CURRENT CONSIDERATIONS IN USING SGLT2 INHIBITORS

The use of sodium glucose co-transporter 2 (SGLT2) inhibitors for the management of diabetes mellitus is the focus of a series of learning opportunities planned by ASHP Advantage. The learning opportunities are designed to build on each other to provide insight into the clinical use of these agents.

A live symposium and webinar on the use of SGLT2 inhibitors for the treatment of type 2 diabetes was conducted on December 10, 2014, during the 49th ASHP Midyear Clinical Meeting and Exhibition in Anaheim, California. Frequently asked questions (FAQs) submitted during the symposium and webinar were later addressed by Initiative Chair Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, and faculty member Curtis L. Triplitt, Pharm.D., CDE, in a live webinar on March 12, 2015. Those FAQs and emerging information serve as the basis for two e-newsletters that are part of the educational initiative. The April 2015 issue focused on the role of SGLT2 inhibitors in combination with insulin in patients with type 2 diabetes and the treatment of adults with type 1 diabetes. This issue focuses on weight loss from SGLT2 inhibitors and use of these drugs in patients with chronic kidney disease (CKD) and hospitalized patients with hyperglycemia.

Other learning opportunities in the series include the following:

- On-demand web-based activity based on the December 10, 2014, symposium and webinar, which provides 1.5 hours of continuing pharmacy education.
- An Engaging the Experts interview exploring important issues related to the use of SGLT2 inhibitors for the management of diabetes.
- On-demand web-based activity based on the Ask the Experts: Practice Pearls for SGLT2 Inhibitors webinar, which provides 1 hour of continuing pharmacy education.

WEIGHT LOSS

Questions have been raised about how the weight loss associated with SGLT2 inhibitors compares with that associated with glucagon-like peptide 1 (GLP-1) agonists in patients with type 2 diabetes mellitus. The GLP-1 agonist liraglutide was approved by the Food and Drug Administration (FDA) as Victoza in 2010 for the treatment of type 2 diabetes. A larger dosage of the drug recently was approved by FDA as Saxenda for use as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults who are (1) obese with a body mass index (BMI) of 30 kg/m² or more or (2) overweight with a BMI of 27 kg/m² or more and have at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia). Victoza is not approved by FDA for use in these patients, and Saxenda is not approved by FDA for the treatment of type 2 diabetes mellitus.

Clinical trials directly comparing weight loss from SGLT2 inhibitors and GLP-1 agonists in adults with type 2 diabetes have not been conducted. A systematic review and meta-analysis of 58 randomized controlled trials comparing SGLT2 inhibitors with placebo or an active agent in this patient population was conducted. These therapies were used as monotherapy or adjunctive therapy for up to 104 weeks, although most (32) studies involved treatment for 12-26 weeks. The active agent was metformin in six studies, the dipeptidyl peptidase (DPP)-4 inhibitor sitagliptin in five studies, and a sulfonylurea in two studies. In most trials, body weight was measured as the absolute change from baseline, but it was reported only as the percentage change from baseline in some studies. The mean absolute reduction from baseline in weight with SGLT2 inhibitors was 1.74 kg greater than with placebo and 1.11 kg greater than with the active treatment. The mean percentage reduction from baseline in weight from SGLT2 inhibitors was 2.37% greater than with placebo and 2.14% greater than with the active treatment.
The effect of GLP-1 agonists on weight in obese or overweight adults with or without type 2 diabetes was assessed in another systematic review and meta-analysis of 25 randomized controlled trials comparing exenatide or liraglutide with placebo, oral antidiabetes therapy (third-generation sulfonylureas, DPP-4 inhibitors, thiazolidinediones, or metformin). The trials lasted for 20-52 weeks. The mean reduction from baseline in weight was 2.9 kg greater with GLP-1 agonists than control therapies.

Any differences between SGLT2 inhibitors and GLP-1 agonists in weight loss are primarily attributed to differences in their mechanism of action. Weight loss from GLP-1 agonists may be the result of central activity in the brain to increase satiety, which can result in weight loss if caloric intake is reduced.

