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Use of sodium-glucose cotransporter-2 inhibitors among older adults with type 2 diabetes mellitus in British Columbia

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Abstract

Aims: Clinical guidelines recommend sodium-glucose cotransporter-2 inhibitors (SGLT2is) for individuals with type 2 diabetes mellitus (T2DM) and established or high risk of cardiorenal disease. This study examined real-world SGLT2i use patterns among older adults with T2DM in British Columbia, Canada.

Materials and Methods: We conducted a drug utilisation study on all individuals aged ≥75 years with T2DM in British Columbia between January 1, 2016, and December 31, 2023, using administrative healthcare databases. We examined prevalence, incidence, characteristics of incident users, and discontinuation.

Results: The prevalence of SGLT2i use increased gradually from 2.0% in the first half of 2016 to 14% in the second half of 2022, then more sharply to 21% in the second half of 2023, with comparable prevalence in individuals with and without cardiorenal disease (20% vs. 22% in 2023). SGLT2i initiation increased from 1.3 to 2.8 per 1000 individuals between 2016 and 2022, spiked to 5.4 per 1000 individuals in January 2023, and then stabilised. Of the 14 320 SGLT2i initiators between 2021 and 2023, 62% had cardiorenal disease, most used other glucose-lowering drugs concomitantly (particularly metformin [68%], sulfonylureas [39%], and insulins [19%]), and 62% were started on treatment by a general practitioner. Additionally, 17% discontinued treatment within a year.

Conclusions: SGLT2i use among older adults with T2DM in British Columbia increased steadily from 2016 to 2022, followed by a spike in 2023, aligned with the expansion in publicly funded drug coverage. By the end of 2023, around one in five used SGLT2is, regardless of cardiorenal disease status.

KEYWORDS
drug utilisation, glucose-lowering drugs, older adults, sodium-glucose cotransporter-2 inhibitors, type 2 diabetes mellitus

1 | INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a newer class of glucose-lowering drugs used to treat type 2 diabetes mellitus (T2DM).[1] These drugs effectively lower blood glucose levels with a low risk of hypoglycaemia. In addition, SGLT2is provide cardiovascular and renal benefits. They have been shown to reduce all-cause mortality, major adverse cardiovascular events, heart failure hospitalisations, and chronic kidney disease progression in individuals with T2DM who have, or are at high risk of, cardiovascular disease, heart failure, or chronic kidney disease.[2] Therefore, current guidelines recommend their use in these populations.[1] Despite evidence supporting their efficacy and safety in older adults with T2DM,[3–5] clinicians may hesitate to prescribe SGLT2is to those aged ≥75 years. This is partly due to concerns about potential adverse effects and underrepresentation of this age group in clinical trials.[6–9] In this drug utilisation study, we explored the real-world use of SGLT2is among individuals aged ≥75 years with T2DM in British Columbia, Canada.

2 | MATERIALS AND METHODS

In this population-based drug utilisation study, we used administrative healthcare databases from British Columbia, Canada, to describe the use of SGLT2is among older adults with T2DM between 2016 and 2023. We assessed the prevalence and incidence of SGLT2i use, characteristics of incident users, and discontinuation. The study was approved by the University of British Columbia Research Ethics Board (H25-02297).

2.1 | Data sources

We used individual-level, linkable data from the administrative healthcare databases of the British Columbia Ministry of Health. In British Columbia, public health insurance is available to eligible residents through the Medical Services Plan (MSP). This program provides coverage for medically necessary physician and hospital services. Residents enrolled in the MSP are also eligible for the PharmaCare program, which helps with the cost of eligible prescription drugs, medical supplies, and pharmacy services. We obtained data on prescriptions filled at community pharmacies in British Columbia (regardless of PharmaCare coverage) from PharmaNet, hospital admissions from the Discharge Abstract Database (DAD), ambulatory care visits from the National Ambulatory Care Reporting System (NACRS), fee-for-service physician services from the MSP, demographics from the Consolidation File, and deaths from BC Vital Events and Statistics Deaths.

