

Sodium-glucose Cotransporter 2 Inhibitors and the Risk for Urosepsis – A Multi-site Prevalent New-user Cohort Study

Anat Fisher MD PhD¹, Michael Fralick MD PhD^{2,3}, Kristian B. Filion PhD^{4,5}, Sophie Dell’Aniello MSc⁵, Antonios Douros MD PhD^{4,5,6}, Éric Tremblay BPharm MSc⁷, Baiju R. Shah MD PhD^{3,8,9}, Paul E. Ronksley PhD¹⁰, Silvia Alessi-Severini PhD^{11,12}, Nianping Hu PhD¹³, Shawn C. Bugden PharmD MSc^{11,14}, Pierre Ernst MD MSc^{5,15}, Lisa M. Lix PhD¹⁶ for the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators*

1. Research Associate, Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver B.C, Canada ORCID ID: <https://orcid.org/0000-0001-9730-5107>
2. Sinai Health System, Toronto, ON, Canada
3. Department of Medicine, University of Toronto, Toronto, Ontario, Canada
4. Departments of Medicine and Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC
5. Centre for Clinical Epidemiology, Lady Davis Institute, Montreal, QC
6. Institute of Clinical Pharmacology and Toxicology, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
7. Institut national d'excellence en santé et en services sociaux (INESSS), Quebec City, Quebec, Canada
8. I.C.E.S, Toronto, Ontario, Canada
9. Division of Endocrinology and Metabolism, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
10. Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
11. College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
12. Manitoba Centre for Health Policy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
13. The Health Quality Council, Saskatoon, Saskatchewan, Canada
14. School of Pharmacy, Memorial University of Newfoundland, St John's, Newfoundland and Labrador, Canada
15. Department of Medicine, McGill University, Montreal, QC

16. Department of Community Health Sciences, University of Manitoba, Winnipeg,
Manitoba, Canada

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Corresponding author:

Lisa Lix PhD

Professor

Department of Community Health Sciences

University of Manitoba

3rd floor, 753 McDermot Ave

Winnipeg, Manitoba, Canada

Telephone: (204) 789-3573

Fax: (204) 789-3905

Email: lisa.lix@umanitoba.ca

*The Canadian Network for Observational Drug Effect Studies (CNODES) Investigators are: Samy Suissa (Principal Investigator); Colin R. Dormuth (British Columbia); Brenda R. Hemmelgarn (Alberta); Jacqueline Quail (Saskatchewan); Dan Chateau (Manitoba); J. Michael Paterson (Ontario); Jacques LeLorier (Québec); Adrian R. Levy (Atlantic: Nova Scotia, Newfoundland and Labrador, New Brunswick, Prince Edward Island); Pierre Ernst and Kristian B. Filion (UK Clinical Practice Research Datalink (CPRD)); Lisa M. Lix (Database); Robert W. Platt (Methods); and Ingrid S. Sketris (Knowledge Translation). CNODES, a collaborating centre of the Drug Safety and Effectiveness Network (DSEN), is funded by the Canadian Institutes of Health Research (Grant Number DSE-146021).

1 Abstract

2 **AIMS:** The United States Food and Drug Administration has warned of an increased
3 risk of serious urinary tract infection (UTI) and Fournier's gangrene in patients with
4 diabetes mellitus type 2 treated with sodium–glucose cotransporter 2 inhibitors
5 (SGLT2i). However, evidence on these risks is limited. We aimed to compare urosepsis
6 rates in SGLT2i users with users of dipeptidyl peptidase-4 inhibitors (DPP4i) in a real-
7 world setting.

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

15 **RESULTS:** We included 208,244 users of SGLT2i and 208,244 users of DPP4i. Among
16 SGLT2i users, 42% initiated canagliflozin, 31% dapagliflozin, and 27% empagliflozin.
17 During a mean follow-up of 0.9 years, patients initiating SGLT2i had a lower rate of
18 urosepsis compared with those receiving DPP4i. The pooled adjusted hazard ratio was
19 0.58; 95% confidence interval (CI): 0.42-0.80. The incidence rates of Fournier's
20 gangrene were numerically similar in SGLT2i (0.08 per 1000 person-years; 95% CI:
21 0.05-0.13) and DPP4i users (0.14; 95% CI: 0.09-0.21).

