St. John Fisher University

Fisher Digital Publications

Pharmacy Faculty/Staff Publications

Wegmans School of Pharmacy

5-2016

SGLT-2 Inhibitors: A Novel Mechanism in Targeting Glycemic Control in Type 2 Diabetes Mellitus

Kobi T. Nathan

St. John Fisher University, knathan@sjf.edu

Nabila Ahmed-Sarwar

St. John Fisher University, nahmed-sarwar@sjf.edu

Paul M. Werner

St. John Fisher University, pmw00581@students.sjf.edu

Follow this and additional works at: https://fisherpub.sjf.edu/pharmacy_facpub

Part of the [Pharmacy and Pharmaceutical Sciences Commons](#)

[How has open access to Fisher Digital Publications benefited you?](#)

Publication Information

Nathan, Kobi T.; Ahmed-Sarwar, Nabila; and Werner, Paul M. (2016). "SGLT-2 Inhibitors: A Novel Mechanism in Targeting Glycemic Control in Type 2 Diabetes Mellitus." *The Consultant Pharmacist* 31.5, 251-260.

Please note that the Publication Information provides general citation information and may not be appropriate for your discipline. To receive help in creating a citation based on your discipline, please visit <http://libguides.sjfc.edu/citations>.

This document is posted at https://fisherpub.sjf.edu/pharmacy_facpub/94 and is brought to you for free and open access by Fisher Digital Publications at . For more information, please contact fisherpub@sjf.edu.

SGLT-2 Inhibitors: A Novel Mechanism in Targeting Glycemic Control in Type 2 Diabetes Mellitus

Abstract

OBJECTIVE: To review the chemistry, pharmacology, pharmacodynamics, pharmacokinetics, clinical efficacy, tolerability, dosing, drug interactions, and administration of canagliflozin, dapagliflozin, and empagliflozin, and comparing the benefit and risk aspects of using these agents in the older adult diabetes patient population.

DATA SOURCES, STUDY SELECTION, DATA EXTRACTION, AND DATA SYNTHESIS: A search of PubMed using the terms "SGLT-2 inhibitors," "canagliflozin," "dapagliflozin," "empagliflozin," "efficacy," and "tolerability" was performed to find relevant primary literature on each of the sodium/glucose cotransporter 2 (SGLT-2) inhibitors currently approved for use in type 2 diabetes. Phase III trials for all agents were included. All English-language articles from 2010 to 2015 appearing in these searches were reviewed for relevance to this paper. In addition, related articles suggested in the PubMed search were also reviewed. The SGLT-2 inhibitors have shown a reduction in hemoglobin A1c values and fasting plasma glucose levels with a low incidence of hypoglycemia. The incidence of mycotic infections is increased in patients taking an SGLT-2 inhibitor.

CONCLUSION: SGLT-2 inhibitors may be a viable treatment option for patients not controlled on other oral agents. The risk of hypoglycemia is small. However, the clinical efficacy and tolerability of these agents has not been fully elucidated in older and frail patients.

Keywords

fsc2016

Disciplines

Pharmacy and Pharmaceutical Sciences

Comments

This article was published in *The Consultant Pharmacist*®, Volume 31, Number 5, May 2016, pp. 251-260(10): <https://doi.org/10.4140/TCP.n.2016.260>

Posted with permission.

SGLT-2 Inhibitors: A Novel Mechanism in Targeting Glycemic Control in Type 2 Diabetes Mellitus

Kobi T. Nathan, Nabila Ahmed-Sarwar, Paul Werner

OBJECTIVE: To review the chemistry, pharmacology, pharmacodynamics, pharmacokinetics, clinical efficacy, tolerability, dosing, drug interactions, and administration of canagliflozin, dapagliflozin, and empagliflozin, and comparing the benefit and risk aspects of using these agents in the older adult diabetes patient population.

DATA SOURCES, STUDY SELECTION, DATA EXTRACTION,

AND DATA SYNTHESIS: A search of PubMed using the terms "SGLT-2 inhibitors," "canagliflozin," "dapagliflozin," "empagliflozin," "efficacy," and "tolerability" was performed to find relevant primary literature on each of the sodium/glucose cotransporter 2 (SGLT-2) inhibitors currently approved for use in type 2 diabetes. Phase III trials for all agents were included. All English-language articles from 2010 to 2015 appearing in these searches were reviewed for relevance to this paper. In addition, related articles suggested in the PubMed search were also reviewed. The SGLT-2 inhibitors have shown a reduction in hemoglobin A1c values and fasting plasma glucose levels with a low incidence of hypoglycemia. The incidence of mycotic infections is increased in patients taking an SGLT-2 inhibitor.

CONCLUSION: SGLT-2 inhibitors may be a viable treatment option for patients not controlled on other oral agents. The risk of hypoglycemia is small. However, the clinical efficacy and tolerability of these agents has not been fully elucidated in older and frail patients.

KEY WORDS: Anti-hyperglycemic agents, Canagliflozin, Dapagliflozin, Empagliflozin, Hypoglycemia, SGLT-2 inhibitors, Type 2 diabetes mellitus.

