



EDITORIAL COMMENT

The risk for urinary tract infections with sodium-glucose cotransporter 2 inhibitors: no longer a cause of concern?

Pantelis A. Sarafidis ¹ and Alberto Ortiz²

¹Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece and ²IIS-Fundacion Jimenez Diaz, School of Medicine, University Autonoma of Madrid, FRIAT and REDINREN, Madrid, Spain

Correspondence to: Pantelis A. Sarafidis; E-mail: psarafidis11@yahoo.gr; Twitter handle: @CKJ_EiC

ABSTRACT

Sodium–glucose co-transporter-2 (SGLT2) inhibitors improve cardiovascular and renal outcomes in patients with type 2 diabetes, including those with diabetic kidney disease. However, the US Food and Drug Administration and European Medicines Agency warnings about potential adverse effects, such as urosepsis and pyelonephritis, based on post-marketing case reports, may deter physicians from prescribing these drugs. A recent evaluation of two large US-based databases of commercial claims failed to find evidence for an increased risk of urinary tract infection (UTI) or severe UTI in type 2 diabetes patients who were prescribed an SGLT2.

Keywords: adverse effects, diabetes mellitus, pyelonephritis, SGLT2 inhibitors, urinary tract infection

Diabetes mellitus (DM) is a major problem of public health; estimates from the World Health Organization suggest that >15% of the global adult population may have DM by 2030 [1]. It is the most common cause of end-stage renal disease [2]. In previous years, new drug classes for the treatment of type 2 DM have emerged, including inhibitors of renal sodium–glucose co-transporter-2 (SGLT2); these drugs inhibit glucose reabsorption into proximal tubular cells, producing mild glycosuria. Thus, apart from blood glucose reduction, they offer mild but clinically meaningful decreases in body weight and blood pressure due to glycosuria-induced calorie loss and natriuresis [3]. Unlike older antidiabetic agents, recent cardiovascular outcome trials have shown that SGLT2 inhibitors reduce cardiovascular events and all-cause mortality in type 2 DM. Furthermore, secondary analyses of the above trials, as well as a recent trial with primary renal outcome, clearly suggest that these agents can largely

retard the progression of renal disease in type 2 DM [4–6]. Current knowledge suggests that SGLT2 inhibitors reduce glomerular hyperfiltration, intraglomerular pressure and urinary albumin excretion through reversal of the vasodilation of the afferent arteriole, that is through a mechanism different to that of renin–angiotensin system blockers, offering a unique opportunity for nephroprotection [4, 6]. Based on the above, recent guidelines and consensus statements recommend the preferred use of SGLT2 inhibitors as a second step (after metformin) in type 2 DM patients with atherosclerotic cardiovascular disease, chronic kidney disease (CKD) or heart failure [4, 7]. Furthermore, these agents are currently being explored as nephroprotective and cardioprotective agents in non-diabetic individuals [8].

In major trials with SGLT2 inhibitors, the overall rates of adverse effects were significantly lower in the active drug groups than in the placebo groups [9–11], indicating a

Received: 27.9.2019; Editorial decision: 31.10.2019

© The Author(s) 2019. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

generally safe profile. However, the mode of action of these agents is theoretically expected to be associated with adverse reactions related to glycosuria [4]. Urinary frequency and volume depletion-associated symptoms have been more common in the SGLT2 inhibitor group in only one [10] of the three major cardiovascular trials [9–11]. Previous reports on increased incidences of acute kidney injury (AKI) with these agents were also not confirmed in clinical trials, as AKI episodes were less frequent in the SGLT2 inhibitor groups [9–11]. Thus genitourinary tract infections appeared to be the most common complication undermining their use. Among them, genital mycotic infections, although generally mild in severity and resolving with topical treatment, were indeed from 4- to 9-fold, more common in the SGLT2 inhibitor groups than in the placebo groups in major trials [9–11]. In contrast to the solid information on genital infections, early data on the incidence of urinary tract infections (UTIs) during SGLT2 treatment were not consistent, generating confusion among treating physicians.

The presence of DM itself increases UTI risk by 1.5- to 4-fold; development of UTIs in individuals with diabetes is a major problem, as it further increases the risk of complications, hospitalizations and death and elevates economic burden [12, 13]. In 2015, the US Food and Drug Administration (FDA) revised labels for all SGLT2 inhibitors to add a warning about increased risk of severe UTIs [14]. This warning followed 19 cases of urosepsis and pyelonephritis reported to the FDA, which by itself was of limited scientific value due to the absence of comparator and denominator. The European Medicines Agency considers UTIs (including pyelonephritis and urosepsis) as common adverse reactions of these drugs, citing post-marketing cases of pyelonephritis and urosepsis for empagliflozin and canagliflozin [15–17]. Such warnings, however, may induce fear of UTIs among treating physicians and cause the underuse of SGLT2 inhibitors, despite their undisputed benefit on cardiovascular outcomes and mortality.