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

25 Introduction

26 In May 2015, the United States Food and Drug Administration (FDA) warned of an
27 increased risk for serious urinary tract infection (UTI) in patients treated with sodium–
28 glucose cotransporter 2 inhibitors (SGLT2i).¹ A second FDA warning, issued in August
29 2018, reported on a possible association between SGLT2i treatment and severe genital
30 infections resulting in necrotizing fasciitis of the perineum (Fournier’s gangrene).² The
31 safety warnings were issued in response to 19 cases of urosepsis^{1,3} and 12 cases of
32 Fournier’s gangrene² identified from the FDA Adverse Event Reporting System and the
33 literature. The FDA reports provided limited evidence on causal relationships between
34 the SGLT2i and these conditions, and rates could not be calculated.⁴

35 Multiple meta-analyses of clinical trial data have examined the association between
36 SGLT2i and UTI. Meta-analyses of randomized clinical trials (RCTs) from 2012 to 2016
37 identified an increased risk of UTI⁵⁻⁹ while more recent large meta-analyses did not.^{10,11}
38 RCTs can underestimate the rate of important adverse events,^{12,13} and the participants
39 may not represent patients treated in routine care;¹⁴ therefore, it is important to also
40 consider real-world studies. Four large observational studies found similar, if not lower,
41 rates of UTI with SGLT2i compared to other second-line medications for type 2
42 diabetes.¹⁵⁻¹⁸ While these studies provided important reassurance regarding the risk of
43 UTI, only one study also assessed urosepsis. This study found no increased risk of
44 urosepsis in patients treated with SGLT2i compared with dipeptidyl peptidase-4
45 inhibitors (DPP4i) and with glucagon-like peptide1 (GLP1) receptor agonists.¹⁶

46 With regards to Fournier’s gangrene, a recent meta-analysis of RCTs did not identify an

47 increased risk of this rare outcome.¹⁹ Similarly, two recent observational studies in users
48 of SGLT2i did not detect an increased rate of Fournier's gangrene compared with users
49 of DPP4i,^{20,21} or non-SGLT2i antidiabetic medications.²⁰ However, because Fournier's
50 gangrene is rare (i.e., incidence is 0.016 per 1000²²), the three epidemiological
51 studies¹⁹⁻²¹ were underpowered to detect a difference. Given the limited available
52 evidence on the risk of urosepsis and Fournier's gangrene, the severity of these
53 outcomes, and the increasing use of SGLT2i among patients with type 2 diabetes,^{23,24}
54 there remains an urgent need to assess these potential safety issues.

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

60

61 **Methods**

62 **Study design and data sources**

63 We conducted matched cohort studies using a prevalent new-user design with time-
64 conditional propensity scores (TCPS).²⁶ Patients were identified from administrative
65 healthcare databases in seven Canadian provinces (Alberta, British Columbia,
66 Manitoba, Nova Scotia, Ontario, Quebec, and Saskatchewan), and primary-care clinical
67 data from the CPRD.²⁷ The Canadian data included physician billing claims,
68 hospitalization discharge diagnoses, and pharmacy dispensations of prescription

69 drugs.²⁵ In Alberta, data were available for individuals aged 19 years or older; in
70 Ontario, data were available for individuals 65 years or older. Quebec data were
71 restricted to 40% of the total Quebec population who were aged 65 years or older,
72 beneficiaries of social assistance, or subscribers to the province's public insurance drug
73 plan. The CPRD data included primary care medical records—with prescription data
74 rather than dispensations—for over 15 million people enrolled from over 700 UK
75 practices. We restricted inclusion to patients who were linkable to hospitalization data
76 (76% of CPRD practices).

