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Complete List of Authors:	Filion, Kristian; McGill University Lix, Lisa; University of Manitoba Yu, Oriana; Sir Mortimer B Davis Jewish General Hospital, Centre for Clinical Epidemiology Dell'Aniello, Sophie; Lady Davis Institute for Medical Research, Centre for Clinical Epidemiology Douros, Antonios; McGill University Shah, Baiju; Sunnybrook Health Sciences Centre St-Jean, Audray; Lady Davis Institute for Medical Research Fisher, Anat; The University of British Columbia, Anesthesiology, Pharmacology & Therapeutics Tremblay, Eric; Institut national d'excellence en sante et en services sociaux du Quebec Bugden, Shawn; Memorial University of Newfoundland Alessi-Severini, Silvia; University of Manitoba, College of Pharmacy Ronksley, Paul; University of Calgary, Community Health Sciences Hu, Nianping; Saskatchewan Health Quality Council Dormuth, Colin; The University of British Columbia, Anesthesiology Pharmacology and Therapeutics Ernst, Pierre; McGill University Suissa, Samy; McGill University, Epidemiology and Biostatistics and Medicine; Lady Davis Institute for Medical Research, Centre for Clinical Epidemiology
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SGLT2 Inhibitors and the Risk of Major Adverse Cardiovascular Events: A Multi-database Study Using a Prevalent New-User Design

Short Title: SGLT2 Inhibitors and MACE

Kristian B. Filion, *Associate Professor of Medicine and Epidemiology*[1,2], Lisa M. Lix, *Professor of Community Health*[3], Oriana H.Y. Yu, *Endocrinologist and Assistant Professor of Medicine*[1,4], Sophie Dell'Aniello, *Statistician*[1], Antonios Douros, *Assistant Professor of Medicine*[1,2,5], Baiju R. Shah, *Scientist and Professor of Medicine*[6,7,8], Audray St-Jean, *Research Assistant*[1], Anat Fisher, *Research Associate*[9], Eric Tremblay, *Pharmacist*[10], Shawn C Bugden, *Dean and Professor of Pharmacy*[11,12], Silvia Alessi-Severini, *Associate Professor of Pharmacy*[11,13], Paul E. Ronksley, *Associate Professor of Community Health Sciences*[14], Nianping Hu, *Analyst*[15], Colin R. Dormuth, *Associate Professor*[9], Pierre Ernst, *Professor of Medicine*[1,2], Samy Suissa, *Professor of Medicine and Epidemiology*[1,2] for the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators[*]

[1] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada
[2] Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[3] Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[4] Division of Endocrinology and Metabolism, Jewish General Hospital, McGill University, Montreal, Quebec, Canada
[5] Institute of Clinical Pharmacology and Toxicology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
[6] ICES, Toronto, Ontario, Canada
[7] Division of Endocrinology and Metabolism, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
[8] Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[9] Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, Canada
[10] Institut national d'excellence en santé et en services sociaux (INESSS), Quebec City, Quebec, Canada
[11] College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[12] School of Pharmacy, Memorial University of Newfoundland, St John's, Newfoundland and Labrador, Canada
[13] Manitoba Centre for Health Policy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[14] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary Alberta, Canada
[15] The Health Quality Council, Saskatoon, Saskatchewan, Canada

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Corresponding Author:
Kristian B. Filion PhD, FAHA
Associate Professor and William Dawson Scholar
Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health
McGill University
3755 Cote Ste-Catherine Road, Suite H410.1
Montreal, Quebec, Canada
Telephone: (514) 340-8222 Ext. 28394
Fax: (514) 340-7564
Email: kristian.filion@mcgill.ca

*The Canadian Network for Observational Drug Effect Studies (CNODES) Investigators are: Samy Suissa (Principal Investigator); Colin R. Dormuth (British Columbia); Brenda R. Hemmelgarn (Alberta); Jacqueline Quail (Saskatchewan); Dan Chateau (Manitoba); J. Michael Paterson (Ontario); Jacques LeLorier (Québec); Adrian R. Levy (Atlantic: Nova Scotia, Newfoundland and Labrador, New Brunswick, Prince Edward Island); Pierre Ernst and Kristian B. Filion (UK Clinical Practice Research Datalink (CPRD)); Lisa M. Lix (Database); 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-146021).

ABSTRACT

Objectives: To compare, in a real-world context of clinical practice, the risk of cardiovascular events with sodium-glucose cotransporter 2 (SGLT2) inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors among patients with type 2 diabetes.

Design: Multi-database retrospective cohort study using a prevalent new-user design with subsequent meta-analysis.

Setting: The Canadian Network for Observational Drug Effect Studies (CNODES), with administrative healthcare databases from seven Canadian provinces and the United Kingdom over the period 2013-2018.

Participants: 209,867 new users of a SGLT2 inhibitor matched to 209,867 DPP-4 inhibitor users on time-conditional propensity scores.

Main outcome measures: The primary outcome was major adverse cardiovascular events (MACE, a composite endpoint of myocardial infarction, ischemic stroke, and cardiovascular death). Secondary outcomes were the individual components of MACE, heart failure, and all-cause mortality. We used Cox proportional hazards models to estimate site-specific adjusted hazards ratios (HRs) and 95% confidence intervals (CIs), comparing exposure to SGLT2 inhibitors with DPP-4 inhibitors using an as-treated approach. Site-specific results were pooled using random-effects meta-analysis.

Results: Compared with DPP-4 inhibitors, SGLT2 inhibitors were associated with decreased risks of MACE (HR: 0.76, 95% CI: 0.69 to 0.84), myocardial infarction (HR: 0.82, 95% CI: 0.70 to 0.96), cardiovascular death (HR: 0.60, 95% CI: 0.54 to 0.67), heart failure (HR: 0.43, 95% CI: 0.37 to 0.51), and all-cause mortality (HR: 0.60, 95% CI: 0.54 to 0.67). SGLT2 inhibitors had more modest benefits for ischemic stroke (HR: 0.85, 95% CI: 0.72 to 1.01). Similar benefits with

respect to MACE were observed with canagliflozin (HR: 0.79, 95% CI: 0.66 to 0.94), dapagliflozin (HR: 0.73, 95% CI: 0.63 to 0.85), and empagliflozin (HR: 0.77, 95% CI: 0.68 to 0.87).

Conclusions: In this large observational study conducted in a real-world clinical practice context, SGLT2 inhibitors were associated with a decreased risk of serious cardiovascular events compared with DPP-4 inhibitors.

Trial registration: NCT03939624.

SUMMARY BOX

Section 1: What is already known on the topic

- Sodium-glucose cotransporter 2 (SGLT2) inhibitors are increasingly being used to treat type 2 diabetes.
- Randomized controlled trials have demonstrated that SGLT2 inhibitors reduce the risk of major adverse cardiovascular events (MACE) and heart failure relative to placebo.

Section 2: What this study adds

- SGLT2 inhibitors are associated with a decreased risk of serious cardiovascular events compared with dipeptidyl peptidase-4 (DPP-4) inhibitors among patients with type 2 diabetes in a real-world setting.
- With consistent results across individual SGLT2 inhibitors, this study suggests a class effect regarding the cardiovascular benefits of SGLT2 inhibitors.

INTRODUCTION

Randomized controlled trials (RCTs) have demonstrated that sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the incidence of major adverse cardiovascular events (MACE) among patients with type 2 diabetes and previous cardiovascular disease.[1 2] In the EMPA-REG OUTCOME (EMPAgliflozin Removal of Excess of Glucose OUTCOME) trial, patients randomized to empagliflozin had decreased rates of MACE (a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (hazard ratio [HR]: 0.86, 95% confidence interval [CI]: 0.74 to 0.99) and of hospitalization for heart failure (HR: 0.65, 95% CI: 0.50 to 0.85) compared to those randomized to placebo.[3] Similar benefits were found in the CANVAS (CANagliflozin cardioVascular Assessment Study) trial of canagliflozin.[4] In contrast, the DECLARE (Dapagliflozin Effect on Cardiovascular Events) TIMI 58 trial[5] found that dapagliflozin was non-inferior to placebo for MACE (HR: 0.93, 95% CI 0.84 to 1.03) and superior for hospitalization due to heart failure (HR: 0.73, 95% CI 0.61 to 0.88).[6] While these RCTs demonstrated that SGLT2 inhibitors are efficacious relative to placebo, their cardiovascular effects relative to other second- to third-line antidiabetic therapies remain unknown. Furthermore, the generalizability of these RCT data to a real-world setting is uncertain.[7]

To date, several observational studies have examined the association between SGLT2 inhibitors and cardiovascular outcomes, with the majority of these studies showing a reduced risk relative to other antidiabetic drugs.[8-15] However, a few of these studies had important limitations that render their results difficult to interpret. These limitations include the presence of immortal time bias[16 17] in three studies.[8 9 13] In addition, all of these studies used new user designs and thus excluded individuals with recent use of the comparator drugs. Given the highly dynamic treatment of type 2 diabetes and the frequent use of other second- to third-line therapies prior to the initiation

of SGLT2 inhibitors, such exclusions can greatly impact the generalizability of study results and may even introduce selection bias.[18] Furthermore, limited data are available regarding the cardiovascular effects of individual SGLT2 inhibitors. Our objective was therefore to compare the risks of MACE, its components, all-cause mortality, and heart failure associated with SGLT2 inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors among patients with type 2 diabetes by applying a prevalent new user design to population-based data from eight jurisdictions. This study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES).[19]

METHODS

Data Sources

We implemented a prevalent new-user design in a retrospective multi-database cohort study using administrative healthcare databases from the Canadian provinces of Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec, and Saskatchewan, and the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). The Canadian databases include population-wide data on physician claims, hospitalization records, and prescription drug claims. Prescription drug data are restricted to those aged ≥18 years in Alberta, those aged ≥65 years in Ontario, and those ≥65 years, social assistance recipients, and those without access to a private insurance plan in Quebec. The CPRD is a primary care database that contains the records of more than 15 million patients registered at over 700 general practitioner practices in the UK.[20] Importantly, it includes clinical data not typically found in administrative databases. CPRD data were linked to the Hospital Episode Statistics database, which contains hospital admission information; linkage is available for general practices in England that have consented to the linkage scheme only (currently representing 75% of all practices in England).

The study protocol was registered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT03939624), and research ethics board approval was obtained at each participating site as needed.

Study Population

In each participating site, we identified a source population of all patients who received an antidiabetic drug (metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, alpha-glucosidase inhibitors, meglitinides, insulin, or combinations of these drugs) between January 1, 2006 and June 30, 2018 (or the latest date of data availability at each site). The dates of data availability at each site are

provided in **Supplementary Table 1**. Due to the availability of prescription drug data, the source population in Nova Scotia was restricted to those with an antidiabetic drug dispensing between November 1, 2017 and June 30, 2018. Entry into the source population was defined by the date of the first dispensing (or prescription for CPRD) of an antidiabetic drug during this period. We selected 2006 as the beginning of observation for the source population as 2006 to 2018 corresponds to the period during which DPP-4 inhibitors and SGLT2 inhibitors were approved.

