



Tropical Journal of Pharmaceutical and Life Sciences

(An International Peer Reviewed Journal)

Journal homepage: <http://informativejournals.com/journal/index.php/tjpls>



Dapagliflozin and Urinary Tract Infection Risk in Type 2 Diabetes: A Comprehensive Critical Review of Mechanistic, Randomized, and Real-World Evidence

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ARTICLE INFO:

Received: 24th Sept. 2026; **Received in revised form:** 29th Sept. 2026; **Accepted:** 27th Oct. 2026; **Available online:** 30th Oct. 2026.

Abstract

Dapagliflozin, a sodium–glucose cotransporter-2 (SGLT2) inhibitor, increases urinary glucose excretion, raising questions about its association with urinary tract infection (UTI) in people with type 2 diabetes mellitus. This critical narrative review examines the biological rationale and clinical evidence concerning UTI risk associated with dapagliflozin, distinguishing urinary infections from genital mycotic infections and considering dose, treatment duration, patient characteristics, and study design. Targeted searches of PubMed/PubMed Central, publisher websites, regulatory sources, clinical trial information, and clinical guidance informed a narrative appraisal of randomized controlled trials, meta-analyses, observational studies, and pharmacovigilance reports. Study selection was not systematic; the review had no prospectively registered protocol, documented duplicate independent screening, or uniform formal risk-of-bias assessment, and published estimates were not re-pooled. Dapagliflozin-specific meta-analyses suggest a possible modest increase in broadly defined UTI, with some subgroup analyses reporting higher estimates at 10 mg or with longer treatment exposure; these findings do not establish a causal dose–duration relationship. Randomized evidence has not demonstrated a consistent increase in serious urinary infections, although a modest increase in non-serious events cannot be excluded. A 2026 class-level trial meta-analysis did not find a statistically significant increase in overall or serious/complicated UTI, while a 2026 multicentre Indian cross-sectional study reported a higher observed UTI prevalence among SGLT2 inhibitor users but could not establish causality or isolate dapagliflozin-specific risk. Genital mycotic infections remain a more consistent adverse-effect signal than UTIs. Clinical decisions should therefore distinguish these outcomes, consider individual urinary-tract risk factors, and balance potential infection risks against established cardiorenal benefits. The proposed Host–Dose–Duration framework is conceptual and requires prospective validation before clinical use.

Keywords: Dapagliflozin; Drug safety; Glycosuria; SGLT2 inhibitors; Type 2 diabetes mellitus; Urinary tract infection.

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DOI: <https://doi.org/10.61280/9h681f91>

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Published by Informative Journals (Jadoun Science Publishing Group India)

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1. Introduction

Dapagliflozin selectively inhibits SGLT2 in the proximal renal tubule, reducing glucose reabsorption and increasing urinary glucose excretion independently of insulin secretion [1]. Its role now extends beyond glycaemic control: in DECLARE–TIMI 58, which enrolled 17,160 people with T2DM, dapagliflozin reduced hospitalization for heart failure or cardiovascular death across a broad population [2], while DAPA-CKD showed slower progression of kidney disease in participants with or without diabetes [3]. At the same time, product labelling includes warnings about serious urinary tract infections (UTIs), Fournier’s gangrene, and genital mycotic infections [1].

Concern about urinary infection intensified after a regulatory action. In 2015, the US Food and Drug Administration revised SGLT2-inhibitor labels to warn about serious UTIs [4], following reports of 19 life-threatening kidney or bloodstream infections that began as UTIs in people taking these drugs between March 2013 and October 2014 [4]. The proposed mechanism is plausible: glucose-rich urine could support bacterial growth or affect adherence, as discussed in literature on pharmacologically induced glucosuria and genitourinary infection [5,6]. However, spontaneous reports lack a denominator and may be influenced by stimulated reporting after a safety warning; they cannot, by themselves, establish incidence or causality [5].

Clinical studies have not fully resolved the question. An early meta-analysis of dapagliflozin trials reported an increased UTI risk [7]; a network meta-analysis identified a signal at 10 mg [8]; a large class-level meta-analysis found no statistically significant increase [9]; and a 2023 dapagliflozin-specific meta-analysis reported higher estimates in the 10-mg subgroup with exposure beyond 24 weeks and in add-on therapy [10]. These differences matter clinically: overstating risk could discourage use of a therapy with established cardiorenal benefits, whereas overstating reassurance could minimize uncertainty for susceptible patients. Indian real-world evidence is also expanding, although dapagliflozin-specific causal estimates remain limited [11,12,35].

This review addresses four connected questions: (1) what biological mechanisms could plausibly link dapagliflozin-associated glycosuria with urinary infection, and what mechanisms might counterbalance that risk; (2) what randomized, observational, regional, and pharmacovigilance evidence shows when outcomes, populations, dose, duration, and confounding are considered; (3) why findings differ across evidence streams; and (4) how the available evidence can inform proportionate clinical assessment and future research. Urinary tract infection and genital mycotic infection are considered separately because their frequency, biological pathways, and evidentiary consistency differ. A Host–Dose–Duration framework is presented as a hypothesis-generating structure for organizing relevant clinical factors, not as a validated risk score.

2. Literature Identification and Critical Appraisal

This article is a comprehensive critical narrative review, not a systematic review. Literature was identified through targeted searches of PubMed/PubMed Central, publisher websites, regulatory sources, and clinical-trial information using web-based search tools; the update search for this revision was conducted on 25 October 2026. Search terms were refined iteratively rather than applied through a prospectively specified exhaustive strategy. Search concepts combined dapagliflozin and SGLT2-inhibitor terms with urinary tract infection, UTI, pyelonephritis, urosepsis, bacteriuria, genital infection, and T2DM. English-language randomized trials, systematic reviews and meta-analyses, cohort studies, pharmacovigilance analyses, clinical guidance, regulatory documents, and mechanistic studies were considered. Greater attention was given to large or long-duration outcome trials, agent- or dose-specific meta-analyses, and population-based cohorts. A prospectively registered protocol, documented multi-reviewer screening, duplicate independent screening, and a uniform formal risk-of-bias instrument were not used. Complete database-specific search histories and screening counts were not retained; therefore, the search is not fully reproducible and selection bias is possible.