2.2 | Study cohort

We identified all residents in British Columbia aged ≥75 years with MSP coverage between January 1, 2016, and December 31, 2023, who had T2DM. T2DM was defined as either a diabetes diagnosis or the use of glucose-lowering drugs. For the diabetes diagnosis, we used a validated definition. This required at least one hospitalisation with diabetes (International Classification of Diseases, 10th Revision [ICD-10] codes in the DAD: E10*, E11*, E13*, or E14*) within the past 5 years, or at least two physician claims for diabetes (International Classification of Diseases, 9th Revision [ICD-9] code in the MSP: 250*) within the past 2 years.[10] Glucose-lowering drug use was defined as at least one filled prescription within the past 180 days for any of the following classes: dipeptidyl peptidase-4 inhibitors (DPP4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), insulins, metformin, or sulfonylureas (SUs) (definitions are provided in Table S1, Supporting Information). While this definition identified diabetes in general, the vast majority of diabetes cases among Canadian adults are type 2 diabetes.[11] Therefore, most individuals in the study cohort likely had T2DM.

2.3 | Study drugs

SGLT2is were identified in PharmaNet using the Anatomical Therapeutic Chemical (ATC) classification system. We included both single-agent and fixed-dose combination products. Three SGLT2is were available in Canada during the study period: canagliflozin, dapagliflozin, and empagliflozin. SGLT2is were not publicly funded in British Columbia until 2019. That year, empagliflozin was added to the PharmaCare formulary as a third-line treatment for patients with T2DM who had failed metformin and either sulfonylureas or insulins. Dapagliflozin was added in 2022 for patients with heart failure with reduced ejection fraction. On January 5, 2023, PharmaCare expanded coverage of SGLT2is. This policy change aimed to align coverage with clinical evidence and improve patient access by reducing out-of-pocket costs. Empagliflozin became available as a second-line treatment for patients with T2DM who had failed metformin. Dapagliflozin became available for all patients with heart failure, T2DM, and chronic kidney disease. Canagliflozin remained uncovered.[12] For eligible patients, covered SGLT2is are reimbursed under the various PharmaCare plans. Coverage varies by income, age, medical condition, and other plan-specific criteria.[13]

2.4 | Prevalence of SGLT2i use

We calculated the 6-month prevalence proportion of SGLT2i use per 100 individuals. The numerator was the number of prevalent users in the study cohort, and the denominator was the number of individuals in the study cohort with MSP coverage on the first day of each period. An individual was considered a prevalent user if the first day of the period fell within the days' supply of a prescription plus a 20% grace period, or if they filled at least one prescription during the period. We used a 20% grace period to allow for minor refill delays without overestimating prevalence.[14,15] This was done overall and stratified by sex, age group (75–84 and ≥85 years), and cardiorenal disease status. Cardiorenal disease was defined as the presence of heart failure, cardiovascular disease, cerebrovascular disease/stroke, and/or chronic kidney disease. A 5-year lookback from the first day of each period was used to identify these comorbidities (definitions are provided in Table S2). Stratified analyses included only individuals within each stratum.

2.5 | Incidence of SGLT2i use

We calculated the monthly incidence rate of SGLT2i use per 1000 individuals. The numerator was the number of incident users in the study cohort, and the denominator was the number of individuals in the study cohort with MSP coverage on the first day of each month. Incident use was defined as not having filled a prescription for an SGLT2i within the past 5 years. This was also done overall and stratified by sex, age group (defined above), and cardiorenal disease status (defined above). Stratified analyses included only individuals within each stratum.

2.6 | Characteristics of incident SGLT2i users

To examine the characteristics of contemporary SGLT2i users, we described incident SGLT2i users between January 1, 2021, and December 31, 2023. Characteristics included the type of SGLT2i initiated (canagliflozin, dapagliflozin, or empagliflozin), sex, age, Charlson Comorbidity Index (CCI),[16] comorbidities, concomitant drug use, number of fee-for-service physician services in the year before treatment initiation, rural residence, long-term care residence, income, and prescriber specialty. Definitions are provided in Tables S1–S3. The CCI was calculated without including sex or age, as it was used to measure comorbidity burden rather than to predict mortality. An individual was considered a concomitant drug user if they filled at least one prescription in the 180 days before treatment initiation. This was done overall and stratified by cardiorenal disease status.

