Received: 27 March 2018 | Revised: 11 July 2018 | Accepted: 15 July 2018

DOI: 10.1111/dom.13477

WILEY

ORIGINAL ARTICLE

Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes

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Funding information
This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit-sector.

Aims: To determine the association between cardiovascular diseases (CVD) and SGLT2 inhibitors compared to sulfonylureas and dipeptidyl peptidase-4 (DPP4) inhibitors and to examine within-class effects of SGLT2 inhibitors.

Methods: A retrospective cohort analysis was conducted using Truven Health MarketScan. New users of SGLT2 inhibitors, sulfonylureas or DPP-4 inhibitors were included. Primary outcome was incident CVD, defined as non-fatal myocardial infarction or non-fatal stroke; secondary outcomes were hospitalization because of heart failure and lower extremity amputation. Proportional hazards models, after propensity score matching, were used to obtain hazard ratios (HR) and 95% confidence intervals (CI).

Results: In fully adjusted models, use of SGLT2 inhibitors was associated with a decreased risk of developing CVD compared with use of sulfonylureas (HR, 0.50; 95% CI, 0.45, 0.55) and DPP-4 inhibitors (HR, 0.57; 95% CI, 0.52, 0.62), respectively. Analyses revealed no evidence of within-class effects: dapagliflozin vs sulfonylureas (HR, 0.55; 95% CI, 0.43, 0.70) or DPP-4 inhibitors (HR, 0.57; 95% CI, 0.46, 0.70); and canagliflozin vs sulfonylureas (HR, 0.61; 95% CI, 0.54, 0.69) or DPP-4 inhibitors (HR, 0.66; 95% CI, 0.54, 0.71). Additionally, SGLT2 inhibitors were associated with lower risk of hospitalization because of heart failure compared to both sulfonylureas and DPP-4 inhibitors, as well as lower risk of lower extremity amputation compared to sulfonylureas.

Conclusion: Using population-based data, incident use of SGLT-2 inhibitors was associated with a decreased incidence of CVD compared to use of sulfonylureas and DPP-4 inhibitors. These findings were consistent between dapagliflozin and canagliflozin, suggesting that CVD reduction is a class effect for SGLT2 inhibitors. In addition, SGLT2 inhibitors portended lower risk of hospitalization because of heart failure (vs sulfonylureas and DPP-4 inhibitors) and lower risk of lower extremity amputation (vs sulfonylureas).

KEYWORDS

antidiabetic drug, cardiovascular disease, SGLT2 inhibitor

1 | INTRODUCTION

Type 2 diabetes now affects more than 350 million patients worldwide,[1] putting these individuals at higher risk of developing micro- and macrovascular complications including cardiovascular diseases (CVDs).[2] Maintaining optimal glycaemic control can delay or reduce the risk of potential complications.[2] However, debate continues regarding which antihyperglycaemic drugs optimally reduce complications. Recent evidence from randomized clinical trials (RCTs) suggests that sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as dapagliflozin, canagliflozin and empagliflozin, may exhibit cardioprotective effects.[3] For example, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) reported a 14% reduction in the risk of CVD (non-fatal myocardial infarction [MI] and non-fatal stroke) and CVD-related death in the empagliflozin group compared to the placebo group.[4] Similarly, the Canagliflozin Cardiovascular Assessment Study (CANVAS) trial reported a lower risk of CVD events with canagliflozin

compared to placebo (hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.75, 0.97).[5] Subsequently, these results were supported by a meta-analysis of RCTs which found a net protective effect of SGLT2 inhibitors against major CVDs (relative risk [RR], 0.85; 95% CI, 0.77, 0.93), heart failure (RR, 0.67; 95% CI, 0.55, 0.80) and all-cause death (RR, 0.79; 95% CI, 0.70, 0.88).[6]

Although RCTs are the gold standard in assessing the effectiveness of medications, the restricted environment of RCTs limits generalizability to real-world settings and often does not allow for assessment of heterogeneity in treatment effects. Evidence generated using real-world data can complement RCTs in guiding prescribing decisions in clinical practice.[7,8]

Several observational studies have recently evaluated the cardiovascular safety of SGLT2 inhibitors among patients with type 2 diabetes.[9–17] One population-based study, which used data from the Health Improvement Network database, found that, compared to use of other glucose-lowering agents, the use of empagliflozin was associated with lower risk of all-cause mortality, irrespective of baseline CVD.[9] Similarly, the first analysis from the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study and two follow-up analyses of the same study showed a lower risk of death and hospitalization as the result of heart failure with use of SGLT2 inhibitors compared to other glucose-lowering medications (eg, sulfonylureas, thiazolidinediones [TZDs]) but showed no difference in incidence of non-fatal MI and non-fatal stroke.[10,11,13] In contrast, the most recent analyses of the CVD-REAL study and two other observational studies, which primarily focused on canagliflozin, reported a lower risk of non-fatal MI and non-fatal stroke but a higher risk of lower extremity amputation with the use of SGLT2 inhibitors compared to other glucose-lowering medications.[12,14,15,17]

