

# Incidence of severe urinary tract infections not increased by initiating sodium–glucose cotransporter 2 inhibitors

Recently, the Food and Drug Administration issued an advisory that sodium–glucose cotransporter 2 (SGLT-2) inhibitors are associated with a risk of severe urinary tract infection (UTI)<sup>1</sup>. They reported 19 patients with life-threatening sepsis due to UTI and severe pyelonephritis after initiating SGLT-2 inhibitors who required hospitalization. Some of them required admission to an intensive care unit or dialysis in order to treat acute renal failure.

An increased risk of genital infection due to initiating SGLT-2 inhibitors has been reported in many studies<sup>2</sup>. However, the risk of severe upper UTI due to initiating SGLT-2 inhibitors was not significant in most of the studies, although some showed a higher risk<sup>2</sup>. Therefore, whether SGLT-2 inhibitors are associated with an increased risk of UTI remains controversial.

After the Food and Drug Administration's advice, Dave *et al.*<sup>3</sup> carried out a population-based cohort study to examine whether patients initiating SGLT-2 inhibitors had an increased risk for severe UTI events. The study included a large number of patients with type 2 diabetes who initiated SGLT-2 inhibitors: 123,752 in cohort 1 and 111,978 patients in cohort 2. The study was based on patients with commercial insurance in the USA, and compared the incidence rate of severe UTI between those using SGLT-2 inhibitors and other second-line antidiabetic drugs; that is dipeptidyl peptidase-4 inhibitors in cohort 1 and glucagon-like peptide-1 receptor agonists in cohort 2,

matched by the propensity score in each pair-wise comparison. In cohort 1, the incidence rate of severe UTI per 1,000 person-years was 1.76 for SGLT-2 inhibitors and 1.77 for dipeptidyl peptidase-4 inhibitors. In cohort 2, the incidence rate per 1,000 person-years was 2.15 for SGLT-2 inhibitors and 2.96 for glucagon-like peptide-1 receptor agonists. They concluded that there was no significantly increased risk of severe UTI due to initiating SGLT-2 inhibitors.

Genitourinary infection means genital infection and UTI. The two infections are different with respect to the pathophysiology. The risk of genital infection evidently increases with the use of SGLT-2 inhibitors<sup>2,4</sup>. This might be caused by an increased amount of glucose in the urine that could be a substrate for bacteria to grow on the genital epithelium. It is also considered that, in cases of developing vaginal infection, the function of the vaginal epithelium to block bacterial growth might be impaired by long-term diabetes, which includes aging, hormonal imbalance, microvascular complications and a decreased immune response<sup>4</sup>. Upper UTI might be caused by the reflux of bacteria from the lower urinary tract if conditions, such as renal abscess, renal papillary necrosis and renal emphysematous pyelonephritis, do not exist. Asymptomatic bacteriuria in the lower urinary tract has been reported to be associated with diabetes<sup>5</sup>, and could be aggravated by an increased amount of urinary glucose caused by SGLT-2 inhibitors. However, it remains unclear whether the impairment of protection against bacteria reflux, which might lead to upper UTI, could be more frequent in patients with diabetes.

The incidence rates of genital infection and severe UTI in patients with the use

of SGLT-2 inhibitors are absolutely different (Table 1). The incidence of severe UTI in the present study<sup>3</sup> was approximately 2.0 per 1,000 person-years, which is markedly lower than that of genital infection (50–900 per 1,000 person-years, depending on whether it is symptomatic and on the studies)<sup>2,4</sup>. The present study is valuable in that it explored the very rare incidence rate of severe UTI through a large number of patients by adjustment for confounding factors using the propensity-match scoring method. Indeed, no such longitudinal study that investigated the incidence rates of severe UTI in patients with type 2 diabetes has been reported.

This study prompts us to explore important clinical factors that could influence developing severe UTI. First of all, high glycosylated hemoglobin might initially be a contributing factor. Second, a diabetes-related condition that includes the duration of diabetes and the presence of microvascular complications is important. In particular, diabetic autonomic neuropathy could lead to atonic or neurogenic bladder, which is likely to cause severe upper UTI. Finally, identifying the presence of lower UTI at the baseline as a risk of developing severe upper UTI would be helpful. It remains to be elucidated whether lower UTI is a strong risk of developing severe upper UTI. Lower UTI, such as cystitis and bacteriuria, can be practically detected by the urinary leukocyte count. It is important to know whether the presence of lower UTI is associated with an increased risk of severe UTI on initiating SGLT-2 inhibitors. All these clinically relevant risk factors were unfortunately not included in the present study, as has been acknowledged by the authors.

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Received 5 November 2019; revised 16 November

2019; accepted 18 November 2019

**Table 1** | Adverse events of genital infections, urinary tract infections including both minor and severe, and severe urinary tract infections after initiating sodium–glucose cotransporter 2 inhibitors


Author	Design of study	n/N	%	Rate/1,000 patients-years	Reference
Genital infections					
Kohler <i>et al.</i>	Clinical trial	124/1,490	8.3	52.0	Cited in ref. <sup>4</sup>
Wu <i>et al.</i>	Clinical trial	1,242/19,835	6.3	NA	Ref. <sup>2</sup>
Yokoyama <i>et al.</i>	Real world practice	18/114	15.8	319.3	Ref. <sup>4</sup>
Urinary tract infections (both minor and severe)					
Kohler <i>et al.</i>	Clinical trial	422/1,490	28.3	217.0	Cited in ref. <sup>4</sup>
Wu <i>et al.</i>	Clinical trial	1,419/19,835	7.2	NA	Ref. <sup>2</sup>
Urinary tract infections (only severe)					
Dave <i>et al.</i>	Population-based (cohort 1)	61/16,147	0.4	1.76	Ref. <sup>3</sup>
Dave <i>et al.</i>	Population-cased (cohort 2)	73/14,645	0.5	2.15	Ref. <sup>3</sup>

NA, not available; Ref., reference.

The take-home message from the present study is that, in terms of adverse effects of the use of SGLT-2 inhibitors, the incidence rates of severe UTI and genital infection are different, and the risk of severe UTI might not be increased with the use of SGLT-2 inhibitors in patients with diabetes. The incidence of severe UTI itself is rare, and it still remains important to caution against the incident case with severe UTI, and consider whether severe UTI is associated with diabetes and the use of SGLT-2 inhibitors in daily clinical practice.

## DISCLOSURE

The author declares no conflict of interest.

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Doi: 10.1111/jdi.13189