Use of Sodium-Glucose Transport Protein 2 Inhibitors and the Incidence of Urolithiasis: A Multi-Database and Cross-Country Study in Patients With Type 2 Diabetes Mellitus

Mu-Chi Chung[1,2,3,4], Chia-Yen Lin[5,6,7], Chao-Hsiang Chang[8], Yi-Huei Chang[8], Po-Jen Hsiao[8], Chi-Shun Lien[8], Laing-You Wu[9], Ming-Ju Wu[2], Jeng-Jer Shieh[10,11], Peir-Haur Hung[12,13], Hsin-Hua Chen[1,4,14,15,16] and Chi-Jung Chung[9,17,*]

The benefits of sodium-glucose transport protein 2 inhibitor (SGLT2i) use on severe urolithiasis requiring surgery remains unclear. All patients with incident T2D in Taiwan National Health Institution databases (2016–2021) and TriNetX datasets (2014–2023) were retrospectively analyzed. The study analyzed a propensity score-matched pairs with T2D treated with SGLT2i or dipeptidyl peptidase 4 inhibitors (DPP4i). The primary outcome was the incidence of urolithiasis and urolithiasis requiring surgery during the study period. Urolithiasis diagnoses were identified using International Classification of Diseases diagnostic codes and categorized into upper and lower urinary tract stones. Cases of urolithiasis requiring surgery were determined by the presence of both diagnostic codes and surgical procedure codes within the same outpatient visit or hospitalization. Conditional and time-dependent Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). During the study period, 5700 participants were diagnosed with urolithiasis, 1297 participants were urolithiasis requiring surgery in Taiwan NHIRD cohort 8438 participants with urolithiasis as well as 289 participants with urolithiasis requiring surgery were in the TriNetX cohort. Adjusted HRs of urolithiasis and urolithiasis requiring surgery were 0.82-fold (95% CI, 0.77–0.87), 0.72-fold (95% CI, 0.63–0.82) in Taiwan NHIRD, 0.84 (95% CI, 0.78–0.90), and 0.62 (95% CI, 0.44–0.88) in TriNetX cohort respectively. Similar protective associations with SGLT2i use against urolithiasis were observed across subgroups in both datasets from Taiwan NHIRD and TriNetX. In conclusion, SGLT2i might protect against kidney stones and severe cases requiring surgery in T2D patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been associated with metabolic benefits, but their impact on urolithiasis risk, particularly cases requiring surgical intervention, remains unclear.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study investigated whether SGLT2i use is associated with a reduced risk of urolithiasis and urolithiasis requiring surgery in patients with T2D, compared to dipeptidyl peptidase 4 inhibitors (DPP4i), using real-world data from Taiwan's NHIRD and the global TriNetX database.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ The study found that SGLT2i use was associated with a significantly lower risk of urolithiasis and urolithiasis requiring surgery across diverse populations. The protective effects were consistent across subgroups, including age, gender, and concomitant medication use.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These findings suggest a potential protective role of SGLT2i against kidney stones in T2D patients, which may influence future treatment guidelines. Further research is needed to elucidate the underlying mechanisms and confirm these benefits in randomized controlled trials.

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[1]Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung, Taiwan; [2]Division of Nephrology, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [3]Division of Clinical Toxicology, Departmentof Medical Toxicology, Taichung Veterans General Hospital, Taichung, Taiwan; [4]Ph.D. Program in Translational Medicine, National Chung Hsing University, Taichung, Taiwan; [5]Department of Urology, Taichung Veterans General Hospital, Taichung, Taiwan; [6]School of Medicine, Chung Shan Medical University, Taichung, Taiwan; [7]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [8]Department of Urology, China Medical University Hospital, Taichung, Taiwan; [9]Department of Public Health, College of Public Health, China Medical University, Taichung, Taiwan; [10]Institute of Biomedical Sciences, National Chung Hsing University, Taichung, Taiwan; [11]Department of Education and Research, Taichung Veterans General Hospital, Taichung, Taiwan; [12]Department of Internal Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan; [13]Department of Applied Life Science and Health, Chia-Nan University of Pharmacy and Science, Tainan, Taiwan; [14]Division of Allergy, Immunology and Rheumatology, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [15]Division of Clinical Informatics, Center for Quality Management, Taichung Veterans General Hospital, Taichung, Taiwan; [16]Big Data Center, National Chung Hsing University, Taichung, Taiwan; [17]Department of Medical Research, China Medical University Hospital, Taichung, Taiwan. *Correspondence: Chi-Jung Chung (cjchung@mail.cmu.edu.tw)

Urolithiasis represents a health concern, imposing both substantial morbidity and economic burden on healthcare systems worldwide.[1] Recent trends indicate a rising prevalence, particularly among individuals with comorbidities.[2] While most patients have a favorable prognosis, those requiring surgical intervention face potential postoperative complications, including sepsis and mortality.[3] Furthermore, a history of urolithiasis has been associated with an elevated risk of chronic kidney disease (CKD), end-stage renal disease (ESRD), and coronary artery disease, highlighting the need for comprehensive management strategies.[4]

Emerging evidence suggests a link between metabolic disorders and urolithiasis. Obesity, metabolic syndrome, and Type 2 diabetes (T2D) are associated with an elevated risk of stone formation, with insulin resistance potentially serving as a common mechanism.[5] The severity of diabetes correlates strongly with urolithiasis risk.[6] Among individuals with T2D, urolithiasis is the predominant urological complication necessitating hospitalization. This results in increased healthcare costs and prolonged hospital stays compared to non-diabetic patients.[7]

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) are a first-line therapy for cardiovascular and diabetic kidney diseases in patients with T2D. Beyond glycemic control, these agents reduce body weight, uric acid levels, and blood pressure,[8] factors linked to a reduced risk of urolithiasis. SGLT2i users exhibit reduced urinary calcium phosphate supersaturation ratios, suggesting a potential protective effect against calcium phosphate stone formation.[9] Conversely, increased uric acid supersaturation ratios and lower urinary pH among SGLT2i users raise concerns about a possible elevated risk for uric acid stones.[9] The relationship between SGLT2i and urolithiasis merits further investigation.

