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ORIGINAL ARTICLE

Sodium-glucose co-transporter-2 inhibitors and the risk of urosepsis: A multi-site, prevalent new-user cohort study

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Abstract

Aim: To compare urosepsis rates in patients with type 2 diabetes treated using sodium-glucose co-transporter-2 inhibitors (SGLT2i) with dipeptidyl peptidase-4 inhibitors (DPP4i) in a real-world setting.

Methods: We conducted a matched cohort study using a prevalent new-user design with time-conditional propensity scores. New users of SGLT2i from seven Canadian provinces and the UK were matched to DPP4i users. The primary outcome was hospitalization with a diagnosis of urosepsis and the secondary outcome was Fournier's gangrene. Site-specific hazard ratios for urosepsis comparing SGLT2i with DPP4i were estimated using Cox proportional hazards models and pooled using a random effects meta-analysis.

Results: We included 208 244 users of SGLT2i and 208 244 users of DPP4i. Among SGLT2i users, 42% initiated canagliflozin, 31% dapagliflozin and 27% empagliflozin. During a mean follow-up of 0.9 years, patients initiating SGLT2i had a lower rate of

urosepsis compared with those receiving DPP4i. The pooled adjusted hazard ratio was 0.58 (95% confidence interval [CI]: 0.42-0.80). The incidence rates of Fournier's gangrene were numerically similar in SGLT2i (0.08 per 1000 person-years; 95% CI: 0.05-0.13) and DPP4i users (0.14; 95% CI: 0.09-0.21).

Conclusions: In this large, multi-site study, we did not observe an increased risk for urosepsis associated with SGLT2i compared with DPP4i among patients with type 2 diabetes in a real-world setting.

KEYWORDS

cohort study, dipeptidyl peptidase-4 inhibitor, observational study, pharmaco-epidemiology, sodium-glucose co-transporter-2 inhibitor, type 2 diabetes

1 | INTRODUCTION

In May 2015, the United States Food and Drug Administration (FDA) warned of an increased risk of serious urinary tract infection (UTI) in patients treated with sodium-glucose co-transporter-2 inhibitors (SGLT2i).[1] A second FDA warning, issued in August 2018, reported on a possible association between SGLT2i treatment and severe genital infections resulting in necrotizing fasciitis of the perineum (Fournier's gangrene).[2] The safety warnings were issued in response to 19 cases of urosepsis[1,3] and 12 cases of Fournier's gangrene[2] identified from the FDA Adverse Event Reporting System and the literature. The FDA reports provided limited evidence on causal relationships between the SGLT2i and these conditions, and rates could not be calculated.[4]

Multiple meta-analyses of clinical trial data have examined the association between SGLT2i and UTI. Meta-analyses of randomized controlled trials (RCTs) from 2012 to 2016 identified an increased risk of UTI[5–9] while more recent large meta-analyses did not.[10,11] RCTs can underestimate the rate of important adverse events,[12,13] and the participants may not represent patients treated in routine care[14]; therefore, it is important to also consider real-world studies. Four large observational studies found similar, if not lower, rates of UTI with SGLT2i compared with other second-line medications for type 2 diabetes.[15–18] While these studies provided important reassurance regarding the risk of UTI, only one study also assessed urosepsis. This study found no increased risk of urosepsis in patients treated with SGLT2i compared with dipeptidyl peptidase-4 inhibitors (DPP4i) and with glucagon-like peptide-1 (GLP1) receptor agonists.[16]

With regards to Fournier's gangrene, a recent meta-analysis of RCTs did not identify an increased risk of this rare outcome.[19] Similarly, two recent observational studies in users of SGLT2i did not detect an increased rate of Fournier's gangrene compared with users of DPP4i,[20,21] or non-SGLT2i antidiabetic medications.[20] However, because Fournier's gangrene is rare (i.e. incidence is 0.016 per 1000[22]), the three epidemiological studies[19–21] were underpowered to detect a difference. Given the limited available evidence on the risk of urosepsis and Fournier's gangrene, the severity of these outcomes, and the increasing use of SGLT2i among patients with type 2 diabetes,[23,24] there remains an urgent need to assess these potential safety issues.

The Canadian Network for Observational Drug Effect Studies (CNODES)[25] used population-based data from seven Canadian provinces and the UK Clinical Practice Research Datalink (CPRD) to test whether SGLT2i were associated with an increased rate of urosepsis compared with DPP4i among adults with type 2 diabetes, and to describe the risk of Fournier's gangrene.

2 | METHODS

2.1 | Study design and data sources

We conducted matched cohort studies using a prevalent new-user design with time-conditional propensity scores (TCPS).[26] Patients were identified from administrative healthcare databases in seven Canadian provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, Quebec and Saskatchewan), and primary care clinical data from the CPRD.[27] The Canadian data included physician billing claims, hospitalization discharge diagnoses, and pharmacy dispensations of prescription drugs.[25] In Alberta, data were available for individuals aged 19 years or older; in Ontario, data were available for individuals aged 65 years or older. Quebec data were restricted to 40% of the total Quebec population who were aged 65 years or older, beneficiaries of social assistance, or subscribers to the province's public insurance drug plan. The CPRD data included primary care medical records—with prescription data rather than dispensations—for over 15 million people enrolled from over 700 UK practices. We restricted inclusion to patients who were linkable to hospitalization data (76% of CPRD practices).