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

81

82 **Study population**

83 The source population included individuals dispensed or prescribed (CPRD) an
84 antidiabetic medication between January 1, 2006 and June 30, 2018 or the end of data
85 availability in each site (Supplement Table S1). Antidiabetic medications included
86 metformin, sulfonylureas, thiazolidinediones, DPP4i, SGLT2i, GLP1 receptor agonists,
87 alpha-glucosidase inhibitors, meglitinides, insulin, or combinations of these drugs. With
88 the source population covering 2006 to 2018, we were able to identify all patients with a
89 previous history of DPP4i use. From the source population, we identified patients who
90 received a first dispensation for an SGLT2i or a dispensation for a DPP4i during the

91 identification period (Supplement Tables S1, S2), which started in each site on the date
92 of the first recorded dispensation of SGLT2i at this site and ended on June 30, 2018 or
93 the last date with available data. We excluded new users of SGLT2i if they had also
94 started using a DPP4i on the same date, and users of a DPP4i if they had used an
95 SGLT2i earlier.

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

103

104 **Matched study cohort**

105 Using the prevalent new-user design,²⁶ we included new users of SGLT2i, who were
106 either incident new-users, i.e., patients who did not receive a DPP4i in the previous
107 year, and prevalent new-users, i.e., those who received treatment with a DPP4i in the
108 year before starting an SGLT2i. For each initial dispensation of a SGLT2i, we selected a
109 comparator dispensation from the cohort of DPP4i patients matched on calendar time,
110 prior treatment, and TCPS. First, we defined an exposure set for each initial
111 dispensation of an SGLT2i. To minimize the risk of calendar time bias, each exposure
112 set included DPP4i dispensations occurring within 120 days of the new SGLT2i

113 prescription. Exposure sets for incident new users of SGLT2i included incident
114 dispensations of DPP4i (i.e., a new DPP4i dispensation for a patient with no DPP4i use
115 in the previous year). Exposure sets for prevalent new users of SGLT2i included DPP4i
116 users who had the same duration of prior use of DPP4i (± 180 days) and did not switch to
117 or add an SGLT2i. All exposure sets were further matched on level of antidiabetic
118 therapy (categorized as insulin use, use of at least two different classes of antidiabetic
119 medications, or 0-1 classes of non-insulin antidiabetic medications) and the use of
120 GLP1 receptor agonists in the previous year. Cohort entry date was the date of the
121 initial SGLT2i dispensation or by the date of the matched DPP4i dispensation in the
122 exposure set. Patients were followed from the day after cohort entry until the occurrence
123 of the outcome, death, end of the study period, end of data, discontinuation of the study
124 drug, or switching from a DPP4i to an SGLT2i, whichever occurred first.

125 Next, we computed the TCPS (i.e., the probability of receiving an SGLT2i versus a
126 DPP4i) using conditional logistic regression stratified by exposure set. Estimation was
127 done separately for incident and prevalent new users, and scores were computed for
128 each individual in each exposure set; hence, an individual may have different scores for
129 exposure sets they enter, depending on the time of entry (i.e., time conditional). The
130 conditional logistic regression models included demographics, duration of diabetes,
131 medical conditions in the three years before cohort entry, and medication and
132 healthcare use in the year before cohort entry, for a total of 47 covariates (Supplement,
133 Table S3). The variables were selected based on clinical expertise and prior literature
134 identifying predictors of UTI (e.g., age, sex, antibiotic use) and variables associated with
135 DPP4i use or SGLT2i use (e.g., presence of cardiovascular disease, chronic kidney

136 disease, peripheral vascular disease). For the CPRD analysis we included additional
137 clinical variables at cohort entry: body mass index, smoking, race, blood pressure level,
138 estimated glomerular filtration rate (GFR), and hemoglobin A1c level. These clinical
139 variables were not included in other databases. Missing values were considered a
140 separate category. To satisfy the positivity assumption, we excluded exposure sets if
141 the TCPS of the patient treated with an SGLT2i was not within the range of the TCPS
142 distribution of the corresponding DPP4i exposure set. Finally, in chronological order, we
143 used the nearest TCPS to match new users of SGLT2i on a one-to-one basis (without
144 replacement) to patients using DPP4i in their exposure set. In sites that experienced
145 more than 10% loss of exposure sets after satisfying the positivity assumption and
146 matching, we allowed matching with replacement using a caliper width of ± 0.2 standard
147 deviations of the log TCPS, to reduce the number of times a given individual was
148 selected in the comparator group. Matching with replacement was done in five sites
149 (Alberta, British Columbia, Manitoba, Nova Scotia, and Saskatchewan).

