

Appendix Table 1: Start and end dates of study period at each site for source population creation

Site	Start and end dates of study period
Alberta	January 1, 2008 – March 31, 2017
British Columbia	January 1, 2006 – June 30, 2018
Manitoba	January 1, 2006 – March 31, 2018
Nova Scotia*	November 1, 2016 – June 30, 2018
Ontario	January 1, 2006 – March 31, 2018
Quebec	January 1, 2006 – June 30, 2018
Saskatchewan	February 13, 2008 – June 30, 2018
Clinical Practice Research Datalink	January 1, 2006 – December 31, 2017

*Due to limitations in prescription drug data availability, patients were only included from November 1, 2017 to June 30, 2018.

Appendix Table 2: List of diagnosis and procedure codes for amputation outcome definitions

Outcome	Diagnosis codes	Procedure codes			
	ICD-10-CA	ICD-9-CM	CCP*	CCI*	OPCS
Below-knee amputation	—	84.11	96.11 96.12 96.13 96.14	1VG93	X095
		84.12		1VQ93	X101
		84.13		1WA93	X102
		84.14		1WE93	X103
		84.15		1WI93	X104
		84.16		1WJ93	X108
				1WK93	X109
				1WL93	X111
				1WM93	X112
				1WN93	X118
					X119

CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CA, International Classification of Diseases, 10th Revision, with Canadian Enhancement; OPCS, Office of Population Censuses and Surveys.

*Source for CCP and CCI codes for below-knee amputation: Huseynova K et al. 2018.

Appendix Table 3: List of sites included in the meta-analysis of the association between the use of SGLT2 inhibitors and the risk of below-knee amputations among patients with type 2 diabetes *

		AB	BC	MB	NS	ON	QC	SK	CPRD
Main analysis		✓	✓	✓		✓	✓	✓	✓
Age	≥70 years		✓			✓	✓		
	<70 years	✓	✓	✓		✓	✓	✓	
Sex	Females		✓			✓	✓		
	Males	✓	✓	✓		✓	✓	✓	
Prior insulin use	Yes	✓	✓	✓		✓	✓	✓	
	No		✓	✓		✓	✓		
SGLT2 inhibitor molecule	Canagliflozin	✓	✓			✓	✓	✓	
	Dapagliflozin		✓	✓		✓	✓		
	Empagliflozin		✓			✓	✓		
Intention-to-treat approach		✓	✓	✓		✓	✓	✓	
Varying grace period	0 day		✓	✓		✓	✓		
	60 days	✓	✓	✓		✓	✓	✓	✓
	365 days	✓	✓	✓		✓	✓	✓	✓
New user status	Incident users	✓	✓	✓		✓	✓	✓	
	Prevalent users		✓			✓	✓		

Abbreviations: AB, Alberta; BC, British Columbia; CPRD, Clinical Practice Research Datalink; DKA, diabetic ketoacidosis; MB, Manitoba; NS, Nova Scotia; QC, Quebec; SK, Saskatchewan.

*Inclusion in each meta-analysis was restricted to sites with at least 5 events in each exposure group.

Appendix Table 4: Additional baseline characteristics of new users of SGLT2 inhibitors and their matched DPP-4 users among patients with type 2 diabetes in the CPRD*

Characteristic	SGLT2 inhibitors[†] (n = 5,388)	DPP-4 inhibitors (n = 5,388)
Blood pressure		
DBP <90 and SBP <140	3484 (64.7)	3548 (65.9)
DPB ≥90 or SBP ≥140	1896 (35.2)	1829 (33.9)
Unknown	8 (0.1)	11 (0.2)
Body mass index (kg/m²)[‡]		
<30	1534 (28.5)	1725 (32.0)
≥30	3835 (71.2)	3634 (67.4)
Unknown	19 (0.4)	29 (0.5)
eGFR (mL/min/1.73m²)		
<60	284 (5.3)	510 (9.5)
≥60	5097 (94.6)	4867 (90.3)
Unknown	7 (0.1)	11 (0.2)
HbA1c, % (mmol/mol)		
≤7% (≤53mmol/mol)	184 (3.4)	216 (4.0)
7.1-8% (54-64mmol/mol)	1047 (19.4)	1081 (20.1)
>8 (>64mmol/mol)	4121 (76.5)	4054 (75.2)
Unknown	36 (0.7)	37 (0.7)
Race		
White	3926 (72.9)	3867 (71.8)
Other	537 (10.0)	575 (10.7)
Unknown	925 (17.2)	946 (17.6)
Smoking status		
Never	2161 (40.1)	s
Ever	3221 (59.8)	3281 (60.9)
Unknown	6 (0.1)	s

Abbreviations: CPRD, Clinical Practice Research Datalink; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter 2.

*Data are presented as n (%). Values suppressed due to privacy restrictions are presented as s.

[†]SGLT2 inhibitors patients were matched to DPP-4 inhibitors patients from their exposure-set (defined on level of antidiabetic therapy, prior use of GLP-1 receptor agonists, time on DPP-4 inhibitors for prevalent new users and calendar time) on time-conditional propensity score.

[‡]The assessment of body mass index, smoking status, blood pressure, eGFR and HbA1c was based on the last measurement before study cohort entry, and race was assessed ever before.

