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Sodium-Glucose Cotransporter-2 Inhibitor Use and the Risk of Acute Kidney Injury in Older Adults in Routine Clinical Practice: A Population-Based Cohort Study

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Abstract

Regulatory agencies warn about acute kidney injury (AKI) risk following sodium-glucose cotransporter-2 (SGLT2) inhibitor use. This population-based retrospective cohort study in Ontario, Canada quantified the 90-day AKI risk in older adults who were newly dispensed either SGLT2 inhibitors or dipeptidyl peptidase-4 (DPP4) inhibitors in an outpatient setting between 2015 and 2017. Risk ratios (RR) were obtained using modified Poisson regression and risk differences using binomial regression. Relative to new use of a DPP4 inhibitor, initiation of an SGLT2 inhibitor was associated with a lower 90-day risk of a hospital encounter with AKI: 216 events in 19,611 patients (1.10%) versus 388 events in 19,483 patients (1.99%); weighted RR 0.79 (95% confidence interval 0.64 to 0.98). In routine care of older adults, new SGLT2 inhibitor use was associated with lower risk of AKI. Together with previous evidence, these findings suggest that regulatory warnings about AKI risk with SGLT2 inhibitors may be unwarranted.

Keywords

Administrative data, retrospective cohort study, SGLT2 inhibitors, type 2 diabetes, acute kidney injury

Summary for Lay Audience

The number of drugs used to treat patients with diabetes has grown significantly. Sodium-glucose costransporter-2 (SGLT2) inhibitors are an example of a new class of diabetes medications that help lower blood sugar by promoting its loss in the urine. Despite the ability of SGLT2 inhibitors to lower blood sugar, the US Food and Drug Administration (FDA) and Health Canada have issued safety warnings of the link between SGLT2 inhibitors and kidney injury. These warnings were made based on individual case reports and case series. We used health administrative databases to examine elderly patients with diabetes who were prescribed SGLT2 inhibitors and we examined kidney injury. We found that, in the first 90 days after being prescribed an SGLT2 inhibitor, patients had lower risk of developing kidney injury, compared to a similar group of people taking different diabetes medications. We suggest that the safety warnings and concerns about SGLT2 inhibitors and the risk of kidney injury might be revisited.

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List of Abbreviations

ACE = angiotensin-converting–enzyme

ACEi = angiotensin-converting-enzyme inhibitor

ACR = albumin-to-creatinine ratio

AKI = acute kidney injury

ARB = angiotensin-receptor blocker

ATT = average treatment effect in the treated

CI = confidence interval

CIHI = Canadian Institute for Health Information

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration

DAD = Discharge Abstract Database

DPP4 = dipeptidyl peptidase-4

DPP4i = dipeptidyl peptidase-4 inhibitor

DVT/PE = deep vein thrombosis and pulmonary embolism

ED = emergency department

eGFR = estimated glomerular filtration rate

ESRD = end-stage renal disease

GLP1 = glucagon-like peptide-1

FDA = Food and Drug Administration

GP/FP = general practice/family practice

HbA1c = glycated hemoglobin

HR = hazard ratio

ICD-10 = International Classification of Diseases, Tenth Revision

IPDB = ICES Physician Database

IPTW = inverse probability of treatment weighting

IQR = interquartile range

KDIGO = Kidney Disease: Improving Global Outcomes

KFRE = kidney failure risk equation

LHIN = Local Health Integration Network

NACRS = National Ambulatory Care Reporting System

NSAID = nonsteroidal anti-inflammatory drug

ODB = Ontario Drug Benefit

OHIP = Ontario Health Insurance Plan

OLIS = Ontario Laboratories Information System

OR = odds ratio

RCT = randomized controlled trial

RD = risk difference

RECORD = REporting of studies Conducted using Observational Routinely-collected health Data

RECORD-PE = REporting of studies Conducted using Observational Routinely-collected health Data for Pharmacoepidemiology

RPDB = Registered Persons Database of Ontario

RR = risk ratio

SCr = serum creatinine

SD = standard deviation

SGLT2 = sodium-glucose cotransporter-2

SGLT2i = sodium-glucose cotransporter-2 inhibitor

Chapter 1

1 Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors (e.g. canagliflozin, empagliflozin and dapagliflozin) are a class of diabetes medications used to treat type 2 disease. Although only newly available in Ontario since 2015 (1,2), their popularity is growing: in 2016, an estimated 2 million prescriptions for SGLT2 inhibitors were filled in Canada alone (3). In addition to effectively lowering blood glucose levels, SGLT2 inhibitors are only one of two new diabetes therapy drug classes with evidence of cardiovascular risk reduction in patients with diabetes (4–7).

SGLT2 inhibitors have however been linked with adverse outcomes. In October 2015 and June 2016 Health Canada and the United States Food and Drug Administration (FDA) issued safety warnings about the risk of acute kidney injury (AKI) after initiation of canagliflozin and dapagliflozin, based on case reports and case series (summarized in Appendix A) (8,9). These safety warnings led to changes in the drug product monographs to include information about the risk of AKI shortly after initiation.

There is a plausible mechanism for SGLT2 inhibitor-induced AKI. By interfering with the co-uptake of glucose and sodium in the proximal nephron, SGLT2 inhibitors can increase sodium delivery to the distal nephron, which can result in afferent arteriole vasoconstriction and an associated reduction in estimated glomerular filtration rate (eGFR) (10–14). Even so, recent clinical trials and population-based studies suggest either no increase or a decrease in AKI risk after SGLT2 inhibitor initiation (4–7,10,15–17).

We conducted a population-based cohort study of older adults with diabetes newly dispensed an SGLT2 inhibitor or a dipeptidyl peptidase-4 (DPP4) inhibitor (a comparator drug also used to manage diabetes) in an outpatient setting. We conducted this study to better understand the association between SGLT2 inhibitor use and the 90-day risk of a hospital encounter (emergency department (ED) visit or hospital admission) for AKI in routine clinical practice.

Chapter 2

2 Literature Review

2.1 Diabetes burden and SGLT2 inhibitor prescribing

According to the Canadian Chronic Disease Surveillance System, approximately 3 million Canadians were living with diagnosed diabetes in 2014 (18). Patients with diabetes are at risk of a number of complications including cardiovascular disease, end-stage renal disease (ESRD) and lower-limb amputations (19), and they face increased mortality (20,21). Patients with diabetes also incur high health care costs. (Rosella et al. showed that patients with diabetes cost the Canadian healthcare system about $16,000, compared with people without diabetes costing the healthcare system $6,000, over an eight-year period (22)).

Over the last several years, there have been a number of drugs developed to reduce blood sugars and diabetes related complications. SGLT2 inhibitors including canagliflozin, empagliflozin and dapagliflozin have been available on the Ontario Drug Benefits Formulary since 2015 and 2016 (2). Standard daily drug doses for each of these drugs are listed in Appendix B. These drugs are also available as combination pills with other oral hypoglycemic medications (2). In 2016, an estimated 2 million prescriptions for SGLT2 inhibitors were filled in Canada alone, as well as 4.4 million prescriptions in the United States (3,23).

2.2 Mechanism of SGLT2 inhibitor glucose lowering

SGLT2 inhibitors inhibit sodium-glucose cotransporters, located in the proximal convoluted tubule of the kidney nephron, from reabsorbing glucose into the bloodstream (24). Inhibition of sodium-glucose cotransporters causes higher urinary concentrations of glucose, and can lower the concentration of serum glucose (25).

2.3 SGLT2 inhibitors and the kidneys

Acute kidney injury (AKI) is a serious condition characterized by a sudden increase in the concentration of serum creatinine (SCr) and a decrease in urine output (26). AKI ranges in severity. According to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline, AKI can be diagnosed if any of the following criteria is met: (i) an increase in SCr $\geq$ 0.3 mg/dl ($\geq$ 26.5 μmol/l within 48 hours; or (ii) an increase in SCr to $\geq$ 1.5 times a baseline measurement within 7 days; or (iii) a reduction in urine output < 0.5 ml/kg/h for 6 hours (27).

According to the International Society of Nephrology, there are more than 13 million cases of AKI ever year (28). The presence of type 2 diabetes increases the risk of AKI (29,30). In addition, elderly patients are more likely to present with AKI (31,32), AKI is associated with a higher risk of all-cause mortality and ESRD, and higher healthcare costs (31,33,34). Therefore efforts to lower the risk of AKI in type 2 diabetes is vital.

The mechanism of AKI following the use of an SGLT2 inhibitor is not entirely understood with a number of mechanisms proposed (35–37). Heerspink *et al.* suggest that by interfering with the co-uptake of glucose and sodium in the proximal nephron, SGLT2 inhibitors can increase sodium delivery to the distal nephron, which can result in afferent arteriole vasoconstriction and an associated reduction in eGFR (10–14).

There are several proposed mechanisms to explain a potential protective effect of SGLT2 inhibitors and the risk of acute and chronic renal adverse events. Through their mechanism of action of decreasing glucose reabsorption at the kidneys, SGLT2 inhibitors may suppress renal swelling (38,39), inflammation (40) and may also affect energy metabolism in renal cells to improve efficiency (41). Since SGLT2 inhibitors also facilitate lower sodium reabsorption at the kidneys, these drugs can have beneficial effects that potentially may involve restoring tubuloglomerular feedback, oxygen consumption changes and improving renal anemia (42). Lastly, the beneficial systemic effects of SGLT2 inhibitors, such as reductions in body weight, blood pressure and insulin levels, can lead to renal protection. A reduction in body weight can lower

albuminuria and reduced insulin levels can lower the risk of hyperinsulinemia which can damage the kidneys (42,43).

2.4 Search strategy and quality assessment of prior studies

We conducted a literature review to identify prior studies that examined the association between SGLT2 inhibitor use and AKI. Both MEDLINE (1946 to July 2019) and EMBASE (1947 to July 2019) were searched, along with the first 5 pages of Google, in order to review the grey literature. For both databases, the final search strategy consisted of keywords such as acute kidney injury, acute kidney failure and sodium glucose cotransporter 2 inhibitor. Full information about the literature search strategies can be found in Appendix C.

Inclusion and exclusion criteria were developed *a priori.* Studies were included if they met the following criteria: (i) full-text English article, (ii) randomized controlled trial (RCT) or cohort study, (iii) more than 1,000 patients, (iv) reported AKI as an outcome (AKI could be assessed in any manner such as diagnostic codes for an adverse event or actual SCr laboratory values). Studies were not included if they (i) were cross-sectional, commentaries, editorials, letters, methodology papers, or narrative review articles, (ii) had a sample size that was less than 1,000 patients, and (iii) did not report the outcome of AKI.

2.5 Summary of previous literature

Seven studies were identified as meeting our inclusion criteria. Four of these studies were RCTs and three were cohort studies. Overall, studies showed no risk or a reduction in both the acute and chronic renal adverse events amongst SGLT2 inhibitor users (summarized in Table 1). Our assessment of study quality using the Modified Downs and Black quality checklist (44) determined that three were of fair quality (16,16,18), one was of good quality (25), and three were of excellent quality (27,28,28).

2.6 SGLT2 inhibitors and acute kidney injury

Two RCTs included in this literature review specifically intended to primarily assess efficacy in terms of renal outcomes associated with SGLT2 inhibitor use: CANVAS-R and the CREDENCE trial (5,7). The CREDENCE trial, published earlier this year, had a primary renal outcome and found that a safety endpoint of AKI was non-significantly lower in the arm randomized to canagliflozin compared with placebo (hazard ratio (HR) 0.85 (95% CI 0.64-1.13)). The primary composite renal outcome of doubling of SCr, ESRD, renal death, and cardiovascular death occurred less frequently among patients randomized to canagliflozin versus placebo (HR 0.70 (95% CI 0.59-0.82)).

Every study included in the literature review consistently showed that there was no increased risk of AKI amongst SGLT2 inhibitor users. However, all four of the major RCTs included in our review showed an initial drop in eGFR within 3 months of the initiation of an SGLT2 inhibitor (4–7,10). This drop in eGFR suggests a hemodynamic effect similar to the one observed following the initiation of angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) (45,46). This initial drop was reported to be reversible.

Additionally, case reports identified through the FDA adverse event reporting system database identified a signal of AKI following SGLT2 inhibitor use (47).

Table 1. Literature review of 7 published studies describing adverse renal events associated with SGLT2 inhibitor use compared with other classes of hypoglycemic medications or hypoglycemic medication non-use for the treatment of hyperglycemia

Author	Study Description	Results	Study Limitations	Study Procedure/Exposure Time	Quality Score[b]
Randomized Controlled Trials					
Zinman et al., 2015 (4)	- The EMPA-REG OUTCOME trial consisted of 7,020 patients at 590 sites in 42 countries - Adult patients ≥18 years of age with type 2 diabetes and established cardiovascular disease were randomized to receive placebo, 10 mg of empagliflozin or 25 mg of empagliflozin	- 2,333 patients received placebo and 4,687 patients received empagliflozin (mean age 63 years in both groups) - Early worsening of eGFR by about 3 ml/min/1.73m^2 within the first 12 weeks, but sustained function over time (10)[a] - The percentage of patients with AKI was lower in the empagliflozin groups compared to placebo - Doubling of the SCr level occurred less among empagliflozin users [HR 0.56 (95% CI 0.39–0.79)] (10)[a] - The risk of renal-	- Renal findings may not be generalizable to patients without established cardiovascular disease - Kidney endpoints were exploratory (AKI was not one of the primary outcomes of interest)	- Patients underwent a 2 week, open-label, placebo run-in period - Patients either took empagliflozin or placebo once daily for a median duration of treatment of 2.6 years - Additional follow-up visit 30 days after the end of treatment - The median observation time was 3.1 years	28

		replacement therapy was lower amongst empagliflozin users [HR 0.45 (95% CI 0.21-0.97)] (10)[a]			
Neal et al., 2017 (5)	- The CANVAS program consisted of integrated data from two trials (CANVAS & CANVAS-R) involving 10,142 participants from 667 centers in 30 countries - Adult patients ≥30 years of age with type 2 diabetes and high cardiovascular risk were randomized to receive placebo, 100 mg canagliflozin or 300 mg of canagliflozin in CANVAS; placebo, 100 mg of canagliflozin with an option to increase to 300 mg of canagliflozin starting at week 13 in CANVAS-R	- 4,347 patients received placebo and 5,795 patients received canagliflozin (mean age of 63 years in both groups) - No higher risk of AKI following canagliflozin use versus placebo - The composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes occurred less frequently in patients receiving canagliflozin [HR 0.60 (95% CI 0.47 to 0.77)]	- Moderate number of events for important outcomes - AKI was not one of the primary outcomes of interest	- Patients underwent a 2-week, single-blind, placebo run-in period - The median follow-up was 126.1 weeks -71.4% of CANVAS-R patients in the canagliflozin treatment group had the dose increased to 300mg - The urinary ACR was measured every 26 weeks in CANVAS-R and at week 12 and annually thereafter in CANVAS - SCr with eGFR measurements were performed at least every 26 weeks in both trials	27
Wiviott et al., 2018 (6)	- The DECLARE–TIMI 58 trial consisted of 17,160 participants at 882 sites in 33 countries - Adult patients ≥40 years of age with type 2 diabetes and who had or were at risk	- 8,578 patients received placebo and 8,582 patients received dapagliflozin (mean age 64 years in both groups) - AKI occurred less frequently in the	- Renal findings may not be generalizable to patients not at risk for atherosclerotic cardiovascular	- Patients underwent a 4-to-8-week, single-blind run-in period during which they received placebo, and blood and urine testing was performed - Patients returned for	28

	for atherosclerotic cardiovascular disease were randomized to receive 10 mg of dapagliflozin or matching placebo	dapagliflozin group compared with placebo [HR 0.69 (95% CI 0.55 to 0.87)] - The renal composite outcome of a sustained decrease of 40% or more in estimated glomerular filtration rate (eGFR), new ESRD, or death from renal or cardiovascular causes occurred less frequently in dapagliflozin users [HR 0.76 (95% CI 0.67 to 0.87)]	disease - AKI was not one of the primary outcomes of interest	follow-up every 6 months - Patients were contacted by telephone every 3 months between in-person visits - Median follow-up time was 4.2 years	
Perkovic et al., 2019 (7)	- The CREDENCE trial consisted of 4,401 participants with type 2 diabetes and albuminuric chronic kidney disease - Adult patients ≥30 years of age were randomized to receive 100 mg of canagliflozin or matching placebo	- 2,199 patients received placebo and 2,202 patients received canagliflozin (mean age 63 years in both groups) - Initial decline in eGFR within the first 3 months of initiation of canagliflozin - There was no difference in the risk of AKI between groups [HR 0.85 (95% CI 0.64 to 1.13)] - The primary composite outcome of ESRD (dialysis, transplantation,	- Findings about AKI may not be generalizable to those without established albuminuric chronic kidney disease - Trial was stopped early which might have limited the power for the AKI outcome	- Patients underwent a 2-week, single-blind, placebo run-in period - Patients were required to be receiving a stable dose of an ACE inhibitor or ARB for at least 4 weeks before randomization - Patients received 100mg once daily of canagliflozin or matching placebo with the use of randomly permuted blocks, with stratification according to the category of eGFR at screening	25