In the first analysis of the CVD-REAL study, which included data from the United States and Europe, the reduction in risk of heart failure and death was reported across countries, regardless of variability in the use of SGLT-2 inhibitors, with canagliflozin dominating the United States and dapagliflozin dominating Europe, suggesting a class effect.[10] Similarly, the results of the CVD-REAL 2 study, which included Asian and Middle Eastern populations, suggested that reduction in cardiovascular outcomes (eg, MI, stroke) with the use of SGLT2 inhibitors was a class effect.[16] Although prior studies have suggested a class effect, none have explicitly evaluated the within-class effect of SGLT2 inhibitors.

Additionally, there has been conflicting evidence regarding the risk of amputation with the use of SGLT2 inhibitors.[18,19] Therefore, our primary objectives were to (1) determine the incidence of CVD with the use of SGLT2 inhibitors compared to other oral, second-line glucose-lowering drugs, namely sulfonylureas and DPP-4 inhibitors, among patients with type 2 diabetes and (2) to compare the within-class effects of SGLT2 inhibitors. Secondarily, we aimed to assess the association between use of SGLT2 inhibitors vs sulfonylureas or DPP-4 inhibitors on and the risk of hospitalization because of heart failure or of lower extremity amputation.

2 | METHODS

2.1 | Data source

We conducted a retrospective cohort study using the Truven Health MarketScan (Truven Health Analytics, Ann Arbor, MI, USA), a commercial and Medicare supplemental claims database from January 2013 to December 2015. The database captures information on outpatient, inpatient, health expenditure, enrollment and prescription drug claims of more than 57 million individuals. The commercial data include privately insured employees and their dependents who are covered under employer-sponsored health insurance programs. The Medicare data represent the healthcare experience of retirees who are covered by Medicare supplemental insurance.

2.2 | Study population and exposure determination

Patients were included if they were 18 years of age or older and had a diagnosis of type 2 diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM], 250.x0 or 250.x2) based on one inpatient or two outpatient encounters at two different service dates within one year prior to treatment initiation. Additionally, patients were required to have 12 months of continuous enrollment in a medical and pharmacy benefits programme prior to the index-date, and to have at least one prescription of an antidiabetic medication of interest including SGLT2 inhibitors (dapagliflozin, canagliflozin or empagliflozin), sulfonylureas (chlorpropamide, tolbutamide, tolazamide, glimepiride, glipizide or glyburide) or DPP-4 inhibitors (sitagliptin, saxagliptin, alogliptin or linagliptin). These specific comparators were chosen to represent commonly used second-line therapies based on the most updated treatment algorithms for patients with type 2 diabetes, and also to avoid time-lag bias.[20,21]

The date of the dispensing of the first eligible prescription was designated as the index date. A new-user design, which avoids the biases introduced by including prevalent users, such as the under-ascertainment of early events or immortal time bias, was employed.[21,22] Patients were considered to be exposed as long as they continued to refill their prescription, allowing a gap of 7 days or less between refills. Patients were excluded if they had a diagnosis of type I diabetes (ICD-9-CM code 250.x1 or 250.x3) or end-stage renal disease (ESRD) (ICD-9-CM: 585.6), of if they had a prescription for any antidiabetic medication of interest during the baseline period or initiated more than one antidiabetic medication of interest on the same day.

Follow-up for outcomes began at the index date and continued until the first occurrence of an outcome of interest, discontinuation of index medications, initiation of study comparator, inpatient death, end of enrollment or end of study period, whichever took place first. In a subgroup analysis, we also examined outcomes associated with use of individual SGLT2 inhibitors including dapagliflozin and canagliflozin, compared to use of sulfonylureas and DPP-4 inhibitors. For this subgroup analysis only, switching within the SGLT2 inhibitor class prompted censoring of follow-up.

2.3 | Study outcomes

The primary study outcome was first occurrence of a composite of a CVD event, defined as non-fatal MI (ICD-9: 410.x) or non-fatal stroke (ICD-9: 433.x1, 434 [excluding 434.x0], or 436), presenting at primary or secondary discharge diagnosis. The same outcome definition, using primary diagnosis only, was also examined in the sensitivity analysis. The secondary outcome of hospitalization because of heart failure was measured using ICD-9-CM codes 402.x1, 404.x1, 404.x3, or 428.xx. Lower extremity amputation was measured using primary and secondary diagnosis, according to ICD-9-CM codes 84.11, 84.12, 84.13, 84.14, 84.15, or 84.16; or, CPT-4 codes 27880, 27881, 27882, 27886, 27888, 28800, 28805, 28810, 28820, or 28825.