This study leveraged two robust data sources: Taiwan's National Health Insurance Research Database (NHIRD) and the global TriNetX platform, to investigate the association between SGLT2i use and urolithiasis risk in patients with T2D. Our analysis compared SGLT2is with dipeptidyl peptidase 4 inhibitors (DPP4is), a widely used class of antidiabetic medications. We extended our investigation to examine the risk of urolithiasis requiring surgical intervention and exploring stone formation at various anatomical locations within the urinary tract. This dual-database approach provided a unique opportunity to assess the relationship between SGLT2i use and urolithiasis risk across diverse populations.

MATERIALS AND METHODS

Data sources

There are two well-known databases used in the present study. First, we utilized medical data from the Taiwan's NHIRD. Following the implementation of the National Health Insurance program in 1995, Taiwan's coverage rate exceeds 99%. This database includes registration documents and claims information such as outpatient visits, hospitalizations, prescription records, and surgical treatments. Access to NHIRD is granted for research purposes without requiring patient consent. Second, TriNetX is a global federated collaborative research platform offering real-time data from electronic health records. In 2022, it included over 220 healthcare organizations across 30 countries. For our study, we utilized the TriNetX Research Network, which represented over 100 million patients across 70 healthcare organizations globally, primarily located in the United States, with some from Latin America and the Asia-Pacific regions.[10] This database includes disease diagnosis, medication records, laboratory results, and procedure treatments. Access to TriNetX is also granted for research purposes without requiring patient consent.[11]

This research was separately approved by the Institutional Review Board of China Medical University Hospital (CRREC-109-018). This was conducted in accordance with the Declaration of Helsinki and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. TriNetX complies with HIPAA and GDPR regulations, ensuring stringent data protection standards. The study was exempt from obtaining individual informed consent due to the anonymized nature of the data utilized. The Western Institutional Review Board has exempted TriNetX from the informed consent process, as it provides aggregated statistics and summaries of de-identified data. We obtained specific approval from the Institutional Review Board of Taichung Veterans General Hospital (IRB approval number: SE22220A-1, TCVGH) to use the TriNetX platform. This multi-layered ethical approach underscores our commitment to maintaining patient privacy while advancing medical research.

Study design and participants

We conducted a nationwide retrospective cohort study using de-identified data from NHIRD and TriNetX. In both databases, disease diagnoses were determined based on diagnostic codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM.

In NHIRD, confirmed T2D was defined as having at least three outpatient visits within 1 year or one hospitalization, a criterion validated in a previous study.[12] We identified 572,514 T2D patients who initiated SGLT2i or DPP-4i between May 2016 (when SGLT2i were included in Taiwan's NHIRD) and December 2021, excluding those with either drug in the previous year. A 1-year washout period was implemented to ensure adequate elimination of prior SGLT2i or DPP-4i effects on urinary stone formation. The index date was defined as the date of the first visit in which a SGLT2i or DPP-4i was prescribed. After excluding T2D patients under the age of 18, those who concurrently used SGLT2i or DPP-4i, and patients with chronic kidney disease (CKD) Stage 4, CKD Stage 5, or end-stage renal disease, 555,914 study participants who used SGLT2 inhibitor or DPP-4 inhibitor without late-stage CKD remained. Furthermore, patients with a diagnosis of urolithiasis or records of urolithiasis-related treatments before using SGLT2i or DPP-4i were excluded, leaving 112,936 SGLT2i users and 280,759 DPP-4i users for the study. This study focused exclusively on incident urolithiasis events. To mitigate baseline comorbidity and prescription medication confounding effects, we conducted a 1:1

propensity score matching based on age, gender, comorbidities, and other medication use, resulting in 112,701 pairs for both SGLT2i and DPP-4i groups. A detailed study flowchart is depicted in **Figure 1** (Left).

An intention-to-treat (ITT) analysis was adopted in this study, analyzing all patients according to their originally assigned treatment groups, regardless of any changes or discontinuation in therapy during the follow-up period.

In TriNetX, confirmed T2D was defined as having at least two outpatient visits within 2 years or one hospitalization, validated in a previous USA study.[13] We identified T2D patients who used SGLT2i or DPP-4i between January 2014 (when SGLT2i were included in TriNetX) and December 2023, without prior prescriptions in the previous year. After the same exclusions criteria as NHIRD and 1:1 propensity score matching, there were 114,052 individuals for both SGLT2i and DPP-4i groups. A detailed study flowchart is depicted in **Figure 1** (Right).

