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Key Points:

Abstract:
Sodium-glucose cotransporter 2 (SGLT2) inhibitors have revolutionized our armamentarium for kidney and heart protection in patients with or without diabetes. Based on early reports of a limited number of cases, a concern for increased risk of urinary tract infections arose, which has become one of the main areas of concern for some clinicians. However, data from large randomized clinical trials and real-world population-based studies have not shown a significantly increased risk of UTI in patients on SGLT2 inhibitors. The goal of this brief review article is to review the literature and provide reassurance to the patients and prescribers for the broader use of these agents.

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Sodium-glucose Cotransporter 2 Inhibitors and Urinary Tract Infection: Is there room for real concern?

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Abstract
Sodium-glucose cotransporter 2 (SGLT2) inhibitors have revolutionized our armamentarium for kidney and heart protection in patients with or without diabetes. Based on early reports of a limited number of cases, a concern for increased risk of urinary tract infections arose, which has become one of the main areas of concern for some clinicians. However, data from large randomized clinical trials and real-world population-based studies have not shown a significantly increased risk of UTI in patients on SGLT2 inhibitors. The goal of this brief review article is to review the literature and provide reassurance to the patients and prescribers for the broader use of these agents.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have become a highly valued agent in our armamentarium in caring for patients with proteinuric kidney disease. Although initially developed to improve glycemic control, the evidence from clinical trials has shown efficacy in kidney and heart protection among even non-diabetic individuals. The initial cardiovascular outcome trials (CVOT) not only showed the effectiveness of SGLT2 inhibitor agents in reducing cardiovascular mortality and hospitalization for heart failure (HF) in patients with diabetes, but secondary outcomes from these early trials also revealed up to 40% reduction in risk of progression of kidney disease. [1-4] The cohort of patients included in these initial COVT mostly had preserved kidney function without significant albuminuria. Subsequent clinical trials focused on patients with various degrees of baseline kidney impairment, and higher albuminuria confirmed the kidney protective effects of these agents in patients with type 2 diabetes. [5] Remarkably, the cardiorenal protective effects of these agents have now been shown even in individuals without diabetes. [6-8]

SGLT2 inhibitors suppress glucose reabsorption in the kidney proximal tubules (PT), resulting in glucosuria. Based on this mechanism of action, a heightened concern for the development of urinary tract infection (UTI) has been one of the barriers to prescribing these agents. In 2015, the US Food and Drug Administration (FDA) added a warning for severe UTI with the use of SGLT2i agents based on a limited number of cases reported to the FDA’s Adverse Event Reporting System. [9] However, data from individual large randomized clinical trials (RCT)
have not shown a significant difference between SGLT2i agents and placebo. [1-6] In addition, a meta-analysis of multiple RCTs and more than 50000 individuals did not find an increased risk of UTI using SGLT-2 inhibitors versus placebo. [10]

Table 1. Studies comparing UTI risk between SGLT2 inhibitors and placebo

| Comparison                  | Study (Publication year) | Patients (n) | Outcome                                            |
|-----------------------------|--------------------------|--------------|----------------------------------------------------|
| **Meta-analysis**           |                          |              |                                                    |
| SGLT2 inhibitor vs placebo  | Puckrin *et al.* (2018)  | 72 trials: 37,116 | Random-effects model risk ratio (95% CI): 1.03 (0.96-1.11)  |
|                            |                          |              | I² (95% CI): 0% (0-0)                              |
| **Randomized controlled trials** |                        |              |                                                    |
| Canagliflozin (100 mg) vs placebo | Perkovic *et al.* (2019) | 4,397 | HR (95% CI): 1.08 (0.90–1.29)                      |
| Canagliflozin (all doses) vs placebo | Neal *et al.* (2017)     | 4,330 | 40 vs 37 participants with an event per 1000 patient-years; p-value 0.38 |
| Dapagliflozin (10 mg) vs placebo | Heerspink *et al.* (2020) | 4,298 | No difference reported; details unpublished         |
|                            | Wiviott *et al.* (2018) | 17,143 | HR (95% CI): 0.93 (0.73-1.18) p-value: 0.54         |
| Empagliflozin (all doses) vs placebo | Wanner *et al.* (2016)  | 7018 | Rate ratio (95% CI): eGFR <60 mL/min/1.73m²: 1.06 (0.86-1.3) eGFR ≥60 mL/min/1.73m²: 0.92 (0.80-1.07) |

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease); HR, hazard ratio; vs, versus. Table by Paolo Nikolai So, MD.