ABBREVIATIONS: ADA = American Diabetes Association, AUC = Area under the curve, CI = Confidence interval, CYP = Cytochrome P450, DPP-4 = Dipeptidyl peptidase-4, eGFR = Estimated glomerular filtration rate, FAERS = Federal Drug Administration Adverse Event Reporting System, FDA = Food and Drug Administration, FPG = Fasting plasma glucose, HbA1c = Hemoglobin A1c, SGLT-2 = Sodium/glucose cotransporter 2, T2DM = Type 2 diabetes mellitus, UGT = UDP-glucuronosyltransferase, UTI = Urinary tract infection, V_d = Volume of distribution.

Consult Pharm 2016;31:251-260.

Introduction

The long-term glycotoxic effects of persistent hyperglycemia in type 2 diabetes (T2DM) is well-known and documented. Treating hyperglycemia can be an arduous and complicated process for both the provider and the patient. A myriad of oral anti-hyperglycemic agents, in addition to insulin, are available to return patients to normoglycemia. The majority of these agents (metformin, sulfonylureas, nonsulfonylurea secretagogues, glucagonlike peptide-1 analog, and dipeptidyl peptidase-4 [DPP-4] inhibitors) are insulin-dependent.¹ Their efficacy diminishes over time as pancreatic islet β -cell function declines over the natural progression of the disease.^{1,2} In addition, use of these agents has its limitations, such as increased risk of hypoglycemia and weight gain with insulin and sulfonylureas.^{3,4} Treating older adults with T2DM poses significant pharmacologic hurdles and challenges. Complex pharmacodynamic and pharmacokinetic variables come into play, such as multiple comorbidities, drug-disease interactions, drug-drug interactions, polypharmacy, and altered pharmacokinetics as a result of changes in metabolic function, adipose, and lean tissue composition.

A novel class of oral anti-hyperglycemic agents, the SGLT-2 (sodium/glucose cotransporter-2) inhibitors may hold promise in managing older adults with T2DM, especially when used as an adjunct to established oral agents. SGLT-2 inhibitors have an insulin-independent mechanism of action, which differentiates them from the other oral anti-hyperglycemic agents. The blood glucose-lowering efficacy of the SGLT-2 inhibitors in T2DM has been clinically demonstrated in prospective randomized clinical trials.^{1,3-8} This effect is seen when the SGLT-2 inhibitors are administered as monotherapy or as adjunct agents with other glucose-lowering medications.⁹ Rapid de-escalations in both basal and postprandial blood glucose levels are seen, with decreases of hemoglobin A1c (HbA1c) averaging 0.6% to 1.2%, with the potential to decrease up to 3% in patients with severely uncontrolled diabetes.^{5,10} There are currently three agents in the SGLT-2 inhibitor drug class: canagliflozin, dapagliflozin, and empagliflozin.¹¹⁻¹⁵ Several more agents that are currently in development are listed in Table 1.¹⁶⁻²⁰

Table 1. SGLT-2 Inhibitors in Development

Agent	Development Phase*
Ertugliflozin	Phase III
Ipragliflozin	Phase III
Luseogliflozin	Phase III
Remogliflozin	Phase IIb
Tofogliflozin	Phase III

Abbreviation: SGLT-2 = Sodium/glucose cotransporter 2.

• Phase III = Confirms effectiveness, monitors side effects, identifies indications, and identifies safety parameters

• Phase IIb = Establishes efficacy and further evaluates safety

Source: References 16-20.

Chemistry

Canagliflozin: The empirical formula is $C_{24}H_{25}FO_5S \cdot 1/2H_2O$, with a molecular weight of 453.53 (Figure 1).¹² The agent is available in a film-coated tablet for oral administration with either 102 or 306 mg of the active drug, equating to 100 and 300 mg of anhydrous canagliflozin, respectively. Canagliflozin is practically insoluble in aqueous media from pH 1.1 to 12.9.^{11,12}

Dapagliflozin: The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$, with a molecular weight of 502.98 (Figure 2).¹⁴ It is available in a film-coated tablet for oral administration with either 5 or 10 mg of the active drug, dapagliflozin propanediol.^{13,14}

Empagliflozin: The empirical formula is $C_{21}H_{25}ClO_6$, with a molecular weight of 450.91 (Figure 3).²¹ It is available in a film-coated tablet for oral administration with either 10 or 25 mg of the active drug base.^{15,21}

Clinical Pharmacology

SGLT-2 is a protein transporter responsible for approximately 90% of glucose reabsorption at the proximal renal tubule. Under normal physiological conditions, the Na^+/K^+ -ATPase pump, located basolaterally within the renal tubules, uses adenosine triphosphate (ATP) to shuttle three sodium ions to the blood while bringing two potassium ions into the intracellular space. This mechanism decreases the sodium content inside the cell and drives the SGLT-2 pump to bring sodium and glucose into the cell. As

Figure 1. Structural Formula of Canagliflozin

Source: Reference 12.

Figure 2. Structural Formula of Dapagliflozin

Source: Reference 14.

