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MINIREVIEWS

Place of sodium-glucose co-transporter type 2 inhibitors for treatment of type 2 diabetes

Nasser Mikhail

Nasser Mikhail, Department of Medicine, Endocrine Division, OliveView-UCLA Medical Center, Sylmar, CA 91342, United States
Author contributions: Mikhail N solely contributed to this paper.
Correspondence to: Nasser Mikhail, MD, MSc, Department of Medicine, Endocrine Division, OliveView-UCLA Medical Center, 14445 Olive View Dr, Sylmar, CA 91342, United States. nmikhail@dhs.lacounty.gov
Telephone: +1-310-2607897
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Abstract

Inhibitors of sodium-glucose co-transporter type 2 (SGLT2), such as canagliflozin and dapagliflozin, are recently approved for treatment of type 2 diabetes. These agents lower blood glucose mainly by increasing urinary glucose excretion. Compared with placebo, SGLT2 inhibitors reduce hemoglobin A1c (HbA1c) levels by an average of 0.5%-0.8% when used as monotherapy or add-on therapy. Advantages of this drug class include modest weight loss of approximately 2 kg, low risk of hypoglycemia, and decrease blood pressure of approximately 4 mmHg systolic and 2 mmHg diastolic. These characteristics make these agents potential add-on therapy in patients with HbA1c levels close to 7%-8.0%, particularly if these patients are obese, hypertensive, and/or prone for hypoglycemia. Meanwhile, these drugs are limited by high frequency of genital mycotic infections. Less common adverse effects include urinary tract infections, hypotension, dizziness, and worsening renal function. SGLT2 inhibitors should be used with caution in the elderly because of increased adverse effects, and should not be used in chronic kidney disease due to decreased or lack of efficacy and nephrotoxicity. Overall, SGLT2 inhibitors are useful addition for treatment of select groups of patients with type 2 diabetes, but their efficacy and safety need to be established in long-term clinical trials.

Key words: Type 2 diabetes; Canagliflozin dapagliflozin; Weight loss; Hypoglycemia; Chronic kidney disease; Genital infection

Core tip: Sodium-glucose co-transporter type 2 inhibitors are recently approved drugs for type 2 diabetes with unique mechanism of action. In this minireview, the author provides a practical approach on how to select the best candidates for these drugs.

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INTRODUCTION

In healthy individuals, almost all glucose filtered by the kidneys is reabsorbed into the circulation, and less than 0.5 g of glucose per day is lost in urine[1]. Ninety per cent of glucose reabsorption from glomerular filtrate is mediated by sodium-glucose co-transporter type 2 (SGLT2) located in early segments (called S1 and S2) of proximal renal tubules[2,3]. The remaining 10% of filtered glucose is reabsorbed by means of SGLT1 located in late segment (S3) of proximal tubule[3]. SGLT2 inhibitors decrease hyperglycemia independently of insulin by lowering the renal threshold for glucose and therefore increasing urinary excretion of glucose[2]. Canagliflozin (Invokana) is the first SGLT2 inhibitor approved in the United States in March 2013 for treatment of type 2 diabetes[4]. Dapagliflozin

Table 1 Differences between canagliflozin and dapagliflozin

	Canagliflozin (Invokana)[4]	Dapagliflozin (Forxiga)[5]
Approved doses	Starting dose 100 mg tablet qd, taken before breakfast. If tolerated, dose can be increased to 300 mg tablet *qd*	Starting dose 5 mg tablet qd taken in the morning with or without food. If tolerated, dose can be increased to 10 mg tablet *qd*
Use in CKD	Contraindicated with eGFR < 45 mL/min per 1.73 m^2. Dose limited to 100 mg/d with eGFR of 45-59 mL/min per 1.73 m^2	Not recommended with eGFR < 60 mL/min per 1.73 m^2. No dose adjustment is needed with milder CKD
Hepatic impairment (Child-Pugh classification: A: mild, B: moderate, C: severe)	No dosage adjustment is needed with mild or moderate hepatic impairment. Not recommended with severe hepatic impairment	No dosage adjustment is needed with mild or moderate hepatic impairment. Start with smaller dose (5 mg/d) in severe hepatic impairment then the high-dose 10 mg/d if tolerated
Drug interactions	Use higher dose (300 mg/d) with UGT enzyme inducers (*e.g.*, rifampin) ↑ C max of digoxin by 36%. Use low starting digoxin doses, and monitor serum digoxin levels closely	No dose adjustment is needed when used with UGT enzyme inducers No interaction with digoxin
Effect on LDL-C levels (mean percentage change *vs* placebo)	↑ 4.5%-8%	↑ 3.9%
Possible increase in cardiovascular events	A trend toward increase in non fatal stroke and cardiovascular events (see text)	Not observed
Possible increase in cancer	Not observed	Possible increase in bladder cancer (0.17% *vs* 0.03% with placebo)

eGFR: Estimated glomerular filtration rate; Cmax: Maximum plasma concentration; CKD: Chronic kidney disease.

