



## Review Article

# Sodium-glucose co-transporter 2 inhibitors use and the risks of genital and urinary tract infection: What should we know?

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### ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have convincingly demonstrated efficacy in reducing cardiovascular (CV) and renal complications in patients with diabetes mellitus, chronic kidney disease, and heart failure. However, their use is also linked to the concern of some adverse events, the most common being genital and urinary tract infections (UTIs). This review summarizes the risks of genital and UTIs of SGLT2 inhibitors across large-scale clinical trials, meta-analyses, and real-world cohort studies. SGLT2 inhibitors are shown to significantly increase the risk of genital infections in clinical trials and real-world observational studies and marginally increase the risk of UTI in meta-analyses. We also discuss the potential pathogenesis of SGLT2 inhibitor-related infections and identify the susceptible risk factors. Since most genital and UTIs associated with SGLT2 inhibitors are mild and treatable and severe infections are rare, the use of SGLT2 inhibitors is highly recommended in patients who meet the inclusion criteria of clinical trials, where the CV and renal benefits outweigh the infection risks. For all users of SGLT2 inhibitors, preventive strategies, patient education, and careful monitoring are essential to minimize the infection risks. Furthermore, we address an unmet need regarding SGLT2 inhibitors among vulnerable populations, such as older adults, frail, and immunocompromised patients, underscoring the importance of observational studies from the real-world data. Future research should focus on identifying the high-risk groups, developing SGLT2 inhibitors with a lower infection profile and establishing effective prevention strategies to mitigate the risk of genital and UTIs associated with these medications.

**KEYWORDS:** *Genital infection, Sodium-glucose co-transporter 2 inhibitors, Urinary tract infection*

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## INTRODUCTION

Diabetes mellitus (DM) is a major public health concern worldwide. According to the International Diabetes Federation, the global prevalence of DM has reached 10.5%, equating to 537 million diabetic patients worldwide. By the year 2045, the number of diabetic patients is projected to increase to 783 million globally [1]. The macrovascular and microvascular complications commonly encountered among diabetic patients contribute significantly to morbidity and mortality, placing a substantial burden on the healthcare systems.

The development of sodium-glucose co-transporter 2 (SGLT2) inhibitors, first approved by the United States Food and Drug Administration in March 2013, has demonstrated notable disease-modifying effects in reducing

cardiovascular (CV) and renal complications in diabetic patients. Beyond their glucose-lowering effects – achieved by inhibiting SGLT2-dependent glucose and sodium reabsorption in the proximal tubules – these inhibitors have consistently shown clinical benefits in CV and renal protection across multiple large-scale randomized controlled trials (RCTs). A recent Cochrane meta-analysis pooling data from 53 RCTs confirmed the efficacy of SGLT2 inhibitors in patients with DM and chronic kidney disease (CKD), including reduced risks of hospitalization for heart failure, all-cause and CV mortality, kidney composite outcomes, and renal failure [2].

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Based on the high-quality evidence of these benefits, current guidelines strongly recommend SGLT2 inhibitors in patients with DM, CKD, and heart failure [3-5].

However, increased adverse events associated with SGLT2 inhibitors have been observed in both clinical trials and real-world data, including urinary tract and genital infections, euglycemic ketoacidosis, bone fractures, and lower limb amputations, which have raised the clinical concerns [6]. These potential risks necessitate carefully evaluating the benefit-risk profile of SGLT2 inhibitors in the clinical practice. Given that genital and urinary tract infections (UTIs) are among the most frequently encountered adverse events associated with SGLT2 inhibitors, this review aims to focus on these risks.

### **THE INCIDENCE AND RISK FACTORS OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS-RELATED GENITAL AND URINARY TRACT INFECTIONS**

The incidence rates of overall UTIs and genital infections have shown wide variability across large-scale clinical trials targeting diverse study populations, ranging from 0.5%–18% to 0.8%–6.4%, respectively [7]. However, the occurrence of severe or complicated UTIs and genital infections has generally been low, ranging from 1.0%–1.9% to <0.1%–0.3%, respectively, over a median follow-up period of 16–28.8 months [8-12]. Most clinical trials have reported a significantly higher risk of genital infections compared to control groups [9-11,13-16]. In contrast, the risk of UTIs among SGLT2 inhibitor users has generally been comparable, except in VERTIS CV (12.2% in 5 mg and 12.0% in 15 mg ertugliflozin group vs. 10.2% in the placebo group) [16] and EMPEROR-Preserved (9.9% in 10 mg empagliflozin group vs. 8.1% in the placebo group) [11] trials. Table 1 summarizes the risks of genital and UTIs based on the data from the large clinical trials of SGLT2 inhibitors.

