Appendix 1 (as submitted by the authors): Supplementary tables and figures

Appendix to: Iskander C, Cherney DZ, Clemens KK, et al. Use of sodium-glucose cotransporter-2 inhibitors and risk of acute kidney injury in older adults with diabetes: a population-based cohort study. *CMAJ* 2020. doi: 10.1503/cmaj.191238.

Appendix 1A. Regulatory warnings surrounding the risk of acute kidney injury following SGLT2 inhibitor use (1,2)

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 (2). - 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 (1).
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 (3).
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 (2). - 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 (1).

Appendix 1B. 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 (5)[a] - The percentage of patients with AKI was lower in the empagliflozin groups compared to placebo - Doubling of the SCr occurred level less among empagliflozin users [HR 0.56 (95% CI 0.39 to 0.79)] (5)[a] - The risk of renal-replacement therapy was lower with empagliflozin users [HR 0.45 (95% CI 0.21-0.97)] (5)[a]	- 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
Neal et al., 2017 (6)	- 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	- 4,347 patients received placebo and 5,795 patients received canagliflozin (mean age 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	- Moderate number of events for important outcomes - Kidney endpoints were exploratory in CANVAS (not the primary purpose of the trial) - 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	27

	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	canagliflozin [HR 0.60 (95% CI 0.47 to 0.77)]		performed at least every 26 weeks in both trials	
Wiviott et al., 2018 (7)	- 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 for atherosclerotic cardiovascular disease were randomized to receive 10 mg of dapagliflozin or matching placebo	- 8, 578 patients received placebo and 8,582 patients received dapagliflozin (mean age 64 years in both groups) - AKI occurred less frequently in the 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)]	- Renal findings may not be generalizable to patients not at risk for atherosclerotic cardiovascular disease - AKI was not one of the primary outcomes of interest	- 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 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	28

Perkovic et al., 2019 (8)	- 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, 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)]	- 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 - 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	25
Population-Based Studies					
Nadkarni et al., 2017 (9)	- 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 different between SGLT2 inhibitor users and nonusers [adjusted HR 0.60 (95% CI 0.40 to 1.10)]	- 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 likely be present	- 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

Cahn et al., 2018 (10)	- 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 (11)	- Retrospective cohort study using data from nationwide health and administrative registers in Sweden and Denmark to compare patients that newly initiated an SGLT2 inhibitor or a GLP1 receptor agonist between July 2013 to December 2016	- 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 0.45 to 1.05)] in SGLT2 inhibitor users compared to GLP1 receptor agonist users	- The use of canagliflozin was rare among SGLT2 inhibitor users - Medication compliance might 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	- 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 most recent prescription - Median follow-up time ranged between 270 and 274 days	18

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).

Appendix 1C. REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement for Pharmacoepidemiology (RECORD-PE) (12)

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.	—	—	Introduction
Objectives				
3	State specific objectives, including any prespecified hypotheses.	—	—	Introduction
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.	Methods: Study Design & Research Setting
Setting				
5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	—	—	Methods: Study Design & Research Setting
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. 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.	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 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	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 multiple entries were permitted. See explanatory document for guidance related to matched designs.	Methods: Data Sources; Cohort Assembly

		with linked data at each stage.		
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. 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.	Methods: Cohort Assembly; Outcomes •Codes for baseline characteristics available upon request
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.	Methods: Data Sources
Bias				
9	Describe any efforts to address potential sources of bias.	—	—	Methods: Additional Outcomes

				Interpretation: Study Strengths
Study size				
10	Explain how the study size was arrived at.	—	—	Figure 1
Quantitative variables				
11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	—	—	Methods: Statistical Analyses
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.	Methods: Additional Outcomes; Statistical Analyses Footnotes of Table 1
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 cleaning methods used in the study.	—	N/A
Linkage				
12	—	12.3: State whether the study included person	—	Methods: Data Sources

		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.		
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.	—	Figure 1
Descriptive data				
14	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential 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).	—	—	Table 1, Appendix 8
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.	—	—	Table 2
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 period.	—	—	Table 2
Other analyses				
17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses.	—	—	Figure 2; Appendix 11
Discussion				
Key results				
18	Summarise key results with reference to study objectives.	—	—	Interpretation
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.	Interpretation: Study Limitations
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.	Interpretation: Conclusion