The study cohort included all patients from the source population who received a SGLT2 inhibitor or a DPP-4 inhibitor between the date of the first dispensing of a SGLT2 inhibitor in each site and June 30, 2018 (or the latest date of data availability at each site). The dates of the first SGLT2 inhibitor dispensing at each site are provided in **Supplementary Table 1**. Using a prevalent new-user cohort design,[21] each SGLT2 inhibitor user was matched to a DPP-4 inhibitor user from its exposure set (described below). The study cohort entry date was defined by the SGLT2 inhibitor dispensation date or the corresponding dispensation date for the DPP-4 inhibitor in the matched exposure set.

Patients aged less than 18 years old (<19 years in Alberta and <66 years in Ontario) and those with less than 365 days of healthcare coverage prior to cohort entry date were excluded. Among incident SGLT2 inhibitor users, patients who also initiated a DPP-4 inhibitor on the same date were excluded. In addition, DPP-4 inhibitor patients with a dispensing for a SGLT2 inhibitor before or on the date of cohort entry were excluded. Patients were followed until the occurrence of an event (defined below) or censoring due to discontinuation of the study drug, death, end of healthcare coverage, or end of the study period, whichever occurred first. Separate follow-up times were determined for each outcome. Patients were eligible to enter the cohorts up to two times, a

first time with a DPP-4 inhibitor prescription, and a second time with a SGLT2 inhibitor prescription (but not vice versa given our use of the prevalent new-user design).

Matching

For each new user of SGLT2 inhibitors, exposure sets were defined on the level of antidiabetic therapy (1st, 2nd, or 3rd line), prior use of GLP-1 receptor agonists, time on DPP-4 inhibitors for prevalent new users, and calendar time (DPP-4 inhibitor prescription within 120 days of SGLT2 inhibitor initiation). Level of antidiabetic therapy was determined as: ≥1 insulin prescription in the prior 365 days (3rd line); ≥2 classes of antidiabetic drugs (excluding insulin) in the prior 365 days (2nd line); or other (including patients without any antidiabetic medication in the prior 365 days) (1st line). Prior use of GLP-1 receptor agonists was not used to define exposure sets in Ontario since they were not reimbursed through provincial drug insurance, and data regarding their use was thus not available. Incident SGLT2 inhibitor users were matched to incident DPP-4 inhibitor users who initiated treatment in the same period, while patients switching from a DPP-4 inhibitor to a SGLT2 inhibitor or adding a SGLT2 inhibitor to a DPP-4 inhibitor (prevalent users) were matched to patients who had been using DPP-4 inhibitors for the same amount of time in their exposure sets. A DPP-4 inhibitor user was considered incident if they had no DPP-4 inhibitor dispensing in the prior 12 months.

Time-conditional propensity scores (TCPS) were constructed using conditional logistic regression stratified by exposure set to predict the probability (or propensity) of receiving a SGLT2 inhibitor compared to a DPP-4 inhibitor using covariates defined *a priori* (see **Supplementary Table 2**). Specifically, comorbidities were assessed using the 8th (Ontario outpatient billing only), 9th, and 10th versions of the International Statistical Classification of Diseases and Related Health Problems with Canadian enhancement (ICD-9-CM and ICD-10-CA) diagnostic codes present in physician billing and hospitalization records in the 3 years before cohort entry. Prescription

medication use and healthcare use were assessed in the year before cohort entry. Comorbidities in the CPRD were assessed using ICD-10 codes and Read codes. In the CPRD, the following covariates were also included in the propensity score model: body mass index, smoking status, race, blood pressure, estimated glomerular filtration rate (eGFR), and hemoglobin A1c (HbA1c). Age and diabetes duration were modeled continuously using restricted cubic splines with four knots.

Patients using SGLT2 inhibitors were matched 1:1 without replacement to patients using DPP-4 inhibitors in their exposure set on nearest TCPS and in chronological order. However, five sites experienced a substantial loss of exposure sets when matching without replacement. In sites where there were >10% of exposure sets in which no suitable match was available after trimming the TCPS distribution, matching with replacement was performed. The matching approach adopted at each site is summarized in **Supplementary Table 3**.

Exposure Assessment

Exposure was classified into one of the two mutually exclusive categories at study cohort entry date: 1) current use of SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) alone or in combination with other antidiabetic drugs; or 2) current use of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) alone or in combination with other non-SGLT2 inhibitor antidiabetic drugs. Vildagliptin is only available in the UK. Exposure was defined using an as-treated approach; specifically, exposure was considered time-fixed and defined by the cohort entry drug, and patients were followed until treatment discontinuation, defined as either a gap of ≥30 days between successive prescriptions or the initiation of a SGLT2 inhibitor within the DPP-4 inhibitor cohort.

DPP-4 inhibitors were used as the reference category as both DPP-4 inhibitors and SGLT2 inhibitors are oral agents usually prescribed as a second- or third-line treatment of type 2 diabetes.

In addition, DPP-4 inhibitors have no known association with the cardiovascular outcomes of interest.[22-25]

Outcomes

The primary outcome was MACE, defined as a composite of myocardial infarction, ischemic stroke, or cardiovascular death. Secondary outcomes included the individual endpoints of MACE, all-cause mortality, and hospitalization for heart failure (see **Supplementary Table 4** for ICD-10-CA codes). Myocardial infarction, ischemic stroke, and heart failure were defined using hospitalization data, with a diagnosis recorded in the primary (i.e., most responsible) position and the event date defined by the date of admission. It was not feasible to use vital statistics data to define cardiovascular death due to the recent entry of SGLT2 inhibitors into the market and the lag in the availability of vital statistics data at several sites. Therefore, cardiovascular death was defined using the following algorithm: 1) in-hospital death with a cardiovascular diagnosis; or 2) out-of-hospital death without documentation of cancer in the prior year or trauma in the preceding month. The date of death defined the event date for both cardiovascular death and all-cause mortality.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of patients using frequencies and percentages for categorical variables and means (standard deviation) for continuous variables. Potential imbalances in covariates after matching were assessed using the absolute value of the standardized difference, with a value ≥0.1 considered to be important.

In our primary analysis, we used Cox proportional hazards models to estimate site-specific adjusted HRs and corresponding 95% CIs for MACE among patients exposed to a SGLT2 inhibitor compared to those exposed to a DPP-4 inhibitor. Models were adjusted for age (in years;

continuous), sex, diabetes duration (in years; continuous), and TCPS decile; sites that implemented matching with replacement used a robust sandwich estimate for the covariance matrix.

We conducted 13 pre-specified secondary analyses. We first repeated our primary analysis for the individual components of MACE (myocardial infarction, ischemic stroke, and cardiovascular death), all-cause mortality, and hospitalization for heart failure. We then conducted stratified analyses for MACE and heart failure by age (≥70 and <70 years), sex, prior insulin use (in the previous year), and SGLT2 inhibitor molecule. In addition, we conducted stratified analyses for MACE by prior history of cardiovascular disease, defined by a diagnosis for coronary artery disease, peripheral arterial disease, or cerebrovascular disease in the previous 3 years. Stratified analyses for heart failure were conducted by history of heart failure, defined by two outpatient codes or one inpatient code for heart failure in the previous 3 years.

In sensitivity analyses, MACE and heart failure were analyzed: 1) using an analysis analogous to an intention-to-treat approach in which exposure was defined at cohort entry and patients were followed until the occurrence of an event or censored due to death, end of healthcare coverage, end of the study period, entry into SGLT2 inhibitor cohort for DPP-4 inhibitor patients, or maximum of 1 year of follow-up, whichever occurred first; 2) varying the grace period to define continuous exposure to 0 and 60 days; 3) stratifying by incident and prevalent new-user status; and 4) stratifying prevalent users by the addition of a SGLT2 inhibitor to a DPP-4 inhibitor versus switching to a SGLT2 inhibitor from a DPP-4 inhibitor. Finally, CPRD analyses were repeated with data restricted to variables found in the Canadian databases to examine the amount of residual confounding removed by the inclusion of these variables in the TCPS.

Meta-Analysis

Site-specific adjusted HRs were pooled using DerSimonian and Laird random-effects meta-analytic models with inverse variance weighting. Between-site heterogeneity was estimated

using the I^2 statistic. All site-specific analyses were conducted using SAS version 9.4, and meta-analyses were conducted using Review Manager version 5.3.

Patient and Public Involvement

This study was a secondary data analysis and was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy, and there are no plans to involve patients in the dissemination of study results.

RESULTS

Patient Characteristics

Among 270,902 eligible new users of SGLT2 inhibitors and 632,114 new users of DPP-4 inhibitors (**Figure 1**), 209,867 matched pairs were included in the study cohort. The study population included 103,797 pairs of incident new users and 106,070 pairs of prevalent new users. Baseline characteristics of new users of SGLT2 inhibitors and their matched DPP-4 inhibitor users are described in **Table 1** and **Supplementary Table 5**. After TCPS matching, baseline covariates were well balanced between the two cohorts. Among 209,867 SGLT2 inhibitor users, 42.3% initiated canagliflozin, 30.7% dapagliflozin, and 27.0% empagliflozin at cohort entry. The distribution of the additional characteristics of SGLT2 inhibitor and DPP-4 inhibitor users in the CPRD are presented in **Supplementary Table 6**. Some imbalance was present in eGFR, with SGLT2 inhibitor users having a lower prevalence of eGFR <60 mL/min/1.73m^2; both groups were balanced on other covariates.

Cardiovascular Outcomes

Overall, the mean duration of follow-up in the matched cohort for the primary outcome of MACE was 0.9 years (standard deviation: 0.76), generating a total of 370,515 person-years of observation time. During follow-up, MACE occurred in 2,146 SGLT2 inhibitor users (incidence rate: 11.4 per 1,000 person-years) and 3,001 DPP-4 inhibitor users (incidence rate: 16.5 per 1,000 person-years) (**Figure 2**). Crude incidence rates and crude and adjusted HRs for all outcomes are reported in **Table 2**. Compared with DPP-4 inhibitors, SGLT2 inhibitors were associated with a decreased risk of MACE (HR: 0.76; 95% CI: 0.69 to 0.84; I^2: 47%; **Figure 3**). They were also associated with decreased risks of myocardial infarction (HR: 0.82; 95% CI: 0.70 to 0.96; I^2: 53%; **Supplementary Figure 1**) and cardiovascular death (HR: 0.60; 95% CI: 0.54 to 0.67; I^2: 14%; **Supplementary Figure 2**), with a more modest effect for ischemic stroke (HR: 0.85; 95% CI:

0.72 to 1.01; I^2: 28%; **Supplementary Figure 3**). In addition, SGLT2 inhibitors were associated with decreased risks of all-cause mortality (HR: 0.60; 95% CI: 0.54 to 0.67; I^2: 42%; **Supplementary Figure 4**) and hospitalization for heart failure (HR: 0.43; 95% CI: 0.37 to 0.51; I^2: 43%; **Figures 4 and 5**).