		or a sustained eGFR of <15 ml per minute per 1.73 m^2), a doubling of the SCr level, or death from renal or cardiovascular cause occurred less frequently among canagliflozin users [HR 0.70 (95% CI 0.59 to 0.82)]		- Follow-up occurred at weeks 3, 13, and 26 and then alternated between telephone calls and in-clinic visits at 13-week intervals - Median follow-up time of 2.62 years	
Population-Based Studies					
Nadkarni et al., 2017 (15)	- Retrospective cohort study using data from the Mount Sinai chronic kidney disease registry, between January 2014 and December 2016, and the Geisinger Health System cohort, between January 2013 and February 2017, in the United States, to compare SGLT2 inhibitor users versus nonusers	- Mount Sinai cohort (mean age 63 years) - SGLT2 inhibitor users: n=372; nonusers: n=372 - Geisinger cohort (mean age 58 years) - SGLT2 inhibitor users: n=1,207; nonusers: n=1,207 - In the Mount Sinai cohort, the adjusted hazards of AKI_{KDIGO} were 60% lower in SGLT2 inhibitor users compared to nonusers [adjusted HR 0.40 (95% CI 0.20 to 0.70)] - In the Geisinger cohort, the adjusted hazards of AKI_{KDIGO} was not	- In the Mount Sinai cohort, users and nonusers were not well matched on race, HbA1c levels, thiazide diuretics, and metformin use - Urine ACR measurements were missing in 85% of the Mount Sinai cohort - Residual confounding and confounding by indication may	- Only patients with type 2 diabetes and available SCr measurements were included - Exposure was a new prescription for canagliflozin, empagliflozin or dapagliflozin - Follow-up time was similar in SGLT2 inhibitor users and nonusers (458 vs. 439 days)	16

		different between SGLT2 inhibitor users and nonusers [adjusted HR 0.60 (95% CI 0.40 to 1.10)]	likely be present		
Cahn et al., 2018 (16)	- Retrospective cohort study using claims data from Israel to compare patients initiated on an SGLT2 inhibitor or DPP4 inhibitor between April 2015 to June 2017	- SGLT2 inhibitor users: n=6,418 (mean age 62 years); DPP4 inhibitor users: n=5,604 (mean age 64 years) - The risk of AKI [OR 0.47 (95% CI 0.27 to 0.80)] was lower in patients initiating an SGLT2 inhibitor versus a DPP4 inhibitor	- May be selection bias in patients who initiated an SGLT2 inhibitor or DPP4 inhibitor - Since canagliflozin is not available in Israel, only patients who initiated empagliflozin or dapagliflozin were included - Residual confounding may be present	- Only dapagliflozin and empagliflozin are available in Israel - The index date was defined as the first date of purchase of SGLT2 inhibitor or DPP4 inhibitor - At least two consecutive prescriptions within 120 days on the index date was required for study inclusion - The first SCr measurement within 2 to 24 weeks after index was defined as the follow-up measurement - Follow-up time was 24 weeks following the index date	16
Ueda et al., 2018 (17)	- Retrospective cohort study using data from nationwide health and administrative registers in Sweden and Denmark to compare patients that newly initiated an SGLT2	- SGLT2 inhibitor users: n=17,213; GLP1 receptor agonists: n=17,213 (mean age 61 years after matching) - No increase in the risk of AKI [HR 0.69 (95%CI	- The use of canagliflozin was rare among SGLT2 inhibitor users - Medication compliance might	- The date of filling the first new prescription was considered the index date - Patients were classified as exposed if prescriptions were refilled before the estimated end date of the	18

	inhibitor or a GLP1 receptor agonist between July 2013 to December 2016	0.45 to 1.05)] in SGLT2 inhibitor users compared to GLP1 receptor agonist users	bias the results of this study towards the null - The codes for AKI have not been validated which may have led to outcome misclassification - Residual confounding may be present	most recent prescription - Median follow-up time ranged between 270 and 274 days	

Abbreviations: ACE= angiotensin-converting–enzyme, ACR= albumin-to-creatinine ratio, AKI= acute kidney injury, ARB= angiotensin-receptor blocker, CI= confidence interval, DPP4= dipeptidyl peptidase-4, eGFR = estimated glomerular filtration rate, ESRD= end-stage renal disease, GLP1= glucagon-like peptide-1, HbA1c= glycated hemoglobin, HR= hazard ratio, KDIGO= kidney disease improving global outcomes, OR= odds ratio, SCr= serum creatinine, SGLT2= sodium-glucose cotransporter-2

[a]Wanner et al. presented the results of a prespecified secondary objective of the EMPAREG-OUTCOME trial, which was to examine the effects of empagliflozin on microvascular outcomes.

[b]We evaluated the quality of studies using the Modified Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies. We gave all studies a score from 0 to 27, grouped into the following four quality levels: excellent (26 to 28), good (20-25), fair (15-19) and poor (14 or less).

Chapter 3

3 Rationale and Research Questions

3.1 The need for research

Many previous studies exploring the link between SGLT2 inhibitors and AKI have been RCTs and may not represent routine clinical practice. In the real-world, for example, patients in routine clinical practice are generally monitored less often and have more comorbidity than patients in clinical trials (48). There may also be low rates of AKI among patients well-managed in a trial setting who receive regimented safety monitoring that is not attainable in real-world clinical practice. This may result in a potential underestimate of relative and absolute safety, as has been observed with limb amputation in some studies (17,49). In addition, in the real-world, clinicians are increasingly educated on appropriate SGLT2 inhibitor use in routine clinical practice which includes counseling patients not to take the drug during an acute illness (50). We conducted this study to better understand the association between SGLT2 inhibitor use and the 90-day risk of a hospital encounter (ED visit or hospital admission) for AKI in routine clinical practice.

3.2 Research questions and hypothesis

3.2.1 Primary Research Question

Does a group of older adults with diabetes newly dispensed SGLT2 inhibitors compared with a group of patients newly dispensed DPP4 inhibitors, who have similar indicators of baseline health, have an altered 90-day risk of a hospital encounter with AKI?

3.2.2 Secondary Research Questions

1) Does a group of older adults with diabetes newly dispensed SGLT2 inhibitors compared with a group of patients newly dispensed DPP4 inhibitors, who have similar indicators of baseline health, have an altered 90-day risk of hospitalization with AKI?

2) Does a group of older adults with diabetes newly dispensed SGLT2 inhibitors compared with a group of patients newly dispensed DPP4 inhibitors, who have similar indicators of baseline health, have an altered 90-day risk of a hospital encounter with moderate to severe AKI?

3) Does a group of older adults with diabetes newly dispensed SGLT2 inhibitors compared with a group of patients newly dispensed DPP4 inhibitors, who have similar indicators of baseline health, have an altered 90-day risk of AKI restricted to the outpatient setting?

4) Does a group of older adults with diabetes newly dispensed SGLT2 inhibitors compared with a group of patients dispensed DPP4 inhibitors, who have similar indicators of baseline health, have an altered 90-day risk of AKI in all settings (outpatient, emergency room, in-patient hospitalization)?

Regulatory warnings and recent literature are conflicting, as the warnings describe a higher risk of AKI after SGLT2 inhibitor initiation, but recent literature showed no difference in risk or lower risk of AKI after SGLT2 inhibitor initiation. Therefore, we are uncertain of the direction of association between SGLT2 inhibitor initiation and the risk of AKI.

Chapter 4

4 Methods

4.1 Study design and setting

We conducted a population-based retrospective cohort study of older adults aged ≥66 years in Ontario between July 1, 2015 and September 30, 2017 using linked healthcare databases in Ontario, Canada. Ontario has >14 million residents, 17% of whom are aged 65 years or older (51). Ontario residents are covered by publicly-funded, universal health insurance. The Ontario Health Insurance Plan (OHIP) covers physician and hospital services for all Ontario residents. Those aged 65 years and older receive prescription drug coverage through the Ontario Drug Benefit (ODB) program. Dispensation records for individuals not covered by the ODB program are not available.

Health administrative databases are increasingly being used for population-based studies (52). Administrative database studies allow investigators to study large samples of patients for long follow-up periods and examine outcomes in a routine-care setting. In addition, loss to follow-up is of little concern since emigration from Ontario is less than 0.1% annually (53). We have successfully used these data sources to study associations between a number of drugs and risk of AKI (54–57).

We conducted this study at ICES, a not-for-profit research institute within Ontario. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. We followed reporting guidelines for observational pharmacoepidemiology studies (Appendix D) (58).

4.2 Databases

We used nine health administrative databases to ascertain patient information, drug exposure status, covariate and outcome information. Databases were linked using unique encoded identifiers and analyzed at ICES. We have used a number of these databases in previous pharmacoepidemiologic studies (55–57,59–62).

Ontario Drug Benefit (ODB) Database: The ODB database contains prescription claims data for individuals aged 65 years or older covered through the ODB Program. This database was used to ascertain SGLT2 inhibitor or DPP4 inhibitor exposure status as well as baseline drug use prior to the cohort entry date. We also acquired patient residential status to remove long-term care residents from our cohort.

Registered Persons Database of Ontario (RPDB): We used this database to acquire information on patient demographics (age and sex), as well as income quintiles (based on neighborhood average incomes), and residence location (urban or rural).

ICES Physician Database (IPDB): The IPDB contains information about all physicians in Ontario, including demographics, specialty, and measures of physician activity (billings and workload data). We used this database to acquire information about the prescribing physician's specialty. We also determined the specialty of the physician for the baseline number of general physician visits, cardiologist, ophthalmologist, endocrinologist and nephrologist consults.

Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS) and Same Day Surgery (SDS) Database: CIHI-DAD contains patient-level information on hospitalizations in Ontario. The NACRS database captures information on patient visits to hospital emergency departments or other community-based ambulatory care clinics. The SDS dataset contains patient-level data for day surgery institutions in Ontario. Diagnostic codes are entered into these databases including the International Classification of Diseases, Tenth Revision (ICD-10) codes. We used these databases to ascertain baseline comorbidities in the 5 years prior to the cohort entry date, as well as the number of hospitalizations and

ED visits. We used ICD-10 codes to ascertain our primary outcome of a hospital encounter with AKI.

Ontario Health Insurance Plan (OHIP) Claims Database: The OHIP Claims Database contains information on health care providers' billing claims for inpatient and outpatient services in Ontario, as well as associated diagnoses. We used this data source to ascertain whether patients received dialysis in the one year prior to the cohort entry date (exclusion criteria). We also gathered additional information on baseline comorbidities and healthcare utilization. Further, we used OHIP billing codes in outcome ascertainment to collect information about acute dialysis.

Ontario Laboratories Information System (OLIS): OLIS is an electronic repository that houses laboratory test results beginning in 2007 in hospitals and community laboratories across the province. Since not all laboratories began submitting their data to OLIS simultaneously, we identified geographical areas across Ontario where residents would likely visit a hospital with linked laboratory data (referred to as the laboratory catchment area). We included only Ontarians that resided within these laboratory catchment areas. We used information from OLIS to determine baseline SCr measurements, other baseline laboratory measurements as well as inpatient and outpatient laboratory data for our outcomes.

Ontario Diabetes Dataset (ODD): The ODD contains all individuals within Ontario with any type of non-gestational diabetes. We used this data source to determine duration of diabetes for all individuals in our cohort.

4.3 Patients

We created a cohort of older adults aged ≥66 years in Ontario who were newly dispensed an SGLT2 inhibitor (canagliflozin, empagliflozin or dapagliflozin) or a DPP4 inhibitor (saxagliptin, sitagliptin or linagliptin) between July 1, 2015 (the earliest date of SGLT2 inhibitor coverage by ODB) (2) and September 30, 2017. We chose DPP4 inhibitors as our comparator as they are also a second to third line medication for diabetes (reduces

concerns of confounding by indication) and unlike SGLT2 inhibitors, have no known risk of AKI (63,64). The dispensing date of their first eligible prescription during the accrual period was considered the cohort entry or index date. We limited our cohort to those aged ≥66 years to establish complete medication history and ensure they were not in their first eligibility year for prescription drug coverage (age 65 years), and to those who fell in OLIS catchment areas, using previously published methods (65). We included only Ontarians who resided within these catchment areas to ensure accurate outcome ascertainment, as not all hospital-based laboratories started contributing to OLIS at the same time, and to date, not all contribute. In order to accurately ascertain outcomes for individuals in our cohort, we ensured individuals resided within areas serviced by OLIS, so that they would be receiving SCr tests in hospitals captured in our data sources. We assessed eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (66). Patients were included if their corresponding baseline eGFR value was above 45 mL/min per 1.73 m^2, as SGLT2 inhibitors were contraindicated in Ontario for patients with a lower eGFR during the study period (67). Lastly, to define new use, we required that patients be free of the study drugs for at least 180 days prior to the index date and studied the first such exposure during accrual period.

We excluded: (i) those with a prescription for more than one type of DPP4 inhibitor or SGLT2 inhibitor on the index date to compare mutually exclusive groups; (ii) those residing in long-term care since these individuals are inherently different than the general population in terms of disease and medication management (68); (iii) those discharged from a hospital in the two days prior to the index date, to ensure new outpatient prescriptions since patients who initiate treatment in hospital typically fill ongoing prescriptions on the discharge date or the day after; and (iv) individuals with non-standard daily drug doses for diabetes treatment to ensure applicability to usual prescribing (5mg/day to 300mg/day depending on the drug) (Appendix B) (69). Finally, for patients with multiple eligible prescriptions we restricted to the first eligible one.

4.4 Baseline characteristics

We assessed baseline comorbidities in the five years prior to the cohort entry date (except the Charlson comorbidity index which had a 2-year look back period) and medication use in the 120 days prior to the cohort entry date. Dispensing of other hypoglycemic medications was examined in the 120 days prior to the cohort entry date, on the cohort entry date and in the one year to 120 days prior to the cohort entry date. Health care utilization was assessed in the year prior to the cohort entry date, except for bone mineral density tests, hearing tests, sputum tests, which were all assessed in the 5 years prior to the cohort entry date. Additionally, wound swabs were measured in the 7 days prior to the cohort entry date, and electroencephalography in the 90 days prior to the cohort entry date. We assessed baseline kidney function using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (66) and baseline SCr measurements for the entire cohort, in the one year prior to the cohort entry date. We had no information about race and assumed all patients to be nonblack for the CKD-EPI equation (<5% of the Ontario population is of black race) (70). For individuals with laboratory data available, we also captured serum potassium values, albumin-to-creatinine (ACR) ratio measurements and glycated hemoglobin (HbA1c) in the one year prior to the cohort entry date (see Appendix E for all coding definitions).

4.5 Inverse probability of treatment weighting

We used inverse probability of treatment weighting (IPTW) based on propensity scores to minimize the systematic differences in the measured baseline characteristics of our SGLT2 and DPP4 groups. By using weights based on propensity scores, we created a synthetic population where the distribution of baseline characteristics was independent of their drug exposure status, while retaining data from all included individuals (71).

To do this, we estimated the propensity scores using a multivariable logistic regression model with 97 baseline characteristics (selected because of their association with both the outcome of AKI and type of oral hypoglycemic agent dispensed (see Appendix F for

variables included in the propensity score). We then used weights to estimate the average treatment effect in the treated (ATT), where SGLT2 inhibitors were considered the treated population (72). Patients in the reference group were weighted as [propensity score/(1 - propensity score)], while patients in the exposed group received a weight of 1. This allowed us to create a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group (71,73,74).

The 97 variables used to estimate propensity scores were complete, except for prescriber specialty (<10% missing), rural residence (<0.5% missing) and neighbourhood income quintile (<0.5% missing). Prior to weighting, we classified missing prescriber specialty as a 'missing' category, missing rural status as non-rural, and imputed the third income quintile for missing income status. Emigration from Ontario is less than 0.1% per year and was the only reason for lost follow-up (53).

4.6 Outcomes

4.6.1 Primary outcome

Our primary outcome was a hospital encounter (hospitalization or ED presentation) with AKI, defined by 2012 KDIGO thresholds: ≥50% increase in SCr concentration over baseline, or an absolute increase of at least 27 µmol/L (0.3 mg/dL) or receipt of dialysis for AKI (27). The baseline value was the most recent outpatient SCr value within the past year. We compared this baseline value to the highest hospital-based SCr value in the 90 days following cohort entry. We chose a 90-day follow-up period based on prior evidence showing that SGLT2 inhibitors lead to an eGFR decline soon after drug initiation (7,10).

4.6.2 Secondary outcomes

As secondary outcomes, we assessed hospital admission with AKI, and hospital encounter with moderate to severe AKI (SCr increase meeting KDIGO threshold of stage 2 or more AKI; defined in Appendix G) (27). We also examined evidence of AKI in the outpatient setting, and AKI in any setting (outpatient, in-hospital or ED).

4.7 Additional analyses

We conducted six additional analyses to assess the robustness of our results.

To assess the possibility of surveillance bias, we examined the proportion of patients in both groups who had at least one outpatient SCr measurement during the follow-up period.

To complement analyses examining increases in SCr as a binary outcome, we assessed absolute and relative changes in SCr measurements after drug initiation.

We completed sub-group analyses to understand potential SGLT2 inhibitor-associated risks in vulnerable segments of the population who are at higher risk of AKI (75–81). We examined the association between SGLT2 inhibitor use (versus DPP4 inhibitor use) and the primary outcome, stratified by presence or absence of four characteristics: (1) baseline eGFR <60 mL/min per 1.73 m^2, (2) concurrent ACE inhibitor or ARB use, (3) concurrent diuretic use, and (4) age >80 years (Appendix H).

We performed a survival analysis of the primary outcome within 365 days of follow-up, censoring on death.

We evaluated the 90-day risk of a hospital encounter with bowel obstruction, as a negative control outcome which was not expected to be associated with SGLT2 inhibitor or DPP4 inhibitor use.

We performed an E-value analysis in order to assess how robust our association was to potential unmeasured confounding (82).

4.8 Statistical analyses

We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, NC, USA). DPP4 inhibitors were the referent group for all analyses. Two-tailed *P* values less than 0.05

were considered statistically significant for all outcomes. We present the 95% confidence intervals (CIs) for all primary outcome estimates, which correspond to a level of significance of 0.05. In addition to statistical significance, clinical significance was also considered by including input from practicing physicians.

We compared baseline characteristics between those newly dispensed SGLT2 inhibitors and DPP4 inhibitors using standardized differences, for which a threshold of ≥10% was considered meaningful (83). The standardized difference was chosen because it is less sensitive to sample size, in comparison to hypothesis testing (84), and has been previously used to compare the distribution of baseline characteristics between treatment groups (85–87).