Subsequently, Dave et al., in a large population-based study, showed that the risk of severe and non-severe UTI events among individuals on SGLT2i therapy was not increased compared to patients on other oral hypoglycemic agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors or glucagon-like peptide-1 receptor (GLP-1) agonists. [11] However, individual comparison of different SGLT2i agents demonstrated a higher risk of UTI associated with the use of dapagliflozin than others.

In another recent study, Varshney et al. compared the risk of genitourinary infections between SGLT2i therapy and GLP-1 receptor agonists use in older adults (age > 65 years) with diabetes mellitus type 2. Their results add to the existing body of evidence showing that SGLT2i use was not associated with an increased risk of composite genitourinary infection compared to other
second-line glycemic controlling agents. [12] Similarly, in a large multi-site real-world study of Canadian and United Kingdom patients with type 2 diabetes, there was no increased risk of urosepsis associated with SGLT2i therapy compared with DPP4i use. [13]

Table 2. Studies comparing UTI risk between SGLT2 inhibitors and active comparators

| Comparison                              | Study (Publication year) | Patients (n) | Outcome                                                                 |
|-----------------------------------------|--------------------------|--------------|-------------------------------------------------------------------------|
| SGLT2 inhibitor vs active comparator     | Puckrin et al. (2018)    | 22 trials: 15,966 | Random-effects model risk ratio (95% CI): 1.08 (0.93-1.25) I² (95% CI): 22 (0-54) |
| Retrospective cohort                     | Varshney et al. (2021)   | 474          | Composite genitourinary infection [HR (95% CI)]: 0.78 (0.26-2.37)         |
| SGLT2i vs DPP4i                          | Fisher et al. (2020)     | 416,488      | Urosepsis [HR (95% CI)]: 0.58 (0.42-0.80)                                 |
| SGLT2i vs DPP4i or GLP1-RA               | Dave et al. (2019)       | SGLT2i vs DPP4i: 123,752; SGLT2i vs GLP1-RA: 111,978 | Severe UTI [HR (95% CI)]:
  • SGLT2i vs DPP4i: 0.98 (0.68, 1.41)
  • SGLT2i vs GLP1-RA: 0.72 (0.53, 0.99)

Treated outpatient UTI:
  • SGLT2i vs DPP4i: 0.96 (0.89, 1.04)
  • SGLT2i vs GLP1-RA: 0.91 (0.84, 0.99)

Abbreviations: CI, confidence interval; DPP4i, dipeptidyl peptidase-4 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonists; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitors; vs, versus. Table by Paolo Nikolai So, MD.

One potential explanation for the lack of real-world evidence of increased clinically significant UTI, despite glucosuria and the resultant favorable environment for bacterial growth, is the increased urinary flow because of osmotic diuresis and natriuresis effects of these medications. [14] Therefore, caution is needed in using SGLT2i agents in the setting of abnormal urinary flow. A reported case of acute pyelonephritis after initiation of dapagliflozin use in an individual with bladder outlet obstruction raises concern that although data from real-world studies do not suggest a higher risk of UTIs associated with SGLT2is in the general population, this risk can theoretically increase in the setting of abnormal urinary flow. [15] Future studies are needed to evaluate this particular clinical question.
To date, data from multiple real-world studies and meta-analysis reports suggest a lack of increased risk of clinically significant UTI with SGLT2i use. These concerns should not become a barrier in considering the initiation of therapeutic agents with so much potential for improving the care of our vulnerable group of patients.

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