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Concomitant Use of Sodium-Glucose Cotransporter 2 Inhibitors and Overactive Bladder Drugs and the Risk of Urinary Tract Infection

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ABSTRACT

Concomitant use of sodium glucose cotransporter-2 inhibitors (SGLT-2i) and overactive bladder (OAB) drugs potentially poses a risk of urinary tract infections (UTI) due to the urinary retention of highly concentrated glucose in the urine. Thus, this study aimed **t**o investigate the risk of UTI among patients who initiated SGLT-2i treatment while taking OAB drugs. This population-based cohort study included new-users of SGLT-2i or comparator antidiabetics (dipeptidyl peptidase-4 inhibitor [DPP-4i]; glucagon-like peptide-1 receptor agonist [GLP-1RA]) with OAB drugs between 2014 and 2020 using claim data from Korea. Primary outcome was a composite UTI event composite endpoint comprising pyelonephritis, cystitis, and urethritis, using both inpatient and outpatient diagnoses. Propensity score fine stratification was used to adjust for potential confounding factors. Weighted hazard ratios (HR) were calculated using the Cox proportional hazards model. In the first cohort, 796 and 9,181 new-users of SGLT-2i and DPP-4i with OAB drugs were identified, respectively. This study found a similar risk of UTI in concomitant users of SGLT-2i and DPP-4i (weighted HR 1.08, 95% CI 0.88–1.32) with OAB drugs. In the second cohort, 2,387 and 280 new-users of SGLT-2i and GLP-1RA with OAB drugs were identified, respectively. Initiation of SGLT-2i while on OAB treatment was not associated with increased risk of UTI (0.89, 0.50–1.60), compared to initiation of GLP-1RA. These results show that the concomitant use of SGLT-2i with OAB drugs was not associated with an increased risk of UTI compared with the concomitant use of DPP-4i or GLP-1RA with OAB drugs.

INTRODUCTION

Overactive bladder (OAB) is a prevalent disease characterized by urinary urgency, commonly accompanied by frequent nocturia, with or without urinary incontinence (1). As patients with diabetes are more likely to be vulnerable to urinary symptoms due to the high concentration of glucose in the urine, the prevalence of OAB among patients with type 2 diabetes is more than 2-fold that of the general population (2, 3). Antimuscarinic drugs and beta-3 adrenoceptor agonists are often used to prevent or mitigate urinary symptoms by increasing urine storage capacity and relaxing the detrusor smooth muscles (4). Although these OAB drugs are widely used and efficacious, they can cause various adverse effects including drug-induced urinary retention (5, 6). Given that urinary glucose likely contributes to urinary tract infections (UTI), urinary retention caused by OAB drugs is a major risk factor for UTI in patients with diabetes.

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) have shown cardiorenal benefits beyond the glucose-lowering effect through their unique mechanism of controlling blood sugar via the renal proximal tubule (7, 8). However, in the process of excreting glucose through urine, several major safety concerns have been raised related to the increased risk of genitourinary tract infection (9). While the increased risk of genital infections associated with SGLT-2i use is widely known, its association with UTI is less clear and conflicting results have been reported (10-13).

As the prevalence of type 2 diabetes and OAB increases, more patients use SGLT-2i and OAB drugs together (14-16). Yet, no population-based study has explored whether their concomitant use is associated with UTI. Thus, we aimed to investigate the risk of UTI among patients who initiated SGLT-2i treatment while taking OAB drugs and compared it with that of those who initiated dipeptidyl peptidase-4 inhibitor (DPP-4i) or glucagon-like peptide-1 receptor agonist (GLP-1RA) treatment while taking OAB drugs.

METHODS

Study Design and Data Source

We conducted an active comparator, new-user cohort study using healthcare claim data from the National Health Insurance Service (NHIS) database of South Korea. South Korea provides universal health insurance coverage through a single provider system for approximately 50 million residents (17). The NHIS database includes demographic information on age, sex, and reimbursed claims in medical diagnostic records by physicians, history of medical facility admissions, health examinations, and inpatient and outpatient prescriptions (17). Diagnosis was recorded using the International Classification of Diseases, 10th revision (ICD-10) coding system, and the positive predictive value for diagnostic codes was reported to be 82% in a previous validation study (18). Medications were recorded using the National Health Insurance (NHI) coding systems, including information on the active ingredient, dosage, route of administration, date of prescription, and days of supply.