2.4 | Adjustment for confounders

To balance comparison groups and minimize potential bias as the result of confounding, propensity score (1:1) matching was used for selection of the paired samples (SGLT2 inhibitors vs sulfonylureas, and SGLT2 inhibitors vs DPP-4 inhibitors). The propensity score was generated by fitting a logistic regression model to predict the probability of receiving the SGLT2 inhibitors vs the comparators in each pairwise comparison. Patients were matched based on the propensity score using a caliber of 0.1 to the nearest neighbor. In development of the study protocol, limitations of prior studies (eg, choice of the comparator group, prevalent vs incident user design) were considered and covariates were extracted from a prior protocol developed by the Mini-Sentinel, an active surveillance program monitored by the food and drug administration.[23] Variables included in the propensity score modeling were patient age and sex, measures of use of health care services (ie, total number of outpatient visits, total number of inpatient visits), presence of comorbidities (ie, asthma, chronic obstructive pulmonary disease, chronic kidney disease [CKD], ischaemic heart disease, depression, stroke, hypoglycaemia, cancer, hypertension, MI, heart failure), use of other diabetes medications (ie, insulin, metformin, TZDs, α-Glucosidase inhibitors, glucagon-like peptide-1 receptor agonists, meglitinides) and use of other medications (ie, angiotensin-converting enzyme inhibitors, aldosterone receptor antagonists, α-blockers, angiotensin receptor blockers, β-blockers, calcium channel blockers, loop diuretics, potassium-sparing diuretics, thiazide diuretics, direct vasodilators). Baseline CVD was defined as history of MI, angina pectoris, stroke, coronary revascularization, coronary artery disease, cerebrovascular diseases, cerebral infarction, transient ischaemic attack, cerebral haemorrhage and subarachnoid haemorrhage.

2.5 | Statistical analysis

Descriptive statistics were summarized using means for continuous variables and proportion for categorical variables. Demographics and clinical characteristics were compared between exposure groups using a chi-square test for categorical variables and independent t-test for continuous variables. Standardized differences were used to examine the balance in baseline characteristics post matching, where imbalance was defined as an absolute value higher than 0.2.[24,25] Following propensity score matching, proportional hazard models were used to obtain the HR and associated 95% CI. Several sensitivity analyses were conducted to examine the robustness of study results, including the exclusion of TZDs and insulin users, and changing the outcome definition to primary diagnosis only. We further evaluated heterogeneity in treatment effect in selected subgroups of diabetic patients, including patients with baseline CVD vs those with baseline CVD, and those aged less than 65 years vs those 65 years and older. Separate propensity score matching was performed within each of the subgroup analyses and for each pair of within-class effect comparisons (eg, dapagliflozin vs DPP-4 inhibitors). For secondary analyses of lower extremity amputation, patients with a history of lower extremity amputation were excluded. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

We identified a total of 147 352 new users of SGLT2 inhibitors, 624 069 new users of sulfonylureas and 300 607 new users of DPP-4 inhibitors. After matching, a total of 125 534 patients were included in the SGLT2 inhibitors vs sulfonylureas cohort (n = 62 767 per exposure group) and a total of 133 266 patients in the SGLT2 inhibitors vs DPP-4 inhibitors cohort (n = 66 633 per exposure group) (Table 1). In both propensity-matched cohorts, patient characteristics including age, sex and presence of comorbid conditions were comparable. Table S1 summarizes baseline characteristics among the three groups before propensity score matching.

3.1 | Incident cardiovascular disease

Table 2 shows the risk of the composite CVD with SGLT2 inhibitors vs sulfonylurea users and DPP-4 inhibitor users in the propensity score-matched cohorts. The composite CVD outcome occurred in 569 of 62 767 (0.91%) SGLT2 inhibitor users and in 1272 of 62 767 (2.02%) sulfonylurea users. The crude incidence of the composite CVD outcome was 9.5 per 1000 person-years in the SGLT2 inhibitor group and 15.7 per 1000 person-years in the sulfonylurea group. In the SGLT2 inhibitor/DPP-4 inhibitor matched cohort, 660 of 66 633 (0.99%) SGLT2 inhibitor users experienced the composite CVD outcome vs 1519 of 66 633 (2.28%) DPP-4 inhibitor users. The crude incidence of the composite CVD was 7.9 per 1000 person-years with SGLT2 inhibitors and 17.2 per 1000 person-years with DPP-4 inhibitors. In the proportional hazard models, use of SGLT2 inhibitors was associated with a decreased risk of developing CVD compared with use of sulfonylureas (HR, 0.50; 95% CI, 0.45, 0.55) and DPP-4 inhibitors (HR, 0.57; 95% CI, 0.52-0.62) after adjusting for baseline demographics, comorbidities and use of other medications (Table 2). We also observed a reduced risk of hospitalization because of heart failure with the use of SGLT2 inhibitors as compared to use sulfonylureas (HR, 0.48; 95% CI, 0.40, 0.57) and DPP-4 inhibitors (HR, 0.54; 95% CI, 0.48, 0.60).