2.7 | Discontinuation of SGLT2is

We calculated the proportion of incident SGLT2i users between January 1, 2021, and December 31, 2022, who discontinued treatment. Early discontinuation was defined as no refill within the days' supply of the first prescription plus a 90-day grace period. We used a 90-day grace period to minimise misclassification of ongoing treatment as discontinuation.[17] One-year discontinuation was defined as no refill within 1 year of treatment initiation. To exclude discontinuations due to death, we restricted the analyses to individuals who survived beyond these periods.

3 | RESULTS

3.1 | Prevalence of SGLT2i use

The overall prevalence of SGLT2i use increased sevenfold between 2016 and 2022, rising from 2.0% in the first half of 2016 to 14% in the second half of 2022. This was followed by a sharper increase to 21% in the second half of 2023. Similar trends were observed across sex, age groups, and cardiorenal disease status. SGLT2i use was most common among men and individuals aged 75–84 years. Individuals with cardiorenal disease had similar but slightly lower SGLT2i use than those without cardiorenal disease throughout the study period. In 2023, SGLT2i use increased more rapidly among individuals with cardiorenal disease. By the second half of 2023, 20% of individuals with cardiorenal disease used SGLT2is, compared with 22% of those without cardiorenal disease (Figure 1).

3.2 | Incidence of SGLT2i use

The overall monthly rate of incident SGLT2i use increased gradually from 1.3 per 1000 individuals in January 2016 to 2.8 per 1000 individuals in December 2022. In January 2023, the incidence rate spiked, nearly doubling to 5.4 per 1000 individuals. It then remained elevated, ending at 4.7 per 1000 individuals in December 2023. This trend was consistent across sex, age groups, and cardiorenal disease status. Incident SGLT2i use was highest among men and individuals aged 75–84 years. Individuals without cardiorenal disease had similar or slightly higher incidence rates than those with cardiorenal disease until mid-2020. After that, incidence rates among individuals with cardiorenal disease slightly surpassed those without cardiorenal disease. The spike observed in January 2023 was also more pronounced among individuals with cardiorenal disease (from 2.9 per 1000 individuals in December 2022 to 6.2 per 1000 individuals in January 2023) compared to those without cardiorenal disease (from 2.5 to 4.4 per 1000 individuals). Incidence rates ended at 5.0 and 4.3 per 1000 individuals, respectively, in December 2023 (Figure 2).

3.3 | Characteristics of incident SGLT2i users

We identified 14 320 incident SGLT2i users between January 1, 2021, and December 31, 2023 (Table 1). Empagliflozin was the most frequently initiated SGLT2i (66%), followed by dapagliflozin (31%) and canagliflozin (3.8%). SGLT2i initiators had a median age of 81 years (interquartile range [IQR]: 77–84), and 60% were men. Common comorbidities included hypertension (69%), chronic kidney disease (46%), heart failure (25%), diabetic retinopathy (18%), and cardiovascular disease (17%). SGLT2i initiators frequently used other glucose-lowering drugs, particularly metformin (68%), sulfonylureas (39%), insulins (19%), and dipeptidyl peptidase-4 inhibitors (18%). They also frequently used cardiovascular drugs, such as lipid-modifying agents (77%). Most SGLT2is (62%) were initiated by general practitioners (GPs). Among SGLT2i initiators, 8883 (62%) had cardiorenal disease. Those with cardiorenal disease had a higher comorbidity burden than those without cardiorenal disease (mean CCI [standard deviation]: 3.7 [2.2] vs. 1.6 [1.2]). They also used more fee-for-service physician services in the past year (median [IQR]: 80 [53–119] vs. 47 [32–67]). Further, cardiovascular drug use was generally higher among SGLT2i initiators with cardiorenal disease, particularly beta

