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Update on the Use of SGLT-2 Inhibitors

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The incidence of type 2 diabetes (T2D) continues to rise in adults and children. In Oregon, approximately 287,000 people have diabetes with an estimated total cost to the state of 3 billion dollars annually.[1] In 2017 there were around 220,000 cases of T2D in children, with the highest incidence in ethnic groups such as Blacks and Hispanics.[2] Pharmacotherapy is the cornerstone for management of T2D. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are often used to help lower glucose levels in those with T2D. While they are associated with moderate hemoglobin A1c (HbA1c) reductions, there is also evidence of cardiovascular (CV) and renal benefits.[3] The purpose of this newsletter is to provide updated guideline recommendations for the use of SGLT-2 inhibitors beyond glucose reductions and review evidence for two recently approved therapies, bexagliflozin and sotagliflozin.

Background

Sodium glucose cotransporter-2 inhibitors block the reabsorption of glucose from the renal glomerular filtrate in the renal proximal tubule.[4] This results in reduction in renal absorption of filtered glucose and increased urinary glucose excretion. Additionally, changes in volume status/diuresis may contribute to the mechanism of action conferring CV benefit that has been demonstrated with select SGLT2 inhibitors. Some of the additional benefits beyond glucose lowering demonstrated with SGLT-2 inhibitors include reduction in adverse CV outcomes (e.g., canagliflozin, dapagliflozin, empagliflozin and ertugliflozin*) and improvements in renal outcomes in those with diabetic nephropathy and albuminuria (e.g., canagliflozin) (**Table 1**).[3] There is also evidence of benefit for SGLT2 inhibitors in adults without diabetes for reduction in adverse HF outcomes (e.g., dapagliflozin, empagliflozin) and in people with chronic kidney disease (e.g., dapagliflozin and empagliflozin*[6]). * Not FDA indicated but evidence supports benefit in specific outcome noted.

Table 1. Approved Indications for SGLT2 Inhibitors[3]*

Indications	Drugs	Results for Approved Indications
In People with Type 2 Diabetes		
Improved glycemic control (HbA1c lowering)	Bexagliflozin (Brenzavvy™),	0.37% to 0.79%
	Canagliflozin (Invokana®),	-0.58%
	Dapagliflozin (Farxiga ®) and	-0.43%
	Empagliflozin (Jardiance ®) and	-0.3%
	Ertugliflozin (Steglatro®)	-0.48% to -0.5%
CV risk reduction in patients with T2D and established CV disease	Canagliflozin (Invokana®) and Empagliflozin (Jardiance ®)	3-point MACE: HR 0.86 (95% CI, 0.75 to 0.97) 3-point MACE: HR 0.86 (95% CI, 0.74 to 0.99)
Reduction in risk of end-stage kidney disease in patients with T2D and diabetic nephropathy with albuminuria >300 mg/day	Canagliflozin (Invokana®)	HR 0.70 (95% CI, 0.59 to 0.82)
HF risk reduction in patients with T2D and established CV disease or multiple CV risk factors	Dapagliflozin (Farxiga ®)	3-point MACE: HR 0.93 (95% CI, 0.84 to 1.03)
In People with or without Type 2 diabetes		
Reduction in risk of eGFR decline and end-stage kidney disease CV death and hospitalization for HF in patients with CKD at risk of progression	Dapagliflozin (Farxiga ®)	HR 0.61 (95% CI, 0.51 to 0.72)
HF risk reduction in patients with HF	Dapagliflozin (Farxiga ®) Empagliflozin (Jardiance ®)	HR 0.74 (95% CI, 0.65 to 0.85) HR 0.75 (95% CI, 0.65 to 0.86)*/ HR 0.79 (95% CI, 0.69 to 0.90)†
Reductions in risk of CV death, HF hospitalization and urgent HF visits in pts with HF or T2D, CKD, and other CV risk factors	Sotagliflozin (Inpefa™)	HR 0.74 (95% CI, 0.63 to 0.88)

Key: * In patients with reduced ejection fractions; † In patients with preserved ejection fractions
Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MACE = major cardiovascular adverse events; T2D= type 2 diabetes.

Guideline Recommendations

The National Institute for Health and Care Excellence (NICE) updated guidance for the use of dapagliflozin and empagliflozin in 2021 and 2022, respectively, for the management of adults with HF.[7] NICE recommends that adults with chronic HF and ejection fraction less than 40% should be offered SGLT2 inhibitors, if appropriate based on patient specific factors, along with other HF medications.