3.2 | Risk of lower extremity amputation

The crude incidence rates of lower extremity amputation were 1.5 per 1000 person-years in the SGLT2 inhibitor group and 1.9 in the sulfonylurea group. In the SGLT2 inhibitor vs DPP-4 inhibitor analysis, the

TABLE 1 Demographics and clinical characteristics in propensity score-matched cohorts of new users of SGLT2 inhibitors, sulfonylureas and DPP-4 inhibitors

Patient characteristics after PS matching	SGLT2 inhibitors (n = 62 767)	Sulfonylureas (n = 62 767)	Std-diff %[a]	SGLT2 inhibitors (n = 66 633)	DPP4 inhibitors (n = 66 633)	Std-diff %[a]
Mean age, y (± SD)	54 (±12.4)	54 (±9.6)	0.10	55 (±9.2)	54 (±11.0)	0.10
Sex, n (%)						
Male	32 827 (52.3)	32 890 (52.4)	0.00	35 915 (53.9)	35 849 (53.8)	0.01
Female	29 940 (47.7)	29 877 (47.6)		30 718 (46.1)	30 784 (46.2)	
Comorbidities, n (%)						
Asthma	3766 (6.0)	3766 (6.0)	0.00	3865 (5.8)	3998 (6.0)	0.00
COPD	2260 (3.6)	2134 (3.4)	0.02	2532 (3.8)	2332 (3.5)	0.02
CKD	2197 (3.5)	2071 (3.3)	0.04	2599 (3.9)	2132 (3.2)	0.02
Ischaemic heart disease	7,469 (11.9)	7030 (11.2)	0.04	8396 (12.6)	7729 (11.6)	0.03
Depression	2636 (4.2)	2636 (4.2)	0.00	2665 (4.0)	2665 (4.0)	0.03
Hypoglycaemia	2699 (4.3)	2636 (4.2)	0.01	2998 (4.5)	2865 (4.3)	0.01
Hyperlipidaemia	41 363 (65.9)	41 175 (65.6)	0.00	44 311 (66.5)	44 244 (66.4)	0.01
Cancer	4268 (6.8)	4143 (6.6)	0.02	4598 (6.9)	4065 (6.1)	0.02
Hypertension	42 242 (67.3)	42 054 (67)	0.02	45 644 (68.5)	45 244 (67.9)	0.00
Use of other diabetes medications, n (%)						
Insulin	14 750 (23.5)	13 872 (22.1)	0.06	14 793 (22.2)	13 860 (20.8)	0.00
Metformin	36 279 (57.8)	36 907 (58.8)	−0.02	39 847 (59.8)	41 312 (62)	−0.03
TZDs	4017 (6.4)	4017 (6.4)	−0.01	4931 (7.4)	4931 (7.4)	0.00
α-Glucosidase inhibitor	251 (0.4)	251 (0.4)	0.00	267 (0.4)	333 (0.5)	0.00
GLP-1	8725 (13.9)	7846 (12.5)	0.05	6930 (10.4)	530 (8.6)	0.01
Meglitinides	1067 (1.7)	1004 (1.6)	0.00	999 (1.5)	933 (1.4)	0.00
Use of other medications, n (%)						
ACE	20 588 (32.8)	20 588 (32.8)	0.00	23 122 (34.7)	23 388 (35.1)	−0.02
Aldosterone receptor antagonists	1506 (2.4)	1506 (2.4)	0.00	1599 (2.4)	1533 (2.3)	0.00
α-Blocker	3138 (5.0)	3138 (5.0)	0.00	3532 (5.3)	3465 (5.2)	0.01
Angiotensin-receptor blocker	10 357 (16.5)	10 357 (16.5)	0.00	10 994 (16.5)	10 928 (16.4)	−0.01
β-Blocker	14 185 (22.6)	14 185 (22.6)	0.01	15 925 (23.9)	15 659 (23.5)	0.00
Calcium-channel blocker	9917 (15.8)	10 043 (16)	0.00	11 194 (16.8)	11 194 (16.8)	−0.01
Loop diuretic	4959 (7.9)	4770 (7.6)	0.02	5464 (8.2)	5264 (7.9)	0.01
Potassium-sparing diuretic	1569 (2.5)	1569 (2.5)	0.01	1732 (2.6)	1599 (2.4)	0.00
Thiazide	1067 (1.7)	1130 (1.8)	0.01	1066 (1.6)	1066 (1.6)	0.00
Vasodilator	527 (0.84)	521 (0.83)	0.00	600 (0.9)	600 (0.9)	0.01
Healthcare utilization, mean (± SD)						
Mean number of inpatient visits	1 (±0.7)	1 (±0.8)	−0.01	1 (±0.7)	1 (±0.8)	−0.01
Mean number of outpatient visits	16 (±17)	17 (±18.7)	−0.07	14 (±13.9)	14 (±14.5)	−0.07