To estimate weighted risk ratios (RRs) and 95% CIs, we used a modified Poisson regression by specifying a generalized linear model assuming a Poisson distribution and log link function with a repeated statement to obtain robust error variances (88). The modified Poisson regression provides estimates of RR for dichotomous outcomes. The clinical interpretation of the RR has more value, when compared with the odds ratio (OR) (88–90). The modified Poisson regression was selected over other models that estimate the RR directly in order to avoid the common convergence issues encountered when using a log-binomial regression model and the conservative results produced from Poisson regression (91–97). To estimate weighted risk differences (RDs) between the groups and 95% CIs, we used binomial regression with an identity link function (92).

To evaluate the effect of SGLT2 inhibitor use on AKI for specific subgroups, we first included an interaction term between our exposure and subgroup indicator in our modified Poisson model. This resulted in an interaction *P* value, which allowed us to assess departure from risk-ratio multiplicativity (98).

To assess absolute and relative changes in SCr measurements after drug initiation, weighted mean differences and 95% CIs were obtained using an ordinary least squares linear regression model with an identity link function. This model was used because we were interested in comparing SCr measurements as a continuous variable (99).

To examine the primary outcome within 365 days of follow-up, we used Cause specific weighted Cox proportional hazards regression, censoring on the competing risk of death to estimate weighted HRs (99). The corresponding 95% CI was obtained using a bootstrap estimator (100). In addition, the proportional hazards assumption was tested by including time dependent covariates in the model and the assumption was not violated. To further explore the competing risk of death, we estimated the subdistributions hazards using a Fine and Gray model treating death as a competing risk (101). However, the applicability of this model when using IPTW has not yet been fully explored in the literature (102). As such, we included this analysis only to explore the potential impact of death in the estimation of AKI within 365 days in SGLT2 users compared to DPP4 users.

In order to assess how robust our association was to potential unmeasured confounding, we performed an E-value analysis to obtain the minimum strength of association that a combination of unmeasured confounders would need to have with both the exposure and outcome to negate the observed results (82,103). The E-value is a measure of a given association's robustness to potential unmeasured confounders (82). We produced a plotted curve using an online E-value calculator that provides the e-value for the point estimate of our primary outcome and for the CI of the primary outcome (104). However, in general with the E-value analysis, caution is warranted when interpreting the E-values as these values are a simplification of the context around the study (i.e. the exposure-outcome association in question, how well all currently measured confounders were accounted for, etc.) (105).

Chapter 5

5 Results

5.1 Cohort characteristics

5.1.1 Unweighted cohort

After exclusions, we identified 19,611 patients newly dispensed an SGLT2 inhibitor and 19,483 patients newly dispensed a DPP4 inhibitor between July 1, 2015 and September 30, 2017 (see Figure 1 for cohort assembly). Baseline characteristics pre- and post-weighting are presented in Table 2. The mean age of the unweighted cohort was 71 years for SGLT2 inhibitor users and 74 years for DPP4 inhibitor users. 48% of DPP4 inhibitor users and 40% of SGLT2 inhibitor users were women. A total of 48% of SGLT2 inhibitor users were dispensed canagliflozin, 37% empagliflozin and 15% dapagliflozin. The median (25^{th}, 75^{th} percentile) doses were 100 (100-300) mg/day for canagliflozin, 10 (10-10) mg/day for empagliflozin, and 10 (5-10) mg/day for dapagliflozin.

Prior to weighting, SGLT2 inhibitor users were more likely to be younger (71 vs. 74 years), more likely to receive their prescription from an endocrinologist (19.3% vs. 7.6%), were less likely to have a prior AKI diagnosis (1.8% vs. 3.6%), were more likely to be taking ACE inhibitors (36.5% vs. 31.5%) and were more likely to have HbA1c levels checked (96.9% vs. 94.4%) than DPP4 users (Table 2). Socioeconomic status was missing for 33 (0.2%) of SGLT2 inhibitor users and 18 (0.1%) of DPP4 inhibitor users. Residential information was not available for 33 (0.2%) SGLT2 inhibitor users and 18 (0.1%) DPP4 inhibitor users. In addition, prescriber information was unavailable for 1,261 (6.5%) of DPP4 inhibitor users and 1,091 (5.6%) of SGLT2 inhibitor users.

5.1.2 Weighted cohort

The mean age was 71 years and 40% were women for both SGLT2 inhibitor users and DPP4 inhibitor users. Baseline SCr was measured a median of 28 days (IQR 9-89) prior for SGLT2 inhibitor users and 23 (8-81) days for DPP4 inhibitor users. After weighting,

groups remained imbalanced on eGFR categories, but where considered as a continuous variable, there was no statistical or clinically meaningful difference between groups. Overall 17% of the cohort had a weighted baseline eGFR between 45 and 60 mL/min per 1.73 m^2.

Over 120 measured baseline characteristics were similar between SGLT2 inhibitor users and DPP4 inhibitor users, including diabetes parameters, diabetes medications and healthcare utilization measures. Prescriber information was missing for 1,131 (5.7%) DPP4 inhibitor users and 1,091 (5.6%) of SGLT2 inhibitor users. General practitioners were the most frequent prescribers (65%) for both SGLT2 inhibitors and DPP4 inhibitors (Table 2).

5.2 Main analysis

5.2.1 Primary outcome

Relative to new DPP4 inhibitor use, new SGLT2 inhibitor use was associated with a lower 90-day risk of a hospital encounter with AKI: 216 events in 19,611 patients (1.10%) versus 388 events in 19,483 patients (1.99%); weighted RR 0.79 (95% CI 0.64 to 0.98), p-value 0.04; weighted RD -0.29% (95% CI -0.57% to -0.01%) (Table 3).

5.2.1 Secondary outcomes

SGLT2 inhibitor use was associated with a lower 90-day risk of hospitalization with AKI: 149 events in 19,611 patients (0.76%) versus 291 events in 19,483 patients (1.49%); weighted RR 0.73 (95% CI 0.56 to 0.95), p-value 0.02; weighted RD -0.28% (95% CI -0.53% to -0.03%) (Table 2). The point estimate for the risk of hospital encounter with moderate to severe AKI following SGLT2 inhibitor use compared with DPP4 inhibitor use was similar to the primary outcome analysis. However with fewer events, there was less precision in the estimate and the between-group difference was not significantly different: 44 events in 19,611 patients (0.22%) versus 74 events in 19,483 patients (0.38%) events; weighted RR 0.81 (95% CI 0.49 to 1.33), p-value 0.40. There was no significant difference in the risk of AKI in an outpatient setting: 573 events in

19,611 patients (2.92%) versus 609 events in 19,483 patients (3.13%); weighted RR 1.13 (95% CI 0.95 to 1.33), p-value 0.16 and AKI in all settings: 716 in 19,611 patients (3.65%) versus 837 events in 19,483 patients (4.30%) events; weighted RR 1.06 (95% CI 0.92 to 1.22), p-value 0.42 (Table 3).

5.3 Additional analyses

Over a 90-day follow-up, SGLT2 inhibitor users were more likely to have at least one SCr measurement in the outpatient setting compared with DPP4 inhibitor users [10,619 (54.2%) of SGLT2 inhibitor users and 9,602 (49.3%) of DPP4 inhibitor users, p-value < 0.01 (Appendix I)].

The change in SCr concentration in follow-up compared to the baseline value for SGLT2 inhibitor users and DPP4 inhibitor users is presented in Appendices J and K. SGLT2 inhibitor users, compared with DPP4 inhibitor users, had a slightly greater change in SCr concentration from baseline during follow-up, however the change was not clinically significant [weighted mean between-group difference in absolute terms was 1 µmol/L (95% CI 0.3 to 1.7), p-value < 0.01; and as a percentage was 1.3% (95% CI 0.4 to 2.1), p-value < 0.01].

Baseline eGFR, ACE inhibitor or ARB use, diuretic use, and older age did not significantly modify the association between SGLT2 inhibitor (versus DPP4 inhibitor) use and the risk of AKI (*P* values for interaction ranged from 0.28-0.83) (Figure 2).

Over a 365-day follow-up period, SGLT2 inhibitor use was associated with a lower risk of hospital encounter with AKI: 2,666 events in 19,611 patients (13.6%) versus 3,712 events in 19,483 patients (19.1%), 172 versus 208 weighted events per 1,000 person-years, respectively; HR 0.83 (95% CI 0.78 to 0.89) (Appendix L). A similar result was observed when death was treated as a competing risk.

A significant difference in hospital encounters with bowel obstruction between SGLT2 inhibitor users and DPP4 inhibitor users was neither expected nor observed: 20 events in

19,611 patients (0.10%) versus 36 events in 19,483 patients (0.18%); weighted RR 1.00 (95% CI 0.49 to 2.06), p-value 1.00 (Appendix M).

The E-values for the relative risk and lower confidence bound for the primary outcome were 1.83 and 1.14, respectively, indicating the amount of unmeasured confounding that would be needed to bias the observed association to the null (Appendix N).

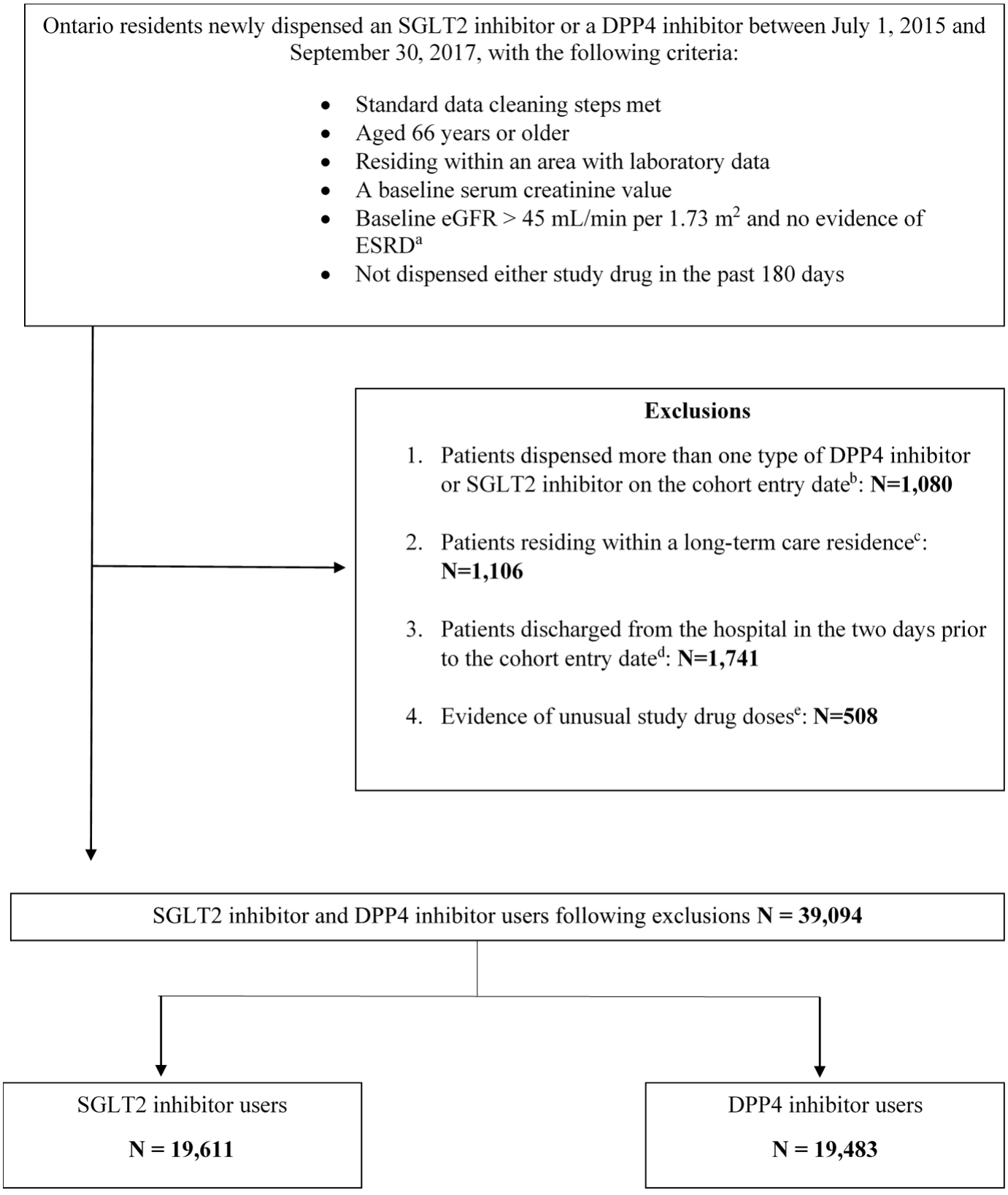

Figure 1. Cohort assembly for patients in the SGLT2 inhibitor user group and the comparator DPP4 inhibitor user group

[a]ESRD defined as evidence of previous dialysis or renal transplant; [b]To ensure two mutually exclusive groups; [c]Individuals are inherently different than the general population in terms of medication management; [d]To ensure new outpatient prescriptions; [e]To ensure applicability to usual prescribing

Table 2. Baseline characteristics of older adults with type 2 diabetes newly dispensed SGLT2 inhibitors (canagliflozin, dapagliflozin or empagliflozin) and DPP4 inhibitors (saxagliptin, sitagliptin or linagliptin) in Ontario, Canada (2015-2017)

Characteristic[a]	Observed data No. (%) of patients			Weighted data[b] No. (%) of patients		
	SGLT2 inhibitors (*n* = 19,611)	DPP4 inhibitors (*n* = 19,483)	Standardized Difference[c] (%)	SGLT2 inhibitors (*n* = 19,611)	DPP4 inhibitors (*n* = 19,775)	Standardized Difference[c] (%)
SGLT2 inhibitor type						
Canagliflozin	9,404 (48.0)					
Empagliflozin	7,311 (37.3)					
Dapagliflozin	2,896 (14.8)					
DPP4 inhibitor type						
Sitagliptin		13,086 (67.2)				
Linagliptin		4,726 (24.3)				
Saxagliptin		1,671 (8.6)				
Demographics						
Age, year, mean ± SD	71.4 ± 4.86	74.1 ± 6.3	47	71.4 ± 4.9	71.4 ± 5.0	1
Age, year, median (IQR)	70 (68 to 74)	73 (69 to 78)	43	70 (68 to 74)	70 (68 to 74)	1
66-74	15,017 (76.6)	11,415 (58.6)	39	15,017 (76.6)	15,224 (77.0)	1
75-84	4,249 (21.7)	6,586 (33.8)	27	4,249 (21.7)	4,153 (21.0)	2
85+	345 (1.8)	1,482 (7.6)	28	345 (1.8)	398 (2.0)	1
Women	7,903 (40.3)	9,325 (47.9)	15	7,903 (40.3)	8,104 (41.0)	1
Rural Residence[d]	2,192 (11.2)	2,088 (10.7)	2	2,192 (11.2)	2,423 (12.3)	3
Year of cohort entry						
2015	3,571 (18.2)	4,260 (21.9)	9	3,571 (18.2)	3,187 (16.1)	6
2016	8,060 (41.1)	9,153 (47.0)	12	8,060 (41.1)	8,940 (45.2)	8

2017	7,980 (40.7)	6,070 (31.2)	20	7,980 (40.7)	7,647 (38.7)	4
Neighbourhood income quintile[e]						
1 (low)	4,350 (22.2)	4,566 (23.4)	3	4, 350 (22.2)	4,397 (22.2)	0
2	4236 (21.6)	4,390 (22.5)	2	4,236 (21.6)	4,328 (21.9)	1
3	4,011 (20.5)	3,953 (20.3)	0	4,044 (20.6)	4,047 (20.5)	0
4	3,679 (18.8)	3,513 (18.0)	2	3,679 (18.8)	3,683 (18.6)	1
5 (high)	3,302 (16.8)	3,043 (15.6)	3	3,302 (16.8)	3,321 (16.8)	0
Local health integration network (LHIN)						
1	36 (0.2)	15 (0.1)	3	36 (0.2)	29 (0.1)	3
2	1,765 (9.0)	1,890 (9.7)	2	1765 (9.0)	1,869 (9.4)	1
3	254 (1.3)	179 (0.9)	4	254 (1.3)	262 (1.3)	0
4	21 (0.1)	19 (0.1)	0	21 (0.1)	23 (0.1)	0
5	1,864 (9.5)	1,954 (10.0)	2	1,864 (9.5)	1,797 (9.1)	1
6	2,121 (10.8)	2,696 (13.8)	9	2,121 (10.8)	2,162 (10.9)	0
7	1,774 (9.0)	1,852 (9.5)	2	1,774 (9.0)	1,873 (9.5)	2
8	3,441 (17.5)	3,332 (17.1)	1	3,441 (17.5)	3,167 (16.0)	4
9	4,897 (25.0)	4,218 (21.6)	8	4,897 (25.0)	5,058 (25.6)	1
10	967 (4.9)	751 (3.9)	5	967 (4.9)	1,019 (5.2)	1
11	290 (1.5)	345 (1.8)	2	290 (1.5)	278 (1.4)	1
12	996 (5.1)	813 (4.2)	4	996 (5.1)	1,00 (5.1)	0
13	825 (4.2)	984 (5.1)	4	825 (4.2)	874 (4.4)	1
14	360 (1.8)	435 (2.2)	3	360 (1.8)	363 (1.8)	0
Prescriber Speciality						
Cardiologist	413 (2.1)	108 (0.6)	13	413 (2.1)	506 (2.6)	3
Endocrinologist	3,786 (19.3)	1,475 (7.6)	35	3,786 (19.3)	3,574 (18.1)	3
General practitioner	12,798 (65.3)	15,685 (80.5)	35	12,798 (65.3)	12,927 (65.4)	0
Internist	1,139 (5.8)	540 (2.8)	15	1,139 (5.8)	1,232 (6.2)	2
Nephrologist	217 (1.1)	97 (0.5)	7	217 (1.1)	234 (1.2)	1
Other	167 (0.9)	317 (1.6)	6	167 (0.9)	171 (0.9)	0
Missing	1,091 (5.6)	1,261 (6.5)	4	1,091 (5.6)	1,131 (5.7)	0
Comorbidities in prior 5 years						

