SGLT2i use in adults with chronic kidney disease: A cross-sectional study identifying care gaps to inform knowledge translation

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Abstract

Background – Recent trials have shown important kidney and cardiovascular benefits of SGLT-2 inhibitors (SLGT2i) in adults with chronic kidney disease (CKD).

Objectives – Among adults with diabetes, characterize the prevalence of CKD (based on trial and guideline criteria), and assess SGLT2i use and its predictors.

Methods – Cross-sectional study using Alberta administrative data in adults with diabetes in 2019. CKD was defined as eGFR < 90 with ≥ moderate proteinuria, or eGFR < 60. The associations of sociodemographics, comorbidities, and health care utilization on SGLT2i use were identified using logistic regression.

Results – We identified 446,315 adults with diabetes, of whom 76,630 (17%) were CKD-indicated for SGLT2i. Combined with cardiovascular disease and heart failure, total SGLT2i-eligibility (adults with cardio-renal benefit) was 37%. In contrast, SGLT2i use was 7% in those with CKD. CKD, older age, lower HbA1c, female sex, lower neighbourhood income, and hospital admission were among variables associated with less SGLT2i use. Family physician visits were associated with greater SGLT2i use. Expanding our perspective to all adults, with and without diabetes, at least 162,012 individuals with CKD (5% of all Alberta adults) will eventually benefit from SGLT2i.

Conclusions – A substantial number of adults with CKD, both with and without diabetes, would derive heart and kidney benefits from SGLT2i. Efforts will be needed to address barriers among adults with CKD, particularly related to older age and lower income; enhance primary care; and promote greater awareness of the heart and kidney benefits of SGLT2i independent from glycemic control.

Background

Chronic kidney disease (CKD) is a risk factor for end-stage renal disease, and is associated with worse cardiovascular outcomes.[1] The CREDENCE and DAPA-CKD trials showed that sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduced clinically meaningful kidney outcomes and cardiovascular events in adults both with [2,3] and without diabetes.[3] SGLT2i are now recommended in diabetes guidelines for end-organ protection in patients with CKD.[4-6] Similar recommendations are expected in adults without diabetes, particularly if similar results are observed in the forthcoming EMPA-KIDNEY trial of empagliflozin.[7]

As SGLT2i are already indicated in adults with diabetes for glycemic control, atherosclerotic cardiovascular disease (CVD), and heart failure, the incremental impact of the CKD indication for SGLT2i among those with diabetes is unknown. In this context, we define the "CKD indication" for SGLT2i specifically as meeting trial and guideline-based criteria for cardiorenal benefit from SGLT2i on the basis of estimated glomerular filtration rate (eGFR) or proteinuria. The Alberta Kidney Health Strategic Clinical Network[8] has identified improving SGLT2i use in adults with CKD as an emerging clinical priority. As a first step in these efforts, we examined a cross-section of adults with diabetes, to answer the following questions: (1) What is the prevalence of "SGLT2i-eligible adults", i.e.: those who have been shown to benefit (in addition to blood glucose control) from SGLT2i according to recent trials and guidelines? (2) What is the incremental effect of the CKD indication alone on SGLT2i eligibility? (3) Among current users of SGLT2i, are sociodemographic factors, health status, diabetes status, and health care utilization associated with SGLT2i use? We examined predictors of SGLT2i use to identify potential directions and opportunities to accelerate SGLT2i use in adults with CKD. (4) What is the

prevalence of the CKD indication for SGLT2i in the general Alberta population, both with and without diabetes? The prevalence of the CKD indication in all Albertan adults, regardless of diabetes status, will foreshadow the magnitude of the knowledge translation challenge to come.