Stratified and Sensitivity Analyses

The stratified analyses for MACE and heart failure are shown in **Table 3**. These analyses revealed no evidence of effect modification by age, sex, prior insulin use, or SGLT2 inhibitor molecule. In addition, there was no difference in the estimated associations with MACE and heart failure among patients with a history of cardiovascular disease or those with a history of heart failure, respectively. Overall, sensitivity analyses produced results that were consistent with those of our primary analyses for both MACE and heart failure (**Table 4**), though our analysis stratified by incident versus prevalent user cannot exclude potentially stronger benefits with SGLT2 inhibitors among prevalent users. In addition, similar estimates were obtained with and without the use of clinical covariates available in the CPRD only for all outcomes except ischemic stroke, where a higher point estimate was obtained in analyses that did not include these variables but 95% CIs largely overlapped (**Supplementary Table 7**).

DISCUSSION

In this large multi-database retrospective cohort study, we found that the use of SGLT2 inhibitors was associated with a decreased risk of MACE compared to DPP-4 inhibitor use among patients with type 2 diabetes (HR: 0.76; 95% CI: 0.69 to 0.84). Beneficial effects were observed for the individual endpoints of MACE. The strong association with MACE was mainly driven by the cardiovascular death endpoint (HR: 0.60; 95% CI: 0.54 to 0.67). We also observed decreased risks of all-cause mortality (HR: 0.60; 95% CI: 0.54 to 0.67) and heart failure (HR: 0.43; 95% CI: 0.37 to 0.51) in patients using SGLT2 inhibitors compared to those using DPP-4 inhibitors. Similar results were observed for canagliflozin, dapagliflozin, and empagliflozin and across patient subgroups defined by age, sex, prior use of insulin, and history of cardiovascular disease or history of heart failure.

Our study has several strengths. The use of an active comparator used at a similar stage of diabetes treatment and rigorous matching minimized potential confounding bias. Our large sample size permitted the calculation of precise estimates for the primary and secondary outcomes. This sample size also allowed for the examination of molecule-specific associations, representing a key addition to the literature. The consistency of results across several sensitivity analyses further supports the robustness of our results. Finally, the registration of our study protocol enhanced the transparency of reporting.

Our study also has potential limitations. First, residual or unmeasured confounding bias remains possible. We used different approaches to minimize this potential bias, including the use of an active comparator, the prevalent new-user design, and propensity score matching. In addition, we assessed the possible effect of residual confounding using the CPRD, which includes clinical measures not typically found in administrative data. Sensitivity analyses conducted in the CPRD

suggest that these variables were not strong confounders in this study. Second, exposure misclassification is possible as prescription drug data represent dispensations (or prescriptions written for the CPRD) and not actual consumption. Third, there is potential outcome misclassification for cardiovascular death defined using our algorithm. A sensitivity analysis restricted to the subset of patients for which vital statistics were available produced results that were consistent with the primary analysis but with wider CIs (HR: 0.78; 95% CI: 0.63 to 0.97). Fourth, although we had a large sample size, the number of events were limited in some stratified analyses. Fifth, ertugliflozin was not available during the study period and was thus excluded from our assessment. Finally, the mean duration of follow-up was 0.9 years only, and it is possible that the observed findings may be related to short-term hemodynamic effects of SGLT2 inhibitors rather than long-term disease-modifying benefits. There remains a need to assess their long-term comparative effectiveness and safety as additional real-world evidence becomes available.

Placebo-controlled RCTs of SGLT2 inhibitors have reported a decreased risk of MACE in patients randomized to canagliflozin or empagliflozin, with dapagliflozin reaching non-inferiority but not superiority with respect to MACE.[3-6] A decrease in hospitalization for heart failure was observed in RCTs for all three molecules. While these placebo-controlled RCTs provided important information regarding the cardiovascular effects of SGLT2 inhibitors, they also had important limitations. All three were conducted in patients with either established cardiovascular disease or at high risk of cardiovascular disease, further limiting the generalizability of their results to a real-world setting. Furthermore, while the use of placebo offers greater assay sensitivity (i.e., the ability to determine if a treatment is effective or not) relative to an active comparator,[26] the differential use of rescue medications among those with poorly controlled blood glucose hampers this sensitivity, particularly given the known cardiotoxic effects of some antidiabetic drugs (e.g.,

thiazolidinedione and heart failure[27], sulfonylureas and cardiovascular death[28]). The use of an active comparator used at the same point in the management of type 2 diabetes overcomes these limitations and provides a more clinically- and policy-relevant comparison.

Previous observational studies also suggest a reduced risk of heart failure and all-cause mortality.[8-15 29] However, observational studies have provided more heterogeneous results for MACE, with some studies finding a protective effect[8 9 13 14] and others finding no benefit.[10 12 15] Of note, the definition of MACE varied across studies.[8-10 12 14] Some of this heterogeneity may also be explained by the use of different comparators, with some studies comparing SGLT2 inhibitors to a reference group consisting of 'other antidiabetic drugs'.[8-10 13] With a heterogeneous reference group, the results can be difficult to interpret and, depending on the distribution of antidiabetic drugs in the reference group, time-lag bias (confounding by disease severity[30]) can occur. In addition, some studies[8 9 13] may have been affected by immortal time bias that tends to exaggerate their effectiveness.[16 17]

Our use of a prevalent new-user design allowed us to include patients with a recent history of DPP-4 inhibitor use, thus better reflecting real-world practice. Indeed, the use of an active comparator new user approach[31] would have resulted in the exclusion of approximately 50% of our study cohort. Thus, this methodological approach, combined with the use of data from seven Canadian provinces and the UK and broad inclusion criteria, has greatly increased the generalizability of results relative to previous studies in this area. Our use of TCPS produced treatment groups that were very well balanced with respect to baseline characteristics. Indeed, the one characteristic for which an imbalance remained was renal insufficiency (defined by eGFR<60 ml/min/1.73m^2) in analyses restricted to the CPRD. This finding is not unexpected given that SGLT2 inhibitors are generally not recommended among patients with renal insufficiency.[32]

Ultimately, with data from eight jurisdictions across two countries, our study adds clarity to the heterogeneous treatment effects reported by previous observational studies, providing precise estimates of the beneficial cardiovascular effects of SGLT2 inhibitors in a real-world setting.

CONCLUSIONS

In this large multi-database cohort study, the use of SGLT2 inhibitors was associated with a decreased risk of MACE compared to the use of DPP-4 inhibitors among patients with type 2 diabetes. Benefits were observed for the individual endpoints of MACE, all-cause mortality, and heart failure. Similar reductions in MACE were observed for canagliflozin, dapagliflozin, and empagliflozin and across patient subgroups defined by age, sex, prior use of insulin, and history of cardiovascular disease. These findings suggest that SGLT2 inhibitors offer cardioprotective benefits among patients with type 2 diabetes in a real-world setting.

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CONTRIBUTIONS OF AUTHORS

KBF drafted the manuscript. All authors contributed to the study design and implementation, interpretation of results, and critically reviewed the manuscript for important intellectual content. LL conducted the meta-analyses. All authors approved the final version of the manuscript. KBF is the guarantor.

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ETHICAL APPROVAL

Research ethics board approval was obtained at each participating site except Ontario, where the need for ethics approval was waived.

DATA SHARING

No additional data available.

TRANSPARENCY DECLARATION

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained. *The manuscript's guarantor.

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Table 1. Baseline characteristics of users of SGLT2 inhibitors and their matched DPP-4 inhibitor users.*

Characteristic	SGLT2 inhibitors (n = 209,867)	DPP-4 inhibitors (n = 209,867)	Standardized difference
Age (years)	63.8 ± 9.5	64.0 ± 9.6	0.028
18-35	3,536 (1.7)	3,636 (1.7)	0.004
36-45	12,456 (5.9)	11,990 (5.7)	0.009
46-55	31,302 (14.9)	30,472 (14.5)	0.011
56-65	48,290 (23.0)	48,486 (23.1)	0.002
66-75	90,031 (42.9)	88,813 (42.3)	0.012
76-85	22,226 (10.6)	24,251 (11.6)	0.031
>85	2,026 (1.0)	2,219 (1.1)	0.009
Site			
Alberta	26,186 (12.5)	26,186 (12.5)	-
British Columbia	44,043 (21.0)	44,043 (21.0)	-
Manitoba	12,204 (5.8)	12,204 (5.8)	-
Nova Scotia	1,119 (0.5)	1,119 (0.5)	-
Ontario	65,556 (31.2)	65,556 (31.2)	-
Quebec	44,504 (21.2)	44,504 (21.2)	-
Saskatchewan	10,832 (5.2)	10,832 (5.2)	-
CPRD	5,423 (2.6)	5,423 (2.6)	-
Females	87,076 (41.5)	87,650 (41.8)	0.006
Calendar year at cohort entry			
2013	323 (0.2)	325 (0.2)	0.000
2014	7,131 (3.4)	8,082 (3.9)	0.024
2015	52,091 (24.8)	51,361 (24.5)	0.008
2016	66,816 (31.8)	66,569 (31.7)	0.003
2017	61,792 (29.4)	61,504 (29.3)	0.003
2018	21,714 (10.3)	22,026 (10.5)	0.005
Diabetes duration (years)	12.5 ± 6.5	12.5 ± 6.5	0.001
<1 year	7,194 (3.4)	7,412 (3.5)	0.006
1-4.9 years	25,401 (12.1)	25,570 (12.2)	0.002
5-10 years	52,681 (25.1)	52,685 (25.1)	0.000
>10 years	124,591 (59.4)	124,200 (59.2)	0.004
Comorbidities†			
Alcohol-related disorders	2,975 (1.4)	2,992 (1.4)	0.001
Aortic aneurysm	1,503 (0.7)	1,568 (0.7)	0.004
Atherosclerosis	4,221 (2.0)	4,226 (2.0)	0.000
Atrial fibrillation	7,336 (3.5)	7,516 (3.6)	0.005
Cancer	21,575 (10.3)	21,882 (10.4)	0.005
Cerebrovascular disease	10,024 (4.8)	10,218 (4.9)	0.004
Cirrhosis	3,586 (1.7)	3,497 (1.7)	0.003