Medications

We focused on two classes of medications: SGLT2is (dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, and sotagliflozin, with the latter two included only in TrinetX and not in NHIRD) and DPP4is (sitagliptin, linagliptin, saxagliptin, alogliptin, and vildagliptin, included in both databases). Comprehensive details, including specific drug types and prescription dates, were collected. DPP4 inhibitors were chosen as our comparison group since they shared a similar therapeutic position (as second- or third-line treatments for glucose control), and prior research has shown no link between these agents and urolithiasis.[14]

Outcome of urolithiasis

The primary outcome was urolithiasis incidence. The diagnosis of urolithiasis in both NHIRD and TrinetX was based on the same ICD-9-CM and ICD-10-CM diagnostic codes (**Table S1**). The coding for urolithiasis has been validated in both Taiwan and the United States, with a positive predictive value of 92.5%[15] and 95.9%, respectively.[16] Urolithiasis requiring surgery was defined as the surgical procedure during the same outpatient visit or hospitalization, including extracorporeal shock wave lithotripsy, nephron-pyelolithotomy, percutaneous nephrolithotomy, ureteroscopy and removal of stone, ureterolithotomy, endoscopic cystolitholapaxy, and vesicolithotomy. Surgical intervention was identified by payment orders in Taiwan, which are necessary for reimbursement in Taiwan. In contrast, we identified surgical intervention by ICD-9 and ICD-10 Current Procedural Terminology (CPT) codes in TrinetX.

In a secondary analysis, we examined the association between SGLT2i use and anatomical locations of stones, dividing outcomes into upper and lower urinary tract stones based on ICD codes. Codes with unspecified locations (including ICD-9592.9/788.0 and ICD-10N22/N23) or patients with diagnoses of both upper and lower urinary tract stones were excluded.

Covariates

The same covariates were analyzed in both databases. Comorbidities encompassed conditions such as hypertension, hyperlipidemia, cerebrovascular disease (CVD), coronary artery disease (CAD), CKD, obesity, gout, hyperparathyroidism, inflammatory bowel disease, and urinary tract infections that occurred in the year preceding the index date. Our model also considered other medications used, including glucagon-like peptide-1 (GLP-1) agonists, insulin, metformin, thiazides, diuretics (except thiazides), statins, aspirin, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and benzbromarone.

Statistical analysis

Propensity score matching was used to establish a comparison group for SGLT2i users. We estimated the probability of initiating SGLT2 inhibitor as a function included all study covariates and further calculated the individual propensity score given their baseline covariates. Greedy nearest neighbor matching was employed to construct a 1:1 PS-matched group with a minimum caliper width of within 0.2 on the log (PS) scale in Taiwan NHIRD and within 0.05 standard deviation in TriNetX.[17] Furthermore, the suitability of covariate comparisons between the propensity score-matched groups was assessed using standardized mean differences (SMD) with a cutoff of 0.10.[18,19] Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. Age was categorized into 10-year groups: below 25 years, 25–34 years, 35–44 years, and so

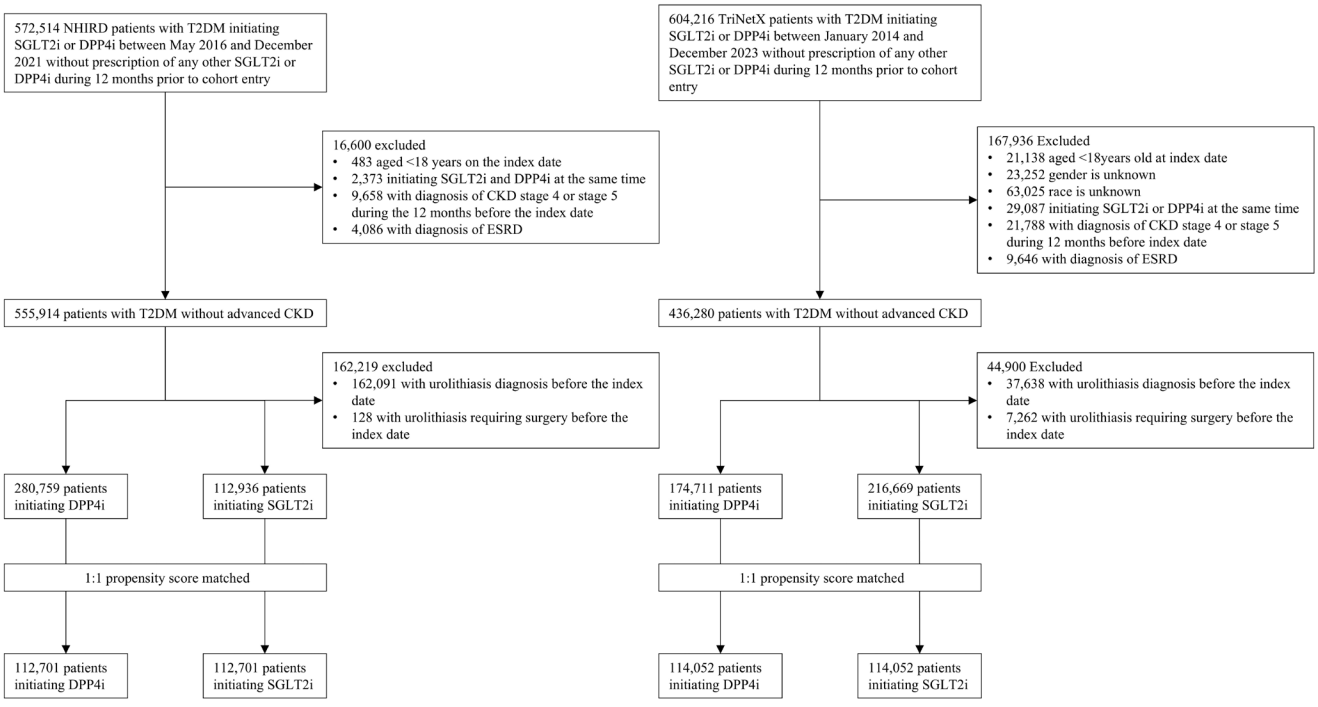

Figure 1 Flow diagram of the study patient selection.