(Forxiga) was approved by the European Medicines Agency in November 2012, and by the Federal Drug Administration (FDA) in the United States in January 2014[5]. While head to head trials are lacking, some important differences exist between canagliflozin and dapagliflozin (Table 1). Many SGLT2 inhibitors such as empagliflozin, ipragliflozin, luseogliflozin are pending approval or still under development[2,6]. The main purpose of this review is to identify the optimum place of SGLT2 inhibitors in management of patients with type 2 diabetes based on both patients' characteristics and drug profile of SGLT2 inhibitors. More emphasis will be placed on the 2 approved SGLT2 inhibitors: canagliflozin and dapagliflozin.

SEARCH METHODOLOGY

PubMed search was conducted until July 2014 to identify all humans studies related to efficacy and safety of all SGLT2 inhibitors published in the English, Spanish and French literature. The search included all clinical trials of various SGLT2 inhibitors, pertinent guidelines of experts, review articles, prescribing information of canagliflozin and dapagliflozin are also reviewed. Search terms included "sodium glucose co-transporters", "diabetes mellitus", "canagliflozin", "dapagliflozin", "empagliflozin", "efficacy", "safety", "adverse effects", "cardiovascular effects", "mortality", "glycosuria".

Potential candidates for SGLT2 inhibitors

As add-on to other oral agents in patients with hemoglobin A1c levels of 7%-8.0%: In general, the efficacy of SGLT2 inhibitors is similar to metformin, sulfonylurea, pioglitazone, but canagliflozin may be slightly superior to sitagliptin [difference in hemoglobin A1c (HbA1c) 0.37%][7,8]. As result of their unique mechanism of action, SGLT2 inhibitors can be virtually combined with any other anti-diabetic therapy. A recent meta-analysis of 58 studies that included 8 different SGLT2 inhibitors showed that these agents reduced mean HbA1c levels by 0.79% when used as monotherapy and 0.61% when used as add-on treatment compared with placebo[7]. Because of universal agreement that metformin is the initial drug of choice for treatment of type 2 diabetes, the use of SGLT2 inhibitors as monotherapy is not justified except in selected patients who cannot tolerate metformin[9]. The place of SGLT2 inhibitors therefore is more appropriate as add-on therapy. For instance, after the addition of canagliflozin, dapagliflozin, and empagliflozin to patients with mean baseline HbA1c of approximately 8.0%, proportions of subjects who achieved HbA1c concentrations less than 7% were: 64% (*vs* 32% with placebo), 41% (*vs* 26% with placebo), and 32% (*vs* 9% with placebo), respectively[6,10,11]. In the previous 3 trials, background diabetes treatment consisted of metformin + pioglitazone, metformin alone, and metformin + sulfonylurea, respectively[6,10,11]. Clearly, in these studies, not all subjects achieved the HbA1c target of less than 7%. Hence, as baseline HbA1c levels become higher than 8.0% (*e.g.*, 8.5%-9%), the addition of a SGLT2 inhibitor may only improve, but unlikely optimize, glycemic control. In the latter setting, initiation of insulin is the most appropriate step.

Obese patients or patients concerned about weight gain: The use of SGLT2 inhibitors is consistently associated with mild weight loss of approximately 2 kg compared with placebo irrespective of presence or type of concomitant anti-diabetes therapy[7]. Weight loss becomes evident after 6 wk then usually reaches a plateau or slight-

