Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study

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ABSTRACT

OBJECTIVE
To evaluate the cardiovascular safety of canagliflozin, a sodium-glucose cotransporter 2 inhibitor for the treatment of type 2 diabetes mellitus, in direct comparisons with DPP-4 inhibitors (DPP-4i), GLP-1 receptor agonists (GLP-1RA), or sulfonylureas, as used in routine practice.

DESIGN
Population based retrospective cohort study.

SETTING
Nationwide sample of patients with type 2 diabetes from a large de-identified US commercial healthcare database (Optum Clinformatics Datamart).

PARTICIPANTS
Three pairwise 1:1 propensity score matched cohorts of patients with type 2 diabetes 18 years and older who initiated canagliflozin or a comparator non-gliflozin antidiabetic agent (ie, a DPP-4i, a GLP-1RA, or a sulfonylurea) between April 2013 and September 2015.

MAIN OUTCOME MEASURES
The primary outcomes were heart failure admission to hospital and a composite cardiovascular endpoint (comprised of being admitted to hospital for acute myocardial infarction, ischemic stroke, or hemorrhagic stroke). Hazard ratios and 95% confidence intervals were estimated in each propensity score matched cohort controlling for more than 100 baseline characteristics.

RESULTS
During a 30 month period, the hazard ratio for heart failure admission to hospital associated with canagliflozin was 0.70 (95% confidence interval 0.54 to 0.92) versus a DPP-4i (n=17 667 pairs), 0.61 (0.47 to 0.78) versus a GLP-1RA (20 539), and 0.51 (0.38 to 0.67) versus a sulfonylurea (17 354). The hazard ratio for the composite cardiovascular endpoint associated with canagliflozin was 0.89 (0.68 to 1.17) versus a DPP-4i, 1.03 (0.79 to 1.35) versus a GLP-1RA, and 0.86 (0.65 to 1.13) versus a sulfonylurea. Results were similar in sensitivity analyses further adjusting for baseline hemoglobin A1c levels and in subgroups of patients with and without prior cardiovascular disease or heart failure.

CONCLUSIONS
In this large cohort study, canagliflozin was associated with a lower risk of heart failure admission to hospital and with a similar risk of myocardial infarction or stroke in direct comparisons with three different classes of non-gliflozin diabetes treatment alternatives as used in routine care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The EMPA-REG OUTCOME and the CANVAS trials, two recent large placebo controlled randomized trials of SGLT2 inhibitors (empagliflozin and canagliflozin, respectively) showed a 35% and a 33% reduced risk of admission to hospital for heart failure in addition to a 14% reduced risk of the prespecified primary composite cardiovascular outcome (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke)

Initial evidence based on in use data supports a potential class effect among SGLT2 inhibitors with regard to a reduced risk of admission to hospital for heart failure, but does not provide information on the cardiovascular effects of individual SGLT2 inhibitors compared with clinically relevant antidiabetic drug alternatives

To date, the comparative potential reduction in hospital stays for heart failure associated with the use of individual SGLT2 inhibitor drugs in routine care and their effects on other cardiovascular outcomes remains uncertain

WHAT THIS STUDY ADDS

A large population based cohort study in which canagliflozin was associated with a 30% to 49% decreased risk of heart failure admission to hospital and with a similar risk of myocardial infarction or stroke as compared with three other non-gliflozin antidiabetic drugs as used in routine care

The reduction in hospital stays for heart failure showed for canagliflozin in the CANVAS trial extends to in use settings and consistently occurs in direct comparisons with three clinically relevant diabetes treatment alternatives

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes. In addition to atherosclerotic heart disease, patients with diabetes are at an increased risk of being admitted to hospital or dying from heart failure.[1] Despite some early indication of benefit,[2] there was no definitive evidence from interventional studies that glucose lowering therapy would improve cardiovascular outcomes in patients with diabetes until recently. Furthermore, intensive glucose lowering or use of specific antihyperglycemic drugs has been associated with adverse cardiovascular outcomes.[3 4]

Multiple sodium glucose cotransporter 2 inhibitors (SGLT2i) that block renal reabsorption of glucose are now available for the management of type 2 diabetes in adults. In addition to a healthy lifestyle, SGLT2i's used as monotherapy or in combination with other drugs, improve glycemia, promote modest weight loss, lower blood pressure, and have positive effects on cardiovascular risk surrogates.[5-7] Two recent large randomized controlled trials of SGLT2i's showed a reduced risk of heart failure admission to hospital (35% for empagliflozin in the EMPA-REG OUTCOME trial and

33% for canagliflozin in the the CANVAS trial)[8][9] and a 14% reduced risk of the prespecified primary composite cardiovascular outcome (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). The decreased risk of heart failure admission to hospital observed in both trials may substantially contribute to the overall cardiovascular benefit and potential improved survival, as it tends to manifest early, before substantial changes in atherosclerosis would be anticipated, and as no meaningful reductions in non-fatal myocardial infarction or stroke were found in either trial.

To date, the potential reduction in the number of patients being admitted to hospital for heart failure associated with the use of individual SGLT2i drugs in routine care and their effects on other cardiovascular outcomes remain uncertain. Initial evidence based on the CVD-REAL study, an in use evaluation sponsored by industry, supports a potential class effect among SGLT2i's with regard to a reduced risk of heart failure admission to hospital,[10] but neither provides information on the cardiovascular effects of individual SGLT2i drugs nor compares these drugs with specific antidiabetic drug alternatives, thus not addressing the clinically relevant questions of which drug or drug class may be more or less beneficial from a cardiovascular point of view. A subanalysis restricted to the participating Nordic countries (CVD-REAL Nordic) has recently provided initial comparative information on an individual SGLT2i, dapagliflozin, showing an association with lower risks of cardiovascular events and mortality.[11] However, the study did not include other SGLT2i's that may be more frequently prescribed outside of the included countries and compared dapagliflozin with only one drug class, that is, DPP-4 inhibitors.

Thus, we sought to conduct a direct comparison of canagliflozin – the first SGLT2i marketed in the USA and the most frequently prescribed SGLT2i during the study period – versus three other non-gliflozin antidiabetic drug classes with regard to the risk of heart failure and other cardiovascular outcomes in a population based cohort of patients with type 2 diabetes as treated in routine care.

