

**Real-life prescribing of SGLT2 inhibitors: How to handle the other medications, including  
glucose-lowering drugs and diuretics**

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## **Introduction**

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have emerged as an effective therapy for improving outcomes in diabetic and non-diabetic kidney disease (1, 2). Clinical trials have demonstrated the benefits of SGLT2is for secondary prevention of adverse cardiovascular (CV) effects in patients with established atherosclerotic disease and/or heart failure with reduced ejection fraction (3-7). It is imperative for clinicians to assess the use of SGLT2is in medically eligible patients and prescribe these agents when appropriate.

Despite the overwhelming evidence of the benefits of SGLT2i therapy, the prescription rate remains dismally low particularly among patients most likely to benefit from cardiorenal protective effects (8). Several potential factors contribute to low SGLT2i prescription rate including prescriber hesitancy, treatment inertia and high drug cost. In this article, we review clinical indications for SGLT2i use, therapeutic and adverse effects, and our approach to handling concomitant medications.

## **Clinical indications for SGLT2i Use**

1. *Type 2 diabetes mellitus (T2DM) and albuminuric kidney disease (albuminuria of  $\geq 200$  mg/gram of creatinine plus eGFR of 25 – 90 ml/min/1.73 m<sup>2</sup>). In the CREDENCE Trial, Canagliflozin decreased the primary cardiorenal endpoint by 30% compared to placebo*

in patients with diabetic kidney disease (1). In the DAPA-CKD trial, Dapagliflozin reduced the primary cardiorenal endpoint by 39% compared to placebo in patients with diabetic and non-diabetic kidney disease (2).

2. *Non-diabetic albuminuric kidney disease (albuminuria  $\geq 200$  mg/day plus eGFR of 25 - 75 ml/min/1.73 m<sup>2</sup>).* In the DAPA-CKD trial, one third of the patients did not have T2DM and the cardiorenal benefits of Dapagliflozin were similar among patients with non-diabetic and diabetic kidney disease (2).
3. *T2DM with cardiovascular disease.* In the EMPA-REG and CANVAS trials, Empagliflozin and Canagliflozin demonstrated a 14% reduction in the primary endpoint of major adverse cardiac events in patients with history of CV disease (3, 4). In DECLARE-TIMI, Dapagliflozin reduced the risk of CV death and hospitalization for heart failure by 17% in patients who had or were at risk for atherosclerotic heart disease (5).
4. *Heart failure with reduced ejection fraction.* In the DAPA-HF trial, Dapagliflozin reduced worsening of heart failure and CV death by 26% in patients with ejection fraction of  $\leq 40\%$  (6). In EMPEROR-Reduced trial, Empagliflozin reduced the primary outcome of CV death and hospitalization for heart failure by 25% in patients with ejection fraction of  $\leq 40\%$  (7).
5. *T2DM and hyperglycemia.* Several professional society guidelines recommend using SGLT2i as either first-line therapy or as an add-on therapy to Metformin, for management of hyperglycemia in patients with T2DM (9-11).

Once the appropriate clinical indications are identified, patients should be screened for conditions that increase risk for adverse effects of SGLT2is. Such conditions include cognitive impairment, advanced age, limited mobility, recurrent urinary tract infections (UTIs), indwelling foley catheter, neurogenic bladder, poor genital hygiene, solitary kidney, bilateral renal artery stenosis, immunosuppressive therapy, and history of diabetic ketoacidosis (DKA). Patients with these underlying conditions must be assessed on an individual basis, weighing the risks and benefits of SGLT2i therapy. The safety of SGLT2is have not been established in kidney transplant recipients, pregnant or lactating women.

### **Therapeutic and Adverse Effects of SGT2is**

SGLT2is cause glucosuria and moderate natriuresis by blocking the sodium-glucose co-transporter-2 in the proximal tubule causing reduction in blood pressure (BP), blood glucose, proximal tubule workload, and weight. SGLT2is confer cardiovascular, renal and metabolic benefits, though the precise underlying mechanistic underpinnings remain to be fully elucidated.