ly rebounds after 26-32 wk until the end of follow-up at 104 wk[12]. The main cause of weight loss is increased urinary glucose loss, estimated to be approximately 100 g of glucose per 24 h[13]. Since each gram of glucose excreted in urine translates into a loss of 4 kcal, a loss of approximately 400 kcal/d is expected with SGLT 2 inhibitors[14]. Two studies using dual-energy X-ray absorptiometry show that approximately two-thirds of the reduction in body weight associated with administration of dapagliflozin and canagliflozin originates from fat mass, whereas the remaining one third is derived from lean body mass[15,16]. Another contributing factor to weight reduction may be fluid loss as result of the diuretic action of SGLT2 inhibitors, particularly during the initial rapid decline in body weight[15]. Since weight gain is a major unwanted effect of insulin therapy, addition of a SGLT2 inhibitor was evaluated in obese patients receiving high insulin doses (77 units/d)[12]. Thus, patients randomized to dapagliflozin lost an average weight of 1.4 kg without changing insulin requirements. Conversely, subjects randomized to placebo gained 1.8 kg, and their insulin requirements increased by 18 units/d[12]. Moreover, the HbA1c levels were 0.4% lower among dapagliflozin-treated group *vs* the placebo group[12]. Therefore, in insulin-treated patients concerned about weight gain, addition of a SGLT2 inhibitor may be a viable option.

Patients prone for hypoglycemia: The use of SGLT2 inhibitors is associated with low risk for hypoglycemia that is generally similar or slightly greater than placebo[11], similar to metformin[17], but 7-11 times less common than sulfonylurea (SU)[16,18]. Thus, in one trial, hypoglycemia occurred in 5% of patients randomized to canagliflozin 300 mg/d *vs* 34% of patients randomized to glimepiride (mean maximum dose 5.6 mg/d)[16]. SGLT2 inhibitors can be therefore a reasonable alternative to SU in patients with frequent hypoglycemia. The low hypoglycemic risk of SGLT2 inhibitors is attributed to the fact that these agents reduce renal glucose threshold to a range close to 76-90 mg/dL, *i.e.*, level that is above the plasma glucose concentration at which hypoglycemic symptoms occur[13,14]. Meanwhile, the incidence of hypoglycemia associated with SGLT2 inhibitors may increase in 3 conditions namely concomitant therapy with insulin and/or SU, in chronic kidney disease (CKD), and in the elderly. Thus, when dapagliflozin 10 mg/d was added to a background of insulin therapy, frequency of hypoglycemia was numerically greater among patients randomized to dapagliflozin than placebo, 57% and 52%, respectively[19]. With respect to CKD, in one study of patients with estimated glomerular filtration rate (eGFR) between 30 and 49 mL/min per 1.73 m^2, the proportions of subjects with documented hypoglycemia were higher with both doses of canagliflozin being 52% *vs* 36% with placebo[20]. Of note, the vast majority (96%) of the previous study population was also taking insulin or SU[20]. Finally, regarding advanced age, in a study of older patients (mean age 64 years), the incidence of hypoglycemia was 36% and 28% with canagliflozin 300 mg/d, and placebo, respectively[21].

Patients with uncontrolled hypertension: In one meta-analysis of 27 randomized trials, the use of various SGLT2 inhibitors was associated with mean reduction of systolic and diastolic blood pressure of 4.0 mmHg and 1.6 mmHg, respectively compared with baseline[22]. Only canagliflozin showed dose-response relationship with systolic blood pressure[22]. The decrease in blood pressure is most likely due to osmotic diuresis, but mild weight loss may be another contributing factor[13]. It is reassuring that the decrease in blood pressure was not associated by an increase in heart rate[8,23].

Patients in whom SGLT2 inhibitors may be used with caution

Women with history of mycotic genital infections and uncircumcised men: Increased vaginal fungal infection is the most common adverse effect of SGLT2 inhibitors reported by 11%-14% of patients who received canagliflozin or dapagliflozin compared with 2%-4% in subjects randomized to placebo or a comparator agent such as glimepiride or sitagliptin[8,16]. The increased genetic mycotic infection is most likely related to the increase in urinary glucose excretion induced by SGLT2 inhibitors. The median time of diagnosis was 19 d after the initiation of canagliflozin, and the most frequently isolated Candida species were Candida albicans (51%) and Candida glabrata (37%)[24]. Infection is frequently recurrent, and patients with previous history of genital mycotic infections are more prone to develop this type of infection[4,19,25].

