



Sodium–Glucose Cotransporter 2 Inhibitors and the Risk of Below-Knee Amputation: A Multicenter Observational Study

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OBJECTIVE

Reports of amputations associated with sodium–glucose cotransporter 2 (SGLT2) inhibitors have been inconsistent. We aimed to compare the risk of below-knee amputation with SGLT2 inhibitors versus dipeptidyl peptidase 4 (DPP-4) inhibitors among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This multicenter observational study used administrative health care databases from seven Canadian provinces and the U.K. Incident SGLT2 inhibitor users were matched to DPP-4 inhibitor users using a prevalent new-user design and time-conditional propensity scores. Cox proportional hazards models were used to estimate site-specific adjusted hazard ratios (HR) and corresponding 95% CIs of incident below-knee amputation for SGLT2 inhibitor versus DPP-4 inhibitor users. Random effects meta-analyses were used to pool the site-specific results.

RESULTS

The study cohort included 207,817 incident SGLT2 inhibitor users matched to 207,817 DPP-4 inhibitor users. During a mean exposed follow-up time of 11 months, the amputation rate was 1.3 per 1,000 person-years among SGLT2 inhibitor users and 1.5 per 1,000 person-years among DPP-4 inhibitor users. The adjusted HR of below-knee amputations associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use was 0.88 (95% CI 0.71–1.09). Similar results were obtained in stratified analyses by specific SGLT2 inhibitor molecule.

CONCLUSIONS

In this large multicenter observational study, there was no association between SGLT2 inhibitor use and incident below-knee amputations among patients with type 2 diabetes compared with DPP-4 inhibitor use. While these findings provide some reassurance, studies with a longer duration of follow-up are needed to assess potential long-term effects.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are the newest antidiabetic agents for type 2 diabetes management (1). They inhibit the SGLTs on renal proximal tubules, leading to glucosuria. This effect not only lowers glycemia but also induces weight loss and blood pressure reduction (2). Indeed, randomized placebo-controlled trials have shown that SGLT2 inhibitors also decrease the risk of cardiovascular outcomes (3,4) and heart failure (3–5). Current guidelines from the American Diabetes Association

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recommend the use of SGLT2 inhibitors as second- or third-line treatment in addition to metformin in the management of type 2 diabetes (1). Owing to the cardiovascular and renal benefits conferred by these agents, SGLT2 inhibitors are recommended as one of the preferred second-line agents for patients who have high risk factors or known cardiovascular disease, heart failure, and chronic renal disease (i.e., estimated glomerular filtration rate [eGFR] of 30–60 mL/min/1.73 m² or urine albumin-to-creatinine ratio of 30 mg/g). Given the cardiovascular benefits of SGLT2 inhibitors and the emphasis on these benefits in recent treatment guidelines, the use of SGLT2 inhibitors has increased substantially among patients with type 2 diabetes (6).

Despite the cardiovascular benefits associated with SGLT2 inhibitor treatment, there are several safety concerns associated with their use, including a reported increased risk of below-knee amputations (3,7). Concerns regarding this adverse event stem from the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program trial, in which participants randomized to the SGLT2 inhibitor canagliflozin had a twofold increased risk compared with participants randomized to placebo (hazard ratio [HR] 1.97; 95% CI 1.41–2.75) (3). As a result of this finding, the U.S. Food and Drug Administration issued a black-box warning of amputation risk for canagliflozin (8). However, there was no increased risk of amputation associated with canagliflozin use among patients with type 2 diabetes and chronic renal disease compared with patients treated with placebo in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CRE-DENCE) trial, which assessed canagliflozin use and renal outcomes (HR 1.11; 95% CI 0.79–1.56) (9). Nevertheless, two pharmacovigilance analyses found an increased reporting of amputation among individuals treated with SGLT2 inhibitors compared with other antidiabetic agents (10,11). Several observational studies have

been conducted to assess the association between SGLT2 inhibitor use and the risk of amputation, with most of the studies using the same employment insurance database in the U.S.; however, their findings have been inconsistent (7,12–18).

In light of the findings from the CANVAS Program trial and the inconsistent results of previous observational studies, further studies are needed to address whether SGLT2 inhibitor use is associated with an increased risk of amputation. This study used data from Canada and the U.K. with the aim of determining whether SGLT2 inhibitor use compared with DPP-4 inhibitor use, is associated with an increased risk of below-knee amputation among patients with type 2 diabetes in a real-world setting.

RESEARCH DESIGN AND METHODS

Source Population

We used administrative health care databases from the Canadian provinces of Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Québec, and Saskatchewan and the U.K. Clinical Practice Research Datalink (CPRD). The Canadian databases contain population-level data on physician claims, hospitalization records, and prescription drug claims. Prescription drug data are only available for individuals aged ≥ 18 years in Alberta, aged ≥ 65 years in Ontario, and those ≥ 65 years receiving social assistance and without access to private drug insurance in Québec.