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide-1 receptor agonists; PS, propensity score; SD, standard deviation; SGLT2, sodium-glucose co-transporter 2 inhibitors; Std-diff, standardized difference; TZDs, thiazolidinediones.
[a] Imbalance in standardized difference is defined as a absolute value >0.20.

crude incidence rates were 1.8 per 1000 person-years in the SGLT-2 inhibitor group and 1.9 per 1000 person-years in the DPP-4 inhibitor groups (Table 2). Use of SGLT2 inhibitors was associated with lower risk of amputation compared to use of sulfonylureas (adjusted HR, 0.74; 95% CI, 0.57, 0.96), but not compared to use of DPP-4 inhibitors (HR, 0.88; 95% CI, 0.65, 1.15).

3.3 | Subgroup and sensitivity analyses

Results of subgroup and sensitivity analyses are shown in Tables 3 and 4. In subgroup analyses, we found a lower risk of CVD among patients 65 years of age or younger who were exposed to SGLT2 inhibitors compared exposure to sulfonylureas (HR, 0.59; 95% CI,

TABLE 2 Risk of cardiovascular diseases with SGLT2 Inhibitors versus comparators in propensity score-matched analyses

Study population	Medications	No. of Patients	Pearson-years	No. of events	Crude incidence	Adjusted HR (95% CI)
SGLT2 inhibitors vs sulfonylureas	SGLT2 inhibitors	62 767	59 678	569	9.5	0.50 (0.45, 0.55)
Composite of CVD (MI and stroke) by outcome	Sulfonylureas	62 767	81 001	1272	15.7	Reference
MI	SGLT2 inhibitors	62 767	70 821	341	4.8	0.70 (0.61, 0.81)
	Sulfonylureas	62 767	68 457	499	7.3	Reference
Stroke	SGLT2 inhibitors	62 767	68 434	381	5.6	0.69 (0.61, 0.78)
	Sulfonylureas	62 767	70 739	571	8.1	Reference
Secondary outcomes						
Heart failure	SGLT2 inhibitors	62 767	68 438	368	5.4	0.48 (0.40, 0.57)
	Sulfonylureas	62 767	70 600	767	10.9	Reference
Lower extremity amputation	SGLT2 inhibitors	59 385	59 499	92	1.5	0.74 (0.57, 0.96)
	Sulfonylureas	59 385	82 092	158	1.9	Reference
SGLT2 inhibitors vs DPP-4 inhibitors	SGLT2 inhibitors	66 633	83 505	660	7.9	0.57 (0.52, 0.62)
Composite of CVD (MI and stroke) by outcome	DPP-4 inhibitors	66 633	88 077	1519	17.2	Reference
MI	SGLT2 inhibitors	66 633	73 853	313	4.2	0.72 (0.63, 0.82)
	DPP-4 inhibitors	66 633	73 206	407	5.6	Reference
Stroke	SGLT2 inhibitors	66 633	60 307	379	6.3	0.61 (0.50, 0.73)
	DPP-4 inhibitors	66 633	59 566	542	9.1	Reference
Secondary outcomes						
Heart failure	SGLT2 inhibitors	66 633	73 824	360	4.9	0.54 (0.48, 0.60)
	DPP-4 inhibitors	66 633	73 031	649	8.9	Reference
Lower extremity amputation	SGLT2 inhibitors	65 847	66 845	120	1.8	0.88 (0.65, 1.15)
	DPP-4 inhibitors	65 847	89 161	171	1.9	Reference

Abbreviations: CI, confidence interval; CVD, cardiovascular diseases; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; MI, myocardial infarction; SGLT2, sodium-glucose co-transporter 2.

0.52, 0.66) and DPP-4 inhibitors (HR, 0.65; 95% CI, 0.57, 0.74). Conversely, we observed no significant difference in outcomes among those above 65 years of age, comparing SGLT2 inhibitor users to sulfonylurea users (HR, 0.80; 95% CI, 0.65, 1.00) and DPP-4 inhibitor users (HR, 0.90; 95% CI, 0.71, 1.14), although the treatment-by-age group interaction tests in each cohort were not statistically significant (P = 0.420 and P = 0.936). We observed no significant difference in effect when stratifying by baseline CVD presence or absence (P value for interaction in each cohort, P = 0.083 and P = 0.092). Finally, we observed no evidence of differential effects comparing individual SGLT2 inhibitors. Compared to sulfonylureas, a similarly lower risk was observed with dapagliflozin (HR, 0.55; 95% CI, 0.43, 0.70) and canagliflozin (HR, 0.61; 95% CI, 0.54, 0.69). Likewise, compared to DPP-4 inhibitors, a similarly lower risk was observed with dapagliflozin (HR, 0.57; 95% CI, 0.46, 0.70) and canagliflozin (HR, 0.66; 95% CI, 0.54, 0.71). Study results remained consistent when using an outcome definition based on primary diagnosis only, and by excluding insulin users or TZD users.