Methods
Data source
Data were collected from the de-identified Clinformatics Datamart (OptumInsight, Eden, Prairie, MN), a health care insurance dataset based in the USA which includes more than 14 million patients yearly. Demographic information, health plan enrollment status, inpatient and outpatient medical encounters coded using ICD-9-CM (international classification of diseases, ninth revision, clinical modification) and CPT-4 (current procedural terminology, fourth edition) codes, and filled prescriptions (including the National Drug Code numbers, quantity dispensed, and days' supply) were recorded for each patient. Claims data from the Clinformatics Datamart were linked to laboratory test results provided by two national laboratories. Through this link, results for outpatient laboratory tests were available for approximately one third of beneficiaries.

Study population and drug exposure
We identified patients aged 18 or older who initiated treatment with canagliflozin, a DPP-4 inhibitor (DPP-4i) (alogliptin, linagliptin, saxagliptin, or sitagliptin), a GLP-1 receptor agonist (GLP-1RA) (albiglutide, dulaglutide, exenatide, or liraglutide), or a second or third generation sulfonylurea (glimepiride, glipizide, or glyburide), between 1 April 2013 (consistent with the marketing of canagliflozin in the US) and 30 September 2015 (the end of data availability in the study dataset). Patients entered the study cohort on the day of their first use of any of the drugs above, defined as not having received that specific class or drug in the previous six months, restricting to individuals who had six or more months of continuous enrollment before drug initiation. A recorded diagnosis of type 2 diabetes (defined as an inpatient or outpatient ICD-9-CM code of 250.x0 or 250.x2) was required at any point before drug initiation. We excluded patients with a history of secondary diabetes, gestational diabetes, malignancy, end stage renal disease, HIV, or organ transplant. Table 1 shows the study populations included in the three pairwise comparisons of patients initiated on either canagliflozin or a non-gliflozin comparator. Patients meeting the inclusion criteria could contribute to each cohort only once but could contribute to multiple different cohorts.

Follow-up started on the day after cohort entry (ie, the date of drug initiation). Initiators of canagliflozin and their comparators were followed in an as treated approach until treatment discontinuation or switch to a comparator, the occurrence of a study event, death, end of continuous health plan enrollment, or end of the study period, whichever came first. We extended the exposure effect window until 45 days after the end of the last prescription's supply.[12]

Study outcomes
The primary outcomes were heart failure admission to hospital and a composite cardiovascular endpoint (comprised of being admitted to hospital for acute myocardial infarction, ischemic stroke, or hemorrhagic stroke). In previous studies, the positive predictive values of these claims based algorithms for cardiovascular events were at least 80% (see web appendix 1 for definitions).[13-16]

We defined several secondary outcomes including a broadly defined heart failure endpoint (to include a new prescription for loop diuretics), an expanded composite cardiovascular endpoint (to include acute unstable angina and coronary revascularization), the individual components of the composite cardiovascular endpoints, and all cause mortality (ascertained through linkage with the Social Security Administration Death Master File).[17]

Patient characteristics
Baseline patient characteristics were measured during the six months preceding and on the date of entry to the cohort. We considered the following covariates as potential confounders: demographics, indicators

Table 1 | Study populations included in the three pairwise comparisons of patients

Cohort	Study population
1	Patients initiating either canagliflozin or a DPP-4 inhibitor (DPP-4i), without any use of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) (canagliflozin, dapagliflozin, or empagliflozin), or a DPP-4i in the six months before drug initiation
2	Patients initiating either canagliflozin or a GLP-1 receptor agonist (GLP-1RA), without any use of a SGLT2i or a GLP-1RA in the six months before drug initiation
3	Patients initiating either canagliflozin or a sulfonylurea, without any use of a SGLT2i or a sulfonylurea in the six months before drug initiation

of diabetes severity, presence of other comorbidities, use of drugs, and measures of health care utilization as proxy for overall disease state and care intensity. Baseline laboratory test results for HbA1c, serum creatinine, serum blood urea nitrogen, and low density lipoprotein levels were available for a subset of the study cohort. We defined comorbidities using ICD-9 and CPT-4 codes. The complete list of baseline patient characteristics is reported in web appendix 2.

Statistical analysis

Baseline characteristics were cross tabulated by each pair of canagliflozin or its comparator. To control for imbalances in patient characteristics between cohorts, we calculated exposure propensity scores as the predicted probability of receiving the treatment of interest (ie, canagliflozin v each comparator) conditional upon the subjects' baseline covariates using three separate multivariable logistic regression models.[18] All variables were included and no further selection was conducted. We 1:1 matched cohorts on their propensity score using a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score.[19] Covariate balance between the cohorts before and after propensity score matching was assessed using standardized differences; meaningful imbalances were defined as a standardized difference greater than 0.1.[20] For each comparison and for all outcomes, we calculated unadjusted and propensity score matched number of events, incidence rates, and hazard ratios with 95% confidence intervals. We assessed the proportional hazards assumption by testing the significance of the interaction term between exposure and time, and confirmed that it was not violated.[21]

We conducted several sensitivity analyses to test the robustness of our primary findings. First, among the patients with baseline HbA1c levels available (approximately one third of the total population depending on the cohort), we re-estimated the propensity score adding HbA1c level in addition to the other baseline covariates to further account for underlying glucose control. Second, to address the potential for unmeasured confounding associated with the high risk for recurrence, we restricted to patients who had not been admitted to hospital for heart failure, acute coronary, or cerebrovascular events during the 60 day period before entry to the cohort. Third, to address potential informative censoring, we carried forward the exposure to the initiated drug for 365 days without considering drug discontinuation or switching, to mimic an intention to treat approach.[22]

In addition, we conducted subgroup analyses stratified by presence of heart failure or cardiovascular disease at baseline for the primary outcomes of heart failure admission to hospital or the composite cardiovascular endpoint respectively (see web appendix 3 for the definition of subgroups).

All analyses were performed using SAS 9.3 Statistical Software (SAS Institute Inc, Cary, NC).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

Study cohort and patient characteristics

Figure 1 shows that after applying inclusion and exclusion criteria, there were 224 999 unique patients initiating canagliflozin, a DPP-4 inhibitor (DPP-4i), a GLP-1 receptor agonist (GLP-1RA), or a sulfonylurea and contributing a total of 164 249 person years in the study database. Of those, 31 725 unique patients initiating canagliflozin (19 352 person years) were included. We identified three cohorts of patients who initiated either canagliflozin or a comparator. The first was a cohort of new users of canagliflozin (n=21 431) or a DPP-4i (77 463). The second was a cohort of new users of canagliflozin (25 806) or a GLP-1RA (32 676). The third was a cohort of new users of canagliflozin (18 924) or a sulfonylurea (115 435) (web appendix 2 and 4). We then identified three pairwise 1:1 propensity score matched cohorts of patients initiating canagliflozin or a DPP-4i (n=17 667 pairs), canagliflozin or a GLP-1RA (20 539), and canagliflozin or a sulfonylurea (17 354) (table 2). Overall, there were 77 956 unique initiators contributing to the three cohorts matched on propensity score (46 774 person years), of which 28 149 were unique initiators of canagliflozin (17 171).

