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Sodium-Glucose Co-transporter 2 Inhibitors: Safety Considerations and Clinical Implications for Healthcare Providers

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Learning Objectives
•Recall fundamental nephron anatomy and physiology
•Describe clinical implications associated with SGLT inhibitors
•Discuss the key evidence behind clinical implications
•Identify which patient populations would apply to these considerations

Abstract

Sodium-Glucose Co-transporter-2 inhibitors have been adopted into the most recent American Diabetes Association Guidelines as a now integral part of diabetes care. These medications may be involved in effective strategies to lower glycosylated hemoglobin (A1C), blood glucose, long-term neuropathies and other diabetic complications. Specifically, these drugs have recently been accepted as the drugs of choice in diabetes care for those with cardiovascular comorbidities. Additionally, recent updates regarding Black Box Warnings with canagliflozin have stated it may cause long term increases in the overall number of amputations. Knowledge concerning the new guidelines and the clinical implications with this class of drugs is essential to providing patient care and optimizing outcomes for patients suffering from type two diabetes mellitus.

There are approximately 30.3 million Americans with type two diabetes mellitus (T2DM) in the world today. This statistic tells us that nearly one in ten people in the United States has T2DM. Research involving safe and effective drug products that may benefit this population have serious implications to the health of our country. A specific class of medications used to treat T2DM are the Sodium Glucose Cotransporter-2 (SGLT-2) inhibitors. Agents within this class include empagliflozin, canagliflozin, and dapagliflozin. Canagliflozin and dapagliflozin have received an FDA indication for the treatment of T2DM, and empagliflozin has received an FDA indication for the treatment of T2DM and reduction of cardiovascular (CV) mortality.

SGLT2 agents exert their glucose lowering effects through a unique mechanism. To understand this mechanism, recall the anatomy and physiology of the nephron. The nephron is the functional unit of the kidney and is composed of many distinct sections that are involved in the filtration and reabsorption of waste and electrolytes. The glomerulus, the proximal convoluted tubule, the Loop of Henle, the distal convoluted tubule, and the cortical collecting ducts are the major sections that make up a nephron. The proximal convoluted tubule contains the SGLT2 transporter and is responsible for glucose reabsorption. This transporter serves as an attractive pharmacologic target as there is evidence of increased expression and activity of the transporter in the presence of hyperglycemia. [1] Inhibition of these channels inhibits glucose reabsorption and lowers the renal threshold for glucose. This subsequent decrease in glucose reabsorption (30-50%) into the bloodstream and urinary excretion has been shown to positively affect patients' blood glucose who have been diagnosed with T2DM.[1] Current evidence suggests a modest but beneficial A1C reduction in T2DM patients in the range of 0.5-1.0%.

As these agents become more widely used in practice, it is important to be aware of clinical implications and nonglycemic outcomes when using these agents in patients with T2DM. Major clinical implications to take into consideration include CV benefits, changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), weight loss, dehydration, diabetic ketoacidosis, bone fractures, renal effects, and potentially severe urinary tract infections.[1-4]

Studies in the past decade have analyzed these clinical endpoints, with The Rationale, Design, and Baseline Characteristics of a Randomized, Placebo-controlled Cardiovascular Outcome Trial of Empagliflozin (EMPA-REG OUTCOME). This study included important cardiovascular outcomes relevant to T2DM patients. The EMPA-REG OUTCOME trial evaluated CV outcomes associated with SGLT2 inhibitors used in T2DM patients with cardiovascular disease (CVD) with the primary outcome of a composite of CV death, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke.[1,2] Collectively, the trial consisted of 7020 patients enrolled and treated with a median treatment time of 2.6 years with a total of 772 outcome events.[2] Noninferiority for the primary outcome was determined if the upper boundary of the confidence interval was less than 1.3.[2] The trial demonstrated that CV related deaths occurred in a significantly

