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An Update on SGLT2 Inhibitors for the Treatment of Diabetes Mellitus

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Abstract

Purpose of review—SGLT2 inhibitors are the newest class of oral anti-hyperglycemic agents that have been approved for the treatment of diabetes mellitus. Over the past year there have been significant developments in both the safety and efficacy of this class of medications that are presented in this review.

Recent findings—Besides data on the glucose lowering effect of SGLT2 inhibitors, other metabolic benefits have been demonstrated for this class of medications. Moreover, there have been 3 FDA Drug Safety Communications issued in 2015 that have led to additional drug labeling. The basic mechanism of action, indications, glucose-lowering benefits, other metabolic benefits, and adverse side effects of SGLT2 inhibitors are presented in this review.

Summary—SGLT2 inhibitors are medications that have a unique mechanism of action and that lower glucose independent of insulin. Given the recent findings on efficacy and benefits, these agents are rapidly establishing their role in the treatment of diabetes. Especially in patients with type 2 diabetes not willing or not ready to start insulin, SGLT2 inhibitors may be another option in those patients requiring additional glucose lowering and in those with acceptable risk factor profiles. Although there appears to be some positive benefits in cardiovascular endpoints, more research on the long term outcomes in people taking SGLT2 inhibitors is warranted.

Keywords

SGLT2 inhibitors; type 2 diabetes; canagliflozin; dapagliflozin; empagliflozin

Introduction

The estimated total prevalence of type 2 diabetes in the United States in 2011–2012 was 14.3% and the estimated prevalence of prediabetes was 38% demonstrating the severity of the disease burden, which has continued to increase over the past 30 years.(1) Type 2 diabetes is a progressive disease typically requiring multiple medications in order to control

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Conflicts of Interest

W.T.C. has served as the principal investigator of research studies awarded to his institution by AstraZeneca, Janssen, Lexicon Pharmaceuticals, and Sanofi and has served as a consultant for Sanofi, Adocia, Mitsubishi-Tanabe Pharma, and Intarcia Therapeutics. No other potential conflicts of interest relevant to this article were reported. D.S.H. has served as the principal investigator of research studies awarded to his institution by Boehringer Ingelheim, Sanofi, and Eli Lilly. No other potential conflicts of interest relevant to this article were reported.

blood glucose levels. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are the latest class of anti-hyperglycemic agents to receive FDA approval. SGLT2 inhibitors function through a novel mechanism of reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release. Other benefits may include favorable effects on blood pressure and weight. The scope of this review will focus on clinical trials published over the past year and especially the new safety concerns that have led to multiple FDA advisories for SGLT2 inhibitors.

Physiology of SGLT Inhibition

Glucosuria has been studied for over 150 years using the botanical extract, phlorizin (2). Phlorizin was later identified as a non-specific inhibitor of sodium-glucose cotransporter (SGLT) proteins and several types of SGLT proteins have since been identified. These proteins function independently of insulin. Inhibition of these proteins was observed to result in changes that favorably improve carbohydrate metabolism, thus becoming an attractive concept for the treatment for diabetes (3–5).

Sodium-glucose cotransporter 1 (SGLT1) proteins are high affinity, low capacity transporters of glucose. They are expressed in the small intestines as well as the proximal tubule of the kidneys (5, 6). Inhibition of SGLT1 may lead to gastrointestinal complications, including severe diarrhea (5). The SGLT1 proteins in the proximal convoluted tubule of the kidneys are responsible for less than 10% of filtered glucose reabsorption (6). The role of SGLT1 proteins in the intestine are still understudied, but may play a role as noted from evidence from dual inhibitors.

Sodium-glucose cotransporter-2 (SGLT2) proteins are expressed in the proximal convoluted tubule of the kidneys. These transporters are an ideal target for the treatment of diabetes because they are responsible for roughly 90% of filtered glucose reabsorption (4–7). The normal renal threshold for reabsorption of glucose corresponds to a serum glucose concentration of 180 mg/dL. In patients with type 2 diabetes, this threshold can increase and the expression of the SGLT2 can be up-regulated causing a maladaptive response that worsens hyperglycemia.(8) Selective inhibition of SGLT2 inhibitors can reduce this threshold to as low as 40 to 120 mg/dL.(9) Comparatively, individuals with the rare “nondisease,” familial renal glucosuria (FRG), have no functional SGLT2 proteins. They present with glucosuria in the presence of normoglycemia. Individuals with FRG rarely have hypotension or hypoglycemia (10, 11) suggesting the safety of both the short and long term use of SGLT2 inhibitors.