The study protocol was registered at clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/; NCT04017221), and research ethics board approval was obtained at each participating site. Site-specific analyses were conducted using SAS, and meta-analyses were conducted using Review Manager version 5.3.

2.2 | Study population

The source population included individuals dispensed or prescribed (CPRD) an antidiabetic medication between 1 January 2006 and 30 June

2018 or the end of data availability in each site (Table S1). Antidiabetic medications included metformin, sulphonylureas, thiazolidinediones, DPP4i, SGLT2i, GLP1 receptor agonists, alpha-glucosidase inhibitors, meglitinides, insulin or combinations of these drugs. With the source population covering 2006 to 2018, we were able to identify all patients with a previous history of DPP4i use. From the source population, we identified patients who received a first dispensation for an SGLT2i or a dispensation for a DPP4i during the identification period (Tables S1 and S2), which started in each site on the date of the first recorded dispensation of SGLT2i at this site and ended on 30 June 2018 or the last date with available data. We excluded new users of SGLT2i if they had also started using a DPP4i on the same date, and users of a DPP4i if they had used an SGLT2i earlier.

We excluded patients who were younger than 18 years or had healthcare coverage for less than 365 days before the first dispensation of an SGLT2i or a DPP4i. Users of SGLT2i were excluded if they had a prior hospitalization for a UTI or acute pyelonephritis within 30 days before cohort entry, spinal cord injury affecting bladder function within 3 years before cohort entry, or a urinary catheter within the last year before cohort entry. For users of DPP4i, we applied the same exclusion criteria for each DPP4i dispensation.

2.3 | Matched study cohort

Using the prevalent new-user design,[26] we included new users of SGLT2i, who were either incident new-users, that is, patients who did not receive a DPP4i in the previous year, and prevalent new users, that is, those who received treatment with a DPP4i in the year before starting an SGLT2i. For each initial dispensation of an SGLT2i, we selected a comparator dispensation from the cohort of DPP4i patients matched on calendar time, prior treatment and TCPS. First, we defined an exposure set for each initial dispensation of an SGLT2i. To minimize the risk of calendar time bias, each exposure set included DPP4i dispensations occurring within 120 days of the new SGLT2i prescription. Exposure sets for incident new users of SGLT2i included incident dispensations of DPP4i (i.e. a new DPP4i dispensation for a patient with no DPP4i use in the previous year). Exposure sets for