Duration of diabetes, years, mean ± SD	13.8 ± 6.9	12.0 ± 7.2	25	13.8 ± 6.9	13.8 ± 7.1	1
Duration of diabetes, years, median (IQR)	14 (9 to 19)	12 (6 to 17)	25	14 (9 to 19)	14 (8 to 20)	1
<1 year	699 (3.6)	1,357 (7.0)	15	699 (3.6)	696 (3.5)	1
1-4 years	1,707 (8.7)	2,435 (12.5)	12	1,707 (8.7)	1,767 (8.9)	1
5-9 years	3,611 (18.4)	4,303 (22.1)	9	3,611 (18.4)	3,733 (18.9)	1
10-19 years	9,319 (47.5)	8,114 (41.6)	12	9,319 (47.5)	8,984 (45.4)	4
20-29 years	4,275 (21.8)	3,274 (16.8)	13	4,275 (21.8)	4,595 (23.2)	3
Diabetic retinopathy	168 (0.9)	140 (0.7)	2	168 (0.9)	172 (0.9)	0
Diabetic neuropathy	231 (1.2)	257 (1.3)	1	231 (1.2)	223 (1.1)	1
Hypoglycemia	115 (0.6)	185 (0.9)	3	115 (0.6)	127 (0.6)	0
Hyperglycemic emergency	47 (0.2)	82 (0.4)	4	47 (0.2)	75 (0.4)	4
Prior acute kidney injury	351 (1.8)	702 (3.6)	11	351 (1.8)	395 (2.0)	1
Prior acute urinary retention	252 (1.3)	452 (2.3)	8	252 (1.3)	237 (1.2)	1
Chronic obstructive pulmonary disease	396 (2.0)	490 (2.5)	3	396 (2.0)	453 (2.3)	2
Chronic lung disease	3,885 (19.8)	3,976 (20.4)	1	3,885 (19.8)	4,049 (20.5)	2
Cancer	5,586 (28.5)	5,987 (30.7)	5	5,586 (28.5)	5,579 (28.2)	1
Stroke	270 (1.4)	556 (2.9)	10	270 (1.4)	256 (1.3)	1
Atrial Fibrillation	717 (3.7)	930 (4.8)	5	717 (3.7)	702 (3.5)	1
Ventricular arrhythmia	61 (0.3)	76 (0.4)	2	61 (0.3)	66 (0.3)	0
Coronary artery bypass graft surgery	513 (2.6)	372 (1.9)	5	513 (2.6)	514 (2.6)	0
Percutaneous coronary intervention	1,051 (5.4)	777 (4.0)	7	1,051 (5.4)	1,010 (5.1)	1
Pacemaker	543 (2.8)	561 (2.9)	1	543 (2.8)	518 (2.6)	1

Congestive heart failure	1,649 (8.4)	1,876 (9.6)	4	1,649 (8.4)	1,674 (8.5)	0
Transplant - hepatic	8 (0.0)	7 (0.0)	4	8 (0.0)	9 (0.0)	0
Chronic liver disease	947 (4.8)	978 (5.0)	1	947 (4.8)	916 (4.6)	1
Coronary artery disease	6,665 (34.0)	5,985 (30.7)	7	6,665 (34.0)	6,669 (33.7)	1
Peripheral vascular disease	202 (1.0)	218 (1.1)	1	202 (1.0)	188 (1.0)	0
Hypertension	15,302 (78.0)	13,528 (69.4)	20	15,302 (78.0)	15,477 (78.3)	1
Hypotension	176 (0.9)	297 (1.5)	6	176 (0.9)	157 (0.8)	1
Hyponatremia	202 (1.0)	393 (2.0)	8	202 (1.0)	203 (1.0)	0
Influenza vaccination	14,066 (71.7)	13,393 (68.7)	7	14,066 (71.7)	13,912 (70.4)	3
Prior respiratory infection	12,540 (63.9)	12,169 (62.5)	3	12,540 (63.9)	12,559 (63.5)	1
Prior skin & soft tissue infection	19,428 (99.1)	19,112 (98.1)	9	19,428 (99.1)	19,602 (99.1)	0
Prior other infections	6,343 (32.3)	6,299 (32.3)	0	6,343 (32.3)	6,391 (32.3)	0
Hyperkalemia	85 (0.4)	131 (0.7)	4	85 (0.4)	86 (0.4)	0
Urinary incontinence	195 (1.0)	209 (1.1)	1	195 (1.0)	177 (0.9)	1
Urinary retention	252 (1.3)	452 (2.3)	8	252 (1.3)	237 (1.2)	1
Prior urinary tract infections	578 (2.9)	1,015 (5.2)	12	578 (2.9)	661 (3.3)	2
Charlson comorbidity index[f]						
Mean ± SD	0.3 ± 0.9	0.5 ± 1.2	14	0.3 ± 0.9	0.3 ± 1.0	1
Median (IQR)	0 (0 to 0)	0 (0 to 0)	13	0 (0 to 0)	0 (0 to 0)	1
0	16,722 (85.3)	15,676 (80.5)	13	16,722 (85.3)	16,998 (86.0)	2
1	943 (4.8)	1,147 (5.9)	5	943 (4.8)	852 (4.3)	2
2	862 (4.4)	1,044 (5.4)	5	862 (4.4)	862 (4.4)	0
3	1,084 (5.5)	1,616 (8.3)	11	1,084 (5.5)	1,063 (5.4)	0
Medications[g]						
ACE inhibitors	7,155 (36.5)	6,128 (31.5)	11	7,155 (36.5)	7,271 (36.8)	1
ARB	4,754 (24.2)	4,095 (21.0)	8	4,754 (24.2)	4,856 (24.6)	1

ACE or ARB	11,796 (60.1)	10,124 (52.0)	16	11,796 (60.1)	12,008 (60.7)	1
ACE and ARB	113 (0.6)	99 (0.5)	1	113 (0.6)	120 (0.6)	0
Acetylsalicyclic acid[h]	436 (2.2)	395 (2.0)	1	436 (2.2)	497 (2.5)	2
Beta blockers	6,427 (32.8)	5,679 (29.1)	8	6,427 (32.8)	6,442 (32.6)	0
Calcium channel blockers	6,167 (31.4)	5,540 (28.4)	7	6,167 (31.4)	6,205 (31.4)	0
NSAIDs[i]	2,076 (10.6)	1,684 (8.6)	7	2,076 (10.6)	2,144 (10.8)	1
Statins	14,887 (75.9)	12,257 (62.9)	28	14,887 (75.9)	15,031 (76.0)	0
Proton pump inhibitors	4,264 (21.7)	4,137 (21.2)	1	4,264 (21.7)	4,352 (22.0)	1
Picosalax	169 (0.9)	169 (0.9)	0	169 (0.9)	158 (0.8)	1
Cephalosporins	823 (4.2)	849 (4.4)	1	823 (4.2)	870 (4.4)	1
Lithium	23 (0.1)	28 (0.1)	0	23 (0.1)	30 (0.2)	3
Amoxicillin	1,518 (7.7)	1,468 (7.5)	1	1,518 (7.7)	1,717 (8.7)	4
Ciprofloxacin	434 (2.2)	561 (2.9)	4	434 (2.2)	494 (2.5)	2
Norfloxacin	51 (0.3)	74 (0.4)	2	51 (0.3)	74 (0.4)	2
Nitrofurantoin	377 (1.9)	566 (2.9)	7	377 (1.9)	501 (2.5)	4
Sulfamethoxazole & trimethoprim	159 (0.8)	220 (1.1)	3	159 (0.8)	203 (1.0)	2
Overactive bladder medications	329 (1.7)	352 (1.8)	1	329 (1.7)	345 (1.7)	0
Loop diuretics	1,289 (6.6)	1,376 (7.1)	2	1,289 (6.6)	1,352 (6.8)	1
Potassium sparing diuretics	610 (3.1)	635 (3.3)	1	610 (3.1)	602 (3.0)	1
Thiazide diuretics	2,700 (13.8)	2,608 (13.4)	1	2,700 (13.8)	2,874 (14.5)	2
Any diuretic type	4,240 (21.6)	4,231 (21.7)	0	4,240 (21.6)	4,460 (22.6)	2
Number of unique diuretic types						
0	15,371 (78.4)	15,252 (78.3)	0	15,371 (78.4)	15,315 (77.4)	2
1	3,892 (19.8)	3,858 (19.8)	0	3,892 (19.8)	4,110 (20.8)	2
2	337 (1.7)	358 (1.8)	1	337 (1.7)	332 (1.7)	0
3	11 (0.1)	15 (0.1)	0	11 (0.1)	18 (0.1)	0
Number of unique drug names						

Mean ± SD	7.87 ± 4.07	6.91 ± 4.43	23	7.87 ± 4.07	8 ± 4.28	3
Median (IQR)	7 (5 to 10)	7 (4 to 9)	24	7 (5 to 10)	8 (5 to 10)	3
0-4 drug names	3,654 (18.6)	5,916 (30.4)	28	3,654 (18.6)	3,837 (19.4)	2
5-9 drug names	10,179 (51.9)	8,698 (44.6)	15	10,179 (51.9)	9,633 (48.7)	6
10-15 drug names	4,924 (25.1)	4,113 (21.1)	10	4,924 (25.1)	5,286 (26.7)	4
15-19 drug names	625 (3.2)	554 (2.8)	2	625 (3.2)	747 (3.8)	3
20+ drug names	229 (1.2)	202 (1.0)	2	229 (1.2)	273 (1.4)	2
Hypoglycemic medications dispensed in prior 120 days						
Insulin	5,229 (26.7)	2,508 (12.9)	35	5,229 (26.7)	5,582 (28.2)	3
Acarbose	366 (1.9)	141 (0.7)	11	366 (1.9)	447 (2.3)	3
Gliclazide	6,606 (33.7)	4,385 (22.5)	25	6,606 (33.7)	6,870 (34.7)	2
Glyburide	719 (3.7)	1,004 (5.2)	7	719 (3.7)	740 (3.7)	0
Metformin	15,765 (80.4)	12,738 (65.4)	34	15,765 (80.4)	15,837 (80.1)	1
Repaglinide	6 (0.0)	10 (0.1)	4	6 (0.0)	23 (0.1)	4
Rosiglitazone maleate	13 (0.1)	16 (0.1)	0	13 (0.1)	12 (0.1)	0
Pioglitazine	100 (0.5)	104 (0.5)	0	100 (0.5)	108 (0.5)	0
Hypoglycemic medications dispensed on the cohort entry date						
Insulin	1,153 (5.9)	803 (4.1)	8	1,153 (5.9)	1,110 (5.6)	1
Acarbose	122 (0.6)	105 (0.5)	1	122 (0.6)	126 (0.6)	0
Gliclazide	2,077 (10.6)	2,176 (11.2)	2	2,077 (10.6)	1,946 (9.8)	3
Glyburide	172 (0.9)	292 (1.5)	6	172 (0.9)	159 (0.8)	1
Metformin	5,589 (28.5)	5,422 (27.8)	2	5,589 (28.5)	5,439 (27.5)	2
Pioglitazine	26 (0.1)	9 (0.0)	4	26 (0.1)	7 (0.0)	4
Hypoglycemic medications dispensed in the 1 year to 120 days before the cohort entry date						
Insulin	5,664 (28.9)	2,877 (14.8)	35	5,664 (28.9)	5,997 (30.3)	3
Acarbose	445 (2.3)	217 (1.1)	9	445 (2.3)	522 (2.6)	2
Gliclazide	7,457 (38.0)	5,459 (28.0)	21	7,457 (38.0)	7,672 (38.8)	2
Glyburide	1,003 (5.1)	1,419 (7.3)	9	1,003 (5.1)	1,025 (5.2)	0
Metformin	16,698 (85.1)	14,552 (74.7)	26	16,698 (85.1)	16,695 (84.4)	2
Repaglinide	7 (0.0)	20 (0.1)	4	7 (0.0)	28 (0.1)	4
Rosiglitazone maleate	19 (0.1)	22 (0.1)	0	19 (0.1)	15 (0.1)	0

Pioglitazine	125 (0.6)	141 (0.7)	1	125 (0.6)	148 (0.7)	1
Healthcare use in the past 1 year						
Number of any hospitalizations						
Mean ± SD	0.12 ± 0.45	0.22 ± 0.65	18	0.12 ± 0.45	0.12 ± 0.44	0
Median (IQR)	0 (0 to 0)	0 (0 to 0)	18	0 (0 to 0)	0 (0 to 0)	1
0 visits	17,821 (90.9)	16,618 (85.3)	17	17,821 (90.9)	18,001 (91.0)	0
1 visit	1,364 (7.0)	1,977 (10.1)	11	1,364 (7.0)	1,378 (7.0)	0
2 visits	314 (1.6)	562 (2.9)	9	314 (1.6)	289 (1.5)	1
3+ visits	112 (0.6)	326 (1.7)	10	112 (0.6)	107 (0.5)	1
Number of any ED visits						
Mean ± SD	0.5 ± 1.24	0.69 ± 1.57	13	0.5 ± 1.24	0.52 ± 1.12	2
Median (IQR)	0 (0 to 1)	0 (0 to 1)	16	0 (0 to 1)	0 (0 to 1)	2
0 visits	14,234 (72.6)	12,840 (65.9)	15	14,234 (72.6)	14,009 (70.8)	4
1 visit	3,292 (16.8)	3,596 (18.5)	4	3,292 (16.8)	3,487 (17.6)	2
2 visits	1,136 (5.8)	1,527 (7.8)	8	1,136 (5.8)	1,256 (6.4)	3
3+ visits	949 (4.8)	1,520 (7.8)	12	949 (4.8)	1,023 (5.2)	2
GP/FP visits						
Mean ± SD	8.22 ± 6.72	9.37 ± 9.93	14	8.22 ± 6.72	8.12 ± 6.79	1
Median (IQR)	7 (4 to 10)	7 (4 to 11)	5	7 (4 to 10)	7 (4 to 10)	1
0 visits	460 (2.3)	493 (2.5)	1	460 (2.3)	597 (3.0)	4
1-2 visits	1,702 (8.7)	1,788 (9.2)	2	1,702 (8.7)	1,707 (8.6)	0
3-4 visits	3,462 (17.7)	3,256 (16.7)	3	3,462 (17.7)	3,457 (17.5)	1
5-6 visits	3,824 (19.5)	3,629 (18.6)	2	3,824 (19.5)	4,090 (20.7)	3
7-8 visits	3,101 (15.8)	2,853 (14.6)	3	3,101 (15.8)	3,076 (15.6)	1
9-10 visits	2,222 (11.3)	1,988 (10.2)	4	2,222 (11.3)	2,033 (10.3)	3
11+ visits	4,840 (24.7)	5,476 (28.1)	8	4,840 (24.7)	4,814 (24.3)	1
Cardiologist visits						
Mean ± SD	1.12 ± 2.36	1.25 ± 2.72	5	1.12 ± 2.36	1.12 ± 2.26	0
Median (IQR)	0 (0 to 1)	0 (0 to 1)	2	0 (0 to 1)	0 (0 to 1)	0
0 visits	11,273 (57.5)	11,042 (56.7)	2	11,273 (57.5)	11,397 (57.6)	0
1 visit	3,882 (19.8)	3,875 (19.9)	0	3,882 (19.8)	3,859 (19.5)	1

2 visits	1,782 (9.1)	1,701 (8.7)	1	1,782 (9.1)	1,723 (8.7)	1
3+ visits	2,674 (13.6)	2,865 (14.7)	3	2,674 (13.6)	2,795 (14.1)	1
Opthamologist visits						
Mean ± SD	1.02 ± 2.24	0.95 ± 2.14	3	1.02 ± 2.24	1.03 ± 2.27	0
Median (IQR)	0 (0 to 1)	0 (0 to 1)	4	0 (0 to 1)	0 (0 to 1)	1
0 visits	12,927 (65.9)	13,196 (67.7)	4	12,927 (65.9)	13,015 (65.8)	0
1 visit	2,828 (14.4)	2,627 (13.5)	3	2,828 (14.4)	2,814 (14.2)	1
2 visits	1,386 (7.1)	1,354 (6.9)	1	1,386 (7.1)	1,399 (7.1)	0
3+ visits	2,470 (12.6)	2,306 (11.8)	2	2,470 (12.6)	2,547 (12.9)	1
Endocrinologist visits						
Mean ± SD	0.6 ± 1.31	0.34 ± 1.21	21	0.6 ± 1.31	0.59 ± 1.37	1
Median (IQR)	0 (0 to 0)	0 (0 to 0)	29	0 (0 to 0)	0 (0 to 0)	1
0 visits	14,809 (75.5)	16,879 (86.6)	29	14,809 (75.5)	15,214 (76.9)	3
1 visit	1,422 (7.3)	957 (4.9)	10	1,422 (7.3)	1,402 (7.1)	1
2 visits	1,485 (7.6)	764 (3.9)	16	1,485 (7.6)	1,301 (6.6)	4
3+ visits	1,895 (9.7)	883 (4.5)	20	1,895 (9.7)	1,858 (9.4)	1
Nephrologist visits						
Mean ± SD	0.11 ± 0.67	0.14 ± 1.12	3	0.11 ± 0.67	0.11 ± 0.57	0
Median (IQR)	0 (0 to 0)	0 (0 to 0)	5	0 (0 to 0)	0 (0 to 0)	0
0 visits	18,607 (94.9)	18,249 (93.7)	5	18,607 (94.9)	18,676 (94.4)	2
1 visit	501 (2.6)	624 (3.2)	4	501 (2.6)	498 (2.5)	1
2 visits	286 (1.5)	333 (1.7)	2	286 (1.5)	350 (1.8)	2
3+ visits	217 (1.1)	277 (1.4)	3	217 (1.1)	250 (1.3)	2
Diabetes management	11,451 (58.4)	10,080 (51.7)	13	11,451 (58.4)	11,805 (59.7)	3
Diabetes incentive	6,855 (35.0)	5,782 (29.7)	11	6,855 (35.0)	7,072 (35.8)	2
Diabetes management by a specialist	964 (4.9)	289 (1.5)	19	964 (4.9)	925 (4.7)	1
Diabetes management by a specialist team	487 (2.5)	112 (0.6)	15	487 (2.5)	447 (2.3)	1
Cholesterol tests	17,740 (90.5)	16,929 (86.9)	11	17,740 (90.5)	17,897 (90.5)	0
Proteinuria	10,453 (53.3)	10,905 (56.0)	5	10,453 (53.3)	10,624 (53.7)	1