Figure 3. Structural Formula of Empagliflozin

Source: Reference 21.

this pump transports glucose into the cell against its gradient, its action is considered to be secondary active transport. The pump cotransports sodium and glucose at 1:1 stoichiometry from the lumen to the intracellular space, after which time GLUT-2 brings the reabsorbed glucose from the intracellular space to the peritubular capillaries, thereby increasing plasma glucose levels.^{9,11-15,21} SGLT-2 has a high capacity, but low affinity for glucose. SGLT-2 inhibitors bind to SGLT-2, preventing them from exerting their action of glucose reabsorption. The result is a greater amount of glucose remaining in the urine and subsequently excreted from the body. SGLT-2 is responsible for approximately 90% of total glucose reabsorption, and it is estimated that the effect of the SGLT-2 inhibitors account for a decrease in glucose reabsorption of about 30%-50%.^{9,11-15,21}

Pharmacokinetics

The pharmacokinetic profiles for each of the three SGLT-2 inhibitors are detailed in Table 2.^{11-15,21}

Clinical Efficacy

Several trials have evaluated the clinical efficacy and tolerability of the three current SGLT-2 inhibitors approved by the Food and Drug Administration (FDA) for the treatment of T2DM. Studies have evaluated this class of medication in comparison to lifestyle modifications and various other oral anti-hyperglycemic agents, including sulfonylureas, metformin, and DPP-4 inhibitors.^{3-8,22-25} This class of medications is not approved as an add-on therapy to insulin. Overall, each individual agent has shown a reduction in HbA1c values and fasting plasma glucose levels with a low incidence of hypoglycemia.^{3,7,8}

Table 2. Pharmacokinetics of SGLT-2 Inhibitors

	Canagliflozin (Invokana)	Dapagliflozin (Farxiga)	Empagliflozin (Jardiance)
Onset of action	Within 24 hours (dose-dependent)	Within 24 hours	Peak plasma: within 1.5 h postdose
Duration of action	24 hours	24 hours	24 hours
Absorption	Not affected by food; taking before first meal may decrease postprandial hyperglycemia	High-fat meal decreases peak plasma concentration by up to 50%	Lower absorption with high-fat and high-calorie meal; AUC ↓16%, but not clinically significant
Distribution	V _d : 119 L	V _d : 118 L	V _d : 73.8L
Protein binding	99% mainly to albumin	91%	86.2%
Metabolism	O-glucuronidation by UGT1A9 & UGT2B4 to 2 inactive metabolites; minor CYP3A4 oxidation	UGT 1A9 to 1 inactive metabolite (Dapagliflozin 3-O-glucuronide), minor CYP	Glucuronidation by UGT2B4, UGT1A2, UGT1A3, UGT1A8, UGT1A9
Bioavailability	~ 65%	78%	N/A
Half-life elimination	100 mg: 10.6 hours 300 mg: 13.1 hours	12.9 hours	12.4 hours
Time to peak	1-2 hours	2 hours	1.5 hours
Excretion	Feces (51.7%) Urine (~ 33%)	Urine (75%) Feces (21%)	Urine (54.4%) Feces (41.2%)

Abbreviations: AUC = Area under the curve, CYP = Cytochrome P450, SGLT-2 inhibitors = Sodium/glucose cotransporter 2, UGT = UDP-glucuronosyltransferase, V_d = Volume of distribution.

Source: References 11-15, 21.

Canagliflozin

Patients with an average HbA1c of 8% who were randomized to canagliflozin 100 mg daily, 300 mg daily, or diet and exercise/placebo; canagliflozin 300 mg once daily produced clinically significant reduction in HbA1c with absolute reduction of 1.03% at 26 weeks. In comparison, the 100 mg daily dose achieved an absolute HbA1c reduction of 0.77% at 26 weeks. Additionally, the reduction in fasting plasma glucose levels of 27 mg/dL and up to 34 mg/dL in the canagliflozin 100 mg daily and 300 mg daily groups, respectively, was observed. The authors concluded that both the 100 mg and 300 mg dosing regimens provided clinical and statistically significant improvements in glycemic control. While acknowledging the ability to improve glycemic targets, the baseline average fasting plasma glucose levels ranged from 166 to 172 mg/dL, and even at doses of 300 mg daily, patients were unable to reach goal fasting blood glucose levels between 80 and 130 mg/dL as recommended by the American Diabetes Association.^{26,27} Acknowledging that goals should be individualized for each patient, the reduction observed with canagliflozin may be clinically significant in certain patient populations. Clinical trials including patients with average baseline HbA1c values ranging from 7.8% to 7.9% determined that canagliflozin as an add-on therapy to metformin was not inferior in comparison to glimepiride plus metformin or sitagliptin plus metformin in reducing HbA1c and fasting plasma glucose (FPG) values. At 52 weeks, canagliflozin 100 mg daily plus metformin did not produce a clinically significant reduction in HbA1c values (0.01%; 95% confidence interval [CI] -0.11%-0.09%). Canagliflozin 300 mg daily plus metformin resulted in an absolute HbA1c reduction of approximately 0.12% (95% CI -0.22% to -0.02%) compared with patients randomized to either glimepiride plus metformin or sitagliptin plus metformin. The results of these studies indicate the combination of canagliflozin and metformin does not provide greater benefits in glycemic control compared with previously available medication classes.^{3,7}

Dapagliflozin

Similar efficacy is demonstrated in noninferiority trials evaluating dapagliflozin.²²⁻²⁴ The safety and efficacy of dapagliflozin has been evaluated in comparison to metformin, as an add-on to metformin or sulfonylureas, and as add-on therapy to metformin and sitagliptin.