Characteristic	SGLT2 inhibitors (n = 209,867)	DPP-4 inhibitors (n = 209,867)	Standardized difference
COPD	20,824 (9.9)	20,885 (10.0)	0.001
Coronary artery disease	45,532 (21.7)	44,871 (21.4)	0.008
Dementia	2,203 (1.0)	2,359 (1.1)	0.007
Diabetic nephropathy	7,610 (3.6)	7,796 (3.7)	0.005
Diabetic neuropathy	4,033 (1.9)	3,944 (1.9)	0.003
Diabetic retinopathy	5,371 (2.6)	5,618 (2.7)	0.007
Dialysis	284 (0.1)	316 (0.2)	0.004
Dyslipidemia	170,806 (81.4)	170,146 (81.1)	0.008
Heart failure	11,625 (5.5)	11,762 (5.6)	0.003
Hypertension	108,231 (51.6)	108,768 (51.8)	0.005
Hypoglycemia	1,051 (0.5)	1,086 (0.5)	0.002
Ischemic stroke	2,499 (1.2)	2,664 (1.3)	0.007
Myocardial infarction	5,585 (2.7)	5,415 (2.6)	0.005
Other kidney disease	10,011 (4.8)	10,939 (5.2)	0.020
Peripheral arterial disease	4,862 (2.3)	4,852 (2.3)	0.000
Use of antidiabetic drugs[†]			
Alpha-glucosidase inhibitors	3,107 (1.5)	3,130 (1.5)	0.001
GLP-1 receptor agonists	9,180 (4.4)	9,180 (4.4)	0.000
Insulin	58,330 (27.8)	58,330 (27.8)	0.000
Meglitinides	4,736 (2.3)	4,773 (2.3)	0.001
Metformin	185,681 (88.5)	185,426 (88.4)	0.004
Sulfonylureas	109,139 (52.0)	109,132 (52.0)	0.000
Thiazolidinediones	5,315 (2.5)	5,114 (2.4)	0.006
Health care use[†]			
Inpatient hospitalizations			
0	178,223 (84.9)	177,700 (84.7)	0.007
1-2	29,226 (13.9)	29,567 (14.1)	0.005
≥3	2,418 (1.2)	2,600 (1.2)	0.008
Number of physician visits			
0-2	15,009 (7.2)	15,281 (7.3)	0.005
3-5	32,078 (15.3)	31,677 (15.1)	0.005
≥6	162,780 (77.6)	162,909 (77.6)	0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2.

[*]Data are presented as n (%) or mean ± SD. SGLT2 inhibitors patients were matched to DPP-4 inhibitors patients from their exposure set (defined on level of antidiabetic therapy, prior use of GLP-1 receptor agonists, time on DPP-4 inhibitors for prevalent new users and calendar time) on time-conditional propensity score. Site-specific cells that contained a value <6 were suppressed due to privacy restrictions and were assumed to have a value of 3.

†Comorbidities were assessed in the 3 years prior to study cohort entry. Medication use and healthcare use were assessed in the year before cohort entry.

Table 2. Crude and adjusted hazard ratios for the association between SGLT2 inhibitors versus DPP-4 inhibitors and the risk of cardiovascular outcomes.

	No. of events	Person-years	Crude incidence rate (per 1,000 person-years)	Crude HR (95% CI)*	Adjusted models*,†	
					HR (95% CI)	I^2
MACE						
SGLT2 inhibitors	2,146	188,782	11.4	0.72 (0.65 to 0.80)	0.76 (0.69 to 0.84)	47%
DPP-4 inhibitors	3,001	181,733	16.5	1.00 (Reference)	1.00 (Reference)	
Myocardial infarction						
SGLT2 inhibitors	995	196,503	5.1	0.81 (0.72 to 0.92)	0.82 (0.70 to 0.96)	53%
DPP-4 inhibitors	1,169	182,398	6.4	1.00 (Reference)	1.00 (Reference)	
Ischemic stroke						
SGLT2 inhibitors	501	190,047	2.6	0.78 (0.68 to 0.89)	0.85 (0.72 to 1.01)	28%
DPP-4 inhibitors	636	182,731	3.5	1.00 (Reference)	1.00 (Reference)	
Cardiovascular death						
SGLT2 inhibitors	738	189,276	3.9	0.55 (0.47 to 0.65)	0.60 (0.54 to 0.67)	14%
DPP-4 inhibitors	1,399	182,746	7.7	1.00 (Reference)	1.00 (Reference)	
All-cause mortality						
SGLT2 inhibitors	1,651	189,278	8.7	0.54 (0.48 to 0.60)	0.60 (0.54 to 0.67)	42%
DPP-4 inhibitors	3,156	183,075	17.3	1.00 (Reference)	1.00 (Reference)	
Heart failure						
SGLT2 inhibitors	587	189,058	3.1	0.40 (0.35 to 0.46)	0.43 (0.37 to 0.51)	43%
DPP-4 inhibitors	1,401	181,956	7.7	1.00 (Reference)	1.00 (Reference)	

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

*SGLT2 inhibitors patients were matched to DPP-4 inhibitors patients from their exposure set (defined on level of antidiabetic therapy, time on DPP-4 inhibitors for prevalent new users only, prior use of GLP-1 receptor agonists, and within 120 days of the SGLT2 prescription) on time-conditional propensity score.

†Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.

Table 3. Summary of results of stratified analyses of pooled adjusted hazard ratios (95% CI) for MACE and heart failure for SGLT2 inhibitor use versus DPP-4 inhibitor use.

		Adjusted HR (95% CI)**	I^2
MACE			
Main analysis		0.76 (0.69 to 0.84)	47%
Age	≥70 years	0.75 (0.67 to 0.85)	19%
	<70 years	0.77 (0.69 to 0.87)	33%
Sex	Females	0.65 (0.58 to 0.72)	2%
	Males	0.81 (0.72 to 0.91)	39%
History of cardiovascular disease*	Yes	0.71 (0.58 to 0.88)	71%
	No	0.77 (0.68 to 0.86)	34%
Prior insulin use†	Yes	0.75 (0.66 to 0.86)	32%
	No	0.76 (0.68 to 0.86)	38%
SGLT2 inhibitor molecule	Canagliflozin	0.79 (0.66 to 0.94)	67%
	Dapagliflozin	0.73 (0.63 to 0.85)	32%
	Empagliflozin	0.77 (0.68 to 0.87)	1%
Heart failure			
Main analysis		0.43 (0.37 to 0.51)	43%
Age	≥70 years	0.46 (0.36 to 0.61)	53%
	<70 years	0.39 (0.30 to 0.50)	49%
Sex	Females	0.42 (0.35 to 0.49)	0%
	Males	0.50 (0.39 to 0.65)	62%
History of heart failure‡	Yes	0.44 (0.35 to 0.55)	33%
	No	0.47 (0.41 to 0.53)	0%
Prior insulin use†	Yes	0.45 (0.39 to 0.52)	1%
	No	0.47 (0.40 to 0.55)	9%
SGLT2 inhibitor molecule	Canagliflozin	0.41 (0.32 to 0.52)	42%
	Dapagliflozin	0.44 (0.36 to 0.54)	0%
	Empagliflozin	0.52 (0.43 to 0.65)	4%

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; MACE, major adverse cardiac events; SGLT2, sodium-glucose cotransporter 2.

*History of cardiovascular disease was defined by coronary artery disease or peripheral arterial disease or cerebrovascular disease in the 3 years prior.

†Prior insulin use was defined as prescription for insulin in the year prior.

‡History of heart failure was defined by two outpatient codes or one inpatient code in the 3 years prior.

**Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.

Note: Nova Scotia had zero events in one of the exposure groups and thus was not included in the cardiovascular disease (yes) analysis for MACE and the age (≥70 years), sex, history of heart failure, and SGLT2 inhibitor molecule analyses for heart failure.

Table 4. Summary of results of sensitivity analyses of pooled adjusted hazard ratios (95% CI) for MACE and heart failure for SGLT2 inhibitor use versus DPP-4 inhibitor use.

	Adjusted HR (95% CI)*	I^2
MACE		
Main analysis	0.76 (0.69 to 0.84)	47%
Intention-to-treat approach	0.80 (0.73 to 0.88)	45%
Grace period		
0 days	0.75 (0.67 to 0.85)	0%
60 days	0.75 (0.69 to 0.81)	34%
New user status		
Incident users	0.81 (0.71 to 0.93)	44%
Prevalent users	0.71 (0.65 to 0.76)	0%
Prevalent users		
Adding a SGLT2 inhibitor	0.72 (0.63 to 0.82)	0%
Switching to a SGLT2 inhibitor	0.70 (0.64 to 0.77)	0%
Heart failure		
Main analysis	0.43 (0.37 to 0.51)	43%
Intention-to-treat approach	0.52 (0.45 to 0.61)	43%
Grace period		
0 days	0.47 (0.32 to 0.69)	48%
60 days	0.43 (0.35 to 0.53)	68%
New user status		
Incident users	0.46 (0.38 to 0.56)	26%
Prevalent users	0.41 (0.30 to 0.55)	55%
Prevalent users		
Adding a SGLT2 inhibitor	0.40 (0.31 to 0.51)	0%
Switching to a SGLT2 inhibitor	0.39 (0.27 to 0.56)	62%

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; MACE, major adverse cardiac events; SGLT2, sodium-glucose cotransporter 2.

* Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.

Note: Nova Scotia had zero events in one of the exposure groups and thus was not included in the following analyses for MACE: grace period (0 day), new user status (prevalent users), and prevalent users. Nova Scotia, Alberta, Saskatchewan, and the CPRD had zero events in one of the exposure groups in the prevalent user analysis involving the addition of a SGLT2 inhibitor and were thus excluded from this analysis.

FIGURE LEGENDS

Figure 1. Flow chart describing the construct of the study cohort. Notes: (a) Numbers may not add up because site-specific cells with a value <6 were suppressed due to privacy restrictions; (b) Patients <19 years in Alberta and <66 years in Ontario were excluded; (c) Patients were eligible to enter the study cohort a maximum of two times, a first time with a DPP-4 prescription and a second time with a SGLT2 prescription. Abbreviations: DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose cotransporter 2.