SCr tests	19,026 (97.0)	18,519 (95.1)	10	19,026 (97.0)	19,180 (97.0)	0
Glucose tests	17,881 (91.2)	17,288 (88.7)	8	17,881 (91.2)	17,948 (90.8)	1
HbA1c tests	18,996 (96.9)	18,401 (94.4)	12	18,996 (96.9)	19,152 (96.8)	0
DVT/PE	21 (0.1)	48 (0.2)	3	21 (0.1)	22 (0.1)	0
Bone mineral density test	1,201 (6.1)	1,357 (7.0)	4	1,201 (6.1)	1,211 (6.1)	0
Hearing test	866 (4.4)	792 (4.1)	1	866 (4.4)	814 (4.1)	1
Sputum	35 (0.2)	52 (0.3)	2	35 (0.2)	54 (0.3)	2
Wound swab	14 (0.1)	18 (0.1)	0	14 (0.1)	17 (0.1)	0
Holter monitoring	1,546 (7.9)	1,605 (8.2)	1	1,546 (7.9)	1,576 (8.0)	0
Cardiac stress test	3,124 (15.9)	2,519 (12.9)	9	3,124 (15.9)	3,064 (15.5)	1
Coronary revascularization	382 (1.9)	292 (1.5)	3	382 (1.9)	338 (1.7)	2
Electrocardiography	9,239 (47.1)	9,809 (50.3)	6	9,239 (47.1)	9,251 (46.8)	1
Pulmonary function test	2,244 (11.4)	2,051 (10.5)	3	2,244 (11.4)	2,156 (10.9)	2
At-home physician service	252 (1.3)	481 (2.5)	9	252 (1.3)	237 (1.2)	1
Urinalysis	10,684 (54.5)	11,202 (57.5)	6	10,684 (54.5)	10,864 (54.9)	1
Cystoscopy	612 (3.1)	778 (4.0)	5	612 (3.1)	600 (3.0)	1
Transurethral resection of the prostate	71 (0.4)	81 (0.4)	0	71 (0.4)	53 (0.3)	2
Carotid ultrasound	901 (4.6)	994 (5.1)	2	901 (4.6)	942 (4.8)	1
Cardiac catheterization	661 (3.4)	503 (2.6)	5	661 (3.4)	587 (3.0)	2
Coronary angiogram	648 (3.3)	494 (2.5)	5	648 (3.3)	575 (2.9)	2
Electroencephalography	51 (0.3)	138 (0.7)	6	51 (0.3)	50 (0.3)	0
Chest x-ray	4,899 (25.0)	5,929 (30.4)	12	4,899 (25.0)	4,964 (25.1)	0
Echocardiography	4,377 (22.3)	4,262 (21.9)	1	4,377 (22.3)	4,387 (22.2)	0
Prostate-specific antigen test	1,124 (5.7)	845 (4.3)	6	1,124 (5.7)	1,109 (5.6)	0

Cervical cancer screening	641 (3.3)	531 (2.7)	4	641 (3.3)	614 (3.1)	1
Laboratory tests[j]						
Baseline eGFR[k], ml/min/1.73m^2						
Mean ± SD	76.7 ± 13.9	72.9 ± 15.6	26	76.7 ± 13.9	76.7 ± 15.6	0
Median (IQR)	78 (66 to 88)	74 (59 to 87)	24	78 (66 to 88)	80 (64 to 90)	0
>60 ml/min/1.73m^2	16,786 (85.6)	14,405 (73.9)	29	16,786 (85.6)	16,009 (81.0)	12[l]
45-60 ml/min/1.73m^2	2,825 (14.4)	5,078 (26.1)	29	2,825 (14.4)	3,766 (19.0)	12[l]
Time from most recent SCr test to cohort entry date						
Mean ± SD	61.9 ± 75.6	63.8 ± 83.6	2	61.9 ± 75.6	59.7 ± 78.5	3
Median (IQR)	28 (9 to 89)	24 (8 to 88)	6	28 (9 to 89)	23 (8 to 81)	3
Baseline SCr, µmol/L						
Mean ± SD	79.7 ± 18.1	81.2 ± 20.2	8	79.7 ± 18.1	79.7 ± 20.3	0
Median (IQR)	78 (66 to 91)	79 (66 to 94)	6	78 (66 to 91)	77 (65 to 92)	1
Baseline potassium, mEq/L						
Potassium data available	5,556 (28.3)	7,072 (36.3)	17	5,556 (28.3)	6,110 (30.9)	6
Mean ± SD	4.5 ± 0.5	4.4 ± 0.5	13	4.5 ± 0.5	4.5 ± 0.4	7
Median (IQR)	5 (4 to 5)	4 (4 to 5)	11	5 (4 to 5)	5 (4 to 5)	5
Time from most recent ACR test to cohort entry date						
Mean ± SD	67.8 ± 90.5	61.4 ± 93.9	7	67.8 ± 90.5	65.2 ± 93.1	3
Median (IQR)	20 (0 to 106)	10 (0 to 91)	19	20 (0 to 106)	16 (0 to 101)	3
Baseline ACR categories, mg/mmol						
ACR data available	14,637 (74.6)	12,381 (63.5)	24	14,637 (74.6)	14,240 (72.0)	6
Undetected	9,424 (48.1)	7,903 (40.6)	15	9,424 (48.1)	9,129 (46.2)	4
3-30	4,263 (21.7)	3,729 (19.1)	6	4,263 (21.7)	4,288 (21.7)	0
>30	950 (4.8)	749 (3.8)	5	950 (4.8)	823 (4.2)	3
Most recent glycated hemoglobin level, %						
Glycated hemoglobin value available	6,516 (33.2)	8,071 (41.4)	17	6,516 (33.2)	7,288 (36.9)	8
Mean ± SD	7.8 ± 1.2	7.7 ± 1.3	12	7.8 ± 1.2	7.8 ± 1.2	2

Median (IQR)	8 (7 to 8)	7 (7 to 8)	16	8 (7 to 8)	8 (7 to 8)	3
<6	89 (1.4)	224 (2.8)	7	89 (1.4)	129 (1.8)	3
6-<6.5	392 (6.0)	686 (8.5)	9	392 (6.0)	468 (6.4)	3
6.5-<7.0	1,018 (15.6)	1,500 (18.6)	10	1,018 (15.6)	1,175 (16.1)	3
7.0-<7.5	1,334 (20.5)	1,688 (20.9)	7	1,334 (20.5)	1,483 (20.3)	3
≥7.5	3,683 (56.5)	3,973 (49.2)	4	3,683 (56.5)	4,032 (55.3)	4
KFRE[m] data, %						
2-year KFRE data available	14,637 (74.6)	12,381 (63.5)	24	14,637 (74.6)	14,240 (72.0)	6
<5%	14,637 (100)	12,381 (100)	1	14,638 (100)	14,240 (100)	6
5-year KFRE data available	14,637 (74.6)	12,381 (63.5)	24	14,637 (74.6)	14,240 (72.0)	6
<5%	14,616 (99.9)	12,345 (99.7)	1	14,616 (99.9)	14,200 (99.7)	6
5%+	21 (0.1)	36 (0.3)	1	21 (0.1)	40 (0.3)	3

Abbreviations: ACE= angiotensin-converting–enzyme, ACR= albumin-to-creatinine ratio, ARB= angiotensin-receptor blocker, DPP4= dipeptidyl peptidase-4, DVT/PE= deep vein thrombosis and pulmonary embolism, ED= emergency department, eGFR = estimated glomerular filtration, GP/FP= general practice/family practice, HbA1c= glycated hemoglobin, IQR= interquartile range, KFRE= kidney failure risk equation, NSAID= nonsteroidal anti-inflammatory drug, SCr= serum creatinine, SD= standard deviation, SGLT2= sodium-glucose cotransporter-2

[a]Unless otherwise specified, baseline characteristics were assessed on the date the patient filled their prescription: the cohort entry date.

[b]Weighted using inverse probability of treatment weighting based on propensity scores, using weights to estimate the average treatment effect in the treated. Patients in the reference group were weighted as [propensity score/(1 - propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group (71,73,74)**.**

[c]The difference between the groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference (83).

[d]Rural residence was defined as a population < 10,000 people. Residential information was not available for 33 (0.2%) SGLT2 inhibitor users and 18 (0.1%) DPP4 inhibitor users in the unweighted cohort. Missing values in the unweighted cohort were re-classified into the "Not rural" category during weighting.

[e]Income was categorized into fifths of average neighborhood income on the cohort entry date. Socioeconomic status was missing for 33 (0.2%) of SGLT2 inhibitor users and 18 (0.1%) of DPP4 inhibitor users.

[f]Charlson comorbidity index (106,107) was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0. A higher score indicates a higher risk of one-year mortality associated with comorbidities.
[g]Medication use was examined in the 120-day period before the cohort entry date (the Ontario Drug Benefit program dispenses a maximum 100-day supply.
[h]Only included dispensed acetylsalicyclic acid use and does not account for over-the-counter acetylsalicyclic acid use.
[i]Excludes acetylsalicylic acid and does not account for over-the-counter NSAID use.
[j]Most recent laboratory test values in the 1-to-365–day period before the cohort entry date.
[k]eGFR was calculated using the Chronic Kidney Disease (CKD)–Epidemiology (EPI) equation: $141 \times \min([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine concentration in } \mu\text{mol/L}/88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] × 1.159 [if African-American]; κ=0.7 if female and 0.9 if male; α=-0.329 if female and -0.411 if male; min=the minimum of serum creatinine concentration/κ or 1; max=the maximum of serum creatinine concentration/κ or 1. Information on race was not available in our data sources and all patients were assumed not to be of African-Canadian race; African-Canadians represented less than 5% of the population of Ontario in 2006.
[l]Although the groups were still imbalanced on eGFR categories after weighting, there was no statistical or clinically meaningful difference when baseline eGFR was assessed as a continuous variable.
[m]KFRE is based on a prediction model for progression to kidney failure (108). The equation includes age, sex, eGFR and albuminuria. A higher percentage indicates a greater 2- and 5-year chance of developing treated end-stage kidney disease.

Table 3. 90-day primary and secondary outcomes of prescription SGLT2 inhibitor new users compared with DPP4 inhibitor new users

	Observed		Weighted[b]				
	No. events (%)		No. events (%)				
	SGLT2 inhibitors (*n*=19,611)	DPP4 inhibitors (*n*=19,483)	SGLT2 inhibitors (*n*=19,611)	DPP4 inhibitors (*n*=19,775)	Risk difference, % (95% CI)	Risk ratio (95% CI)	*P*-value
Primary outcome							
Hospital encounter with acute kidney injury[c]	216 (1.10%)	388 (1.99%)	216 (1.10%)	275 (1.39%)	-0.29% (-0.57% to -0.01%)	0.79 (0.64 to 0.98)	0.04
Secondary outcomes							
Hospitalization with acute kidney injury	149 (0.76%)	291 (1.49%)	149 (0.76%)	206 (1.04%)	-0.28% (-0.53% to -0.03%)	0.73 (0.56 to 0.95)	0.02
Hospital encounter with moderate to severe acute kidney injury[d]	44 (0.22%)	74 (0.38%)	44 (0.22%)	55 (0.28%)	-0.05% (-0.18% to 0.08%)	0.81 (0.49 to 1.33)	0.40
Acute kidney injury restricted to outpatient setting	573 (2.92%)	609 (3.13%)	573 (2.92%)	513 (2.60%)	0.33% (-0.12% to 0.77%)	1.13 (0.95 to 1.33)	0.16
Acute kidney injury in all settings	716 (3.65%)	837 (4.30%)	716 (3.65%)	681 (3.44%)	0.21% (-0.28% to 0.70%)	1.06 (0.92 to 1.22)	0.42

Abbreviations: CI= confidence interval, DPP4= dipeptidyl peptidase-4, SGLT2= sodium-glucose cotransporter-2

[a]Reference group: DPP4 inhibitor users.

[b]Weighted using inverse probability of treatment weighting based on propensity scores, using weights to estimate the average treatment effect in the treated.

[c]Based on hospital presentation (emergency department or hospitalization) assessed using the Ontario Laboratories Information System serum creatinine values. This was defined by the 2012 KDIGO thresholds: compared with baseline, a serum creatinine increase ≥ 50% or an absolute increase of at least 27 µmol/L (0.3 mg/dL) (27).

[d]Defined according to KDIGO staging thresholds of stages 2 and 3 combined (27).

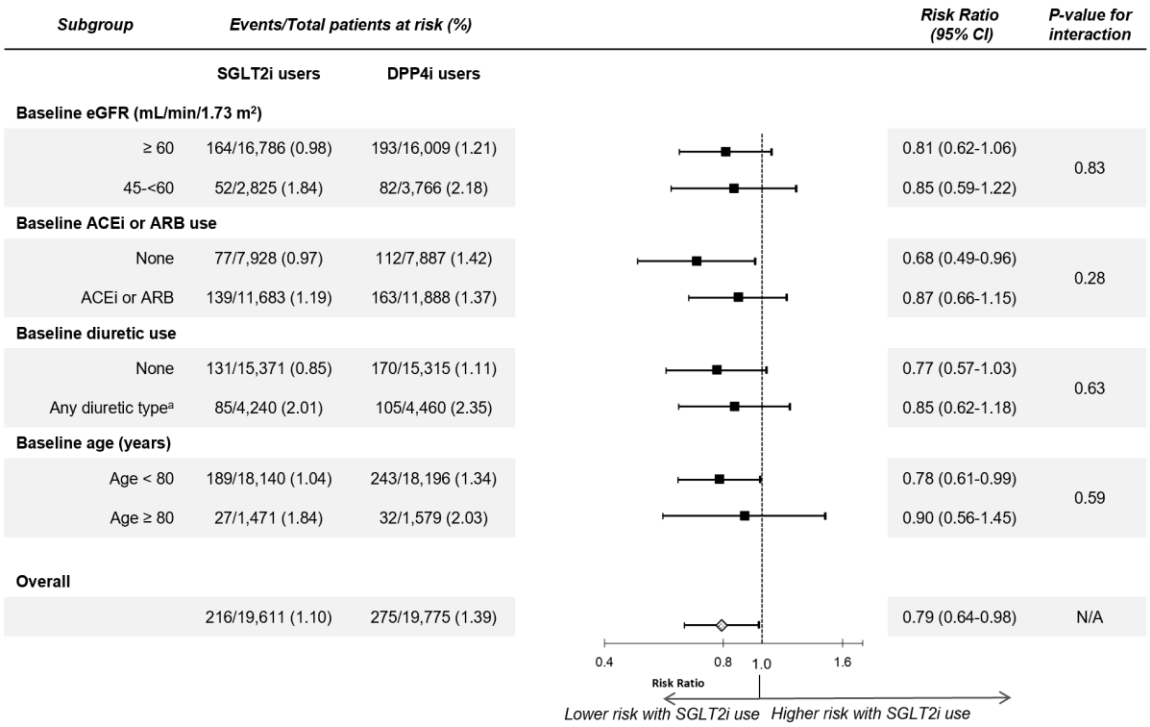

Figure 2. Association between SGLT2 inhibitor new use (canagliflozin, dapagliflozin or empagliflozin) and the 90-day risk of hospital encounter with AKI examined in subgroups defined by baseline eGFR, ACEi or ARB use, diuretic use and age

Abbreviations: ACEi= angiotensin-converting-enzyme inhibitor, ARB= angiotensin receptor blocker, CI= confidence interval, DPP4i= dipeptidyl peptidase-4 inhibitor, eGFR= estimated glomerular filtration rate, N/A= not applicable, SGLT2i= sodium-glucose cotransporter-2 inhibitor

[a]Diuretic types included loop diuretics, potassium sparring diuretics and thiazide diuretics

Chapter 6

6 Discussion

6.1 Summary and interpretation of study results

In this large population-based cohort study of older adults, we did not observe a higher risk of AKI in new users of SGLT2 inhibitors compared with DPP4 inhibitors in any analysis. Rather, we observed that new use of an SGLT2 inhibitor was associated with a lower 90-day risk of a hospital encounter with AKI. Results remained robust when the follow-up was extended to one year. When four subgroups of higher risk patients were examined, none showed evidence of a higher 90-day risk of AKI following new SGLT2 inhibitor use compared to DPP4 inhibitor use.

These findings are reassuring for the safety of SGLT2 inhibitors as currently prescribed in routine care. A likely explanation to this observed protective effect is the, now better understood, mechanism by which SGLT2 inhibitors have demonstrated several nephroprotective features akin to ACE inhibitors and ARB initiation (45,46,109), including a reduction in albuminuria and risk of progressive chronic kidney disease (110,111). The cardiovascular benefits of SGLT2 inhibitors may also result in renal benefits, given how dependent the kidney is on cardiac function.

Our demonstration of a 21% lower relative risk of AKI is consistent with three published observational cohort studies (15–17). Two of these studies also used laboratory data to define AKI (albeit in relatively smaller sample sizes) and both found a >50% lower AKI risk following SGLT2 inhibitor use (15,16). The most recent observational study with the most comparable sample size to this current study found SGLT2 inhibitor use versus GLP1 receptor agonist use resulted in a 31% reduction in AKI risk, but was not statistically significant (17).