Patients with T2DM inadequately controlled on metformin were randomized to receive dapagliflozin 5 mg and 10 mg in addition to continuing their high-dose metformin therapy.²² A reduction in HbA1c of 0.7% in patients receiving 5 mg and 0.84% in patients receiving 10 mg from an average baseline HbA1c of 8.1% was observed at 24 weeks, in comparison to an HbA1c reduction of 0.3% seen in patients continuing metformin monotherapy. The addition of high-dose dapagliflozin has demonstrated the overall ability to provide an additional 0.54% HbA1c decrease in comparison to metformin alone. In a small subset of patients with baseline HbA1c values $\geq 9\%$, an overall reduction of 0.84% in HbA1c was observed at 24 weeks when compared with patients receiving metformin monotherapy. The absolute difference in FPG in patients receiving the combination of dapagliflozin and metformin was no greater than 17 mg/dL when compared with metformin monotherapy. The authors of this study concluded at 24 weeks that the addition of dapagliflozin to patients inadequately controlled on metformin resulted in a significant reduction in HbA1c and FPG. Acknowledging that a statistically significant improvement is observed, the limited HbA1c reduction achieved may have an inadequate impact on reducing long-term complications of diabetes. The potential for a greater HbA1c reduction observed in patients with higher baseline HbA1c values may provide a greater clinical impact.

Additionally, dapagliflozin has been studied as an add-on therapy for patients inadequately controlled on glipizide or glimepiride.^{23,24} Patients with an average baseline HbA1c of 7.8% did not achieve a statistically or clinically relevant difference in HbA1c reduction when comparing dapagliflozin 10 mg with glipizide (-0.5% vs. -0.52%; $P = \text{NS}$, respectively).²⁴ In patients with a baseline HbA1c of approximately 8.1%, the difference in HbA1c reduction was observed to be no greater than 0.27% when comparing patients receiving dapagliflozin in addition to

glimepiride versus glimepiride monotherapy. Although a greater HbA1c reduction was seen in patients receiving the combination, approximately 30% of these patients required additional therapies as a result of poor control, indicating that the additional HbA1c reduction cannot be contributed to the addition of dapagliflozin alone.²³

In contrast to the findings of canagliflozin, dapagliflozin in addition to sitagliptin + metformin compared with sitagliptin ± metformin demonstrated an additional reduction of 0.4% from baseline in patients with baseline HbA1c of 7.9% at 24 weeks. Dapagliflozin did demonstrate that patients with baseline HbA1c > 8% achieved a greater HbA1c reduction from baseline of 0.8% and absolute reduction in fasting plasma glucose of -27.9 mg/dL compared with placebo. The authors concluded the addition of dapagliflozin in patients inadequately controlled on sitagliptin with or without metformin therapy provides additional clinical benefits.⁶ Although the clinical benefit of an overall reduction of 0.4% is questionable, the greater A1c reduction observed in patients with higher baseline HbA1c levels may provide a greater clinical impact in prevention of long-term complications of hyperglycemia.

Empagliflozin

In contrast, the most recently FDA-approved SGLT-2 inhibitor, empagliflozin, has been largely studied as an add-on therapy to metformin, being compared with the combination of metformin with either a sulfonylurea or DPP-4 inhibitor.^{4,5,25} When compared with placebo plus metformin as an add-on to metformin, empagliflozin 10 mg daily and 25 mg daily plus metformin produced similar absolute HbA1c reductions, 0.57% and 0.64%, respectively, at 24 weeks.⁴ Similarly, when both strengths of empagliflozin plus metformin were compared with sitagliptin plus metformin, the HbA1c reductions achieved were consistent with those found when compared with placebo plus metformin and remained consistent at 78 weeks.⁵ A comparison of empagliflozin 25 mg daily plus metformin and glimepiride plus metformin found no difference in reducing HbA1c levels between the two treatment groups.²⁵ The overall reductions in FPG seen with empagliflozin in clinical trials, regardless of comparator, were similar to those in trials evaluating canagliflozin.

In a subgroup analysis of patients with baseline HbA1c > 10% (n = 69), a significantly greater absolute HbA1c reduction of 3.23% and FPG reduction of 38 mg/dL compared with placebo was achieved. This indicates the potential for empagliflozin to provide a greater impact on improving glycemic control in patients with higher baseline HbA1c levels.⁴ A limitation of these findings is the study protocol allowed for the use of rescue medication use in patients with elevated fasting blood glucose levels or patients with HbA1c > 8.5% at scheduled follow-ups during the 24-week period. The empagliflozin trials concluded a significant improvement in glycemic control compared with other oral anti-hyperglycemic agents.^{4,5,25} The subgroup analysis of patients with HbA1c > 10% provides compelling data to hypothesize hyperglycemia-dependent clinical efficacy.