The CPRD is a large primary care database containing medical information documented by primary care physicians on ~ 13 million patients enrolled in >680 general practices in the U.K. (19,20). This database documents demographic characteristics, diagnoses, laboratory test results, procedures, prescriptions, medical history, administrative information, and clinical data, including smoking, BMI, and alcohol use. The CPRD is regularly audited, and the data have been shown to be valid and of high quality (19,21). CPRD data were linked to the Hospital Episodes Statistics database,

which contains full hospitalization data from 1997 to the present. Hospital Episodes Statistics linkage for this study was from 1 April 1997 to 31 December 2017.

The study protocol was registered at ClinicalTrials.gov (NCT04017221). Ethics approval was obtained at each participating site. The study protocol received ethical and scientific approval from the Independent Advisory Scientific Committee of the CPRD (protocol number: 19_007A2).

Individuals aged ≥ 18 years with type 2 diabetes were identified by prescriptions for an antidiabetic medication (α -glucosidase inhibitors, DPP-4 inhibitors, glucagon-like peptide [GLP]-1 receptor agonists, insulin, meglitinides, metformin, SGLT2 inhibitors, sulfonlureas, thiazolidinediones, or combinations of these drugs) between 1 January 2006 and 30 June 2018 or the most recent date of data availability at each site. Potentially eligible subjects were identified as of 2006 to cover the period of general availability of DPP-4 inhibitors and SGLT2 inhibitors. In Nova Scotia, due to limitations in prescription drug data availability, individuals who received antidiabetic medications between 1 November 2017 and 30 June 2018 were eligible to be included in the study cohort.

From this source population, we constructed the study cohort of users of SGLT2 inhibitors and users of DPP-4 inhibitors with a prescription after the date of introduction of SGLT2 inhibitors at each study site (Supplementary Table 1). Identifiable information was not accessible, and we complied with all privacy requirements of the data custodians at each site. A prevalent new-user design (22) was used to match each user of an SGLT2 inhibitor to a user of a DPP-4 inhibitor. Study cohort entry among SGLT2 inhibitor users was defined by the date of the first SGLT2 dispensing (or prescription in CPRD). Study cohort entry for DPP-4 inhibitor users was the date of the matched (see below) DPP-4 inhibitor prescription during the period defined by the first prescription

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of SGLT2 inhibitors and 30 June 2018. Individuals with a prior history of amputation at any time before or on study cohort entry were excluded.

Matching

We created exposure sets that were defined by user type (incident vs. prevalent), level of antidiabetic treatment, prior use of GLP-1 agonists, and calendar time (DPP-4 inhibitor prescription within 120 days of the SGLT2 inhibitor initiation). Incident users were defined as using SGLT2 inhibitor or DPP-4 inhibitor for the first time (i.e., new users). Incident SGLT2 inhibitor users were matched to incident DPP-4 inhibitor users. Patients treated with DPP-4 inhibitors who switched to or added an SGLT2 inhibitor to their treatment regimen (prevalent new users) were matched to patients treated with DPP-4 inhibitors for the same duration but who remained on DPP-4 inhibitor treatment (Supplementary Fig. 1). We also matched, on the level of antidiabetic treatment, a three-level categorical variable created as a proxy for severity of diabetes. Three levels of antidiabetic treatment were created to mirror the severity of type 2 diabetes based on the type and number of different antidiabetic agents in the prior 365 days. The first level was defined as patients treated with only one antidiabetic agent or treated with lifestyle modifications (i.e., they did not receive an antidiabetic agent during the prior 365 days). The second level included patients who required at least two noninsulin antidiabetic agents. Finally, the third level included patients who received insulin treatment (alone or in combination with other antidiabetic agents). Time conditional propensity scores (TCPS) were then constructed separately for incident and prevalent new users by using conditional logistic regression stratified by exposure set to estimate the propensity of receiving a SGLT2 inhibitor versus a DPP-4 inhibitor using the covariates shown in the COVARIATES section. Scores were computed for each individual in each exposure set; hence, an individual may have different scores for exposure sets they enter, depending on the time of entry (i.e., time conditional). Additional covariates were included in the TCPS in the CPRD cohort (please see COVARIATES section). SGLT2 inhibitor users were matched 1:1 without replacement to users of DPP-4

inhibitors from their exposure set with the closest TCPS and in chronological order. However, in five sites, there was a loss of >10% of exposure sets after trimming the areas of non-overlap of the TCPS distribution and matching. In these sites, matching with replacement was performed using a caliper width of ± 0.2 SDs of log TCPS.