Some might suggest cohort studies suffer from residual confounding leading to spurious associations. For example, before weighting patients in this study, newly dispensed SGLT2 inhibitor users demonstrated less comorbidity and better maintained kidney

function than DPP4 inhibitor users, which might explain the observed lower risk of AKI with SGLT2 inhibitors even after weighting. However, our results were very similar to the findings of large recent RCTs and meta-analyses of RCTs. In the CREDENCE study, patients with type 2 diabetes and chronic kidney disease, who were randomized to receive canagliflozin, had a lower non-significant risk of AKI compared with placebo (7). A recent systematic review and meta-analysis by Neuen *et al.* of over 38,723 participants from RCTs demonstrated a similar significant 25% reduction in AKI risk with SGLT2 inhibitor use versus placebo (111). A systematic review and meta-analysis by Toyama *et al*, of over 7,000 patients from RCTs demonstrated a 31% reduction in AKI risk with SGLT2 inhibitor use versus placebo, but was not statistically significant (112). Another meta-analysis of the three major RCTs demonstrated a 34% statistically significant relative risk reduction in the likelihood of AKI amongst those randomized to receive SGLT2 inhibitors versus placebo (113).

The totality of randomized and routine care evidence suggests regulatory warnings and prescribing references about a higher AKI risk with SGLT2 inhibitors may be unwarranted and might be reconsidered (1,114).

6.2 Strengths and limitations

Our study has several strengths. It is the largest population-based study to date to assess the risk of a clinically important complication of SGLT2 inhibitor use among older adults. It is the first Canadian study to evaluate AKI risk in association with an important medication that is likely to be used more often in response to recent trials demonstrating its benefits (4,6,7). We used laboratory values, as opposed to diagnostic codes, to more specifically capture AKI events associated with SGLT2 inhibitor initiation (115,116). We selected patients who filled a prescription for a different class of oral hypoglycemic medications as our comparator group to avoid confounding by indication bias that would arise if we simply examined SGLT2 inhibitor non-users.

There are several limitations to our study. Given the observational study design, causality cannot be inferred. Although we chose an active comparator drug that is also 2nd or 3rd line medication for diabetes and we balanced on 97 measured baseline characteristics, confounding by indication cannot be ruled out. When estimating eGFRs using the CKD-EPI equation, we had no information about race and assumed all patients to be non-black for the CKD-EPI equation (<5% of the Ontario population is of black race) (70). Thus, eGFR values for black patients may not be estimated accurately. In addition, we cannot account for whether strategies such as sick day management of diabetes medications (i.e. stopping SGLT2 inhibitors during acute illness) altered the risk of AKI. Although residual confounding cannot be eliminated, we attempted to reduce it using IPTW and balanced patients on over 95 characteristics. We also conducted several additional sensitivity analyses which supported the main findings. In particular, the magnitude of the E-value, along with the entire context of this study, suggest the observed association is unlikely to be explained by unmeasured confounding. Some confounders that could not be captured in our datasets may be smoking status, body mass index, and oral water intake which when poor may predispose to volume depletion (30,117–120). However, we have no reason to believe that these factors would be differentially more prevalent amongst SGLT2i users compared to DPP4i users.

Additional limitations were that we could only identify prescriptions dispensed by a pharmacy but had no information about medication use or adherence. We only included patients aged over 66 years, but our study findings are consistent with studies that included adults of all ages (16,17). The 2012 KDIGO definition of AKI includes timing elements for when SCr measurements needed to be taken within (increase in SCr within 48 hours and a baseline measurement presumed to have occurred within the prior 7 days), which were not considered in the current study outcome definitions (27). The SCr measurements were done as per routine care and about half of the patients did not have a SCr measurement during the 90-day follow-up period. While we observed a significant between-group difference in the likelihood of SCr measurement in follow-up, the absolute difference was not large and we believe it unlikely to affect the overall results. Following SGLT2 inhibitor initiation clinicians may be more likely to check SCr, especially in higher risk patients, compared to our comparator group, which could lead to

a greater (not lower) risk of SGLT2 inhibitor-associated AKI. Lastly, it is important to note that the population studied was of lower risk of AKI, largely based on well-preserved kidney function and minimal or no albuminuria. Extrapolation of the findings to higher risk patients should be done with caution.

6.3 Implications

In older adults in routine clinical practice, new initiation of an SGLT2 inhibitor compared with DPP4 inhibitors was associated with a lower 90-day AKI risk. This is reassuring for prescribers, as SCr expectedly increased following SGLT2 inhibitor initiation, but did not appear to lead to AKI. Taken together with consistent information from other studies, regulatory warnings about a higher risk of AKI with SGLT2 inhibitors may be unwarranted and should be revisited.

Consideration can be given to future trials of SGLT2 inhibitor use in patient settings where the timing and risk of AKI is both predictable and high, such as in the perioperative setting. As the uptake of SGLT2 inhibitors expands, we will likely see the drug used by more patients with advanced chronic kidney disease, where the risk-benefit balance requires attention. Also, better information on the effects of withholding these drugs in the context of acute illness or infection warrants attention.

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Appendices

Appendix A. Regulatory warnings on the risk of acute kidney injury with SGLT2 inhibitor use (8,9)

Study Drug	Summary of Warning
Canagliflozin	- In October 2015, Health Canada released a summary of the safety review which reported a risk of acute kidney injury following canagliflozin use. This review was based on reports of acute kidney injury both to Health Canada and international reports. In addition, scientific literature was reviewed at the time and it was noted that the drug's renal effects might be a potential problem (8). - In June 2016, the United States Food and Drug Administration (FDA) strengthened kidney warnings for canagliflozin based on a search of the FDA adverse event reporting system identifying 101 patients with sufficient detail to confirm the diagnosis and show a temporal relationship with canagliflozin (9).
Empagliflozin	- No warning about the risk of acute kidney injury following the use of empagliflozin. - However, in an FDA briefing document discussing the supplemental new drug application for empagliflozin using data from the EMPA-REG OUTCOME trial (released shortly after the warnings were issued for canagliflozin and dapagliflozin), there was a section stating that the risk of acute kidney injury with empagliflozin is slightly increased compared to placebo due to the diuretic activity of the drug leading to an early hemodynamic effect on renal function. In both the first 30 days and first 90 days following empagliflozin use, the incidence of early renal adverse events was greater in empagliflozin users (121).
Dapagliflozin	- In October 2015, Health Canada released a summary of the safety review which reported a risk of acute kidney injury following dapagliflozin use. This review was based on reports of acute kidney injury both to Health Canada and international reports. In addition, scientific literature was reviewed at the time it was noted that the drug's renal effects might be a potential problem (8). - In June 2016, the United States Food and Drug Administration (FDA) strengthened kidney warnings for dapagliflozin based on a search of the FDA adverse event reporting system identifying 101 patients with sufficient detail to confirm the diagnosis and show a temporal relationship with dapagliflozin (9).

Appendix B. Standard daily doses of SGLT2 inhibitors and DPP4 inhibitors

Drug	Standard daily drug doses (mg)
SGLT2 inhibitors	
Canagliflozin	100 or 300
Empagliflozin	10 or 25
Dapagliflozin	5 or 10
DPP4 inhibitors	
Saxagliptin	2.5 or 5
Sitagliptin	25, 50 or 100
Linagliptin	5

Appendix C. Search strategies for literature review

Database		Search Terms
OVID Medline	1	Acute Kidney Injury/
	2	((kidney or renal) adj3 (insufficien* or injur* or fail*)).mp.
	3	1 or 2
	4	Sodium-Glucose Transporter 2/
	5	(empagliflozin or dapagliflozin or canagliflozin or invokana or forxiga or jardiance).mp.
	6	4 or 5
	7	3 and 6
	RESULTS	**261**
		Ovid MEDLINE(R) ALL <1946 to July 10, 2019>
OVID Embase	1	acute kidney failure/
	2	((kidney or renal) adj3 (insufficien* or injur* or fail*)).mp.
	3	sodium glucose cotransporter 2/ or sodium glucose cotransporter 2 inhibitor/
	4	(empagliflozin or dapagliflozin or canagliflozin or invokana or forxiga or jardiance).mp.
	5	1 or 2
	6	3 or 4
	7	5 and 6
	RESULTS	**983**
		Embase Classic+Embase <1947 to 2019 July 10>

Appendix D. REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement for Pharmacoepidemiology (RECORD-PE) (58)

Item No	STROBE items	RECORD items	RECORD-PE items	Section
Title and abstract				
1	(a) Indicate the study's design with a commonly used term in the title or the abstract. (b) Provide in the abstract an informative and balanced summary of what was done and what was found.	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. 1.2: If applicable, the geographical region and timeframe within which the study took place should be reported in the title or abstract. 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	—	Title & Abstract
Introduction				
Background rationale				
2	Explain the scientific background and rationale for the investigation being reported.	—	—	Chapter 1 & 2
Objectives				
3	State specific objectives, including	—	—	Chapter 3

	any prespecified hypotheses.			
Methods				
Study design				
4	Present key elements of study design early in the paper.	—	4.a: Include details of the specific study design (and its features) and report the use of multiple designs if used. 4.b: The use of a diagram(s) is recommended to illustrate key aspects of the study design(s), including exposure, washout, lag and observation periods, and covariate definitions as relevant.	Chapter 4
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	Chapter 4
Participants				
6	(a) Cohort study—give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Case-control study—give the eligibility criteria, and the sources and methods of case ascertainment and control selection.	6.1: The methods of study population selection (such as codes or algorithms used to identify participants) should be listed in detail. If this is not possible, an explanation should be provided. 6.2: Any validation studies of	6.1.a: Describe the study entry criteria and the order in which these criteria were applied to identify the study population. Specify whether only users with a specific indication were included and whether patients were allowed to enter the study population once or if	Chapter 4

	Give the rationale for the choice of cases and controls. Cross sectional study—give the eligibility criteria, and the sources and methods of selection of participants. (b) Cohort study—for matched studies, give matching criteria and number of exposed and unexposed. Case-control study—for matched studies, give matching criteria and the number of controls per case.	the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	multiple entries were permitted. See explanatory document for guidance related to matched designs.	
Variables				
7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1.a: Describe how the drug exposure definition was developed. 7.1.b: Specify the data sources from which drug exposure information for individuals was obtained. 7.1.c: Describe the time window(s) during which an individual is considered exposed to the drug(s). The rationale for\ selecting a particular time window should be provided. The extent of potential left truncation or left censoring should be specified.	Chapter 4 •Codes for baseline characteristics available upon request

			7.1.d: Justify how events are attributed to current, prior, ever, or cumulative drug exposure. 7.1.e: When examining drug dose and risk attribution, describe how current, historical or time on therapy are considered. 7.1.f: Use of any comparator groups should be outlined and justified. 7.1.g: Outline the approach used to handle individuals with more than one relevant drug exposure during the study period.	
Data sources/measurement				
8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.		8.a: Describe the healthcare system and mechanisms for generating the drug exposure records. Specify the care setting in which the drug(s) of interest was prescribed.	Chapter 4
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	Chapter 4 Chapter 6
Study size				
10	Explain how the study size was arrived at.	—	—	Chapter 5: Figure 1
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If	—	—	Chapter 4

	applicable, describe which groupings were chosen, and why.			
Statistical methods				
	(a) Describe all statistical methods, including those used to control for confounding. (b) Describe any methods used to examine subgroups and interactions. (c) Explain how missing data were addressed. (d) Cohort study—if applicable, explain how loss to follow-up was addressed. Case-control study—if applicable, explain how matching of cases and controls was addressed. Cross sectional study—if applicable, describe analytical methods taking account of sampling strategy. (e) Describe any sensitivity analyses.	—	12.1.a: Describe the methods used to evaluate whether the assumptions have been met. 12.1.b: Describe and justify the use of multiple designs, design features, or analytical approaches.	Chapter 4
Data access and cleaning methods				
12	—	12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. 12.2: Authors should provide information on the data	—	N/A

		cleaning methods used in the study.		
Linkage				
12	—	12.3: State whether the study included person level, institutional level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	—	Chapter 4
Results				
Participants				
13	(a) Report the numbers of individuals at each stage of the study (eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed). (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram.	13.1: Describe in detail the selection of the individuals included in the study (that is, study population selection) including filtering based on data quality, data availability, and linkage. The selection of included individuals can be described in the text or by means of the study flow diagram.	—	Chapter 5: Figure 1
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential	—	—	Chapter 5: Table 2

	confounders. (b) Indicate the number of participants with missing data for each variable of interest. (c) Cohort study—summarise follow-up time (eg, average and total amount).			
Outcome data				
15	Cohort study—report numbers of outcome events or summary measures over time. Case-control study—report numbers in each exposure category, or summary measures of exposure. Cross sectional study—report numbers of outcome events or summary measures.	—	—	Chapter 5: Table 3
Main results				
16	(a) Give unadjusted estimates and, if applicable, confounder adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included. (b) Report category boundaries when continuous variables are categorised. (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time	—	—	Chapter 5: Table 3

	period.			
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	Chapter 5: Figure 2 Appendices I-M
Discussion				
Key results				
18	Summarise key results with reference to study objectives.	—	—	Chapter 6
Limitations				
19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1.a: Describe the degree to which the chosen database(s) adequately captures the drug exposure(s) of interest.	Chapter 6
Interpretation				
20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	—	20.a: Discuss the potential for confounding by indication, contraindication or disease severity or selection bias (healthy adherer/sick stopper) as alternative explanations for the study findings when relevant.	Chapter 6

Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	Chapter 6
Other information				
Funding				
22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	—	—	N/A
Accessibility of protocol, raw data, and programming code				
22	—	22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	—	N/A

Appendix E. Coding definitions for demographics, comorbid conditions, healthcare utilization measures and laboratory measurements

Variable	Database	Codes
Demographics		
Age	RPDB	
Sex	RPDB	
Location of residence – Rural status	RPDB	RURAL
Socioeconomic status (neighbourhood income quintiles)	RPDB	INCQUINT
Local Health Integration Network (LHIN)	RPDB	LHIN
Entry year		
Prescribing physician	IPDB	MAINSPECIALTY
Comorbidities		
Duration of diabetes	ODD	
Acute kidney injury	CIHI-DAD	ICD-10: N17
Chronic kidney disease	CIHI-DAD OHIP	ICD-10: E102, E112, E132, E142, I12, I13, N00, N01, N02, N03, N04, N05, N06, N07, N08, N10, N11, N12, N13, N14, N15, N16, N17, N18, N19, N20, N21, N22, N23 OHIP dx: 403, 585
Acute urinary retention	CIHI-DAD	ICD-10: R33
Chronic obstructive pulmonary disease	CIHI-DAD	ICD-10: J41, J43, J44
Chronic lung disease	CIHI-DAD CIHI-NACRS OHIP	ICD-10: I272, I278, I279, J40, J41, J42, J43, J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J701, J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99 OHIP dx: 491, 492, 493, 494, 496, 501, 502, 515, 518, 519 OHIP fee: J889, J689
Cancer	CIHI-DAD OHIP	ICD-10: 80003, 80006, 80013, 80023, 80033, 80043, 80102, 80103, 80106, 80113, 80123, 802, 803, 80413, 80423, 80433, 80443, 80453, 80502, 80503, 80513, 80523, 807, 808, 80903, 80913, 80923, 80933, 80943, 80953, 81103, 81202, 81203, 81213, 81223, 81233, 81243, 81303, 81402, 81403, 81406,

		81413, 81423, 81433, 81443, 81453, 81473, 81503, 81513, 81523, 81533, 81543, 81553, 81603, 81613, 81623, 81703, 81713, 81803, 81903, 82003, 82013, 82102, 82103, 82113, 82203, 82213, 823, 82403, 82413, 82433, 82443, 82453, 82463, 82473, 82503, 82513, 82603, 82612, 82613, 82623, 82632, 82633, 82703, 82803, 82813, 82903, 83003, 83103, 83123, 83143, 83153, 83203, 83223, 83233, 83303, 83313, 83323, 83403, 83503, 83703, 83803, 83813, 83903, 84003, 84013, 84103, 84203, 84303, 84403, 84413, 84423, 84503, 84513, 84603, 84613, 84623, 84703, 84713, 84723, 84733, 84803, 84806, 84813, 849, 85002, 85003, 85012, 85013, 85023, 85032, 85033, 85042, 85043, 851, 852, 85303, 854, 85503, 85603, 85623, 857, 85803, 86003, 86203, 86303, 86403, 86503, 86803, 86933, 87003, 87103, 87202, 87203, 87213, 87223, 87233, 87303, 87403, 87412, 87413, 87422, 87423, 87433, 87443, 87453, 87613, 87703, 87713, 87723, 87733, 87743, 87803, 88003, 88006, 88013, 88023, 88033, 88043, 88103, 88113, 88123, 88133, 88143, 88303, 88323, 88333, 88403, 88503, 88513, 88523, 88533, 88543, 88553, 88583, 88903, 88913, 88943, 88953, 88963, 89003, 89013, 89023, 89103, 89203, 89303, 89333, 89403, 89413, 895, 89603, 89633, 89643, 897, 89803, 89813, 89903, 89913, 90003, 90203, 90403, 90413, 90423, 90433, 90443, 90503, 90513, 90523, 90533, 906, 90703, 90713, 90723, 90803, 90813, 90823, 90833, 90843, 90853, 90903, 91003, 91013, 91023, 91103, 91203, 91243, 91303, 91333, 91403, 91503, 91703, 91803, 91813, 91823, 91833, 91843, 91853, 91903, 92203, 92213, 92303, 92313, 92403, 92503, 92513, 92603, 92613, 92703, 92903, 93103, 93303, 93623, 93643, 93703, 93803,

		93813, 93823, 93903, 93913, 93923, 940, 941, 942, 94303, 944, 945, 94603, 947, 948, 94903, 95003, 95013, 95023, 95033, 95043, 951, 952, 95303, 95393, 95403, 95603, 95613, 95803, 95813, 959, 965, 966, 967, 968, 969, 970, 971, 972, 973, 97403, 97413, 97603, 97613, 97623, 97633, 97643, 980, 982, 98303, 984, 98503, 986, 98703, 98803, 989, 99003, 99103, 993, 994, C00, C01, C02, C03, C04, C05, C06, C07, C08, C09, C10, C11, C12, C13, C14, C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26, C30, C31, C32, C33, C34, C37, C38, C39, C40, C41, C43, C44, C45, C46, C47, C48, C49, C50, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C69, C70, C71, C72, C73, C74, C75, C76, C77, C78, C79, C80, C81, C82, C83, C84, C85, C86, C88, C90, C91, C92, C93, C94, C95, C96, C97, D00, D01, D02, D03, D04, D05, D06, D07, D09, Z85 OHIP dx: 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164,165, 170, 171, 172, 173, 174, 175, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 230, 231, 232, 233, 234
Stroke	CIHI-DAD	ICD-10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340
Atrial fibrillation	CIHI-DAD	ICD-10: I48
Ventricular arrhythmia	CIHI-DAD NACRS	ICD-10: I472, I4900
Coronary artery bypass graft surgery	CIHI-DAD OHIP	CCI: 1IJ76 OHIP fee: R742, R743, E654, E645, E652, E646
Percutaneous coronary intervention	CIHI-DAD	CCI: 1IJ50, 1IJ57GQ, 1IJ54GQAZ OHIP fee: Z434, G262, G298