Generalisability				
21	Discuss the generalisability (external validity) of the study results.	—	—	Interpretation
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.	—	—	Funding
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 1D. Data sources[a] and details about the information used in the study

Ontario Drug Benefit (ODB) database	- Identified prescription claims for individuals aged 65 years or older. This database contains accurate records of all dispensed outpatient prescriptions (13).
Ontario Laboratory Information System (OLIS)	- Studied laboratory values from hospital and community laboratories, to assess changes in serum creatinine to diagnose AKI and estimated glomerular filtration rate (eGFRs) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (14).
Canadian Institute for Health Information's Discharge Abstract Database (DAD) and National Ambulatory Care Reporting System (NACRS)	- Ascertained information on hospitalizations and emergency department visits, respectively
Ontario Health Insurance Plan (OHIP) Database	- Ascertained information on physician billings
ICES Physician Database (IPDB)	- Ascertained information on prescribing physicians
Registered Persons Database (RPDB)	- Ascertained information on demographic characteristics and vital status

[a]We used the 10th edition of the International Classification of Diseases diagnosis codes to define comorbidities.

Appendix 1E. 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 OHIP	CCI: 1IJ50, 1IJ57GQ, 1IJ54GQAZ OHIP fee: Z434, G262, G298
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 1F. Standard daily drug doses of SGLT2 inhibitors and DPP4 inhibitors (15)

Drug	Standard daily drug doses (mg/day)
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 1G. 2012 KDIGO thresholds for AKI stages (16)

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 1H. 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 1I. Variables included in the propensity score model

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 endorcrinologist 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 Glycosylated 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 1J. All 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)	Stan. Diff.[c] (%)	SGLT2 inhibitors (*n* = 19,611)	DPP4 inhibitors (*n* = 19,775)	Stan. Diff.[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						
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 score[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 agents 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 agents 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 agents 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
Serum creatine 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 in prior year						
eGFR[j], 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+	16,786 (85.6)	14,405 (73.9)	29	16,786 (85.6)	16,009 (81.0)	12
45-<60	2,825 (14.4)	5,078 (26.1)	29	2,825 (14.4)	3,766 (19.0)	12
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
Most recent SCr value, 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
Most recent potassium value, 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
Most recent 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 glycosylated hemoglobin level, %						
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 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, ASA= acetylsalicyclic acid, 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= hemoglobin A1c, IQR= interquartile range, KFRE= kidney failure risk equation, NSAID= nonsteroidal anti-inflammatory drug, SCr= serum creatinine, Stan. Diff.= standardized difference, 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. (17–19)

[c]The difference between the groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference. (20)

[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.

[f]Charlson comorbidity score (21,22)was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0.

[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.

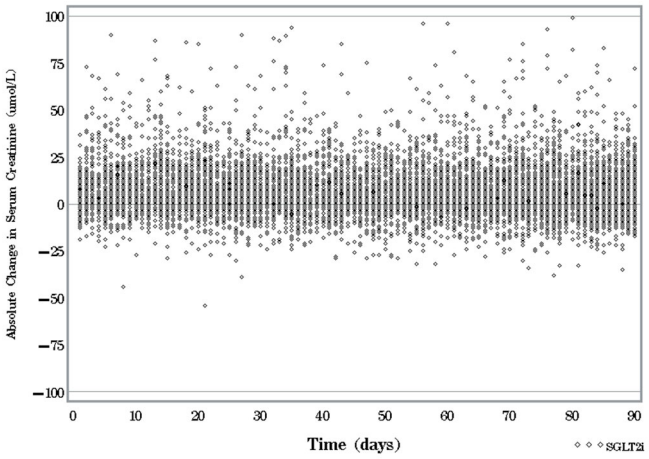
[j]The most recent eGFR measurement in the 1-to-365–day period before the index date; eGFR was calculated using the Chronic Kidney Disease (CKD)–Epidemiology (EPI) equation: 141 × min([serum creatinine concentration in μmol/L/88.4]/κ, 1)α × max([serum creatinine concentration in μmol/L/88.4]/κ, 1)-1.209 × 0.993Age × 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.