Sources were appraised narratively with attention to UTI definitions and ascertainment, study population and exclusions, dose and exposure duration, comparator selection, potential confounding, reported risk of bias, and statistical power for rare events. Estimates are presented as reported by the original authors and were not recalculated or pooled for this review. Relative risks, odds ratios, and hazard ratios are distinct measures and

should not be interpreted as interchangeable; where displayed together, they provide descriptive context only (Figure 2). Meta-analyses may include overlapping trials and therefore should not be treated as independent confirmations. Because study selection and appraisal were not conducted through a formal systematic process, the synthesis is interpretive and should be read with these limitations in mind.

Table 1: Literature search and appraisal summary

Element	Description
Sources	PubMed/PubMed Central records, publisher websites, regulatory documents and clinical-trial information accessed through web-based searches; full search logs were not retained.
Example PubMed string	(dapagliflozin[tiab] OR Farxiga[tiab] OR "SGLT2 inhibitor"[tiab]) AND ("urinary tract infection"[tiab] OR UTI[tiab] OR pyelonephritis[tiab] OR urosepsis[tiab] OR bacteriuria[tiab] OR "genital infection*" [tiab]) AND ("type 2 diabetes"[tiab] OR T2DM[tiab])
Eligible designs	Randomised trials, systematic reviews and meta-analyses, cohort studies, pharmacovigilance analyses, guidance documents, mechanistic and regulatory sources
Limits	English-language sources; update search conducted 25 October 2026; narrative selection, not a systematic screening process.
Appraisal focus	Outcome definition; population and exclusions; dose and duration; comparator and confounding; risk of bias; power for rare events

3. Pharmacological and Mechanistic Rationale

3.1 Glycosuria as the central mechanism

Dapagliflozin produces glucosuria in a dose-dependent manner [13]. How large the effect is depends on baseline glycaemic control and renal filtration, not on insulin [10]. The agents also differ in their dose–response: urinary glucose excretion plateaus at roughly the starting doses of empagliflozin and canagliflozin but keeps rising across the dapagliflozin dose range [5]. This pharmacodynamic difference is one plausible reason why a dose-related UTI signal has been reported for dapagliflozin and not for the class as a whole [5,8]. Figure 1 summarises the proposed pathways.

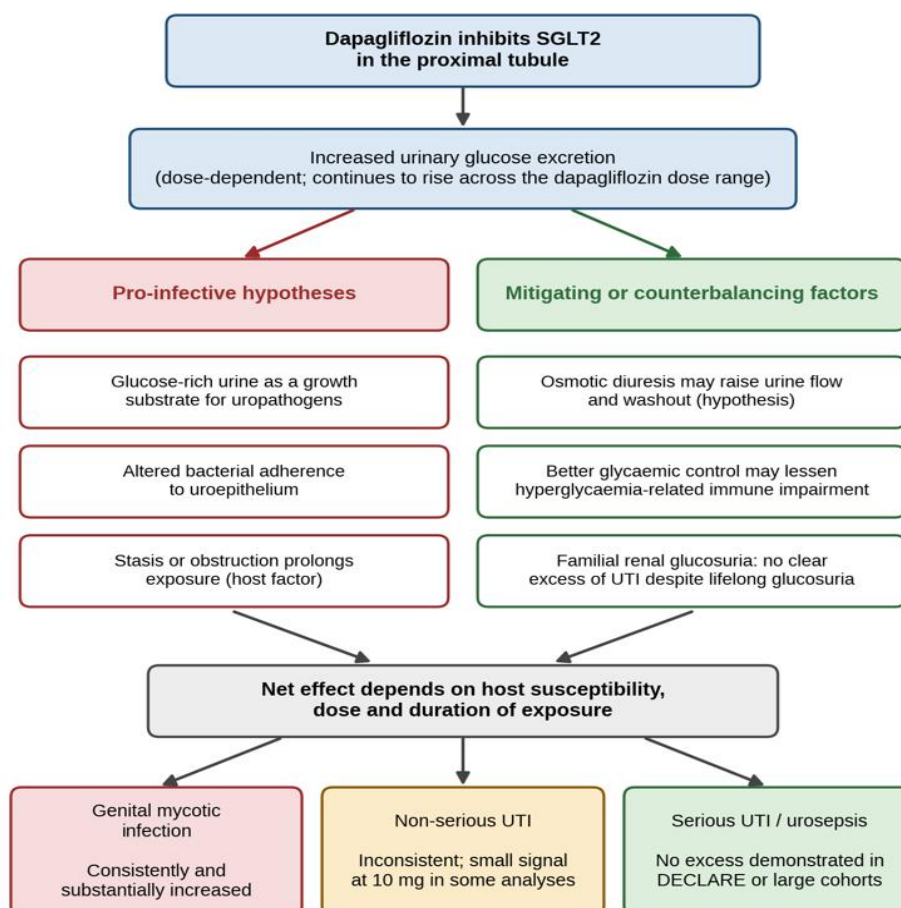


Figure 1. Proposed mechanisms linking dapagliflozin-induced glycosuria to urinary and genital infection; several are hypothetical. SGLT2, sodium-glucose cotransporter-2; UTI, urinary tract infection.

3.2 Why risk might rise

Glucose-rich urine could serve as a growth substrate for uropathogens and could alter bacterial adherence to the uroepithelium, an effect already described in diabetic women before SGLT2 inhibitors existed [5,14]. Urinary stasis or obstruction would lengthen the exposure of the urinary tract to such urine. The hypothesis is biologically reasonable at the level of the host, but dapagliflozin trials have not tested it directly.

3.3 Why risk might not rise

Several observations count against a simple glucose-substrate model. People with familial renal glucosuria excrete glucose throughout life, yet no clear excess of UTI has been linked to the condition [10,15]. Chronic hyperglycaemia itself weakens innate immunity [16], so better glycaemic control could, in theory, lower susceptibility to infection [10]. Osmotic diuresis may also raise urine flow and promote bladder emptying, which could mechanically limit colonisation; this is plausible but unproven in humans. The route from glucosuria to infection is therefore still poorly characterised [5].