In contrast to the above, in major outcome studies, the risk of UTIs with SGLT2 inhibitors was similar to that with placebo. In Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME), the overall occurrence of UTIs was 18.0 and 18.1% and that of complicated UTI (defined as pyelonephritis, urosepsis or a serious adverse event consistent with UTI) was 1.7 and 1.8% in the empagliflozin and placebo groups, respectively [9]. In the CANagliflozin cardioVascular Assessment Study (CANVAS) programme, the relevant incidence with canagliflozin and placebo was 40 versus 37 UTI events per 1000 patient-years ($P=0.38$) [10], while in the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI) trial, UTIs were reported in 1.5 and 1.6% of dapagliflozin- or placebo-treated patients ($P=0.54$) [11]. These results are strengthened by a recent meta-analysis including data from 86 randomized clinical trials with 50 880 patients [18]. Therein there was no significant difference in the risk of UTIs when SGLT2 inhibitors were compared with placebo {relative risk [RR] 1.03 [95% confidence interval (CI) 0.96–1.11]} or active drugs [RR 1.08 (95% CI 0.93–1.25)]. In drug-specific analyses, empagliflozin [RR 0.99 (95% CI 0.91–1.08)] and canagliflozin [RR 1.10 (95% CI 0.90–1.33)] were not associated with increased risk of UTI versus placebo, but dapagliflozin was [RR 1.23 (95% CI 1.03–1.46)]; the latter was a dose-dependent association evident with dapagliflozin 10 mg but not with dapagliflozin 5 mg daily. In comparisons against active drugs, no individual SGLT2 inhibitor demonstrated an increased risk of UTI.

As the findings of clinical trials with regards to safety outcomes are not always directly generalizable to everyday clinical practice, in a recent observational study, Dave *et al.* [19] aimed to answer this question. They used data from two US databases of patients with employer-based insurance. Within each database they created through 1:1 propensity score matching one cohort of adult type 2 DM patients that were initiating SGLT2 inhibitors versus dipeptidyl peptidase-4 (DPP-4) inhibitors (Cohort 1) or SGLT2 inhibitors versus glucagon-like peptide-1 (GLP-1) receptor agonists (Cohort 2). New use was defined as no use of the relevant drugs for a 180-day window before study entry. Cohort entry was restricted to between March 2013 and September 2015. Patients with evidence of nursing home or hospice care, gestational DM, type 1 DM, cancer, human immunodeficiency virus or renal insufficiency (CKD, acute renal failure or end-stage renal disease), as well as those with a high risk of UTI (hydronephrosis, vesicoureteral reflux, spinal cord injuries or catheter use) and those with a history of UTI were excluded from the analysis. With propensity score matching performing adjustment for >90 baseline characteristics, Cohort 1 included 123 752 patients and Cohort 2 included 111 978 patients. The primary outcome (severe UTI event, defined as a hospitalization for primary UTI, hospitalization for sepsis with UTI or pyelonephritis) occurred in 61 individuals newly starting SGLT2 inhibitors (1.76 events/1000 person-years) and 57 individuals starting DPP-4 inhibitors (1.77 events/1000 person-years) in Cohort 1 [hazard ratio (HR) 0.98, (95% CI 0.68–1.41)]. In Cohort 2, the relevant rates were 2.15 versus 2.96 events/1000 person-years for those starting SGLT2 inhibitors versus GLP-1 agonists [HR 0.72 (95% CI 0.53–0.99)]. The individual components of the primary outcome showed similar trends, with a significant difference for hospitalization for sepsis with UTI favouring SGLT2 inhibitors in Cohort 2 [HR 0.54 (95% CI 0.36–0.82)]. SGLT2 inhibitors were also not associated with an increased risk for treated outpatient UTIs [Cohort 1: HR 0.96 (95% CI 0.89–1.04); Cohort 2: HR 0.91 (95% CI 0.84–0.99)] [19].

These important results suggest that SGLT2 inhibitors are not associated with an increased risk of severe or outpatient UTIs compared with DPP-4 inhibitors or GLP-1 agonists in everyday practice. Among the study's strengths, one can list the large samples that provided an adequate number of events, especially with regards to the rare outcome of severe UTI, which is a clinically relevant endpoint. A thorough process of propensity score matching enabled the formation of balanced groups for a wide set of factors. Furthermore, the authors performed sensitivity and subgroup analyses, indicating the robustness of their findings [19]. However, some limitations are also present.