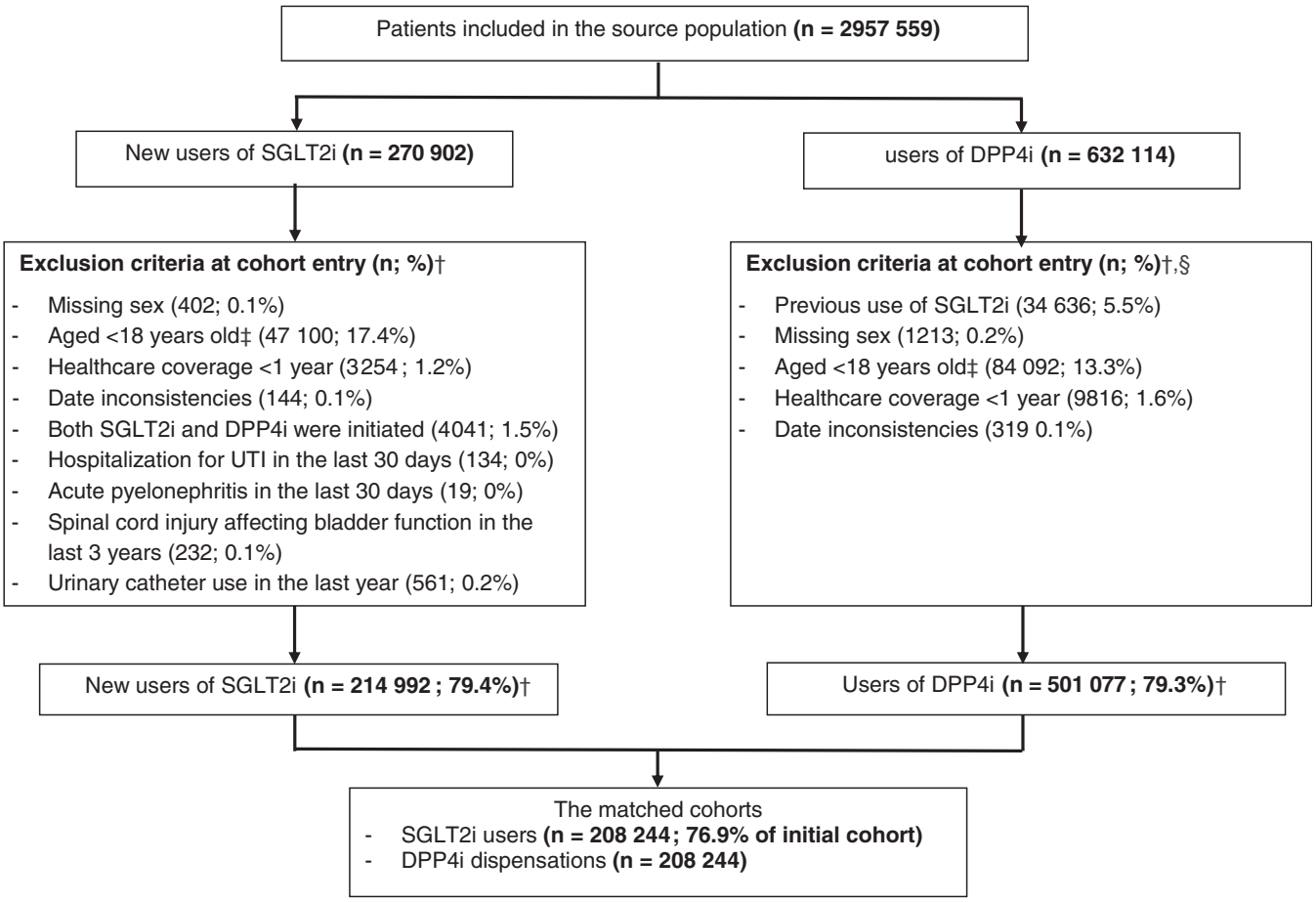

FIGURE 1 Flowchart of study cohort. DPP4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose co-transporter 2 inhibitor; UTI, urinary tract infection. †Numbers may not add up because of small cells suppressed and replaced by a value of 3 due to privacy restrictions; ‡Patients <19 years in Alberta and <66 years in Ontario; §The last four exclusions in the DPP4i cohort were applied to each DPP4i dispensation (rather than patients), thus they are not listed

TABLE 1 Baseline characteristics of users of sodium-glucose co-transporter-2 inhibitors (SGLT2i) and their matched users of dipeptidyl peptidase-4 inhibitors (DPP4i)[a]

	SGLT2i (n = 208 244)	DPP4i (n = 208 244)
Site *n* (% from the final cohort)		
Alberta	26 120 (12.5)	26 120 (12.5)
British Columbia	43 311 (20.8)	43 311 (20.8)
CPRD	5422 (2.6)	5422 (2.6)
Manitoba	12 074 (5.8)	12 074 (5.8)
Nova Scotia	1135 (0.5)	1135 (0.5)
Ontario	64 928 (31.2)	64 928 (31.2)
Quebec	44 442 (21.3)	44 442 (21.3)
Saskatchewan	10 812 (5.2)	10 812 (5.2)
Incident new-user status	102 743 (49.3)	102 743 (49.3)
Age (y) mean ± SD[b]	63.8 ± 9.5	64.0 ± 9.5
18-35	3477 (1.7)	3696 (1.8)
36-45	12 305 (5.9)	11 757 (5.6)
46-55	31 042 (14.9)	30 194 (14.5)
56-65	48 018 (23.1)	48 485 (23.3)
66-75	89 451 (43.0)	88 171 (42.3)
76-85	21 968 (10.5)	23 788 (11.4)
>85	1983 (1.0)	2153 (1.0)
Females	86 320 (41.5)	86 413 (41.5)
Calendar year at cohort entry		
2013	325 (0.2)	342 (0.2)
2014	6990 (3.4)	7425 (3.6)
2015	51 645 (24.8)	51 141 (24.6)
2016	66 398 (31.9)	66 351 (31.9)
2017	61 321 (29.4)	61 122 (29.4)
2018	21 565 (10.4)	21 863 (10.5)
SGLT2i molecule		
Canagliflozin	88 096 (42.3)	—
Dapagliflozin	63 980 (30.7)	—
Empagliflozin	56 168 (27.0)	—
Diabetes duration (y) mean ± SD	12.6 ± 6.6	12.6 ± 6.6
<1 y	7154 (3.4)	7441 (3.6)
1-4.9 y	25 214 (12.1)	25 187 (12.1)
5-10 y	52 568 (25.2)	52 757 (25.3)
>10 y	123 308 (59.2)	122 859 (59.0)
Co-morbidities[c]		
Alcohol-related disorders	3620 (1.7)	3639 (1.7)
Cancer	21 599 (10.4)	22 094 (10.6)
Myocardial infarction	5371 (2.6)	5254 (2.5)
Ischaemic stroke	2465 (1.2)	2553 (1.2)
Peripheral arterial disease	4818 (2.3)	4839 (2.3)
Diabetic retinopathy	5381 (2.6)	5512 (2.6)
Diabetic neuropathy	3951 (1.9)	4017 (1.9)
Diabetic nephropathy	7530 (3.6)	7715 (3.7)
Cystitis	11 577 (5.6)	11 744 (5.6)
Pyelonephritis	1062 (0.5)	1082 (0.5)
Stones or urinary tract obstruction	7263 (3.5)	7251 (3.5)
Urinary tract infection in the year prior	6770 (3.3)	6702 (3.2)
Use of medications[c,d]		
Metformin	180 954 (86.9)	180 831 (86.8)
Sulphonylureas	108 623 (52.2)	108 599 (52.1)
Thiazolidinediones	5193 (2.5)	4954 (2.4)
Glucagon-like peptide-1 receptor agonists	8585 (4.1)	8585 (4.1)
Alpha-glucosidase inhibitors	3043 (1.5)	2932 (1.4)
Meglitinides	4709 (2.3)	4695 (2.3)
Insulin	57 622 (27.7)	57 622 (27.7)
Angiotensin-converting enzyme inhibitors	94 809 (45.5)	94 380 (45.3)
Angiotensin II receptor blockers	66 831 (32.1)	66 521 (31.9)
Beta-blockers	59 026 (28.3)	58 496 (28.1)
Calcium channel blockers	63 521 (30.5)	63 516 (30.5)
Loop diuretics	21 375 (10.3)	21 657 (10.4)
Thiazide diuretics	45 175 (21.7)	44 846 (21.5)
Other diuretics	18 550 (8.9)	18 544 (8.9)
Direct renin inhibitors	104 (0.0)	84 (0.0)
Aldosterone antagonists	6159 (3.0)	6046 (2.9)
Digitalis-like agents	2604 (1.3)	2688 (1.3)
Statins	160 128 (76.9)	159 741 (76.7)
Other lipid-lowering therapy	23 569 (11.3)	22 908 (11.0)
Acetylsalicylic acid	37 071 (17.8)	36 871 (17.7)
Non-acetylsalicylic acid antiplatelet drugs	14 100 (6.8)	13 816 (6.6)
Nonsteroidal anti-inflammatory drugs	40 396 (19.4)	40 109 (19.3)
Oral anticoagulants	13 439 (6.5)	13 420 (6.4)
Oral glucocorticoids	12 957 (6.2)	13 054 (6.3)
Antibiotics to treat urinary tract infection		
From 90 d prior to or on cohort entry	23 464 (11.3)	23 324 (11.2)
From 91 to 365 d prior to cohort entry	51 213 (24.6)	51 034 (24.5)
Number of different classes of non-antidiabetic drugs[d]		
0-1	8478 (4.1)	8650 (4.2)
2-5	66 064 (31.7)	66 670 (32.0)
≥6	133 702 (64.2)	132 924 (63.8)
Healthcare use[c]		