Tolerability

SGLT-2 inhibitors have demonstrated to be well tolerated in clinical trials, resulting in a low study-withdrawal rate.^{3-5,8,22} The trials consistently reported no significant changes in renal function and serum electrolytes in patients randomized to either SGLT-1 inhibitors or comparator oral anti-hyperglycemic agents. This is in contrast to the postmarketing reports and subsequent FDA warning regarding the increase in risk of ketoacidosis associated with this class of medication.²⁸

In early 2016, FDA added new warnings and precautions to labels of all SGLT-2 inhibitors following a review of the FDA Adverse Event Reporting System (FAERS) database from March 2013 to May 2015. Seventy-three cases of ketoacidosis in patients with type 1 and type 2 diabetes were reported. Presentation was serious enough to warrant hospitalization or treatment in the emergency department. In several instances, ketoacidosis was not identified, and treatment was delayed because of patients presenting in a euglycemic state. Additionally, 19 cases of life-threatening urosepsis and pyelonephritis were added to the FAERS database from March 2013 to October 2014. All patients required hospitalization, with some requiring admission to an intensive care unit or dialysis to treat acute kidney injury.²⁸

The rates of hypoglycemia for patients randomized to receive this class of medication was not significantly different

Table 3. Reports of Adverse Drug Reactions

Percentage of patients reporting adverse drug reaction for each agent

Adverse Drug Reaction	Dapagliflozin + Metformin	Empagliflozin + Metformin	Canagliflozin + Metformin	Metformin	Sitagliptin + Metformin	Glimepiride + Metformin
Hypoglycemia	2%-4%	1.8%-2.4% (0.9%-1.8% monotherapy)	2%-6%	0.5%-3.6%	3.6%-5%	N/A
Osmotic diuresis	N/A	N/A	3%-5%	N/A	N/A	< 1%
UTIs	4%-8%	9%-12.7% (3.8%-6.4% monotherapy)	6%-12%	4.9%-8%	12.5%	5%
Genital infections	8%-13%	3%-3.6% (3.7%-5.8% monotherapy)	3%-11.1%	0%-5%	0%	1.6%

Abbreviations: N/A = Not reported in study, UTI = Urinary tract infection.

Source: References 3-5, 8, 9.

in comparison to metformin, sitagliptin, and sulfonylureas.³⁻⁵ The reported increase in urinary glucose excretion of approximately 20 g in patients receiving an SGLT-2 inhibitor in comparison to metformin.²² Adverse reactions resulting from an increase in glucose in the renal and genital urinary tract can be expected. Adverse drug reactions such as occurrence of urinary tract infections (UTIs), genital infections, and osmotic diuresis for each of the SGLT-2 inhibitors are listed in Table 3. No significant difference in the occurrence of osmotic diuresis was observed in patients randomized to receive SGLT-2 inhibitors.^{3,8}

The occurrence of UTIs for all three agents—dapagliflozin, empagliflozin, and canagliflozin—was not different when compared with metformin or glimepiride after 24 weeks of therapy.^{3,5,22} Patients receiving empagliflozin were followed for an extended duration of 78 weeks; the rate of UTIs were lower in patients receiving empagliflozin monotherapy in comparison to those on combination empagliflozin and metformin (3.8%-6.4% vs. 12.7%). No significant difference in the rate of UTIs was observed in patients receiving empagliflozin and metformin in comparison to those receiving sitagliptin and metformin (12.7% vs. 12.5%, respectively).⁵

Unlike UTIs, the reports of genital infections described as mild to moderate were significantly higher in patients receiving SGLT-2 inhibitors in comparison to metformin, sitagliptin, and sulfonylureas.^{3-5,22} In comparison to canagliflozin and dapagliflozin, the reports of genital infections occurred less frequently in patients receiving empagliflozin, with a higher incidence in female than male patients.^{4,5,8,22}

SGLT-2 inhibitors were associated with reductions in systolic blood pressure; reductions were slightly higher when SGLT-2 inhibitors were used in combination with metformin therapy.^{4,22,24,25} The greatest reduction in systolic blood pressure was reported to be 5.4 mmHg from baseline in patients randomized to receive canagliflozin 300 mg daily.²⁸ Reports of orthostatic hypotension were reported in < 1% of patients randomized to canagliflozin as an add-on to metformin in comparison to no reports in patients receiving glimepiride and metformin.³ At 48 weeks, no difference was found between patients randomized to dapagliflozin as an add-on therapy to sitagliptin with or without metformin in the occurrence of hypotension, dehydration, and hypovolemia.⁶