Covariates

The following covariates, defined a priori, were used to construct the TCPS in all study cohorts: age, sex, calendar year at cohort entry, and diabetes duration (<1 year, 1–4.9 years, 5–10 years, and >10 years). We included comorbidities identified during the 3 years before study cohort entry such as alcohol-related disorders, cancer, cerebrovascular disease, cirrhosis, coronary artery disease, diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, dialysis, hypertension, ischemic stroke, myocardial infarction, other kidney diseases, and peripheral arterial disease. We also included medication use in the year before study cohort entry, such as acetylsalicylic acid, aldosterone antagonists, α -glucosidase inhibitors, angiotensin II receptor blockers, ACE inhibitors, β -blockers, calcium channel blockers, digitalis-like agents, direct renin inhibitors, GLP-1 receptor agonists, insulin, loop diuretics, meglitinides, metformin, nonacetylsalicylic acid antiplatelet drugs, nonsteroidal anti-inflammatory drugs, oral anticoagulants, other diuretics, other lipid-lowering therapy, statins, sulfonyleureas, thiazide diuretics, and thiazolidinediones. Finally, we included covariates that are indicators of health care use in the year before study cohort entry, including the number of inpatient hospitalizations (0, 1–2, and ≥ 3) and number of physician visits (0–2, 3–5, and ≥ 6).

In the CPRD study cohort, additional a priori defined covariates were included in the TCPS models. These covariates included BMI, smoking status (never, ever, and unknown), race, blood pressure, estimated glomerular filtration rate, and glycated hemoglobin A_{1c}.

Exposure Assessment

Patients were classified as being current users of SGLT2 inhibitors (canagliflozin, dapagliflozin, or empagliflozin) alone or combined with other antidiabetic agents, or current users of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin,

or vildagliptin) alone or in combination with non-SGLT2 inhibitor antidiabetic agents. Exposure was defined using an as-treated approach whereby exposure was time-fixed and defined by the cohort entry drug. Patients were monitored until they discontinued treatment, defined as a gap of ≥ 30 days after the end of a prescription (grace period) or the initiation of an SGLT2 inhibitor for users of DPP-4 inhibitors, or censored due to death, end of health care coverage, or end of study period, whichever occurred first. DPP-4 inhibitor use was the comparator because this class of antidiabetic agent is also a second- or third-line treatment and has not been shown to be associated with increased amputation risk (23).

Study Outcomes

The primary study outcome was incident below-knee amputation, defined as having transtibial amputations or amputations involving the ankle and foot using procedure codes documented during hospitalization or physician claims data (24). Below-knee amputation was assessed, given that 71% of amputations that occurred in the CANVAS Program trial were at the toe and metatarsal level (3,25). Furthermore, given that this study excluded individuals with a prior history of amputation, it would be clinically unlikely for individuals to develop incident above-knee amputation associated with SGLT2 inhibitor use. The diagnostic and procedure codes used to define this outcome are reported in Supplementary Table 2.

Statistical Analyses

Patient characteristics were summarized in each study cohort using frequencies and percentages for categorical variables and means \pm SD for continuous variables. Multivariable Cox proportional hazards models were used to estimate the site-specific adjusted HR and the corresponding 95% CI for the risk of incident below-knee amputation among SGLT2 inhibitor users versus DPP-4 inhibitor users. Cox models were adjusted for age, sex, diabetes duration, and deciles of TCPS. In secondary analyses, we stratified by age to determine whether the risk of amputation associated with SGLT2 inhibitor use was higher among the elderly population (≥ 70 and <70 years),

sex, prior insulin use (defined as insulin use in the previous year), and SGLT2 inhibitor molecule.

Finally, we completed five sensitivity analyses. First, we repeated the primary analysis using grace periods of 0, 60, and 365 days to define continuous use of the study drug. Second, we stratified the primary analysis by incident and prevalent new user status among SGLT2 inhibitor users. Third, we defined exposure using an intention-to-treat approach in which exposure was defined at cohort entry and patients were monitored until occurrence of the outcome or censored due to death, end of health care coverage, end of study period, entry into the SGLT2 inhibitor cohort for DPP-4 inhibitor users, or a maximum of 1 year of follow-up, whichever occurred first. Fourth, given that SGLT2 inhibitor use is not indicated for patients on dialysis, we repeated the primary analysis after excluding individuals with a prior history of dialysis using the study cohort from Ontario because this cohort contained the highest number of individuals with a prior history of dialysis. Kaplan-Meier curves for each site were visually evaluated to assess potential departures from the assumption of proportional hazards. This assessment revealed no indication that the assumption was violated at any of the sites. Finally, we repeated the primary analysis using a fixed-effects model.

Meta-analysis

We pooled the adjusted HRs from each site using DerSimonian and Laird random-effects meta-analysis with inverse variance weighting (26). Inclusion in the meta-analysis was restricted to sites with at least five events in each exposure group (Supplementary Table 3). Between-site heterogeneity was assessed using the I^2 statistic. Analyses were conducted using RevMan version 5.3 software.

