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

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

Abstract

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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.

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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, Vd = Volume of distribution.

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Clinical Review

Table 1. SGLT-2 Inhibitors in Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Development Phase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertugliflozin</td>
<td>Phase III</td>
</tr>
<tr>
<td>Ipragliflozin</td>
<td>Phase III</td>
</tr>
<tr>
<td>Luseogliflozin</td>
<td>Phase III</td>
</tr>
<tr>
<td>Remogliflozin</td>
<td>Phase IIb</td>
</tr>
<tr>
<td>Tofogliflozin</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

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}F\text{O}_{5}\text{S}\cdot\frac{1}{2}\text{H}_{2}\text{O}, with a molecular weight of 453.53 (Figure 1).\textsuperscript{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.\textsuperscript{11,12}

Dapagliflozin: The empirical formula is C_{21}H_{25}Cl\text{O}_{6}\cdot\text{C}_{3}H_{8}\text{O}_{2}\cdot\text{H}_{2}\text{O}, with a molecular weight of 502.98 (Figure 2).\textsuperscript{14} It is available in a film-coated tablet for oral administration with either 5 or 10 mg of the active drug, dapagliflozin propanediol.\textsuperscript{13,14}

Empagliflozin: The empirical formula is C_{21}H_{25}Cl\text{O}_{6}, with a molecular weight of 450.91 (Figure 3).\textsuperscript{21} It is available in a film-coated tablet for oral administration with either 10 or 25 mg of the active drug base.\textsuperscript{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
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.\textsuperscript{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\%.\textsuperscript{9,11-15,21}

### Pharmacokinetics

The pharmacokinetic profiles for each of the three SGLT-2 inhibitors are detailed in Table 2.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3,7,8}

<table>
<thead>
<tr>
<th>Table 2. Pharmacokinetics of SGLT-2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of action</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Within 24 hours</td>
</tr>
<tr>
<td>(dose-dependent)</td>
</tr>
<tr>
<td><strong>Duration of action</strong></td>
</tr>
<tr>
<td><strong>Absorption</strong></td>
</tr>
<tr>
<td>taking before first meal</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
</tr>
<tr>
<td><strong>Protein binding</strong></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
</tr>
<tr>
<td><strong>Half-life elimination</strong></td>
</tr>
<tr>
<td>300 mg: 13.1 hours</td>
</tr>
<tr>
<td><strong>Time to peak</strong></td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AUC = Area under the curve, CYP = Cytochrome P450, SGLT-2 inhibitors = Sodium/glucose cotransporter 2, UGT = UDP-glucuronosyltransferase, V\textsubscript{d} = Volume of distribution.

**Source:** References 11-15, 21.
Clinical Review

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.28

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 ≥ 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 = 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
SGLT-2 Inhibitors: Targeting Glycemic Control

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. 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.

Tolerability

SGLT-2 inhibitors have demonstrated to be well tolerated in clinical trials, resulting in a low study-withdrawal rate. 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. 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.

The rates of hypoglycemia for patients randomized to receive this class of medication was not significantly different.
in comparison to metformin, sitagliptin, and sulfonylureas.\textsuperscript{3-5} The reported increase in urinary glucose excretion of approximately 20 g in patients receiving an SGLT-2 inhibitor in comparison to metformin.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{26} 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.\textsuperscript{7} 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.\textsuperscript{6}
Drug Interactions
Drug interactions with SGLT-2 inhibitors are relatively limited in comparison to other oral anti-hyperglycemic agents. The potential to enhance the hypoglycemic effects of SGLT-2 inhibitors is possible when combined with insulin and insulin secretagogues. 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. 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. Additionally, canagliflozin has the potential to increase the AUC and mean peak drug concentration of digoxin. 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. 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 ≥ 60 mL/min. The use of dapagliflozin is not recommended in patients with eGFR < 60 mL/min. Canagliflozin and empagliflozin are not recommended in patients with an eGFR < 45 mL/min. The use of dapagliflozin is not recommended in patients with eGFR < 45 mL/min. The dose of canagliflozin should not exceed 100 mg daily in patients with eGFR between 45-59 mL/min. 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

<table>
<thead>
<tr>
<th>Product</th>
<th>Available strengths</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farxiga (dapagliflozin)</td>
<td>5 mg and 10 mg tablets</td>
<td>Every morning</td>
</tr>
<tr>
<td>Invokana (canagliflozin)</td>
<td>100 mg and 300 mg tablets</td>
<td>Every morning</td>
</tr>
<tr>
<td>Jardiance (empagliflozin)</td>
<td>10 mg and 25 mg tablets</td>
<td>Every morning</td>
</tr>
<tr>
<td><strong>Combination products</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xigduo XR (dapagliflozin/metformin)</td>
<td>5/500 mg, 5/1,000 mg, 10/500 mg, 10/5,000 mg tablets</td>
<td>Every morning</td>
</tr>
<tr>
<td>Invokamet (canagliflozin/metformin)</td>
<td>50/500 mg, 50/1,000 mg, 150/500 mg, 150/5,000 mg tablets</td>
<td>Every morning</td>
</tr>
<tr>
<td>Glyxambi (empagliflozin/linagliptin)</td>
<td>10/5 mg, 25/5 mg tablets</td>
<td>Every morning</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial Dose*</th>
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</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana)</td>
<td>100 mg once daily ($340)</td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga)</td>
<td>5 mg once daily ($340)</td>
</tr>
<tr>
<td>Empagliflozin (Jardiance)</td>
<td>10 mg once daily ($340)</td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>Adverse Drug Reaction</th>
<th>Signs and Symptoms Requiring Referral to Clinician</th>
</tr>
</thead>
</table>
| Mycotic infections    | • Vaginal itching or burning  
                        | • Abnormal vaginal discharge  
                        | • Urinary frequency         |
| Urinary tract infections | • Urinary frequency  
                        | • Flank pain  
                        | • Fever                      |
| Hypovolemia            | • Orthostasis  
                        | • Dizziness  
                        | • Elevated skin turgor  
                        | • Dry mucus membranes         |
| Renal dysfunction      | • Dark urine  
                        | • Weakness/fatigue  
                        | • Urinary frequency  
                        | • Hypotension                 |
| Ketoacidosis           | • 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. 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. 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.

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