Drug Interactions

Drug interactions with SGLT-2 inhibitors are relatively limited in comparison to other oral anti-hyperglycemic agents.²⁹⁻³¹ The potential to enhance the hypoglycemic effects of SGLT-2 inhibitors is possible when combined with insulin and insulin secretagogues.²¹ Initiating lower doses of the SGLT-2 inhibitors in combination with reduction in dose of prandial insulin doses and short-acting sulfonylureas can reduce the risk of hypoglycemic events. Additionally, the potential for osmotic diuresis leading to volume depletion, resulting from increases in urine volume and polyuria, is higher in patients concurrently receiving SGLT-2 inhibitors and diuretics.²¹ Dose reductions of loop diuretics (i.e., furosemide and torsemide) should be considered when concurrently used with SGLT-2 inhibitors. Drug interactions specific to canagliflozin include UDP-glucuronosyltransferase (UGT) enzyme inducers and digoxin. Concurrent use of nonselective UGT enzyme inducers (i.e., rifampin, phenytoin, phenobarbital, ritonavir) significantly reduces the area under the curve (AUC) of canagliflozin. Patients on concurrent UGT enzyme-inducer therapy are likely to require canagliflozin 300 mg daily to achieve therapeutic drug levels.¹² Additionally, canagliflozin has the potential to increase the AUC and mean peak drug concentration of digoxin.¹² Monitoring digoxin levels in patients receiving concurrent digoxin and canagliflozin therapy

after initiation or adjustments in canagliflozin dosing can be utilized to monitor for digoxin toxicity. Canagliflozin did not inhibit 1A2, 2A6, 2C19, or 2E1 isoenzymes and weakly inhibited 2B6, 2C8, 2C9, and 3A4.

Dosing and Administration

The currently available dosage formulations for products containing SGLT-2 inhibitors are available in Table 4.^{12,14,21,29-31} This class of medication is approved for use in patients with T2DM and has primarily been studied in individuals older than 18 years of age. No specific hepatic dosage adjustments are required in patients with hepatic impairment. The efficacy of this medication class is significantly dependent on renal clearance; the recommendations are based on estimated glomerular filtration rate (eGFR) for each agent and vary slightly. All three agents are determined to be safe and efficacious in patients with eGFR $\geq$ 60 mL/min.^{12,14,21,29-31} The use of dapagliflozin is not recommended in patients with eGFR < 60 mL/min.¹⁴ Canagliflozin and empagliflozin are not recommended in patients with an eGFR < 45 mL/min.^{12,21} The dose of canagliflozin should not exceed 100 mg daily in patients with eGFR between 45-59 mL/min.¹² To maximize efficacy it is ideal to instruct patients to administer these medications once daily prior to their morning meal. Appropriate adjustments to timing of the medication should be made for patients to align with

Table 4. Commercially Available Formulation of SGLT-2 Inhibitors

Product	Available strengths	Frequency of administration
Farxiga (dapagliflozin)	5 mg and 10 mg tablets	Every morning
Invokana (canagliflozin)	100 mg and 300 mg tablets	Every morning
Jardiance (empagliflozin)	10 mg and 25 mg tablets	Every morning
Combination products		
Xigduo XR (dapagliflozin/metformin)	5/500 mg, 5/1,000 mg, 10/500 mg, 10/5,000 mg tablets	Every morning
Invokamet (canagliflozin/metformin)	50/500 mg, 50/1,000 mg, 150/500 mg, 150/5,000 mg tablets	Every morning
Glyxambi (empagliflozin/linagliptin)	10/5 mg, 25/5 mg tablets	Every morning
Abbreviation: SGLT-2 = Sodium/glucose cotransporter 2. Source: References 12, 14, 21, 33-35.		

timings when dietary intake is consistent with a longer duration of time (i.e., night-shift workers).

Pharmacoeconomics

Currently, there are no pharmacoeconomic studies comparing the cost-effectiveness of the SGLT-2 inhibitors as a drug class. The average wholesale price pricing for each agent in this drug class is outlined in Table 5.^{12,14,21,32}

Discussion and Recommendations

Overall, SGLT-2 inhibitors have been shown to reduce HbA1c values and FPG levels with a low incidence of hypoglycemia. The safety and efficacy of each agent in this novel drug class has been evaluated against the other established oral antidiabetic agents, such as metformin, the sulfonylureas, and the DPP-4 inhibitors. However, for patients with HbA1c 7.8%-8.1%, the clinical significance of these reductions may prove to be questionable in the larger scenario of effective glycemic control in patients with type 2 diabetes. Notably, the modest reduction in HbA1c percentage for each agent as discussed in the various studies fail to make a clinically relevant reduction in HbA1c values, limiting their benefits to patients within 1% from achieving their goal HbA1c. However, the SGLT-2 inhibitor class has demonstrated, but not established, the possibility of providing a greater HbA1c reduction in patients with significantly elevated HbA1c values (> 10.0%), suggesting a potential to provide clinically significant reductions in HbA1c values in this subset of diabetic patients.⁴ For these individuals, the SGLT-2 inhibitors may provide a viable alternative to insulin therapy. Conversely, cost may prove to be prohibitive in its use as an adjunct treatment option; the cost of insulin is significantly less than this novel class of agents. Providers and patients will have to weigh the benefits versus risks of insulin therapy over SGLT-2 inhibitor therapy.