on. Cumulative incidences of urolithiasis or urolithiasis requiring surgery occurrence between two groups receiving SGLT2i or DPP-4i were estimated and visualized using Kaplan–Meier survival curves and were compared using the log-rank test. All participants were followed from the index date to the first occurrence of death, study outcome, or end of follow-up. The proportional hazards assumption was assessed by means of scaled Schoenfeld residuals. Because the proportional hazards assumption was violated, conditional and time-varying Cox proportional hazard regression with yearly time intervals was used to determine the crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) for the risks of urolithiasis or urolithiasis requiring surgery. Subgroup analyses were conducted among study participants with various comorbidities and prescription medications to evaluate the association between SGLT2i use and urolithiasis incidence. All hypothesis tests were two-tailed, with significance defined as $\alpha = 0.05$. Statistical analysis was performed using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Characteristics of study participants

After propensity score matching, we compared 112,701 pairs of SGLT2i or DPP-4i users from the Taiwan's NHIRD and 114,052 pairs from TriNetX (**Table 1**). All standardized mean differences between groups were less than 0.1, indicating well-balanced covariate distributions. Compared to SGLT2i users in TriNetX, those in the NHIRD were younger, had a higher proportion of males, and higher prevalence of hypertension, hyperlipidemia, CVD, gout, and urinary tract infections. They also used more metformin and benzbromarone.

SGLT2i use and urolithiasis risk

During the study period, 2559 SGLT2i users and 3141 DPP4i users were diagnosed with urolithiasis, while 517 SGLT2i users and 780 DPP4i users underwent urolithiasis-related surgery in NHIRD cohort (**Table 2**). In TriNetX, 3776 SGLT2i users and 4642 DPP4i users were diagnosed with urolithiasis, while 148 SGLT2i users and 141 DPP4i users required surgery. The median duration time from initiation of SGLT2i or DPP4i to the occurrence of urolithiasis was 1.91 years (interquartile range [IQR], 2.33 years) in the Taiwan NHIRD cohort and 3.35 years (IQR, 3.65 years) in the TriNetX cohort.

Log-rank tests in both datasets indicated that SGLT2i users had a lower cumulative incidence of urolithiasis compared to DPP4i users. In NHIRD cohort, the incidence of urolithiasis was 10.26 vs. 12.78 cases per 1000 patient-years ($P < 0.0001$) for SGLT2i and DPP4i users, respectively (**Figure 2a**). The incidence of urolithiasis requiring surgery was 2.04 vs. 3.12 cases per 1000 patient-years ($P < 0.0001$) (**Figure 2c**). Similarly, in the TriNetX cohort, the incidence of urolithiasis was 9.16 vs. 10.98 cases per 1000 patient-years ($P < 0.0001$) (**Figure 2b**), and the incidence of urolithiasis requiring surgery was 0.46 vs. 0.75 cases per 1000 patient-years ($P < 0.0001$) (**Figure 2d**). After adjusting for age, gender, diabetes duration, comorbidities, and medications, the SGLT2i group in NHIRD cohort had an adjusted hazard ratio (HR) of 0.82 (95% CI, 0.77–0.87; $P < 0.0001$) for urolithiasis and 0.72 (95% CI, 0.63–0.82; $P < 0.0001$) for urolithiasis requiring surgery. In TriNetX, the adjusted HRs were 0.84 (95% CI, 0.78–0.90; $P < 0.0001$) for urolithiasis and 0.71 (95% CI, 0.56–0.89; $P = 0.0027$) for urolithiasis requiring surgery after adjusting for age, gender, race, diabetes duration, comorbidities, and medications (**Table 2**).

Among SGLT2i users, dapagliflozin and empagliflozin were the most commonly used medication in NHIRD (52.5%) and in TriNetX (58.4%), respectively. In NHIRD, users of dapagliflozin and empagliflozin exhibited significantly reduced risks of both urolithiasis and urolithiasis requiring surgery (adjusted HRs ranged from 0.66 to 0.83). In TriNetX, empagliflozin or canagliflozin use was both associated with a reduced risk for urolithiasis. However, only dapagliflozin with protect effect for urolithiasis requiring surgery was significantly found in the analysis.

Subgroup analyses

Due to the small number of cases requiring surgery, we only assessed the relationships between SGLT2i use and urolithiasis under different stratifications of comorbidities and prescription medications in the propensity score-matched population (**Table S2**). In NHIRD cohort, protective associations with SGLT2i use against urolithiasis were observed in T2D patients without CVD, CKD, gout, obesity, hyperparathyroidism, inflammatory bowel disease, cystitis, and in those not using GLP-1, insulin, thiazides, diuretics (except thiazides), aspirin, or benzbromarone. SGLT2i use significantly reduced the risk of urolithiasis regardless of age, gender, hypertension, hyperlipidemia, CKD, urinary tract infection, and the use of metformin, statin, and ACEI/ARB.

In TriNetX, similar protective associations of SGLT2i use against urolithiasis were observed in patients without hypertension, hyperlipidemia, CVD, CAD, gout, hyperparathyroidism, inflammatory bowel disease, cystitis, urinary tract infection, and in those not using insulin, thiazides, diuretics (except thiazides), or benzbromarone. SGLT2i use significantly reduced the risk of urolithiasis irrespective of gender, CKD, obesity, and use of GLP-1, metformin, statins, aspirin, and ACE inhibitors/ARBs.