	OHIP	
Pacemaker	CIHI-DAD CIHI-NACRS OHIP	CCI: 1HZ37, 1HD53GRJA, 1HD54GRJA, 1HZ53GRNK, 1HZ53GRNL, 1HZ53GRNM, 1HZ54LANJ, 2HZ07NK 2HZ07NL, 2HZ07NM, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR, 1HD55, 1HZ09, 1HZ55, 2HZ24, 1Hz53GRNN OHIP fee: G303, Z433, Z435, Z443, Z444, Z445, R752, Z412, Z428, E628, G176, G177, G115
Congestive heart failure	CIHI-DAD OHIP	ICD-10: I099, I420, I425, I426, I427, I428, I429, I43, I500, I501, I509, I255, J81 CCP: 4961, 4962, 4963, 4964 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR OHIP fee: R701, R702, Z429 OHIP dx: 428
Transplant - hepatic	CIHI-DAD OHIP	ICD-10: T86400, T86401, T86402, Z944, CCI: 1OA85 OHIP fee: S294, S295, E765, G254
Chronic liver disease	CIHI-DAD OHIP	ICD-10: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77 OHIP dx: 571, 573, 070 OHIP fee: Z551, Z554
Coronary artery disease	CIHI-DAD OHIP	ICD-10: I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822 CCI: 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76 CCP: 4801, 4802, 4803, 4804, 4805, 481, 482, 483 OHIP fee: R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448 OHIP dx: 410, 412, 413
Diabetic retinopathy	CIHI-DAD	ICD-10: E1030, E1031, E1032, E1033, E1130, E1131, E1132, E1133, E1330, E1331, E1332, E1333, E1430, E1431, E1432, E1433, H360
Diabetic neuropathy	CIHI-DAD	ICD-10: E1040, E1041, E1042, E1048, E1049, E1440, E1441, E1442, E1448, E1140, E1141, E1142, E1148, E1340, E1341, E1342, E1348, E1349, G590,

		G632, G990
Peripheral vascular disease	CIHI-DAD OHIP	ICD-10: I700, I702, I708, I709, I731, I738, I739, K551 CCP: 5125, 5129, 5014, 5016, 5018, 5028, 5038, 5126, 5159 CCI: 1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76MI, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87, 1KA87LA, 1KE57 OHIP fee: R787, R780, R797, R804, R809, R875, R815, R936, R783, R784, R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649
Hypertension	ODB	
Hypotension	CIHI-DAD	ICD-10: I95
Hypoglycemia	CIHI-DAD	ICD-10: E15, E160, E161, E162, E1063, E1163, E1363, E1463
Hyperglycemic emergency	CIHI-DAD	ICD-10: E1410, E1412, E1010, E1012, E1110, E1112, E1300, E140
Hyponatremia	CIHI-DAD	ICD-10: E871
Influenza vaccination	OHIP	OHIP fee: G590, G591
Respiratory infection	CIHI-DAD OHIP	ICD-10: 462, 5191, 5180, 5181, 5812, 51889, 5192, 5193, 5194, 5198, 5199, 3821, 3822, 3823, 3824, 3829, 463, 4660, 485, 481, 514, 486, 4919, 4650, 4658, 4659, 4740, 4741, 4749, 4610, 4611, 4612, 4613, 4618, 4619, 496, 0340 ICD-10: J22, J02, J98, H66, J03, H65, J20, J18, J42, J06, J35, J01, J44 OHIP dx: 519, 460, 382, 463, 381, 466, 486, 491, 474, 461, 496, 034
Skin & soft tissue infection	CIHI-DAD OHIP	ICD-10: L08, L03, T01, L01, T814, A46 OHIP dx: 709, 686, 698, 682, 998, 879, 894, 884, 684, 250
Infections, other	CIHI-DAD OHIP	ICD-10: A49 OHIP dx: 786, 136, 040, 039
Hyperkalemia	CIHI-DAD	ICD-10: E875
Urinary incontinence	CIHI-DAD	ICD-10: N393, N394, R32
Urinary retention	CIHI-DAD	ICD-10: R33
Urinary tract infections	CIHI-DAD	ICD-10: N10, N11, N12, n136, N151, N159, N160, N300, N308, N309, N340, N390, N410, N411, N412, N413, N431, N45, T835
Charlson comorbidity index	CIHI-DAD	

Healthcare Utilization		
Number of any hospitalizations	CIHI-DAD	
Number of any emergency room visits	NACRS	
GP/FP visits	OHIP IPDB	
Cardiologist visits	IPDB	
Opthamologist vists	IPDB	
Endocrinologist vists	IPDB	
Nephrologist visits	OHIP IPDB	
Diabetes management	OHIP	OHIP fee: K030
Diabetes incentive	OHIP	OHIP fee: Q040
Diabetes management by a specialist	OHIP	OHIP fee: K045
Diabetes management by a specialist team	OHIP	OHIP fee: K046
Cholesterol tests	OHIP	OHIP fee: L055
Proteinuria	OHIP	OHIP fee: L253, L254, L255, G009, G010
Serum creatine tests	OHIP	OHIP fee: L065, L067, L068
Glucose tests	OHIP	OHIP fee: L104, L253, L103, L111
HbA1c tests	OHIP	OHIP fee: L093
DVT/PE	CIHI-DAD	ICD-10: I26, I743, I801, I802, I803
Bone mineral density test	OHIP	OHIP fee: J654, J688, J854, J888, X149, X152, X153, X155, Y654, Y688, Y854, Y888
Hearing test	OHIP	OHIP fee: G153, G154, G440, G441, G442, G443, G448, G450, G451, G452, G525, G526, G529, G530, G533, G815, G816
Sputum	OHIP	OHIP fee: L629, L716, L815
Wound swab	OHIP	OHIP fee: L628
Holter monitoring	CIHI-DAD OHIP	CCI: 2HZ24JAKH OHIP fee: G311, G320, G647, G648, G649, G650, G651, G652, G653, G654, G655, G656, G657, G658, G659, G660, G661, G682, G683, G684, G685, G686, G687, G688, G689, G690, G692, G693
Cardiac stress test	CIHI-DAD OHIP	CCP: 0341, 0342, 0343, 0344, 0605 CCI: 2HZ08, 3IP70 OHIP fee: G315, G174, G111, G112, G319, G582, G583, G584, J607, J608, J807, J808, J809, J866, J609, J666

Coronary revascularization	CIHI-DAD OHIP	CCP: 481, 482, 483, 480 CCI: 1IJ50, 1IJ26, IIJ27, 1IJ57, 1IJ76, 1IJ57GQ, 1IJ54GQAZ OHIP fee: R741, R742, R743, E651, E652, E654, E646, G298, Z434, G262
Electrocardiography	CIHI-DAD OHIP	CCI: 2HZ24JAKE OHIP fee: G310, G313
Pulmonary function test	OHIP	OHIP fee: L354, L358
At-home physician service	OHIP	OHIP fee: A901, B960, B961, B962, B963, B964, B966, B990, B992, B993, B994, B996, B997, B998
Urinalysis	OHIP	OHIP Fee: L253, L254, L255, L633, L634, L641, G009, G010
Cystoscopy	OHIP	OHIP fee: Z606, Z607, Z628, Z632, Z633, Z634
Transurethral resection of the prostate	CIHI-DAD OHIP	CCI: 1QT59BAAD, 1QT59BAAG, 1QT59BAAW, 1QT59BAAZ, 1QT59BACG, 1QT59BAGX, 1QT87BA, 1QT87BAAG, 1QT87BAAK CCP: 721 OHIP fee: S655
Carotid ultrasound	CIHI-DAD OHIP	CCP: 0281 CCI: 3JE30, 3JG30 OHIP fee: J201, J501, J190, J191, J490, J491, J492
Cardiac catheterization	CIHI-DAD OHIP	CCP: 4995, 4996, 4997, 4892, 4893, 4894, 4895, 4896, 4897, 4898 CCI: 3IJ30GP, 3HZ30GP, 2HZ24GPKJ, 2HZ24GPKL, 2HZ24GPKM, 2HZ24GPXJ, 2HZ28GPPL, 2HZ71GP, 3IP10, 3IS10 OHIP fee: G296, G297, G299, G300, G301, G304, G305, G306, G297, G509
Coronary angiogram	CIHI-DAD OHIP	CCP: 4892, 4893, 4894, 4895, 4896, 4897, 4898 CCI: 3IP10, 3IS10 OHIP fee: G297, G509
Electroencephalography (EEG)	OHIP	OHIP fee: G414, G415, G416, G417, G418, G540, G542, G544, G545, G546, G554, G555
Chest x-ray	OHIP	OHIP fee: X090, X091, X092, X195
Echocardiography	CIHI-DAD OHIP	CCP: 0282 CCI: 3IP30 OHIP fee: G560, G561, G562, G566, G567, G568, G570, G571, G572, G574,

		G575, G576, G577, G578, G581
Prostate-specific antigen test	OHIP	OHIP fee: Q005, Q118, Q119, Q120, Q121, Q122, Q123, Q133
Cervical cancer screening	OHIP	OHIP fee: E430, G365, G394, L713, L812
Laboratory Measurements		
eGFR (using serum creatinine)	OLIS	
Serum creatinine	OLIS	OLIS: 14682-9
Serum potassium	OLIS	OLIS: 2823-3, 6298-4,39789-3
Albumin-to-creatinine ratio	OLIS	OLIS: 14959-1, 30000-4, 32294-1
Glycated hemoglobin	OLIS	OLIS: 4548-4, 71875-9, 59261-8, 17855-8, 17856-6, 41995-2

Appendix F. Variables included in the propensity score

Variables included in the propensity score	
Demographics	Age Sex Entry year Rural residence Neighbourhood income quintile Local Health Integration Network
Comorbidities	Duration of diabetes Acute kidney injury Chronic kidney disease Acute urinary retention Chronic obstructive pulmonary disease Chronic lung disease Percutaneous coronary intervention Pacemaker Cancer Stroke Atrial fibrillation Ventricular arrhythmia Coronary artery bypass graft surgery Congestive heart failure Chronic liver disease Coronary artery disease Diabetic retinopathy Diabetic neuropathy Peripheral vascular disease Hypertension Hypotension Hypoglycemia Hyponatremia Hyperkalemia Charlson comorbidity index
Medications	Angiotensin-converting enzyme inhibitors Angiotensin receptor blockers Acetylsalicyclic acid Beta blockers Calcium channel blockers Loop diuretics Potassium sparing diuretics Nonsteroidal anti-inflammatory drugs Statins Thiazide diuretics

	Proton pump inhibitors Picosalax Insulin use 120 days prior to the cohort entry date Acarbose use 120 days prior to the cohort entry date Gliclazide use120 days prior to the cohort entry date Glyburide use 120 days prior to the cohort entry date Metformin use 120 days prior to the cohort entry date Pioglitazine use 120 days prior Insulin use on the cohort entry date Acarbose use on the cohort entry date Gliclazide use on the cohort entry date Glyburide use on the cohort entry date Metformin use on the cohort entry date Insulin use in the 1 year to 120 days prior to the cohort entry date Acarbose use in the 1 year to 120 days prior to the cohort entry date Gliclazide use in the 1 year to 120 days prior to the cohort entry date Glyburide use in the 1 year to 120 days prior to the cohort entry date Metformin use in the 1 year to 120 days prior to the cohort entry date Pioglitazine use in the 1 year to 120 days prior to the cohort entry date
Healthcare Utilization	Number of any hospitalizations Number of emergency department visits Number of general practice or family practice visits Number of cardiologist visits Number of opthamologist visits Number of endocrinologist visits Number of nephrologist visits Diabetes management Diabetes incentive Diabetes management by a specialist Diabetes management by a specialist team Cholesterol test Proteinuria Serum creatinine test Glucose test

	Glycated hemoglobin test Bone mineral density test Hearing test Holter monitoring Cardiac stress test Coronary revascularization Electrocardiography Pulmonary function test At-home physician service Urinalysis Cystoscopy Carotid ultrasound Cardiac catheterization Coronary angiogram Electroencephalography Chest x-ray Echocardiography Prostate-specific antigen test Cervical cancer screening
Other	Prescribing physician specialty Number of medications Estimated baseline glomerular filtration rate

Appendix G. 2012 KDIGO thresholds for AKI stages (27)

Stage	Definition
1	50 to <100% increase in serum creatinine from baseline or an absolute increase ≥0.3 mg/dL, but does not meet stage two or three criteria
2	100 to <200% increase from baseline
3	≥200% increase from baseline, absolute serum creatinine value of 4.0 mg/dL, or receipt of acute dialysis

Appendix H. ACE inhibitors, ARBs and all type of diuretic drugs included in the subgroup analysis

Drug Name	Drug Identification Numbers
ACE inhibitor	
Captopril	00546283, 00546291, 00546305, 00695661, 00851639, 00851647, 00851655, 00851833, 00893595, 00893609, 00893617, 00893625, 01913824, 01913832, 01913840, 01913859, 01942964, 01942972, 01942980, 01942999, 02163551, 02163578, 02163586, 02163594, 02230203, 02230204, 02230205, 02230206, 02237861, 02237862, 02237863, 02242788, 02242789, 02242790, 02242791
Lisinopril	00839329, 00839337, 00839388, 00839396, 00839418, 00839442, 02049333, 02049376, 02049384, 02217481, 02217503, 02217511, 02256797, 02256800, 02256819, 02271443, 02271451, 02271478, 02274833, 02274841, 02274868, 02285061, 02285088, 02285096, 02285118, 02285126, 02285134, 02289199, 02289202, 02289229, 02292203, 02292211, 02292238, 02294230, 02294249, 02294257, 02294591, 02299879, 02299887, 02299895, 02332167, 02332175, 02332183, 02361531, 02361558, 02361566, 02394472, 02394480, 02394499, 09853685, 09853960, 09854010, 09857272, 09857286, 09857287
Enalapril sodium	00670901, 00670928, 00708879, 00708887, 00851795, 02019884, 02019892, 02019906, 02020025, 02233005, 02233006, 02233007, 02291878, 02291886, 02291894, 02291908, 02299933, 02299941, 02299968, 02299976, 02299984, 02299992, 02300001, 02300028, 02300036, 02300044, 02300052, 02300060, 02300079, 02300087, 02300095, 02300109, 02300117, 02300125, 02300133, 02300141, 02300680, 02352230, 02352249, 02352257, 02352265
Benazepril chlorohydrate	00885835, 00885843, 00885851
Cilazapril	01911465, 01911473, 01911481, 02266350, 02266369, 02266377, 02280442, 02280450, 02280469, 02283778, 02283786, 02283794, 02285215, 02285223, 02291134, 02291142, 02291150
Quinapril	01947664, 01947672, 01947680, 01947699, 02248499, 02248500, 02248501, 02248502, 02290987, 02290995, 02291002, 02291010
Ramipril	02050943, 02050951, 02050978, 02050986, 02221829, 02221837, 02221845, 02221853, 02247917, 02247918, 02247919, 02247945, 02247946, 02247947, 02251515, 02251531, 02251574, 02251582, 02255316, 02255324, 02255332, 02283891, 02287692, 02287706, 02287714, 02287722, 02287927, 02287935, 02287943, 02291398, 02291401, 02291428, 02291436, 02295369, 02295482, 02295490, 02295504, 02295512, 02299372, 02301148, 02301156, 02301164, 02301172, 02310503, 02310511, 02310538, 02310546, 02331101, 02331128, 02331136, 02331144, 02332299, 02332302, 02332310, 02332329, 02374846, 02374854, 02374862, 02387387, 02387395, 02387409, 02387417, 02420457, 02420465, 02420473, 02420481,

	02421305, 02421313, 02421321, 02438860, 02438879, 02438887, 02438895
Perindopril tert-butylamine	02123274, 02123282, 02246624
Trandolapril	02231459, 02231460, 02239267
Fosinopril	02242733, 02242734, 02262401, 02262428, 02331004, 02331012
Fosinopril sodium	02247802, 02247803, 02255944, 02255952, 02266008, 02266016, 02275252, 02275260, 02294524, 02294532, 02332566, 02332574, 01907107, 01907115
Benazapril HCL	02273918, 02290332, 02290340
Hydrochlorothiazide & Lisinopril	02301768
ARB	
Losartan potassium	02182815, 02182874, 02182882, 02309750, 02309769, 02309777, 02313332, 02313340, 02313359, 02353504, 02353512, 02354829, 02354837, 02354845, 02357968, 02357976, 02368277, 02368285, 02368293, 02379058, 02380838, 02398834, 02398842, 02398850, 02403323, 02403331, 02403358, 02404451, 02404478, 02404486, 02405733, 02405741, 02405768, 02422468, 02422484, 02424967, 02424975, 02424983, 02426595, 02426609, 02426617
Valsartan	02236808, 02236809, 02244781, 02244782, 02289504, 02313006, 02313014, 02337495, 02337509, 02337517, 02344564, 02356651, 02356678, 02356686, 02356759, 02356767, 02356775, 02363100, 02363119, 02371529, 02371537, 02371545, 02383535, 02383543, 02383551, 02414228, 02414236, 02414244
Irbesartan	02237923, 02237924, 02237925, 02315971, 02315998, 02316005, 02316390, 02316404, 02316412, 02317060, 02317079, 02317087, 02328070, 02328089, 02328100, 02328461, 02328488, 02328496, 02347296, 02347318, 02347326, 02386968, 02386976, 02386984, 02406810, 02406829, 02406837, 02418193, 02418207, 02418215, 02422980, 02422999, 02423006, 02427087, 02427095, 02427109
Candesartan Cilexetil	02239090, 02239091, 02239092, 02311658, 02326957, 02326965, 02326973, 02365340, 02365359, 02365367, 02366312, 02366320, 02366339, 02376520, 02376539, 02376547, 02376555, 02379120, 02379139, 02379147, 02379155, 02379260, 02379279, 02379287, 02379295, 02380684, 02380692, 02380706, 02380714, 02386496, 02386518, 02386526, 02386534, 02391171, 02391198, 02391201, 02391228, 02392267, 02399105, 02417340
Eprosartan Mesylate	02240431, 02240432, 02243942
Telmisartan	02240769, 02240770, 02320177, 02320185, 02375958, 02375966, 02376717, 02376725, 02391236, 02391244, 02393247, 02393255, 02407485, 02407493, 02420082, 02420090, 02432897, 02432900, 02434164
Eprosartan Mesylate & Hydrochlorothiazide	02253631
Olmesartan Medoxomil	02318660, 02318679