Methods

We performed a cross-sectional study using data from the Alberta Kidney Disease Network, comprised of linked administrative databases of Alberta Health over the period April 1, 2002-March 31, 2019 (see Supplement).[9]

Defining SGLT2i-eligibility and the CKD indication for SGLT2i

For adults with diabetes, indications for SGLT2i were defined as (1) CVD, (2) heart failure, and (3) CKD, and (4) glycemic control (see Table 1 for detailed definitions). Indications (1) through (3) were considered "end-organ" indications with evidence of clinically important benefits (kidney, cardiovascular, mortality) beyond glycemic control. Indication (3) was the focus of this study. Both dapagliflozin and canagliflozin have formal indications for CKD; dapagliflozin's indication covers adults both with and without diabetes. These indications are well supported by clinical trials and have also been adopted by the most recent Canadian guidelines. Notably, the CKD trials of dapagliflozin and canagliflozin included patients with severe proteinuria, though diabetes guidelines,[5,6] the KDIGO diabetic kidney disease guidelines,[4] and the Health Canada indication apply to "CKD" generally, presumably based on evidence from cardiovascular trials showing renal benefits agnostic to CKD stage and proteinuria.[10,11] Thus, we defined the

Commented [DL1]: Previously written as moderate

CKD indication as (3a) eGFR >= 25mL/min/1.73m^2 and < 90mL/min/1.73m^2 with evidence of severe or greater proteinuria (KDIGO A3, equivalent to UACR >= 30 mg/mmol), reflecting the kidney trial inclusion criteria; and (3b) eGFR >= 24mL/min/1.73m^2 and < 60mL/min/1.73m^2, or evidence of moderate or greater proteinuria (KDIGO A2, equivalent to UACR >= 3 mg/mmol), reflecting the broader guideline-based definition of CKD. Sub-indication (3a) was nested in (3b), the latter being more inclusive. Indication (4), glucose reduction, was defined as HbA1c >= 7%. All current SGLT2i users, whatever their HbA1c and other SGLT2i indications, were also considered to be using SGLT2i for glucose lowering, presuming that very few adults in 2019 would have been using SGLT2i for end-organ reasons alone.

Inclusion and exclusion criteria

We included all Alberta adults with diabetes on March 31, 2019, with at least one serum creatinine measurement between April 1, 2002 and the index date. Diabetes status was determined using an established administrative data definition.[12,13] We additionally classified patients with one or more HbA1c >= 6.5%,[14] or one or more pharmacy dispensations for insulin, as having diabetes. Patients with most recent eGFR < 25mL/min/1.73m^2, end-stage renal failure on dialysis, diagnostic codes specifying type 1 diabetes, or no indicators of proteinuria since 2002 were excluded.

Identifying adults with CKD and other SGLT2i indications

eGFR was estimated from serum creatinine using the CKD-Epi equations and categorized based on the most recent serum creatinine measurement, with at least 2 consecutive measurements meeting these criteria > 90 days apart. Proteinuria was categorized using the most recent

community urine albumin:creatinine ratio (UACR), urine protein:creatinine ratio, or semi-quantitative urine dipstick interchangeably (see Supplement Table S1). CAD, stroke, and heart failure were defined using validated definitions.[15] All individuals with heart failure were considered to benefit from SGLT2i.

SGLT2i use and other study variables

In Alberta, pharmacies report medication dispensations at the point of sale.[16] Patients were considered current SGLT2i users if, from their most recent dispensation, the day's supplied plus an additional 30 days for stockpile covered March 31, 2019.

Explanatory variables were sociodemographic quantities, diabetes indicators, other comorbidities,[15,17] Elixhauser comorbidity summary index,[18] and health care utilization (family physician [FP] visits, specialist visits, and hospitalizations) in the preceding year (Table 1).

Analysis

The characteristics of included adults were described with means (sd) and proportions. We then reported the prevalence of each SGLT2i indication, and the proportion of SGLT2i use for each. The association of various characteristics on current SGLT2i use was determined using logistic regression in adults with diabetes, with variables added on in purposeful blocks, and statistically significant variables ($p < 0.05$) retained. The regression was repeated in adults with CKD only as a subgroup. Finally, we broadened our focus to identify all adults in Alberta with >= 1 serum creatinine value since April 1, 2002, who met the CKD indication for SGLT2i (indication (3a) or (3b)), including adults both with or without diabetes. The prevalence of adults with the CKD indication in Alberta was calculated using the census-derived adult population of Alberta

(3.5 million) as a denominator. The analysis was performed in Stata 17 (Stata Corp, College Station, TX). This study was approved by the research ethics boards at the Universities of Alberta and Calgary.