Analysis of upper and lower urinary tract stones

We further investigated the impact of SGLT2i use on the risk of urolithiasis, focusing on the locations of the stones within the urinary tract (**Figure 3**). After excluding codes with unspecified locations or diagnoses of both upper and lower urinary tract stones, there were 4880 cases of upper urinary tract stones and 221 cases of lower urinary tract stones in NHIRD (89% of total events) and 7906 cases of upper urinary tract stones and 223 cases of lower urinary tract stones in TriNetX (97% of total events). SGLT2i users had significantly reduced risks of upper urinary tract stones (HR, 0.80; 95% CI, 0.75–0.85; $P < 0.0001$), but no significant association was observed with lower urinary tract stones (HR, 0.78; 95% CI, 0.54–1.14; $P = 0.2015$) in NHIRD cohort. In TriNetX, SGLT2i users showed significantly reduced risks for both upper urinary tract stones (HR, 0.84; 95% CI, 0.78–0.91; $P < 0.0001$) and lower urinary tract stones (HR, 0.54; 95% CI, 0.34–0.85; $P = 0.0377$).

Table 1 Baseline characteristics comparisons between study populations in TriNetX and Taiwan NHIRD

	Taiwan NHIRD cohort			TriNetX cohort		
	DPP4i (*N* = 112,701)	SGLT2i (*N* = 112,701)	SMD	DPP4i (*N* = 114,052)	SGLT2i (*N* = 114,052)	SMD
Index year			−0.02			0.09
2014				2571 (2.25%)	3248 (2.85%)	
2015				4301 (3.77%)	5458 (4.79%)	
2016	5978 (5.30%)	6628 (5.88%)		6511 (5.71%)	6551 (5.74%)	
2017	12,859 (11.41%)	13,478 (11.96%)		10,892 (9.55%)	9091 (7.97%)	
2018	15,813 (14.03%)	15,272 (13.55%)		15,064 (13.21%)	10,982 (9.63%)	
2019	21,503 (19.08%)	21,245 (18.85%)		17,759 (15.57%)	14,834 (13.01%)	
2020	28,701 (25.47%)	27,993 (24.84%)		16,630 (14.58%)	14,945 (13.10%)	
2021	27,847 (24.71%)	28,085 (24.92%)		16,220 (14.22%)	18,114 (15.88%)	
2022				13,448 (11.79%)	17,197 (15.08%)	
2023				10,656 (9.34%)	13,632 (11.95%)	
Age, Mean ± SD	58.69 ± 13.33	58.82 ± 13.19	0.01	61.96 ± 13.01	61.72 ± 12.24	−0.02
Stratify age, *n* (%)						
< 25	981 (0.87%)	768 (0.68%)		550 (0.48%)	368 (0.32%)	
26–34	3854 (3.42%)	3838 (3.41%)		2702 (2.37%)	2109 (1.85%)	
35–44	12,690 (11.26%)	12,604 (11.18%)		8386 (7.35%)	7754 (6.80%)	
45–54	22,320 (19.80%)	22,084 (19.60%)		19,096 (16.74%)	20,095 (17.62%)	
55–64	33,354 (29.60%)	33,728 (29.93%)		31,442 (27.57%)	33,936 (29.75%)	
65–74	26,937 (23.90%)	27,184 (24.12%)		31,784 (27.87%)	32,644 (28.62%)	
75–84	10,515 (9.33%)	10,497 (9.31%)		17,811 (15.62%)	15,292 (13.41%)	
≥85	2050 (1.82%)	1998 (1.77%)		2281 (2.00%)	1854 (1.63%)	
Gender (Women), *n* (%)	50,330 (44.66%)	49,579 (43.99%)	0.01	55,172 (48.37%)	54,726 (47.98%)	0.01
Race						
White				78,315 (68.67%)	76,196 (66.81%)	0.04
Black or African American				20,429 (17.91%)	21,582 (18.92%)	−0.03
Asian				9362 (8.21%)	9661 (8.47%)	−0.01
Other Race				5946 (5.21%)	6613 (5.80%)	−0.03
Comorbidity, *n* (%)						
Hypertension (HTN)	68,525 (60.80%)	68,337 (60.64%)	0.00	23,600 (20.69%)	25,772 (22.60%)	−0.05
Hyperlipidemia (HPL)	76,475 (67.86%)	75,536 (67.02%)	0.02	14,941 (13.10%)	16,656 (14.60%)	−0.04
Cerebral vascular disease (CVD)	6450 (5.72%)	6922 (6.14%)	−0.02	6110 (5.36%)	6807 (5.97%)	−0.03
Coronary artery disease (CAD)	20,220 (17.94%)	21,398 (18.99%)	−0.03	67,566 (59.24%)	70,582 (61.89%)	−0.05
Chronic kidney disease (CKD)	12,450 (11.05%)	13,376 (11.87%)	−0.03	77,637 (68.07%)	81,232 (71.22%)	−0.07
Gout	6926 (6.15%)	7495 (6.65%)	−0.02	4462 (3.91%)	5084 (4.46%)	−0.03
Obesity	2181 (1.94%)	2647 (2.35%)	−0.03	29,158 (25.57%)	31,767 (27.85%)	−0.05
Hyperparathyroidism (HPTH)	26 (0.02%)	32 (0.03%)	0.00	705 (0.62%)	819 (0.72%)	−0.01
Inflammatory bowel disease (IBD)	141 (0.13%)	191 (0.17%)	−0.01	3284 (2.88%)	3576 (3.14%)	−0.01
Cystitis	2140 (1.90%)	2363 (2.10%)	−0.01	2271 (1.99%)	2494 (2.19%)	−0.01
Urinary tract infection (UTI)	6730 (5.97%)	7084 (6.29%)	−0.01	5766 (5.06%)	6147 (5.39%)	−0.01

(Continued)

Table 1 (Continued)

