Sodium-Glucose Cotransporter 2 Inhibitors and Severe Urinary Tract Infections: Reassuring Real-World Evidence

Short title: SGLT-2 Inhibitors and Severe UTI

Kristian B. Filion PhD^{1,2} and Oriana H Yu MD MSc^{2,3}

¹ Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

² Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada

³ Division of Endocrinology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada

Word Count: 997

Address for Correspondence:

Kristian B. Filion, PhD

Associate Professor and William Dawson Scholar

Departments of Medicine and of Epidemiology, Biostatistics, and Occupational Health, McGill University

Centre For Clinical Epidemiology, Lady Davis Institute - Jewish General Hospital

3755 Cote Ste-Catherine, H-410.1

Montreal, Quebec H3T 1E2 Canada

Tel: (514) 340-8222 x 28394

Fax: (514) 340-7564

E-mail: kristian.filion@mcgill.ca

Dr. Filion holds a Chercheur-Boursier Junior II award from the *Fonds de recherche du Québec – santé* (FRQS; Quebec Foundation for Health Research) and a William Dawson Scholar award from McGill University. Dr. Yu holds a *Chercheur-Boursier Clinicien* Junior 1 award from the FRQS.

June 21, 2019

Sodium glucose cotransporter-2 (SGLT-2) inhibitors are the most recently approved class of anti-diabetic drugs that reduce glycemia by inhibiting the reabsorption of glucose on the renal proximal tubule (1). Through this mechanism of action, SGLT-2 inhibitors also induce weight loss and confer cardiovascular benefits, including reductions in major adverse cardiovascular events and heart failure (2). As a result, they were the first class of anti-diabetic drugs approved for cardiovascular disease prevention and are now recommended as one of the preferred second-line therapies among patients with type 2 diabetes and known atherosclerotic cardiovascular disease who are unable to attain glycemic control with metformin (3).

Given the mechanism of action of SGLT-2 inhibitors, there is a strong biological rationale supporting a potential increased risk of urinary tract infections (UTIs). Indeed, the higher glucose concentration in the urine with SGLT-2 inhibitor use may promote bacterial growth (4). In 2015, the Food and Drug Administration (FDA) issued a warning of an increased risk of serious UTIs with SGLT-2 inhibitors (5). This warning was based on 19 reported cases of urosepsis and pyelonephritis reported to the FDA Adverse Event Reporting System. Given the underlying UTI risk among patients with type 2 diabetes and the inherent limitations of such systems (e.g., no comparator, no denominator), the strength of the conclusions that can be drawn from these data are limited. Subsequent meta-analyses of data from randomized controlled trials (RCTs) did not find an increased UTI risk with SGLT-2 inhibitors versus placebo overall (relative risk [RR]: 1.03, 95% confidence interval [CI]: 0.96-1.11). However, molecule-specific analyses suggested that dapagliflozin may be associated with an increased risk compared to placebo (RR: 1.23, 95% CI: 1.03-1.46)(6).

Importantly, the generalizability of RCT data in this area to everyday clinical practice is unclear.

In this issue of the *Annals of Internal Medicine*, Dave and colleagues examine the association between SGLT-2 inhibitors and the risk of severe UTI in a real-world setting (7). Using data from two large, US insurance databases (MarketScan and Optum), they conducted two propensity-matched cohort studies comparing the risk of severe UTIs of SGLT-2 inhibitors to those of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists. The primary endpoint was severe UTI, defined as a composite of hospitalizations with 1) sepsis and UTI, 2) pyelonephritis, or 3) UTI as a primary diagnosis. When data were pooled across databases, SGLT-2 inhibitors were not associated with an increased risk of severe UTI compared with either DPP-4 inhibitors (hazard ratio [HR]: 0.98, 95% CI: 0.68-1.41) or GLP-1 receptor agonists (HR: 0.72, 95% CI: 0.53-0.99). Similar results were obtained when examining the individual components of the primary endpoint and across several secondary and sensitivity analyses. Molecule-specific analyses revealed no important differences between canagliflozin and dapagliflozin versus DPP-4 inhibitors (HR: 0.83, 95% CI: 0.57-1.21 and HR: 0.57, 95% CI 0.29-1.14, respectively) or GLP-1 receptor agonists (HR: 0.66, 95% CI: 0.47-0.92 and HR: 0.52, 95% CI: 0.28-0.97, respectively).