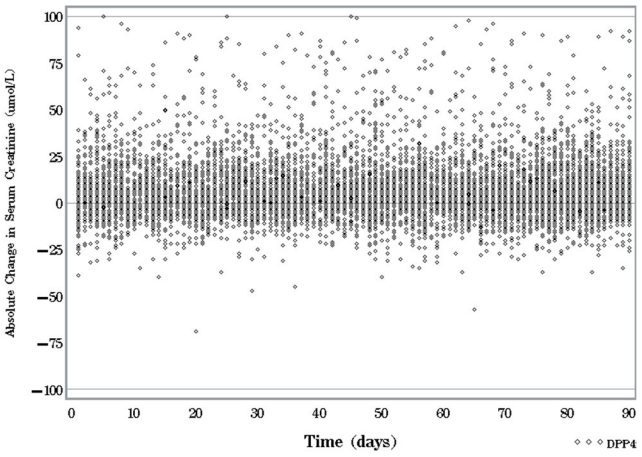
Appendix 1K. The proportion of patients who had at least one serum creatinine measurement during the follow-up period

	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)	*P* value	Relative risk (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)	< 0.01	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 (17–19). Weighted relative risks and 95% CIs were obtained using modified Poisson regression (23) 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 1L. Absolute changes (µmol/L) in serum creatinine after SGLT2 inhibitor and DPP4 inhibitor use





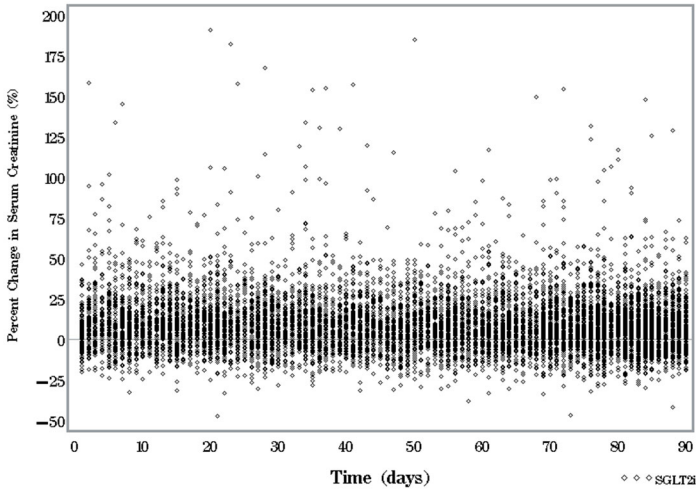
SGLT2i users			
	Unit change (weighted)		
N	Mean (SD)	95% CI	Median (IQR)
10,936	8 (26)	7-8	5 (-1,12)

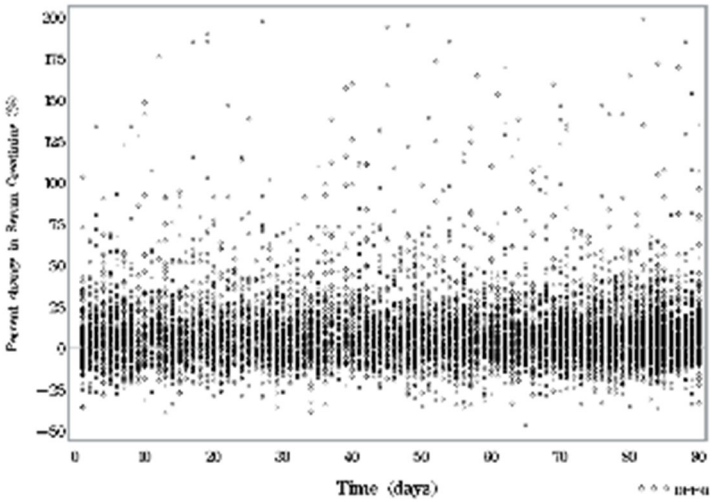
DPP4i users			
	Unit change (weighted)		
N	Mean (SD)	95% CI	Median (IQR)
10,070	7 (26)	6-7	4 (-2,11)