Hydrochlorothiazide & Quinopril	02408775
Hydrochlorothiazide & Telmisartan	02433214
Loop Diuretics	
Bumetanide	00728276, 00728284, 02176076
Ethacrynic acid	00016497, 02258528
Furosemide	00012580, 00217743, 00289590, 00332275, 00337730, 00337749, 00344079, 00353612, 00362166, 00380016, 00380024, 00396249, 00396788, 00432342, 00527033, 01900943, 01987585, 01987615, 01987739, 01987798, 01988832, 02224690, 02224704, 02224720, 02224755, 09857208
Potassium Sparring Diuretics	
Amiloride HCL	00487805, 02249510
Amiloride HCL & Hydrochlorothiazide	00487813, 00784400, 00886106, 01937219, 02174596, 02257378
Eplerenone	02323052, 02323060
Hydrochlorothiazide & Spironolactone	00180408, 00594377, 00613231, 00657182
Hydrochlorothiazide & Trimolol Maleate	00509353
Hydrochlorothiazide & Triamterene	00181528, 00441775, 00532657, 00865532, 01910191, 01919547
Spironolactone	00028606, 00285455, 00613215, 00613223
Triamterene	00027138, 00299715, 01919563, 01919571
Thiazide Diuretics	
Chlorthalidone	00010413, 00010421, 00293881, 00298964, 00337447, 00337455, 00360279, 00360287, 00398365, 00398373
Hydrochlorothiazide	00016500, 00016519, 00021474, 00021482, 00092681, 00092703, 00263907, 00312800, 00326844, 02247386, 02247387
Indapamide	00564966, 02049341, 02153483, 02179709, 02223597, 02223678, 02227339, 02231184, 02239619, 02239620, 02240067, 02245246, 02373904, 02373912
Metolazone	00301663, 00301671, 00301698, 00888400, 00888419, 00888427

Appendix I. Serum creatinine measurement during the follow-up period

	Observed		Weighted[b]				
	No. events (%)		No. events (%)				
	SGLT2 inhibitors (n=19,611)	DPP4 inhibitors (n=19,483)	SGLT2 inhibitors (n=19,611)	DPP4 inhibitors (n=19,775)	Risk difference, % (95% CI)	Risk Ratio (95% CI)	P value
At least one serum creatinine measurement[c]	10,619 (54.15)	9,602 (49.28)	10,619 (54.15)	9,718 (49.14)	5.00 (3.65 to 6.36)	1.10 (1.07 to 1.13)	< 0.01

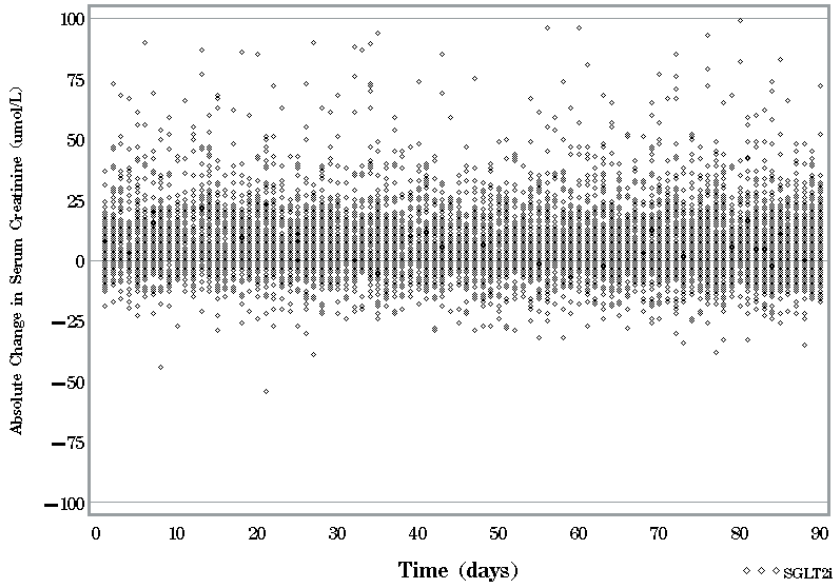
Abbreviations: CI= confidence interval, DPP4= dipeptidyl peptidase-4, SGLT2= sodium-glucose cotransporter-2

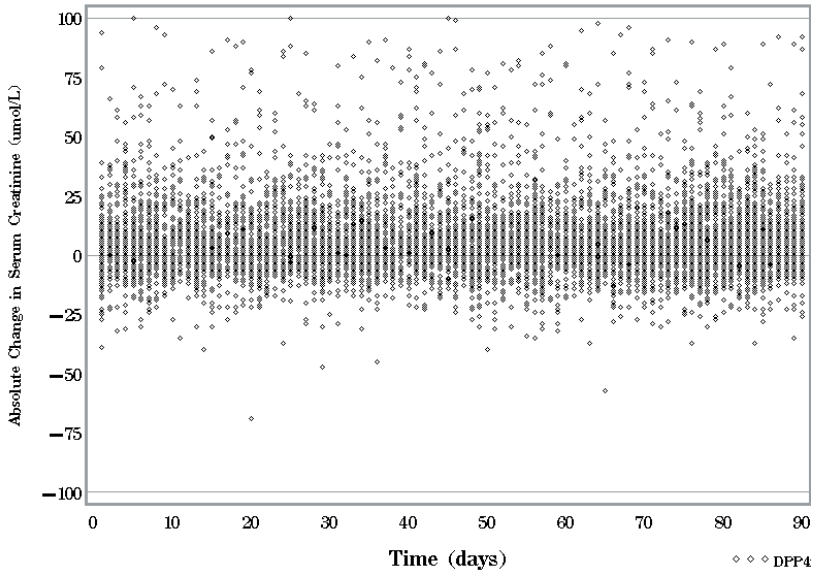
[a]Reference group: DPP4 inhibitor users.

[b]Weighted using inverse probability of treatment weighting based on propensity scores, using weights to estimate the average treatment effect in the treated. Patients in the reference group were weighted as [propensity score/(1 - propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group (71,73,74)**.** Weighted relative risks and 95% CIs were obtained using modified Poisson regression (88) and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function.

[c]Based on tests done in an outpatient setting assessed using the Ontario Laboratories Information System serum creatinine values.

Appendix J. Absolute changes (µmol/L) in serum creatinine after SGLT2 inhibitor and DPP4 inhibitor initiation





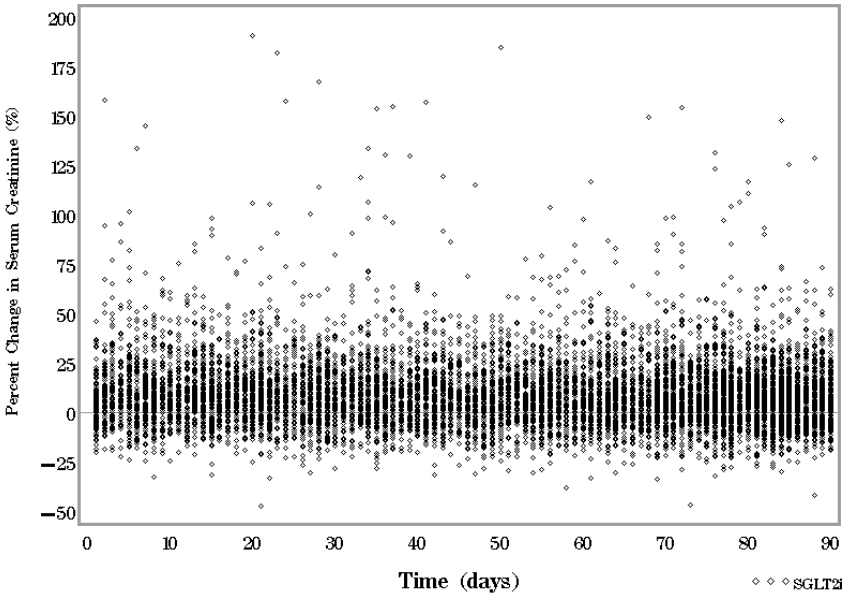
SGLT2i users			
	Unit change (weighted)		
N	Mean (SD)	95% CI	Median (IQR)
10,936	8 (26)	7-8	5 (-1,12)

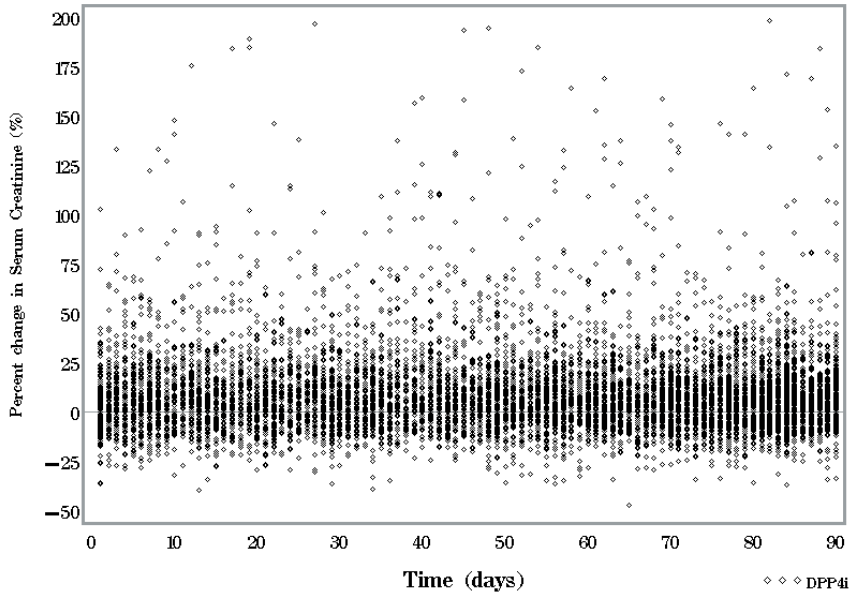
DPP4i users			
	Unit change (weighted)		
N	Mean (SD)	95% CI	Median (IQR)
10,070	7 (26)	6-7	4 (-2,11)

Weighted mean difference		p-value
Estimate	95% CI	
1 .01	0.30-1.71	0.005

[a]Weighted mean difference and 95% CIs were obtained using a normal regression model with an identity link function.

Appendix K. Percent changes in serum creatinine after SGLT2 inhibitor and DPP4 inhibitor initiation





SGLT2i users			
	Unit change (weighted)		
N	Mean (SD)	95% CI	Median (IQR)
10,936	10 (32)	9-11	7 (-1,16)

DPP4i users			
	Unit change (weighted)		
N	Mean (SD)	95% CI	Median (IQR)
10,070	9 (29)	8-9	5 (-3,14)

Weighted mean difference		p-value
Estimate	95% CI	
1.27	0.45-2.10	0.002

[a]Weighted mean difference and 95% CIs were obtained using a normal regression model with an identity link function.

Appendix L. Risk of hospital encounter with acute kidney injury[a] within 365 days among SGLT2 inhibitor new users compared with DPP4 inhibitor new users

	Observed			Weighted[c]				
	No. patients	**No. events (%)**	**Event rate per 1000 person-years**	**No. patients**	**No. events (%)**	**Event rate per 1000 person-years**	**Hazard ratio (95% CI)**	**P value**
SGLT2 inhibitors	19,611	2,666 (13.59)	172.42	19,611	2,666 (13.59)	172.42	0.83 (0.78 to 0.89)[d]	<.0001
DPP4 inhibitors[b]	19,483	3,712 (19.05)	245.77	19,775	3,164 (16.00)	207.51		

Abbreviations: CI= confidence interval, DPP4= dipeptidyl peptidase-4, SGLT2= sodium-glucose cotransporter-2

[a]365- day risk of acute kidney injury, based on hospital presentation (emergency department or hospitalization) assessed using the Ontario Laboratories Information System serum creatinine values.

[b]Reference group: DPP4 inhibitor users.

[c]Weighted using inverse probability of treatment weighting based on propensity scores, using weights to estimate the average treatment effect in the treated. Patients in the reference group were weighted as [propensity score/(1 - propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group (71,73,74)**.**

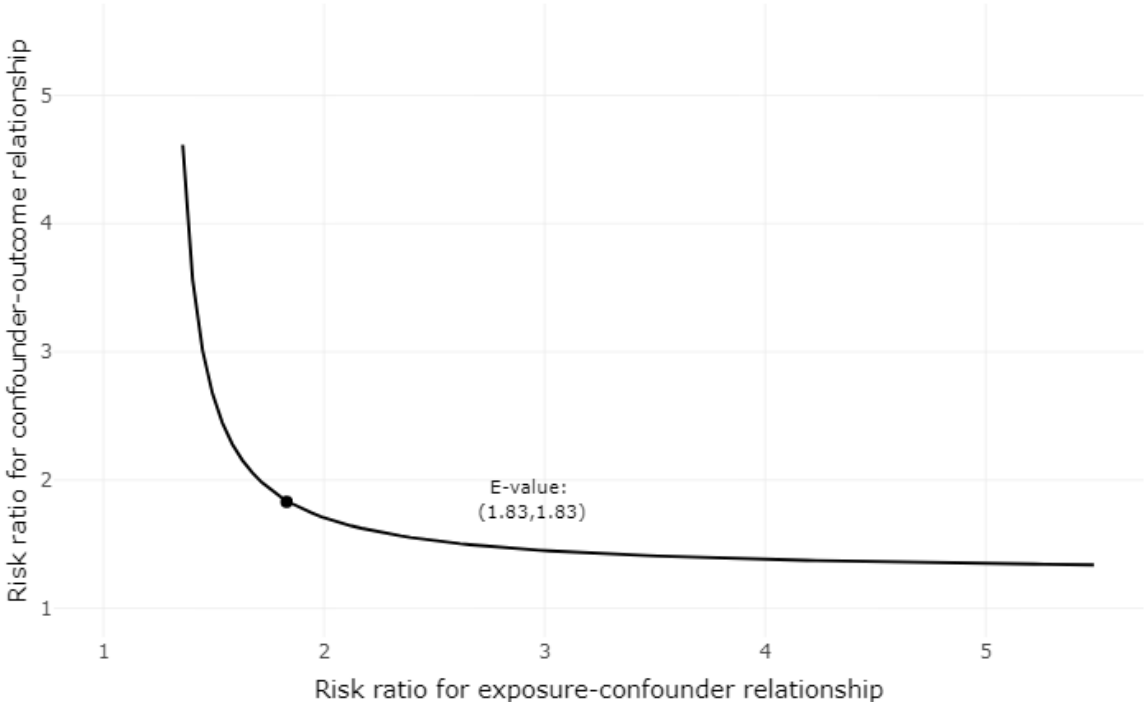
[d]Weighted hazard ratio and 95% CI were obtained using Cox regression (with 365-day follow-up censoring on death). A similar result was observed when death was treated as a competing risk. 95% CI was obtained using a bootstrap estimator (100). In addition, the proportional hazards assumption was tested by including time dependent covariates in the model and the assumption was not violated.

Appendix M. 90-day risk of hospital encounter with bowel obstruction

	Observed		Weighted[b]					
	No. events (%)		No. events (%)		Risk difference, % (95% CI)	P value	Risk ratio (95% CI)	P value
	SGLT2 inhibitors (n=19,611)	DPP4 inhibitors (n=19,483)	SGLT2 inhibitors (n=19,611)	DPP4 inhibitors (n=19,775)				
Outcome								
Bowel obstruction[c]	20 (0.10)	36 (0.18)	20 (0.10)	20 (0.10)	0 (-0.07 to 0.07)	1.00	1.00 (0.49 to 2.06)	1.00

Abbreviations: CI= confidence interval, DPP4= dipeptidyl peptidase-4, SGLT2= sodium-glucose cotransporter-2.
[a]Reference group: DPP4 inhibitor users.
[b]Weighted using inverse probability of treatment weighting based on propensity scores, using weights to estimate the average treatment effect in the treated. Patients in the reference group were weighted as [propensity score/(1 - propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group (71,73,74). Weighted risk ratios and 95% CIs were obtained using modified Poisson regression (88) and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function.
[c]Based on hospital presentation (emergency department or hospitalization) assessed using diagnostic codes.

Appendix N. Post-hoc E-value analysis



E-value for point estimate: 1.83 and for confidence interval: 1.14

Each point along the curve defines a joint relationship between the two sensitivity parameters that could potentially explain away the estimated effect. If one of the two parameters is smaller than the E-value, the other must be larger, as defined by the plotted curve

Curriculum Vitae

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Post-secondary Education and Degrees:
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2012-2016 B.MSc. Interdisciplinary Medical Sciences

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Honours and Awards:
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Ontario Drug Policy Research Network Student Training Program Trainee Award
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Iskander, Carina, et al. (2019). Identifying Ontario geographic regions to assess adults who present to hospital with laboratory-defined conditions: a population-based study. CMAJ Open, 7(4): E624-E629