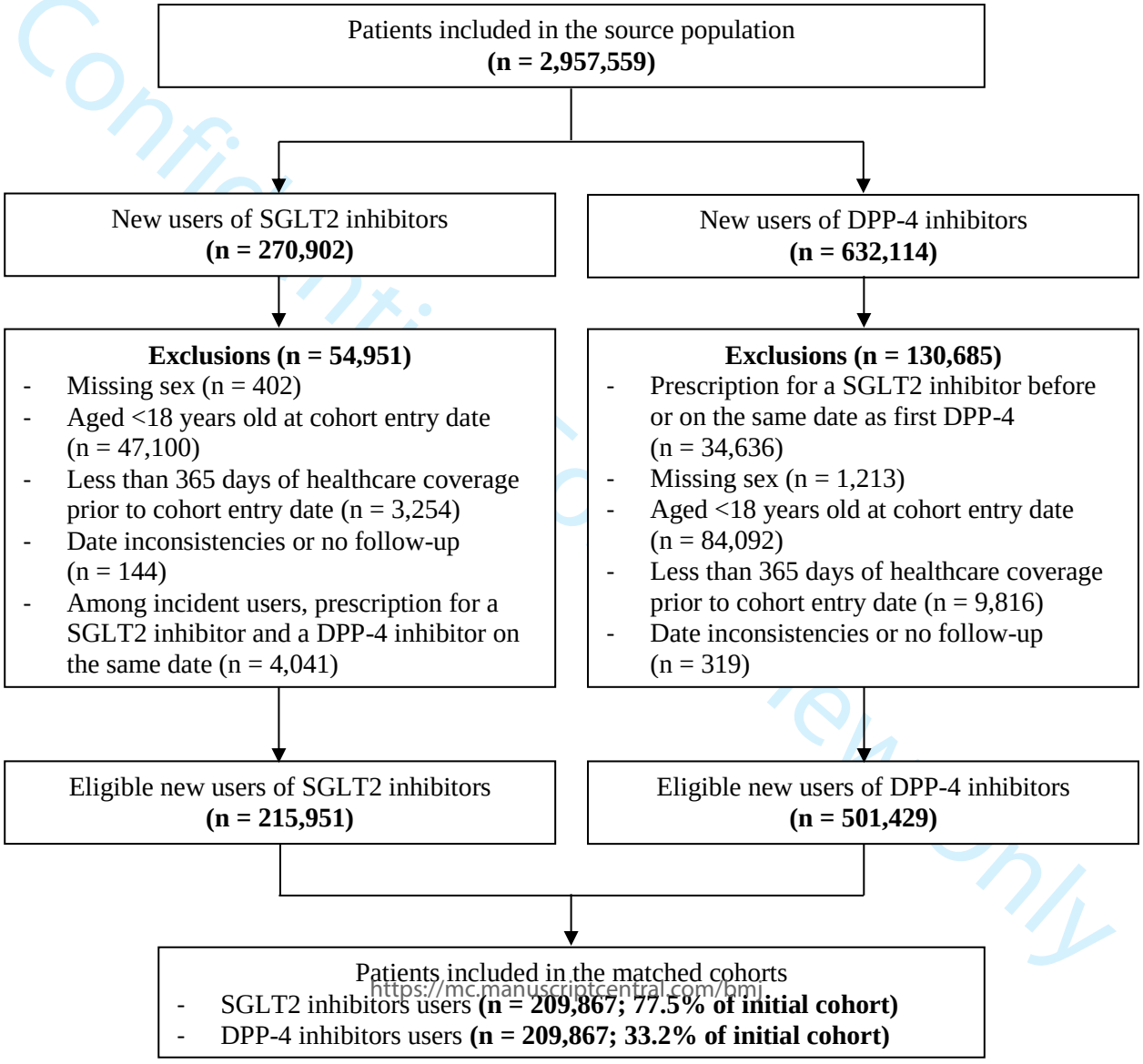
Figure 2. Cumulative incidence of MACE among SGLT2 inhibitor users and matched DPP-4 inhibitor users in the two largest sites: a) Ontario; b) Quebec.

Figure 3. Adjusted hazard ratios (95% CI) of MACE associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use. Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score. Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; MACE, major adverse cardiac events; SGLT2, sodium-glucose cotransporter 2.

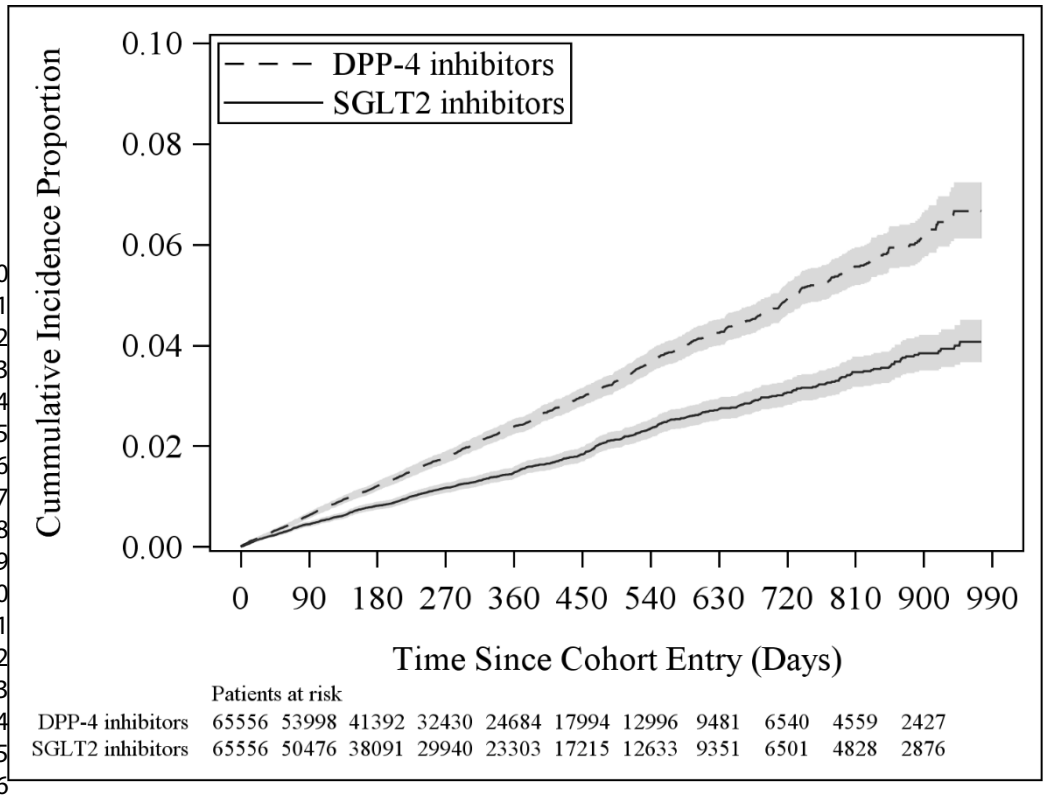
Figure 4. Cumulative incidence of heart failure among SGLT2 inhibitor users and matched DPP-4 inhibitor users in the two largest sites: a) Ontario; b) Quebec.

Figure 5. Adjusted hazard ratios (95% CI) of heart failure associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use. Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score. Abbreviations: CI, confidence interval; DPP-4, dipeptidyl

Figure 1.



a) Ontario



b) Quebec

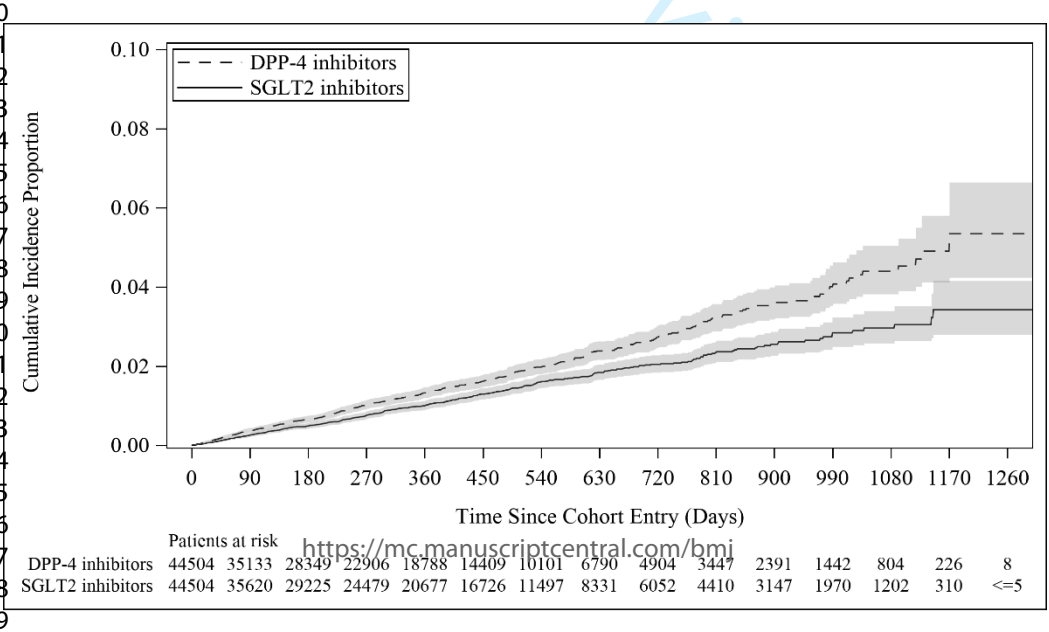
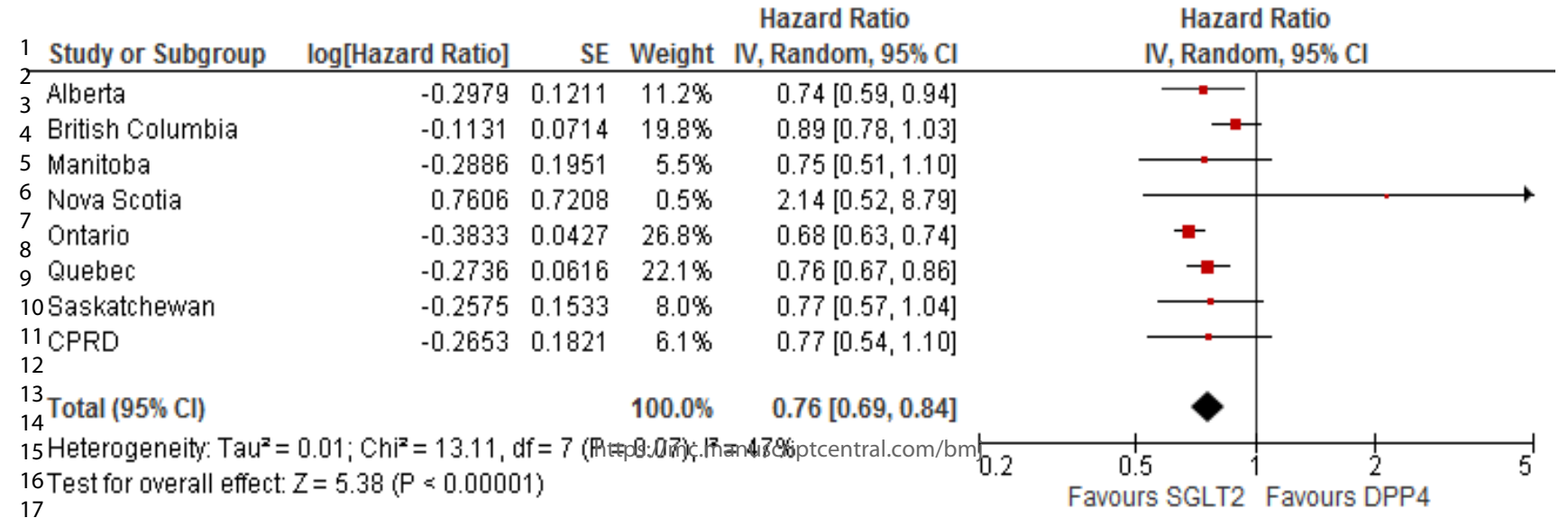
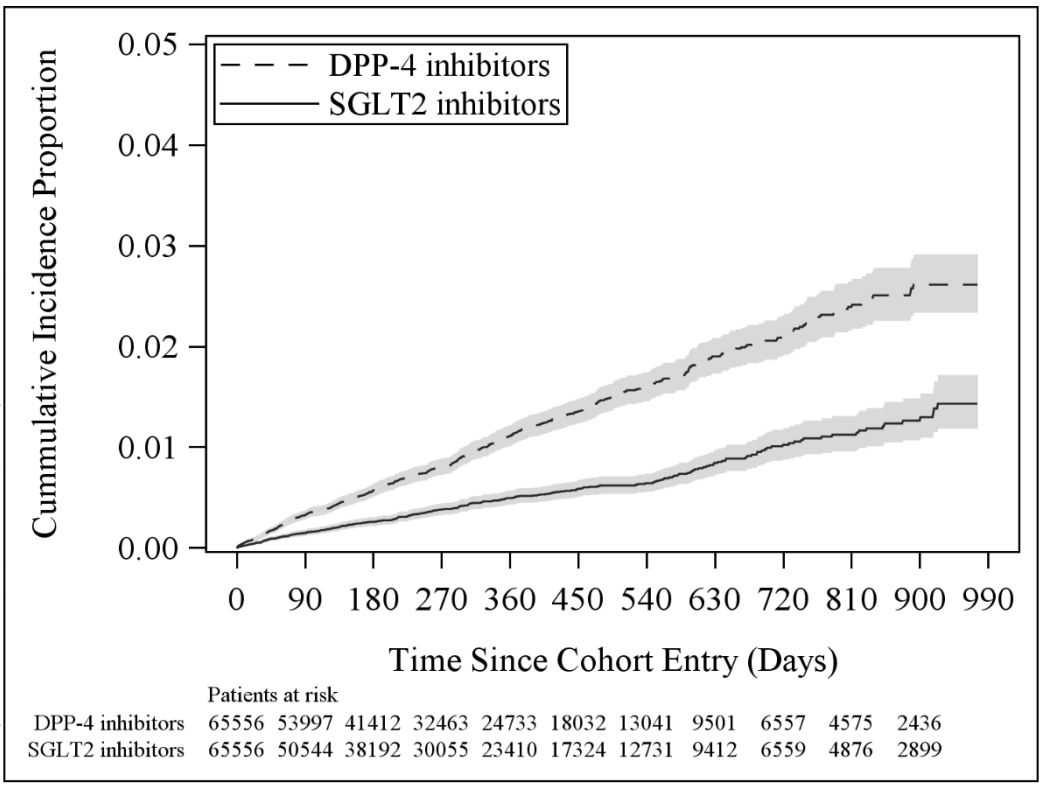