However, the limited observation duration and small number of adverse events in these trials may preclude robust statistical inference from the clinical trials. In this regard, a network meta-analysis and meta-regression, which included 264 randomized trials and 271,415 patients, showed that SGLT2 inhibitors were associated with a significantly elevated risk of both UTIs (odds ratio [OR] = 1.11, 95% confidence interval [CI] = 1.06–1.16) and a more pronounced increase in the risk of genital infections (OR = 3.5, 95% CI = 3.1–3.9) [17]. Notably, among SGLT2 inhibitor users, the authors identified females, those with a treatment duration of  $\geq 6$  months, and individuals with a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> were more susceptible to these infections [17]. Another meta-analysis evaluating dapagliflozin use and risk of UTI from 42 RCTs involving 35,938 type 2 DM patients showed that dapagliflozin users had a higher risk of UTI (OR = 1.17, 95% CI = 1.04–1.31) and the particular concern raised from those with high-dose, long duration, and add-on therapy of dapagliflozin [18]. Arshad *et al.* pooled the data from four landmark studies – CANVAS,

CREDENCE, DECLARE–TIMI 58, and EMPA-REG – and found a significantly increased risk of genital infections among SGLT2 inhibitor users, but no significant increase in UTI risk [19]. Wanner *et al.* reported that empagliflozin was not associated with serious genital infections or serious UTIs based on data from four empagliflozin clinical trials [20].

In the real-world settings, a large cohort study evaluating the risk factors of genital infection among 21,004 people initiating SGLT2 inhibitors and 55,471 controls initiating dipeptidyl peptidase-4 inhibitors using UK primary care database confirmed the significantly higher incidence of genital infection within 1 year (8.1% for SGLT2 inhibitors and 1.8% for dipeptidyl peptidase-4 inhibitors) and identified female sex (hazard ratio [HR] 3.64; 95% CI 3.23–4.11) and previous history of genital infection (HR 4.38; 95% CI 3.73–5.13) as the two major risk factors for genital infections among SGLT2 inhibitors initiators [21]. Consistently, the Association of British Clinical Diabetologists nationwide dapagliflozin audit collected data on 1,049 patients treated with dapagliflozin from 59 diabetes centers showed that women (OR 4.22; 95% CI 2.48–7.19) and patients with previous genital fungal infections (OR 2.41; 95% CI 1.04–5.57) had increased risks of developing genital fungal infections [22]. Using US commercial claims databases from 2013 to 2017, which included 129,994 women and 156,074 men, SGLT2 inhibitors were linked to a threefold higher risk of genital infections compared to DPP-4 inhibitors or GLP-1 agonists in both sexes. This increased risk became evident within the 1<sup>st</sup> month of treatment and remained elevated throughout therapy [23]. Table 2 summarizes the risks of genital and UTIs of SGLT2 inhibitors from the meta-analyses and real-world cohort studies.

### **POTENTIAL PATHOGENESIS REGARDING THE ASSOCIATION OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS AND GENITAL AND URINARY TRACT INFECTIONS**

Although the exact mechanisms linking the usage of SGLT2 inhibitors to genital and UTIs remain unclear, glycosuria is widely accepted as the crucial pathogenic factor for this phenomenon.

In experimental and animal studies, evidence has suggested that uropathogenic characteristics are altered in a glycosuria environment. Experimental studies have shown that either plain glycosuria or adding glucose to human urine enhances the bacterial growth rate and alters the gene expression and virulence of uropathogenic *Escherichia coli* strains [25,26] and group B Streptococcus [27]. In animal studies, mice with hyperglycosuria induced by dapagliflozin exhibited an increased load of transurethral-inoculated *E. coli* and *Klebsiella pneumoniae* in the urinary tract, which conferred a higher risk of developing bacteremia and renal abscesses. The hyperglycosuria condition also resulted in poor neutrophil mobilization and a delayed increase in interleukin-1 $\beta$  and interleukin-6 levels in the urine [28].