Clinical studies suggest that the SGLT-2 inhibitors are well-tolerated by patients, with the most common events being osmotic diuresis and mycotic infections. The incidence of these adverse events was low in the trials; however, the average age of patients included in currently available SGLT-2 inhibitor studies ranged from 51.0 to 60.8 years. The limited number of patients older than 70

Table 5. Approximate Cost of SGLT-2 Inhibitors

Agent	Initial Dose*
Canagliflozin (Invokana)	100 mg once daily (\$340)
Dapagliflozin (Farxiga)	5 mg once daily (\$340)
Empagliflozin (Jardiance)	10 mg once daily (\$340)

* Approximate cost for 30-day supply.

Abbreviation: SGLT-2 = Sodium/glucose cotransporter 2.

Source: Reference 32.

Table 6. Education Points for Patients on SGLT-2 Inhibitor Therapy

Adverse Drug Reaction	Signs and Symptoms Requiring Referral to Clinician
Mycotic infections	<ul style="list-style-type: none"> • Vaginal itching or burning • Abnormal vaginal discharge • Urinary frequency
Urinary tract infections	<ul style="list-style-type: none"> • Urinary frequency • Flank pain • Fever • Dysuria • Urinary frequency
Hypovolemia	<ul style="list-style-type: none"> • Orthostasis • Dizziness • Elevated skin turgor • Dry mucus membranes
Renal dysfunction	<ul style="list-style-type: none"> • Dark urine • Weakness/fatigue • Urinary frequency • Hypotension
Ketoacidosis	<ul style="list-style-type: none"> • Mental confusion • Extreme fatigue • Nausea and vomiting • Abdominal pain • Hyperventilation

Source: References 12, 14, 21.

years of age poses a challenge in extrapolating the safety endpoints in geriatric patients.¹ Consequently, the safety and efficacy of these agents has not been ascertained in the older and frail patient population with multiple comorbid conditions. Older patients, because of natural biophysical changes, are more prone to the deleterious effects of dehydration and UTIs. Use of the SGLT-2 inhibitors, with resultant osmotic diuresis, decreased intravascular volume, and possible electrolyte derailment, may lead to potentially harmful consequences in older adults. In addition, older patients, especially women and those with diabetes, are at increased risk for genital infections. An increase in rates of such events has been reported in all studies of the SGLT-2 inhibitors.^{1,3-8} Older adults manifest hypoglycemia differently than the general younger population, and are also more prone to its effects. The consequences of these adverse drug reactions have the potential to cause harm to elderly patients. Pharmacists should ensure patients are adequately educated on signs and symptoms that indicate the need for provider intervention, as listed in Table 6. While the studies show a low incidence of hypoglycemic events, use of these agents may not be appropriate in certain patients, and should warrant close scrutiny and vigilance by medical providers and caretakers.

Conclusion

The SGLT-2 inhibitors are a novel class of oral anti-hyperglycemic agents that have been shown to decrease HbA1c values in patients with T2DM. These drugs may be used as adjunct treatment with other oral anti-hyperglycemic agents belonging to the biguanide, sulfonylurea, and DPP-4 inhibitor drug classes. Studies suggest HbA1c decreases may be more clinically relevant in patients with higher HbA1c values. The safety and tolerability of SGLT-2 inhibitors has not been elucidated in older patients. Although reports of SGLT-2 inhibitors negatively affecting renal clearance are limited, and no significant differences in the occurrence of hypotension and volume-related complications were observed in clinical trials, elderly patients may be at greater risk for developing these adverse effects. Frequent monitoring of renal function, volume status, and blood pressure may be required to ensure safe medication use. Caution, clinical

prudence, and careful weighing of benefits versus risks is recommended when use of these agents is contemplated in these patients.

Kobi T. Nathan, PharmD, MEd, CGP, is assistant professor of pharmacy practice, St. John Fisher College, Wegmans School of Pharmacy, and clinical pharmacy specialist, Monroe Community Hospital, Rochester, New York. **Nabila Ahmed-Sarwar, PharmD, BCPS, CDE**, is assistant professor of pharmacy practice, St. John Fisher College, Wegmans School of Pharmacy, clinical pharmacy specialist, Highland Family Medicine, and University of Rochester Family Medicine Residency Program, Rochester. **Paul Werner, PharmD**, is a 2015 graduate, St. John Fisher College, Wegmans School of Pharmacy.

For correspondence: Kobi T. Nathan, PharmD, MEd, CGP, St. John Fisher College, Wegmans School of Pharmacy, 3690 East Avenue, Rochester, NY 14618; Phone: 585-385-8033; Fax: 585-385-5295; E-mail: knathan@sjfc.edu.

Disclosure: No funding was received for the development of this manuscript. The authors have no potential conflicts of interest.

© 2016 American Society of Consultant Pharmacists, Inc.
All rights reserved.

Doi:10.4140/TCP.n.2016.260.