Compared with initiators of other non-gliflozin antidiabetic drugs, patients initiating canagliflozin were generally younger, more frequently male, and with a lower general burden of comorbidities measured by the Combined Comorbidity Score and by the prevalence of individual comorbidities at baseline (web appendix 2).[23] For the subset of the population with laboratory values available, patients initiating canagliflozin had higher mean HbA1c and estimated glomerular filtration rate compared with initiators of other drugs.[24] Table 2 and web appendix 5 show that all differences in patient characteristics between initiators of canagliflozin and new users of other comparator drugs were well balanced after propensity score matching.

After propensity score matching the mean follow-up time was 0.6 (SD 0.5) years for all cohorts. Most
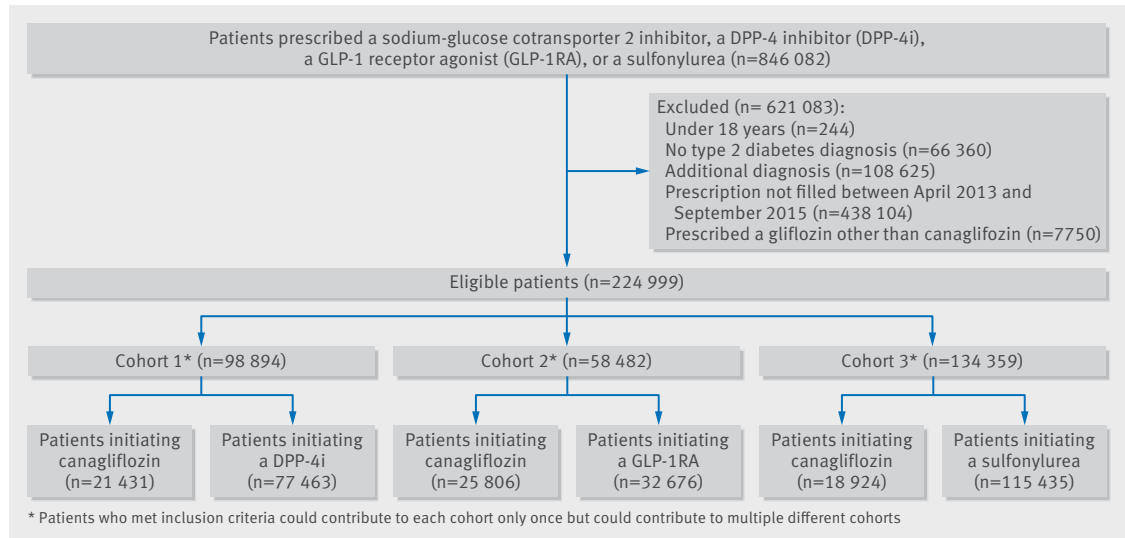
Fig 1 | Flowchart of study cohort

patients were censored owing to the end of the study period (between 55% and 68%).

Absolute and relative hazards of primary and secondary outcomes

Table 3 shows that after propensity score matching, for the heart failure admission to hospital primary outcome, the number of events for canagliflozin and the non-gliflozin comparator were 91 and 124 respectively (8.9 *v* 12.8 per 1000 person years; hazard ratio 0.70, 95% confidence interval 0.54 to 0.92) in cohort 1; 94 and 148 (7.5 *v* 12.4; 0.61, 0.47 to 0.78) in cohort 2; and 77 and 154 (7.3 *v* 14.4; 0.51, 0.38 to 0.67) in cohort 3.

For the composite cardiovascular endpoint primary outcome, the number of events for canagliflozin and the non-gliflozin comparator were 101 and 108 respectively (9.9 *v* 11.1 per 1000 person years; hazard ratio 0.89, 95% confidence interval 0.68 to 1.17) in cohort 1; 111 and 102 (8.8 *v* 8.5; 1.03, 0.79 to 1.35) in cohort 2; and 93 and 110 (8.8 *v* 10.3; 0.86, 0.65 to 1.13) in cohort 3. Table 4 shows that among propensity score matched pairs with no use of loop diuretics or heart failure at baseline, canagliflozin initiators had a decreased risk of the broadly defined heart failure endpoint, compared with initiators of other non-gliflozin antidiabetic drugs (hazard ratio 0.64, 95% confidence interval 0.53 to 0.76 in cohort

1; 0.68, 0.58 to 0.81 in cohort 2; and 0.47, 0.39 to 0.56 in cohort 3). In all cohorts, canagliflozin initiators had no meaningfully increased or decreased risk for the expanded composite cardiovascular endpoint, the individual components of the cardiovascular endpoint, and all cause mortality, though the estimate for all cause mortality was imprecise owing to the low death rate in the study cohort (table 4).

Figure 2 shows Kaplan-Meier curves comparing the cumulative incidence of heart failure admission to hospital and the composite cardiovascular endpoint between the propensity score matched canagliflozin and other comparator groups were consistent with our findings. For the heart failure admission to hospital endpoint, Kaplan-Meier curves for the three comparisons tended to separate early (ie, within six months after treatment initiation).

Sensitivity and subgroup analyses
Our findings remained consistent when we further adjusted for baseline HbA1c level, though with wider confidence intervals owing to the smaller size of the population included in this analysis, and when we restricted to patients without the occurrence of heart failure admission to hospital, acute coronary events, or acute cerebrovascular events during the 60 day period before initiation of the index drug. Table 5 shows that

Table 2 | Selected baseline characteristics in propensity-score matched cohorts of patients initiating canagliflozin or a comparator. Values are numbers (percentages) unless stated otherwise

Baseline patient characteristics	Cohort 1 (n=17 667 pairs)		Cohort 2 (n=20 539 pairs)		Cohort 3 (n=17 354 pairs)	
	Canagliflozin	DPP-4i	Canagliflozin	GLP-1RA	Canagliflozin	Sulfonylurea
Demographics						
Mean (SD) age (years)	56.5 (10.6)	56.5 (10.7)	56.8 (10.9)	56.7 (10.8)	55.9 (10.5)	55.8 (10.5)
Female	7931 (44.9)	7954 (45.0)	9716 (47.3)	9702 (47.2)	7809 (45.0)	7835 (45.2)
Comorbidities						
Mean (SD) combined comorbidity score	0.1 (1.3)	0.2 (1.4)	0.2 (1.4)	0.2 (1.4)	0.1 (1.3)	0.1 (1.4)
Obese or overweight	3768 (21.3)	3805 (21.5)	4572 (22.3)	4582 (22.3)	3673 (21.2)	3677 (21.2)
Smoker	1333 (7.6)	1304 (7.4)	1553 (7.6)	1523 (7.4)	1321 (7.6)	1297 (7.5)