Current Selective SGLT2 Inhibitors

A handful of SGLT2 inhibitors have been approved for the treatment of type 2 diabetes or are currently undergoing clinical trials. Currently there are three SGLT2 selective inhibitors approved by the Food and Drug Administration (FDA) for mono, dual, and triple therapy: canagliflozin (Invokana®), dapagliflozin (Farxiga®) and empagliflozin (Jardiance®) (5, 11, 12). In addition, there are several other similar compounds in the pipeline that may be approved in the near future. Of the three FDA approved drugs, empagliflozin has the greatest

selectivity for SGLT2 compared to SGLT1, while canagliflozin is the least selective (5). Four combination drugs have also been approved by the FDA: canagliflozin/metformin (Invokamet®), dapagliflozin/metformin (Xigduo XR®), empagliflozin/metformin (Synjardy®) and empagliflozin/linagliptin (Glyxambi®) (11) as illustrated in Table 1.

Indications for Use of SGLT2 Inhibitors

SGLT2 inhibitors may be a useful option in obese and hypertensive patients because of their weight loss and antihypertensive benefits. Patients who are at high risk for hypoglycemia may benefit from a combination of metformin and an SGLT2 inhibitor because the risk of hypoglycemia with SGLT2 inhibitors is small when compared to insulin and sulfonylureas. (9) SGLT2 inhibitors are contraindicated for patients with renal insufficiency (GFR < 45 mL/min/1.73m^2). However, they may be very useful without regard to diabetes duration because their action is independent of β-cell function and insulin secretion. Therefore, they can be used in patients with longstanding diabetes provided renal function is acceptable.

Benefits of SGLT2 Inhibitors

Glucose Control

In a meta-analysis published in 2014, 24-week reduction of HbA1c with SGLT2 inhibitors was greater in trials enrolling patients with a lower mean age, shorter duration of diabetes, and a higher baseline BMI, HbA1c, and fasting glucose.(13) Based on recent clinical trials, reduction in HbA1c in comparison to placebo reaches its maximum at approximately 6 months and is maintained up to 1 year.(13) Treatment with SGLT2 inhibitors has been associated with a similar hypoglycemic risk as that of metformin and DPP-4 inhibitors.

When compared with other oral anti-hyperglycemic agents, SGLT2 inhibitors have demonstrated non-inferiority along with additional metabolic benefits. As an example, in a randomized, double-blind study of 1,450 patients, HbA1c decreased −0.65% with canagliflozin 100, decreased −0.74% with canagliflozin 300 mg, and decreased −0.55% with glimepiride 6 or 8 mg over a 104 week period.(14) Moreover, when added to other anti-hyperglycemic medications (both oral medications and insulin), SGLT2 inhibitors have shown additional improvement in glucose control. Dapagliflozin added to patients already taking metformin and sulfonylurea showed a decrease in HbA1c of −0.86% compared to a decrease in HbA1c of −0.17% in the placebo group at 24 weeks.(15) In patients with type 2 diabetes inadequately controlled on basal insulin, Rosenstock et al. in a 78 week randomized, double-blind, placebo-controlled trial demonstrated that empagliflozin significantly reduced HbA1c (−0.5±0.1% with 10mg and −0.6±0.1% with 25mg, both $p<0.001$).(16) Moreover, while the placebo group had to increase their basal insulin dose by 5.5±1.6 units, the empagliflozin 10 mg group lowered their dose by 1.2 ± 1.5 units and the 25 mg group lowered their dose by 0.5 ± 1.6 units demonstrating that SGLT2 inhibitors may reduce insulin dose requirements and mitigate insulin-induced weight gain.(16) In a sub-study of patients taking ≥ 20 units/day of insulin at baseline in the CANagliflozin CardioVascular Assessment Study (CANVAS), HbA1c decreased by −0.62% in the Canagliflozin 100mg group and decreased by −0.73% in the 300 mg group versus placebo at 18 weeks. The HbA1c improvement remained essentially the same at 52 weeks.(17)

Other Metabolic Effects

Weight loss—In clinical trials of the SGLT2 inhibitors as monotherapy or add-on treatment, weight loss of ~1 to 4 kg occurred over 18 to 104 weeks.(14–17) It has been reported that weight-loss-independent and weight-loss-associated mechanisms contributed to both HbA1c and systolic blood pressure (SBP) lowering with SGLT2 inhibition.(16)

Blood Pressure—To date, all studies with SGLT2 inhibitors have found significant reductions in BP, with greater reductions seen in systolic (1.66 to 6.9mmHg) than diastolic (0.88 to 3.5mmHg) BP.(9) Interestingly, similar levels of blood pressure reduction are seen in people with eGFR of 45 mL/min/1.73 m^2 as those with 85 mL/min/1.73 m^2, and patients do not develop hyponatremia as many do with diuretics.(18) The initial reductions in BP are believed to be due to the diuretic and volume depletion effects. However, longer-term effects may be attributable to inhibition of the renin-angiotensin system and weight loss. SGLT2 inhibitors may be an ideal class of medications for patients with type 2 diabetes and hypertension.