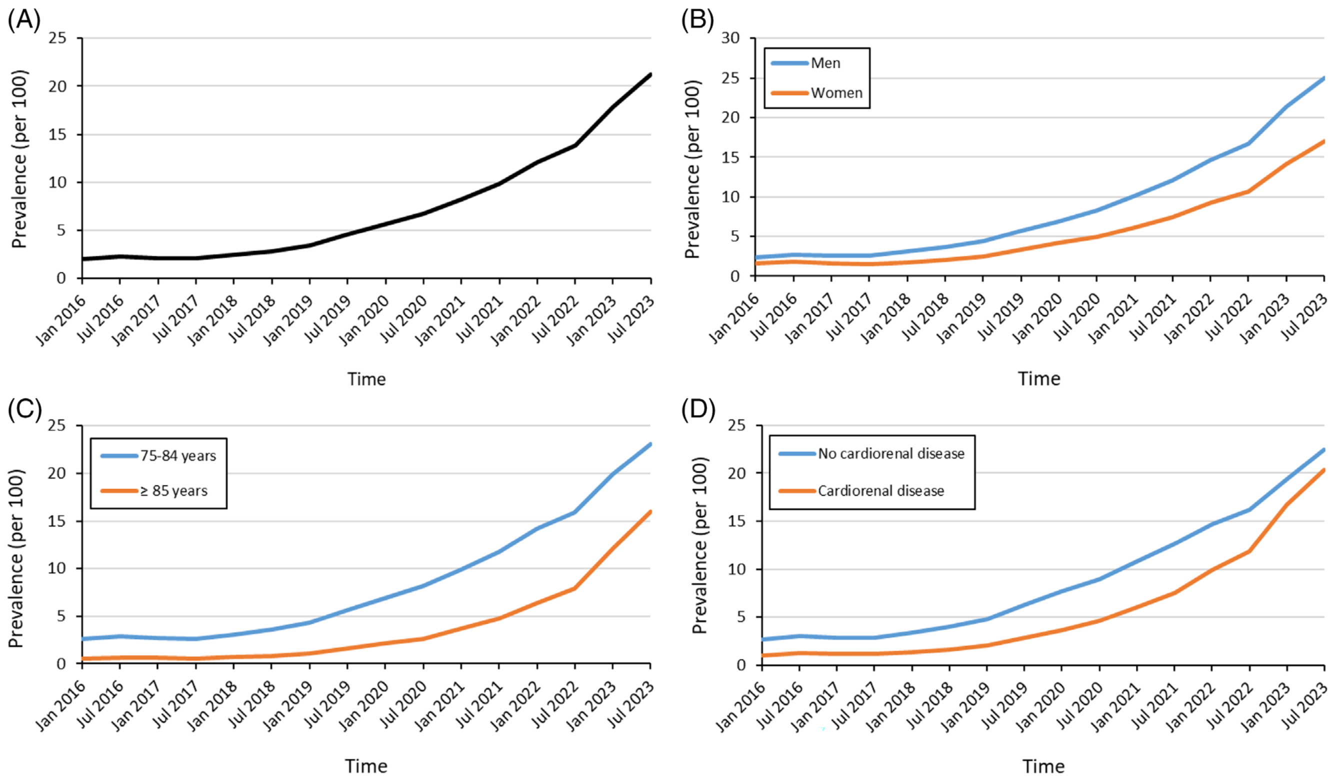

FIGURE 1 Six-month prevalence of sodium-glucose cotransporter-2 inhibitor use among older adults (≥75 years) with type 2 diabetes mellitus in British Columbia, Canada. Denominators included those enrolled in the Medical Services Plan of British Columbia at the start of each period. Results are shown overall (panel A) and stratified by sex (panel B), age group (panel C), and cardiorenal disease status (panel D). Stratified analyses were limited to individuals within each stratum.

blockers (57% vs. 28%), loop diuretics (36% vs. 6.1%), and direct oral anticoagulants (27% vs. 9.8%). Among SGLT2i initiators with cardiorenal disease, treatment was less often initiated by GPs (53% vs. 77%) and more often by nephrologists (11% vs. 0.33%) or cardiologists (9.1% vs. 2.6%).