3.4 The genital–urinary asymmetry

Genital infection is the most reproducible signal. One meta-analysis of dapagliflozin trials gave a relative risk of 3.23 (95% CI 2.50–4.18) [7], and a network meta-analysis gave an odds ratio of 3.21 (2.08–4.93) for dapagliflozin 2.5 mg [8]. In DECLARE-TIMI 58, genital infections that were serious or led to discontinuation occurred in 0.9% of dapagliflozin and 0.1% of placebo patients (HR 8.36, 4.19–16.68) [2], although genuinely serious genital infections were few and balanced between arms [17]. Urinary results are much less consistent, so genital and urinary infections should be reported and discussed separately (contrast in Figure 2).

4. Evidence from randomized trials

Randomised evidence comes in two kinds that have to be read together: meta-analyses that pool many mostly short glycaemic trials, and large outcome trials that followed patients for years.

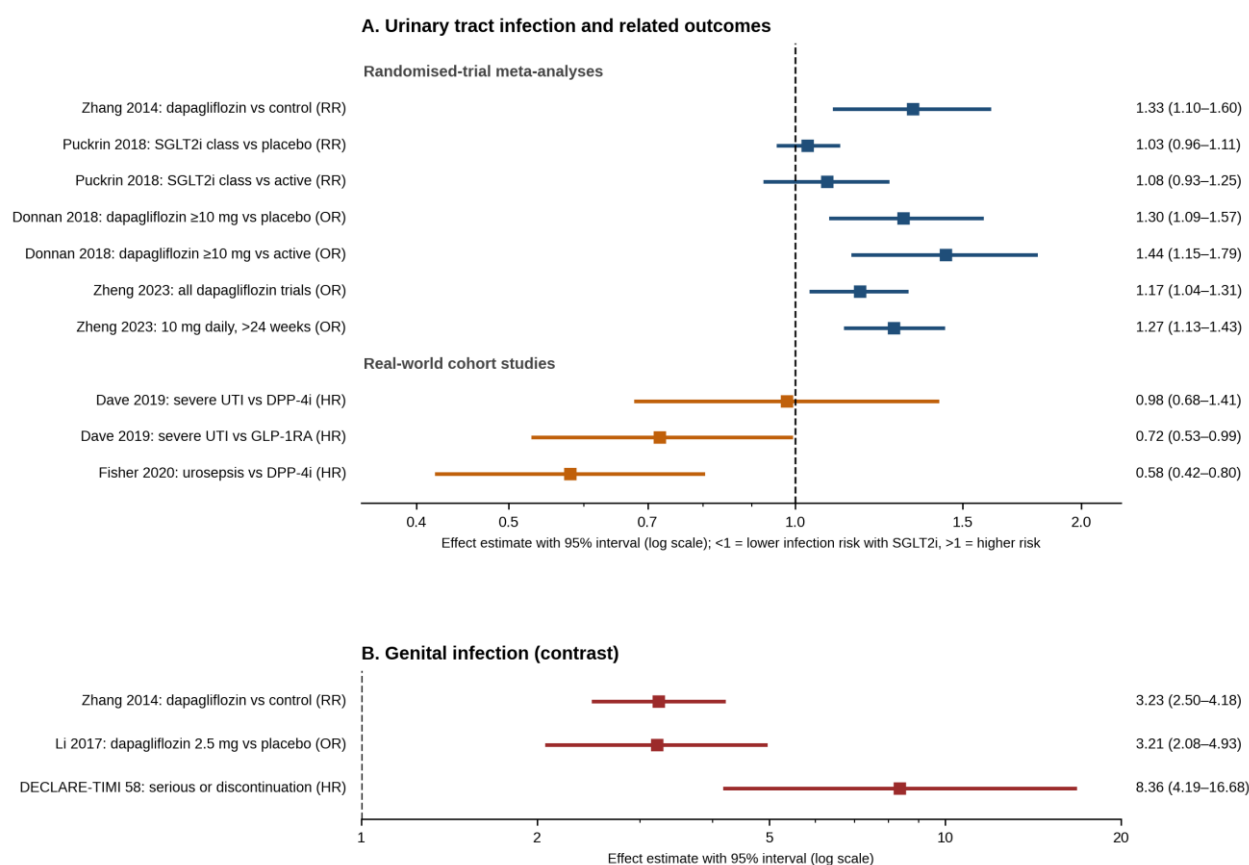


Figure 2. Published effect estimates for UTI (A) and genital infection (B) with dapagliflozin or SGLT2 inhibitors; measures differ and were not re-pooled. RR, relative risk; OR, odds ratio; HR, hazard ratio; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist.

4.1 Meta-analyses of randomised trials

Table 2 lists the main meta-analyses. An early pooled analysis of dapagliflozin trials had looked at UTI in people with diabetes [18], and the first dapagliflozin-specific meta-analysis reported a 33% higher UTI risk [7]. A network meta-analysis of 52 trials and 36,689 patients found that only dapagliflozin 10 mg caused significantly more UTIs than placebo, with a dose–response relationship seen for dapagliflozin alone [8]. A class-level analysis of 86 randomised trials in 50,880 patients found no rise in UTI against placebo (RR 1.03) or active comparators (RR 1.08), although genital infections were more common [5,9]. The largest network meta-analysis, which covered 105 publications, 60,082 individuals and 4,348 UTIs, found higher odds of UTI with dapagliflozin at 10 mg or more than with placebo (OR 1.30, 1.09–1.57) and active comparators (OR 1.44, 1.15–1.79); every difference lost significance, however, when the analysis was limited to trials at low risk of bias [5].

The dapagliflozin-specific meta-analysis by Zheng et al. pooled 42 trials of at least 12 weeks in 35,938 patients [10]. The overall odds ratio was 1.17 (95% CI 1.04–1.31); the reported signal was concentrated in the 10-mg subgroup with exposure beyond 24 weeks (OR 1.27, 1.13–1.43) and in combination therapy (OR 1.27, 1.09–1.48), while estimates for 2.5 mg and 5 mg and for monotherapy were not statistically significant [10]. These are subgroup findings and do not, by themselves, establish a causal dose-duration relationship. A 2026 trial-level meta-analysis of 14 randomized trials across T2DM, chronic kidney disease and heart failure reported a pooled RR of 1.14 (95% CI 0.99–1.32; $I^2=76\%$) for any UTI and 0.99 (0.78–1.27) for serious/complicated urinary infection [34]. The any-UTI result was not statistically significant but remained compatible with a modest increase, and heterogeneity was substantial. The analysis was class-level rather than a definitive dapagliflozin-only estimate, so it complements rather than replaces agent-specific evidence. A separate review of landmark outcome trials also concluded that genitourinary infection was the main area of increased risk [19].

