Lower urinary tract symptoms should be queried when initiating Sodium Glucose
Co-Transporter 2 inhibitors

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The sodium-glucose co-transporter 2 inhibitors (SGLT2i) reduce risk of both macrovascular (myocardial infarctions and stroke) (1) and microvascular events (progression of chronic kidney disease) (2) in persons with type 2 diabetes. The beneficial effects of SGLT2i are derived from a cascade of effects subsequent to inhibition of glucose reabsorption in the S1 segment of the proximal tubule. Clinical trials have shown that SGLT2i reduce the absolute risk of kidney failure by 35% relative to placebo (95% CI 54%, 81%).(2) Thus, SGLT2i may be one of the most important interventions provided for adults at high risk for kidney failure. With any intervention, side effects and adverse effects must be considered in order to identify patients appropriate for the intervention and ensure that treated patients are educated regarding potential side effects and the appropriate coping mechanisms for bothersome side effects. For the SGLT2i drug class, adverse events includes hypoglycemia, ketoacidosis, volume depletion (especially when combined with loop diuretics), and genital urinary infections.(3-6) Other important side effects that are not life threatening but nevertheless bothersome are lower urinary tract symptoms (LUTS). Below, we describe reasons why LUTS should be queried in patients before initiating SGLT2i and methods for managing LUTS in order to maintain adherence with this drug class.

Lower urinary tract symptoms include urinary frequency, and urgency with or without incontinence. Urinary urgency, or sudden urge to urinate that may or may not be accompanied by urinary incontinence is termed overactive bladder (OAB) syndrome.(7) Over 10% of older adults cope with some degree of OAB, and prevalence increases with advancing age.(7) Adults with diabetes, especially those with poor glucose control, are particularly at risk for OAB due to bladder dysfunction from neuropathy and osmotic diuresis which can lead to detrusor muscle hypertrophy and reduction in bladder storage capacity.(8) Approximately half of adults with diabetes cope with some degree of bladder dysfunction, and in a few patients, the dysfunction can progress to bladder failure necessitating bladder catheterization. (8) OAB may not be life-threatening, but OAB symptoms reduce quality of life
and add financial burden due to a lack of insurance coverage for pads and briefs.(7) Most older adults with OAB will never seek treatment due to stigma and fear of embarrassment.(7)

Nocturia, also part of LUTS, is defined as awakening from sleep at least once to urinate and it affects most older adults. In fact, over half of all adults age 65 and older void 2 or more times nightly, and prevalence and severity of nocturia may be even higher among older adults with CKD depending on the CKD stage.(9) Nocturia arises from multiple factors including disruption of nocturnal arginine vasopressin secretion, fluid intake behaviors, and decreased bladder storage capacity.(9) Due to changes in bladder wall compliance with age, the sensation of bladder fullness and urge to urinate occurs at lower bladder fill volumes. Among adults with CKD, lack of nocturnal dip in blood pressure and reduced kidney response to arginine vasopressin may also contribute to nocturia and its severity.(9) Overall, nocturia is a function of increased nocturnal urine production. Thus, medications that solely target bladder function are not effective for mitigating symptoms. Nocturia often leads to sleep disturbances and lower sleep quality and is associated with increased risk for slipping and falling. (9)

Any intervention that increases urine output, including SGLT2i, can exacerbate LUTS. SGLT2i reduces both glucose and sodium reabsorption in a 1:1 molar ratio. As the filtered glucose blocked from reabsorption by SGLT2i use travels through the tubules, glucose concentration increases as water is reabsorbed. The high tubular fluid osmolality in distal tubules then leads to a reduced osmotic gradient between the fluid inside the tubule and the fluid outside the tubule (interstitial fluid) with luminal fluid having higher osmolality.(10) Within the collecting duct, this reduction in osmotic gradient reduces passive reabsorption of water which is modulated by vasopressin. (10) In healthy adults treated for 7 days with dapagliflozin, bumetanide, or both, Hallow et al. showed that dapagliflozin increased urine volume and free water excretion.(10) The increase in free water excretion with SGLT2i did not increase blood sodium concentrations and the investigators hypothesized that the lack of change in blood sodium
concentrations is due to redistribution of sodium to peripheral storage sites and/or inhibition of Na\(^+/\)H\(^+\) exchanger 3 sodium reabsorption. (10)

Most people will not experience large and sustained increases in urine output with SGLT2i. (11) In fact, among persons with normal extracellular volume, urine volume increases modestly during the first few days of SGLT2i use and then returns to baseline levels after a week. (10) SGLT2i use in persons with expanded extracellular volume may show a more robust and sustained increase in urine volume. In a study of 30 patients with type 2 diabetes and kidney disease, those with a high ratio of bioimpedance measured extracellular weight to total body weight (> 0.4) showed significantly greater reductions in extracellular body weight with dapagliflozin administration compared to those with a low ratio (≤ 0.4); this association was not noted with administration of loop diuretics (≤ 0.4). (12)

In the RECEDE-CHF trial, a randomized controlled trial of empagliflozin in patients with diabetes and heart failure treated with loop diuretics, empagliflozin use was associated with an approximate 500 ml/day increase in urine volume compared to placebo. (13) This increase in urine output with SGLT2i use occurred within a day of drug initiation and was sustained at 6 weeks. The increase in urine output was due to higher free water clearance with no significant differences in fractional excretion of Na noted between empagliflozin and placebo arms. (13) Total blood volume with empagliflozin did not appear to change as reflected by stable levels of serum urea and hematocrit. Fluid intake was not assessed.