lower proportion of patients receiving empagliflozin versus those receiving placebo (10.5% vs 12.1%; hazard ratio [HR] 0.86, 95.02%, CI 0.74–0.99, p<0.001 for noninferiority; p=0.04 for superiority).[2] The rate of myocardial infarctions and strokes were not significantly reduced with empagliflozin versus placebo (4.8% vs 5.4%; HR 0.87, 95% CI 0.70–1.09, p=0.23, and 3.5% vs 3.0%; HR 1.18, 95% CI 0.89–1.56, p=0.26 respectively). However, when compared with placebo, there was a 38% relative risk reduction in CV mortality in the empagliflozin group (3.7% for empagliflozin vs 5.9% for placebo; HR 0.62, 95% CI 0.49–0.77, p<0.001), a 35% relative risk reduction in hospital admission for heart failure (2.7% for empagliflozin vs 4.1% for placebo; HR 0.65, 95% CI 0.50–0.85, p=0.002), and a 32 percent relative risk reduction in death from any cause (5.7% for empagliflozin vs 8.3% for placebo; HR 0.68, 95% CI 0.57–0.82, p<0.001).[2] The mechanism of said benefits is unclear.[5]

Additionally, the Canagliflozin Cardiovascular Assessment Study (CANVAS) program (consisting of both the CANVAS and renal outcome specific CANVAS-R trials) was designed to compare canagliflozin vs placebo and subsequent CV and renal outcomes.[6] The primary outcome measured was a composite of death from CV disease, nonfatal myocardial infraction, and nonfatal stroke. The study concluded that the primary outcome was lower when comparing canagliflozin vs placebo. The primary outcome occurred in 26.9 vs 31.5 participants per 1000 patient years (HR, 0.86; 95% CI, 0.75 to 0.97; p<0.001 for noninferiority, p=0.02 for superiority). CV safety was to be shown if the upper boundary of the 95% confidence interval of the hazard ratio with canagliflozin as compared with placebo was less than 1.3, and superiority was to be shown if the upper boundary was less than 1.0.[6] Due to the hazard ratio of 0.86, this study concludes that there was cardiovascular superiority demonstrated by the administration of canagliflozin to T2DM patients.

In terms of blood pressure changes, studies have demonstrated a reduction of SBP and DBP without a compensating increase in heart rate.[1] The mechanism of both systolic and diastolic blood pressure reduction is not well understood, but it is thought to be due to modest osmotic diuresis and mild natriuresis.[1] These effects are important to take into consideration in patient populations who are already susceptible to volume depletion. These patients include those with renal impairment, concomitant diuretic use, elderly patients, and patients taking Renin-Angiotensin-Aldosterone-System (RAAS) modulators.

Previously described volume depletion is likely not a contributing factor to weight loss, as changes in blood pressure are typically seen long before quantifiable weight loss occurs. These agents have demonstrated weight loss properties in patients taking them.[1] In clinical trials, weight loss was sustained for up to 104 weeks in patients taking SGLT2 inhibitors.[1] Weight loss is thought to be due to medication induced urinary glucose excretion, resulting in a loss of approximately 200kcal/day in caloric load.[1]

In the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 inhibitors (CVD-REAL) study, over 300,000 participants across 6 different

countries were enrolled to evaluate whether long term clinical outcomes were better when a diabetic patient was started on an SGLT2 inhibitor versus another diabetic medication.[5] It was found that SGLT2 inhibitors reduced the risk of hospitalization caused from heart failure by about 39% and reduced all-cause mortality by 51%.[5] These numbers reflect a sample that was tested with primarily canagliflozin (53%) and dapagliflozin (42%), with empagliflozin reflecting only about 5% of the sample.

A secondary analysis of the EMPAREG OUTCOME trial also found substantial benefit on progression of kidney outcomes.[7] There appeared to be a protective effect on estimated glomerular filtration rate (eGFR), with a lower rate of decline in the empagliflozin group compared to placebo group.[7] Of the treated patients 59% had normoalbuminuria at baseline, 29% had microalbuminuria, and 11% had macroalbuminuria. Reductions in urinary albumin-to-creatinine ratios of 7%, 25%, and 32% were seen after 12 weeks of treatment in the normo-, micro- and macroalbuminuria groups, respectively.[7] These reductions were maintained after a median follow-up of 3.1 years.[7] The general hypothesis is that a reduction of albuminuria following an intervention is primarily reflecting a reduction in intraglomerular pressure, thereby decreasing filtration of large proteins such as albumin.[7] This in turn leads to a reduction in inflammation, endothelial dysfunction, oxidative stress and fibrosis, leading to less long-term damage to the kidney.[7] This data is supported by the CANVAS-R study. The purpose of this study was to assess the effect of canagliflozin compared to placebo on the progression of albuminuria in T2DM patients who have inadequate glucose control and are at an elevated risk of cardiovascular disease but have had standard diabetes care. Results for the primary endpoint of the progression to micro or macoalbuminuria with an albumin/creatinine ratio of greater than 30% from baseline showed no statistically significant change, but did show modest benefit in renal outcomes (HR 0.73; 95% CI 0.67-0.79).