	Taiwan NHIRD cohort			TriNetX cohort		
	DPP4i (*N* = 112,701)	SGLT2i (*N* = 112,701)	SMD	DPP4i (*N* = 114,052)	SGLT2i (*N* = 114,052)	SMD
Diabetes medications, *n* (%)						
GLP-1 Agonist	580 (0.51%)	1164 (1.03%)	−0.06	6500 (5.70%)	9823 (8.61%)	−0.10
Insulin	9944 (8.82%)	11,640 (10.33%)	−0.06	38,811 (34.03%)	42,885 (37.60%)	−0.07
Metformin	59,457 (52.76%)	59,657 (52.93%)	0.00	48,288 (42.34%)	50,970 (44.69%)	−0.05
Other medications, *n* (%)						
Thiazides	2926 (2.60%)	3508 (3.11%)	−0.03	16,608 (14.56%)	18,949 (16.61%)	−0.05
Diuretics (except Thiazides)	4875 (4.33%)	5651 (5.01%)	−0.03	24,625 (21.59%)	26,921 (23.60%)	−0.05
Statin	41,981 (37.25%)	43,061 (38.21%)	−0.02	51,902 (45.51%)	56,090 (49.18%)	−0.07
Aspirin	15,285 (13.56%)	16,545 (14.68%)	−0.03	22,458 (19.69%)	24,929 (21.86%)	−0.05
ACEI/ARB	38,589 (34.24%)	39,655 (35.19%)	−0.02	48,428 (42.46%)	51,958 (45.56%)	−0.06
Benzbromarone	2911 (2.58%)	3248 (2.88%)	−0.02	48 (0.04%)	50 (0.04%)	0.00

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; GLP-1, glucagon-like peptide-1.

DISCUSSION

This multi-center, multi-ethnic study demonstrated that, compared to DPP-4i use, SGLT2i was associated with an approximately 15%–30% lower risk of urolithiasis and urolithiasis requiring surgery in T2D patients. Findings from both the Taiwan's NHIRD and TriNetX cohort indicate that the benefits of SGLT2is in reducing urolithiasis risk, especially for upper urinary stones, were observed across subgroups, including gender, use of metformin, statins, or ACE inhibitors/ARBs.

Understanding the protective effects of glucose-lowering drugs against urolithiasis in T2D is crucial, given the poor outcomes associated with urolithiasis in these patients. While urolithiasis is considered in SGLT2i clinical trials, it has not been a prespecified outcome, highlighting the need for dedicated research.[20] Our study provides robust evidence on the association between SGLT2i use and urolithiasis incidence.

Previous studies suggested a reduced risk of nephrolithiasis among SGLT2i users compared to other antidiabetic medications, with hazard ratios ranging from 0.5 to 0.6.[20,21] However, these studies had limitations, including neutral[20] or unspecified risks for bladder stones,[21,22] lack of examination of surgical intervention risk,[20,21] and invalidated renal stone diagnoses. Only one previous study discussed the potential of SGLT2i to reduce the risk of urolithiasis requiring surgical intervention, which was consistent with our study, further confirming the reliability of this result.[22] Our study offers a deeper understanding of SGLT2i benefits and risks in T2D patients prone to urolithiasis, informing tailored treatment strategies.

The lower risk of urolithiasis with SGLT2i use may be due to several mechanisms: increased urinary flow rate and fluid intake, changes in urinary composition (e.g., lower pH, higher citrate levels),[9] and upregulation of uromodulin.[21] These changes could inhibit the formation of calcium phosphate and calcium oxalate stones.[23–25] SGLT2i was supposed to suppress renal stone formation through anti-inflammatory effects.[26,27] This finding is particularly relevant given the involvement of the NLRP3 inflammasome in calcium oxalate stone formation.[28]

Our study is the first to show the association between SGLT2i and decreased risk of lower urinary tract stone. This finding is particularly significant as lower urinary tract stones arise not only from descended upper tract calculi but also from conditions promoting urinary stasis, such as myogenic bladder dysfunction and benign prostatic hyperplasia (BPH). Recent evidence shows SGLT2i users have a lower occurrence of BPH compared to non-users.[29] This observation is supported by data demonstrating canagliflozin mitigated experimentally induced BPH in a rodent model.[30] An emerging hypothesis suggests SGLT2is may benefit myogenic bladder dysfunction, similar to their efficacy in heart failure,[31] but this requires further validation.

The strengths of our study include consistent outcomes in a multi-center approach from diverse populations. NHIRD offers extensive sample size and national coverage in Taiwan, while TriNetX expands to over 220 HCOs and 30 countries. Those broad scopes enhance the reliability and generalizability of the findings. Additionally, the accuracy of T2D[12,13] and urolithiasis diagnoses[15,16] within Taiwan's NHIRD and USA claims data were well-validated, providing a robust foundation for the study's conclusions.

The study acknowledges several limitations. One key limitation is the inability to access detailed serum and urine laboratory values from ICD codes in NHIRD, which hinders precise identification of the nature of urolithiasis. Furthermore, factors like dietary habits, and fluid intake, which can influence urolithiasis risk, were absent in both databases. A previous study revealed the possibility of participants having undiagnosed, asymptomatic stones,[32] which are difficult to identify in our study. Next, despite employing propensity score matching to minimize confounders between SGLT2i and DPP4i users, residual confounding by indication may still exist in both databases. Additionally, there are no existing reports directly validating the TriNetX database. Since this database primarily consists of data from USA populations, we relied on validation data from other USA databases instead. Finally, despite the multi-center and multi-ethnic approach of this study, the generalizability is still limited to populations primarily from the USA and Taiwan.