(Continued)

Table 2 | Selected baseline characteristics in propensity-score matched cohorts of patients initiating canagliflozin or a comparator. Values are numbers (percentages) unless stated otherwise (*Continued*)

Baseline patient characteristics	Cohort 1 (n=17 667 pairs)		Cohort 2 (n=20 539 pairs)		Cohort 3 (n=17 354 pairs)	
	Canagliflozin	DPP-4i	Canagliflozin	GLP-1RA	Canagliflozin	Sulfonylurea
Indicators of diabetes severity:						
Nephropathy	1217 (6.9)	1216 (6.9)	1530 (7.5)	1524 (7.4)	1103 (6.4)	1104 (6.4)
Neuropathy	2436 (13.8)	2412 (13.7)	3003 (14.6)	3058 (14.9)	2352 (13.6)	2323 (13.4)
Retinopathy	1279 (7.2)	1260 (7.1)	1606 (7.8)	1632 (8.0)	1269 (7.3)	1285 (7.4)
Mean (SD) number of diabetes drugs on the day of entry to the cohort	2.2 (0.9)	2.2 (0.9)	2.4 (1.0)	2.4 (1.0)	2.2 (0.9)	2.2 (0.9)
Diabetes drug on the day of entry to the cohort:						
Metformin	10 429 (59.0)	10 508 (59.5)	11 655 (56.8)	11 647 (56.7)	9969 (57.4)	9956 (57.4)
DPP-4i	0 (0.0)	17 667 (100.0)	3875 (18.9)	3884 (18.9)	3342 (19.3)	3508 (20.2)
GLP-1RA	1047 (5.9)	1008 (5.7)	0 (0.0)	20 539 (100.0)	1760 (10.1)	1634 (9.4)
Sulfonylurea	4862 (27.5)	4945 (28.0)	5846 (28.5)	5810 (28.3)	0 (0.0)	17 354 (100.0)
Insulin	3817 (21.6)	3724 (21.1)	4863 (23.7)	4938 (24.0)	4102 (23.6)	3913 (22.6)
Glitazone	1149 (6.5)	1220 (6.9)	1431 (7.0)	1421 (6.9)	1123 (6.5)	1126 (6.5)
Hypertension	9170 (51.9)	9164 (51.9)	10 910 (53.1)	10 994 (53.5)	8821 (50.8)	8873 (51.1)
Ischemic heart disease	2018 (11.4)	1975 (11.2)	2431 (11.8)	2454 (12.0)	1895 (10.9)	1906 (11.0)
History of coronary revascularization	385 (2.2)	391 (2.2)	465 (2.3)	491 (2.4)	351 (2.0)	340 (2.0)
Congestive heart failure	563 (3.2)	594 (3.4)	694 (3.4)	709 (3.5)	517 (3.0)	530 (3.1)
Atrial fibrillation	507 (2.9)	517 (2.9)	622 (3.0)	613 (3.0)	500 (2.9)	488 (2.8)
Stroke	222 (1.3)	227 (1.3)	251 (1.2)	272 (1.3)	202 (1.2)	195 (1.1)
Transient ischemic attack	121 (0.7)	119 (0.7)	153 (0.7)	155 (0.8)	120 (0.7)	126 (0.7)
Peripheral vascular disease	619 (3.5)	623 (3.5)	762 (3.7)	786 (3.8)	624 (3.6)	595 (3.4)
Other cardiovascular disease	883 (5.0)	922 (5.2)	1068 (5.2)	1076 (5.2)	841 (4.9)	840 (4.8)
Edema	818 (4.6)	840 (4.8)	1024 (5.0)	1030 (5.0)	720 (4.2)	738 (4.3)
Disorders of fluid electrolyte and acid-base balance	652 (3.7)	656 (3.7)	763 (3.7)	820 (4.0)	612 (3.5)	590 (3.4)
Hypoglycemia	1781 (10.1)	1814 (10.3)	2094 (10.2)	2117 (10.3)	1707 (9.8)	1726 (10.0)
Hyperlipidemia	8600 (48.7)	8556 (48.4)	10 246 (49.9)	10 342 (50.4)	8544 (49.2)	8532 (49.2)
Chronic obstructive pulmonary disease	742 (4.2)	764 (4.3)	888 (4.3)	894 (4.4)	706 (4.1)	667 (3.8)
Pneumonia	261 (1.5)	288 (1.6)	320 (1.6)	314 (1.5)	250 (1.4)	237 (1.4)
Obstructive sleep apnea	1720 (9.7)	1667 (9.4)	2113 (10.3)	2102 (10.2)	1702 (9.8)	1682 (9.7)
Osteoarthritis	1707 (9.7)	1688 (9.6)	2079 (10.1)	2093 (10.2)	1680 (9.7)	1617 (9.3)
Non-diabetes kidney disease	1484 (8.4)	1487 (8.4)	1922 (9.4)	1921 (9.4)	1347 (7.8)	1348 (7.8)
Drugs						
No use of any antidiabetic drug in previous six months	2089 (11.8)	2016 (11.4)	1999 (9.7)	1955 (9.5)	2102 (12.1)	2059 (11.9)
Past use of metformin	2780 (15.7)	2728 (15.4)	3465 (16.9)	3453 (16.8)	2823 (16.3)	2859 (16.5)
Past use of a DPP-4i	0 (0.0)	0 (0.0)	2250 (11.0)	2287 (11.1)	1567 (9.0)	1617 (9.3)
Past use of a GLP-1RA	1040 (5.9)	1039 (5.9)	0 (0.0)	0 (0.0)	1024 (5.9)	1001 (5.8)
Past use of a sulfonylurea	1828 (10.4)	1811 (10.3)	2256 (11.0)	2311 (11.3)	0 (0.0)	0 (0.0)
Past use of insulin	1524 (8.6)	1510 (8.6)	1808 (8.8)	1826 (8.9)	1616 (9.3)	1628 (9.4)
Past use of a glitazone	508 (2.9)	477 (2.7)	623 (3.0)	642 (3.1)	472 (2.7)	473 (2.7)
ACE inhibitors	7488 (42.4)	7486 (42.4)	8815 (42.9)	8850 (43.1)	6934 (40.0)	6879 (39.6)
Angiotensin II receptor blockers	4460 (25.2)	4515 (25.6)	5367 (26.1)	5393 (26.3)	4484 (25.8)	4508 (26.0)
Beta blockers	4619 (26.1)	4606 (26.1)	5574 (27.1)	5582 (27.2)	4265 (24.6)	4244 (24.5)
Calcium channel blockers	3517 (19.9)	3505 (19.8)	4198 (20.4)	4178 (20.3)	3273 (18.9)	3266 (18.8)
Thiazides	4964 (28.1)	5031 (28.5)	5966 (29.1)	5936 (28.9)	4629 (26.7)	4593 (26.5)
Loop diuretics	1427 (8.1)	1450 (8.2)	1742 (8.5)	1764 (8.6)	1257 (7.2)	1248 (7.2)
Other diuretics*	762 (4.3)	784 (4.4)	918 (4.5)	944 (4.6)	717 (4.1)	720 (4.2)
Nitrates	528 (3.0)	541 (3.1)	645 (3.1)	677 (3.3)	470 (2.7)	469 (2.7)
Digoxin	156 (0.9)	185 (1.1)	195 (1.0)	199 (1.0)	130 (0.8)	118 (0.7)
Statins	10 634 (60.2)	10 650 (60.3)	12 659 (61.6)	12 707 (61.9)	10 441 (60.2)	10 309 (59.4)
Anticoagulants	600 (3.4)	611 (3.5)	701 (3.4)	707 (3.4)	557 (3.2)	552 (3.2)
Antiplatelets	1093 (6.2)	1075 (6.1)	1320 (6.4)	1380 (6.7)	988 (5.7)	1001 (5.8)
Measures of healthcare utilization						
Any hospital stay within previous 30 days	197 (1.1)	181 (1.0)	215 (1.1)	215 (1.1)	175 (1.0)	170 (1.0)
Any hospital stay during previous 31 to 183 days	696 (3.9)	715 (4.1)	800 (3.9)	845 (4.1)	631 (3.6)	646 (3.7)
Mean (SD) number of any physician visit	4.4 (3.4)	4.4 (3.4)	4.6 (3.5)	4.6 (3.5)	4.4 (3.4)	4.4 (3.4)
Visit to endocrinologist	1968 (11.1)	2065 (11.7)	2822 (13.7)	2859 (13.9)	2299 (13.3)	2292 (13.2)
Visit to cardiologist	1355 (7.7)	1392 (7.9)	1631 (7.9)	1659 (8.1)	1366 (7.9)	1455 (8.4)
Mean (SD) number of distinct prescriptions	9.6 (5.2)	9.6 (5.2)	10.1 (5.2)	10.2 (5.2)	9.5 (5.3)	9.4 (5.0)
Laboratory tests						
Patients with HbA1c levels available	6591 (37.3)	6806 (38.5)	7727 (37.6)	7338 (35.7)	6436 (37.1)	6557 (37.8)
Mean (SD) HbA1c (%)	8.8 (1.9)	8.8 (1.9)	8.8 (1.8)	8.8 (1.9)	8.7 (1.9)	8.9 (2.0)
Patients with creatinine levels available	7023 (39.8)	7198 (40.7)	8217 (40.0)	7909 (38.5)	6959 (40.1)	6906 (39.8)
Mean (SD) creatinine (mg/dL)	0.9 (0.2)	1.0 (0.3)	0.9 (0.2)	1.0 (0.3)	0.9 (0.2)	1.0 (0.3)
Mean (SD) eGFR (mL/min/1.73m^2)	100.4 (18.3)	97.8 (22.2)	99.3 (18.7)	97.4 (21.5)	100.9 (18.1)	98.8 (21.3)