150

151 **Exposure**

152 Exposure was defined using an as-treated approach (i.e., defined at cohort entry and
153 considered time-fixed). Patients were assigned one of the two mutually exclusive
154 categories: 1) user of SGLT2i (canagliflozin, dapagliflozin, or empagliflozin) alone or in
155 combination with other antidiabetic drugs; or 2) user of DPP4i (alogliptin, linagliptin,
156 saxagliptin, sitagliptin, or vildagliptin) alone or in combination with other non-SGLT2i
157 antidiabetic drugs. Treatment discontinuation was defined by a treatment gap of 30
158 days or more between successive prescriptions. Patients from the SGLT2i groups were

159 allowed to add on a DPP4i, but they were censored if they discontinued the SGLT2i and
160 switched to a DPP4i. DPP4i users were censored when they initiated an SGLT2i
161 (regardless of whether or not they discontinued their DPP4i) and were allowed to move
162 to the SGLT2i exposure group.

163

164 **Outcomes**

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

172

173 **Statistical analysis**

174 Rates and corresponding 95% confidence intervals (CI) were estimated using the
175 Poisson distribution for both outcomes. We used time-dependent Cox proportional
176 hazards models to estimate hazard ratios and 95% CIs for urosepsis with SGLT2i
177 versus DPP4i, with follow-up time as the underlying time axis. The outcome model
178 included age (continuous variable), sex, diabetes duration (continuous variable), and
179 decile of TCPS. In sites where matching with replacement was required, we corrected
180 for dependence of observations of the same patient, by using the robust sandwich

181 estimate for the covariance. Site-specific results were pooled using DerSimonian and
182 Laird random-effects models with inverse variance weighting.²⁸ We estimated between-
183 site heterogeneity using the I^2 -statistic. To avoid overfitting the data, sites with fewer
184 than five events in each exposure group were not included in the meta-analysis (CPRD,
185 Manitoba, Nova Scotia). Power calculations are provided in the Supplement (page S12).

186

187 **Additional analyses**

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

197

198 **Results**

199 We identified 270,902 patients who initiated an SGLT2i, and 632,114 patients who
200 initiated a DPP4i (Figure 1). After applying the exclusion criteria, 214,992 new users of
201 SGLT2i and 501,077 new users of DPP4i were considered for matching. The matched

202 study cohorts included 208,244 new users of SGLT2i and 208,244 users of DPP4i. Of
203 these, 102,743 (49%) matched pairs were incident new users of SGLT2i and the
204 remaining 105,501 (51%) were prevalent new users.

205 After matching, baseline characteristics were well balanced between the two treatment
206 groups, with the exception of age and GFR in the CPRD, and prior use of metformin in
207 the Saskatchewan database (Table 1, Supplement Table S4). Patients were mostly
208 male (58%) with a mean age of 64 years. About 60% of the patients had a duration of
209 diabetes of over 10 years. In the previous year, 87% of the patients were treated with
210 metformin and 28% were treated with insulin. Among 208,244 users of SGLT2i, 42.3%
211 initiated treatment with canagliflozin, 30.7% dapagliflozin, and 27.0% empagliflozin. We
212 observed a similar distribution of SGLT2i molecules in incident new users and prevalent
213 new users. Additional characteristics of the matched users of SGLT2i and DPP4i in the
214 CPRD are provided in Table 2. Approximately 5% of adults in the CPRD prescribed an
215 SGLT2i had GFR less than 60 mL/min/1.73m² compared with 10% of users of DPP4i.
216 Patients were followed for a mean duration of 0.9 years (standard deviation 0.76), until
217 the event, censoring, or treatment discontinuation, for a total of 369,753 person-years.
218 During follow-up, there were 189 events of urosepsis among users of SGLT2i
219 (incidence rate of 1.00 per 1000 person-years; 95% CI: 0.87-1.16), and 368 events
220 among the users of DPP4i (incidence rate 2.03 per 1000 person-years; 95% CI: 0.83-
221 2.24). For the primary outcome of urosepsis, we pooled hazard ratios from five sites and
222 found that the use of SGLT2i was associated with a decreased risk of urosepsis
223 compared with DPP4i. The unadjusted hazard ratio was 0.53; 95% CI 0.41-0.68. The
224 adjusted hazard ratio was 0.58, 95% CI: 0.42-0.80 (I²: 56%; Figure 2).