Data Source

This study was made possible through data sharing agreements between the Canadian Network for Observational Drug Effect Studies member research centers and the respective provincial governments of Alberta, British Columbia, Manitoba (HIPC # 2018/2019-58), Nova Scotia, Ontario, Québec, and Saskatchewan. This study was approved by the Independent Scientific Advisory Committee (protocol

19_007A2) of the CPRD, and the approved protocol was made available to journal reviewers. The British Columbia (BC) Ministry of Health approved access to and use of BC data for this study. Data sources were as follows (<https://www.popdata.bc.ca/data>): BC Ministry of Health (creator) (2018): Medical Services Plan (MSP) Payment Information File, BC Ministry of Health (publisher). Ministry of Health (2018), BC Ministry of Health (creator) (2018): Consolidation File (MSP Registration & Premium Billing), BC Ministry of Health (publisher). Ministry of Health (2018), BC Ministry of Health (creator) (2018): PharmaNet, BC Ministry of Health (publisher). Data Stewardship Committee (2018) and Canadian Institute for Health Information (creator) (2018): Discharge Abstract Database (Hospital Separations), BC Ministry of Health (publisher). Ministry of Health (2018). BC Ministry of Health (publisher). Ministry of Health (2018), BC Vital Statistics Agency (creator) (2018): Vital

Statistics Deaths, V2, BC Ministry of Health (publisher). Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health and Long-Term Care. This study was supported by Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ministry of Health and Long-Term Care. Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health information.

RESULTS

The study cohort included 207,817 SGLT2 inhibitor users matched to 207,817 DPP-4 inhibitor users (Fig. 1). Among the users of SGLT2 inhibitors, 102,263 were classified as incident new users and 105,554 as prevalent new users. Baseline characteristics were well balanced after TCPS matching (Table 1 and Supplementary Table 4). In the CPRD, the number of patients with renal insufficiency, defined as having an eGFR <60 mL/min/1.73 m²

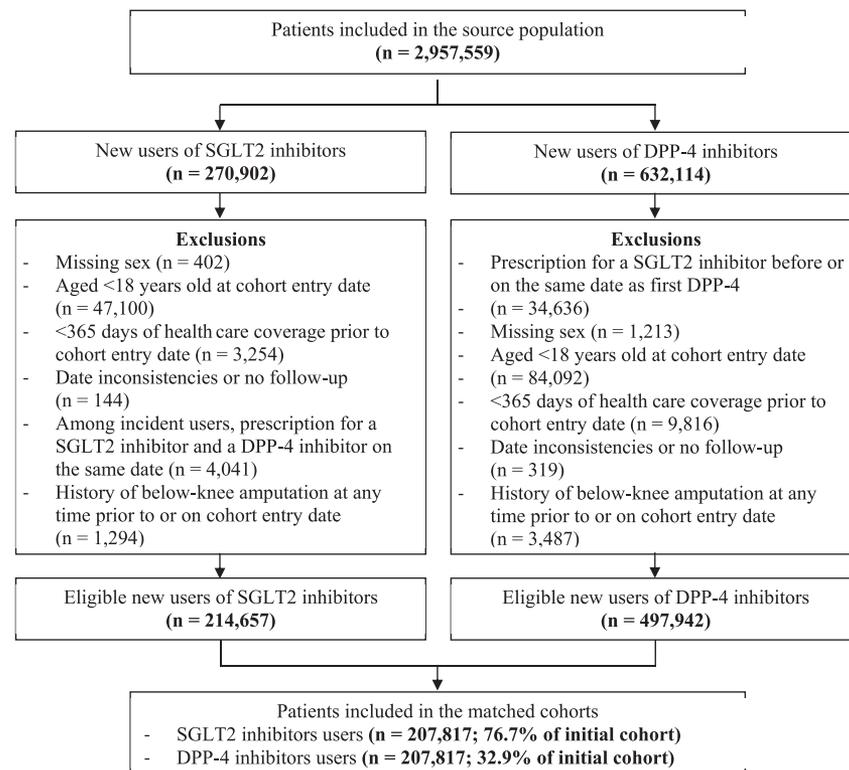


Figure 1—Flowchart describing construction of the study cohort. Numbers may not add up because small cells were suppressed due to privacy restrictions. Patients <19 years in Alberta and <66 years in Ontario were included to ensure that patients had at least 1 year of data before cohort entry. Patients were eligible to enter the study cohort a maximum of two times, a first time with a DPP-4 inhibitor prescription and a second time with an SGLT2 inhibitor prescription.