(Continues)

TABLE 1 (Continued)

	SGLT2i (n = 208 244)	DPP4i (n = 208 244)
Inpatient hospitalizations		
0	177 415 (85.2)	176 920 (85.0)
1-2	28 544 (13.7)	28 967 (13.9)
≥3	2284 (1.1)	2356 (1.1)
Number of physician visits		
0-2	14 999 (7.2)	14 950 (7.2)
3-5	31 902 (15.3)	32 298 (15.5)
≥6	161 343 (77.5)	160 996 (77.3)

Numbers may not add up because of small cells suppressed and replaced by 3 because of privacy restrictions. d, days.
[a]Data are presented as n (%) unless otherwise specified.
[b]SD, standard deviation.
[c]Unless otherwise specified, co-morbidities were assessed in the 3 years prior to cohort entry, and medications and healthcare use were assessed in the year prior to cohort entry.
[d]In Saskatchewan, Quebec and the Clinical Practice Research Datalink (CPRD), the Anatomical Therapeutic Chemical (ATC) codes are unavailable; the number of non-antidiabetic drug classes were defined using British National Formulary (BNF_codes (CPRD), American Hospital Formulary Service (AHFS) classification (Quebec) and the number of distinct medications in the covariates list (Saskatchewan).

prevalent new users of SGLT2i included DPP4i users who had the same duration of prior use of DPP4i (±180 days) and did not switch to or add an SGLT2i. All exposure sets were further matched on level of antidiabetic therapy (categorized as insulin use, use of at least two different classes of antidiabetic medications, or 0-1 classes of non-insulin antidiabetic medications) and the use of GLP1 receptor agonists in the previous year. Cohort entry date was the date of the initial SGLT2i dispensation or by the date of the matched DPP4i dispensation in the exposure set. Patients were followed from the day after cohort entry until the occurrence of the outcome, death, end of the study period, end of data, discontinuation of the study drug, or switching from a DPP4i to an SGLT2i, whichever occurred first.