This study has several strengths. With its propensity-matched design, use of active comparators used at a similar point in the management of type 2 diabetes, and rigorous statistical adjustment (including the use of a frailty score), it has reduced confounding by indication and by other variables. With over 100,000 patients per cohort, the authors were able to restrict analysis to severe UTIs, a clinically-important endpoint among patients with type 2 diabetes. Furthermore, their results were consistent across several different analyses,

suggesting that their findings are robust to study assumptions. Finally, with its use of real-world data, the findings of this study are more generalizable to everyday clinical practice than those obtained from RCTs in this area.

This study does have some limitations worth noting. As discussed by the authors, the study was restricted to insured individuals in the US, and the generalizability of its findings to uninsured individuals and those in other jurisdictions is unclear. Furthermore, patients with renal insufficiency, those at high risk of UTI, and those with a history of UTI were excluded. While such exclusions may have increased validity, they may have adversely impacted generalizability. These exclusions also prevented subgroup analyses among those at greatest risk of the outcome of interest. With the use of an active comparator, new user design (8), patients with a history of recent use of the comparator drugs were excluded; given the dynamic nature of the management of type 2 diabetes, this can result in a large number of excluded patients. Indeed, as described in Table 1, ~30% of SGLT-2 inhibitor users had a history of DPP-4 inhibitor use, and the exclusion of such individuals can reduce generalizability (a strength of real-world evidence)(9). This represents an ongoing methodological challenge in studies of conditions with escalating, multi-step treatments. Finally, despite the use of rigorous methods, the potential for residual confounding remains, which likely explains the unexpected protective effects observed in comparisons with GLP-1 receptor agonists.

This study has several important implications and represents a key addition to the literature. While concerns emerged regarding a potential increased risk of genitourinary tract infections with SGLT-2 inhibitors, accumulating evidence suggests that harms are restricted to genital tract infections (6). Although some limitations are noted, this study is

methodologically rigorous and provides reassuring real-world evidence regarding this potential safety issue. This reassurance comes with some caveats. First, the present study excluded high-risk patients and those with a history of UTI, a key subgroup for which further evidence is needed. Second, some analyses of secondary outcomes such as urosepsis and molecule-specific analyses had more modest statistical power, and safety data from RCTs suggest that the risk may vary by molecule (6). Safety assessments by networks such as the Sentinel System or the Canadian Network for Observational Drug Effect Studies may be needed to conclusively address these issues. Ultimately, while some uncertainty remains, the study by Dave and colleagues (7) provides encouraging evidence of the real-world safety of SGLT-2 inhibitors, allowing patients to benefit from their use with greater confidence in the safety of SGLT-2 inhibitors with respect to severe UTI.

Acknowledgements

Dr. Filion holds a Chercheur-Boursier Junior II award from the *Fonds de recherche du Québec – santé* (FRQS; Quebec Foundation for Health Research) and a William Dawson Scholar award from McGill University. Dr. Yu holds a *Chercheur-Boursier Clinicien* Junior 1 award from the FRQS. The authors thank Dr. Laurent Azoulay for his helpful suggestions regarding an earlier version of this editorial.

Disclosures

The authors have no relationships to disclose.

REFERENCES

1. Ghezzi C, Loo DDF, Wright EM. Physiology of renal glucose handling via SGLT1, SGLT2 and GLUT2. *Diabetologia*. 2018;61(10):2087-97.
2. Home P. Cardiovascular outcome trials of glucose-lowering medications: an update. *Diabetologia*. 2019;62(3):357-69.
3. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. *Diabetes Care*. 2019;42(Suppl 1):S90-s102.
4. Geerlings SE, Brouwer EC, Gaastra W, et al. Effect of glucose and pH on uropathogenic and non-uropathogenic *Escherichia coli*: studies with urine from diabetic and non-diabetic individuals. *J Med Microbiol*. 1999;48(6):535-9.
5. Food and Drug Administration. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. 2015; <https://wayback.archive-it.org/7993/20170112031533/http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm> Accessed on June 19, 2019.
6. Puckrin R, Saltiel MP, Reynier P, et al. SGLT-2 inhibitors and the risk of infections: a systematic review and meta-analysis of randomized controlled trials. *Acta Diabetol*. 2018;55(5):503-14.
7. Dave CV, Schneeweiss S, Kim D, et al. Sodium-glucose cotransporter 2 inhibitors and the risk of severe urinary tract infections. *Ann Intern Med*. 2019.

8. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep.* 2015;2(4):221-8.
9. Filion KB, Suissa S. DPP-4 Inhibitors and heart failure: some reassurance, some uncertainty. *Diabetes Care.* 2016;39(5):735-7.