Weighted mean difference[a]		p-value
Estimate	95% CI[a]	
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 1M. Percent changes in serum creatinine after SGLT2 inhibitor and DPP4 inhibitor use





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[a]		p-value
Estimate	95% CI[a]	
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 1N. 90-day risk of hospital encounter with acute kidney injury using diagnostic codes

	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								
Acute kidney injury[c]	65 (0.33)	155 (0.80)	65 (0.33)	83 (0.42)	-0.09 (-0.23 to 0.05)	0.23	0.79 (0.55 to 1.14)	0.22

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 (17–19)**.** Weighted risk ratios and 95% CIs were obtained using modified Poisson regression (23) 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 1O. Risk of hospital encounter with acute kidney injury[a] within 365 days among SGLT2 inhibitor users compared with DPP4 inhibitor 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 (17–19)**.**

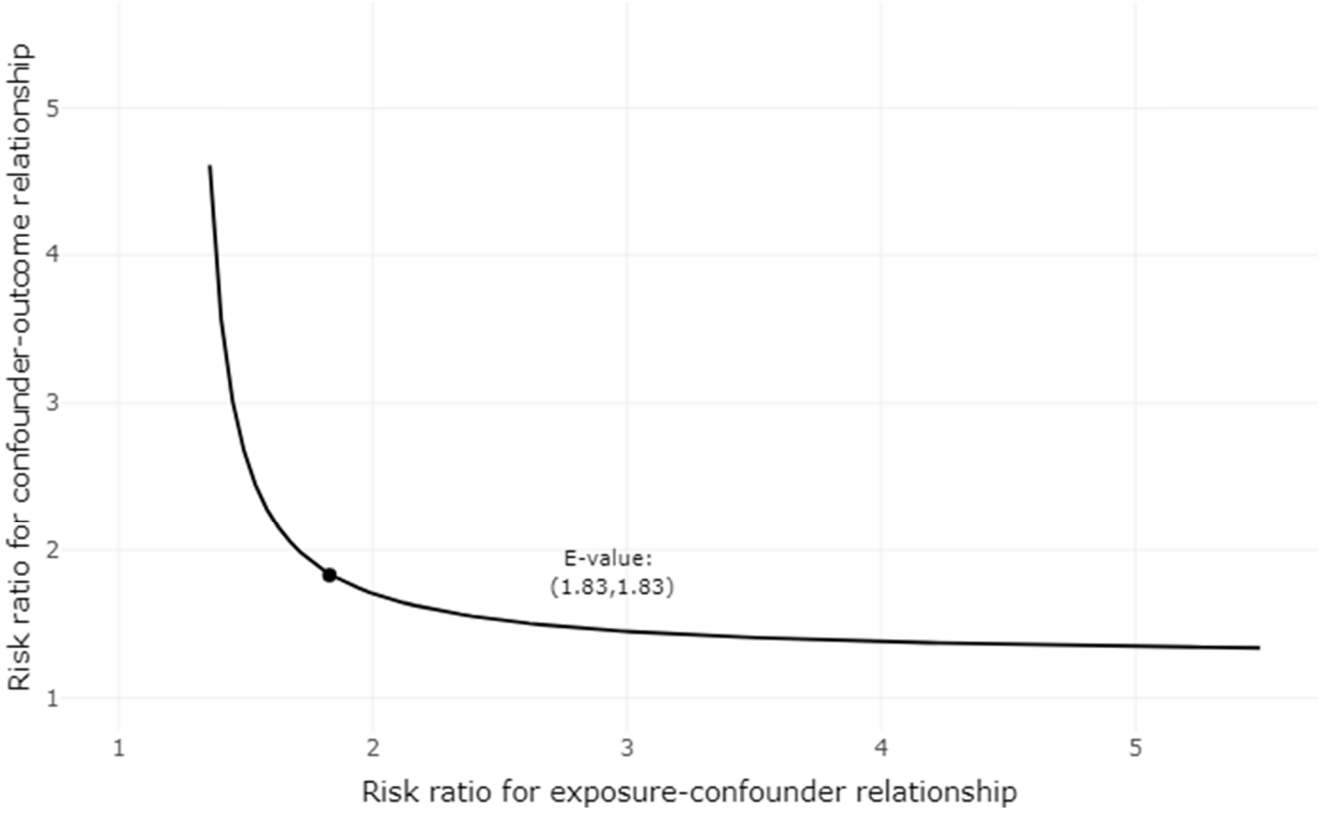
[d]Weighted hazard ratio and 95% CI were obtained using Cox regression (with 365-day follow-up censoring on death). A similar result was observed when death was treated as a competing risk, with a HR 0.83 (95% CI 0.79 to 0.88). 95% CI was obtained using a bootstrap estimator (24). In addition, the proportional hazards assumption was tested by including time dependent covariates in the model and the assumption was not violated.