Next, we computed the TCPS (i.e. the probability of receiving an SGLT2i vs. a DPP4i) using conditional logistic regression stratified by exposure set. Estimation was performed separately for incident and prevalent new users, and 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). The conditional logistic regression models included demographics, duration of diabetes, medical conditions in the 3 years before cohort entry, and medication and healthcare use in the year before cohort entry, for a total of 47 covariates (Table S3). The variables were selected based on clinical expertise and prior literature identifying predictors of UTI (e.g. age, sex, antibiotic use) and variables associated with DPP4i use or SGLT2i use (e.g. presence of cardiovascular disease, chronic kidney disease, peripheral vascular disease). For the CPRD analysis we included additional clinical variables at cohort entry: body mass index, smoking, race, blood pressure level, estimated glomerular filtration rate (eGFR) and HbA1c level. These clinical variables were not included in other databases. Missing values were considered a separate category. To satisfy the positivity assumption, we excluded exposure sets if the TCPS of the patient treated with an SGLT2i was not within the range of the TCPS distribution of the corresponding DPP4i exposure set. Finally, in chronological order, we used the nearest TCPS to match new users of SGLT2i on a one-to-one basis (without replacement) to patients using DPP4i in their exposure set. In sites that experienced more than 10% loss of exposure sets after satisfying the positivity assumption and matching, we allowed matching with replacement using a caliper width of ±0.2 standard deviations of the log TCPS, to reduce the number of times a given individual was selected in the comparator group. Matching with replacement was performed in five sites (Alberta, British Columbia, Manitoba, Nova Scotia and Saskatchewan).

2.4 | Exposure

Exposure was defined using an as-treated approach (i.e. defined at cohort entry and considered time-fixed). Patients were assigned to one of the two mutually exclusive categories: (1) user of SGLT2i (canagliflozin, dapagliflozin or empagliflozin) alone or in combination with other antidiabetic drugs; or (2) user of DPP4i (alogliptin, linagliptin, saxagliptin, sitagliptin or vildagliptin) alone or in combination with other non-SGLT2i antidiabetic drugs. Treatment discontinuation was defined by a treatment gap of 30 days or more between successive prescriptions. Patients from the SGLT2i groups were allowed to add on a DPP4i, but they were censored if they discontinued the SGLT2i and switched to a DPP4i. DPP4i users were censored when they initiated an SGLT2i (regardless of whether or not they discontinued their DPP4i) and were allowed to move to the SGLT2i exposure group.

2.5 | Outcomes

The primary outcome was urosepsis, defined as a hospitalization with a diagnostic code for acute pyelonephritis, UTI or acute cystitis in any position (International Classification of Diseases [ICD] version 10 Canadian Version, ICD-10-CA codes N10, N15.1, N39.0 or N30.0) and a corresponding code for sepsis (ICD-10-CA codes A41.xx, R57.2 or R65.2). The secondary outcome was Fournier's gangrene, defined by inpatient ICD-10-CA diagnostic codes N49.3, N76.8x or N76.88 in any diagnosis position. The date of hospital admission defined the event date.

2.6 | Statistical analysis

Rates and corresponding 95% confidence intervals (CI) were estimated using the Poisson distribution for both outcomes. We used time-dependent Cox proportional hazards models to estimate hazard ratios and 95% CIs for urosepsis with SGLT2i versus DPP4i, with follow-up time as the underlying time axis. The outcome model

TABLE 2 Additional characteristics of new users of sodium-glucose co-transporter-2 inhibitors (SGLT2i) and their matched users of dipeptidyl peptidase-4 inhibitors (DPP4i) in the Clinical Practice Research Datalink (CPRD)

Characteristics[a,b]	SGLT2i (n = 5422)	DPP4i (n = 5422)
Body mass index (kg/m^2)		
<30	1529 (28.2)	1730 (31.9)
≥30	3875 (71.5)	3665 (67.6)
Unknown	18 (0.3)	27 (0.5)
Smoking status		
Never	s[c]	2121 (39.1)
Ever	3249 (59.9)	3294 (60.8)
Unknown	s[c]	7 (0.1)
Race		
White	3955 (72.9)	3894 (71.8)
Other	534 (9.8)	602 (11.1)
Unknown	933 (17.2)	926 (17.1)
Blood pressure (mmHg)		
DBP <90 and SBP <140	3506 (64.7)	3563 (65.7)
DPB ≥90 or SBP ≥140	1908 (35.2)	1846 (34.0)
Unknown	8 (0.1)	13 (0.2)
eGFR (mL/min/1.73 m^2)		
<60	284 (5.2)	531 (9.8)
≥60	5131 (94.6)	4884 (90.1)
Unknown	7 (0.1)	7 (0.1)
HbA1c (%)		
≤7	181 (3.3)	230 (4.2)
7.1-8	1048 (19.3)	1075 (19.8)
>8	4157 (76.7)	4077 (75.2)
Unknown	36 (0.7)	40 (0.7)

Abbreviations: DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.
[a]Data are presented as n (%).
[b]Assessment of body mass index, smoking status, blood pressure, eGFR and HbA1c was based on the last measurement before study cohort entry and race was assessed before study cohort entry.
[c]Values suppressed because of privacy restrictions are presented as s.

included age (continuous variable), sex, diabetes duration (continuous variable) and decile of TCPS. In sites where matching with replacement was required, we corrected for dependence of observations of the same patient, by using the robust sandwich estimate for the covariance. Site-specific results were pooled using DerSimonian and Laird random effects models with inverse variance weighting.[28] We estimated between-site heterogeneity using the I^2 statistic. To avoid overfitting the data, sites with fewer than five events in each exposure group were not included in the meta-analysis (CPRD, Manitoba, Nova Scotia). Power calculations are provided in the supporting information (Supplement [p. S12]).