4 | DISCUSSION

In this large, contemporary cohort of patients with type 2 diabetes, we found that the use of SGLT2 inhibitors was associated with a 43% to 50% reduced risk of developing nonfatal CVD when compared to use of sulfonylureas or to use of DPP-4 inhibitors. These results were consistent among patients with and without pre-existing CVD. We also found that use of SGLT2 inhibitors was associated with a 46% to 52% reduction in the risk of hospitalization because of heart failure, a finding that complements those reported in the EMPA-REG, CANVAS trials and in recent observational studies.[4–6,10,15,17,26] Finally, we observed a modestly lower risk of lower extremity amputation comparing use of SGLT2 inhibitors to use of sulfonylureas, but not to use of DPP-4 inhibitors.

Unlike the EMPA-REG OUTCOME trial and the CANVAS study, which compared SGLT2 inhibitors to placebo, the current study used active comparators which is more relevant to guidance concerning prescribing decisions in routine clinical practice.[4,5] Observational studies, such as the CVD-REAL study, have compared SGLT2 inhibitors to other glucose-lowering agents, with conflicting findings.[10,13,16,17] In the first follow-up analysis of the CVD-REAL study, the authors did not find a significant difference between use of dapagliflozin and use of DPP-4 inhibitors in risk of MI and stroke, but subsequent analyses reported a reduction in risk.[13] Compared to our study, the first follow-up analysis was limited by the small sample size (10 227 vs 66 633) and the outcome sources (outcome definition based on inpatient and outpatient claims vs inpatients claims only). Our case definition of MI was based only on inpatient discharge diagnoses as this approach has a high sensitivity (94%) and specificity (99%).[27] Additionally, the CVD-REAL study used a different exposure definition. Patients who

TABLE 3 Risk of cardiovascular disease with SGLT2 inhibitors versus sulfonylureas in propensity score matched sensitivity and subgroup analyses

Study population	Medications	No. of patients	Pearson-years	No. of CVD Events	Crude incidence	Adjusted HR of CVD (95% CI)	*P*-value for interaction
Subgroup analysis							
Age							
≤65 y	SGLT2 inhibitors	55 805	53 055	420	7.9	0.59 (0.52, 0.66)	0.420
	Sulfonylureas	55 805	70 094	890	12.7	Reference	
>65 y	SGLT2 inhibitors	5517	5109	122	23.9	0.80 (0.65, 1.00)	
	Sulfonylureas	5517	8292	298	35.9	Reference	
Baseline CVD							
With baseline CVD	SGLT2 inhibitors	8962	8900	220	24.7	0.51 (0.43, 0.60)	0.083
	Sulfonylureas	8962	12 007	494	41.1	Reference	
Without baseline CVD	SGLT2 inhibitors	53 242	50 259	337	6.7	0.56 (0.49, 0.64)	
	Sulfonylureas	53 242	68 902	715	10.4	Reference	
Drug							
Dapagliflozin vs. DPP-4 inhibitors	Dapagliflozin	13 816	13 896	126	9.1	0.55 (0.43, 0.70)	0.585
	Sulfonylureas	13 816	15 420	234	15.2	Reference	
Canagliflozin vs. DPP-4 inhibitors	Canagliflozin	32 603	33 682	428	12.7	0.61 (0.54, 0.69)	
	Sulfonylureas	32 603	41 483	695	16.8	Reference	
Sensitivity analysis							
Excluding insulin users	SGLT2 inhibitors	45 844	43 239	323	7.5	0.45 (0.41, 0.49)	
	Sulfonylureas	45 844	59 404	696	11.7	Reference	
Excluding TZD users	SGLT2 inhibitors	58 149	74 922	526	7.0	0.49 (0.41, 0.50)	
	Sulfonylureas	58 149	55 061	1145	20.8	Reference	
Using primary diagnosis	SGLT2 inhibitors	62 767	46 664	371	8.0	0.51 (0.45, 0.59)	
	Sulfonylureas	62 767	66 582	984	14.8	Reference	

Abbreviations: CI, confidence interval; CVD, cardiovascular diseases; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium-glucose co-transporter 2; TZDs, thiazolidinediones.

received a comparator drug but switched to SGLT2 inhibitors were classified as SGLT2 inhibitor-exposed, whereas patients who received a comparator drug and died were classified as comparator-exposed. To address this in our study, we employed an incident new-user design and we censored follow-up when patients switched from one drug to another. Two other recent analyses of real-world data reported findings similar to those of our study.[12,15]

In this study, we found no evidence of within-class effect in risk of CVD between the SGLT2 inhibitors dapagliflozin and canagliflozin. Unfortunately, we were unable to examine empagliflozin because of the limited sample size in this group. Nevertheless, a class effect would appear to be supported by the fact that these drugs seem to exhibit similar effects on the metabolic and non-metabolic surrogate markers associated with cardiovascular risk. Qualitatively similar findings concerning cardiovascular risk have also been observed in the EMPA-REG OUTCOME and CANVAS studies.