3.4 | Discontinuation of SGLT2is

Among the 14 110 SGLT2i initiators who survived beyond the duration of the first prescription plus a 90-day grace period, 20% (2808) did not refill their prescription within that time. One year after SGLT2i initiation, 13 252 individuals were still alive. Of these, 17% (2318) had not refilled their prescription by the end of the year.

4 | DISCUSSION

SGLT2i use among individuals aged ≥75 years with T2DM in British Columbia, Canada, increased gradually between 2016 and 2022 and then more sharply in 2023. By the end of 2023, around one-fifth of this population used SGLT2is, with similar use among those with and without cardiorenal disease. Incident SGLT2i users commonly used other glucose-lowering drugs. Most had cardiorenal disease and used related drugs. Nearly one-fifth of incident SGLT2i users did not refill their prescriptions within the first year.

4.1 | Strengths and limitations

The key strengths of this study are its population-based design, which minimises the risk of selection bias, and the fact that it is the first to examine SGLT2i use among older adults with T2DM in British Columbia. The study also has limitations. First, we used a validated definition to capture T2DM, which includes codes for other types of diabetes.[10] However, since T2DM remains the most prevalent type of diabetes in older adults,[18] our definition likely captured mostly T2DM cases. Second, using GLP-1RAs to identify individuals with T2DM may have introduced some misclassification, as these drugs have more recently been prescribed for indications other than T2DM, such as chronic weight management.[19] However, GLP-1RAs were first added to the British Columbia PharmaCare formulary in 2020, and coverage is limited to T2DM.[12] Consequently, GLP-1RA use during our study period (2016–2023) is expected to primarily reflect T2DM treatment. Additionally, GLP-1RA use in our study was low (4.9%; Table 1). Therefore, any potential misclassification of users treated for indications other than T2DM is expected to be minimal and unlikely to affect our results. Third, because the study relied on pharmacy dispensing data,