Lipids—While some trials have shown no change in lipid parameters, others have shown a modest but statistically significant increase in both HDL and LDL cholesterol with no effect on triglycerides or the LDL/HDL ratio.(9) The clinical significance of these lipid changes, including the increase in LDL, is unknown.

Cardiovascular Benefits

In a recent meta-analysis of 21 phase 2b/3 dapagliflozin clinical trials, there was no suggestion of increased risk for major adverse cardiovascular events (MACE) with dapagliflozin compared with control.(19) In addition, studies that have evaluated type 2 diabetes patients who were at high risk for future cardiovascular disease events, SGLT2 inhibition (i.e. dapagliflozin administration) had significantly greater effects in reducing HbA1c, body weight, and SBP without adversely impacting cardiovascular (CV) safety when compared with placebo treatment.

One of the most significant trials with reported results over the past year was the EMPA-REG OUTCOME study. The randomized double-blind, placebo-controlled study included 7020 participants with established cardiovascular disease and demonstrated a 38% relative risk reduction in death from cardiovascular causes in the empagliflozin group versus the placebo group.(18) Whether these results were due to improved glycemic control or the secondary benefits of SGLT2 inhibitors as discussed above can only be speculated at this point and requires further investigation (see Table 2).

Adverse Side Effects and Warnings

The most common adverse side effect to SGLT2 inhibitors appears to be genital infections, which were increased up to four-fold in clinical trials.(13) Detectable concentrations of glucose in the urine can facilitate the onset of mycotic infections, as observed in patients who experience severe hyperglycemia with glycosuria. Because of the osmotic diuresis induced by glycosuria resulting from SGLT2 inhibition, volume depletion is a possibility.

This is usually accompanied by increased urinary frequency, thirst, and rarely orthostatic hypotension. Risk factors for volume depletion are age >75 years, GFR <60 mL/min/ 1.73m^2, and use of loop diuretics.(9). Incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related adverse events were higher in clinical trials but were generally mild to moderate in intensity and led to few discontinuations.(14, 16, 17)

Ketoacidosis and SGLT2 Inhibitors

In diabetic ketoacidosis (DKA), absolute insulin deficiency leads to reduced glucose utilization and enhanced lipolysis; increased free fatty acids (FFAs) in the liver coupled with high glucagon levels promote FFA oxidation and production of ketone bodies.(15) DKA presents with hyperglycemia (glucose >250 mg/dL), glycosuria, and hyperketonemia. Euglycemic DKA (euDKA) involves a different mechanism. Full-dose SGLT2 inhibition induces a rapid increase in urinary glucose excretion, ranging 50–100 g/day.(15) Because of the decline in glucose by 20–25 mg/dL, plasma insulin levels also decrease (by ~10 pmol/L fasting and ~60 pmol/L postmeal) with a compensatory increase in glucagon levels. This shift in hormones causes a released inhibition of gluconeogenesis in the liver as well as augmented endogenous glucose production both in the fasting and fed states.(15) Most importantly, renal glucose clearance (i.e., the ratio of glycosuria to prevailing glycemia) is twice as much with euDKA compared to DKA.(15) Thus, in SGLT2-treated type 2 diabetes patients with euDKA, the lower insulin-to-glucagon ratio stimulates lipolysis augmenting FFA delivery to the liver and resulting in mild stimulation of ketogenesis. If insulin deficiency is more profound, as can happen in type 1 diabetes patients, or if carbohydrate availability is drastically restricted, the mild ketosis would evolve toward ketoacidosis. All in all, euDKA is pathophysiologically similar to DKA except for the circumstance of SGLT2-induced glycosuria that “artificially” lowers plasma glucose levels and predisposes to increased ketogenesis.(15) These lower glucose levels make identifying euDKA more difficult and may lead to delayed treatment.(14)

Another rare side effect that has been observed with the use of canagliflozin has been acute pancreatitis. Two case reports of acute pancreatitis associated with DKA in patients with temporal exposure to canagliflozin were published in 2015.(20, 21) The exact mechanism for the development of pancreatitis and whether there is a similar risk with other drugs in the SGLT2 inhibitor class remains unknown.