Table 2: Principal meta-analyses of randomised trials on dapagliflozin or SGLT2 inhibitors and urinary tract infection.

Study	Design	Principal findings for UTI
Zhang et al., 2014 [7]	Meta-analysis of dapagliflozin RCTs	RR 1.33 (1.10–1.60); genital infection RR 3.23 (2.50–4.18)
Li et al., 2017 [8]	Network meta-analysis; 52 RCTs; 36,689 patients	Only dapagliflozin 10 mg gave significantly more UTI than placebo; dose–response for dapagliflozin only
Puckrin et al., 2018 [9]	Class-level meta-analysis; 86 RCTs; 50,880 patients	RR 1.03 (0.96–1.11) vs placebo; RR 1.08 (0.93–1.25) vs active comparator; genital infection increased
Donnan et al., 2018 [5]	Bayesian network meta-analysis; 105 publications; 60,082 individuals; 4,348 UTIs	Dapagliflozin ≥ 10 mg: OR 1.30 (1.09–1.57) vs placebo and 1.44 (1.15–1.79) vs active; non-significant in low-risk-of-bias trials
Zheng et al., 2023 [10]	Meta-analysis of dapagliflozin RCTs ≥ 12 weeks; 42 RCTs; 35,938 patients	Overall OR 1.17 (1.04–1.31); 10 mg > 24 weeks OR 1.27 (1.13–1.43); no significant rise at 2.5 or 5 mg; higher with combination therapy
Matteucci et al., 2026 [34]	Trial-level meta-analysis; 14 RCTs across T2DM, CKD and heart failure	Any UTI RR 1.14 (95% CI 0.99–1.32; $I^2=76\%$); serious/complicated UTI RR 0.99 (0.78–1.27); neither statistically significant

4.2 Outcome trials

DECLARE-TIMI 58 randomised 17,160 patients to dapagliflozin 10 mg or placebo, with a median follow-up of 4.2 years [2,17]. In the dedicated safety analysis, UTIs, acute pyelonephritis and urosepsis were balanced between groups [17]. Fournier’s gangrene was rare (one case on dapagliflozin, five on placebo), whereas diabetic ketoacidosis was more common with dapagliflozin (0.3% vs 0.1%) [2]. Its size, duration and systematic capture of serious events make DECLARE-TIMI 58 the most informative single source on severe

urinary outcomes. Its participants, though, had preserved kidney function (creatinine clearance of at least 60 mL/min) [2].

DAPA-CKD randomised 4,304 adults with chronic kidney disease, with or without T2DM, to dapagliflozin 10 mg or placebo for a median of 2.4 years [3]. In the prespecified analysis by diabetes status, serious adverse events of UTI were uncommon but numerically more frequent on dapagliflozin: 1.6% versus 1.0% in participants with T2DM and 0.9% versus 0.6% in those without diabetes, with discontinuation for UTI in 0.5% versus 0.2% of participants with T2DM [20]. These are descriptive proportions without confidence intervals and need cautious reading, but they suggest that a small absolute excess of serious UTI events cannot be ruled out when kidney function is reduced. The other SGLT2 inhibitor outcome trials give a consistent class picture: in EMPA-REG OUTCOME and the CANVAS Program, overall UTI rates were reported as similar to placebo, while genital infections were more frequent [21,22] (Table 3).

Table 3: Urinary and genital infection findings in SGLT2 inhibitor outcome trials.

Trial	Population and agent	Infection findings
DECLARE-TIMI 58 [2,17]	17,160 patients with T2DM; dapagliflozin 10 mg; median 4.2 years	UTI, pyelonephritis and urosepsis balanced; serious or discontinuation-causing genital infection 0.9% vs 0.1% (HR 8.36)
DAPA-CKD [3,20]	4,304 patients with CKD; dapagliflozin 10 mg; median 2.4 years	Serious UTI adverse events 1.6% vs 1.0% (T2DM) and 0.9% vs 0.6% (no diabetes); UTI discontinuation 0.5% vs 0.2% (T2DM); descriptive only
EMPA-REG OUTCOME [21]	Patients with T2DM and cardiovascular disease; empagliflozin	Overall UTI similar to placebo; genital infection more frequent
CANVAS Program [22]	Patients with T2DM and high cardiovascular risk; canagliflozin	Overall UTI similar to placebo; genital infection more frequent

4.3 Reading the trial evidence critically

The meta-analyses differ in drug specificity, outcome definitions, trial inclusion, statistical power and handling of studies at risk of bias. Dapagliflozin-specific analyses report a modest overall or subgroup signal [7,8,10], whereas class-level analyses have generally found no statistically significant increase [9,34]. The 2026 trial-level meta-analysis is particularly relevant because it separated any UTI from serious/complicated infection: neither pooled estimate was statistically significant, but the confidence interval for any UTI (RR 1.14, 95% CI 0.99–1.32) does not rule out a small increase, and heterogeneity was substantial [34]. The largest long-term dapagliflozin outcome trial found similar rates of UTI, pyelonephritis and urosepsis between treatment groups [17], while DAPA-CKD showed small numerical differences in serious UTI events [20]. The balanced interpretation is that a small increase in non-serious UTI remains possible, particularly in some dose/duration subgroups, but a consistent increase in serious urinary outcomes has not been demonstrated. The evidence does not establish that dose or duration causes the observed subgroup differences, and high-risk patients remain insufficiently studied.

5. Real-world, regional, and pharmacovigilance evidence

5.1 Large observational cohorts

Dave et al. compared new users of SGLT2 inhibitors with new users of DPP-4 inhibitors (cohort 1) or GLP-1 receptor agonists (cohort 2) in two large US commercial claims databases [23]. Severe UTI, defined as hospitalisation for UTI, urosepsis or pyelonephritis, occurred at 1.76 versus 1.77 per 1,000 person-years against DPP-4 inhibitors (HR 0.98, 0.68–1.41) and at 2.15 versus 2.96 against GLP-1 receptor agonists (HR 0.72,

0.53–0.99). Outpatient UTI treated with antibiotics was not increased (HR 0.96 and 0.91) [23]. Sensitivity analyses by age, sex, frailty and canagliflozin versus dapagliflozin left the conclusion unchanged [23].