Since these agents require adequate renal function to be effective in hyperglycemia management, their use is contraindicated in patients with severe renal impairment (those patients with an eGFR of <30mL/min/1.73m2) and those requiring dialysis.[1,8] It is recommended to avoid starting canagliflozin or empagliflozin in patients with moderate impairment (those patients with an eGFR of <45 mL/min/1.73m^2).[1,8] No dosage adjustment is needed for empagliflozin if eGFR is ≥ 45 ml/minute/1.73 m^2, whereas the dose of canagliflozin is limited to 100 mg once/day in patients with moderate renal impairment or CKD with an eGFR of 45 to < 60 ml/minute/1.73 m^2. Dapagliflozin should not be initiated if the eGFR is <60 ml/minute/1.73 m^2 and is not recommended if eGFR is persistently between 30 and < 60 ml/minute/1.73 m^2.[1] Renal function should be assessed before the initiation of SGLT2 inhibitor therapy and subsequently monitored on a regular basis.[1]

In a study from the University of Birmingham Diabetes Centre, the effect of empagliflozin in treatment of patients with CKD stage 2 and stage 3 achieved reductions in HbA1c, but no change in HbA1c was observed in patients with stage

4 CKD.[1,9] Canagliflozin use in patients with T2DM and stage 3 CKD was also analyzed in two studies and was associated with reductions in HbA1c, BP, and body weight and was generally well tolerated in this vulnerable population.[1] In both analyses (one 26-week study and one analysis of four studies of 18–26 weeks' duration), eGFR declined roughly 10–15% during the initial weeks of therapy but then returned toward baseline levels by the end of each study.[1,10,11]

Knowledge Check: True or False? SGLT-2 inhibitors have demonstrated a beneficial A1C reduction in T2DM patients up to 2 percent.

Answer: False

Black box warnings for canagliflozin and dapagliflozin include an increased risk for acute kidney injury (AKI) (and an increased risk of mineral loss resulting in bone fractures). An AKI is defined by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines as an increase in serum creatinine (SCr) of >0.3mg/dL in 48 hours, an increase in SCr more than 1.5 times baseline known to have occurred within the past seven days or a urine output of less than 0.5ml/kg/hr for 6 hours. If a patient is found to have an AKI and has been on either aforementioned SGLT2 inhibitors, it is important be aware that the SGLT2 inhibitors may have had some influence on the development of the AKI. The FDA recommends that if an AKI has occurred, then the SGLT2 inhibitor should be discontinued and if there is an infection it should be treated. Furthermore, the FDA recommends that patients should exhibit caution if taking SGLT2 inhibitors with congestive heart failure or if taking with ACE inhibitors, NSAIDs, or angiotensin receptor blockers.

Evidence has shown that some patients may be at risk for bone fractures when taking specific SGLT inhibitors. Studies show that canagliflozin may increase the risk for bone fractures in all patient populations, whereas dapagliflozin was only found to increase the risk of bone fractures in patients with some form of renal impairment.[12] According to the product label for canagliflozin, reported data does indicate an increased risk of bone fractures in patients taking 100mg doses and 300mg doses (incidence rates of 1.4 and 1.5 per 100 patient years respectively).[1,13] Currently, there is no evidence that empagliflozin causes any bone mineral density disorders. According to the CANVAS study, canagliflozin was shown to increase the concentration of a bone resorptive marker, 1 beta-carboxy telopeptide, while having very little change in parathyroid hormone and serum calcium.[13] The Invokana product label sites a study discussing changes in bone mineral density (BMD) in patients taking Invokana. The CANVAS program showed that canagliflozin increased fracture risk by 4% vs placebo at 2.6%.[13] Conversely, one meta-analysis indicated that there was no increased risk of bone fracture among T2DM patients being treated with SGLT2 inhibitors when compared with placebo.[2] The authors did indicate that results were potentially limited