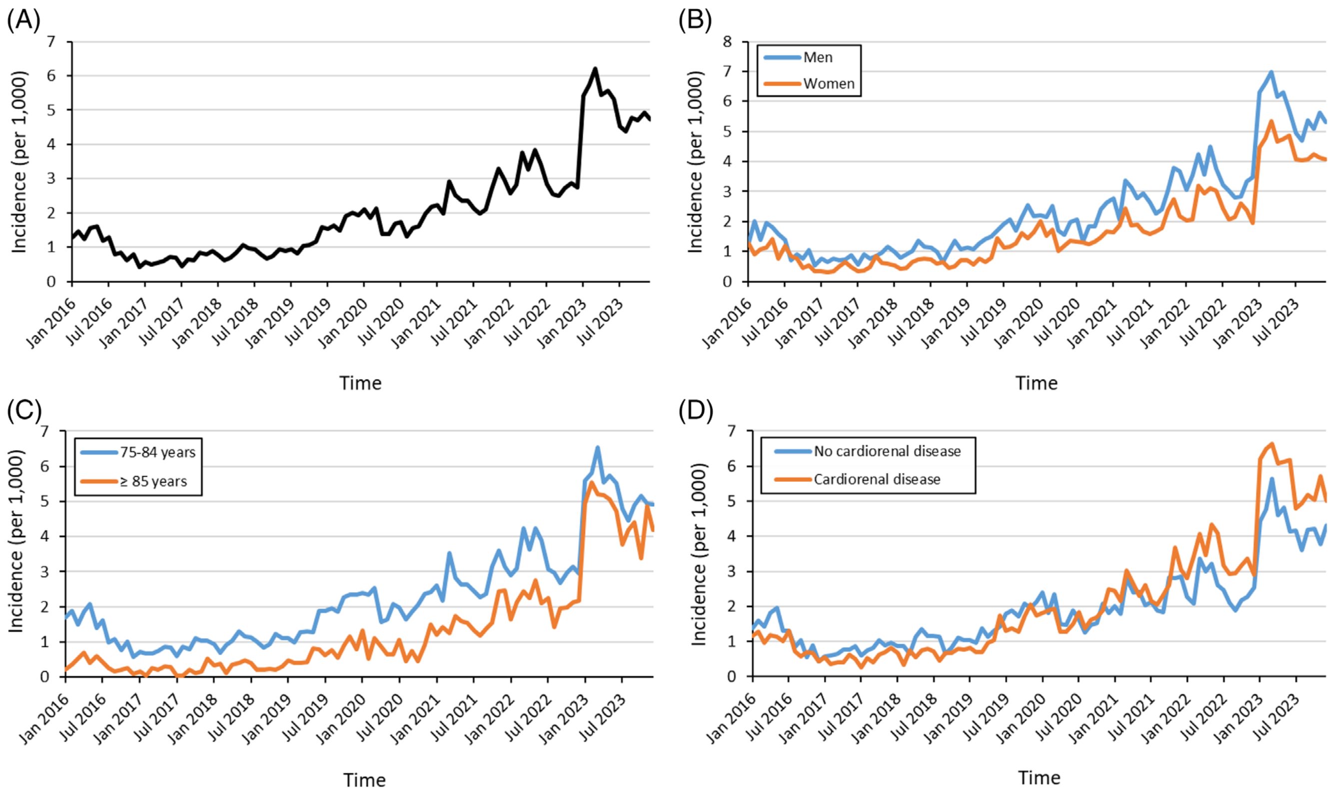

FIGURE 2 Monthly incidence of sodium-glucose cotransporter-2 inhibitor use among older adults (≥75 years) with type 2 diabetes mellitus in British Columbia, Canada. Denominators included those enrolled in the Medical Services Plan of British Columbia at the start of each period. Results are shown overall (panel A) and stratified by sex (panel B), age group (panel C), and cardiorenal disease status (panel D). Stratified analyses were limited to individuals within each stratum.

we could not account for individuals who filled their prescription but did not take the drug as prescribed (secondary non-adherence). Fourth, to calculate the prevalence of SGLT2i use and the proportion of early discontinuation, we introduced a grace period to account for irregular dispensing. However, some exposure misclassification may still have occurred. Fifth, we did not include frailty in the characterisation of incident SGLT2i users, despite its relevance in older adults with T2DM. We used the CCI to capture multimorbidity, which, while not a direct measure of frailty, provides insight into patient complexity. Last, because SGLT2i initiation was defined as no filled prescription in the past 5 years, some former users could have been misclassified as initiators. This could potentially lead to a slight overestimation of incidence rates. However, since SGLT2is were first listed on the PharmaCare formulary in 2019 and use before that was relatively low (Figure 1), any resulting bias is likely minimal.

4.2 | Comparison with existing literature

Previous studies also reported increasing prevalence[20–24] and incidence[20,21] of SGLT2i use, including among those with cardiorenal disease,[20,21] as well as lower use with increasing age.[23] However, most of these studies did not focus specifically on older adults or those with T2DM. The 1-year discontinuation of 17% is lower than observed in other studies.[20,25] This is likely due to differences in definitions and study populations. The spike in SGLT2i use in January 2023 coincided with British Columbia PharmaCare expanding coverage to all individuals with T2DM, after restrictions since their introduction to the formulary in 2019.[12] SGLT2i use similarly spiked in France after expanding indications and allowing general practitioners to initiate treatment.[20]

4.3 | Perspectives

Guidelines for older adults with T2DM recognise that SGLT2is offer benefits comparable to, or even greater than, those seen in younger adults. However, they also recommend caution due to potential adverse effects.[26] While we cannot specify the optimal prevalence and incidence of SGLT2i use in this population, our findings suggest that many potential candidates are not receiving these drugs. SGLT2i use was relatively low among individuals aged ≥75 years with T2DM and lower among those aged ≥85 years compared to those aged 75–84 years. This may reflect caution due to concerns about, and limited data on, their safety in this population, particularly in older adults with frailty or limited life expectancy, who may have a less favourable risk–benefit profile.[27] Indeed, a commonly reported barrier to prescribing SGLT2is is the concern about

TABLE 1 Characteristics of older adults (≥75 years) with type 2 diabetes mellitus in British Columbia, Canada, who initiated sodium-glucose cotransporter-2 inhibitors[a] between January 1, 2021, and December 31, 2023, overall and stratified by cardiorenal disease status.