Increased frequency of genetic mycotic infections also occurs in men exposed to SGLT2 inhibitors, albeit to a lesser extent than in women[25]. These include balanitis or balanoposthitis. In the trial of Cefalu *et al*[16], frequency of genetic mycotic infections in men exposed to canagliflozin 100 mg/d, canagliflozin 300 mg/d, and glimepiride was 7%, 8%, and 1%, respectively. Rates of infection are relatively higher in uncircumcised men and those with history of balanitis[4,25]. In general, genital mycotic events in both genders were considered mild to moderate in severity, were treated with topical or oral anti-fungal agents without interruption of the drug, and uncommonly led to withdrawals[8]. The frequency of UTI is also increased with the use of SGLT2 inhibitors, being 7.2%, 5.1%, and 4.2% among patients randomized to canagliflozin 100 mg/d, 300 mg/d, and placebo, respectively[23]. Candida spp. was cultured from the urine specimens of 4.4% of canagliflozin-treated patients compared with 1.1% of control subjects[26]. This increased frequency of candiduria may reflect contamination from vaginal colonization[26].

Elderly patients: Two main reasons make the use of SGLT2 inhibitors in the elderly not an attractive option: diminished efficacy and increased frequency of some adverse effects. Thus, mean reduction of HbA1c with the highest dose of canagliflozin (300 mg/d) *vs* placebo was

0.8% and 0.5% after 26 wk among patients younger than 65 years and those who were older than 65 years, respectively[21]. This decreased efficacy was also demonstrated in a pooled analysis of 4 other canagliflozin studies[27]. Likewise, in one trial of dapagliflozin, reduction in HbA1c levels in patients younger than 65 (mean age 58 years) and older than 65 (mean age 70 years) was 0.4% and 0.3%, respectively after 24 wk compared with baseline[28]. Since the anti-hyperglycemic action of SGLT2 inhibitors rely on enhancing urinary glucose excretion, the decreased efficacy of the agents with old age is in large part attributed to the reduction in eGFR that normally occurs with aging[21]. Besides decreased efficacy, available data suggest that several adverse effects of SGLT2 inhibitors may increase with advanced age. First, elderly patients exposed to SGLT-2 inhibitors are more prone for worsening renal function than younger patients. Thus, in patients aged 65 and older, renal impairment and renal failure occurred among 14.8% of patients randomized to dapagliflozin *vs* 8.0% with placebo, whereas corresponding proportions in patients younger than 65 were 4.7% and 0.4%[28]. Second, elderly patients receiving canagliflozin and dapagliflozin may be more prone for volume-depletion adverse effects such as hypotension, dizziness, and syncopy[4,5,27]. Third, as mentioned earlier, elderly patients may be more susceptible to hypoglycemia associated with SGLT2 inhibitors[21].

Patients with significant history of vascular disease: The Canagliflozin Cardiovascular Assessment Study (CANVAS) is an ongoing large randomized trial that primarily examines the effects of canagliflozin on cardiovascular events and mortality in patients with long-standing type 2 diabetes and elevated cardiovascular risk[29]. An imbalance in the incidence of cardiovascular events was recorded during the first 30 d of CANVAS. Thus, 13 of 2889 patients had an event in the canagliflozin group compared with 1 of 1441 patients in the placebo group yielding a hazard ratio of 6.5 (95%CI: 0.85-49.6). This imbalance was not evident after 30 d[7]. In addition, the FDA reported a trend toward an increase in nonfatal stroke in patients who received canagliflozin [HR = 1.46 (95%CI: 0.83-2.58)][7]. Regarding dapagliflozin, the limited available data is somewhat reassuring. Thus, one trial of older patients (mean age 64 years) with advanced type 2 diabetes and history of cardiovascular disease did not show difference in cardiovascular events or mortality between patients randomized to dapagliflozin compared to placebo after 52 wk of intervention[28].

Patients with osteoporosis: Incidence rate of bone fractures derived from pooled data of 8 trials were 18.7, 17.6, and 14.2 per 1000 patient years of exposure to canagliflozin 100 mg/d, 300 mg/d, and comparator, respectively[4]. In one study of patients with moderate renal impairment (mean age 67 years), 13 of 85 (7.7%) patients randomized to dapagliflozin experienced fracture compared to none of the 84 subjects randomized to placebo[30]. The reasons of excess fractures in patients exposed to canagliflozin and dapagliflozin are unclear. No notable changes in serum or urine calcium, 1.25 dihydroxy vitamin D, or parathyroid hormone were reported[19]. However, in 2 canagliflozin studies, there was a modest increase in one marker of bone resorption, serum collagen type 1 β-carboxy-terminal telopeptide[14,21]. Nevertheless, until further data become available, SGLT2 inhibitors should be used with caution in patients having history of osteoporosis or fractures.