In 2022, Kidney Disease: Improving Global Outcomes (KDIGO), updated their 2020 recommendations with an emphasis on glucose lowering therapies in patients with chronic kidney disease (CKD), focusing on the use of SGLT-2 inhibitors.[8] First-line drug therapy recommendations include: SGLT2 inhibitors, metformin, renin-angiotensin-system [RAS] inhibitors and moderate- or high-intensity statins. In addition to the composite kidney outcomes (e.g., reduction in end-stage kidney disease, CV death and

hospitalizations for HF), select SGLT2 inhibitors conferred less annual estimated glomerular filtration rate (eGFR) decline and a reduction in albuminuria or decreased progression to severely increased albuminuria.[8]

KDIGO Recommendations for SGLT2 Utilization in CKD[8]:

- SGLT2 inhibitors should be used to treat people with T2D and CKD with an eGFR ≥20 ml/min per 1.73 m^2, with or without hyperglycemia.
- SGLT2 inhibitors with evidence of kidney and CV benefit (e.g., canagliflozin 100 mg, dapagliflozin 10 mg and empagliflozin 10 mg) should be considered as treatment options.
- If a patient has been initiated on a SGLT2 inhibitor, it may be continued even if the eGFR falls below 20 ml/min per 1.73 m^2 unless it is not tolerated or kidney replacement therapy is initiated.

The annual 2023 update from the American Diabetes Association (ADA) on the Standards of Care in Diabetes include recommendations for the use of SGLT2 inhibitors with an updated recommendation based on evidence showing slowed progression of CKD.[9,10] The guidelines strongly recommend the use of SGLT2 inhibitors that have demonstrated CV benefit, irrespective of glucose levels, in those who are high risk or have atherosclerotic CV disease, HF (with preserved or reduced ejection fraction), and/or CKD to reduce cardiorenal risk as part of their glucose lowering regimen (based on high-quality evidence).[9,10]

Bexagliflozin

Bexagliflozin is a SGLT-2 inhibitor approved for use as an adjunct to diet and exercise for controlling glucose levels in adults with T2D.[11] There are 4 published trials demonstrating evidence of efficacy and safety. Bexagliflozin was compared to placebo in 2 trials and compared to active treatment, sitagliptin and glimepiride, in the remaining 2 trials.[12–15] Participants in the trials had T2D with baseline HbA1c levels ranging from 7.98% to 8.3%.[4] The participants were a mean age of 61 years and were predominately White. All of the trials were small (n= 283 - 426). In one trial, the participants had moderate renal impairment.[12] The primary outcome was change in HbA1c for all of the trials. Changes in body mass and the percent of patients obtaining an HbA1c <7% were relevant secondary endpoints.

Bexagliflozin lowered HbA1c in all the trials with difference from placebo ranging from 0.37% to 0.79% in trials lasting up to 96 weeks .[12–14] Bexagliflozin was found to be non-inferior to both sitagliptin and glimepiride, as add-on therapy to metformin. Bexagliflozin demonstrated reductions in body mass in both placebo and active treatment comparison trials ranging from -2.0 kg to -3.75 kg. Mean number of patients obtaining a HbA1c <7% was 34% with bexagliflozin vs. 21.5% for placebo.[12]

The most common adverse reactions with bexagliflozin are female genital mycotic infections, urinary tract infections and increased urination.[8] Bexagliflozin should not be used in people with a GFR less than 30 mL/min/1.73 m^2 and is contraindicated in people on dialysis. There is no data to evaluate how bexagliflozin compares to other SGLT2 inhibitors and evidence to evaluate the impact on long-term cardiovascular or renal outcomes are not currently published.

Sotagliflozin

Sotagliflozin is a SGLT2 inhibitor indicated to reduce the risk of CV death, hospitalization for HF and urgent HF visits in adults with HF or T2D, CKD and other CV risk factors.[16] Sotagliflozin inhibits both SGLT2 and SGLT1.