Figure 3



a) Ontario



b) Quebec

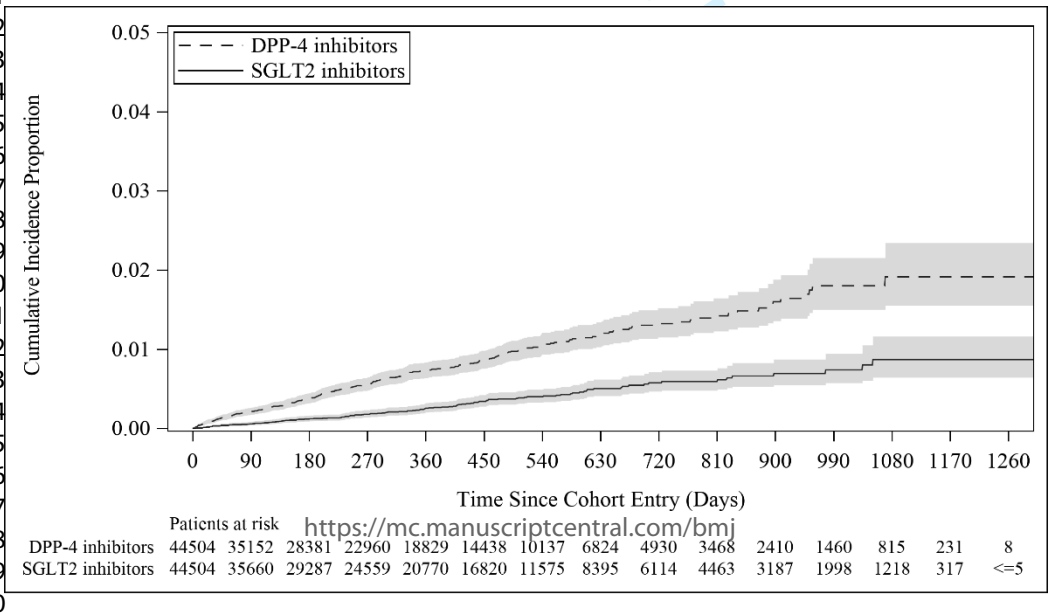
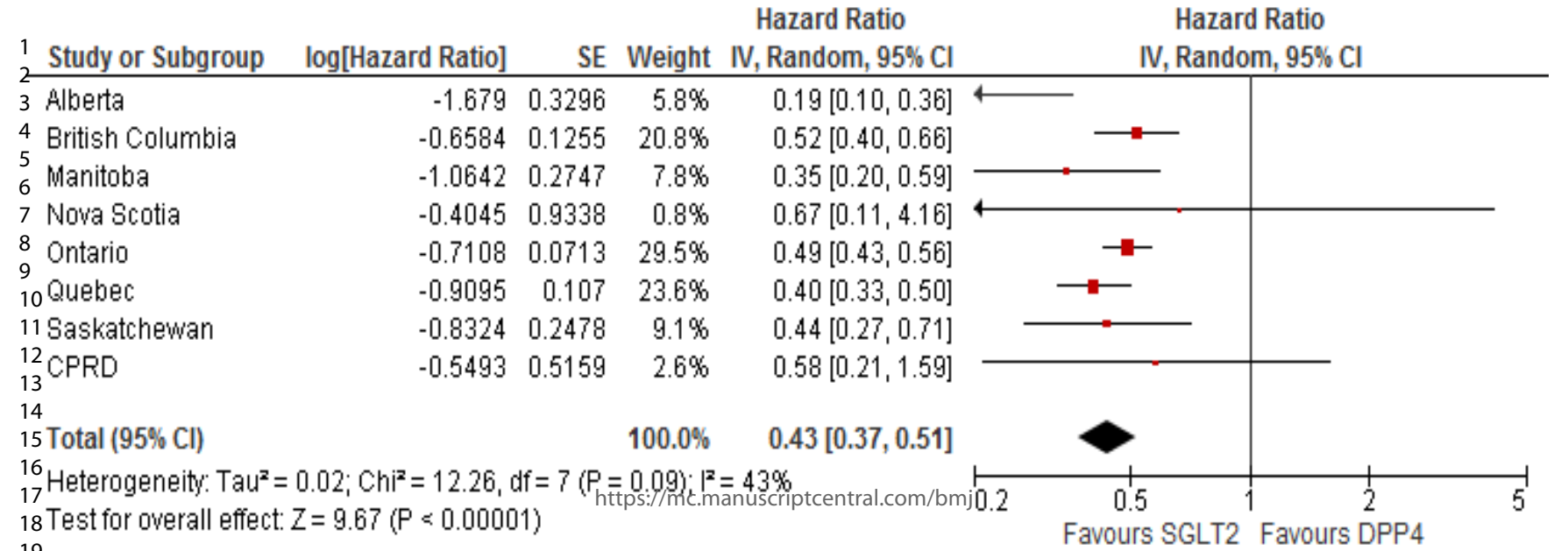


Figure 5



SUPPLEMENTARY MATERIAL

Supplementary Table 1. Start and end dates of study period at each participating site for the identification of the source population and date of first recorded SGLT2 inhibitor dispensing.

	Dates for identification of source population		
Site	**Start date**	**End date**	**Date of first SGLT2 inhibitor**
Alberta	January 1, 2008	March 31, 2017	June 6, 2014
British Columbia	January 1, 2006	June 30, 2018	June 3, 2014
Manitoba	January 1, 2006	March 31, 2018	June 9, 2014
Nova Scotia*	November 1, 2016	June 30, 2018	November 1, 2017
Ontario	January 1, 2006	March 31, 2018	July 29, 2015
Quebec	January 1, 2006	June 30, 2018	September 4, 2014
Saskatchewan	February 13, 2008	June 30, 2018	June 27, 2014
CPRD	January 1, 2006	December 31, 2017	February 4, 2013

Abbreviations: CPRD, Clinical Practice Research Datalink; SGLT2, sodium-glucose cotransporter 2.

*Due to limitations in prescription drug data availability, patients were only included from November 1, 2017 to June 30, 2018.

Supplementary Table 2. Covariates included in the time-conditional propensity score model*.