Study population

We identified two new-user, active-comparator cohorts, wherein initiators of SGLT-2i (dapagliflozin, empagliflozin, ertugliflozin, and ipragliflozin) were compared with initiators of DPP-4i (alogliptin, anagliptin, evogliptin, gemigliptin, linagliptin, saxagliptin, sitagliptin, teneligliptin, and vildagliptin) and GLP-1RA (albiglutide, dulaglutide, exenatide, and lixisenatide) (19). For both cohorts, patients entered the cohort on the date of their first prescription of either SGLT-2i or a comparator drug during the study period (hereafter, cohort entry). New-users were defined as receiving no record of study glucose-lowering drugs in the prior year of cohort entry. The study population included adults aged 18 years or older who initiated SGLT-2i or DPP-4i (for cohort 1), and SGLT-2i or GLP-1RA (for cohort 2) while receiving OAB drugs between September 1, 2014 (first date of SGLT-2i cover in South Korea)

and December 31, 2020. We defined concomitant use of OAB drugs and study glucose-lowering drugs as the use of OAB drugs on the date of study glucose-lowering drugs drug initiation, with days' supply overlapping the date of study antidiabetic drug initiation (**Supplementary material 1**).

Patients aged <18 years at cohort entry and those prescribed both SGLT-2i and a comparator drug upon cohort entry were excluded. Considering that end-stage renal disease (ESRD) is a contraindication for SGLT-2i we also excluded patients with a history of ESRD or dialysis within 365 days prior to cohort entry. We further excluded patients with records related to cancer within 365 days prior to cohort entry to prevent any potential bias caused by cancer or chemotherapy. Finally, patients with a history of UTI within 365 days prior to cohort entry were excluded.

Exposure

We applied an as-treated approach to define exposure. Patients were followed from the day after initiation of study antidiabetic drug treatment while receiving OAB drugs until the occurrence of a UTI, discontinuation of the cohort entry drug, initiation of the comparator class, and discontinuation of the OAB treatment, all-cause death, and the end of the study (December 31, 2020). Patients were considered to have discontinued the index medication or OAB treatment when they failed to refill within 90 days. OAB drugs included antimuscarinic drugs (solifenacin, oxybutynin, tolterodine, trospium, fesoterodine, propiverine) and β-3 adrenoceptor agonists (mirabegron) (4, 5). DPP-4i and GLP-1RA were chosen as the active comparators because SGLT-2i, DPP-4i, and GLP-1RA are second- or third-line glucose-lowering drugs indicated for the management of type 2 diabetes in South Korea.

Outcome

The primary outcome was a UTI event composite endpoint comprising pyelonephritis, cystitis, and urethritis using both inpatient and outpatient diagnoses. Secondary outcomes included individual endpoints of the primary outcomes and severe UTI events, which were defined as hospitalization for UTI. Since the NHIS database provides information on which diagnosis was most accountable for the visit or hospitalization (primary) and differentiates between secondary and other, outcomes were defined as those occurring in primary and secondary diagnosis positions only (**Supplementary material 2**).

Covariates

Baseline characteristics including age, sex, calendar year of cohort entry, prior use of antidiabetic medications and the level of antidiabetic treatment, diabetes-related complications (nephropathy, neuropathy, retinopathy, hypoglycemia), comorbidities, prior medication use, healthcare use (number of hospitalizations [0, 1–2, ≥3], number of physician visits [0–2, 3–5, ≥6]), duration of OAB treatment, and Charlson comorbidity index (0, 1–2, ≥3) were assessed (**Supplementary material 3**). The level of antidiabetic treatment was defined as following criteria: 1) patients without any glucose-lowering drugs (i.e., only treated with lifestyle modification) or received only one glucose-lowering drug; 2) patients receiving more than two different classes of non-insulin glucose-lowering drugs; and 3) patients receiving insulin either alone or in combination with other glucose-lowering drugs. These covariates were measured during the year prior to the cohort entry, which was defined as the initiation date of SGLT-2i and comparator drugs. All variables were included in the propensity score (PS) models for the main analysis.