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

	SGLT2 inhibitors (n = 207,817)	DPP-4 inhibitors (n = 207,817)
Age (years)	63.8 ± 9.5	64.0 ± 9.6
18–35	3,479 (1.7)	3,612 (1.7)
36–45	12,288 (5.9)	11,915 (5.7)
46–55	30,845 (14.8)	30,105 (14.5)
56–65	47,711 (23.0)	48,079 (23.1)
66–75	89,410 (43.0)	87,993 (42.3)
76–85	22,074 (10.6)	23,920 (11.5)
>85	2,010 (1.0)	2,193 (1.1)
Female sex	86,360 (41.6)	87,030 (41.9)
Calendar year at cohort entry		
2013	320 (0.2)	343 (0.2)
2014	6,954 (3.3)	7,322 (3.5)
2015	51,464 (24.8)	50,921 (24.5)
2016	66,242 (31.9)	66,422 (32.0)
2017	61,291 (29.5)	61,013 (29.4)
2018	21,546 (10.4)	21,796 (10.5)
New user status		
Incident users	102,263 (49.2)	102,263 (49.2)
Prevalent users	105,554 (50.8)	105,554 (50.8)
SGLT2 inhibitor molecule		
Canagliflozin	87,922 (42.3)	–
Dapagliflozin	63,792 (30.7)	–
Empagliflozin	56,103 (27.0)	–
Diabetes duration (years)	12.6 ± 6.6	12.5 ± 6.6
<1	7,166 (3.4)	7,341 (3.5)
1–4.9	25,204 (12.1)	25,766 (12.4)
5–10	52,543 (25.3)	52,758 (25.4)
>10	122,904 (59.1)	121,952 (58.7)
Comorbidities†		
Alcohol-related disorders	3,626 (1.7)	3,658 (1.8)
Cancer	21,692 (10.4)	21,937 (10.6)
Cerebrovascular disease	9,892 (4.8)	10,156 (4.9)
Cirrhosis	3,621 (1.7)	3,606 (1.7)
Coronary artery disease	44,710 (21.5)	43,939 (21.1)
Diabetic nephropathy	7,476 (3.6)	7,478 (3.6)
Diabetic neuropathy	3,807 (1.8)	3,844 (1.8)
Diabetic retinopathy	5,266 (2.5)	5,296 (2.5)
Dialysis	277 (0.1)	315 (0.2)
Hypertension	111,130 (53.5)	111,332 (53.6)
Ischemic stroke	2,448 (1.2)	2,535 (1.2)
Myocardial infarction	5,326 (2.6)	5,113 (2.5)
Other kidney diseases	10,222 (4.9)	10,850 (5.2)
Peripheral arterial disease	4,472 (2.2)	4,471 (2.2)
Use of medications‡		
Acetylsalicylic acid	36,875 (17.7)	36,792 (17.7)
Aldosterone antagonists	6,146 (3.0)	6,182 (3.0)
α-Glucosidase inhibitors	3,057 (1.5)	2,949 (1.4)
Angiotensin II receptor blockers	66,747 (32.1)	66,301 (31.9)
ACE inhibitors	94,489 (45.5)	94,092 (45.3)
β-Blockers	58,854 (28.3)	58,371 (28.1)
Calcium channel blockers	63,281 (30.5)	63,671 (30.6)
Digitalis-like agents	2,586 (1.2)	2,624 (1.3)
Direct renin inhibitors	104 (0.1)	92 (0.0)
GLP-1 receptor agonists	8,464 (4.1)	8,464 (4.1)
Insulin	57,143 (27.5)	57,143 (27.5)
Loop diuretics	21,314 (10.3)	21,559 (10.4)
Meglitinides	4,680 (2.3)	4,707 (2.3)
Metformin	180,662 (86.9)	180,828 (87.0)
Nonacetylsalicylic acid antiplatelet drugs	14,034 (6.8)	13,655 (6.6)
Nonsteroidal anti-inflammatory drugs	40,470 (19.5)	40,263 (19.4)

Continued on p. 2449

was higher among DPP-4 inhibitor users compared with SGLT2 inhibitor users (Supplementary Table 4).

The mean exposed follow-up time for the matched cohort was 11 ± 9 months, generating 369,458 person-years of observation. The rate of incident below-knee amputation was similar among SGLT2 inhibitor users (1.3 per 1,000 person-years) versus DPP-4 inhibitor users (1.5 per 1,000 person-years) in the matched cohort. There was no significant increased risk of incident below-knee amputation associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use (HR 0.88; 95% CI 0.71–1.09; $I^2 = 18%$) (Table 2 and Fig. 2).

In secondary analyses, the risk of incident below-knee amputation associated with SGLT2 inhibitor use versus DPP-4 inhibitor use did not differ according to age (≥ 70 vs. < 70 years), sex, or history of prior insulin use or SGLT2 inhibitor molecule (Table 3). The results remained consistent across most sensitivity analyses, including among patients with no prior history of dialysis (Supplementary Table 5). However, there was a trend toward an increased risk of incident below-knee amputation among prevalent new users of SGLT2 inhibitors versus DPP-4 inhibitor users (HR 1.29; 95% CI 0.97–1.70) (Table 3).