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

231 Discussion

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

241 The effect of SGLT2i on the risk for UTI has been studied in over 35 meta-analyses of
242 randomized controlled trials and four real-world observational studies. Meta-analyses
243 from 2012 to 2016 often reported an increase in risk for UTI with SGLT2i monotherapy
244 or as add-on to other pharmacological therapies.⁵⁻⁹ However, the recent meta-analyses
245 did not find an increased risk.^{10,11} This inconsistency in the results could be explained
246 by differences in comparators among the included studies. Meta-analyses comparing

247 SGLT2i to active treatments usually found no difference in UTI.^{10,29,30} On the other
248 hand, compared with placebo or a combination of placebo and active treatment, SGLT2i
249 treatment had an increased UTI risk.^{7-9,31-33} In three meta-analyses, SGLT2i had similar
250 risk for UTI compared with DPP4i.^{30,31,34} Inconsistencies in the results of the meta-
251 analyses could also be related to the specific SGLT2i molecule studied; early meta-
252 analyses, which included mainly studies on dapagliflozin, often found an increase in
253 UTI.³⁵⁻³⁸ Similarly, more recent large meta-analyses found that dapagliflozin was
254 associated with an increased risk of UTI, while canagliflozin and empagliflozin were
255 not.^{10,11,39}

256 As for the outcome of the current study, urosepsis, a recent meta-analysis found no
257 significant increase in the risk of urosepsis compared to placebo (22 cases reported in 9
258 studies, risk ratio 1.41; 95% CI: 0.57-3.48) or active comparators (1 case reported in 2
259 studies, risk ratio 1.39; 95% CI: 0.07-28.33).¹⁰ One study using data from routine care
260 found no increase in risk for urosepsis in patients treated with SGLT2i compared with
261 DPP4i and with GLP1 receptor agonists.¹⁶ The incidence rate of urosepsis with SGLT2i
262 was similar to that estimated in our study (1.8-2.3 per 1000 person-years).¹⁶

263 Other observational studies examined UTI, but not urosepsis and found a similar or
264 lower rate of UTI with SGLT2i compared to DPP4i,^{15,17} GLP1 receptor agonists,¹⁸ or
265 both.¹⁶ Most of these studies used an active comparator, new-user design with one-to-
266 one propensity score matching. Two of the studies examined serious UTI (defined by a
267 UTI diagnosis with hospitalization) and found no increased risk in users of SGLT2i, with
268 hazard ratios of 0.89, 95% CI: 0.67-1.19, compared with GLP1 receptor agonists¹⁸ and
269 0.98, 95% CI: 0.68-1.41, compared with DPP4i and GLP1 receptor agonists.²¹ Two

270 other studies examined outpatient UTI, with the outcome defined using antibiotics
271 prescription refills and/or UTI diagnoses. These two studies found that patients treated
272 with SGLT2i had a similar or lower UTI risk compared with DPP4i, with hazard ratios
273 0.90; 95% CI: 0.66-1.24¹⁵ and 0.89; 95% CI: 0.78-1.00.¹⁷

274 Few studies have examined the association between SGLT2i use and Fournier's
275 gangrene. A recent meta-analysis pooled data from three RCTs and failed to detect any
276 association between SGLT2i and Fournier's gangrene, perhaps due to the small
277 number of events detected (9 events in over 28,000 patients, odds ratio 0.41; 95% CI:
278 0.09-1.82).¹⁹ Because Fournier's gangrene is rare, real-world data can provide
279 important information that may not be apparent from clinical trials. Three observational
280 studies conducted using data from the United States found that the rates of Fournier's
281 gangrene in patients treated with SGLT2i were (numerically or statistically) similar to
282 those treated with DPP4i^{20,21,40}. However, the number of events in SGLT2i users in the
283 three real-world studies, including ours, remains small (105 events overall).