	Overall ($n = 14\ 320$)	Cardiorenal disease ($n = 8883$)	No cardiorenal disease ($n = 5437$)
Woman, *n* (%)	5765 (40)	3413 (38)	2352 (43)
Age			
Median (IQR)	81 (77–84)	81 (77–84)	80 (76–82)
75–79 years, *n* (%)	7123 (50)	3952 (44)	3171 (58)
80–84 years, *n* (%)	4215 (29)	2753 (31)	1462 (27)
85–89 years, *n* (%)	2213 (15)	1577 (18)	636 (12)
90–94 years, *n* (%)	665 (4.6)	519 (5.8)	146 (2.7)
≥ 95 years, *n* (%)	104 (0.73)	82 (0.92)	22 (0.40)
Charlson Comorbidity Index			
Mean (SD)	2.9 (2.1)	3.7 (2.2)	1.6 (1.2)
0, *n* (%)	268 (1.9)	55 (0.62)	213 (3.9)
1–2, *n* (%)	6943 (48)	2652 (30)	4291 (79)
3–4, *n* (%)	4295 (30)	3490 (39)	805 (15)
≥5, *n* (%)	2814 (20)	2686 (30)	128 (2.4)
Comorbidities, *n* (%)			
Heart failure	3628 (25)	3628 (41)	0 (0.00)
Chronic kidney disease	6569 (46)	6569 (74)	0 (0.00)
Hypertension	9935 (69)	7056 (79)	2879 (53)
Cardiovascular disease	2371 (17)	2371 (27)	0 (0.00)
Cerebrovascular disease/stroke	688 (4.8)	688 (7.7)	0 (0.00)
Diabetic retinopathy	2559 (18)	1935 (22)	624 (11)
SGLT2i initiated, *n* (%)			
Canagliflozin	543 (3.8)	315 (3.5)	228 (4.2)
Dapagliflozin	4386 (31)	3355 (38)	1031 (19)
Empagliflozin	9391 (66)	5213 (59)	4178 (77)
Concomitant drug use[b], *n* (%)			
DPP4is	2552 (18)	1604 (18)	948 (17)
Metformin	9795 (68)	5414 (61)	4381 (81)
SUs	5633 (39)	3115 (35)	2518 (46)
GLP-1RAs	702 (4.9)	478 (5.4)	224 (4.1)
Insulins	2772 (19)	1944 (22)	828 (15)
ACEIs	6742 (47)	4232 (48)	2510 (46)
ARBs	4171 (29)	2786 (31)	1385 (25)
Alpha blockers	373 (2.6)	305 (3.4)	68 (1.3)
Beta blockers	6594 (46)	5057 (57)	1537 (28)
Calcium channel blockers	5365 (37)	3626 (41)	1739 (32)
Centrally acting antihypertensives	68 (0.47)	54 (0.61)	14 (0.26)
Thiazide diuretics	2445 (17)	1272 (14)	1173 (22)
Potassium-sparing diuretics	1676 (12)	1496 (17)	180 (3.3)
Loop diuretics	3503 (24)	3173 (36)	330 (6.1)
ARNIs	405 (2.8)	395 (4.4)	10 (0.18)
Lipid-modifying agents	11 057 (77)	7116 (80)	3941 (72)
Platelet aggregation inhibitors[c]	2652 (19)	2077 (23)	575 (11)
Vitamin K antagonists	463 (3.2)	376 (4.2)	87 (1.6)
Direct oral anticoagulants	2933 (20)	2402 (27)	531 (9.8)

TABLE 1 (Continued)