Fisher et al. pooled eight population-based cohorts from seven Canadian provinces and the United Kingdom, with more than 400,000 patients, and found no increase in urosepsis with SGLT2 inhibitors compared with DPP-4 inhibitors (pooled HR 0.58, 0.42–0.80); results were similar for canagliflozin, dapagliflozin and empagliflozin [24]. A meta-analysis of 11 cohort studies covering 679,617 people with T2DM also reported no increased risk of severe UTI [25]. In diabetic chronic kidney disease, a retrospective cohort found no rise in UTI with SGLT2 inhibitors and identified advanced age and female sex as independent risk factors [26]. A recent review of randomised and population-based data concluded that SGLT2 inhibitors have not been shown to raise UTI risk significantly, while noting case reports of pyelonephritis, including one after starting dapagliflozin in a patient with bladder outlet obstruction [27].

5.2 Indian and South Asian data

Indian evidence remains limited, although a large multicentre cross-sectional study published in 2026 now provides an important regional comparison. Earlier Indian studies were generally uncontrolled or short in duration. In FOREFRONT, a real-world study of dapagliflozin in Indian patients with T2DM, 2.9% of participants had at least one adverse event, 0.2% had a UTI, one participant had a serious UTI, and none stopped treatment because of an adverse event [11]. A prospective Indian real-world study that measured culture-proven bacterial UTI in people on SGLT2 inhibitors concluded that the risk of significant bacteriuria or symptomatic UTI was minimal [12]. In a 24-week phase 4 study of a dapagliflozin–saxagliptin combination added to metformin in Indian patients, UTI was the commonest adverse event at 2.6%, genital tract infection occurred in 1.5%, and there were no serious adverse events or discontinuations [28]. A multicentre cross-sectional study of 15,611 adults with T2DM from 42 Indian sites reported UTI in 7.7% of SGLT2 inhibitor users versus 5.4% of non-users; overall urogenital infection was also more common among SGLT2 inhibitor users [35]. Dapagliflozin accounted for most SGLT2 inhibitor exposure, but the analysis was class-level, cross-sectional and vulnerable to residual confounding, outcome-ascertainment differences and treatment-selection bias. It adds important regional context without establishing a causal dapagliflozin-specific effect.

5.3 Pharmacovigilance signals

Spontaneous-report databases regularly flag infection-related signals for SGLT2 inhibitors. A FAERS analysis covering 2013 to 2021 detected significant signals in the infections and infestations class, with pyelonephritis, genital fungal infection and UTI among the frequently reported events [29]. A later FAERS analysis found that most dapagliflozin reports concerned infections, investigations and reproductive-system disorders, notably inflammatory urinary and reproductive conditions in line with the labelling [30], and urogenital infection has also been examined specifically in FAERS [31]. A disproportionality signal shows that an event is reported more often than expected, not that it happens more often, and such signals are open to stimulated reporting after regulatory warnings. They are best used to generate hypotheses and to flag rare serious events for formal study.

Table 4: Selected real-world and regional studies of SGLT2 inhibitors and urinary infection.

Study	Design	Principal findings
Dave et al., 2019 [23]	Two US claims databases; propensity-matched new users; 123,752 patients (vs DPP-4i) and 111,978 (vs GLP-1RA)	Severe UTI HR 0.98 (0.68–1.41) and 0.72 (0.53–0.99); treated outpatient UTI HR 0.96 (0.89–1.04) and 0.91 (0.84–0.99)
Fisher et al., 2020 [24]	Eight cohorts from seven Canadian provinces and the UK; more than 400,000 patients; vs DPP-4i	Urosepsis pooled HR 0.58 (0.42–0.80); similar across canagliflozin, dapagliflozin and empagliflozin
Aboukaoud et al. [25]	Meta-analysis of 11 cohort studies; 679,617 people with T2DM	No increased risk of severe UTI

Yavuz et al., 2025 [26]	Retrospective cohort of diabetic CKD patients with urine cultures; 12-month follow-up	No increase in UTI with SGLT2i; advanced age and female sex independent risk factors
FOREFRONT [11]	Real-world dapagliflozin study in Indian patients with T2DM; uncontrolled	UTI 0.2%; one serious UTI; no discontinuation for adverse events
Indian culture-based study [12]	Prospective real-world study of culture-proven bacterial UTI on SGLT2i; uncontrolled	Risk of significant bacteriuria or symptomatic UTI judged minimal
Phase 4 FDC study [28]	24-week single-arm study of dapagliflozin–saxagliptin added to metformin; India	UTI 2.6%; genital tract infection 1.5%; no serious adverse events
Singh et al., 2026 [35]	Multicentre cross-sectional study; 15,611 adults with T2DM at 42 Indian sites	UTI 7.7% among SGLT2i users vs 5.4% among non-users; dapagliflozin was the most frequently used SGLT2i. Cross-sectional, class-level association; residual confounding and causal inference limitations.

6. Discussion

The apparent disagreement across evidence streams is partly explained by differences in the questions each design can answer. Table 5 summarizes the principal sources of divergence, and Figure 3 presents them schematically.