2.7 | Additional analyses

We used stratified analysis to evaluate effect modification by age (≥70 or <70 years), sex and prior insulin use to explore the risk of specific SGLT2i molecules. We also conducted three sensitivity analyses. First, we broadened the main outcome definition to include all hospitalizations with UTI as the primary diagnosis. Next, we varied the treatment gap used to define discontinuation to 0 and 60 days after the exhaustion of a dispensation. Last, we assessed the effect separately in incident and prevalent new users of SGLT2i. We also considered conducting an intention-to-treat analysis with a maximum follow-up of 1 year; however, the mean follow-up in our primary analysis was 0.9 years and we did not anticipate that results would differ substantially.

3 | RESULTS

We identified 270 902 patients who initiated an SGLT2i and 632 114 patients who initiated a DPP4i (Figure 1). After applying the exclusion criteria, 214 992 new users of SGLT2i and 501 077 new users of DPP4i were considered for matching. The matched study cohorts included 208 244 new users of SGLT2i and 208 244 users of DPP4i. Of these, 102 743 (49%) matched pairs were incident new users of SGLT2i and the remaining 105 501 (51%) were prevalent new users.

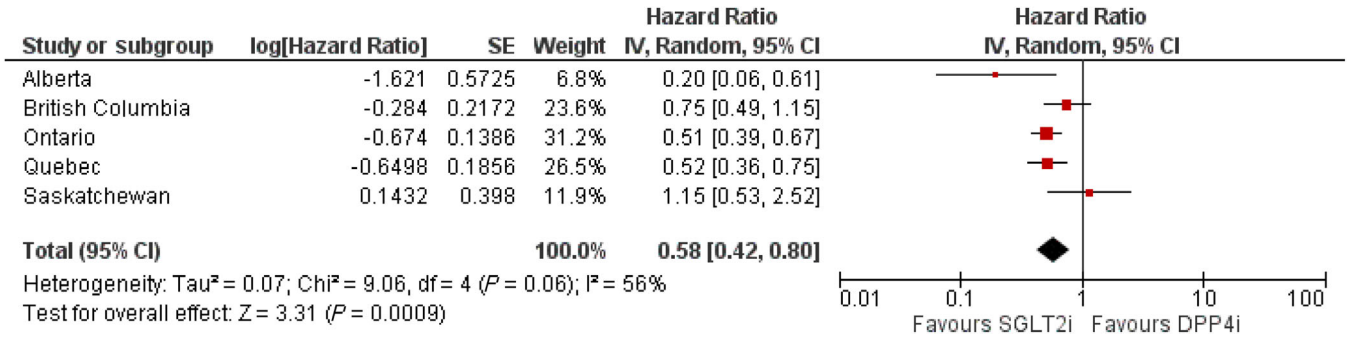

FIGURE 2 Adjusted hazard ratios and 95% confidence intervals of urosepsis associated with sodium-glucose co-transporter-2 inhibitor (SGLT2i) use compared with dipeptidyl peptidase-4 inhibitor (DPP4i) use among patients with type 2 diabetes. CI, confidence interval; df, degree of freedom; IV, inverse variance. Sites with fewer than five events in each exposure group were not included in the meta-analysis

TABLE 3 Summary of results of stratified and sensitivity analyses of pooled adjusted hazard ratios (95% confidence interval [CI]) for sodium-glucose co-transporter-2 inhibitor (SGLT2i) use versus dipeptidyl peptidase-4 inhibitor (DPP4i) use among patients with type 2 diabetes

		Number of sites included	Alberta	British Columbia	Manitoba	Nova Scotia	Ontario	Quebec	Saskatchewan	CPRD[a]	Adjusted hazard ratio (95% CI)	I^2
Main analysis		5	✓	✓			✓	✓	✓		0.58 (0.42-0.80)	56%
Age, y	≥70	3		✓			✓	✓			0.57 (0.45-0.74)	0%
	<70	5	✓	✓			✓	✓	✓		0.52 (0.36-0.75)	33%
Sex	Females	4		✓			✓	✓	✓		0.67 (0.45-0.99)	44%
	Males	3		✓			✓	✓			0.53 (0.41-0.69)	0%
Prior insulin use[b]	Yes	5	✓	✓			✓	✓	✓		0.49 (0.34-0.72)	34%
	No	3		✓			✓	✓			0.70 (0.42-1.17)	72%
SGLT2i molecule	Canagliflozin	5	✓	✓			✓	✓	✓		0.70 (0.44-1.10)	59%
	Dapagliflozin	3					✓	✓			0.63 (0.36-1.12)	44%
	Empagliflozin	1					✓				0.38 (0.24-0.61)	-
Broader outcome[c]		7	✓	✓	✓		✓	✓	✓	✓	0.61 (0.55-0.68)	0%
Varying grace period, d	0	2		✓			✓				0.74 (0.28-1.97)	74%
	60	5	✓								0.58 (0.46-0.74)	36%
New-user status	Incident	4									0.58 (0.35-0.97)	61%
	Prevalent	3									0.70 (0.40-1.23)	77%

I^2 is a test for heterogeneity between the sites. A check mark indicates that site-specific data were available for the analysis.