In May 2015, the U.S. Food and Drug Administration (FDA) issued a Drug Safety Communication warning that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis.(22) From March 2013 to June 6, 2014, 20 cases of acidosis reported as diabetic ketoacidosis (DKA), ketoacidosis, or ketosis in patients treated with SGLT2 inhibitors were reported to the FDA Adverse Events Reporting System (FAERS); all of these patients required emergency treatment or hospitalization.(22) These FAERS cases were atypical for DKA because most of the patients had type 2 diabetes and their blood sugar levels were only slightly increased compared to the high blood sugar levels seen in typical cases of DKA.(22)

In June 2015, the European Medicines Agency (EMA) announced that as of May 2015 a total of 101 cases of DKA have been reported worldwide in EudraVigilance in type 2

diabetes patients treated with SGLT2 inhibitors, with an estimated exposure over 0.5 million patient-years.(15). Peters et al. identified 13 episodes of SGLT-2 inhibitor-associated euDKA or ketosis in nine individuals, seven with type 1 diabetes and two with type 2 diabetes, from various practices across the U.S.(14) They reported that the absence of significant hyperglycemia in these patients delayed recognition of the emergent nature of the problem by patients and providers. They concluded that SGLT-2 inhibitors seem to be associated with euDKA and ketosis, perhaps as a consequence of their noninsulin-dependent glucose clearance, hyperglucagonemia, and volume depletion. However, in an elegant commentary on the topic, Rosenstock and Ferrannini provide comment on the pathophysiology and clinical lessons from the observations to date with euglycemic DKA.(15) They stated “this potential complication related to SGLT2 inhibition is *predictable*, *detectable*, *and preventable* (*or mitigable*) so that the balance of benefits and risks favors the use of SGLT2 inhibitors in the T1D population, which is in desperate need of adjunct therapies.(15) This adverse event was also studied in the canagliflozin type 2 diabetes clinical program. It was observed that DKA and related events occurred at a low frequency in over 17,000 subject evaluated I the clinical program. They also reported that the incidence was “consistent with limited existing observational data in the general population with type 2 diabetes”.(23)

In September 2015, the FDA strengthened the warnings related to the increased risk of bone fractures and added new information about decreased bone mineral density to the labels for canagliflozin (Invokana®) and canagliflozin/metformin (Invokamet®).(24) In 9 pooled clinical trials with a mean duration of exposure to canagliflozin of 85 weeks, the incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator (includes placebo and active comparators), canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively.(24) Fractures occurred as early as 12 weeks after treatment initiation and were more likely to be due to low trauma and affect the upper extremities.(24) A double-blind, placebo-controlled clinical trial was conducted in 714 patients (mean age 64 years, range 55 to 80 years) with type 2 diabetes inadequately controlled on current diabetes therapy as part of an FDA-issued postmarketing requirement. (24) At 2 years, patients randomized to canagliflozin 100 mg and canagliflozin 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively.(24) A 1.2% decline in BMD translates into a decrease of approximately 0.1 T-score units or 1% of peak bone mass. In post-hoc analysis, change in body weight appeared to explain about 40% of the observed difference in total hip BMD between the pooled canagliflozin group and the placebo group.(25) Evaluation of the risk of bone fractures with other drugs in the SGLT2 inhibitor class is ongoing.

Furthermore, in December 2015 as a follow up to the warnings issued in May 2015, the FDA decided to add specific warnings to the labels of all SGLT2 inhibitors indicating the risk of ketoacidosis and serious urinary tract infections. Review of the FAERS database from March 2013 to May 2015 identified 73 cases of ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors (canagliflozin [n=48], dapagliflozin [n=21], and empagliflozin [n=4]).(26) Forty-four of the 73 cases occurred in patients with type 2 diabetes mellitus. Fifteen cases were reported in patients with type 1 diabetes (SGLT2 inhibitors are not approved for use in this population). Blood glucose levels were reported in

40 of the 73 cases and ranged from 90 mg/dL to 1,366 mg/dL (median 211 mg/dL).(26) The range of time from initiation of an SGLT2 inhibitor or an increase in dose to the onset of the reported ketoacidosis was 1 day to 1 year (median 43 days).(26) In the 73 cases of ketoacidosis, potential risk factors for developing ketoacidosis with an SGLT2 inhibitor included: infection, low carbohydrate diet or an overall reduction of caloric intake, reduction in dose of exogenous insulin or discontinuation of exogenous insulin, discontinuation of an oral insulin secretagogue, and alcohol use.(26)

In addition, 19 cases of urosepsis and pyelonephritis that started as urinary tract infections while taking a SGLT2 inhibitor (canagliflozin [n=10] and dapagliflozin [n=9]) were reported to FAERS from March 2013 through October 2014. All 19 patients were hospitalized while 4 patients required admission to the intensive care unit, and 2 required hemodialysis to treat renal failure.(26) The range of time to onset of urosepsis or pyelonephritis was 2 to 270 days (median 45 days). Eight of the 19 cases had documented blood culture results with E. coli as the isolated organism, and there were no reports of fungal urosepsis.(26) The FDA continues to encourage reporting adverse events involving SGLT2 inhibitors to the FDA MedWatch program.