Results

Adults with diabetes with a CKD indication for SGLT2i were older, had more comorbidities, and more frequent health care utilization

We identified 446,315 adults with diabetes (Figure 1). Included adults averaged 62 years old (sd 15), with roughly equal males/females (Table 2). Mean HbA1c was 7.1% with the majority of adults (61%) having HbA1c <= 7.0%. Mean eGFR was 80mL/min/1.73m^2. Adults with diabetes saw their FPs frequently (mean 5.5 visits per year). Contact with medical specialists was less frequent (mean 0.5 visits per year). A substantial minority (10%) had been hospitalized in the previous year.

While there were 12,867 adults (3%) with diabetes with renal indices meeting inclusion criteria for the SGLT2i renal outcome trials (indication 3a), a larger number of adults – 76,630 (17% of all adults with diabetes) – met the broader guideline-based CKD definition (indication 3b) used to guide SGLT2i initiation (Table 3). These individuals tended to be older, more likely to have coronary artery disease, stroke, and heart failure, had more frequent healthcare utilization than those not meeting the CKD indication for SGLT2i (Table 2). Differences in glycemic control were minor.

The CKD indication made an additional 11% of adults with diabetes "SGLT2i-eligible"

Though 17% of adults with diabetes met CKD criteria for SGLT2i, many of them already had CVD or heart failure. In fact, CVD was the most common end-organ indication for SGLT2i in adults with diabetes (26%) (Table 3). The combination of CVD and heart failure together identified 28% of adults with diabetes as having significant clinical benefit from SGLT2i (Figure 1). The total prevalence of adults with diabetes with cardiorenal benefit from SGLT2i was 37% after including CKD as an additional end-organ indication for SGLT2i. Thus, CKD increased SGLT2i-eligibility by an absolute increment of 9% in adults with diabetes.

If glucose reduction is included as an SGLT2i indication, albeit one without evidence of additional clinical benefits, then 55% of all adults with diabetes have an indication for SGLT2i.

Use of SGLT2i was low among adults with CKD and other end-organ indications

The overall rate of SGLT2i use was 8% (Table 3). SGLT2i use was highest in those for whom it was indicated for glucose control (24%). SGLT2i use by end-organ indication was lower: CVD (9%), HF (7%), CKD (7%).

SGLT2i use was associated with multiple factors in adults with diabetes

Among adults with diabetes, CKD was associated with slightly lower SGLT2i use (crude OR = 0.92), unchanged after adjustment (adjusted OR 0.91, 95% CI 0.88-0.95) (Table 4). The strongest associations with SGLT2i use were observed for HbA1c, age, and frequency of FP contact.

Those with HbA1c <= 7.0% had a lower odds of SGLT2i current use than those with HbA1c > 7.0% (OR 0.23). Insulin use was also associated with higher odds of SGLT2i use. In terms of

other indications for SGLT2i, coronary artery disease increased the odds of SGLT2i use, but heart failure and stroke were associated with lower SGLT2i use.

The relationship between age and SGLT2i use was non-linear, with reduced use observed in young individuals and in patients aged 65 or above, but particularly at the upper extreme of age, with odds ratios as low as 0.13 (age >= 84 vs 55-64). Adults in lower quintiles of neighbourhood income also had lower odds of SGLT2i use, with a gradient observed from highest to lowest income quintile, the lowest income quintile being associated with an adjusted 0.81-fold reduced odds of SGLT2i use compared to the highest. Among other sociodemographic variables, female sex was associated with reduced odds of SGLT2i use (OR = 0.73).

Patients were more likely to be using SGLT2i with more frequent FP exposure (OR = 5.82 with > 4 visits). Seeing a nephrologist in the previous year was associated with reduced SGLT2i use, while seeing a cardiologist, internist or endocrinologist exposure increased the odds of SLGT2i use. Hospital admission was associated with lower odds of SGLT2i use (OR 0.66). All of the above associations were statistically significant and were similar in models featuring only those adults with diabetes and concomitant CKD.

Many adults *without* diabetes who meet the CKD indication would benefit from SGLT2i

Among adults without diabetes, we identified 85,382 adults (Figure 1) who met the CKD indication for SGLT2i (indication 3b), 8,716 of whom individuals had severe proteinuria (indication 3a). Combined with the 76,630 similar adults with diabetes, the total number of Alberta adults who would have clinical benefits from SGLT2i due to CKD was 162,012, representing approximately 5% of Alberta's census-derived adult population of 3.5 million.