DPP-4i=DPP-4 inhibitor; GLP-1RA=GLP-1 receptor agonist; SD=standard deviation; ACE=angiotensin converting enzyme; HbA1c=hemoglobin A1c; eGFR=estimated glomerular filtration rate.
*Including eplerenone, spironolactone, amiloride, and triamterene.

Table 3 | Risk of heart failure admission to hospital and composite cardiovascular endpoint associated with canagliflozin versus comparators in propensity score matched analyses

Characteristics	Cohort 1 (n=17 667 pairs)		Cohort 2 (n=20 539 pairs)		Cohort 3 (n=17 354 pairs)	
	Canagliflozin	DPP-4i	Canagliflozin	GLP-1RA	Canagliflozin	Sulfonylurea
Mean (SD) follow-up (years)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6 (0.5)
Heart failure admission to hospital						
No of events (*)	91 (8.9)	124 (12.8)	94 (7.5)	148 (12.4)	77 (7.3)	154 (14.4)
Hazard ratio (95% CI)	0.70 (0.54 to 0.92)	NA	0.61 (0.47 to 0.78)	NA	0.51 (0.38 to 0.67)	NA
Composite cardiovascular endpoint†						
No of events (*)	101 (9.9)	108 (11.1)	111 (8.8)	102 (8.5)	93 (8.8)	110 (10.3)
Hazard ratio (95% CI)	0.89 (0.68 to 1.17)	NA	1.03 (0.79 to 1.35)	NA	0.86 (0.65 to 1.13)	NA

DPP-4i=DPP-4 inhibitor; GLP-1RA=GLP-1 receptor agonist; NA=not applicable.
*Incidence rate per 1000 person years.
†Defined as being admitted to hospital for acute myocardial infarction, ischemic stroke, or hemorrhagic stroke.

the intention to treat analysis was also consistent with the main findings of decreased risk of heart failure admission to hospital and similar risk of the composite cardiovascular endpoint associated with canagliflozin compared with non-gliflozin comparators.

Table 5 shows that in the subgroup analysis stratified by history of heart failure, canagliflozin was consistently associated with a decreased risk of heart failure admission to hospital compared with other non-gliflozin antidiabetic drugs, though with wider confidence intervals. Similarly, the risk of composite cardiovascular endpoints was not meaningfully different in any of the three cohorts, independent of the presence of cardiovascular disease at baseline.