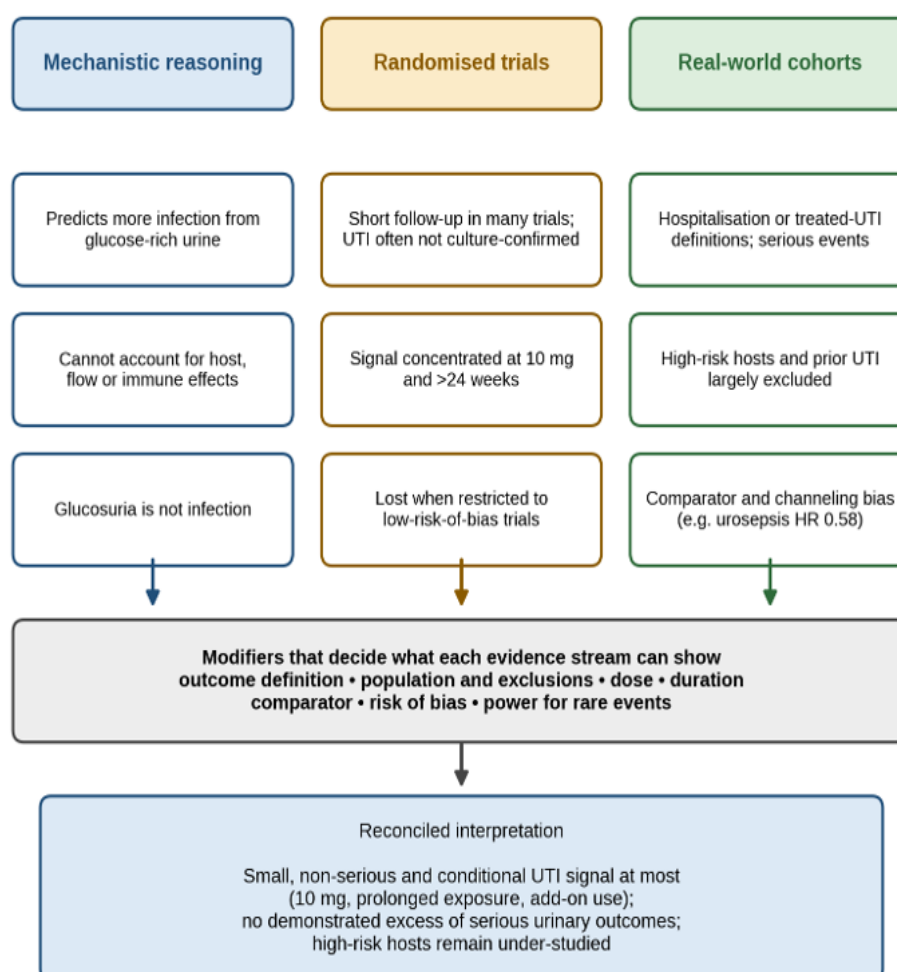


Figure 3. Why mechanistic, randomised and real-world evidence on dapagliflozin and UTI appear to disagree. UTI, urinary tract infection.

Outcome definition. Trials usually record UTI as a reported adverse event, and the diagnostic criteria across dapagliflozin trials range from signs and symptoms to laboratory confirmation [10]. Claims-based cohorts instead capture hospitalisations or antibiotic-treated episodes [23]. These are different clinical phenomena: a small rise in mild, treated episodes can sit alongside no rise in hospitalisation, so studies may all be correct and still look contradictory.

Population and exclusions. DECLARE-TIMI 58 enrolled patients with preserved kidney function [2], and the large claims analysis excluded high-risk patients and those with a previous UTI [23]. The patients clinicians worry about most, those with recurrent UTI, obstruction, urinary diversion or frailty, are therefore the least represented, and neutral results should not be carried over to them without care. The numerically higher serious UTI events in DAPA-CKD [20] show why this matters.

Dose, duration and agent. The statistically positive analyses cluster at 10 mg and at exposures beyond 24 weeks [8,10]. This may reflect cumulative risk, or simply the larger number of events and greater statistical power in long, high-dose arms. Because urinary glucose excretion keeps rising across the dapagliflozin dose range [5], a graded dose response is biologically credible, yet meta-analyses still disagree on whether one exists [10]. The same uncertainty applies to agent versus class: several analyses place the signal with dapagliflozin 10 mg rather than the class [5,8], whereas the class-level estimate is null [9] and real-world analyses gave similar results for the individual agents [24]. Whether dapagliflozin truly differs, or the trial signal is an artefact of dose and power, is unresolved.

Dependence on trial quality. The loss of significance when the largest network meta-analysis was limited to trials at low risk of bias [5] warns that part of the apparent signal may come from methodological weakness, such as unclear blinding or incomplete adverse-event reporting, rather than from the drug.

Comparator and confounding. The pooled hazard ratio of 0.58 for urosepsis against DPP-4 inhibitors [24] is biologically odd, because a genuine protective effect is hard to justify mechanistically. Residual confounding, channelling of healthier patients towards SGLT2 inhibitors or differences in surveillance are more likely explanations. Observational reassurance should therefore be read as absence of evidence of harm, not proof of safety.

Intermediate endpoints. Asymptomatic bacteriuria and pyuria, the physiological steps between glycosuria and clinical infection, were not the focus of the main trials and cohorts discussed here. Culture-based Indian data are an exception but are small and uncontrolled [12]. Without controlled bacteriuria data, we cannot say whether dapagliflozin increases colonisation without increasing disease.

Power for rare, serious events. Progression of UTI to serious infection was rarely reported in randomised trials, so trial data alone can neither support nor refute the concern about serious infections [5]. The 2015 regulatory signal came from spontaneous reports [4,5], and pharmacovigilance databases cannot establish incidence [29,30]. Neither trials nor cohorts can fully exclude a very small absolute excess of severe outcomes.

Generalisability. Most controlled evidence comes from North American, European and multinational trials. South Asian patients differ in body habitus, diabetes duration and background infection risk, and the Indian data available are small and uncontrolled [11,12,28]. It is unknown whether the neutral or small signals seen elsewhere hold equally here.

Table 5: Main reasons why mechanistic, randomised and real-world evidence on dapagliflozin and UTI appear to disagree.

Source of divergence	Effect on the findings	Evidence stream most affected
Outcome definition	Mild treated episodes and hospitalisations can move in different directions	Trials versus claims cohorts
Excluded populations	Neutral results under-represent high-risk hosts	Trials and claims cohorts
Dose, duration and agent	Signal confined to 10 mg and exposure beyond 24 weeks; may reflect power	Meta-analyses of trials
Trial quality	Apparent excess lost in trials at low risk of bias	Network meta-analyses
Comparator and confounding	May exaggerate apparent safety (urosepsis HR 0.58)	Observational cohorts
Intermediate endpoints	Bacteriuria and pyuria rarely measured, so colonisation is unknown	All streams
Power for rare events	A very small excess of severe outcomes cannot be excluded	Trials and cohorts; pharmacovigilance gives no incidence
Generalisability	South Asian data small and uncontrolled	Regional studies

7. Special populations

Chronic kidney disease. Lower filtration reduces the delivery of glucose to the tubule, and therefore the glycosuric effect, which may blunt any infection effect; but CKD populations also carry a higher baseline risk of infection. DAPA-CKD showed a small numerical excess of serious UTI events [20], whereas a retrospective cohort of diabetic CKD found no increase in UTI with SGLT2 inhibitors and identified age and female sex as independent risk factors [26]. The evidence is too limited to settle the matter.