Discussion

We examined a provincial cross section of adults with diabetes. Among them, 17% met the CKD indication for clinical benefit from SGLT2i (an increment of 9% when considered in addition to well-established CVD and heart failure indications for SGLT2i), yet only 7% of these individuals were using SGLT2i. The CREDENCE trial had been published only 8 months prior to the index date. This study was therefore not meant to be evaluative, but, rather, to identify and explore this gap between current prescribing and the emerging evidence of cardiorenal benefit in CKD.

We observed a steady decline in SGLT2i use beyond 65 years, which includes most adults with CKD. SGLT2i are publicly funded in Alberta for all adults aged >= 65 by special authorization, primary for hyperglycemia.[19] Indeed, meeting glycemic control targets (HbA1c <= 7.0%) was associated with a 4-fold reduced odds of SGLT2i use, consistent with the origin of SGLT2i's as anti-diabetes medications. A second explanation for lower SGLT2i use in older adults may be the perception of increased adverse event risk in these individuals.[20] SGLT2i do increase the risk of euglycemic DKA, and, possibly, lower limb amputations (hazard ratios ~2-3), though the absolute background risks of these events are low (<5/1000 patient years).[21-23] These adverse events are probably less of a barrier for adults with CKD than concerns about orthostatic hypotension, acute kidney injury (AKI) and urinary tract infections, despite evidence showing no association between SGLT2i use and the latter two.[24-26] It will be important not to short-change older adults with cardiac and kidney comorbidities, who will benefit the most, in absolute terms, from SGLT2i. Efforts will be needed to facilitate access to SGLT2i for adults with CKD,

irrespective of diabetes status and glycemic control, and to promote the understanding that these agents should be prescribed as kidney and heart medications.[5,20]

Individuals residing in lower income neighbourhoods were less likely to be SGLT2i users. The reasons for this association may include lower access to employment-derived drug benefits, and competing acute issues.[27] Women were also less likely to be prescribed SGLT2i. Sex-based disparities exist with other cardiovascular risk-reducing medications,[28] though for SGLT2i, the disparity may simply be due to genital mycotic infections. Equitable access to SGLT2i will be an important consideration for quality improvement.[29]

FP exposure was associated with higher SGLT2i use. FP contacts were much more frequent than specialist contacts. Efforts to improve SGLT2i use in CKD-indicated adults will largely depend on further empowering and enhancing exposure to primary care providers alongside their specialist colleagues. Prescriber education and quality improvement initiatives will be needed to accelerate the evidence-based uptake of SGLT2 among those with CKD.[20] Hospital discharge may be an important opportunity to recommend or prescribe SGLT2i for a substantial minority of adults.[30,31]

Limitations

First, missing measurements were common. Of the adults with diabetes and non-missing creatinine and proteinuria values included here, many of their proteinuria measurements were over 2 years old (33%). The prevalence of SGLT2i-indications will depend on how conscientiously they are sought out, and may be higher than estimated here. Second, these data precede the formal indication of CKD as an indication for SGLT2i, but our study is intended

to provide anticipatory insights relevant to the eventual roll out of SGLT2i for as many as 5% of all adults.

Conclusions

Among adults with diabetes in Alberta, a substantial proportion (17%) meet the CKD indication for SGLT2i and would have important cardiorenal benefits apart from glucose reduction. In contrast, rates of SGLT2i use remain low (7%). Barriers to SGLT2i use will be important to address as SGLT2i are recast as kidney and heart medications, indicated equally for adults with and without diabetes. In Alberta, at least 5% of the total adult population (162,012 individuals) met the CKD-indication and would benefit from SGLT2i. Future efforts will need to address SGLT2i use in older adults, women, and those in lower income quintiles (including modifications to restrictive public drug insurance criteria); and promote the new understanding that SGLT2i are indicated for end-organ protection regardless of diabetes status or glycemic control.

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Contributions

DL (corresponding author) conceived the study, analyzed the data, and wrote the manuscript. SWK obtained the data. All authors interpreted the results, made critical manuscript revisions, and approved the final manuscript for publication.