	Overall (n = 14 320)	Cardiorenal disease (n = 8883)	No cardiorenal disease (n = 5437)
Opioids	1922 (13)	1335 (15)	587 (11)
NSAIDs	505 (3.5)	237 (2.7)	268 (4.9)
Antidepressants	2834 (20)	1918 (22)	916 (17)
Immunosuppressants	195 (1.4)	151 (1.7)	44 (0.81)
Osteoporosis drugs	668 (4.7)	440 (5.0)	228 (4.2)
Glucocorticoids	1194 (8.3)	849 (9.6)	345 (6.3)
FFS physician services in past year, median (IQR)	65 (42–100)	80 (53–119)	47 (32–67)
Rural location, n (%)	1405 (9.8)	846 (9.5)	559 (10)
Long-term care residence, n (%)	189 (1.3)	128 (1.4)	61 (1.1)
Low income, n (%)	3609 (25)	2280 (26)	1329 (24)
Prescriber speciality, n (%)			
General practitioner	8877 (62)	4702 (53)	4175 (77)
Nurse practitioner	429 (3.0)	308 (3.5)	121 (2.2)
Endocrinologist	834 (5.8)	449 (5.1)	385 (7.1)
Cardiologist	951 (6.6)	810 (9.1)	141 (2.6)
Nephrologist	974 (6.8)	956 (11)	18 (0.33)
Geriatrician	77 (0.54)	46 (0.52)	31 (0.57)
Other	2178 (15)	1612 (18)	566 (10)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ARNIs, angiotensin receptor-neprilysin inhibitors; DPP4is, dipeptidyl peptidase-4 inhibitors; IQR, interquartile range; FFS, fee-for-service; GLP-1RAs, glucagon-like peptide-1 receptor agonists; NSAIDs, nonsteroidal anti-inflammatory drugs; SD, standard deviation; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SUs, sulfonylureas.

[a]Incident sodium-glucose cotransporter-2 inhibitor use was defined as not having filled a prescription for a sodium-glucose cotransporter-2 inhibitor in the past 5 years.

[b]Concomitant drug use was defined as at least one filled prescription in the 180 days before sodium-glucose cotransporter-2 inhibitor initiation.

[c]Low-dose aspirin is primarily available over the counter in British Columbia, Canada, and therefore its use is generally not captured.

potential adverse effects.[6–9] The risk of adverse effects may be higher in older adults due to age-related physiological changes, multimorbidity, and polypharmacy.[28] SGLT2is have been linked to adverse effects such as urogenital infections, diabetic ketoacidosis, and volume depletion.[3] While clinical trials did not find an increased risk of adverse effects in older adults compared to younger adults, they included only a small number of individuals aged ≥75 years.[3–5,27] This highlights the need for further research on the safety of SGLT2is in this population to inform clinical decisions, given their increasing use. Interestingly, SGLT2i use was slightly lower among those with cardiorenal disease compared to those without cardiorenal disease, a finding that has also been reported in other studies.[29] This may reflect limited early evidence of their efficacy and prescriber caution in individuals with comorbidities, leading to selective use in relatively healthier individuals. Additionally, uptake of guideline recommendations prioritising those with cardiorenal disease may have been gradual. From mid-2020 onward, however, treatment initiation among those with cardiorenal disease exceeded that of those without cardiorenal disease, and the gap between the two groups widened. This likely reflects growing evidence supporting both the efficacy and safety of SGLT2is as well as broader adoption of guideline recommendations.

5 | CONCLUSION

The use of SGLT2is among individuals aged ≥75 years with T2DM in British Columbia has increased over time. This increase has been particularly pronounced since 2023, aligned with the expansion in publicly funded drug coverage. Around one in five individuals in this population used SGLT2is by the end of 2023, regardless of cardiorenal disease status. Our findings underscore the need for further research on the safety and efficacy of SGLT2is in those aged ≥75 years, given their increasing use in this population.

AUTHOR CONTRIBUTIONS

Hanin Harbi and Wade Thompson conceptualised the study. Wade Thompson and Gregory Carney acquired the data. Gregory Carney analysed the data. Hanin Harbi drafted the manuscript. All authors contributed to study design and data interpretation, critically revised the manuscript, and approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

Guillaume Grenet has received a grant from the French Association for Thermal Research—"Association Française pour la Recherche Thermale" (AFRETh, http://www.afreth.org/), which was not related to this study. The remaining authors have no conflicts to disclose.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70375.

DATA AVAILABILITY STATEMENT

Access to data provided by the British Columbia Ministry of Health under the Information Sharing Agreement 16-036 is subject to approval but can be requested for research projects through the Data Stewards or their designated service providers. Summary data are available upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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