**Table 1: Summary of the large trials on sodium-glucose co-transporter 2 inhibitors and risk of genital and urinary tract infections**

Author, year (study name)	Participants	SGLT2 inhibitor	Follow-up duration	Main findings	Genital infection	UTI
Zinman <i>et al.</i> , 2015 (EMPA-REG outcome) [9]	7020 patients with type 2 DM at high CV risk	Empagliflozin - 10 mg or 25 mg	Median - 3.1 years	Reduced primary CV outcome (CV death, nonfatal MI, or stroke): HR=0.86; 95% CI=0.74–0.99	Both genders <sup>†</sup> Placebo - 1.8% 10 mg empagliflozin - 6.5% 25 mg empagliflozin - 6.3% Males <sup>†</sup> Placebo - 1.5% 10 mg empagliflozin - 5.4% 25 mg empagliflozin - 4.6% Females <sup>†</sup> Placebo - 2.6% 10 mg empagliflozin - 9.2% 25 mg empagliflozin - 10.8%	Complicated UTI Placebo - 1.8% 10 mg empagliflozin - 1.4% 25 mg empagliflozin - 2.0%
Packer <i>et al.</i> , 2020 (EMPEROR-reduced) [10]	3730 patients with class II–IV HF and EF ≤40%	Empagliflozin - 10 mg	Median - 16 months	Reduced risk of CV death or hospitalization for HF: HR=0.75; 95% CI=0.65–0.86	Genital infection <sup>†</sup> Placebo - 0.6% Empagliflozin - 1.7% Complicated genital infection Placebo - 0.3% Empagliflozin - 0.3%	UTI Placebo - 4.5% Empagliflozin - 4.9% Complicated UTI Placebo - 0.8% Empagliflozin - 1.0%
Anker <i>et al.</i> , 2021 (EMPEROR-preserved) [11]	5988 patients with class II–IV HF and EF >40%	Empagliflozin - 10 mg	Median - 26.2 months	Reduced the combined risk of CV death or hospitalization: HR=0.79; 95% CI=0.69–0.90	Genital infection <sup>†</sup> Placebo - 0.7% Empagliflozin - 2.2% Complicated genital infection Placebo - 0.3% Empagliflozin - 0.3%	UTI <sup>†</sup> Placebo - 8.1% Empagliflozin - 9.9% Complicated UTI Placebo 1.5% Empagliflozin - 1.9%
The EMPA kidney collaborative group, 2023 (EMPA-kidney) [8]	6609 CKD patients with 1) eGFR 20–45 mL/min 2) eGFR 40–90 mL/min with UACR >200 mg/g	Empagliflozin - 10 mg	Median - 2.0 years	Reduced risk of progression of kidney disease or death from CV causes: HR=0.72; 95% CI=0.64–0.82	Serious genital infection Placebo - <0.1% Empagliflozin - <0.1%	Serious UTI Placebo - 1.6% Empagliflozin - 1.6%
Wiviott <i>et al.</i> , 2019 (DECLARE-TIMI) [15]	17,160 patients with type 2 DM who had or were at risk for ASCVD	Dapagliflozin - 10 mg	Median - 4.2 years	Reduced risk of CV death or hospitalization for HF: HR=0.83; 95% CI=0.73–0.95	Genital infection <sup>†</sup> Placebo - 0.1% Dapagliflozin - 0.9%	UTI Placebo - 1.6% Dapagliflozin - 1.5%
Heerspink <i>et al.</i> , 2020 (DAPA-CKD) [12]	4304 CKD patients with eGFR 25–75 mL/min with UACR 200–5000 mg/g	Dapagliflozin - 10 mg	Median - 2.4 years	Reduced the composite outcome of a sustained decline in the eGFR ≥50%, ESRD, or death from renal or CV causes: HR=0.61; 95% CI=0.51–0.72	-	Serious UTI Dapagliflozin - 0.9% Placebo - 0.7%