References

1. Sun YN, Zhou Y, Chen X et al. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *BMJ Open* 2014;4:e004619.
2. Pretki M, Nolan CJ. Islet beta cell failure in type 2 diabetes. *J Clin Invest* 2006;116:1802-12.
3. Cefalu WT, Leiter LA, Yoon KH et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomized, double-blind, phase 3 non-inferiority trial. *Lancet* 2013;382:941-5.
4. Häring HU, Merker L, Seewaldt-Becker E et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2014;37:1650-9.
5. Ferrannini E, Berk A, Hantel S et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. *Diabetes Care* 2013;36:4015-21.
6. Jabbour SA, Hardy E, Sugg J et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care* 2014;37:740-50.

7. Lavallo-González FJ, Januszewicz A, Davidson J et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013;56:2582-92.
8. Rosenstock J, Aggarwal N, Polidori D et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 2012;35:1232-8.
9. Bailey CJ. The Current Drug Treatment Landscape for Diabetes and Perspectives for the Future. *Clin Pharmacol Ther* 2015;98:170-84.
10. Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. *Lancet Diabetes Endocrinol* 2013;1:140-51.
11. Canagliflozin [Internet]. Hudson, OH: Lexi-Comp (US); c2015. Available at http://online.lexi.com.pluma.sjfc.edu/lco/action/doc/retrieve/docid/patch_f/4230722. Accessed February 24, 2015.
12. Invokana [package insert]. Titusville, NJ: Janssen; 2013.
13. Dapagliflozin [Internet]. Hudson, OH: Lexi-Comp (US); c2015. Available at http://online.lexi.com.pluma.sjfc.edu/lco/action/doc/retrieve/docid/patch_f/4927422. Accessed February 24, 2015.
14. Farxiga [package insert]. Wilmington, DE: AstraZeneca; 2014.
15. Empagliflozin [Internet]. Hudson, OH: Lexi-Comp (US); c2015. Available at http://online.lexi.com.pluma.sjfc.edu/lco/action/doc/retrieve/docid/patch_f/5279964. Accessed February 24, 2015.
16. Merck Sharp & Dohme Corp. A phase III, multicenter, randomized, double-blind, active-comparator-controlled clinical trial to study the safety and efficacy of the addition of ertugliflozin (MK-8835/PF-04971729) compared with the addition of glimepiride in subjects with type 2 diabetes mellitus who have inadequate glycemic control on metformin. In *ClinicalTrials.gov* [Internet]. Bethesda, MD: National Library of Medicine (US); 2000. Available at <https://clinicaltrials.gov/ct2/show/NCT01999218?term=ertugliflozin&rank=3> NLM Identifier: NCT01999218. Accessed August 29, 2015.
17. Fonseca VA, Ferrannini E, Wilding JP et al. Active- and placebo-controlled dose-finding study to assess the efficacy, safety, and tolerability of multiple doses of ipragliflozin in patients with type 2 diabetes mellitus. *J Diabetes Complications* 2013;27:268-73.
18. Seino Y, Sasaki T, Fukatsu A et al. Efficacy and safety of luseogliflozin as monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, phase 3 study. *Curr Med Res* 2014;30:1245-55.
19. Sykes AP, Kemp GL, Dobbins R et al. Randomized efficacy and safety trial of once-daily remogliflozin etabonate for the treatment of type 2 diabetes. *Diabetes Obes Metab* 2015;17:98-101.
20. Kaku K, Watada H, Iwamoto Y et al. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. *Cardiovasc Diabetol* 2014;13:65.
21. Jardiance [package insert]. Ridgefield, CT: Boehringer Ingelheim; 2014.
22. Bailey CJ, Gross JL, Pieters A et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010;375:2223-33.
23. Strojek K, Yoon KH, Hrubá V et al. Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycaemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. *Diabetes Ther* 2014;5:267-83.
24. Nauck MA, Del Prato S, Meier JJ et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. *Diabetes Care* 2011;34:2015-22.
25. Ridderstråle M, Andersen KR, Zeller C et al. EMPA-REG H2H-SU trial investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endocrinol* 2014;2:691-700.
26. American Diabetes Association. Standards of medical care in diabetes-2015 abridged for primary care providers. *Clin Diabetes* 2015;33:97-111.
27. Stenlöf K, Cefalu WT, Kim KA et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 2013;15:372-82.
28. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Available at <http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm>. Accessed November 1, 2015.
29. Glumetza [Package Insert]. Raleigh, NC: Salix Pharmaceuticals, Inc.; 2014.
30. Januvia [Package Insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2015.
31. Actos [Package Insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2013.
32. Drugs for Type 2 Diabetes. Pharmacist's Letter. 2012; 28: Detail-Document#: 280601. Full Update May 2015. Available at <http://pharmacistsletter.therapeuticresearch.com/pl/ArticleDDpx?nidchk=1&cs=&s=PL&pt=2&segment=4407&dd=280601&AspxAutoDetectCookiSupport=1>. Accessed August 12, 2015.
33. Xigduo [package insert]. Wilmington, DE: AstraZeneca; 2014.
34. Invokamet [package insert]. Titusville, NJ: Janssen; 2014.
35. Glyxambi [package insert]. Ridgefield, CT: Boehringer Ingelheim; 2015.