by the short duration of treatment/follow up and low incidence of the event of interest. Overall, it is important to consider the clinical consequences of this information such as hospitalization, death, and/or disability, especially for patients that are at a high risk for fractures, who have a comorbidity of osteoporosis or related mineral bone disorders. These treatment studies may imply that those with a strong family history, or those with a high risk of fractures may benefit from a different therapy rather than an SGLT-2 inhibitor. In select patients, it may be more advisable to step up therapy to injectables rather than try an SGLT-2 inhibitor if the risk for amputation is high enough and clinical judgement validates the decision.

Information concerning the increase in risk for amputations was derived from the CANVAS and CANVAS R trials over longer than a five year period.[13] There were approximately 5.9 amputations per 1000 people on canagliflozin enrolled in the study compared to about 2.8 amputations per 1000 people in the placebo group. Toe and foot amputations were the most common in the study, however there were amputations involving the leg. Leg amputations were performed both above and below the knee. Some patients had more than one amputation done in the study. A new black box warning was introduced in May 2017 for canagliflozin that showed that there was an increased risk of leg and foot amputations in Type 2 Diabetic patients. This evidence has not yet surfaced for empagliflozin or dapagliflozin, however it may be important to consider clinically for patients at high risk for leg and foot amputation. Considerations before initiating canagliflozin, per the FDA, include whether or not the patient has a history of peripheral vascular disease, prior amputation, neuropathy, and diabetic foot ulcers. A possible implication of these recent results include special considerations prior to prescribing an SGLT2 inhibitor for patients at a high risk of developing a diabetic foot infection.

Overall clinical impression of the SGLT2 inhibitors as a class shows that in specific populations they can potentially be beneficial to improving patient outcomes for T2DM patient, especially in patients with a high ASCVD risk. In terms of CV health, there seems to be a small benefit to using SGLT2 inhibitors versus other medications. The EMPA-REG OUTCOME trial did demonstrate that CV related deaths occurred in a significantly lower proportion of patients receiving empagliflozin versus those receiving placebo, and the CVD-REAL study demonstrated that SGLT2 inhibitors reduced the risk of hospitalization caused from heart failure by about 39% and reduced all-cause mortality by 51%. Beneficial changes in urinary albumin-to-creatinine ratios may also be seen and maintained in patients taking empagliflozin, and could allow empagliflozin to be a possible therapeutic consideration given renal function is adequate. Conversely, SGLT2 inhibitors have varying effects in CKD patients and some evidence does suggest risk for acute kidney injury. Therefore, special consideration should be given in this patient population and these agents should be used with caution.

The CANVAS program did conclude that the composite primary outcome of death from CV disease, nonfatal myocardial infraction, and nonfatal stroke was lower with canagliflozin vs placebo, with the

primary outcome occurring in 26.9 vs 31.5 participants per 1000 patient years. With that being said, it is difficult to determine if this difference is significant enough to suggest canagliflozin over other second line agents, especially when taking into consideration the risk of amputations and fractures. Recent findings highlight the importance of taking special consideration before initiating an SGLT2 inhibitor in patients with a high risk of diabetic foot infections and those that have a history of mineral bone disorders or kidney dysfunction.

In conclusion, SGLT2 inhibitors may have more safety precautions for certain patients, however they are drugs that successfully lower A1C, blood glucose, and may lead to positive patient health outcomes. While SGLT2 inhibitors are often very well tolerated, dehydration, hypoglycemia, bone fractures, UTIs and DKA can occur and become life threatening. It is important to educate patients on signs and symptoms of these complications, what to do if any of these complications do occur, and how to prevent their occurrences. The SGLT2 inhibitors are effective drugs for lowering blood glucose and serum A1C for T2DM patients. These drugs also do not cause weight gain and may be beneficial in patients where this is a particular concern. While there seem to be various minor clinical benefits that may sway prescribers to use these agents over others especially patients with an elevated ASCVD risk, it is difficult to definitively say that these agents do cause a reduction in certain outcomes.

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