CONCLUSIONS

In this large, multicenter observational study, using administrative data from seven Canadian provinces and the U.K. CPRD, we found no increased risk of incident below-knee amputation associated with SGLT2 inhibitor versus DPP-4 inhibitor use among patients with type 2 diabetes (HR 0.88; 95% CI 0.71–1.09). Results were consistent across subgroups defined by age, sex, and prior insulin use. Similarly, there was no increased risk of below-knee amputation associated with individual SGLT2 inhibitor use, including canagliflozin, compared with DPP-4 inhibitor use.

Concerns regarding an increased risk of amputation associated with the use of SGLT2 inhibitors arose when the CANVAS Program trial found a nearly twofold increased risk associated with canagliflozin use versus placebo (HR 1.97; 95% CI 1.41–2.75) (3). In light of this finding, further analyses were conducted in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)

Table 1—Continued

	SGLT2 inhibitors (n = 207,817)	DPP-4 inhibitors (n = 207,817)
Oral anticoagulants	13,393 (6.4)	13,359 (6.4)
Other diuretics	18,497 (8.9)	18,406 (8.9)
Other lipid-lowering therapy	23,524 (11.3)	22,937 (11.0)
Statins	159,742 (76.9)	159,061 (76.5)
Sulfonylureas	108,451 (52.2)	108,327 (52.1)
Thiazide diuretics	45,019 (21.7)	44,788 (21.6)
Thiazolidinediones	5,175 (2.5)	4,863 (2.3)
Different classes of non-antidiabetic drugs, n‡		
0–1	8,465 (4.1)	8,666 (4.2)
2–5	65,919 (31.7)	66,729 (32.1)
≥6	133,433 (64.2)	132,422 (63.7)
Health care use†		
Inpatient hospitalizations, n		
0	176,833 (85.1)	176,723 (85.0)
1–2	28,687 (13.8)	28,697 (13.8)
≥3	2,296 (1.1)	2,398 (1.2)
Physician visits, n		
0–2	14,963 (7.2)	15,117 (7.3)
3–5	31,883 (15.3)	32,206 (15.5)
≥6	160,971 (77.5)	160,494 (77.2)

Data are presented as n (%) or mean ± SD. *Patients on SGLT2 inhibitors were matched to patients on DPP-4 inhibitors 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 TCPS. Because of privacy restrictions, values of <6 were replaced by 3 before pooling. †Comorbidities were assessed in the 3 years before study cohort entry, and medications and health care use were assessed in the year before study cohort entry. ‡In Saskatchewan, the number of non-antidiabetic drug classes was defined using the list of medication covariates rather than Anatomical Therapeutic Chemical–defined classes due to unavailability of Anatomical Therapeutic Chemical codes. In Québec and the CPRD, drug classification was performed using the American Hospital Formulary Service and the British National Formulary, respectively.

trial to assess amputation risk (27). These analyses revealed no increased risk of amputation with empagliflozin (HR 1.00; 95% CI 0.70–1.44) (27). However, as acknowledged by the authors, the ascertainment of amputations may have been inaccurate, and the results of such post hoc analyses must be interpreted with caution. In the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 trial (DECLARE-TIMI 58) trial, there was no increased risk of amputation associated with

randomization to dapagliflozin versus placebo (HR 1.09; 95% CI 0.84–1.40) (5). Recently, the CREDENCE trial, which enrolled patients with type 2 diabetes and chronic renal disease to study renal outcomes associated with canagliflozin use, did not find an increased risk of amputation among patients treated with canagliflozin (HR 1.11; 95% CI 0.79–1.56) (9).

The safety signal regarding an increased risk of amputation identified in the CANVAS Program trial was supported by

pharmacovigilance analyses conducted using the U.S. Food and Drug Administration Adverse Event Reporting System, which found an increased reporting of amputation specifically among canagliflozin users (proportional reporting ratio [PRR] 5.33; 95% CI 4.04–7.04) compared with users of non-SGLT2 inhibitor antidiabetic agents (10). Subsequently, another pharmacovigilance analysis conducted using the World Health Organization global database of individual case safety reports (Vigibase) found that the PRR was increased for all available SGLT2 inhibitors compared with other antidiabetic medications (canagliflozin: PRR 7.09; 95% CI 5.25–9.57; empagliflozin: PRR 4.96; 95% CI 2.89–8.50; and dapagliflozin: PRR for toe-amputations 2.62; 95% CI 1.33–5.14) (11). Nevertheless, there are well-recognized limitations to using adverse event reporting data, which include difficulties with adverse event recognition, underreporting of adverse events, absence of a denominator, biases that affect event reporting, and variations in report quality (28).