[a]CPRD, the UK Clinical Practice Research Datalink.

[b]Prior insulin use was defined as prescription for insulin in the year prior.

[c]The broader outcome included all hospitalizations for urinary tract infection (UTI) and was defined as a hospital discharge with UTI as the primary diagnosis.

After matching, baseline characteristics were well balanced between the two treatment groups, with the exception of age and eGFR in the CPRD, and prior use of metformin in the Saskatchewan database (Table 1, Table S4). Patients were mostly male (58%) with a mean age of 64 years. About 60% of the patients had a duration of diabetes of more than 10 years. In the previous year, 87% of the patients were treated with metformin and 28% were treated with insulin. Among 208 244 users of SGLT2i, 42.3% initiated treatment with canagliflozin, 30.7% dapagliflozin and 27.0% empagliflozin. We observed a similar distribution of SGLT2i molecules in incident new users and prevalent new users. Additional characteristics of the matched users of SGLT2i and DPP4i in the CPRD are provided in Table 2. Approximately 5% of adults in the CPRD prescribed an SGLT2i had an eGFR less than 60 mL/min/1.73 m^2 compared with 10% of users of DPP4i.

Patients were followed for a mean duration of 0.9 years (standard deviation 0.76) until the event, censoring or treatment discontinuation, for a total of 369 753 person-years. During follow-up, there were 189 events of urosepsis among users of SGLT2i (incidence rate of 1.00 per 1000 person-years; 95% CI: 0.87-1.16), and 368 events among the users of DPP4i (incidence rate 2.03 per 1000 person-years; 95% CI: 0.83-2.24). For the primary outcome of urosepsis, we pooled hazard ratios from five sites and found that the use of SGLT2i was associated with a decreased risk of urosepsis compared with DPP4i. The unadjusted hazard ratio was 0.53 (95% CI 0.41-0.68). The adjusted hazard ratio was 0.58 (95% CI: 0.42-0.80; I^2: 56%; Figure 2).

The incidence rates of Fournier's gangrene were numerically similar between users of SGLT2i and users of DPP4i (number of events: 15 vs. 25; incidence rate 0.08 per 1000 person-years; 95% CI: 0.05-0.13 vs. 0.14; 95% CI: 0.09-0.21). Results from the additional analyses are summarized in Table 3. We found no evidence of effect modification by age, sex, prior insulin use or SGLT2i molecule. The overall results of the sensitivity analyses were consistent with results from our primary analysis.

4 | DISCUSSION

Our study, including data from seven Canadian provinces and the CPRD, is one of the largest real-world studies assessing the occurrence of urosepsis and Fournier's gangrene among patients with type 2 diabetes treated with SGLT2i. We found a lower rate of urosepsis with SGLT2i compared with DPP4i (adjusted hazard ratio 0.58; 95% CI: 0.42-0.80). The risk reduction was similar for each of the SGLT2i molecules studied, namely, canagliflozin, dapagliflozin or empagliflozin. The incidence rate of Fournier's gangrene was numerically similar for SGLT2i and DPP4i (0.08 vs. 0.14 per 1000 person-years with overlapping CIs); however, this finding should be interpreted with caution given the lack of statistical adjustment and wide 95% CIs.

The effect of SGLT2i on the risk of UTI has been studied in over 35 meta-analyses of RCTs and four real-world observational studies. Meta-analyses from 2012 to 2016 frequently reported an increase in risk of UTI with SGLT2i monotherapy or as add-on to other pharmacological therapies.[5–9] However, recent meta-analyses did not find an increased risk.[10,11] This inconsistency in the results could be explained by differences in comparators among the included studies. Meta-analyses comparing SGLT2i with active treatments usually found no difference in UTI.[10,29,30] On the other hand, compared with placebo or a combination of placebo and active treatment, SGLT2i treatment had an increased UTI risk.[7–9,31–33] In three meta-analyses, SGLT2i had a similar risk of UTI compared with DPP4i.[30,31,34] Inconsistencies in the results of the meta-analyses could also be related to the specific SGLT2i molecule studied; early meta-analyses, which mainly included studies on dapagliflozin, often found an increase in UTI.[35–38] Similarly, more recent large meta-analyses found that dapagliflozin was associated with an increased risk of UTI, while canagliflozin and empagliflozin were not.[10,11,39]