Appendix 1P. 90-day risk of hospital encounter with bowel obstruction

	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,[a] % (95% CI)	*P* value	Risk ratio[a] (95% CI)	*P* value
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 (17–19)**.** Weighted risk ratios and 95% CIs were obtained using modified Poisson regression (23) 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.

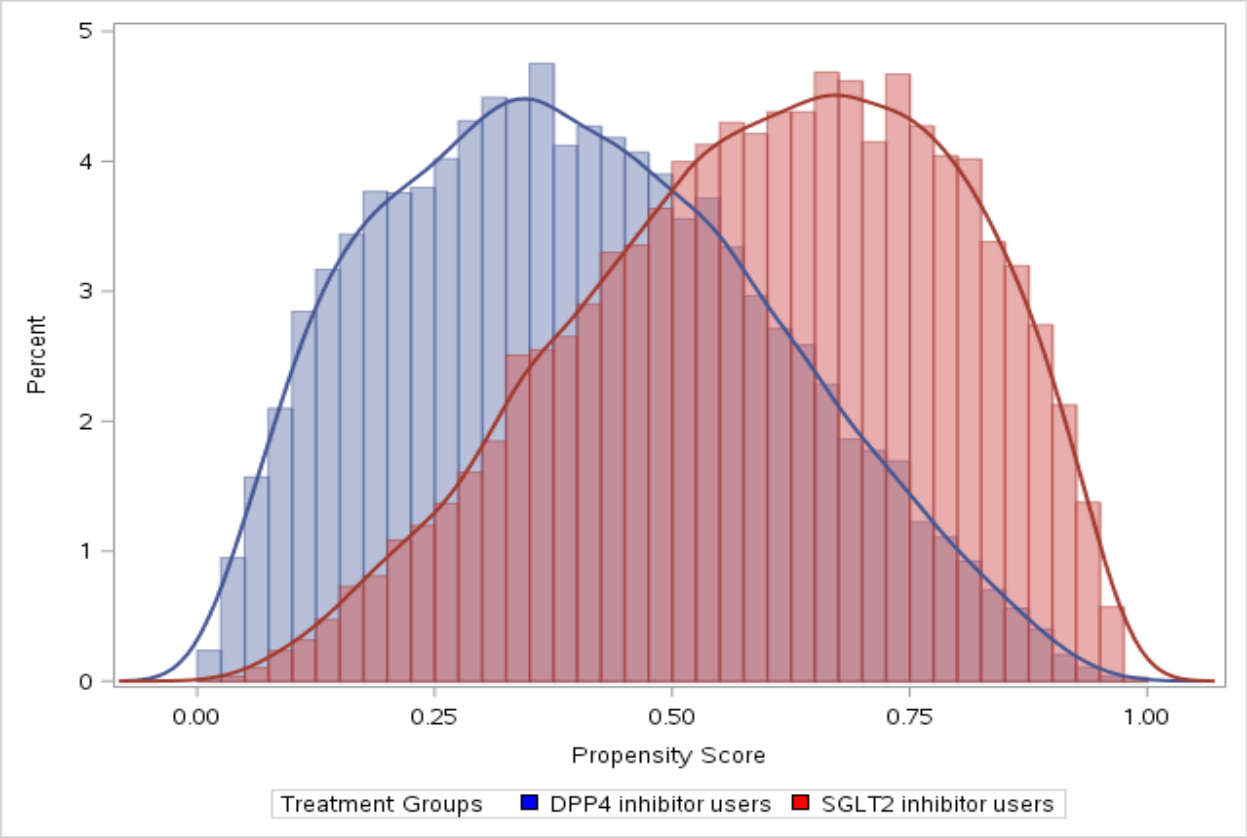
Appendix 1Q. Post-hoc E-value analysis to assess the extent of unmeasured confounding that would be required to negate the observed results