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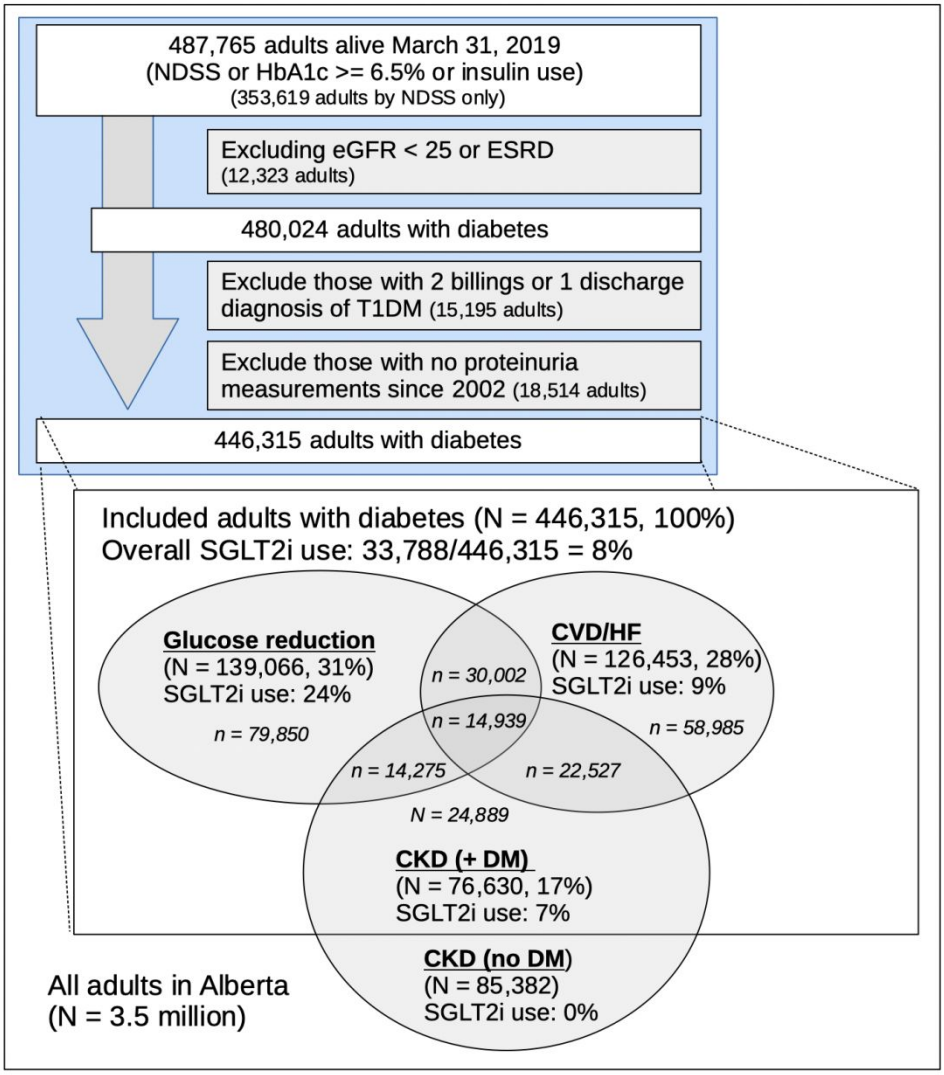
Figures

Figure 1: Adults with diabetes and indications for SGLT2i



Encircled areas show SGLT2i-indications, in the style of a Venn diagram, and are not drawn to scale. Abbreviations: NDSS – National Diabetes Surveillance System, referring to a well accepted administrative-database case definition for diabetes, HbA1c – glycated hemoglobin, eGFR –

estimated glomerular filtration rate, ESRD – end-stage renal disease, T1DM – type 1 diabetes, SGLT2i – sodium glucose-lowering co-transporter 2-inhibitor, CVD – cardiovascular disease, HF – heart failure, CKD – chronic kidney disease (per definitions in Table 1), DM – diabetes.