Conclusion

SGLT2 inhibitors are the newest class of oral anti-hyperglycemic agents available to treat patients with type 2 diabetes. Their novel mechanism of action makes these medications an intriguing option for patients throughout the natural history of type 2 diabetes and as a possible adjunct therapy for type 1 diabetes with close supervision. Although there are a wide range of side effects including recently identified episodes of ketoacidosis related to SGLT2 inhibitor use, this class may be a good option in the carefully selected patient. Longer term cardiovascular safety trials are ongoing and will ultimately test the staying power of this class of medications.

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Key Points

- SGLT2 inhibitors function through a novel mechanism of reducing renal tubular glucose reabsorption, producing a reduction in blood glucose without stimulating insulin release.
- Because their action is independent of β-cell function and insulin secretion, SGLT2 inhibitors can be used in patients with longstanding diabetes provided renal function is acceptable.
- When compared with other oral anti-hyperglycemic agents, SGLT2 inhibitors have demonstrated non-inferiority along with additional metabolic benefits of weight loss and blood pressure lowering.
  - Incidences of genital mycotic infections, urinary tract infections, and osmotic diuresis–related adverse events were higher in clinical trials but were generally mild to moderate in intensity.
  - Euglycemic DKA related to SGLT2 use is pathophysiologically similar to DKA except for the SGLT2-induced glycosuria that “artificially” lowers plasma glucose levels and predisposes to increased ketogenesis.

Table 1

List of current SGLT2 inhibitors.

Generic Name	Brand Name	Available Doses (mg)	Administration
canagliflozin[a]	Invokana®	100, 300	qam before 1st meal
dapagliflozin[a]	Farxiga™	5, 10	qam
empagliflozin[a]	Jardiance®	10, 25	qam
canagliflozin/metformin[a]	Invokamet®	50/500, 50/1000, 150/500, 150/1000	BID with meals, max dose 300mg/2000mg
dapagliflozin/metformin[a]	Xigduo™ XR	5/500, 5/1000, 10/500, 10/1000	qam with food, max dose 10mg/2000mg
empagliflozin/metformin[a]	Synjardy®	5/500, 5/1000, 12.5/500, 12.5/1000	BID with meals, max dose 25mg/2000mg
empagliflozin/linagliptin[a]	Glyxambi®	10/5, 25/5	qam
Ipragliflozin[b]	Suglat®	25, 50	qam, max dose 100mg
tofogliflozin[bc]	Apleway®, Deberza®	20	qam
luseogliflozin[c]			
remogliflozin etabonate[c]			
ertugliflozin[c]			
sotagliflozin[c]			

[a]FDA and EMA approved,

[b]Ministry of Health, Labour and Welfare approved in Japan,

[c]currently in clinical trials or seeking market approval; qam taken once daily in the morning, BID twice daily

Table 2

Prospective cardiovascular safety trials for SGLT2 inhibitors(9)

Name of Trial	Intervention	Primary Endpoint	No. of Patients	Duration of Trial (y)	Projected Year of Completion
Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)	Empagliflozin 10 or 25 mg daily	Time to the first occurrence of any of the following adjudicated components of the primary composite endpoint: CV death (including fatal stroke and fatal MI), nonfatal MI, and nonfatal stroke	7000	5	2015
Canagliflozin cardiovascular Assessment Study (CANVAS)	Canagliflozin 100 or 300 mg daily	Major adverse cardiovascular events, including CV death, nonfatal MI, and nonfatal stroke	4330	≥ 4	2017
Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE)	Canagliflozin 100 mg daily	Time to the first occurrence of an event in the primary composite endpoint: ESRD, doubling of serum creatinine, renal or CV death	3627	5.5	2019
Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58)	Dapagliflozin 10 mg daily	Time to first event included in the composite end point of CV death, MI or ischemic stroke	17150	6	2019
Cardiovascular Outcomes Following Treatment With Ertugliflozin in Participants With Type 2 Diabetes Mellitus and Established Vascular Disease (NCT01986881)	Ertugliflozin 5 or 15 mg daily	Time to first occurrence of any component of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke	3900	6.3	2020

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