Statistical Analysis

We used PS fine stratification to adjust for any potential confounding factors (20). The PS is the likelihood of initiating SGLT-2i and is estimated using a multivariate logistic regression model with covariates measured as independent variables. In each cohort, we generated 50 strata based on the PS distribution of SGLT-2i and comparator drugs. As we estimated the average treatment effect among those treated within each stratum, new-users of SGLT-2i were assigned a weight of 1, whereas new-users of DPP-4i and GLP-1RA were reweighted to be proportional to the number of exposed populations in the corresponding stratum (20). Potential differences between each exposure group were assessed using the absolute standardized difference (aSD), with <0.1 representing an appropriate balance. Covariates that remained imbalanced after weighting were further adjusted in the survival analysis (21, 22). The weighted incidence of UTI with a 95% confidence interval (CI) was also measured. Lastly, weighted Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% CI for UTI associated with the concomitant use of OAB drugs with SGLT-2i versus OAB drugs with comparator drugs (DPP-4i and GLP-1RA).

Potential effect modification was evaluated through subgroup analyses, and patients were stratified according to age at cohort entry (<65 vs ≥65 years), sex, duration of OAB drug use (<90 days vs ≥90 days), prevalent OAB drug use (yes vs no), OAB drug classes (β-3 adrenoceptor agonist vs antimuscarinic drugs), and ingredient of SGLT-2i (dapagliflozin vs empagliflozin). For subgroup analysis, we re-estimated the PS and PS fine stratification weighting within each subgroup of interest.

The robustness of our findings was assessed using several sensitivity analyses. First, we applied an intention-to-treat approach to prevent any informative censoring, where patients were followed from the day after initiation of study antidiabetic drug treatment while receiving OAB drugs until the occurrence of a UTI, death, 365 days after the cohort entry date, or the end of the study date (December 31, 2020), whichever came first. Second, we modified the

definition of UTI to include diagnosis and antibiotic use on the same date to increase the specificity of the outcome definition. Third, we repeated the analysis using 1:1 PS matching to verify whether the results were consistent with those of the primary analysis with PS fine stratification. Patients were matched 1:1 on their PS, using the nearest-neighbor methods and a caliper of 0.05 of the PS. Fourth, the grace period used to define discontinuation of OAB or antidiabetic treatment varied to 30 days, aiming to prevent potential misclassification of exposure.

RESULTS

SGLT-2i Versus DPP-4i

In the first cohort, we identified 796 patients who were receiving OAB drugs at the time of SGLT-2i initiation and 9,181 patients who were receiving OAB drugs at the time of DPP-4i initiation (**Supplementary material 4**). The mean duration of exposure to OAB drugs did not differ significantly between the two groups. Before weighting, users of SGLT-2i with OAB drugs were younger and more likely to have heart failure, coronary artery disease, and a history of statin use than users of DPP-4i with OAB drugs. After weighting, all covariates were well-balanced between the two groups (**Supplementary material 5** and **Table 1**). The first cohort showed a median follow-up of 95 days (IQR 61-115), and the difference in follow up between the two groups was not significant (SGLT-2i: 91 days [IQR 45-111]; DPP-4i: 96 days [IQR 62-115]). 83% of patients were censored for discontinuation of OAB drugs (**Supplementary material 6**).

In our primary analysis, we observed 1,424 UTI events: 103 events in concomitant users of SGLT-2i with OAB drugs (weighted incidence rate, 21.06 per 100 person-years) and 1,321 events in concomitant users of DPP-4i with OAB drugs (19.48 per 100 person-years). Compared with the initiation of DPP-4i while on OAB treatment, there was no difference in the risk of composite UTI events with the initiation of SGLT-2i while on OAB treatment (weighted HR 1.08, 95% CI 0.88–1.32). No difference in risk was observed between the two groups in the individual and severe UTI events (**Table 2**). In addition, no increased risk of UTI was observed in the subgroup analyses stratified by age at cohort entry, sex, duration of OAB drug use, prevalent OAB drug use, OAB drug classes, and ingredient of SGLT-2i (**Figure 1**). The results of the sensitivity analyses were generally consistent with those of the primary analysis (**Figure 2**).