Table 2 Risk for urolithiasis between SGLT2i users and non-users in TriNetX and Taiwan NHIRD

	Event	Person year	Incidence rate	Crude HR (95% CI)	*P*-value	Model 1 HR (95% CI)	*P*-value	Model 2 HR (95% CI)	*P*-value
Urolithiasis (Taiwan NHIRD)									
DPP4i (*N*=112,701)	3141	245,680.53	12.78	REF		REF		REF	
SGLT2i (*N*=112,701)	2559	249,454.37	10.26	0.81 (0.76–0.86)	<0.0001	0.82 (0.77–0.88)	<0.0001	0.82 (0.77–0.87)	<0.0001
Canagliflozin (*N*=9,135)	131	13,076.65	10.02	0.96 (0.73–1.26)	0.7815	0.98 (0.75–1.29)	0.9033	1.00 (0.76–1.31)	0.983
Dapagliflozin (*N*=59,154)	1398	133,183.72	10.50	0.83 (0.76–0.90)	<0.0001	0.84 (0.77–0.91)	<0.0001	0.83 (0.77–0.91)	<0.0001
Empagliflozin (*N*=44,412)	1030	103,194	9.98	0.78 (0.71–0.85)	<0.0001	0.79 (0.72–0.87)	<0.0001	0.79 (0.71–0.87)	<0.0001
Urolithiasis requiring surgery (Taiwan NHIRD)									
DPP4i (*N*=112,701)	780	249,803.36	3.12	REF		REF		REF	
SGLT2i (*N*=112,701)	517	252,854.64	2.04	0.68 (0.60–0.77)	<0.0001	0.72 (0.63–0.82)	<0.0001	0.72 (0.63–0.82)	<0.0001
Canagliflozin (*N*=9,135)	33	13,178.63	2.50	0.89 (0.51–1.54)	0.6746	0.96 (0.55–1.69)	0.8956	0.89 (0.50–1.59)	0.6984
Dapagliflozin (*N*=59,154)	277	135,110.53	2.05	0.72 (0.60–0.85)	0.0002	0.75 (0.63–0.90)	0.0019	0.75 (0.62–0.90)	0.0015
Empagliflozin (*N*=44,412)	207	104,565.48	1.98	0.61 (0.50–0.74)	<0.0001	0.65 (0.53–0.80)	<0.0001	0.66 (0.53–0.81)	<0.0001
Urolithiasis (TriNetX)									
DPP4i (*N*=114,052)	4642	422,829.77	10.98	REF		REF		REF	
SGLT2i (*N*=114,052)	3776	412,006.01	9.16	0.80 (0.75–0.86)	<0.0001	0.81 (0.76–0.87)	<0.0001	0.84 (0.78–0.90)	<0.0001
Canagliflozin (*N*=21,281)	1107	126,682.04	8.74	0.79 (0.71–0.89)	<0.0001	0.81 (0.72–0.90)	0.0002	0.84 (0.75–0.95)	0.0058
Dapagliflozin (*N*=25,370)	797	82,391.35	9.67	0.79 (0.67–0.92)	0.0027	0.84 (0.71–0.99)	0.0325	0.85 (0.72–1.00)	0.0538
Empagliflozin (*N*=66,587)	1856	200,430.65	9.26	0.82 (0.73–0.91)	0.0002	0.81 (0.73–0.91)	0.0002	0.82 (0.74–0.92)	0.0006
Ertugliflozin (*N*=814)	16	2501.97	6.39	0.67 (0.24–1.87)	0.4417	0.69 (0.24–1.97)	0.4893	0.65 (0.22–1.87)	0.4212
Urolithiasis requiring surgery (TriNetX)									
DPP4i (*N*=114,052)	325	435,461.81	0.75	REF		REF		REF	
SGLT2i (*N*=114,052)	195	422,299.51	0.46	0.67 (0.55–0.81)	<0.0001	0.68 (0.55–0.84)	0.0003	0.71 (0.56–0.89)	0.0027
Canagliflozin (*N*=21,281)	64	130,727.18	0.49	0.69 (0.48–0.99)	0.0408	0.75 (0.52–1.10)	0.1425	0.72 (0.48–1.08)	0.1144
Dapagliflozin (*N*=25,370)	38	84,400.23	0.45	0.56 (0.35–0.88)	0.0118	0.62 (0.38–1.01)	0.0523	0.57 (0.34–0.96)	0.0353
Empagliflozin (*N*=66,587)	93	204,633.47	0.45	0.70 (0.53–0.93)	0.0136	0.66 (0.49–0.89)	0.0063	0.76 (0.55–1.06)	0.1077
Ertugliflozin (*N*=814)	0	2538.63	0.00						

Incident rates were calculated as events of urolithiasis per 1000 person-years. Model 1 adjusted for age, gender, and DM duration in the Taiwan NHIRD cohort; age, gender, race, and DM duration in the TriNetX cohort. Model 2 adjusted for age, gender, race (only in the TriNetX cohort), DM duration, comorbidities, and medications.

CONCLUSION

The study found that the use of SGLT2 inhibitors in patients with T2D was associated with a reduced risk of both urolithiasis and urolithiasis requiring surgery, compared to the use of DPP4 inhibitors. This suggests that SGLT2i may have a protective effect against the development of kidney stones and severe cases requiring surgery in T2D patients.