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**Table 1: Contd...**

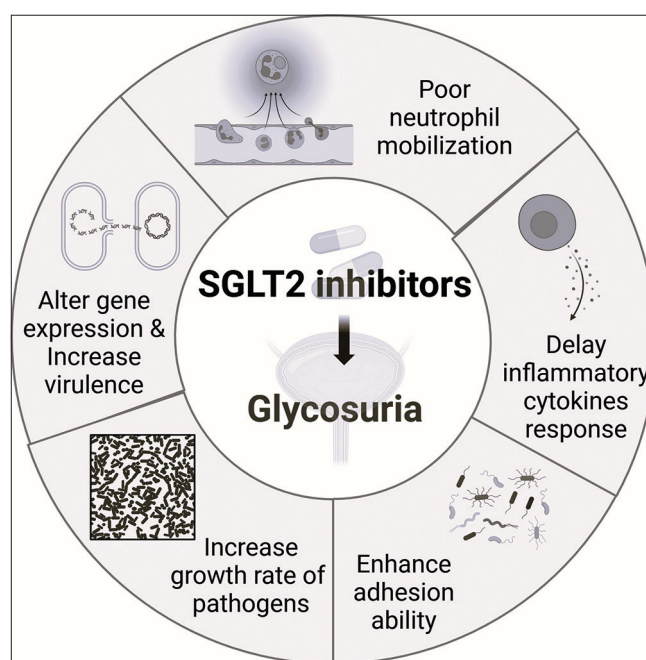
Author, year (study name)	Participants	SGLT2 inhibitor	Follow-up duration	Main findings	Genital infection	UTI
Neal <i>et al.</i> , 2017 (CANVAS) [13]	10,142 participants with type 2 DM and high CV risk	Canagliflozin - 100 mg or 300 mg	Mean - 47 months	Reduced primary outcome (death from CV causes, nonfatal MI or stroke): HR=0.86; 95% CI=0.75-0.97	Genital infection in women (events/1000 pt-yr) <sup>†</sup> Placebo - 17.5 Canagliflozin - 68.8	UTI (events/1000 pt-yr) Placebo - 37.0 Canagliflozin - 40.0
Perkovic <i>et al.</i> , 2019 (CREDENCE) [14]	4401 patients with type 2 DM and albuminuric CKD	Canagliflozin - 100 mg	Median - 2.62 years	Lower relative risk of the primary outcome (ESRD, doubling serum Cr, or death from renal or CV causes): HR=0.70; 95% CI=0.59-0.82	Genital infection in men (events/1000 pt-yr) <sup>†</sup> Placebo - 0.9 Canagliflozin - 8.4 Genital infection in women (events/1000 pt-yr) <sup>†</sup> Placebo - 6.1 Canagliflozin - 12.6	UTI (events/1000 pt-yr) Placebo - 45.1 Canagliflozin - 48.3
Cannon <i>et al.</i> , 2020 (VERTIS CV) [16]	8246 patients with type 2 DM and ASCVD	Ertugliflozin - 5 mg or 15 mg	Mean - 3.5 years	Noninferior to placebo with respect to major adverse CV events: HR=0.97; 95% CI=0.85-1.11; P<0.001 for noninferiority	Genital infection in men <sup>†</sup> Placebo - 1.2% 5 mg ertugliflozin - 4.4% 15 mg ertugliflozin - 5.1% Genital infection in women <sup>†</sup> Placebo - 2.4% 5 mg ertugliflozin - 6.0% 15 mg ertugliflozin - 7.8%	UTI <sup>†</sup> Placebo - 10.2% 5 mg ertugliflozin - 12.2% 15 mg ertugliflozin - 12.0% Severe UTI Placebo - 0.8% 5 mg ertugliflozin - 0.9% 15 mg ertugliflozin - 0.4%

<sup>†</sup>Higher infection rate with SGLT2 inhibitors compared to placebo. SGLT2: Sodium-glucose co-transporter 2, UTI: Urinary tract infection, DM: Diabetes mellitus, CV: Cardiovascular, MI: Myocardial infarction, HR: Hazard ratio, CI: Confidence interval, HF: Heart failure, EF: Ejection fraction, CKD: Chronic kidney disease, eGFR: Estimated glomerular filtration rate, UACR: Urine albumin-to-creatinine ratio, ASCVD: Atherosclerotic cardiovascular disease, ESRD: End-stage renal disease, pt-yr: Patient-year, Cr: Creatinine

Similarly, female mice treated with dapagliflozin and canagliflozin showed increased colony-forming units of viable transurethral-inoculated *Candida albicans* in the kidneys, indicating an ascending infection [29]. In addition, the number of viable *C. albicans* cells correlated with the dose and duration of dapagliflozin treatment.

Regarding the pathogenesis of SGLT2 inhibitors-related genital tract infection, an *in vitro* study demonstrated that in human vaginal epithelial cells cultured in a high-glucose environment, the adhesion of *C. albicans* increased due to the upregulation of ICAM-1, which serves as a ligand for adhesion [30]. In a double-blind study investigating women with type 2 DM, the increased incidence of vaginal *Candida* species colonization was observed among canagliflozin users at week 12 (31% of canagliflozin vs. 14% of placebo/sitagliptin group; OR 2.8; 95% CI 1.0-7.3), linking to a higher incidence of symptomatic vulvovaginal adverse events (10% vs. 3%) [31].