The mechanisms by which SGLT2 inhibitors may exert cardioprotective effects are not fully understood. Improvement in glycaemic indices may play a role, but do not fully explain the differences in cardiovascular risk between antidiabetic classes. Beyond these effects, SGLT2 inhibitors are also known to modify other possibly important parameters, including metabolic factors (weight loss, improved insulin sensitivity, reduced glucose toxicity) and non-metabolic factors (reduced blood pressure (BP), reduced uric acid, modulation of renal hemodynamics and attenuation of albuminuria).[28] The latter group is of particular interest with regard to explaining the differential cardiovascular risk with the use of SGLT2 inhibitors and other classes. For example, lowering of BP seems to be fairly consistent across SGLT2 inhibitors and among individuals with and without hypertension, averaging a reduction of 4 mm Hg in systolic and 1.6 mm Hg in diastolic BP, which is sufficient to prompt clinically important reductions in cardiovascular outcomes and death.[29,30] These beneficial effects on BP may be related to volume contraction, similar in magnitude to the early phase of thiazide diuretic treatment, to reduced arterial stiffness or to weight loss.[28,31] Additionally, the EMPA-REG trial demonstrated a 39% reduction in the composite renal outcome of new albuminuria, doubling of serum creatinine, renal replacement therapy or death from renal disease. In comparison, use of sulfonylureas and DPP-4 inhibitors does not appreciably lower BP or weight, and only use of DPP-4

TABLE 4 Risk of cardiovascular disease with SGLT2 inhibitors versus DPP-4 inhibitors in propensity score matched sensitivity and subgroup analyses

Study population	Medications	No. of patients	Pearson-years	No. of CVD events	Crude incidence	Adjusted HR of CVD (95% CI)	*P* value for interaction
Subgroup analysis							
Age							
≤65 y	SGLT2 inhibitors	56 240	53 523	465	8.7	0.65 (0.57, 0.74)	0.936
	DPP-4 inhibitors	56 240	67 155	840	12.5	Reference	
>65 y	SGLT2 inhibitors	5472	5,133	145	28.2	0.90 (0.71, 1.14)	
	DPP-4 inhibitors	5472	7671	275	35.8	Reference	
Baseline CVD							
With baseline CVD	SGLT2 inhibitors	8477	8498	231	27.2	0.58 (0.50, 0.67)	0.092
	DPP-4 inhibitors	8477	11 290	511	45.3	Reference	
Without baseline CVD	SGLT2 inhibitors	55 274	69 471	394	5.7	0.60 (0.53, 0.68)	
	DPP-4 inhibitors	55 274	52 564	908	17.3	Reference	
Drug							
Dapagliflozin vs DPP-4 inhibitors	Dapagliflozin	18 483	15 689	139	8.9	0.57 (0.46, 0.70)	0.626
	DPP-4 inhibitors	18 483	22 594	286	12.7	Reference	
Canagliflozin vs DPP-4 inhibitors	Canagliflozin	49 191	48 683	548	11.3	0.66 (0.54, 0.71)	
	DPP-4 inhibitors	49 191	60 525	934	15.4	Reference	
Sensitivity analysis							
Excluding insulin users	SGLT2 inhibitors	50 489	48 040	413	8.6	0.56 (0.50, 0.63)	
	DPP-4 inhibitors	50 489	64 642	1009	15.6	Reference	
Excluding TZD users	SGLT2 inhibitors	60 391	57 662	622	10.8	0.59 (0.54, 0.65)	
	DPP-4 inhibitors	60 391	76 535	1391	18.2	Reference	
Using primary diagnosis	SGLT2 inhibitors	66 633	83 505	301	3.6	0.65 (0.58, 0.73)	
	DPP-4 inhibitors	66 633	88 077	836	9.5	Reference	

Abbreviations: CI, confidence interval; CVD, cardiovascular diseases; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium-glucose co-transporter 2; TZDs, thiazolidinediones.

inhibitors comparably lowers uric acid and offer renoprotective effects, but these appear to be modest.[32]

Results from our subgroup analyses suggest that the beneficial effects of use of SGLT2 inhibitors on cardiovascular risk occur irrespective of the presence of baseline CVD. These findings are in disagreement with those reported by Birkeland et al. from a study which, although limited in sample size, reported a lower risk of major CVD in SGLT2 inhibitor-exposed patients with baseline CVD (HR, 0.70; 95% CI, 0.59, 0.83) but not in those without baseline CVD (HR, 0.90; 95% CI, 0.76, 1.07).[11] Our findings, however, are consistent with those of the CVD-REAL 2 study which found that the beneficial effect of use of SGLT2 inhibitors extends to both low- and high-risk patients.[17] Additionally, although there was a minimal overlap in confidence intervals of the different age groups (>65 years, ≤65 years), the *P* value for interaction was not significant, suggesting an absence of difference in the cardiovascular benefits of use of SGLT2 inhibitors between the different age groups.