Covariates	Comment (if applicable)*
Demographic	
Age	Defined at cohort entry date
Sex	
Socioeconomic status	A site-specific definition was applied
Diabetes duration	Time since the first diabetes diagnosis or treatment
Comorbidities	
Alcohol-related disorders	
Aortic aneurysm	
Atherosclerosis	
Atrial fibrillation	
Cancer	Excluding non-melanoma skin cancer
Cerebrovascular disease	
Chronic obstructive pulmonary disease	
Cirrhosis	
Coronary artery disease	
Dementia	Defined by a diagnosis of dementia (in the prior 3 years) or a prescription for cholinesterase inhibitors or memantine (in the prior year)
Diabetic nephropathy	
Diabetic neuropathy	
Diabetic retinopathy	
Dialysis	Defined using diagnosis and procedure codes
Dyslipidemia	Diagnosis of dyslipidemia (in the prior 3 years) or a prescription for a statin or other lipid lowering therapy (in the prior year)
Heart failure	
Hypertension	
Hypoglycemia	Hospitalization with a diagnosis in any position in the prior 3 years
Ischemic stroke	
Myocardial infarction	
Other kidney disease	
Peripheral arterial disease	
Use of medications	
Acetylsalicylic acid	
Aldosterone antagonists	
Alpha-glucosidase inhibitors	
Angiotensin II receptor blockers	
Angiotensin-converting enzyme inhibitors	
Beta-blockers	
Calcium channel blockers	

Covariates	Comment (if applicable)*
Digitalis-like agents	
Insulin	
Loop diuretics	
Meglitinides	
Metformin	
Non-acetylsalicylic acid antiplatelet drugs	
Nonsteroidal anti-inflammatory drugs	
Oral anticoagulants	
Oral glucocorticoids	
Other diuretics	
Sulfonylureas	
Thiazide diuretics	
Thiazolidinediones	
No. of different classes of non-antidiabetic medications	Measured by drug class using site-specific approaches and assessed in the 365 days prior to and including study cohort entry. Categorized as 0-1, 2-5, or ≥6
Healthcare use	
Number of inpatient hospitalizations	In the 365 days prior to and including study cohort entry Categorized as 0, 1-2, or ≥3
Number of physician visits	Included inpatient and outpatient visits in the 365 days prior to study cohort entry Categorized as 0-2, 3-5, or ≥6
Additional CPRD covariates	
Blood pressure (mm Hg)	Based on the last measurement before study cohort entry Categorized as DBP <90 mm Hg and SBP <140 mm Hg, DBP ≥90 mm Hg or SBP ≥140 mm Hg, or missing
Body mass index (kg/m^2)	Based on the last measurement before study cohort entry Categorized as <30 kg/m^2, ≥30 kg/m^2, or missing
eGFR (mL/min/1.73 m^2)	Based on the last measurement before study cohort entry Categorized as <60, ≥60, or missing
HbA1c (%)	Based on the last measurement before study cohort entry Categorized as ≤7, 7.1-8, >8, or missing
Race	Assessed ever before study cohort entry Categorized as white, other, or missing
Smoking status	Based on the last measurement before study cohort entry Categorized as never, ever, or missing

Abbreviations: ATC, Anatomical Therapeutic Chemical; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; SBP, systolic blood pressure.

*Unless otherwise specified, comorbidities were ascertained from hospitalization or physician claims data in the three years prior to study cohort entry. Medications and healthcare use were assessed in the year prior to study cohort entry. Comorbidities were measured using ICD-9-CM for outpatient claims (except Ontario, which used ICD-8 codes, and CPRD, which used Read

codes) and ICD-10-CA for hospitalization records, and procedures were defined using ICD-9-CM, CCP and CCI + site-specific procedure codes.

Supplementary Table 3. Approach implemented to match SGLT2 inhibitor users to DPP-4 inhibitor users within each exposure risk set at each participating site.

Site	Without replacement	With replacement
Alberta		✓
British Columbia		✓
Manitoba		✓
Nova Scotia		✓
Ontario	✓	
Quebec	✓	
Saskatchewan*		✓
CPRD	✓	

Abbreviations: CPRD: Clinical Practice Research Datalink.
*Matching with replacement by randomly selecting a match using a caliper of ± 0.2 standard deviations of the ln (time-conditional propensity score).

Supplementary Table 4. Diagnoses codes used in outcome definitions.

Variable	ICD-10-CA code
Myocardial infarction	I21.x Acute myocardial infarction
Ischemic stroke	I63.x Cerebral infarction I64.x Stroke, not specified as haemorrhage or infarction

Cardiovascular death	Defined using the following algorithm:
	• In-hospital death with a cardiovascular diagnosis [ICD-10-CA: I00.x-I77.x (except I46.9)] recorded as the most responsible diagnosis or present on admission; or
	• Out-of-hospital death (including death in the emergency department if data available) without:
	  ○ Documentation of cancer (ICD-9-CM: 140-172, 174-209; ICD-10-CA: C00-C43, C45-C97) in hospital, emergency department or physician claims data in the prior year; or
	  ○ Documentation of trauma (ICD-9-CM: 800-999, E000-E999; ICD-10-CA: S00-T98, V01-Y98) in hospital, emergency department or physician claims data in the preceding month.

Heart failure	I11.0 Hypertensive heart disease with (congestive) heart failure I13.0 Hypertensive heart and renal disease with (congestive) heart failure I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal failure I50.x Heart failure

Abbreviations: ICD-10-CA, International Classification of Diseases, 10th revision, with Canadian Enhancement. ICD-9-CM, International Classification of Diseases, 9th revision.

Supplementary Table 5. Baseline non-antidiabetic medication use among users of SGLT2 inhibitors and their matched DPP-4 inhibitor users.*

Medications†	SGLT2 inhibitors (n = 209,867)	DPP-4 inhibitors (n = 209,867)	Standardized difference
ACEI	95,629 (45.6)	94,973 (45.3)	0.006
Acetylsalicylic acid	37,258 (17.8)	37,223 (17.7)	0.000
Aldosterone antagonists	6,259 (3.0)	6,068 (2.9)	0.005
ARB	67,320 (32.1)	66,996 (31.9)	0.003
Beta-blockers	59,531 (28.4)	59,009 (28.1)	0.006
Calcium channel blockers	64,200 (30.6)	64,322 (30.6)	0.001
Cholinesterase inhibitors or memantine	1,282 (0.6)	1,366 (0.7)	0.005
Digitalis-like agents	2,631 (1.3)	2,702 (1.3)	0.003
Loop diuretics	17,285 (8.2)	17,530 (8.4)	0.004
Non-acetylsalicylic acid antiplatelet drugs	14,279 (6.8)	13,879 (6.6)	0.008
Nonsteroidal anti-inflammatory drugs	40,816 (19.4)	40,054 (19.1)	0.009
Oral anticoagulants	13,610 (6.5)	13,874 (6.6)	0.005
Oral glucocorticoids	13,083 (6.2)	13,149 (6.3)	0.001
Other diuretics	19,739 (9.4)	19,766 (9.4)	0.000
Other lipid lowering therapy	23,879 (11.4)	22,185 (10.6)	0.026
Statins	161,370 (76.9)	160,529 (76.5)	0.009
Thiazide diuretics	53,776 (25.6)	53,343 (25.4)	0.005
No. of different classes of non anti-diabetic medications			
0-1	9,962 (4.7)	10,322 (4.9)	0.008
2-5	65,731 (31.3)	66,311 (31.6)	0.006
≥6	134,174 (63.9)	133,234 (63.5)	0.009

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2.

*Data are presented as n (%). SGLT2 inhibitors patients were matched to DPP-4 inhibitors patients from their exposure set (defined on level of antidiabetic therapy, prior use of GLP-1 receptor agonists, time on DPP-4 inhibitors for prevalent new users and calendar time) on time-conditional propensity score.

†Medications were assessed in the year before cohort entry.

Supplementary Table 6. Additional baseline characteristics of new users of SGLT2 inhibitors and their matched DPP-4 users in the CPRD.*

Characteristics	SGLT2 inhibitors (n = 5,423)	DPP-4 inhibitors (n = 5,423)	Standardized difference
Blood pressure			
DBP <90 mm Hg and SBP <140 mm Hg	3,503 (64.6)	3,534 (65.2)	0.012
DPB ≥90 mm Hg or SBP ≥140 mm Hg	1,912 (35.3)	1,883 (34.7)	0.011
Missing	8 (0.1)	6 (0.1)	0.010
Body mass index			
<30 kg/m^2	1,533 (28.3)	1,719 (31.7)	0.075
≥30 kg/m^2	3,873 (71.4)	3,680 (67.9)	0.078
Unknown	17 (0.3)	24 (0.4)	0.021
eGFR			
<60 mL/min/1.73m^2	285 (5.3)	540 (10.0)	0.178
≥60 mL/min/1.73m^2	5,131 (94.6)	4,876 (89.9)	0.177
Missing	7 (0.1)	7 (0.1)	0.000
HbA1c			
≤7 %	183 (3.4)	223 (4.1)	0.039
7.1-8 %	1,050 (19.4)	1,059 (19.5)	0.004
>8 %	4,154 (76.6)	4,100 (75.6)	0.023
Missing	36 (0.7)	41 (0.8)	0.011
Race			
White	3,968 (73.2)	3,954 (72.9)	0.006
Other	533 (9.8)	574 (10.6)	0.025
Missing	922 (17.0)	895 (16.5)	0.013
Smoking status			
Never	2,166 (39.9)	2,108 (38.9)	0.022
Ever	3,251 (59.9)	3,308 (61.0)	0.022
Missing	6 (0.1)	7 (0.1)	0.005

Abbreviations: DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; CPRD: Clinical Practice Research Datalink; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporter 2.

*Data are presented as n (%). SGLT2 inhibitors patients were matched to DPP-4 inhibitors patients from their exposure set (defined on level of antidiabetic therapy, prior use of GLP-1 receptor agonists, time on DPP-4 inhibitors for prevalent new users and calendar time) on time-conditional propensity score. The assessment of body mass index, smoking status, blood pressure, eGFR and HbA1c was based on the last measurement before study cohort entry, and race was assessed ever before. Missing data were included in regression models through the use of an indicator variable.

Supplementary Table 7. Summary of the CPRD results for the study outcomes for SGLT2 inhibitor use versus DPP-4 inhibitor use with and without the inclusion of additional covariates in the time-conditional propensity score.*

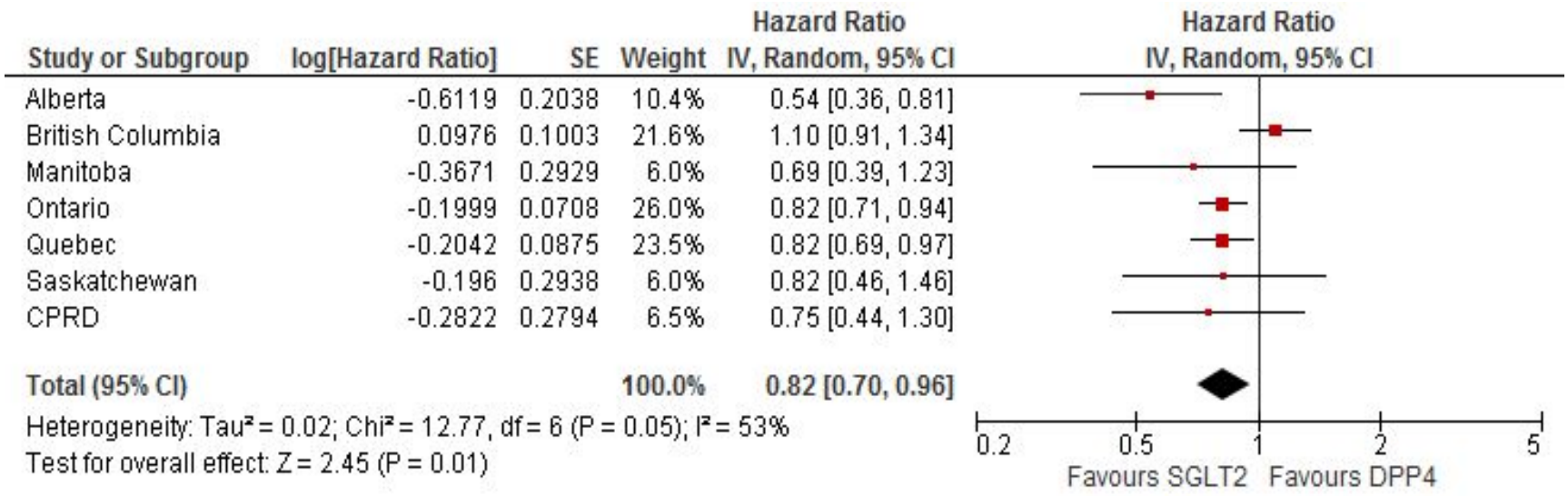
	Adjusted HR (95% CI)*	
Outcome	**With additional covariates†**	**Without additional covariates**
MACE	0.77 (0.54 to 1.10)	0.69 (0.48 to 1.00)
Myocardial infarction	0.75 (0.44 to 1.30)	0.64 (0.37 to 1.12)
Ischemic stroke	1.15 (0.51 to 2.58)	1.63 (0.66 to 4.05)
Cardiovascular death	0.59 (0.33 to 1.05)	0.48 (0.26 to 0.89)
All-cause mortality	0.67 (0.42 to 1.06)	0.64 (0.39 to 1.04)
Heart failure	0.58 (0.21 to 1.59)	0.57 (0.19 to 1.70