Together, these experimental and clinical studies suggest that glycosuria may alter the characteristics of uropathogens, compromise host immunity, and facilitate vaginal *Candida* adhesion and colonization, thereby increasing the risk of genital and UTI [Figure 1].



**Figure 1:** Proposed mechanisms linking the association of sodium-glucose co-transporter 2 inhibitors and genital and urinary tract infections. SGLT2: Sodium-glucose co-transporter 2

**Table 2: Summary of meta-analyses and cohort studies on sodium-glucose co-transporter 2 inhibitors and risk of genital and urinary tract infections**

Author, year (study name)	Participants	SGLT2 inhibitor	Genital infection	UTI
<b>Meta-analyses</b>				
Sridharan and Sivaramakrishnan, 2024 [17]	264 studies, 150,140 and 121,275 patients for UTI and genital infection, respectively	All	SGLT2 inhibitors increase genital infection risk <sup>†</sup> (OR=3.5; 95% CI=3.1–3.9)	SGLT2 inhibitors increase UTI risk <sup>‡</sup> (OR=1.11; 95% CI=1.06–1.16)
Zheng <i>et al.</i> , 2023 [18]	42 RCTs, 35,938 type 2 DM patients	Dapagliflozin	-	Dapagliflozin increases UTI risk <sup>‡</sup> (OR=1.17; 95% CI=1.04–1.31)
Arshad <i>et al.</i> , 2024 [19]	4 studies, 38,723 patients (CANVAS, CREDENCE, DECLARE-TIMI 58, EMPA-REG)	Canagliflozin, dapagliflozin, empagliflozin	SGLT2 inhibitor: 2.24% <sup>†</sup> (placebo: 0.40%)	SGLT2 inhibitor: 1.04% (placebo: 1.15%)
Wanner <i>et al.</i> , 2024 [20]	4 studies, 10,472 patients in empagliflozin group; 10,461 patients in placebo group (EMPA-REG, EMPEROR-reduced, EMPEROR-preserved, EMPA-kidney)	Empagliflozin 10 mg once daily	Serious genital infection (rate/100 pt-yr) Empagliflozin: 0.04 Placebo: 0.07	Serious UTI (rate/100 pt-yr) Empagliflozin: 0.78 Placebo: 0.76
<b>Real-world large cohort studies</b>				
McGovern <i>et al.</i> , 2020 [21]	21,004 people with type 2 DM initiating SGLT2 inhibitors and 55,471 controls initiating DPP4i (UK primary care database)	All	SGLT2 inhibitor: 8.1% within 1 year <sup>†</sup> DPP4i: 1.8% within 1 year	-
Thong <i>et al.</i> , 2018 [22]	1049 patients with type 2 DM (The association of British Clinical Diabetologists nationwide dapagliflozin audit)	Dapagliflozin	Dapagliflozin: 7.8% No control group available	-
Dave <i>et al.</i> , 2019 [23]	286,068 patients with type 2 DM (from 2 US commercial claims databases)	All	Genital infection in women <sup>†</sup> HR for SGLT2 inhibitors versus DPP4i: 2.81 (95% CI=2.64–2.99) Genital infection in men <sup>†</sup> HR for SGLT2 inhibitors versus DPP4i: 2.68 (95% CI=2.31–3.11)	-
Fisher <i>et al.</i> , 2020 [24]	208,244 SGLT2 inhibitors users and 208,244 DPP4i users in type 2 DM (7 Canadian provinces and the UK)	All	-	Urosepsis <sup>‡</sup> : SGLT2 inhibitors users had a lower rate compared with DPP4i users (HR=0.58, 95% CI=0.42–0.80) Fournier's gangrene (rate/1000 pt-yr): Similar in SGLT2i (0.08, 95% CI=0.05–0.13) and DPP4i users (0.14, 95% CI=0.09–0.21)

<sup>†</sup>Higher infection rate with SGLT2 inhibitors compared to placebo, <sup>‡</sup>Lower infection rate with SGLT2 inhibitors compared to placebo. SGLT2: Sodium-glucose co-transporter 2, UTI: Urinary tract infection, OR: Odds ratio, CI: Confidence interval, RCT: Randomized control trial, DM: Diabetes mellitus, pt-yr: Patient-year, DPP4i: Dipeptidyl peptidase-4 inhibitors, UK: United Kingdom, US: United States, HR: Hazard ratio

## SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS USE AND THE SEVERITY OF GENITAL AND URINARY TRACT INFECTIONS

Since UTIs and genital infections, which are mostly curable, are among the most common infections in the real-world clinical practice, one crucial factor in evaluating the use of SGLT2 inhibitors is the risk of severe and life-threatening infections. A meta-analysis evaluating the safety of Empagliflozin, which pooled data from four large clinical trials involving 10,472 patients in the empagliflozin group and 10,461 patients in the placebo group, showed a comparable incidence rate of serious UTIs (0.78 vs. 0.76 events per 100 patient-years). In subgroup analyses,

empagliflozin users tended to have an increased risk of serious UTIs among women (rate ratio [RR] = 1.33, 95% CI = 0.97–1.82) and patients with a history of heart failure (RR = 1.18, 95% CI = 0.89–1.56). Otherwise, the event rates between empagliflozin and placebo were comparable across different categories of age, BMI ( $\geq 25$  and  $< 25$  kg/m<sup>2</sup>), and DM status [20].

In the real-world data, a large-scale observational cohort study including 208,244 patients on SGLT2 inhibitors and 208,244 patients on dipeptidyl peptidase-4 inhibitors from the Canadian Network for Observational Drug Effect Studies and the UK Clinical Practice Research Datalink did not observe an increased risk of urosepsis among SGLT2 inhibitor users.

Instead, a reduced risk of urosepsis among SGLT2 inhibitor users (adjusted hazard ratio = 0.58, 95% CI = 0.42–0.80) was noted compared to those on dipeptidyl peptidase-4 inhibitors [24]. However, this paradox finding should be interpreted cautiously regarding the unmeasured confounders and selection bias commonly in the observational studies.

Fournier gangrene, a rare but life-threatening necrotizing fasciitis in the perineum, predominantly occurs in patients with DM. The US Food and Drug Administration Adverse Event Reporting System identified 542 cases of Fournier gangrene among SGLT2 inhibitor users from 2004 to 2019. An increased trend in the number of events was observed, corresponding with the widespread prescription of SGLT2 inhibitors. Among them, 391 patients (72.14%) were hospitalized and 26 (4.81%) died. In addition, male patients appeared to be more susceptible to Fournier gangrene than female patients (64.3% vs. 27.9%) [32].

Emphysematous UTIs, a severe form of UTI characterized by gas formation, confer a high mortality rate, predominantly affecting patients with DM. Recently, a few case reports have noted the development of emphysematous UTIs in patients using SGLT2 inhibitors [33-35]. Notably, an unusual case of emphysematous UTIs developed in a patient without DM [36].

Given the limited number of cases experiencing severe genital and UTIs, it is impossible to infer the causal relationships of SGLT2 inhibitor exposure with severe infections, and keeping postmarketing surveillance is crucial. The low incidence of severe genital and UTIs and a lack of evidence demonstrating the association between SGLT2 inhibitors use and severe forms of infections suggest a favorable safety profile for SGLT2 inhibitors in the clinical practice.

## **WEIGH THE BENEFITS AND INFECTION RISKS OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS**

Given that most infections associated with SGLT2 inhibitors are mild and treatable, with severe cases being rare, their use should be recommended for patients with type 2 diabetes, CKD, or heart failure, where the strong and consistent CV and renal protective effects of SGLT2 inhibitors have been demonstrated. The benefits and infection risks of SGLT2 inhibitors may also be assessed by considering the number needed to treat (NNT) and the number needed to harm (NNH). Chiang *et al.* pooled the data from randomized, placebo-controlled trials for SGLT2 inhibitors and categorized them into high CV risk type 2 DM, heart failure with reduced ejection fraction (HFrEF), and CKD. For patients with HFrEF, the NNTs to prevent heart failure hospitalization, CV mortality, total mortality, and renal deterioration were 18, 93, 76, and 143, respectively, while NNHs for UTIs and mycotic genital infections were 557 and 356. In CKD patients, the NNTs were 116, 245, 138, and 63, with NNHs for UTI and mycotic genital infections at 309 and 291. For type 2 DM with high-CV risk, the NNTs to prevent the same outcomes were 139, 851, 601, and 558, whereas NNHs for UTI and mycotic genital infections were 239 and 69 [37].