SGLT-2i Versus GLP-1RA

In the second cohort, we identified 2,387 patients receiving OAB drugs at the time of SGLT-2i treatment initiation and 280 patients receiving OAB drugs at the time of GLP-1RA treatment initiation (**Supplementary material 7**). No significant difference was observed in the mean duration of exposure to OAB drugs between the two groups. Before weighting, users of SGLT-2i with OAB drugs were less likely to use insulin or have diabetic complications, chronic kidney disease, or peripheral artery disease than users of GLP-1RA with OAB drugs. After weighting, calendar year, diabetic retinopathy, dyslipidemia, history of statin use, and history of thiazolidinediones use remained unbalanced with aSD of 0.1, but other covariates were well-balanced (**Supplementary material 8** and **Table 1**). The second cohort demonstrated a median follow-up of 94 days (IQR 56-116), and the disparity in follow-up between the two groups was not significant (SGLT-2i: 94 days [IQR 56-117]; GLP-1RA: 91 days [IQR 62-110]). 80% of patients were censored for discontinuation of OAB drugs (**Supplementary material 9**).

In the primary analysis, we observed 402 UTI events: 363 in concomitant users of SGLT-2i with OAB drugs (weighted incidence rate, 19.53 per 100 person-years), and 39 in concomitant users of GLP-1RA with OAB drugs (22.03 per 100 person-years). There was no difference in the risk of composite UTI events between patients who initiated SGLT-2i or GLP-1 RA while on OAB treatment (weighted HR 0.89, 95% CI 0.50-1.60) (**Table 3**). Subgroup analyses yielded results with wide 95% confidence intervals that were, for the most part, consistent and in line with the results in the overall cohort (**Figure 1**). The sensitivity analysis results were robust and consistent with those of the main analysis (**Figure 2**).

DISCUSSION

In this population-based cohort study using claim data, we found no increased risk of UTI when SGLT-2i were added to OAB treatment, as compared to concomitant use of DPP-4i with OAB drugs or GLP-1RA with OAB drugs. Risk of UTI was not elevated across subgroups when stratified according to age, sex, duration of OAB drug use, SGLT-2i ingredients, or OAB drug class. The results of the sensitivity analyses were generally consistent with those of the main analyses, demonstrated the robustness of our findings.

To our knowledge, this is the first study to evaluate the safety of the concomitant use of SGLT-2i and OAB drugs in patients with type 2 diabetes. Nonetheless, the findings of this study are similar to those from indirect evidence from patients with type 2 diabetes who used SGLT-2i without OAB drugs. A meta-analysis of 72 trials reported no increased risk for overall UTI events (HR 1.03, 95% CI 0.96–1.11), urosepsis (1.41, 0.57–3.48), or pyelonephritis (0.78, 0.52–1.18) (12). Another cohort study used claim data from the United States and found that the use of SGLT-2i did not elevate the risk of severe UTI compared with that of DPP-4i (0.98, 0.68–1.41) and GLP-1RA (0.72, 0.53–0.99) (10). Also, an observational study of 408,506 new-users of SGLT-2i in South Korea found a null association between SGLT-2i and UTI risk compared with that of DPP-4i and UTI risk (1.05, 1.00–1.11) (11). Likewise, the results of our study suggest that the risk of UTI was not elevated among new-users of SGLT-2i who were on OAB treatment, which is an independent risk factor for UTI events.

OAB and type 2 diabetes are chronic diseases prevalent in elderly patients (23). Elderly patients with diabetes often have more severe stages of diabetes than younger patients and a higher chance of urine system infection (24). Moreover, the use of OAB drugs can further increase the risk of UTI by causing urinary retention as an adverse effect (25). UTI significantly reduces quality of life and worsens glycemic control in patients. In addition, urinary tract sepsis

and pyelonephritis are known to affect renal function and mortality; thus, UTI management in elderly patients with type 2 diabetes is clinically important (26). Given that the use of SGLT-2i will increase in the elderly population owing to its cardiorenal effect, identifying potential drug-drug interactions of SGLT-2i is needed to elucidate the safety profile among drug classes (14-16). Although not statistically significant, the point estimate of UTI risk increased in both the DPP-4i (<65 years: HR 1.05; ≥65 years: HR 1.12) and GLP-1RA (<65 years: HR 0.65; ≥65 years: HR 1.44) when stratified by age at age 65. Thus, clinicians should carefully monitor elderly patients under concomitant OAB drugs and SGLT-2i treatment.