To date, there have been eight observational studies, to our knowledge, that have assessed the risk of amputation associated with SGLT2 inhibitor use; these studies have produced heterogeneous results (7,12–17). Six of these studies used the MarketScan Commercial Claims and Encounters Database, with five studies showing no association between SGLT2 inhibitor use and amputation (12–15) and one study showing an increased risk of amputation with SGLT2 inhibitor use compared with DPP-4 inhibitor use (HR 1.69; 95% CI 1.20–2.38) (7). Interestingly, in that study, SGLT2 inhibitor use was not associated with an increased risk of lower-extremity amputation compared with sulfonylurea

Table 2—Crude and adjusted HR for the association between the use of SGLT2 inhibitors and the risk of below-knee amputation among patients with type 2 diabetes

Treatment group	Patients (n)	Events (n)	Mean follow-up time (years)	Person-years	Crude incidence rate (per 1,000 person-years)*	Crude HR (95% CI)†	Adjusted models‡	
							HR (95% CI)	I ² (%)
SGLT2 inhibitors	207,817	253	0.90	187,641	1.3	0.87 (0.69–1.10)	0.88 (0.71–1.09)	18
DPP-4 inhibitors	207,817	281	0.88	181,817	1.5	Reference	Reference	

*Incidence rate was calculated using all study cohorts. †Patients on SGLT2 inhibitors were matched to patients on DPP-4 inhibitors from their exposure set (defined on the 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 inhibitor prescription) on TCPS. HR estimation was restricted to sites with at least five events in each exposure group. ‡Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of TCPS.

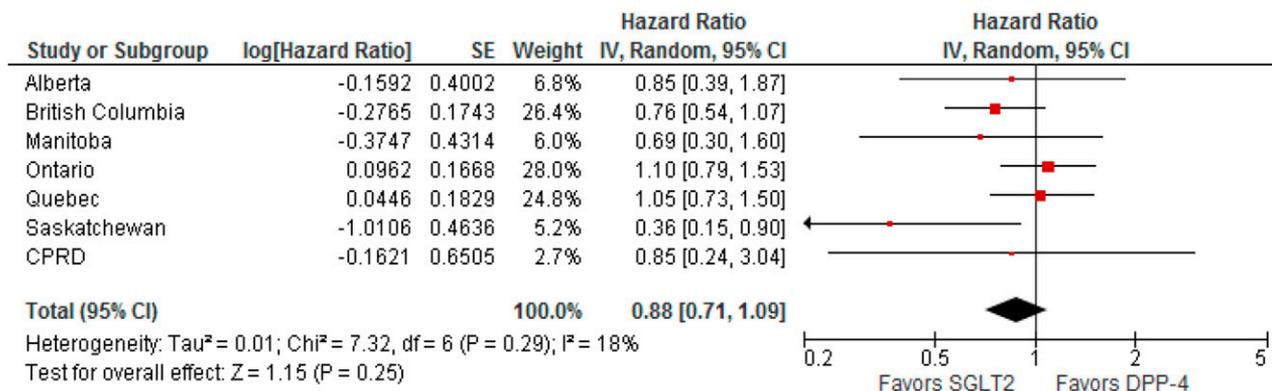


Figure 2—HR (95% CI) of below-knee amputation associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use among patients with type 2 diabetes. Nova Scotia was not included in this analysis because there were fewer than five events in one of the two exposure groups. IV, inverse variance.

use (7). Udell et al. (16) performed an observational study using the U.S. Department of Defense Health System and found that patients initiating an SGLT2 inhibitor had a nearly twofold increased risk of lower-extremity amputation compared with patients treated with non-SGLT2 inhibitor antidiabetic agents (HR 1.99; 95% CI 1.12–3.51). However, most

of the amputations in the SGLT2 inhibitor group were among patients treated with canagliflozin. This finding was also observed in the study performed by Ueda et al. (17), using the Swedish/Danish National Register, which found that SGLT2 inhibitor users had an increased risk of incident amputation compared with GLP-1 receptor agonist users (HR

2.48; 95% CI 1.14–5.40). The heterogeneity of the findings of these previous studies may be due to a number of factors, including differences in the populations assessed, methodologies used, comparator drug used, differences in the extent of amputation (i.e., some studies included above-knee amputations) (14,18), duration of follow-up time, and the inclusion of patients with prior history of amputation (7,13,17,18). Some of these inconsistencies were observed within the same study when the researchers varied the exclusion criteria for their study population (i.e., excluding patients with prior history of amputation, insulin use, renal insufficiency, and baseline cardiovascular disease) and when different comparators were used in the analyses (7).

Our study has several strengths, including the use of DPP-4 inhibitors as comparators because they are prescribed at a similar stage of type 2 diabetes as SGLT2 inhibitors (i.e., as second- or third-line treatment). The use of the prevalent new-user design allowed inclusion of patients who switched to or added an SGLT2 inhibitor, which is reflective of clinical practice and allows our findings to be more generalizable to the realities of clinical practice. Indeed, we noted ~50% of SGLT2 inhibitor users had previously used DPP-4 inhibitors. Finally, with data from eight databases across two countries, our study is the largest observational study conducted examining this safety issue to date, increasing the precision and generalizability of our results.

Our study also has potential limitations. First, residual confounding is possible given that this is an observational study.