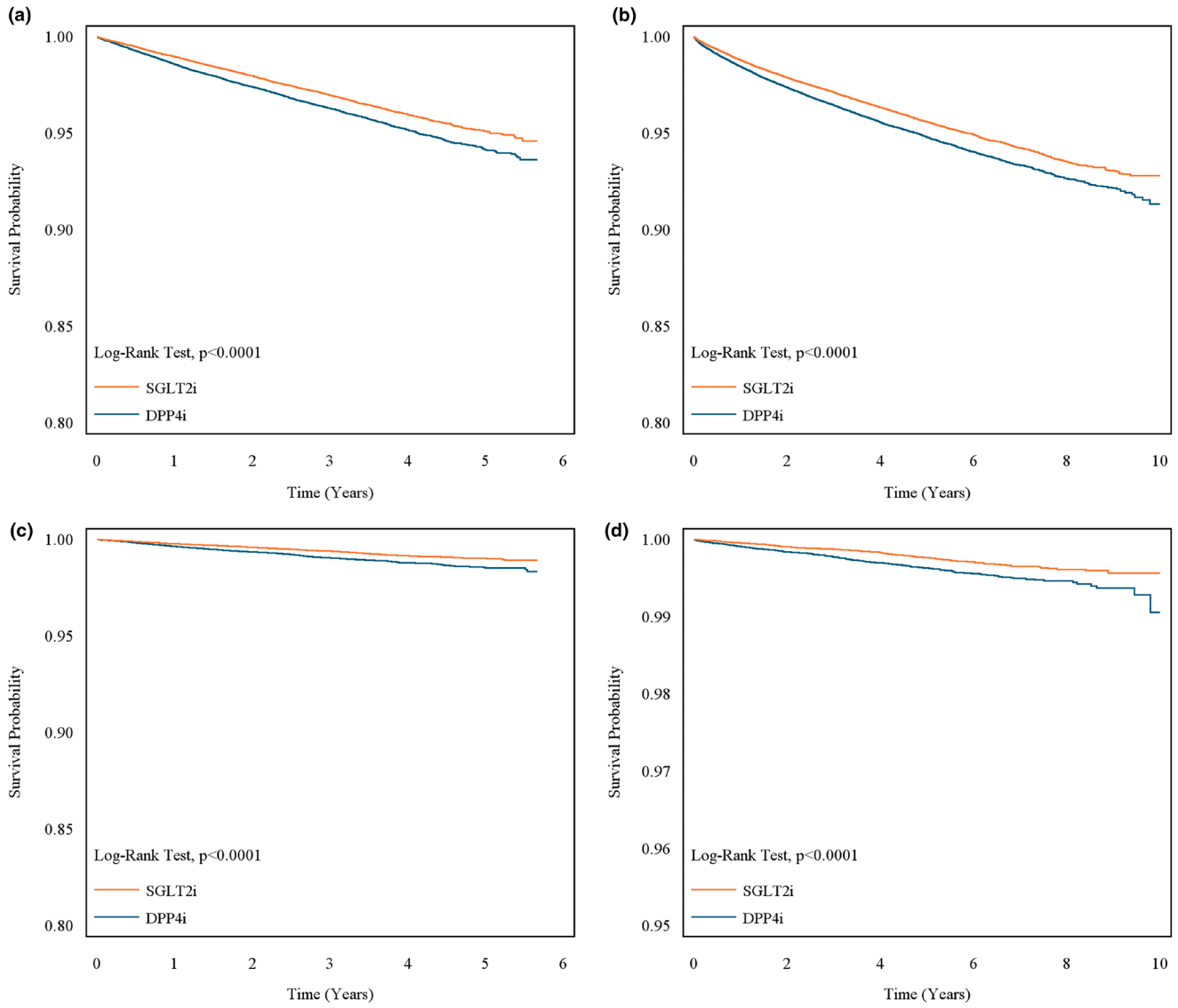

Figure 2 Cumulative incidence of urolithiasis and urolithiasis requiring surgery among patients with type 2 diabetes mellitus treated with SGLT2 inhibitors or DPP-4 inhibitors. Kaplan–Meier curves showing the cumulative incidence of (**a**) urolithiasis and (**c**) urolithiasis requiring surgery in the Taiwan National Health Insurance Research Database cohort, and (**b**) urolithiasis and (**d**) urolithiasis requiring surgery in the TriNetX cohort. DPP-4i, dipeptidyl peptidase-4 inhibitors; SGLT2i, sodium-glucose cotransporter-2 inhibitors.

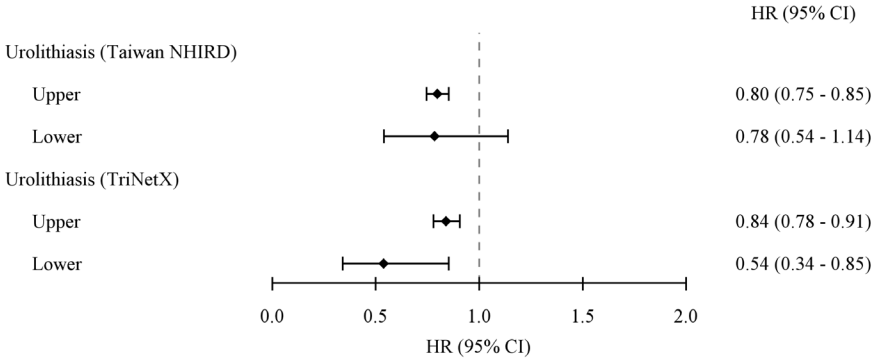

Figure 3 Associations between SGLT2i use and urolithiasis in different locations using conditional Cox regression models.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.-C.C., L.-Y.W., and C.-J.C. wrote the manuscript and performed the research. M.-C.C., C.-Y.L., P.-J.H., C.-H.C., Y.-H.C., C.-S.L., P.-H.H., M.-J.W., J.-J.S., H.-H.C., C.-J.C. designed the research. L.Y.W. analyzed the data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Taiwan National Health Insurance Research Database and TrinetX but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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