Abbreviations: CI, confidence interval; CPRD, Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HR, hazard ratios; SGLT2, sodium-glucose cotransporter 2.

* Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.

†Additional covariates included in the time-conditional propensity score were body mass index, smoking status, race, blood pressure, eGFR, and HbA1c.

Supplementary Figure 1. Adjusted hazard ratios (95% CI) of myocardial infarction associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use*.

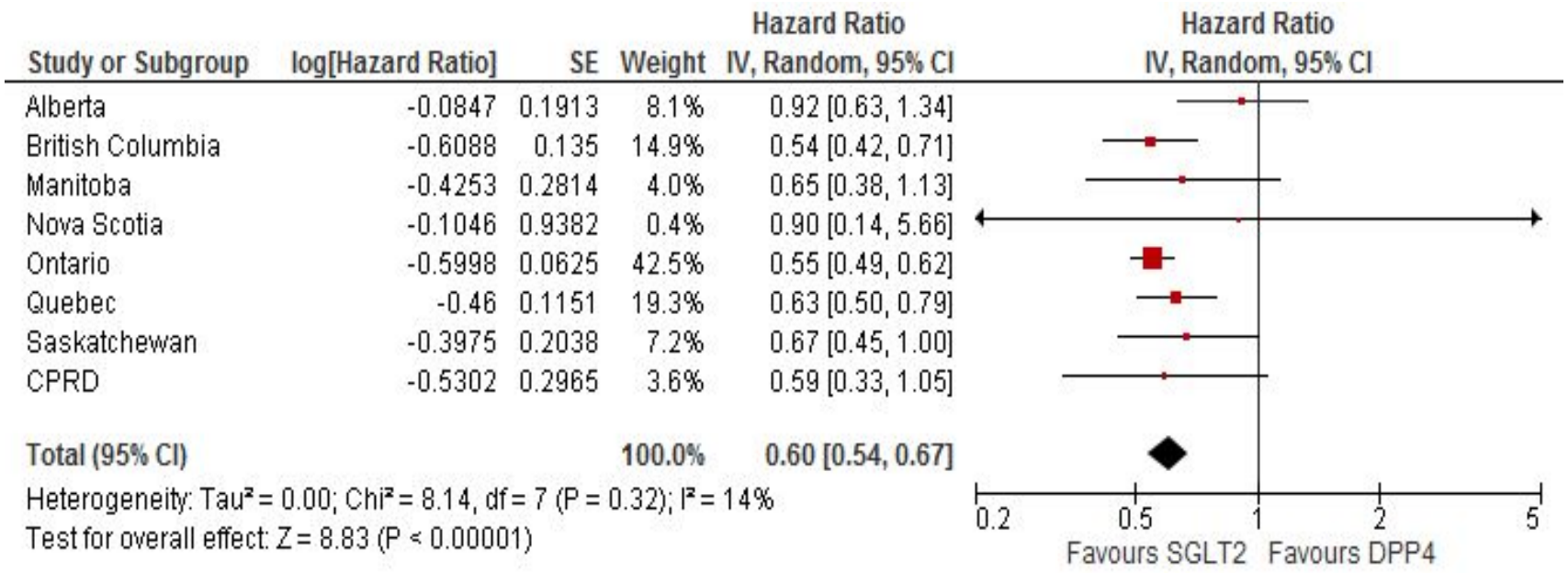


Abbreviations: CI, confidence interval; CPRD: Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

* Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.

Note: Nova Scotia had zero events in one of the exposure groups and thus was not included in this analysis.

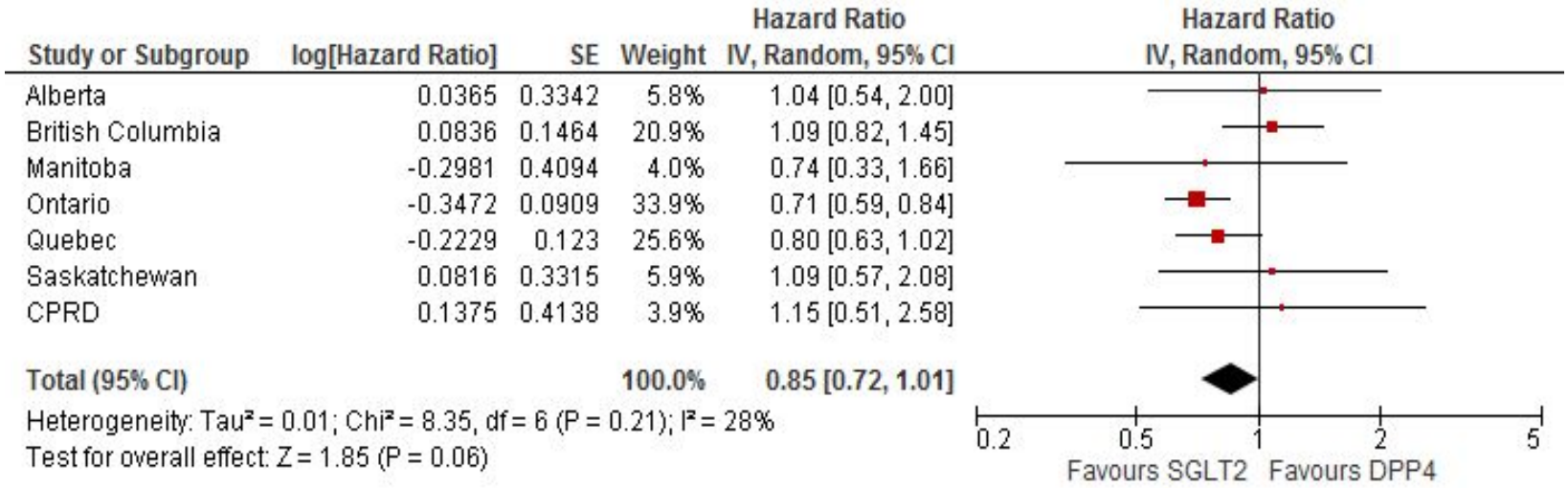
Supplementary Figure 2. Adjusted hazard ratios (95% CI) of cardiovascular death associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use*.



Abbreviations: CI, confidence interval; CPRD: Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

* Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.

Supplementary Figure 3. Adjusted hazard ratios (95% CI) of ischemic stroke associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use*.

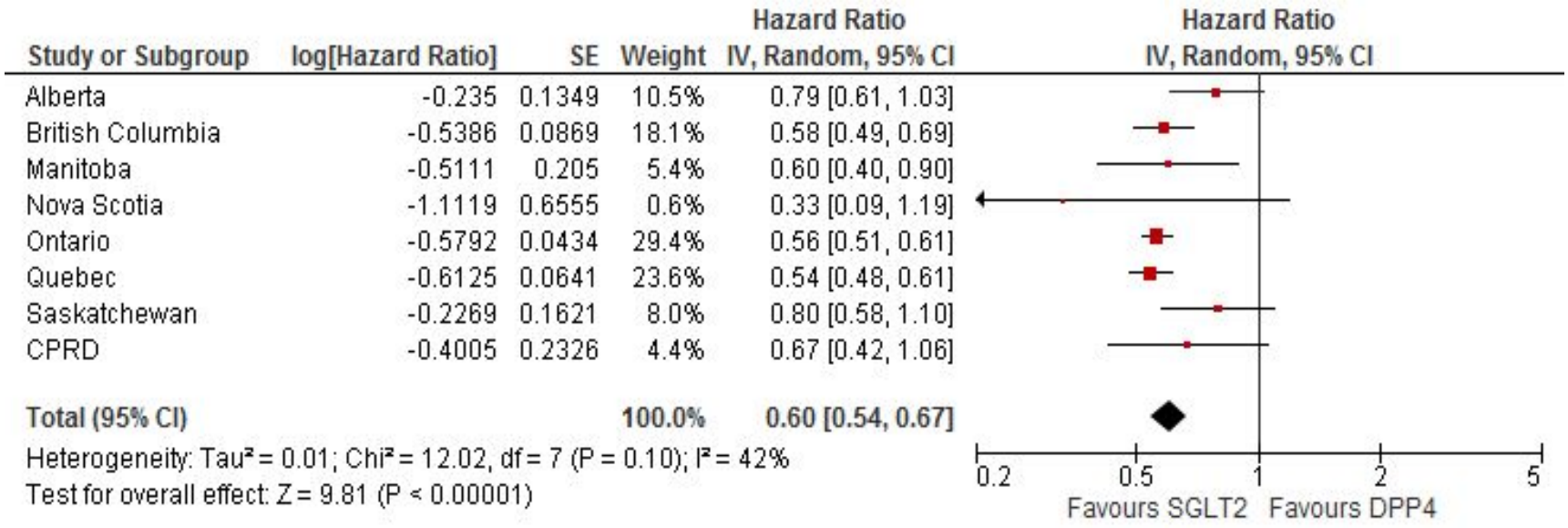


Abbreviations: CI, confidence interval; CPRD: Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

* Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.

Note: Nova Scotia had zero events in one of the exposure groups and thus was not included in this analysis.

Supplementary Figure 4. Adjusted hazard ratios (95% CI) of all-cause mortality associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use*.



Abbreviations: CI, confidence interval; CPRD: Clinical Practice Research Datalink; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

* Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of time-conditional propensity score.