Tables

Table 1: Indications for SGLT2i in adults with diabetes

	Indication	Cardio-renal benefit?	Definition
(1)	CVD	Yes	• Patient has history of coronary artery disease or stroke
(2)	Heart failure	Yes	• Patient has history of heart failure
(3a)	CKD	Yes	Based on inclusion criteria for SGLT2i renal outcome trials • eGFR < 90 mL/min/1.73m^2 with evidence of severe or greater proteinuria • eGFR >= 25 mL/min/1.73m^2
(3b)	CKD[a]	Yes[b]	Based on Diabetes Canada and KDIGO guidelines • eGFR < 60mLmin/1.73m^2 regardless of proteinuria, or moderate or greater proteinuria regardless of eGFR • eGFR >= 25 mL/min/1.73m^2
(4)	Glucose lowering	No	Adults requiring additional pharmacotherapy as add-on to existing therapy, or as monotherapy if metformin is not tolerated, to meet glycemic targets. • HbA1c > 7.0%, or • Any HbA1c with current use of SGLT2i or GLP-1-RA [c]

Collectively indications (1)-(3) are the "end-organ indications", with dedicated trials showing kidney and cardiovascular benefits of SGLT2i in these patients.

[a] CKD criteria (3b) was also applied in this cross-sectional study to adults without diabetes.

[b] Benefits extrapolated from renal outcome trials, which enrolled adults meeting criteria (3a), and also shown in sub-group analyses of cardiovascular outcome trials showing renal benefit in adults with CKD not meeting criteria (3a). Indication (3b) is more inclusive and contains indication (3a) as a subset.

[c] On the presumption that all current users of SGLT2i or GLP-1RA have been started on it for glucose control, given low rates of SGLT2i / GLP-1RA use purely for end-organ interventions.

Abbreviations: SGLT2i – Sodium-glucose lowering cotransporter-2 inhibitor. CVD – Cardiovascular disease. CKD – Chronic kidney disease. eGFR – estimated glomerular filtration rate (CKD-Epi). HbA1c – Hemoglobin A1c (glycated hemoglobin). eGFR – Estimated glomerular filtration rate.

Table 2: Characteristics of Alberta adults with diabetes, stratified by the presence or absence of the CKD indication for SGLT2i

Variable		All adults with DM (n = 469,829) n / mean	freq / SD	DM + CKD (n = 90,316) n / mean	freq / SD	Diabetes with no CKD indication (n = 374,513) n / mean	freq / SD
Sociodemographics							
Age	(mean, SD)	62	15	74	12	60	14
Sex	Female	212808	48%	35932	47%	176876	48%
Residence	Rural	54697	12%	10961	14%	43736	12%
Neighbourhood income quintile	1	100047	23%	18721	25%	81326	23%
	2	90845	21%	16678	22%	74167	21%
	3	84445	20%	14733	20%	69712	20%
	4	83318	19%	13425	18%	69893	20%
	5	72009	17%	11092	15%	60917	17%
Renal function							
Serum creatinine (umol/L)	(mean, SD)	83	23	108	28	77	17
eGFR (CKD-EPI)	(mean, SD)	80	20	55	16	85	17
CKD stage by eGFR	None / Stage 1	160063	36%	0	0%	160063	43%
	Stage 2	238707	53%	29085	38%	209622	57%
	Stage 3	46297	10%	46297	60%	0	0%
	Stage 4	1248	0%	1248	2%	0	0%
Proteinuria	None / mild	376565	84%	32305	42%	344260	93%
	Moderate	51551	12%	31458	41%	20093	5%
	Severe	17173	4%	12038	16%	5135	1%
	Nephrotic	1026	0%	829	1%	197	0%
ACEi or ARB, current use	Yes	184630	41%	47264	62%	137366	37%
Diabetes characteristics							
HbA1c	(mean, SD)	7.1	1.6	7.2	1.5	7.1	1.6
HbA1c	<= 7.0%	201726	61%	36425	56%	165301	62%
	7.1% - 9.0%	95703	29%	21353	33%	74350	28%
	> 9.0%	34447	10%	6699	10%	27748	10%
HbA1c	Missing	114439	--	12153	--	102286	--
Insulin intensity	None	383073	86%	60365	79%	322708	87%
	Basal only	26267	6%	7028	9%	19239	5%
	Bolus +/- basal	36975	8%	9237	12%	27738	8%
Comorbidities							
Coronary artery disease	Yes	89530	20%	25896	34%	63634	17%
Stroke	Yes	45260	10%	15006	20%	30254	8%
Heart Failure	Yes	33239	7%	15127	20%	18112	5%
Elixhauser index	(mean, SD)	10	10	16	11	9	9
Health care utilization							
FP - Number of visits	(mean, SD)	5.5	6.0	6.9	7.5	5.2	5.6
FP visits - Any	>= 1	385926	86%	68675	90%	317251	86%
FP visits - Frequency	0 visits	60389	14%	7955	10%	52434	14%
	1-4 visits	177319	40%	25728	34%	151591	41%
	> 4 visits	208607	47%	42947	56%	165660	45%
IM - Number of visits	(mean, SD)	0.3	1.0	0.5	1.3	0.3	1.0
IM visits - Any	>= 1	70290	16%	16415	21%	53875	15%
CARD - Number of visits	(mean, SD)	0.1	0.5	0.2	0.7	0.1	0.4
CARD visits - Any	>= 1	30219	7%	8976	12%	21243	6%
ENDO - Number of visits	(mean, SD)	0.0	0.3	0.0	0.3	0.0	0.3
ENDO visits - Any	>= 1	6184	1%	1158	2%	5026	1%
NEPH - Number of visits	(mean, SD)	0.0	0.2	0.1	0.5	0.0	0.1
NEPH visits - Any	>= 1	8541	2%	6219	8%	2322	1%
NEPH / ENDO / IM / CARD visits	(mean, SD)	0.5	1.3	0.8	1.8	0.4	1.2
NEPH / ENDO / IM / CARD visits - Any	>= 1	98159	22%	25671	33%	72488	20%
Hospitalization	>= 1	43047	10%	11654	15%	31393	8%