Discussion

In this large population based cohort study, we found a markedly decreased risk of heart failure admission to hospital in canagliflozin initiators compared with initiators of non-gliflozin antidiabetic agents (DPP-4i, GLP1-RA, and sulfonylureas) and no meaningful difference in the occurrence of a composite of myocardial infarction or stroke. Analysis of secondary outcomes that included a broader definition of heart failure (ie, heart failure admission to hospital or a new use of loop diuretics), canagliflozin initiators consistently had a lower risk compared with other diabetes drugs. These results were robust in a sensitivity analysis that further adjusted for HbA1c and importantly, in subgroups of patients with and without a history of heart failure and cardiovascular disease. Furthermore, reductions in rates of heart failure admission to hospital are manifested early, over a relatively short duration of use.

This study has important clinical implications. Our results suggest a potential beneficial effect of

Table 4 | Risk of secondary outcomes associated with canagliflozin versus comparators in propensity score matched analyses

Characteristics	Cohort 1		Cohort 2		Cohort 3	
	Canagliflozin	DPP-4i	Canagliflozin	GLP-1RA	Canagliflozin	Sulfonylurea
Broadly defined heart failure endpoint*						
No of patients	15 959	15 959	18 482	18 482	15 898	15 898
No of events (†)	208 (22.5)	309 (35.7)	236 (20.7)	330 (30.5)	179 (18.5)	381 (39.3)
Hazard ratio (95% CI)	0.64 (0.53 to 0.76)	NA	0.68 (0.58 to 0.81)	NA	0.47 (0.39 to 0.56)	NA
Other secondary outcomes						
No of patients	17 667	17 667	20 539	20 539	17 354	17 354
Composite cardiovascular endpoint‡						
No of events (†)	155 (15.3)	152 (15.7)	172 (13.7)	173 (14.5)	138 (13.1)	155 (14.5)
Hazard ratio (95% CI)	0.97 (0.78 to 1.22)	NA	0.95 (0.77 to 1.17)	NA	0.90 (0.72 to 1.13)	NA
Myocardial infarction						
No of events (†)	60 (5.9)	63 (6.5)	69 (5.5)	64 (5.3)	53 (5.0)	63 (5.9)
Hazard ratio (95% CI)	0.91 (0.64 to 1.29)	NA	1.03 (0.73 to 1.44)	NA	0.85 (0.59 to 1.23)	NA
Stroke						
No of events (†)	42 (4.1)	50 (5.2)	43 (3.4)	38 (3.2)	41 (3.9)	48 (4.5)
Hazard ratio (95% CI)	0.81 (0.54 to 1.22)	NA	1.07 (0.69 to 1.66)	NA	0.87 (0.57 to 1.31)	NA
Unstable angina						
No of events (†)	27 (2.6)	23 (2.4)	31 (2.5)	40 (3.3)	20 (1.9)	28 (2.6)
Hazard ratio (95% CI)	1.13 (0.65 to 1.96)	NA	0.73 (0.46 to 1.17)	NA	0.72 (0.41 to 1.28)	NA
Coronary revascularization						
No of events (†)	90 (8.8)	80 (8.2)	107 (8.5)	101 (8.4)	81 (7.7)	78 (7.3)
Hazard ratio (95% CI)	1.07 (0.79 to 1.45)	NA	1.01 (0.77 to 1.32)	NA	1.05 (0.77 to 1.43)	NA
All cause mortality						
No of events (†)	7 (0.7)	10 (1.0)	9 (0.7)	11 (0.9)	8 (0.8)	6 (0.6)
Hazard ratio (95% CI)	0.66 (0.25 to 1.74)	NA	0.77 (0.32 to 1.85)	NA	1.34 (0.47 to 3.87)	NA

DPP-4i=DPP-4 inhibitor; GLP-1RA=GLP-1 receptor agonist; NA=not applicable.
*Defined as heart failure admission to hospital or new use of loop diuretics. For this outcome, the analysis was restricted to patients with no loop diuretics or heart failure diagnosis at baseline.
†Incidence rate per 1000 person years.
‡Expanded composite cardiovascular endpoint was defined as being admitted to hospital for myocardial infarction, stroke, unstable angina, or coronary revascularization.
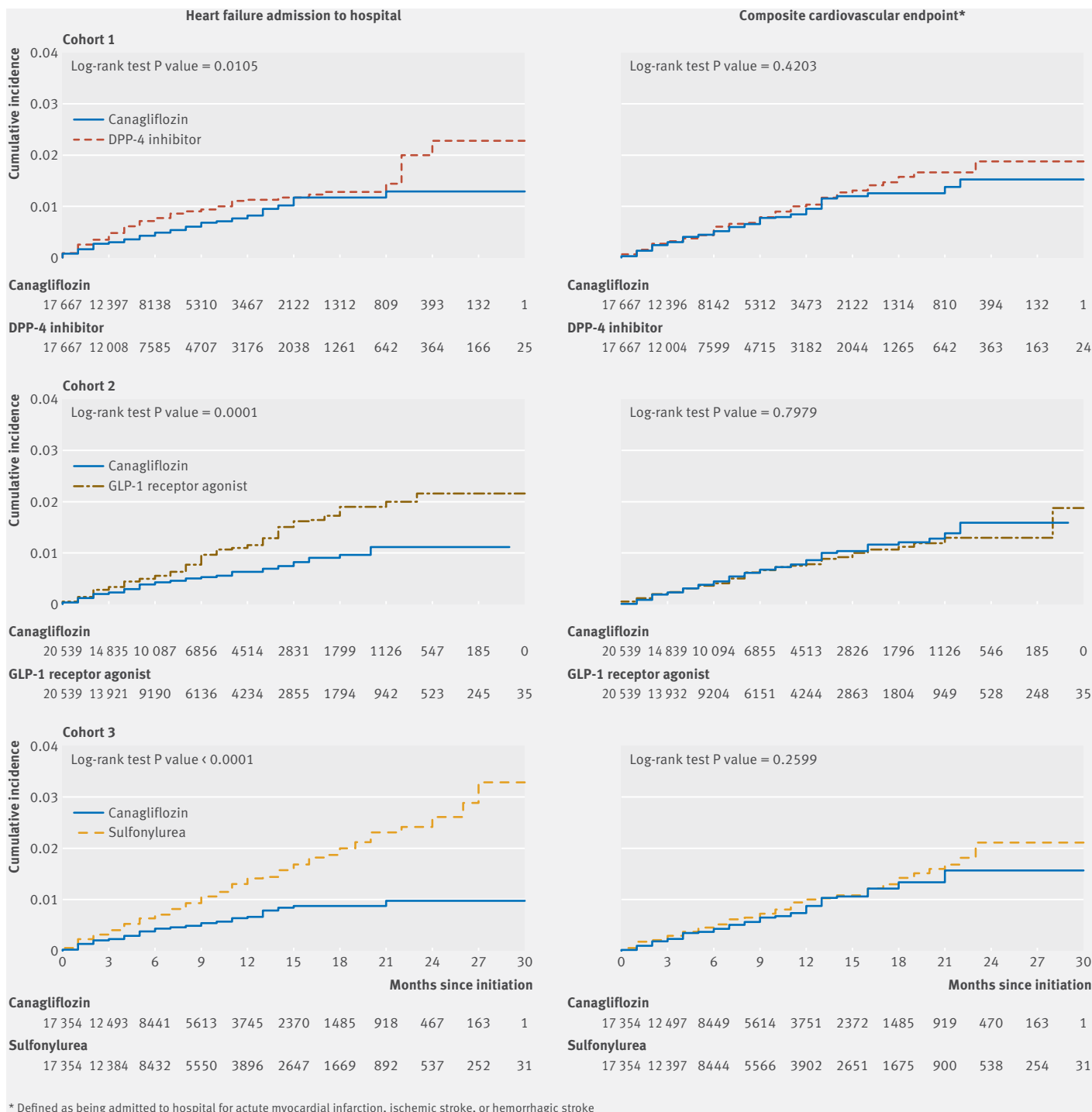
Fig 2 | Propensity score matched Kaplan-Meier curves for cumulative incidence of heart failure admission to hospital and composite cardiovascular endpoint since treatment initiation