Appendix Table 5: Crude and adjusted hazard ratios for the association between SGLT2 inhibitor use and the risk of below-knee amputation among patients with type 2 diabetes and no prior history of dialysis in the past 3 years, Ontario site only

Treatment group	No. patients	No. events	Person-years	Crude incidence rate per 1,000 person-years*	Crude HR (95% CI) †	Adjusted HR (95% CI) ‡
SGLT2 inhibitors	65,021	77	56,145	1.4	1.17(0.84-1.62)	1.13 (0.81-1.57)
DPP-4 inhibitors	64,994	68	58,721	1.2	Reference	Reference

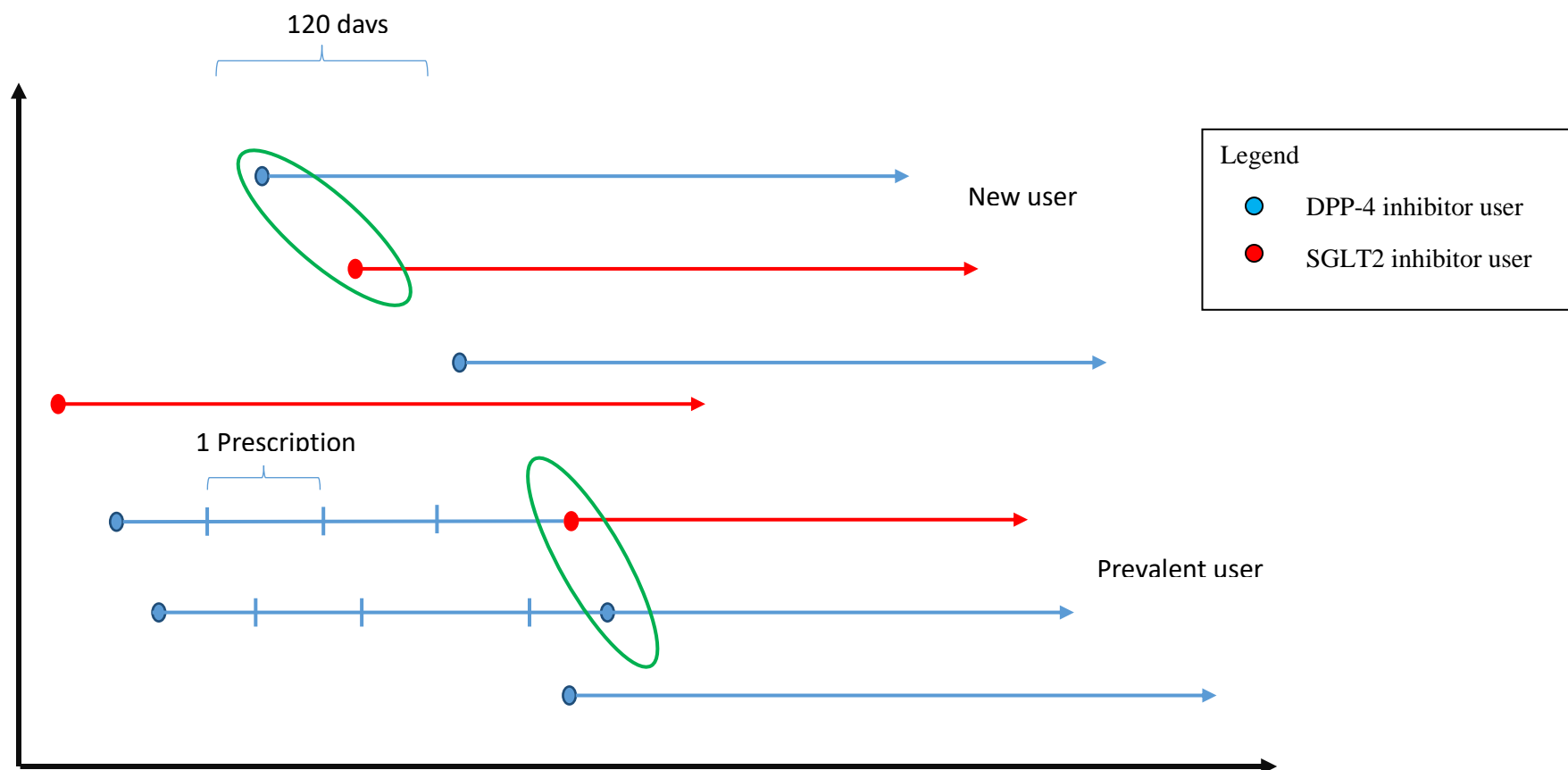
Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; HR, hazard ratio; SGLT2, sodium glucose cotransporter 2.

*Incidence rate was calculated using all study cohorts.

†SGLT2 inhibitors patients were matched to DPP-4 inhibitors patients from their exposure-set (defined on level of anti-diabetic therapy, time on DPP-4 inhibitors [for prevalent new users only], prior use of GLP-1 receptor agonists, and within 120 days of the SGLT2 prescription) on time-conditional propensity score.

‡Outcome models were adjusted for age (continuous), sex, diabetes duration (continuous) and deciles of time-conditional propensity score.

Appendix Figure 1: Study design for matching SGLT2 inhibitor user and DPP-4 inhibitor user*



*New users refer to incident SGLT2 inhibitor users who were matched to incident DPP-4 inhibitor users. Prevalent new users of SGLT2 inhibitor users were matched to DPP-4 inhibitor users who were treated with DPP-4 inhibitors for the same duration. Note SGLT2 inhibitor users were matched to DPP-4 inhibitor users on calendar time (i.e. DPP-4 inhibitor prescription within 120 days of SGLT2 inhibitor initiation).

Abbreviations: DPP-4, dipeptidyl peptidase-4; SGLT2, sodium-glucose co-transporter 2.

Sodium Glucose Co-transporter-2 Inhibitors and the Risk of Below-knee Amputation: a Multicenter Observational Study

List of the Canadian Network for Observational Drug Effect Studies (CNODES) Investigators:

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

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