Since the risk of UTI may be strongly driven by OAB drugs, we also investigated the duration-response of OAB treatment. While the statistical power to detect effect heterogeneity across subgroups was limited, we did not observe any substantial difference in the estimates across the subgroups of OAB duration. Likewise, in previous study that assessed the risk of UTIs with respect to adherence to OAB treatment regimens, it was consistently observed that the risk of UTIs remained unaffected by the level of adherence to OAB drugs (5). Similarly, in a prior study that explored the risk of UTI in relation to adherence to OAB treatment regimens, a consistent finding emerged, that the risk of UTI did not differ regardless of the level of adherence to OAB medications. These results support our cautious interpretation that there is no increased risk of UTI due to drug-drug interactions between SGLT-2i and OAB drugs.

Several RCTs have reported that SGLT-2i may induce UTI events (12, 27). Although RCTs are the gold standard for evaluating the efficacy and safety of drugs, they usually have low statistical power to detect differences in certain safety events, such as UTIs, leading to inconclusive results (28). Moreover, patients on co-medications represent only a small subset of randomized study population, and trials are rarely, if ever, set up to evaluate concomitant use or potential drug-drug interactions (29). Using a real-world database, this study identified

a large number of patients taking new antidiabetic drugs concomitantly with OAB treatment, which provided an opportunity to evaluate the potential pharmacodynamic interaction between SGLT-2i and OAB drugs.

Our study has several limitations. First, as this was an observational study, the results may be affected by residual confounding factors. Our new-user, active-comparator study design, restriction of the cohort to individuals on OAB treatment on cohort entry, and PS-based adjustment for multiple potential confounders ensured robust confounding control. Moreover, we adjusted and stratified the analyses on the duration of OAB treatment before cohort entry to ensure the comparability of exposure groups. Nevertheless, the results of this study could still be affected by unmeasured confounders, such as the duration of diabetes, HbA1c levels, and stages of frailty, particularly, if these differed substantially across initiators of SGLT-2i, DPP-4i and GLP-1RA. Second, we defined the concomitant use of glucose-lowering drugs and OAB drugs based on the date of dispensing and the number of days of supply; however, we were unable to evaluate whether patients took these drugs simultaneously. In addition, since we evaluated the comparative risk of adding a new glucose-lowering drug to OAB treatment, we cannot rule that all three agents increase the risk of UTI in patients on OAB treatment. However, given that no increase in UTI risk has been reported for DPP-4i or GLP-1RA, it is unlikely. Third, although the UTI events were defined using validated diagnostic codes from previous studies, the results of this study may not be free of potential outcome misclassifications. However, our findings were robust across the secondary outcomes of hospitalization for UTI and sensitivity analyses that applied alternative outcome definitions with antibiotic use. Finally, given the small number of GLP-1RA initiators in our study, we cannot exclude that our study was underpowered to detect small, but clinically meaningful increase in UTI risk for SGLT-2i initiators, as compared to GLP-1RA initiators.

CONCLUSIONS

In this population-based cohort study using nationwide claims database from South Korea, the initiation of SGLT-2i was not associated with an increased risk of UTI compared with the initiation of either DPP-4i or GLP-1RA while on OAB treatment. While our study provides reassurance evidence for people with OAB and diabetes who would benefit from cardiorenal benefits of SGLT-2i, future studies in larger cohorts and other countries are needed to confirm our findings.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Use of sodium glucose cotransporter-2 inhibitors (SGLT-2i) potentially poses a risk of urinary tract infections (UTI) due to the highly concentrated glucose in the urine.

What question did this study address?

Is the concomitant use of SGLT-2i with OAB drugs associated with an increased risk of UTI?

What does this study add to our knowledge?

In this population-based cohort study using two independent cohorts, the concomitant use of SGLT-2i with OAB drugs was not associated with an increased risk of UTI compared with that of dipeptidyl peptidase-4 inhibitors or glucagon-like peptide-1 receptor agonists with OAB drugs.

How might this change clinical pharmacology or translational science?

While our study provides reassurance evidence for people with OAB and diabetes who would benefit from cardiorenal benefits of SGLT-2i, future studies in larger cohorts and other population are needed to confirm the risk of UTI following concomitant use of SGLT-2i and OAB drugs.

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Table 1. Baseline characteristics of the concomitant users of SGLT-2i with OAB drugs versus the concomitant users of incretin-based drugs with OAB drugs before and after propensity score fine weighting.