canagliflozin, a drug widely available internationally, on heart failure hospital stays in routine care similar to what was noted in exploratory endpoint analyses in the CANVAS trial for canagliflozin,[9] and in the EMPA-REG OUTCOME trial for empagliflozin;[8] thus, our study responds to the need of confirmatory evidence raised by these exploratory data, in line with the discussion at a recent meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the US Food and Drug Administration.[25] Our study also suggests that the potential beneficial effect of canagliflozin with regard to heart failure admission to hospital tends to occur early, within the first six months after treatment initiation. This is consistent with both the CANVAS and the EMPA-REG OUTCOME trials,[8 9] which showed a similarly early reduction in the risk of admission to hospital for heart failure associated with canagliflozin and empagliflozin, respectively.

Table 5 | Risk of heart failure admission to hospital and composite cardiovascular endpoint associated with canagliflozin versus comparators in propensity score matched sensitivity and subgroup analyses

Analysis	Cohort 1		Cohort 2		Cohort 3	
	Canagliflozin	DPP-4i	Canagliflozin	GLP-1RA	Canagliflozin	Sulfonylurea
Heart failure admission to hospital						
First exposure carried forward for 365 days*:						
No of patients	17 667	17 667	20 539	20 539	17 354	17 354
No of events (†)	103 (9.9)	140 (13.3)	113 (8.9)	167 (13.0)	96 (9.2)	159 (15.0)
Hazard ratio (95% CI)	0.74 (0.57 to 0.95)	NA	0.68 (0.54 to 0.86)	NA	0.61 (0.47 to 0.79)	NA
HbA1c adjusted analysis:						
No of patients	6661	6661	7453	7453	6488	6488
No of events (†)	28 (7.6)	46 (12.9)	32 (7.2)	36 (8.5)	28 (7.3)	36 (9.2)
Hazard ratio (95% CI)	0.58 (0.37 to 0.93)	NA	0.85 (0.53 to 1.37)	NA	0.78 (0.48 to 1.29)	NA
No acute cardiovascular events in previous 60 days‡:						
No of patients	17 571	17 571	20 439	20 439	17 283	17 283
No of events (†)	88 (8.7)	107 (11.1)	95 (7.6)	139 (11.7)	72 (6.9)	134 (12.6)
Hazard ratio (95% CI)	0.79 (0.59 to 1.04)		0.65 (0.50 to 0.84)		0.54 (0.41 to 0.72)	
No heart failure history§:						
No of patients	15 959	15 959	18 482	18 482	15 898	15 898
No of events (†)	40 (4.3)	48 (5.5)	39 (3.4)	59 (5.4)	31 (3.2)	54 (5.5)
Hazard ratio (95% CI)	0.79 (0.52 to 1.21)	NA	0.63 (0.42 to 0.94)	NA	0.58 (0.37 to 0.90)	NA
Heart failure history§:						
No of patients	1654	1654	1991	1991	1430	1430
No of events (†)	52 (58.2)	88 (99.1)	50 (45.1)	77 (72.3)	45 (56.5)	80 (93.3)
Hazard ratio (95% CI)	0.59 (0.42 to 0.82)	NA	0.62 (0.44 to 0.89)	NA	0.59 (0.41 to 0.86)	NA
Composite cardiovascular endpoint¶						
First exposure carried forward for 365 days*:						
No of patients	17 667	17 667	20 539	20 539	17 354	17 354
No of events (†)	117 (11.2)	126 (11.9)	120 (9.4)	125 (9.8)	99 (9.4)	117 (11.0)
Hazard ratio (95% CI)	0.94 (0.73 to 1.21)	NA	0.97 (0.75 to 1.24)	NA	0.86 (0.66 to 1.12)	NA
HbA1c-adjusted analysis:						
No of patients	6661	6661	7453	7453	6488	6488
No of events (†)	33 (8.9)	32 (9.0)	39 (8.7)	34 (8.0)	32 (8.3)	47 (12.0)
Hazard ratio (95% CI)	0.99 (0.61 to 1.61)	NA	1.09 (0.69 to 1.73)	NA	0.70 (0.45 to 1.10)	NA
No acute cardiovascular events in previous 60 days‡:						
No of patients	17 571	17 571	20 439	20 439	17 283	17 283
No of events (†)	91 (9.0)	85 (8.8)	106 (8.4)	100 (8.4)	92 (8.8)	113 (10.6)
Hazard ratio (95% CI)	1.02 (0.76 to 1.37)	NA	1.00 (0.76 to 1.32)	NA	0.82 (0.63 to 1.08)	NA
No cardiovascular history**:						
No of patients	14 587	14 587	16 903	16 903	14 525	14 525
No of events (†)	58 (6.8)	53 (6.6)	62 (5.9)	62 (6.2)	58 (6.5)	60 (6.7)
Hazard ratio (95% CI)	1.04 (0.72 to 1.51)	NA	0.95 (0.67 to 1.35)	NA	0.97 (0.67 to 1.39)	NA
Cardiovascular history**:						
No of patients	3009	3009	3600	3600	2800	2800
No of events (†)	42 (24.9)	45 (27.6)	44 (20.9)	47 (23.5)	37 (22.9)	54 (32.5)
Hazard ratio (95% CI)	0.90 (0.59 to 1.38)	NA	0.89 (0.59 to 1.35)	NA	0.70 (0.46 to 1.06)	NA

DPP-4i=DPP-4 inhibitor; GLP-1RA=GLP-1 receptor agonist; NA=not applicable.
*Follow-up started on the day following treatment initiation and ended at the occurrence of a study outcome, insurance disenrollment, end of a 365 day period, or end of the study period (15 September 2015), whichever came first.
†Incidence rate per 1000 person years.
‡Occurrence of acute cardiovascular or heart failure events requiring a hospital stay during the 60 day period before initiation of the index drug.
§Heart failure history was defined as the presence of heart failure diagnosis or use of loop diuretics at baseline.
¶Composite cardiovascular outcome was defined as being admitted to hospital for myocardial infarction or stroke.
**Cardiovascular history was defined as history of coronary heart disease, cerebrovascular disease, peripheral vascular disease, or heart failure.