A recent meta-analysis found no significant increase in the risk of urosepsis compared with placebo (22 cases reported in nine studies, risk ratio 1.41; 95% CI: 0.57-3.48) or active comparators (one case reported in two studies, risk ratio 1.39; 95% CI: 0.07-28.33).[10] One study using data from routine care found no increase in the risk of urosepsis in patients treated with SGLT2i compared with DPP4i and GLP1 receptor agonists.[16] The incidence rate of urosepsis with SGLT2i was similar to that estimated in our study (1.8-2.3 per 1000 person-years).[16]

Other observational studies examined UTI but not urosepsis and found a similar or lower rate of UTI with SGLT2i compared with DPP4i,[15,17] GLP1 receptor agonists[18] or both.[16] Most of these studies used an active comparator, new-user design with one-to-one propensity score matching. Two of the studies examined serious UTI (defined by a UTI diagnosis with hospitalization) and found no increased risk in users of SGLT2i, with hazard ratios of 0.89 (95% CI: 0.67-1.19) compared with GLP1 receptor agonists[18] and 0.98 (95% CI: 0.68-1.41) compared with DPP4i and GLP1 receptor agonists.[21] Two other studies examined outpatient UTI, with the outcome defined using antibiotics prescription refills and/or UTI diagnoses. These two studies found that patients treated with SGLT2i had a similar or lower UTI risk compared with DPP4i, with hazard ratios of 0.90 (95% CI: 0.66-1.24)[15] and 0.89 (95% CI: 0.78-1.00).[17]

Few studies have examined the association between SGLT2i use and Fournier's gangrene. A recent meta-analysis pooled data from three RCTs and failed to detect any association between SGLT2i and Fournier's gangrene, perhaps because of the small number of events detected (nine events in over 28 000 patients, odds ratio 0.41; 95% CI: 0.09-1.82).[19] Because Fournier's gangrene is rare, real-world data can provide important information that may not be apparent from clinical trials. Three observational studies conducted using data from the United States found that the rates of Fournier's gangrene in patients treated with SGLT2i were (numerically or statistically) similar to those treated with DPP4i.[20,21,40] However, the number of events in SGLT2i users in the three real-world studies, including ours, remains small (105 events overall).

Our study has several strengths. The use of the prevalent new-user design allowed us to include SGLT2i patients who had recently switched from treatment with a DPP4i. By using this study design, we avoided the exclusion of 50% of SGLT2i users and were therefore

better able to reflect real-world diabetes treatment. Although there were changes in the standard of care for patients with type 2 diabetes during the study period, we matched on calendar time (caliper 120 days), minimizing the possibility of residual confounding because of these temporal changes. Additionally, the inclusion of multiple data sources and the large number of patients examined permitted the calculation of precise estimates for urosepsis.

The findings resulting from our study should be interpreted in light of its limitations. First, while the observed baseline characteristics were well balanced, this does not guarantee that unmeasured characteristics were also well balanced (residual confounding). The duration of follow-up was comparatively short (i.e. mean 0.9 years) and thus our results do not provide risk estimates for long-term SGLT2i use. Our results might be partly explained by confounding by indication (or contraindication) if patients at the highest risk of UTI had preferentially received a DPP4i following the FDA warning on SGLT2i in 2015. Also, matching with replacement in some sites may have caused atypical patients to be selected repeatedly. However, the hazard ratios were consistent across the sites, regardless of the matching strategy, and therefore we are confident that this had minimal impact on our results. Finally, although the prevalent new-user design offers several advantages, it is not without limitations. The design included a mixing of causal contrasts, that is, initiating SGLT2i versus DPP4i compared with switching from a DPP4i to SGLT2i versus maintaining DPP4i. We cannot rule out confounding by indication in the prevalent-user subcohort, that is, the reason for switching to an SGLT2i as opposed to maintaining DPP4i treatment may also be related to the outcome. We allowed for previous use of DPP4i among SGLT2i users but not vice versa to mimic an RCT: we focused on new users of SGLT2i and censored those who switched to DPP4i. This censoring was minimal (5.5% of DPP4i dispensations) and unlikely to have had a significant impact upon our results. We are confident that this did not increase the bias, as comparable results were found among incident new users and prevalent new users (Table 3).

In this large, multi-site, cohort study, patients with type 2 diabetes treated with SGLT2i had a lower rate of urosepsis compared with those treated with DPP4i, a medication used at a similar stage in the treatment of diabetes. Given the FDA warnings on the possible increased risk of serious UTI associated with SGLT2i, confounding by contraindication is a consideration. Our results provide reassurance regarding the risk of urosepsis associated with this increasingly used drug class; however, considering all available evidence, SGLT2i treatment may not be safer than DPP4i.

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CONFLICT OF INTEREST

S.A.S. received research grants from Pfizer and Merck for projects not involving SGLT2i or DPP4i. The remaining study investigators have no relevant conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

AF drafted the manuscript. All authors contributed to the study design and implementation, interpretation of results, and critically reviewed the manuscript for important intellectual content. LML conducted the meta-analyses. All authors approved the final version 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 this article.

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