	After propensity weighting					
Baseline characteristics	**SGLT-2i (n=796)**	**DPP-4i (n=9181)**	**aSD**	**SGLT-2i (n=2387)**	**GLP-1RA (n=280)**	**aSD**
Age (years; mean, SD)	61 (12.9)	61 (14.2)	0.002	64.6 (11.7)	64.9 (14.1)	0.020
Female	235 (29.5)	2715 (29.6)	0.001	762 (31.9)	81 (28.8)	0.069
OAB drugs duration (days); mean (SD)	290.1 (605.4)	288.6 (611.7)	0.002	355.7 (560.3)	360.9 (553.8)	0.009
Calendar year						
2014	16 (2.0)	185 (2.0)	0.000	0 (0.0)	0 (0.0)	n/a
2015	49 (6.2)	564 (6.1)	0.000	99 (4.1)	10 (3.5)	0.032
2016	65 (8.2)	740 (8.1)	0.004	257 (10.8)	32 (11.4)	0.021
2017	148 (18.6)	1698 (18.5)	0.003	401 (16.8)	42 (15.1)	0.048
2018	140 (17.6)	1598 (17.4)	0.005	478 (20)	71 (25.3)	0.127
2019	183 (23.0)	2137 (23.3)	0.007	564 (23.6)	63 (22.4)	0.029
2020	195 (24.5)	2259 (24.6)	0.003	588 (24.6)	62 (22.3)	0.056
Level of antidiabetic treatments[§]						
1	533 (67.0)	6198 (67.5)	0.012	464 (19.4)	60 (21.5)	0.051
2	168 (21.1)	1929 (21.0)	0.002	1392 (58.3)	156 (55.6)	0.054
3	95 (11.9)	1055 (11.5)	0.014	531 (22.2)	64 (22.9)	0.015
Antidiabetic drugs use[‡]						
Insulin	95 (11.9)	1055 (11.5)	0.014	531 (22.2)	64 (22.9)	0.015
α-glucosidase inhibitors	26 (3.3)	304 (3.3)	0.002	72 (3.0)	8 (2.9)	0.007
Meglitinides	4 (0.5)	46 (0.5)	0.001	12 (0.5)	1 (0.4)	0.008
Metformin	389 (48.9)	4492 (48.9)	0.001	1897 (79.5)	214 (76.3)	0.077
Sulfonylureas	207 (26.0)	2344 (25.5)	0.011	1284 (53.8)	158 (56.4)	0.053
Thiazolidinediones	59 (7.4)	651 (7.1)	0.012	421 (17.6)	65 (23.2)	0.137
GLP-1RA	3 (0.4)	34 (0.4)	0.001	N/A	N/A	N/A
Dipeptidyl peptidase-4 inhibitor	N/A	N/A	N/A	1569 (65.7)	179 (64.1)	0.035
Diabetes related conditions; n (%)						
Diabetic nephropathy	39 (4.9)	429 (4.7)	0.011	148 (6.2)	14 (5.2)	0.045
Diabetic neuropathy	78 (9.8)	886 (9.6)	0.005	480 (20.1)	55 (19.8)	0.009
Diabetic retinopathy	137 (17.2)	1601 (17.4)	0.006	637 (26.7)	62 (22.3)	0.102
Hypoglycaemia	4 (0.5)	43 (0.5)	0.005	26 (1.1)	3 (0.9)	0.015
Comorbidities; n (%)						
Dyslipidemia	303 (38.1)	3475 (37.9)	0.004	970 (40.6)	100 (35.7)	0.102
Hypertension	408 (51.3)	4691 (51.1)	0.003	1329 (55.7)	150 (53.4)	0.045
Atrial fibrillation	22 (2.8)	256 (2.8)	0.001	66 (2.8)	6 (2.0)	0.050
Heart failure	57 (7.2)	637 (6.9)	0.009	155 (6.5)	20 (7.3)	0.030
Coronary artery disease	53 (6.7)	580 (6.3)	0.014	179 (7.5)	16 (5.7)	0.073
Cerebrovascular disease	57 (7.2)	636 (6.9)	0.009	229 (9.6)	28 (9.9)	0.012
Peripheral artery disease	71 (8.9)	819 (8.9)	0.000	231 (9.7)	21 (7.5)	0.078
Liver cirrhosis	4 (0.5)	42 (0.5)	0.006	21 (0.9)	1 (0.5)	0.051
Chronic kidney disease	11 (1.4)	119 (1.3)	0.007	72 (3.0)	7 (2.6)	0.026
Chronic respiratory disease	113 (14.2)	1310 (14.3)	0.002	376 (15.8)	35 (12.6)	0.092
Dementia	14 (1.8)	155 (1.7)	0.005	72 (3)	8 (2.8)	0.013
Depression	67 (8.4)	760 (8.3)	0.005	211 (8.8)	22 (7.9)	0.033
Hypothyroidism	20 (2.5)	229 (2.5)	0.001	62 (2.6)	5 (1.8)	0.053
Hyperthyroidism	11 (1.4)	131 (1.4)	0.004	18 (0.8)	1 (0.5)	0.034
Comedications; n (%)						
Acetaminophen	495 (62.2)	5668 (61.7)	0.009	1581 (66.2)	191 (68.4)	0.045
ACE inhibitors	28 (3.5)	300 (3.3)	0.014	82 (3.4)	12 (4.4)	0.049
Antiplatelets	311 (39.1)	3552 (38.7)	0.008	1196 (50.1)	139 (49.7)	0.007
ARB	362 (45.5)	4145 (45.1)	0.007	1362 (57.1)	154 (55)	0.041
β-blockers	182 (22.9)	2060 (22.4)	0.010	1137 (47.6)	132 (47.2)	0.010