Table 3—Summary of results of stratified and sensitivity analyses of pooled adjusted HR (95% CI) for below-knee amputation for SGLT2 inhibitor use versus DPP-4 inhibitor use among patients with type 2 diabetes

	Number of sites included	Adjusted HR (95% CI)*	I ² (%)
Main analysis	7	0.88 (0.71–1.09)	18
Age			
≥70 years	3	1.13 (0.81–1.56)	0
<70 years	6	0.80 (0.58–1.12)	46
Sex			
Females	3	1.04 (0.64–1.70)	17
Males	6	0.87 (0.65–1.15)	38
Prior insulin use†			
Yes	6	0.69 (0.46–1.03)	51
No	4	1.14 (0.87–1.50)	0
SGLT2 inhibitor molecule			
Canagliflozin	5	0.98 (0.77–1.25)	0
Dapagliflozin	4	0.69 (0.45–1.06)	0
Empagliflozin	3	1.08 (0.70–1.68)	0
Varying grace period			
0 day	4	1.12 (0.74–1.69)	0
60 days	7	0.90 (0.73–1.12)	28
365 days	7	0.90 (0.72–1.11)	46
New user status			
Incident users	6	0.68 (0.53–0.88)	0
Prevalent users	3	1.29 (0.97–1.70)	0
Intention-to-treat approach‡	6	0.81 (0.63–1.05)	35
No prior history of dialysis	1	1.13 (0.81–1.57)	NA
Fixed-effects model analysis	7	0.90 (0.75–1.08)	18

Inclusion in each meta-analysis was restricted to sites with at least five events in each exposure group. NA, not applicable. *Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous), and deciles of TCPS. †Prior insulin use was defined as a prescription for insulin in the year prior. ‡In the intention-to-treat approach, maximum follow-up was 1 year.

However, we used various approaches to minimize confounding by using an active comparator and extensive matching.

Second, there is potential confounding by contraindication as physicians may have been less likely to prescribe SGLT2 inhibitors to patients who were at higher risk for amputation. Furthermore, there is an imbalance in the proportion of SGLT2 inhibitor versus DPP-4 inhibitor users with renal insufficiency (eGFR <60 mL/min/1.73 m²) noted in the CPRD cohort, because use of SGLT2 inhibitors is not recommended for patients with significant renal insufficiency (i.e., eGFR <45 mL/min/1.73 m²) (1,29). Although the eGFR findings from the CPRD comprised a small percentage of the total cohort (3.3% of the weight of the meta-analysis), there may be residual confounding because patients with renal insufficiency have a higher risk of amputation compared with patients with normal renal function (30). As such, DPP-4 inhibitor users may have an underlying higher risk of amputation compared with SGLT2 inhibitor users, and this could mask the higher risk of amputation associated with SGLT2 inhibitor use. However, in our sensitivity analysis, our results remained consistent among patients with no prior history of dialysis (i.e., during the 3 years before study cohort entry).

Third, the databases used in this study capture dispensing of medications (i.e., Canadian databases) or prescriptions (i.e., CPRD) without any guarantee that these medications were taken by the patient.

Fourth, we did not study the specific site of below-knee amputation because we anticipated insufficient events per site.

Fifth, we included users of SGLT2 inhibitors who had (prevalent new users) and had not (incident new users) used DPP4 inhibitors previously, which may consist of individuals that differ in the severity of diabetes and risk for complications associated with diabetes. In stratified analyses, the risk of below-knee amputation associated with SGLT2 inhibitor use compared with DPP-4 inhibitor use was higher among prevalent new users of SGLT2 inhibitors, but this did not reach statistical significance.

Finally, the duration of follow-up was modest, and future studies with a longer duration of follow-up are needed to determine whether long-term use of SGLT2 inhibitors is associated with below-knee amputation risk, because the increased risk of amputation associated

with canagliflozin treatment in the CANVAS Program trial was observed near the end of the study period (mean follow-up of ~3.6 years) (3). Furthermore, our study focused on patients with no prior history of amputation, whereas the CANVAS Program trial and the CREDENCE trial involved patients with a prior history of amputation. Thus, the patients in these trials have an underlying higher risk of amputation compared with the population cohort of our study (the rate of amputation in our study was 1.3 per 1,000 person-years vs. 6.3 per 1,000 person-years in the CANVAS Program trial and 12.3 per 1,000 person-years in the CREDENCE trial) (3,9).

In conclusion, in this multicenter observational study, we found no evidence of an association between SGLT2 inhibitor use and incident below-knee amputation compared with DPP-4 inhibitor use among patients with type 2 diabetes. Similarly, there was no increased risk of below-knee amputation associated with specific SGLT2 inhibitor molecule use compared with DPP-4 inhibitor use. Future studies will be needed to further address whether SGLT2 inhibitor use increases the risk of incident below-knee amputation over the longer term.

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