Recurrent UTI and urinary tract abnormalities. These patients were largely excluded from key studies [23], so their risk has not been measured. Guidance advises caution when prescribing to people with recurrent UTI [32] and temporary discontinuation during acute pyelonephritis or urosepsis [33].

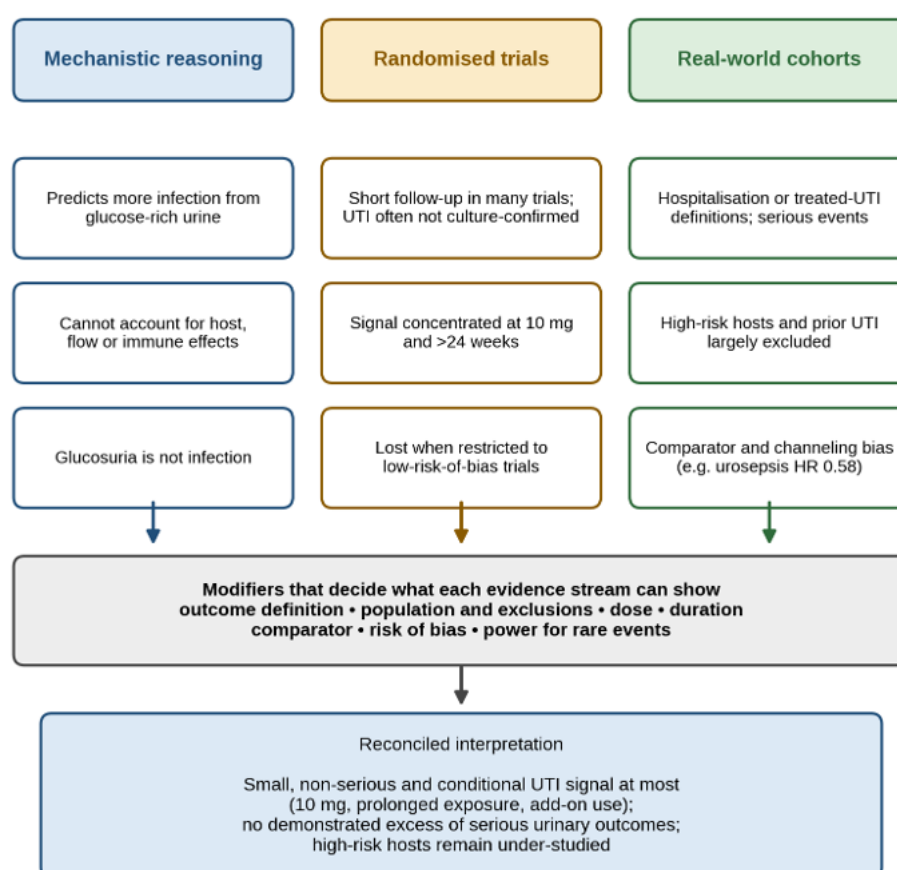
Transplant and other high-risk groups. An expert consensus on genitourinary adverse effects has specifically addressed prevention and management in groups such as renal and cardiac transplant recipients [32]. Controlled infection outcome data for these groups remain scarce.

8. A Host–Dose–Duration framework for risk stratification

The evidence supports treating risk as conditional rather than uniform. We therefore propose a conceptual Host–Dose–Duration (HDD) framework (Table 6, Figure 4) that groups the available signals into three domains. It is our own synthesis and has not been validated, so it should be tested in prospective cohorts before it is used to guide practice.

Table 6: Host–Dose–Duration (HDD) framework: features that raise concern and their evidential basis.

Domain	Features raising concern	Basis
Host	Previous or recurrent UTI; urinary obstruction, prostatic enlargement, neurogenic bladder or urinary diversion; older age and female sex; reduced kidney function; high glycosuric load (poor glycaemic control with preserved renal filtration)	Under-represented in key studies [23]; age and sex as risk factors in diabetic CKD [26]; serious UTI events in DAPA-CKD [20]; glycosuria depends on glycaemia and filtration [10]; stasis hypothesis (untested)
Dose	10 mg daily	Signal, where present, concentrated at 10 mg [5,8,10]; no significant rise at 2.5 or 5 mg [10]; but outcome-trial evidence comes from 10 mg [2]
Duration and context	Exposure beyond about 24 weeks at 10 mg; add-on or combination use	Subgroup findings in a trial meta-analysis [10]; early versus late risk unresolved

**Figure 4.** Conceptual Host–Dose–Duration (HDD) framework for urinary infection risk with dapagliflozin; not validated. BPH, benign prostatic hyperplasia; eGFR, estimated glomerular filtration rate.

In practice, patients with none of the host features can generally start treatment with counselling alone. Those with one or more host features merit an individualised benefit–risk discussion, a baseline urinary history and an explicit plan for reporting symptoms early. The dose should follow the indication, because the cardiovascular and renal outcome evidence is tied to 10 mg dosing [2,3].

9. Clinical implications and current guidance

Figure 5 turns these points into a practical pathway covering assessment before treatment, counselling, follow-up and temporary withholding. It draws on current labelling and guidance [1,32,33] and on the HDD framework (Table 6, Figure 4); it is a conceptual aid and has not been validated.