Finally, we found that use of SGLT2 inhibitors was associated with a decreased risk of lower extremity amputation compared to use of sulfonylureas, but not compared to use of DPP-4 inhibitors. Given the relatively low number of lower amputation events, we cannot be certain whether our findings represent a true differential effect between these classes or an underpowered analysis. Our findings are consistent with those from the studies by Yuan et al. and Adimadhyam et al. which found no difference in the risk of amputation with use of SGLT2 inhibitors compared to use of other glucose-lowering medications (Yuan et al.[18]) and compared to use of DPP-4 inhibitors (Adimadhyam et al.[19]). The results, however, are discordant with those from the EASEL study which found a higher risk of lower extremity amputation comparing SGLT-2 inhibitors to other glucose-lowering medications (HR, 1.99; 95% CI, 1.12, 3.51).[15] The discordant findings between the EASEL study and our own may be explained by a greater than 5-fold difference in sample size and study populations (military vs commercially and Medicare insured), and by some methodological differences (prevalent-user design vs new-user design). For instance, EASEL allowed users of SGLT2 inhibitors to use other glucose lower medications including insulin in the baseline period. As a result, patients in the SGLT2 inhibitor group were probably more ill, that is, in an advanced stage of diabetes, and presumably at greater risk of amputation.

The clinical implications of the current analysis are several-fold. First, our results suggest that SGLT2 inhibitors may be the preferred

second-line oral agent, after metformin, for reducing cardiovascular risk in patients with type 2 diabetes. Although we were unable to directly assess the effect of underlying cardiovascular risk on the differential effects of treatment, our finding of no interaction between baseline CVD and reduced outcomes with use of SGLT2 inhibitors suggests that the preference for SGLT2 inhibitors may be prudent across the cardiovascular risk spectrum. However, the CVD benefits observed here also must be considered alongside other concerns, including greater costs with use of SGLT2 inhibitors.

The current study has several strengths. We used the Truven Marketscan database, which is nationally representative of patients enrolled in employer-based insurance programmes (approximately 55% of the US population) or with Medicare supplementary insurance. This large sample size allowed us to examine the within-class effect of use of SGLT2 inhibitors between dapagliflozin and canagliflozin, and we adjusted for measured confounders using propensity score matching to minimize the impact of confounding by indication. Finally, we conducted numerous sensitivity analyses to ensure the robustness of our results.

Several limitations of this analysis should be noted. First, we cannot exclude the possibility of residual confounding as the result of missing lab values such as HbA1c and missing data concerning lifestyle variables such as smoking status, which were not captured in the administrative data used in this study. Residual confounding as the result of unmeasured variables would occur if the distribution of risk factors (eg, obesity, smoking status) were not balanced between the two groups. However, we tried to minimize this risk by balancing differences among measured variables between the exposure groups, using propensity score matching. Second, the average follow-up period was approximately 12 months in our study, which may be insufficient to fully evaluate the long-term risk of CVD with use of SGLT2 inhibitors. This limitation reflects the relatively recent introduction of the SGLT2 inhibitors. Third, we did not have access to mortality in the outpatient setting.

In conclusion, this retrospective, cohort, propensity score-matched study supports that the use of SGLT2 inhibitors is associated with a reduced risk of developing CVD compared to use of sulfonylureas and DPP-4 inhibitors. These findings were consistent between dapagliflozin and canagliflozin users, although a low sample size of empagliflozin users precluded analysis of this group separately. These findings suggest that CVD risk reduction is a class effect of SGLT2 inhibitors. In addition, use of SGLT2 inhibitors portended lower risk of hospitalization because of heart failure, as compared to use of sulfonylureas and DPP-4 inhibitors, and lower risk of lower extremity amputation as compared to use of sulfonylureas. Future studies, with longer follow-up periods, are needed to confirm these findings.

ACKNOWLEDGMENT

G. D. is a recipient of the American Association of Graduate Women (AAUW) fellowship for the 2017 to 2018 year.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

G. D. and H. P. created the study concept and design. G. D. analyzed data. Data interpretation was performed by G. D. and H. P., with assistance from S. S. The manuscript was written primarily by G. D. and was revised by H. P and S. S.

Each author has substantially contributed to this project. In addition, each author has read and approved the manuscript and assumes responsibility of the content of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Dawwas GK, Smith SM, Park H. Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes. *Diabetes Obes Metab*. 2019;21:28–36. https://doi.org/10.1111/dom.13477