Due to the initial diuresis with SGLT2i, patients may be counseled by providers to drink more fluid after initiating these drugs. Recommendations to increase fluid intake is often unnecessary because diuresis appears transient in most situations. Loop diuretic medications may need to be reduced with initiation of SGLT2i to reduce diuresis and patients should pause SGLT2i use during an acute illness to
prevent volume depletion. In contrast, encouraging fluid intake with SGLT2i use could be harmful. Animal models have shown that increased free water excretion with SGLT2i may increase vasopressin levels, thirst, and fluid intake. Both increased thirst and increased urine output have been reported as adverse effects with SGLT2i. Coaching patients to drink a lot of water after initiation of SGLT2i may lead to higher urine output which could exacerbate LUTS and lead to drug discontinuation or noncompliance.

Few studies have reported the impact of SGLT2i use on LUTS outside of clinical trials, but one case series of 50 men with type 2 diabetes reported an increase in urinary frequency and nocturia after initiating SGLT2i with almost all men affected. Increased urination and nocturia in clinical trials with canagliflozin was reported in 5.1% with the 100-mg dose and 4.6% with the 300-mg dose vs. 0.7% with placebo. All other SGLT2i also showed higher rates of increased urination vs. placebo but definitions of increased urination differed across drugs. Because LUTS are so prevalent among older adults with diabetes, the low reported rates of such symptoms among participants in the clinical trials reflects the better overall health of clinical trial participants compared to the general population with diabetes. Thus, LUTS may be more frequent when SGLT2i are instituted in clinical practice vs. rates reported in clinical trials. Currently, information on exacerbation of LUTS and the requirement to alter or terminate use of SGLT2i due to LUTS remains limited.

Due to high prevalence of LUTS in adults with type 2 diabetes, providers should query the presence and severity of LUTS prior to initiation of SGLT2i, especially in patients 75 years and older. SGLT2i use should be avoided in adults with severe LUTS such as poor bladder contractility and need for catheterization or frequent urinary incontinence requiring use of adult briefs and pads. The requirement for bladder catheterization will increase the risk of UTIs with SGLT2i while severe urinary
incontinence with frequent use of adult briefs or pads will increase susceptibility to mycotic genital infections. When LUTS is not severe enough to preclude SGLT2i use, patients should be educated that SGLT2i may increase thirst and or urine output and potentially exacerbate existing LUTS such as urinary frequency and nocturia. However, such symptoms can often be managed with behavior modifications such as restriction of fluid intake if fluid intake is excessive and avoidance of drinking liquids for several hours prior to bedtime. Due to the dangers of falls in frail adults with nocturia, patients with nocturia should be counseled to use a nightlight to brighten the route to the bathroom, wear slippers or shoes when going to the bathroom, and remove all loose rugs and items in bathroom route.

In summary, SGLT2i reduce risk of kidney disease progression and cardiovascular disease including heart failure in adults with type 2 diabetes. This drug class can increase urine output that may exacerbate LUTS, a common problem among older adults with diabetes. Discussions of LUTS with patients prior to SGLT2i initiation will ensure that providers identify patients who should not be treated with this drug class and help treated patients cope with bothersome side effects such as LUTS to ensure medication continuance and compliance.
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<thead>
<tr>
<th>Medication</th>
<th>Listed Adverse Reactions</th>
<th>Most Common Adverse Reactions (&gt;5% incidence)</th>
<th>Increased Urination</th>
<th>Definition of Increased Urination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>Hypotension, ketoacidosis, AKI, urosepsis/pyelonephritis, Fournier’s gangrene, genital mycotic infections, hypersensitivity reactions, increased LDL</td>
<td>Female genital mycotic infections, urinary tract infections</td>
<td>3.4%/3.2% (10 mg/25 mg) compared to 1.0% placebo. N=1976 in pool of four 24-week placebo-controlled trials</td>
<td>Polyuria, pollakiuria and nocturia</td>
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<td>(Jardiance)(3)</td>
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<tr>
<td>Ertugliflozin</td>
<td>Hypotension, ketoacidosis, AKI, urosepsis/pyelonephritis, lower limb amputation, hypoglycemia, genital mycotic infections, increased LDL</td>
<td>Female genital mycotic infections</td>
<td>2.7%/2.4% (5 mg/15 mg) compared to 1% placebo. N=1029 in pool of three 26-week trials.</td>
<td>Pollakiuria, micturition urgency, polyuria, increased urine output, and nocturia</td>
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<td>(Steglatro)(4)</td>
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<td>Canagliflozin</td>
<td>Lower limb amputation, hypotension, ketoacidosis, AKI, urosepsis/pyelonephritis, hypoglycemia, Fournier’s gangrene, genital mycotic infections*, hypersensitivity reactions, bone fracture</td>
<td>Female genital mycotic infections Urinary tract infections Increased urination</td>
<td>5.1%/4.6% (100 mg/300 mg) compared to 0.7% placebo. N=1667 in pool of four 26-week placebo-controlled trials</td>
<td>Polyuria, pollakiuria, increased urine output, micturition urgency and nocturia</td>
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<tr>
<td>(Invokana)(5)</td>
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<td>Dapagliflozin</td>
<td>Hypotension, ketoacidosis, AKI, urosepsis/pyelonephritis, hypoglycemia, Fournier’s gangrene, genital mycotic infections*</td>
<td>Female genital mycotic infections Urinary tract infections Nasopharyngitis</td>
<td>2.9%/3.8% (5 mg/15 mg) compared to 1.7% placebo. N=2338 in pool of twelve 12-24 week placebo-controlled trials</td>
<td>Pollakiuria, polyuria and increased urine output</td>
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<td>(Farxiga)(6)</td>
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*Female genital mycotic infections include: vulvovaginal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, vulvovaginitis, vaginal infection, vulvitis, and genital infection fungal; Male genital infections include: balanitis or balanoposthitis, balanitis candida, and genital infection fungal.