Sotagliflozin has been studied for HF, CKD, and type 1 diabetes (T1D); however, it is only approved to reduce CV risk in patients with and without diabetes.[16] Sotagliflozin was approved in Europe as an adjunct to insulin therapy to improve glucose control in people with T1D and later withdrawn due to commercial reasons.[17] The FDA did not approve sotagliflozin for glucose lowering in patients with T1D due to increased incidence of diabetic ketoacidosis (DKA) compared to placebo.[18]

The SOLOIST and SCORED trials were used for FDA approval of sotagliflozin (**Table 2**).[19,20] The CV benefits demonstrated in the SCORED trial were driven by reductions in HF hospitalizations (HR 0.67 (95% CI, 0.55 to 0.82; P<0.001). There were no statistical differences in the incidence of CV death between sotagliflozin and placebo in both the SOLOIST and SCORED trials. Additional glucose lowering studies in patients with stage 3 CKD demonstrated slight HbA1c reductions with 400 mg sotagliflozin (mean difference from placebo -0.24%; 95% CI, -0.39 to 0.09; P=0.002) and no statistical difference in HbA1c lowering between sotagliflozin and placebo in those with severe renal impairment (eGFR 15 to 30 ml/min/1.73 m^2).[21,22] In overweight patients, sotagliflozin was associated with weight loss of -1.0 kg to -3.45 kg in studies lasting up to 52 weeks.

Table 2. Trials Demonstrating Sotagliflozin Efficacy

Trial	Participants	Composite of total CV deaths, hospitalizations for HF, and urgent visits for HF
SCORED Trial[20]	Adults with T2D and CKD	1.Sotagliflozin: 5.6 events per 100 patient-years 2. Placebo: 7.5 events per 100 patient-years HR 0.74 (95% CI, 0.63 to 0.88); P<0.001
SOLOIST Trial[19]	Adults with T2D and worsening HF	1. Sotagliflozin: 245 events (51.0%) 2. Placebo: 355 events (76.3%) HR 0.67 (95% CI, 0.52 to 0.85); P<0.001

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; CV = cardiovascular; HF = heart failure; HR = hazard ratio; T2D = type 2 diabetes.

Common sotagliflozin adverse events occurring in placebo controlled trials in 5% or more of patients include the following: urinary tract infection, volume depletion, diarrhea, and hypoglycemia.[16] Sotagliflozin carries a warning of increased risk of DKA. There is insufficient comparative evidence to support the use of sotagliflozin over other SGLT2 inhibitors.

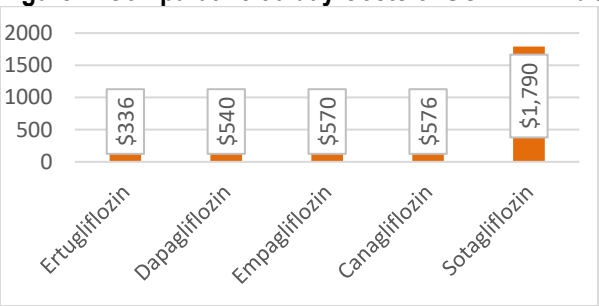
Pediatric Indication

In June of 2023 empagliflozin and empagliflozin/metformin (Jardiance® and Synjardy®), respectively, were approved for use in children and adolescents, 10 years and older with T2D, to improve blood sugar control as an adjunct to diet and exercise.[23] Evidence for efficacy was demonstrated in a 26-week, placebo-controlled, randomized, double-blind study which evaluated HbA1c reductions with the use of empagliflozin and linagliptin.[24] Empagliflozin is the only oral T2D therapy, besides metformin, indicated for use in pediatric patients.

Comparative Pricing

The cost for a thirty-day supply of a SGLT2 inhibitor is displayed in Figure 1. The costs are considered high compared to other oral therapies to treat T2D, such as metformin and sulfonylureas. There is no direct comparative evidence suggesting superior efficacy to support the use of the highest cost therapy, sotagliflozin. There is currently no cost data available for the new agent bexagliflozin.

Figure 1. Comparative 30-day Costs of SGLT2 Inhibitors[25,26]



Oregon Fee-For-Service Policy for SGLT2 Inhibitors:

- Preferred therapies are: canagliflozin, dapagliflozin, and empagliflozin
- Non-preferred therapies are: ertugliflozin, bexagliflozin and sotagliflozin

Conclusion

An increasing body of evidence has demonstrated benefits of SGLT2 inhibitors in people with and without diabetes. While cardiovascular and renal benefits appear to be a class effect, current guidelines recommend that therapies with demonstrated evidence be preferentially utilized (**Table 1**). Adverse events associated with SGLT2 inhibitors should be weighed against the benefits of moderate glucose reductions and reduced risk of adverse CV and renal outcomes. As with all pharmacotherapy, patient specific characteristics and comorbidities should be considered when determining the optimal treatment regimen.

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