Patients in whom SGLT2 inhibitors should be avoided

Patients with chronic kidney disease: As mentioned earlier, the risk of hypoglycemia associated with the use of SGLT2 inhibitors in patients with CKD is increased[20]. Other reasons to avoid the use of these drugs in CKD are decreased or lack of efficacy and worsening renal function. Thus, in patients with stage 3 CKD, defined as eGFR between 30 and 49 mL/min per 1.73 m^2, the efficacy of canagliflozin was only modest with mean HbA1c reduction of 0.4% as compared with placebo[20]. Furthermore, in another trial of patients with eGFR of 30 to 59 mL/min per 1.73 m^2, dapagliflozin did not have any significant effect on HbA1c levels compared with placebo[30]. This decreased or absent efficacy of SGLT2 inhibitors in CKD is most likely the result of reduction of renal glucose clearance as eGFR declines[21,31]. Patients with CKD are particularly susceptible to the nephrotoxic effects of SGLT2 inhibitors. Indeed, increase in serum creatinine, and decrease in eGFR were demonstrated after 1-3 wk of exposure to dapagliflozin and canagliflozin, respectively[20,30]. Therefore, the use of dapagliflozin and canagliflozin is contraindicated in patients with eGFR < 60 mL/min per 1.73 m^2, and 45 mL/min per 1.73 m^2, respectively[4,5].

Patients with high low density lipoprotein-cholesterol (LDL-C) concentrations: For unclear reason, canagliflozin was found to increase plasma levels of LDL-C in a dose-related fashion. In pooled data from 4 placebo-controlled trials, mean percentage increases over baseline values were 4.5% and 8% with 100 mg/d and 300 mg/d, respectively relative to placebo[4]. In one study of 26 wk-duration, slight increases in plasma levels of apolipoprotein B of 1.2% and 3.5% were reported among patients randomized to canagliflozin 100 mg/d, and 300 mg/d, respectively compared with 0.9% increase with placebo[23]. Canagliflozin also increased levels of high density lipoprotein-cholesterol, with mean percentage increase of 6.1%-6.8% relative to placebo[23], and 8%-9% relative to glimepiride[16]. Clearly, the increase in plasma levels of LDL-C and apolipoprotein B is concerning, and its impact on cardiovascular events needs to be carefully examined. The effect of dapagliflozin on LDL-C levels is inconsistent. In pooled data from 13 placebo-controlled trials, mean percentage increase in LDL-C levels was 2.9% in dapagliflozin groups *vs* -1% in placebo groups after 24 wk[5]. Yet, in one trial lasting 2 years, no change in LDL-C

levels was recorded in dapagliflozin-treated subjects[12].

Patients with history of bladder cancer: Possible increased risk of bladder cancer was observed in dapagliflozin trials[5]. Accordingly, dapagliflozin should not be used in patients with history of bladder cancer until further data become available[5].

OTHER LIMITATIONS OF SGLT2 INHIBITORS

Although almost all clinical trials of SGLT2 inhibitors are randomized and double-blind, they are sponsored by corresponding manufacturers, and therefore open to various bias, *e.g.*, using comparator drug in submaximal doses, or not mentioning its actual doses[16,18]. Moreover, the meta-analysis of Vasilakou *et al*[7] revealed that reduction in HbA1c levels by these agents may be overstated because of high discontinuation rates and handling missing data by the use of "last observation carried forward". Indeed, the latter method is considered inappropriate and can potentially inflate drug efficacy[32]. The high cost, and absence of long-term data (*e.g.*, 5 years or more) are further limitations of this new class of drugs.

CONCLUSION

Owing to their unique mechanism of action and acceptable efficacy, SGLT2 inhibitors represent a useful add-on therapy in patients with uncontrolled type 2 diabetes. Patient subgroups that would potentially benefit the most from this class are those with HbA1c levels in the range of 7%-8%, subjects concerned about weight gain, patients prone for hypoglycemia, or those with uncontrolled hypertension. On the other hand, these agents are not recommended in CKD, and should be used with caution in the elderly. It may be wise not to use canagliflozin in patients with established cardiovascular disease and high LDL-C levels until further data become available. The results of the ongoing large randomized trials should clarify the long-term safety of different members of SGLT2 inhibitors with respect to cardiovascular morbidity and mortality, incidence of cancer and fractures[29,33].

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