Prior to initiation of SGLT2is, the patient's BP, volume status and blood glucose control must be assessed. SGLT2is must not be initiated in hypotensive/hypovolemic patients. In hypotensive patients, the anti-hypertensive medications, including diuretics may need to be stopped or reduced to restore normotension. If the patient is hypervolemic/hypertensive, then SGLT2i

therapy can be initiated without adjusting the dose of other anti-hypertensive medications. If the patient is euvolemic/normotensive then the anti-hypertensive agents, including diuretics, may need to be reduced or stopped if the BP decreases. The BP lowering and natriuretic effect of SGLT2is is modest resulting in ~ 3-5mm Hg reduction in systolic BP (Figure 1). In the SGLT2i CV and kidney outcome trials, patients were required to be on maximally tolerated dose of renin angiotensin system (RAS) blockers prior to randomization to the SGLT2i or placebo groups. A similar strategy to continue RAS blockers must be adopted in clinical practice. Monotherapy with SGLT2i is reasonable in patients who are unable to tolerate RAS blockers.

SGLT2i therapy can cause an acute drop in eGFR, however subsequently the decline in eGFR is attenuated with continuation of SGLT2i therapy. In the absence of hemodynamic instability or an alternate cause of acute kidney injury (AKI), the initial decline in eGFR of up to 30% following SGLT2i initiation is likely due to reduction in intra-glomerular pressure. It may be difficult to distinguish whether the decline in eGFR is due to the hemodynamic effect SGLT2i or due to AKI. Periodic monitoring of the kidney function over 2-4 weeks can help in distinguishing these two entities as the decline in eGFR due to the hemodynamic effects of SGLT2is is typically not progressive. In the absence of hemodynamic instability, SGLT2i do not increase the risk of AKI. In fact, an overall reduction in AKI has been observed with SGLT2i use (12).

Prescriber hesitancy due to concern for hypoglycemia can be decreased by following a simple SGLT2i initiation strategy (Figure 1). Patients already on glucose-lowering agents require

assessment of current glycemic control along with the underlying risk factors for hypoglycemia. Glycemic control is typically determined by the Hemoglobin A1C (HbA1C) level but patients with chronic kidney disease, liver disease, erythrocyte disorders and those with frequent hypoglycemic episodes can have falsely low HbA1c values rendering the test unreliable. In such cases, fructosamine levels, self-monitored blood glucose readings, or continuous glucose monitor data must be used. In most non-pregnant adult patients, an HbA1C target of less than 7% is reasonable but for those at high risk of hypoglycemia, a less stringent HbA1C target of less than 8% can be used (13, 14).

The risk of hypoglycemia is not increased in patients only taking Metformin, Dipeptidyl peptidase 4 inhibitors, Glucagon-like peptide-1 receptor agonist and Thiazolidinediones, hence these agents do not require dose adjustment at the time of SGLT2i initiation. On the other hand, Insulin, Sulfonylurea (SU) and Meglitinides (Mgl) increase the risk of hypoglycemia and require dose adjustment at the time of SGLT2i initiation in patients with optimal glycemic control or already experiencing hypoglycemia. In such patients, SU/Mgls must either be stopped, or the dose decreased by 50%, and Insulin doses, particularly the rapid acting (bolus) insulin for patients on a traditional basal-bolus insulin regimen, must be reduced by 10-20%. Patients only using basal insulin can have their doses reduced by 10%. A stepwise dose reduction strategy of insulin doses is preferred rather than complete discontinuation to mitigate the risk of DKA. Patients who are above their glycemic target without frequent

hypoglycemia, should not require dose adjustment of other anti-glycemic agents at the time of SGLT2i initiation. All patients should be counseled on the risk, identification, and treatment of hypoglycemia. It is worth noting that SGLT2is have not been shown to cause hypoglycemia in patients without diabetes (2, 6).

In the SGLT2i trials, the absolute risk of DKA in T2DM is low but the relative risk of DKA associated with SGLT2is has been 2-11 times higher compared to placebo (1, 3-5). The DKA associated with SGLT2i can be euglycemic (blood glucose of less than 250 mg/dL) and its diagnosis is established by the presence of a high anion gap metabolic acidosis and ketonemia. The absence of hyperglycemia can cause a diagnostic delay; any patient on a SGLT2i with symptoms of DKA such as nausea, vomiting, and abdominal pain should be evaluated for euglycemic DKA (euDKA). The pathogenesis of SGLT2i induced euDKA is thought to be due to SGLT2i-induced suppression of insulin, increase in glucagon and masking of hyperglycemia due to enhanced glucosuria (15). It is important to note that DKA has not been observed in patients without diabetes in the large SGLT2i trials.