All p <= 0.001 for comparisons between adults with and without a CKD indication for SGLT2i (T-test and chi^2 tests).
Abbreviations: DM – diabetes. CKD – chronic kidney disease. N – Number of adults. Freq – frequency. SD – standard deviation. eGFR – Estimated glomerular filtration rate. CAD – coronary artery disease. ACEi – angiotensin converting enzyme-inhibitor. ARB – angiotensin receptor blocker. HbA1c – Hemoglobin A1c / glycated hemoglobin. FP – family physician. IM – internal medicine physician. CARD – cardiologist. ENDO – endocrinologist. NEPH – nephrologist.

Table 3: Indications for SGLT2i in adults with diabetes

Indication number	Indication	Number of adults with the indicated condition (proportion of all adults with diabetes)	SGLT2i users (proportion of SGLT2i users, out of adults with the specified indication)
	All adults with diabetes	446,315 (100%)	33,788 / 446,315 = 8%
Indications for SGLT2i			
1	CVD (CAD / stroke)	116,652 (26%)	10,446 / 116,652 = 9%
2	Heart failure	33,239 (7%)	2,271 / 33,239 = 7%
3a	CKD stage >= 2 *and* at least severe proteinuria	12,867 (3%)	988 / 12,867 = 8%
3b	CKD stage >= 3 *or* at least moderate proteinuria	76,630 (17%)	5,460 / 76,630 = 7%
4	Glycemic control (HbA1c > 7.0% or any current SGLT2i use)	139,066 (31%)	33,788 / 139,066 = 24%
Combinations of indications			
1 or 2	CVD + heart failure	126,453 (28%)	11,037 / 126,453 = 9%
1 or 2 or 3b	CVD + heart failure + CKD	165,617 (37%)	13,8545 / 165,617 = 8%
All indications combined			
1 or 2 or 3b or 4	All indications combined	245,467 (55%)	33,788 / 245,467 = 14%

Indication (3a) is a subset of (3b). Indication (3a) reflects trial inclusion criteria of the CREDENCE and DAPA-CKD trials, while indication (3b) reflects a broader definition of CKD for SGLT2i eligibility adopted in the Diabetes Canada and KDIGO Diabetic Kidney Disease guidelines. CKD stage >= 2 refers to eGFR < 90 mL/min/1.73m^2. CKD stage >= 3 refers to eGFR < 60 mL/min/1.73m^2.