284 Our study has several strengths. The use of the prevalent new-user design allowed us
285 to include SGLT2i patients who had recently switched from treatment with a DPP4i. By
286 using this study design, we avoided the exclusion of approximately 50% of SGLT2i
287 users and were therefore better able to reflect real-world diabetes treatment. Although
288 there were changes in the standard of care for patients with type 2 diabetes during the
289 study period, we matched on calendar time (caliper 120 days), minimizing the possibility
290 of residual confounding due to these temporal changes. Additionally, the inclusion of
291 multiple data sources and the large number of patients examined permitted the
292 calculation of precise estimates for urosepsis.

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

315 In this large multi-site cohort study, patients with type 2 diabetes treated with SGLT2i
316 had a lower rate of urosepsis compared with those treated with DPP4i, a medication
317 used at a similar stage in the treatment of diabetes. Given the FDA warnings on the
318 possible increased risk of serious UTI associated with SGLT2i, confounding by
319 contraindication is a consideration. Our results provide reassurance regarding the risk of
320 urosepsis associated with this increasingly used drug class; however, considering all
321 available evidence, SGLT2i treatment may not be safer than DPP4i.
322

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Legends to figures

FIGURE 1. Flowchart of study cohort.

DPP4i: dipeptidyl peptidase-4 inhibitors; SGLT2i: sodium-glucose cotransporter 2 inhibitors; 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.

FIGURE 2. Adjusted hazard ratios and 95% confidence intervals of urosepsis associated with sodium-glucose cotransporter 2 inhibitor (SGLT2i) use compared with dipeptidyl peptidase-4 inhibitor (DPP4i) use among patients with type 2 diabetes

Tables

TABLE 1. Baseline characteristics of users of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and their matched users of dipeptidyl peptidase-4 inhibitors (DPP4i)[†]

	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)
Clinical Practice Research Datalink (CPRD)	5,422 (2.6)	5,422 (2.6)
Manitoba	12,074 (5.8)	12,074 (5.8)
Nova Scotia	1,135 (0.5)	1,135 (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 (years) mean ± SD[‡]	63.8 ± 9.5	64.0 ± 9.5
18-35	3,477 (1.7)	3,696 (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	1,983 (1.0)	2,153 (1.0)
Females	86,320 (41.5)	86,413 (41.5)
Calendar year at cohort entry		
2013	325 (0.2)	342 (0.2)
2014	6,990 (3.4)	7,425 (3.6)
2015	51,645 (24.8)	51,141 (24.6)
2016	66,398 (31.9)	66,351 (31.9)

	SGLT2i	DPP4i
	(n=208,244)	(n=208,244)
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 (years) mean ± SD		
<1 year	12.6 ± 6.6	12.6 ± 6.6
1-4.9 years	7,154 (3.4)	7,441 (3.6)
5-10 years	25,214 (12.1)	25,187 (12.1)
>10 years	52,568 (25.2)	52,757 (25.3)
	123,308 (59.2)	122,859 (59.0)
Comorbidities[§]		
Alcohol-related disorders	3,620 (1.7)	3,639 (1.7)
Cancer	21,599 (10.4)	22,094 (10.6)
Myocardial infarction	5,371 (2.6)	5,254 (2.5)
Ischemic stroke	2,465 (1.2)	2,553 (1.2)
Peripheral arterial disease	4,818 (2.3)	4,839 (2.3)
Diabetic retinopathy	5,381 (2.6)	5,512 (2.6)
Diabetic neuropathy	3,951 (1.9)	4,017 (1.9)
Diabetic nephropathy	7,530 (3.6)	7,715 (3.7)
Cystitis	11,577 (5.6)	11,744 (5.6)
Pyelonephritis	1,062 (0.5)	1,082 (0.5)
Stones or urinary tract obstruction	7,263 (3.5)	7,251 (3.5)
Urinary tract infection in the year prior	6,770 (3.3)	6,702 (3.2)
Use of medications^{§,¶}		
Metformin	180,954 (86.9)	180,831 (86.8)
Sulfonylureas	108,623 (52.2)	108,599 (52.1)
Thiazolidinediones	5,193 (2.5)	4,954 (2.4)
Glucagon-like peptide-1 (GLP1) receptor agonists	8,585 (4.1)	8,585 (4.1)