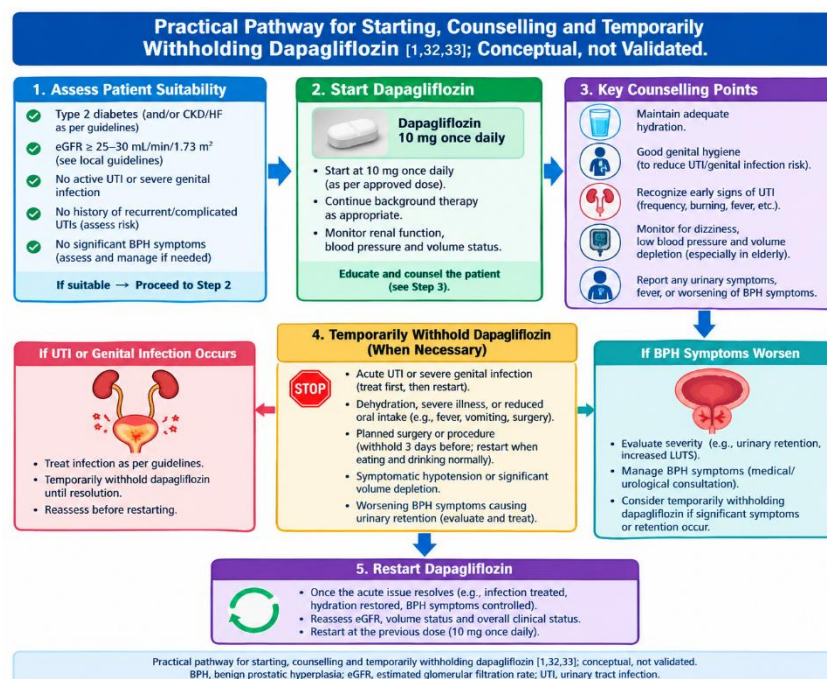


Figure 5. Practical pathway for starting, counselling and temporarily withholding dapagliflozin [1,32,33]; conceptual, not validated. BPH, benign prostatic hyperplasia; eGFR, estimated glomerular filtration rate; UTI, urinary tract infection.

- Counsel every patient about genital hygiene, adequate fluid intake and early reporting of dysuria, fever, flank pain or genital symptoms; the labelling advises prompt medical review for such symptoms [1], and guidance recommends counselling on infection risk and self-care before treatment [33].
- Separate genital from urinary infection when discussing risk. Genital mycotic infection is a more consistent adverse-effect signal; available trials have not demonstrated a consistent increase in serious UTI, but a small excess cannot be excluded [2,17,34].
- Consider temporary interruption during acute pyelonephritis or urosepsis, consistent with the cited UK Kidney Association guidance, and reassess treatment after clinical recovery. Prescribing in patients with recurrent UTI or urinary tract abnormalities should be individualized rather than treated as an automatic contraindication [32,33].
- Do not treat glycosuria or isolated dipstick pyuria as infection. Glycosuria is an expected drug effect [13], and treating asymptomatic bacteriuria in diabetes is generally of no benefit.
- Withholding the drug temporarily during acute severe illness with poor oral intake is common sick-day practice and is reasonable, although controlled evidence on infection outcomes is lacking [33].
- In patients with high-risk urinary tracts, cardiorenal benefit may still outweigh risk, but an individualised plan with urological input is advisable [27,32].

10. Research gaps and future directions

1. Pre-specify culture-confirmed, centrally adjudicated UTI as an outcome in future trials.
2. Include older, frail and anatomically high-risk patients in pragmatic trials and real-world cohorts.
3. Conduct controlled safety studies in South Asian populations, going beyond small uncontrolled series.
4. Compare dapagliflozin 5 mg and 10 mg directly, using urine culture endpoints.

5. Follow glycosuria, pyuria, bacteriuria and urinary microbiome changes over time and relate them to clinical infection.
6. Use time-to-event analyses to show whether risk is concentrated early or accumulates.
7. Validate risk-stratification tools such as the HDD framework prospectively.

11. Strengths and limitations of this review

The main strength of this review is its comparison of mechanistic, randomized, observational, regional and pharmacovigilance evidence while keeping urinary and genital outcomes separate. Its limitations include non-systematic study selection; no prospectively registered protocol; no documented multi-reviewer or duplicate independent screening; no uniform formal risk-of-bias assessment across all evidence streams; incomplete retention of database-specific search histories and screening counts; and possible overlap between meta-analyses that include many of the same trials. Published estimates were not pooled again, several studies use different UTI definitions, and spontaneous-report data cannot estimate incidence. These limitations mean that the review should be interpreted as a critical narrative synthesis rather than an exhaustive systematic review. The proposed Host–Dose–Duration framework is hypothesis-generating and has not been prospectively validated.

12. Conclusion

The available evidence does not justify a categorical conclusion that dapagliflozin routinely causes urinary tract infection (UTI), nor does it establish that urinary risk is absent. Dapagliflozin-specific meta-analyses leave open the possibility of a modest increase in non-serious UTI, particularly in some 10-mg or longer-exposure subgroups; these subgroup findings do not establish a causal dose–duration relationship. Large outcome trials and a 2026 class-level trial meta-analysis have not demonstrated a statistically significant increase in serious or complicated urinary infection, although their estimates do not exclude risk in every population [17,20,34]. The 2026 Indian cross-sectional study reported a higher observed UTI prevalence among SGLT2-inhibitor users, but its design cannot establish causality or isolate dapagliflozin-specific risk [35]. Importantly, genital mycotic infections represent a more consistent adverse-effect signal than UTIs and should not be conflated with urinary infections. Patients with recurrent infection, urinary obstruction, frailty, or other characteristics under-represented in trials warrant individualized assessment. Clinical practice should distinguish urinary from genital infection, provide symptom counselling, evaluate suspected infection promptly, and balance potential harms against established cardiorenal benefits. The proposed Host–Dose–Duration framework is a conceptual, hypothesis-generating aid for organizing clinical questions; it has not been validated and should not be used as a validated risk score or prescribing rule.

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; CKD, chronic kidney disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; FAERS, FDA Adverse Event Reporting System; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDD, Host–Dose–Duration; HR, hazard ratio; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SGLT2, sodium-glucose cotransporter-2; T2DM, type 2 diabetes mellitus; UTI, urinary tract infection.

Acknowledgements: The Authors acknowledge to the CMR college of Pharmacy Management and the Principal for providing resources and support for the work.

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How to cite this article: Jenny Sandal Maisangala, Mugdha Vikasita Gannavaram, Akhila Mudavath, Ankem Kovidha, Dr. Vattikutti uma Maheshwara Rao “Dapagliflozin and Urinary Tract Infection Risk in Type 2 Diabetes: A Comprehensive Critical Review of Mechanistic, Randomized, and Real-World Evidence”. *Tropical Journal of Pharmaceutical and Life Sciences*, vol. 13, no. 5, Oct. 2026,53-68 <https://doi.org/10.61280/9h681f91>.

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