Table 4: Logistic regression of current SGLT2i use in adults with diabetes

Variable			OR (95% CI)	P-value
CKD indication			0.91 (0.88-0.95)	<0.001
Sociodemographics				
Sex	Female		0.73 (0.71-0.75)	<0.001
Age	<= 44 years		0.59 (0.56-0.62)	<0.001
	45-54 years		0.98 (0.95-1.02)	0.278
	55-64 years (REF)		1.00 (1.00-1.00)	.
	65-74 years		0.79 (0.76-0.81)	<0.001
	75-84 years		0.38 (0.36-0.40)	<0.001
	>= 85 years		0.13 (0.12-0.15)	<0.001
Neighbourhood income quintile		1	0.81 (0.78-0.85)	<0.001
		2	0.93 (0.90-0.97)	0.001
		3	0.94 (0.90-0.98)	0.003
		4	1.00 (0.96-1.05)	0.864
		5 (REF)	1.00 (1.00-1.00)	.
Comorbidities and diabetes				
Heart failure			0.91 (0.86-0.96)	0.001
Coronary artery disease			1.18 (1.14-1.21)	<0.001
Stroke			0.94 (0.90-0.98)	0.004
Elixhauser index (per 5 units)			0.94 (0.94-0.95)	<0.001
HbA1c	<= 7.0%		0.23 (0.22-0.23)	<0.001
	> 7.0% and <= 9.0% (REF)		1.00	.
	> 9.0%		0.76 (0.74-0.79)	<0.001
Insulin	Basal insulin only		2.42 (2.34-2.50)	<0.001
	Bolus +/- basal insulin		1.27 (1.22-1.32)	<0.001
Health care utilization in the previous year				
FP visits	No FP visits (REF)		1.00 (1.00-1.00)	.
	1-4 FP visits		4.61 (4.25-5.01)	<0.001
	>4 FP visits		5.82 (5.36-6.31)	<0.001
Nephrologist	>= 1 visit		0.73 (0.67-0.80)	<0.001
Cardiologist	>= 1 visit		1.27 (1.21-1.32)	<0.001
Internist	>= 1 visit		1.65 (1.60-1.70)	<0.001
Endocrinologist	>= 1 visit		2.46 (2.31-2.63)	<0.001
Hospital admission	>= 1 admission		0.66 (0.63-0.69)	<0.001

Rural residence originally included in the sociodemographics block but was dropped due to OR close to 1.00 and p > 0.05 when examined with other variables in that block. Abbreviations: OR – odds ratio (adjusted simultaneously for all other reported variables). 95% CI – 95% confidence interval. DM – diabetes. CKD – chronic kidney disease. REF – reference group or level. HbA1c – hemoglobin A1c / glycated hemoglobin. FP – family physician

SGLT2i use in patients with chronic kidney disease: Identifying challenges and opportunities for diffusion of an effective treatment

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SUPPLEMENTAL MATERALS

Administrative Databases Used

We performed a cross-sectional study using administrative databases of Alberta Health and Alberta Health Services, in the Canadian province of Alberta. The specific databases used were Population Registry, Vital Statistics – Deaths, Practitioner Claims, Ambulatory Care, Discharge Abstract Database, laboratory results repository, and Pharmaceutical Information Network (PIN) database. The Ambulatory Care database captures visits to the Emergency Department and other health care facilities for day procedures. While pharmaceuticals are not universally funded in Alberta, all point-of-sale drug dispensations are uploaded to PIN from Alberta pharmacies, with over > 95% participation since 2008.

Supplement Table S1: Classification of proteinuria

Proteinuria severity	UACR	UPCR	Semi-quantitative dipstick
None / mild	<3 mg/mmol	<15 mg/mmol	Negative or trace
Moderate	3-30 mg/mmol	15-50 mg/mmol	1+
Severe	31-220 mg/mmol	51-359 mg/mmol	2+ or 3+
Nephrotic range	> 220 mg/mmol	> 350 mg/mmol	4+

UACR – Spot urine albumin-to-creatinine ratio
UPCR – Spot urine protein-to-creatinine ratio