CCB	348 (43.7)	3997 (43.5)	0.004	609 (25.5)	81 (28.9)	0.075
Diuretics (loop)	72 (9.0)	800 (8.7)	0.012	306 (12.8)	32 (11.4)	0.045
Diuretics (other)	192 (24.1)	2214 (24.1)	0.000	624 (26.1)	71 (25.2)	0.021
NSAIDS	551 (69.2)	6320 (68.8)	0.008	1685 (70.6)	198 (70.6)	0.000
Oral anticoagulants	22 (2.8)	244 (2.7)	0.007	81 (3.4)	8 (3.0)	0.021
Opioids	96 (12.1)	1087 (11.8)	0.007	350 (14.7)	42 (15.0)	0.009
Systemic antibiotics	588 (73.9)	6804 (74.1)	0.005	1757 (73.6)	214 (76.3)	0.062
Systemic corticosteroids	436 (54.8)	4985 (54.3)	0.009	1356 (56.8)	158 (56.5)	0.006
Statin	430 (54.0)	4911 (53.5)	0.011	1676 (70.2)	183 (65.2)	0.107
Charlson Comorbidity Index; n (%)						
0	226 (28.4)	2643 (28.8)	0.002	317 (13.3)	36 (12.8)	0.012
1-2	301 (37.8)	3486 (38.0)	0.003	948 (39.7)	124 (44.2)	0.090
≥3	269 (33.8)	3052 (33.2)	0.012	1122 (47.0)	120 (43.0)	0.081
Healthcare use[‡]						
Inpatient hospitalizations						
0	577 (72.5)	6716 (73.2)	0.015	1581 (66.2)	182 (64.9)	0.029
1-2	188 (23.6)	2113 (23)	0.014	683 (28.6)	88 (31.3)	0.058
≥3	31 (3.9)	352 (3.8)	0.003	123 (5.2)	11 (3.8)	0.063
Number of physician visits						
0-2	21 (2.6)	243 (2.7)	0.001	38 (1.6)	7 (2.5)	0.061
3-5	54 (6.8)	644 (7.0)	0.009	50 (2.1)	7 (2.5)	0.027
≥6	721 (90.6)	8293 (90.3)	0.008	2299 (96.3)	266 (95.0)	0.062

Abbreviations: aSD, absolute standard deviation; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; CCB, calcium channel blockers; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon like peptide 1 receptor agonists; NSAIDs, nonsteroidal anti-inflammatory drugs; OAB, overactive bladder; SGLT-2i, sodium glucose cotransporter 2 inhibitors

Table 2. Hazard ratios of urinary tract infection associated with the concomitant use of SGLT-2i with OAB drugs vs DPP-4i with OAB drugs.