Patients must be counseled to monitor their BP, weight and blood glucose at home when initiating SGLT2is (Table 1). SGLT2is must not be initiated or continued in hypovolemic patients. Patients must be advised to hold SGLT2is when their oral intake of food and water is restricted due to a planned surgery or due to an underlying illness in order to prevent DKA, hypovolemia and hypotension – this is also referred to as the ‘Sick-day Rule’.

SGLT2i therapy must be initiated at the lowest recommended daily dose (Empagliflozin 10 mg, Canagliflozin 100 mg, Dapagliflozin 5 mg or Ertugliflozin 5 mg). SGLT2i titration to a higher dose is not necessary for maximal cardiorenal benefits (3). Although a higher dose of SGLT2i can be used to improve glycemic control, it is important to recognize that the glucose-lowering effect of SGLT2i declines at lower eGFR. Based on the evidence from CREDENCE and DAPA-CKD trials, once the SGLT2i therapy is initiated at the recommended level of eGFR then it can be continued till the patient initiates dialysis therapy.

Due to its glucosuric effect, SGLT2is increase the risk of genital mycotic infections by 3-4-fold in patients with diabetes. The vast majority of the SGLT2i related genital mycotic infections are treatable with topical anti-fungal agents or single oral dose of Fluconazole, and do not necessitate discontinuation of SGLT2i therapy. Clinicians must counsel the patients regarding maintenance of genital hygiene (Table 1). It is not known if SGLT2is increases the risk of genital mycotic infections among non-diabetic patients.

Fournier's gangrene is a serious medical condition, and it remains unclear whether SGLT2is increase the risk of Fournier's gangrene or not, however it is worth noting that such an association has not been observed in any of the large SGLT2i clinical trials.

SGLT2is do not increase the risk of UTIs, however their use in patients at high risk for UTIs, such as those with an indwelling foley catheter, recurrent UTIs, neurogenic bladder, has not been studied.

SGLT2is and their association with bone fractures and lower extremity amputation remains weak as this association was only been observed with the use of Canagliflozin in the CANVAS Trial, and not in the other large SGLT2i Trials.

### **Conclusion**

SGLT2is offer cardiorenal protection for patients with and without T2DM. Employing a simple strategy for assessing the risks, and modifying ant-hypertensive, diuretic, anti-glycemic agents can mitigate the potential adverse effects of SGLT2is. With the growing evidence for safe use and renal protective effects of SGLT2is, Nephrologists now have a therapeutic agent to combat the pandemic of diabetic kidney disease.

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**Table 1. Handout for the Patients when initiating Sodium Glucose Cotransporter-2 Inhibitor Therapy**

- **Increase in Urine Output**
  - You may notice an increase in your urine output after starting this medication
  - Monitor your weight at home
  
- **Blood Pressure**
  - Monitor your blood pressure at home as this medicine may lower blood pressure
  - Inform your doctor if your blood pressure is too low, or if you experience light-headedness or dizziness
  
- **Blood Glucose**
  - Monitor your blood glucose level at home as this medicine may lower blood glucose
  - Inform your doctor if your blood glucose is low
  
- **Follow the 'Sick Day Rule'**
  - On days that you are unable to eat because you are feeling sick due to fever, infection, poor appetite, nausea, vomiting or diarrhea then hold this medicine.
  - You can resume the medicine once you are able to eat and drink.
  - If you continue to feel sick, then call your doctor as you may need to have blood tests to rule out Diabetic ketoacidosis
  
- **Stop the medication 3 to 4 days before a scheduled surgery that requires you to be NPO (meaning you are instructed to not eat or drink anything for several hours before your surgery)**
  
- **Avoid very low Carbohydrate diet and Keto diet as it may increase the risk of Diabetic Ketoacidosis**
  
- **Wound on your feet or legs**
  - If you notice a wound, ulcer or skin breakdown on your feet or legs, then hold this medicine and inform your doctor
  
- **Burning or pain during urination**
  - If you experience pain or burning on urination, then inform your doctor as you may need further evaluation
  
- **Redness or itching in the genital area, or foul smelling vaginal or penile discharge**
  - Keep the genital area clean
  
  - If you notice redness or itching in the genital area, or foul-smelling vaginal or penile discharge, then inform your doctor. You may need a cream or oral medication to treat an underlying infection

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**Figure 1.** Algorithm for Sodium Glucose Co-transporter-2 Inhibitor Initiation