Strengths and weaknesses in relation to other studies

Randomized controlled trials are the best way to assess drug efficacy. Over the past decade, large scale postmarketing randomized controlled trials of newly licensed antidiabetic drugs have been conducted for cardiovascular outcomes and safety.[26] The strengths of randomized controlled trials include baseline randomization, high adherence, and prespecified and adjudicated outcomes. On the other hand, strict inclusion and exclusion criteria and rigorous safety monitoring limit the generalizability of randomized controlled trial results. Our study was based on approximately 225 000 unique patients with type 2 diabetes contributing 165 000 person years across the USA, allowing better generalizability to routine care. Second, our study provides data from direct comparisons of canagliflozin and other commonly used antidiabetic drugs. In routine clinical care, physicians and patients need to choose drug A versus drug B rather than drug A versus usual care as defined in most cardiovascular outcome trials of antidiabetic drugs. Furthermore, because use of open label alternative antidiabetic agents is permitted for appropriate glycemic control in these trials, the drug of interest is not directly compared with specific alternative diabetes

treatment options. In this regard, the CVD-REAL study, the first published in use investigation assessing the risk of heart failure admission to hospital and death associated with the class of SGLT2i's compared with an unspecified group of diabetes treatment alternatives,[10] also does not provide comparative information on the cardiovascular effects of SGLT2i's versus specific antidiabetic drug options. A subanalysis restricted to the participating Nordic countries (CVD-REAL Nordic) has recently provided initial comparative information on dapagliflozin, though the study only included one comparator class, DPP-4i's.[11] Therefore, evidence based on direct comparisons of specific drugs such as our findings is needed to enhance treatment decision making for patients with diabetes. Third, current cardiovascular outcome trials evaluate drug effects in patients with established cardiovascular disease or multiple risk factors in order to achieve an adequate statistical power in the timeframe of the trials. In this study, we examined the comparative effects of these drugs in patients with and without established heart failure or cardiovascular disease; results suggested no treatment heterogeneity between the subgroups. Lastly, this study is based on recent data up to September 2015, which has the advantage that the study period precedes the publication of both the EMPA-REG OUTCOME and the CANVAS results, thus excluding a possible influence on physicians' selective prescribing.[8 9]

Limitations of this study

This study has several limitations. First, even though primary and secondary outcomes were defined using previously validated claims based algorithms with a positive predictive value ≥84%,[13-16] outcome misclassification is a possibility. However, a broader definition of heart failure that included outpatient dispensing for a new loop diuretic drug did not change our main conclusions. Second, we were unable to study cardiovascular mortality or all cause mortality as the primary outcome, as the information on cause of death was not available in the study dataset; and as the capture of all cause mortality in administrative data was limited by a policy change in 2011 concerning the extent of the Social Security Administration disclosure of death records received from states.[27] This under reporting, the non-restriction to patients with baseline cardiovascular disease, and the short duration of follow-up, explain the lower observed death rates compared with the EMPA-REG OUTCOME and CANVAS trials. Third, while we used propensity score matching to balance more than 100 baseline characteristics between the groups, residual confounding by some unmeasured characteristic(s) cannot be ruled out. Fourth, since canagliflozin is a newly marketed drug approved by the FDA in March 2013, its long term effects will need to be further studied. Similarly, the in use evaluation of the most recently marketed SGLT2i's (dapagliflozin and empagliflozin) in the USA, will also require further accumulation of routine care data, owing to their limited use in routine care in the USA

during the study period. Fifth, our study focused only on the association of canagliflozin with cardiovascular endpoints, without consideration of other potential outcomes (eg, factures and lower-limb amputations) that may be relevant for treatment decisions in diabetes care. Sixth, diabetes duration or body mass index are not captured in claims data. However, it has been shown sufficient balance in these characteristics after adjusting for proxies of diabetes severity and duration in a new user cohort study based on claims data linked to inpatient electronic medical records.[28] The absence of information in diabetes duration also precluded the evaluation of the effects of canagliflozin in early versus late stage diabetes. Lastly, our results may not be generalizable to patients with different insurance types or no insurance coverage, as commercially insured patients are more likely to have differential socioeconomic status, drug adherence, and risk factors for cardiovascular disease. However, the biological effect of a SGLT2i on cardiovascular events is unlikely to differ by insurance status, thus our results may apply to other populations outside the USA. Despite these limitations, our results complement cardiovascular outcome trials by enriching the understanding of the cardiovascular effects of these drugs compared directly with clinically relevant diabetes treatment alternatives among patients with type 2 diabetes in routine practice.

Conclusions

In this large population based cohort of patients with type 2 diabetes with and without baseline cardiovascular disease, canagliflozin was associated with a decreased risk of heart failure admission to hospital compared with three clinically relevant antidiabetic drug alternatives including a DPP4i, a GLP1-RA, and a sulfonylurea, which was similar in magnitude and time of occurrence to what was reported by the CANVAS trial for canagliflozin and by the EMPA-REG OUTCOME trial for empagliflozin.[8 9] The risk of myocardial infarction or stroke was similar between canagliflozin and non-gliflozin antidiabetic drugs, in line with what was reported by the two trials. Our investigation shows the potential cardiovascular benefits of canagliflozin versus other diabetes drugs as used in routine care. Our study also supports the increasing role of large pharmacoepidemiologic studies based on longitudinal data routinely generated in the provision of healthcare for millions of patients, to provide valid and timely information on the safety and effectiveness of glucose lowering drugs in use as a complement to and in anticipation of study results on cardiovascular outcomes.[29]

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Appendix: Supplementary materials