Exposure	SGLT-2i with OAB drug			DPP-4i with OAB drug			Hazard Ratio (95% CI)[†]	
	Events	Person-years	Weighted Incidence rate[*]	Events	Person-years	Weighted Incidence rate[*]	Crude	Weighted
Primary outcome								
Composite of UTI	103	489	21.06 (17.19-25.55)	1321	6164	19.48 (18.37-20.64)	0.97 (0.80-1.19)	1.08 (0.88-1.32)
Secondary outcome								
Cystitis	20	502	3.99 (2.44-6.17)	321	6322	4.35 (3.84-4.91)	0.77 (0.49-1.21)	0.91 (0.57-1.44)
Ureteritis	43	499	8.63 (6.25-11.63)	564	6294	7.93 (7.23-8.67)	0.96 (0.71-1.31)	1.09 (0.80-1.50)
Pyelonephritis	20	502	3.98 (2.43-6.15)	367	6323	4.08 (3.58-4.62)	0.68 (0.44-1.07)	0.98 (0.62-1.54)
Severe UTI events	14	503	2.79 (1.52-4.68)	278	6337	3.06 (2.64-3.54)	0.63 (0.37-1.08)	0.91 (0.53-1.57)

Abbreviations: CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitors; HR, hazard ratio; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; OAB, overactive bladder; UTI, urinary tract infection

[*]Per 100 person-years.

[†]The models were weighted with the use of propensity score fine stratification.

Table 3. Hazard ratios of urinary tract infection associated with the concomitant use of SGLT-2i with OAB drugs vs GLP-1RA with OAB drugs.

Exposure	SGLT-2i with OAB drug			GLP-1RA with OAB drug			Hazard Ratio (95% CI)[†]	
	Events	Person-years	Weighted Incidence rate[*]	Events	Person-years	Weighted Incidence rate[*]	Crude	Weighted
Primary outcome								
Composite of UTI	363	1845	19.53 (17.48-21.75)	39	181	22.03 (15.67-30.12)	0.92 (0.66-1.28)	0.89 (0.50-1.60)
Secondary outcome								
Cystitis	65	1890	3.21 (2.43-4.17)	12	185	4.37 (1.89-8.61)	0.54 (0.29-0.99)	0.80 (0.26-2.52)
Ureteritis	173	1874	9.27 (7.89-10.82)	11	186	8.84 (5.05-14.36)	1.57 (0.85-2.89)	1.04 (0.36-3.04)
Pyelonephritis	88	1888	4.71 (3.75-5.85)	15	185	6.04 (3.02-10.81)	0.58 (0.33-1.00)	0.78 (0.38-1.61)
Severe UTI events	57	1892	2.93 (2.18-3.85)	12	186	4.37 (1.89-8.61)	0.47 (0.25-0.88)	0.66 (0.23-1.94)

Abbreviations: CI, confidence interval; GLP-1RA, glucagon like peptide 1 receptor agonists; HR, hazard ratio; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; OAB, overactive bladder; UTI, urinary tract infection

[*]Per 100 person-years.

[†]The models were weighted with the use of propensity score fine stratification.

Figure Legends

Figure 1. Subgroup analyses of the association between concomitant exposure to SGLT-2i and OAB drugs and urinary tract infection.

Abbreviations: CI, confidence interval; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; OAB, overactive bladder; SGLT-2, sodium glucose cotransporter 2 inhibitors
[*]Duration of OAB drug use prior to cohort entry.

Figure 2. Sensitivity analyses of the association between concomitant exposure to SGLT-2i and OAB drugs and urinary tract infection.

Abbreviations: DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1RA, glucagon-like peptide 1 receptor agonists; HR, hazard ratio; OAB, overactive bladder; UTI, urinary tract infection; SGLT-2i, sodium glucose co-transporter 2 inhibitors

[*]Patients were followed from the day after initiation of study antidiabetic drug treatment while receiving OAB drugs until the occurrence of a UTI, death, 365 days after the cohort entry date, or the end of the study date (December 31, 2020), whichever came first.
[†]Analysis using 1:1 propensity score matching
[‡]Modified the definition of UTI to include diagnosis and antibiotic use on the same date to increase the validity of the outcome definition
[§]Patients were considered to have discontinued the index medication or OAB treatment when they failed to refill within 30 days (time frame of 90 days were used in the main analysis)