The authors excluded patients at high risk of UTI or with a previous history of UTI; such patients are not uncommon in the diabetic population. They also excluded patients with CKD, a fact that introduces a considerable gap in the literature, as SGLT2 inhibitors may have much wider use in such patients, following recent evidence of nephroprotection [4–6]. The authors had no information to perform adjustments for DM duration and severity (indicated by haemoglobin A1c), which are clinically relevant factors. Furthermore, even with the best methodology, the presence of residual confounding cannot be excluded, as in all retrospective cohort studies. Confounding by indication is obviously possible [20], that is doctors could have intentionally not prescribed SGLT2 inhibitors in patients they consider at risk for a UTI or in patients with a previous history of UTIs (which can be present and not reported in a claims database, as patients with mild UTIs are often self-treated). To minimize such an effect, the authors performed subgroup analyses of risk factors for UTI (use of steroids, antibiotics, anti-rheumatic drugs and history of mycotic

infections), but this is restricted to 180 days before cohort entry and the lifetime UTI history is not considered. Findings suggesting that indication biases are present is the unexpected lower incidence of severe UTIs, UTI hospitalizations and outpatient UTIs with SGLT2 inhibitors versus GLP-1 receptor agonists. For this to have biological plausibility, background data suggesting that GLP-1 receptor agonists predispose to UTIs or SGLT2 inhibitors protect against them had to exist, but in both cases, they are obviously absent.

Overall, data from major outcome trials clearly suggest that SGLT2 inhibitors are not associated with an increased risk of UTIs [9–11]. The recent analysis from Dave *et al.* [19] added a set of real-world data pointing in the same direction. Observational studies including patients with a UTI history or specific populations (CKD, the elderly) are pieces of evidence that would advance our knowledge in the field. However, already existing data on the association of SGLT2 inhibitors with UTIs are largely reassuring and should enable more extended use of these drugs for the benefit of our patients.

FUNDING

Research by A.O. is supported by FIS PI16/02057, PI19/00588, PI19/00815, DTS18/00032, ERA-PerMed-JTC2018, KIDNEY ATT ACK AC18/00064 and PERSTIGAN AC18/00071, ISCI-RETIC REDinREN RD016/0009 Fondos FEDER, FRIAT, Sociedad Española de Nefrología, Comunidad de Madrid B2017/BMD-3686 CIFRA2-CM.

CONFLICT OF INTEREST STATEMENT

P.A.S. is an advisor/speaker for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Elpen Pharmaceuticals, Genesis Pharma, Menarini, Innovis Pharma and Winmedica and has received research support for an investigator-initiated study from AstraZeneca. A.O. is a consultant for Sanofi Genzyme and received speaker fees from Shire, Amicus, Amgen, Otsuka, Mundipharma, Fresenius Medical Care and Menarini.

REFERENCES

- World Health Organization. *Global Report on Diabetes*. 2016. <http://www.who.int/diabetes/global-report/en/> (19 September 2019, date last accessed)
- Kramer A, Pippias M, Noordzij M *et al.* The European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015: a summary. *Clin Kidney J* 2018; 11: 108–122
- Loutradis C, Papadopoulou E, Theodorakopoulou M *et al.* The effect of SGLT-2 inhibitors on blood pressure: a pleiotropic action favoring cardio- and nephroprotection. *Future Med Chem* 2019; 11: 1285–1303
- Sarafidis P, Ferro CJ, Morales E *et al.* SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant* 2019; 34: 208–230
- Perkovic V, Jardine MJ, Neal B *et al.* Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306
- Fernandez-Fernandez B, Fernandez-Prado R, Górriz JL *et al.* Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation and Study of Diabetic Nephropathy with Atrasentan: what was learned about the treatment of diabetic kidney disease with canagliflozin and atrasentan? *Clin Kidney J* 2019; 12: 313–321
- Davies MJ, D'Alessio DA, Fradkin J *et al.* Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; 41: 2669–2701
- Herrington WG, Preiss D, Haynes R *et al.* The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. *Clin Kidney J* 2018; 11: 749–761
- Zinman B, Wanner C, Lachin JM *et al.* Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128
- Neal B, Perkovic V, Mahaffey KW *et al.* Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657
- Wiviott SD, Raz I, Bonaca MP *et al.* Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357
- Nitzan O, Elias M, Chazan B *et al.* Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. *Diabetes Metab Syndr Obes* 2015; 8: 129–136
- Davis-Ajami ML, Pakyz A, Wu J *et al.* A payer perspective of the costs of urinary tract and skin and soft tissue infections in adults with diabetes and the relationship to oral antidiabetic medication nonadherence. *J Manag Care Spec Pharm* 2019; 25: 1409–1419
- U.S. 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*. 4 December 2015. <http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm> (19 September 2019, date last accessed)
- Summary of product characteristics. Jardiance. https://www.ema.europa.eu/en/documents/product-information/jardiance-epar-product-information_en.pdf (25 September 2019, date last accessed)
- Summary of product characteristics. Invokana. https://www.ema.europa.eu/en/documents/product-information/invokana-epar-product-information_en.pdf (25 September 2019, date last accessed)
- Summary of product characteristics. Forxiga. https://www.ema.europa.eu/en/documents/product-information/forxiga-epar-product-information_en.pdf (25 September 2019, date last accessed)
- 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: 503–514
- Dave CV, Schneeweiss S, Kim D *et al.* Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections. A population-based cohort study. *Ann Intern Med* 2019; 171: 248–256
- Kyriacou DN, Lewis RJ. Confounding by indication in clinical research. *JAMA* 2016; 316: 1818–1819