## **DO THE RISKS OF GENITAL AND URINARY TRACT INFECTIONS DIFFER AMONG DIFFERENT SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS?**

There is limited evidence comparing the infection risks among different SGLT2 inhibitors. A comparative cohort study using the MarketScan® Commercial and Medicare Supplemental databases showed that, among the three widely available SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin), there were no differences in the risk of genital and UTIs among patients with heart failure with preserved ejection fraction [38]. Similarly, a network meta-analysis involving 96,196 participants from 21 RCTs showed comparable hazard risks for genital and UTIs across empagliflozin, ertugliflozin, dapagliflozin, canagliflozin, and sotagliflozin [39].

In an experimental study, some natural SGLT2 inhibitors, such as formononetin, (+)-pteryxin, and quinidine, were shown to exhibit superior inhibition of FimH, an adhesin protein on the surface of *E. coli* compared to canagliflozin and might be associated with reducing the risks of UTI [40]. However, further research is required to confirm and extend the preliminary findings.

## **SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS USAGE IN PATIENTS SUSCEPTIBLE TO INFECTION**

While SGLT2 inhibitors should be strongly recommended for patients who meet the inclusion criteria for clinical trials, the results should be cautiously extrapolated to populations excluded from these trials, considering the gap between the clinical trial outcomes and real-world practice. Vulnerable populations often excluded from clinical trials, such as the elderly, frail individuals, those with multiple comorbidities, immunocompromised individuals, malnourished patients, those on immunosuppressants, and transplant recipients, may be at a greater risk of infection than suggested by the clinical trial data. For example, the aging population is accelerating growing worldwide. However, a meta-analysis evaluating the adverse events risk of SGLT2 inhibitors on elderly diabetic patients ( $\geq 65$  years) showed that among 130 RCTs identified, only six studies (4.6%) involved elderly patients. They revealed that, among 19,986 elderly patients, SGLT2 inhibitors were associated with a markedly enhanced risk of genital infection (RR = 6.55, 95% CI 2.09–20.5) but not with UTI [41]. In the real-world data, the SOLD (SGLT2i in Older diabetic patients) study, a multicenter observational study, evaluated the safety of SGLT2 inhibitors in 739 DM patients  $\geq 70$  years. They observed 20.3% and 23.5% interrupted treatment at 6 months and 1 year, with genito-UTI as the main reason for discontinuation, accounting for more than 40%. The infection events were mild to moderate in severity, responding to the standard treatment. As expected, the discontinuation rate was the highest among those aged  $\geq 80$  years [42]. Unfortunately, the active comparator was not included in this analysis.

A large-scale national study using hospital-linked UK primary care data showed that, in type 2 DM patients, the overall risk of genital infection was increased compared to dipeptidyl peptidase-4 inhibitors, but with comparable risk between those with <70 and ≥70 years [43]. Utilizing Medicare data in the USA to investigate the safety of type 2 DM patients ≥66 years initiating SGLT2 inhibitors or glucagon-like peptide-1 receptor agonists, SGLT2 initiators have a 3.4-fold increase in the risk of genital infection but not severe UTI requiring hospitalization [44].

In renal transplant recipients with diabetes, a multicenter, retrospective, and observational study found that among 339 SGLT2 inhibitor initiators, UTIs were the most common adverse effect, with an incidence of 14% within 6 months of SGLT2 inhibitor treatment. Female gender (OR 2.46, 95% CI = 1.19–5.03) and a history of UTI in the prior 6 months (OR = 7.90, 95% CI = 3.63–17.21) were identified as the significant risk factors [45].

Beyond older adults and the transplant population, data on the safety of SGLT2 inhibitors in other at-risk populations – such as those with frailty, urolithiasis, neurogenic bladder, urinary tract outlet obstruction or other structural abnormalities, those requiring urethral catheterization, and immunocompromised individuals – are largely lacking. Whether SGLT2 inhibitors use confers more protective benefits than risks in these vulnerable groups remains unknown and further clinical trials and real-world observational studies should be encouraged to mitigate the gap.

## SHOULD SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS BE RE-ADDED AFTER CURING URINARY TRACT AND GENITAL INFECTIONS?