	SGLT2i	DPP4i
	(n=208,244)	(n=208,244)
Alpha-glucosidase inhibitors	3,043 (1.5)	2,932 (1.4)
Meglitinides	4,709 (2.3)	4,695 (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	6,159 (3.0)	6,046 (2.9)
Digitalis-like agents	2,604 (1.3)	2,688 (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 (UTI)		
From 90 days prior to or on cohort entry	23,464 (11.3)	23,324 (11.2)
From 91 to 365 days prior to cohort entry	51,213 (24.6)	51,034 (24.5)
Number of different classes of non-antidiabetic drugs [¶]		
0-1	8,478 (4.1)	8,650 (4.2)
2-5	66,064 (31.7)	66,670 (32.0)
≥6	133,702 (64.2)	132,924 (63.8)
Health care use[§]		

	SGLT2i	DPP4i
	(n=208,244)	(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	2,284 (1.1)	2,356 (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)

† Data are presented as n (%) unless otherwise specified.

‡ SD, standard deviation.

§ Unless otherwise specified, comorbidities were assessed in the 3 years prior to cohort entry, and medications and healthcare use were assessed in the year prior to cohort entry.

¶ In Saskatchewan, Quebec, and the CPRD, the Anatomical Therapeutic Chemical (ATC) codes are unavailable; the Number of non-antidiabetic drug class were defined using BNF code (CPRD), AHFS classification (Quebec), number of distinct medication in the covariates list (Saskatchewan).

Numbers may not add up because of small cells suppressed and replace by 3 due to privacy restrictions.

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

Characteristics^{†,‡}	SGLT2i (n=5,422)	DPP4i (n=5,422)
Body mass index (kg/m²)		
<30	1,529 (28.2)	1,730 (31.9)
≥30	3,875 (71.5)	3,665 (67.6)
Unknown	18 (0.3)	27 (0.5)
Smoking status		
Never	s [§]	2,121 (39.1)
Ever	3,249 (59.9)	3,294 (60.8)
Unknown	s [§]	7 (0.1)
Race		
White	3,955 (72.9)	3,894 (71.8)
Other	534 (9.8)	602 (11.1)
Unknown	933 (17.2)	926 (17.1)
Blood pressure		
Diastolic blood pressure (DBP) <90 and systolic blood pressure (SBP) <140	3,506 (64.7)	3,563 (65.7)
DPB ≥90 or SBP ≥140	1,908 (35.2)	1,846 (34.0)
Unknown	8 (0.1)	13 (0.2)
Glomerular filtration rate (mL/min/1.73m²)		
<60	284 (5.2)	531 (9.8)
≥60	5,131 (94.6)	4,884 (90.1)
Unknown	7 (0.1)	7 (0.1)
Hemoglobin A1c (%)		
≤7	181 (3.3)	230 (4.2)
7.1-8	1,048 (19.3)	1,075 (19.8)
>8	4,157 (76.7)	4,077 (75.2)

Characteristics^{†,‡}	SGLT2i (n=5,422)	DPP4i (n=5,422)
Unknown	36 (0.7)	40 (0.7)

† Data are presented as n (%).

‡ Assessment of body mass index, smoking status, blood pressure, eGFR and hemoglobin A1c was based on the last measurement before study cohort entry, and race was assessed ever before.

§ Values suppressed due to privacy restrictions are presented as s.