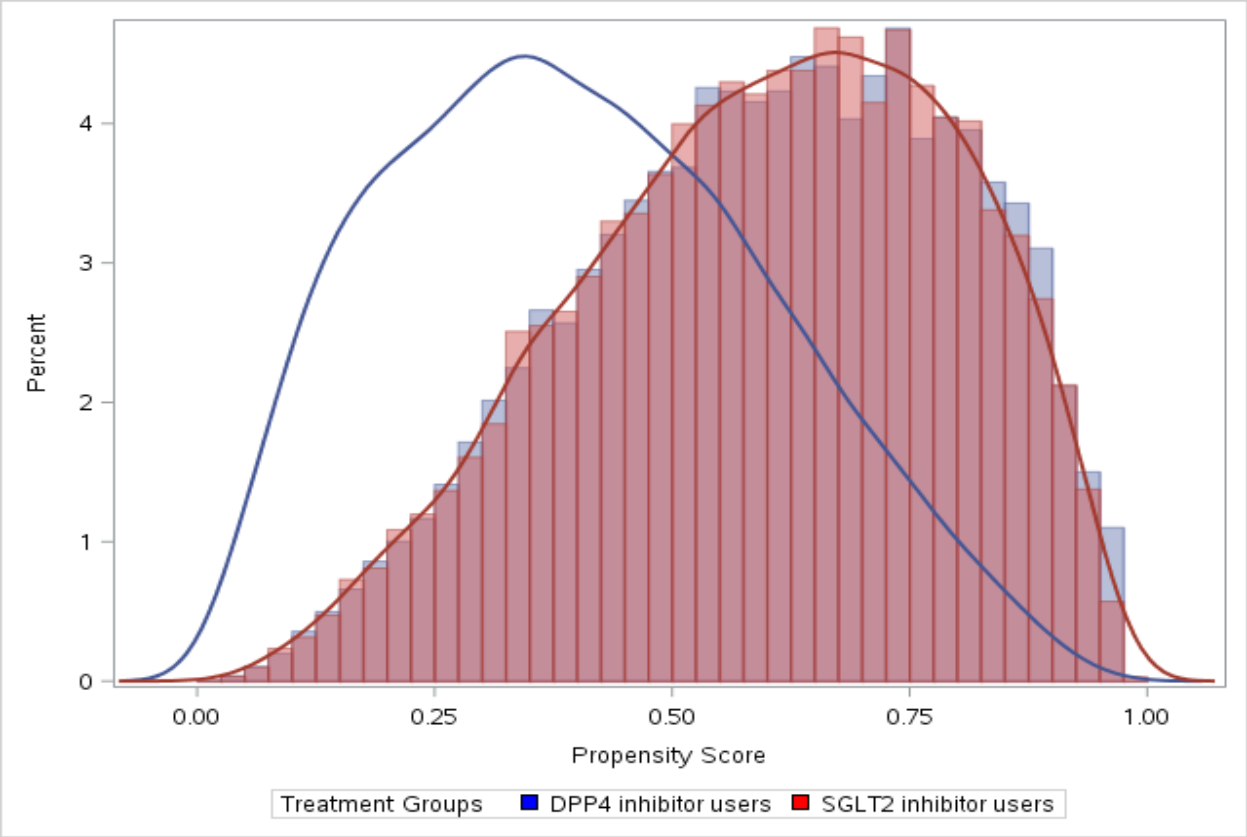
E-value for point estimate: 1.83 and for confidence interval: 1.14

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

Appendix 1R. Observed distribution of propensity scores in SGLT2 inhibitor users and DPP4 inhibitor users



Appendix 1S. Weighted distribution[a] of propensity scores in SGLT2 inhibitor users and DPP4 inhibitor users



[a]Please refer to Table 1 in the manuscript to see that weighting achieved balance on the measured covariates.

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