An observational study conducted at a single medical center in Taiwan reported that the rate of first UTI was approximately 3.43% ( $n = 438$ ) among 12,757 type 2 DM patients on SGLT2 inhibitors over 19 months. Among the 438 patients experiencing their first UTI, 117 of them were rechallenged with SGLT2 inhibitors, and up to 28.2% ( $n = 33$ ) experienced recurrent UTIs [46]. However, given the limitation of lacking an active comparator group, it is difficult to clarify the high recurrent infection contributed by rechallenged SGLT2 inhibitors or patients' characteristics susceptible to infection. Therefore, whether patients who have experienced a first UTI can be safely re-administered for SGLT2 inhibitors remains unanswered. The decision to continue SGLT2 inhibitor treatment should be made on an individual basis, considering the benefits and risks for each patient. However, for those who experience severe infection, it is prudent not to re-administer SGLT2 inhibitors from a safety perspective.

## STRATEGIES TO PREVENT SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS-RELATED URINARY TRACT AND GENITAL INFECTIONS

Cranberries exhibit an anti-adhesive property by blocking FimH and *P* pili and have been widely used for UTI prevention for the decades. A meta-analysis from the Cochrane

database of systemic reviews pooling 26 RCTs and including 6,211 participants showed moderate certainty evidence that cranberry products reduced the risk of UTIs (RR = 0.70, 95% CI = 0.58–0.84). In subgroup analysis, this protective effect was observed in women with recurrent UTIs, children, and participants with a susceptibility to UTIs due to an intervention [47]. In a small-scale RCT involving diabetic postmenopausal women on SGLT2 inhibitors, a highly standardized cranberry extract phytosome tended to reduce the risk of UTIs over 6 months [48]. However, given the limitation of sample size, follow-up duration, and infection events, further larger studies are needed to confirm the preventive effects of cranberry products on high-risk UTIs in SGLT2 inhibitor users, such as females and those with a history of prior UTIs.

Furthermore, several emerging and novel preventive strategies for UTI are developing. FimH antagonist, which acts by binding to FimH and blocking its interaction with mannose receptors on the bladder epithelial cells [49], might effectively prevent recurrent UTI caused by uropathogenic *E. coli* strains. Vaccines against common uropathogens, such as Janssen 9-valent Extraintestinal Pathogenic *E. Coli* Vaccine (ExPEC9V) targeting O-antigens of the surface lipopolysaccharide of 9 *E. coli* serotypes [50,51] and sublingual MV 140 against *K. pneumoniae*, *E. coli*, *Proteus vulgaris*, and *E. faecalis* [52], are promising and currently being tested for effectiveness. Moreover, with the advancements in personalized medicine and genome-wide association studies, it is essential to identify the genes or biomarkers that can predict an individual's susceptibility to infections related to SGLT2 inhibitors.

Although SGLT2 inhibitors are more likely to contribute to genital infections than UTIs, high-quality evidence regarding strategies for preventing genital infections is scarce. Given the widespread use of SGLT2 inhibitors, more preventive studies targeting individuals at high risk for genital and UTIs should be encouraged. Until more robust evidence becomes available, it is reasonable to implement general prevention strategies in clinical practice, such as ensuring adequate fluid intake, maintaining proper hygiene, promoting behavioral modifications, optimizing glycemic control, and managing comorbidities. In addition, all patients on SGLT2 inhibitors should be educated to recognize the symptoms and signs of genital and UTIs to facilitate the early diagnosis and treatment if infections occur.

## CONCLUSION

In summary, while SGLT2 inhibitors are shown to significantly increase the risk of genital infections in clinical trials and real-world observational studies and slightly increase the risk of UTIs in meta-analyses, it is generally mild to moderate in severity. The incidence of severe UTIs and genital infections is relatively low. In this regard, SGLT2 inhibitors should be strongly recommended for immunocompetent patients with DM, CKD, and heart failure, as CV and renal protection benefits largely outweigh the risks of urinary tract and genital infections. However, female patients and those with a history of previous infections are at higher risk of

developing genital and UTIs after initiating SGLT2 inhibitors. General preventive strategies and education should be provided, along with the careful monitoring for symptoms and signs of infection.

However, there is an evidence gap regarding the safety of SGLT2 inhibitors for patients with immunocompromised status, frailty, or other susceptible populations with increased risk of infections. Further studies should be addressed on identifying the vulnerable groups susceptible to severe infection, developing new SGLT2 inhibitors with less infection profile, and developing effective strategies to prevent infection during SGLT2 inhibitors use among those with high infection risk.

#### Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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#### Conflicts of interest

Dr. Bang-Gee Hsu, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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