Inhibitors of SGLT2 interfere with the reabsorption of filtered glucose in the proximal renal tubule, thereby increasing urinary glucose excretion and reducing blood glucose concentrations. Because the amount of glucose excreted in the urine in a 24-hour period often amounts to 50-75 g in patients receiving SGLT2 inhibitor therapy and each gram of glucose contains 4 kcal of energy, the potential daily energy loss amounts to 200-300 kcal. The maximum weight loss from both SGLT2 inhibitors and GLP-1 agonists usually is achieved within 6 months after starting treatment. Weight loss usually is maintained on a long-term basis if therapy is continued.

CHRONIC KIDNEY DISEASE

Because SGLT2 inhibitors act on the kidneys and CKD is a common progressive complication of diabetes, questions about the efficacy and safety of these agents in patients with CKD have been raised. Inhibitors of SGLT2 inhibitors exert their antihyperglycemic effect by interfering with the reabsorption of filtered glucose in the proximal renal tubule. Therefore, a reduction in glomerular filtration rate (GFR) associated with CKD reduces the impact of SGLT2 inhibitor therapy on urinary glucose excretion and blood glucose concentrations. As the GFR decreases, the glycemic efficacy of SGLT2 inhibitors becomes less pronounced.

In a randomized, double-blind, placebo-controlled trial of 269 patients with type 2 diabetes and stage 3 CKD (mean estimated GFR 39 mL/min/1.73 m²), adding canagliflozin 100 mg/day or 300 mg/day to antidiabetes therapy produced significantly greater reductions from baseline in systolic blood pressure and weight than placebo over a 52-week period. Decreases from baseline in estimated GFR (eGFR) were significantly greater in the canagliflozin 300-mg/day group than in the placebo group. Non-significant decreases in the urinary albumin-to-creatinine ratio were seen with canagliflozin 100 mg/day and 300 mg/day over 52 weeks.

Renal function should be monitored during SGLT2 inhibitor therapy, with frequent monitoring provided for patients receiving canagliflozin or empagliflozin with an eGFR <60 mL/min/1.73 m². Dapagliflozin should not be initiated in patients who develop this degree of renal impairment (Table 1), and the drug should be discontinued in patients with an eGFR that decreases below 60 mL/min/1.73 m². Canagliflozin and empagliflozin should not be initiated in patients with an eGFR less than 45 mL/min/1.73 m², and these drugs should be discontinued in patients who develop this degree of renal impairment.

Reports of renal injury in clinical trials of SGLT2 inhibitors were rare. The possibility of renal protection from SGLT2 inhibitors in patients with type 2 diabetes and CKD has been suggested but remains unproven.

<table>
<thead>
<tr>
<th>Drug</th>
<th>eGFR (mL/min/1.73 m²)</th>
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<tbody>
<tr>
<td>Canagliflozin</td>
<td>45-59: do not exceed 100 mg daily</td>
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<td></td>
<td>&lt;45: discontinue/do not initiate therapy</td>
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<tr>
<td>Dapagliflozin</td>
<td>&lt;60: discontinue/do not initiate therapy</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>&lt;45: discontinue/do not initiate therapy</td>
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eGFR = estimated glomerular filtration rate; SGLT = sodium glucose co-transporter

Table 1. SGLT2 Inhibitor Use Restrictions and Dosing Adjustments for Patients with Renal Insufficiency

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ROLE IN HOSPITALIZED PATIENTS WITH HYPERGLYCEMIA

Insulin is preferred for the management of hyperglycemia in hospital inpatients. Evidence-based guidelines from the American Diabetes Association, American Association of Clinical Endocrinologists, and The Endocrine Society recommend against the use of noninsulin therapies for hyperglycemia in the hospital setting due to a lack of safety and efficacy data in this setting, irregular dietary intake, and the high likelihood of the presence of contraindications to use of noninsulin drug therapy (e.g., metformin in a patient with renal insufficiency or a need for use of contrast media). The onset of action of many oral antihyperglycemic therapies is too slow to meet the rapidly changing needs for glycemic control in hospitalized patients with stress hyperglycemia.

The SGLT2 inhibitors should be used with caution if at all in hospitalized patients with hyperglycemia because these drugs have been associated with reductions in the GFR, small transient increases in serum creatinine, and renal adverse effects (e.g., genitourinary infections).

OVERCOMING BARRIERS TO SUCCESS

After participating in an educational activity, intentions are usually good to bring those ideas back to your practice site. But does that really happen? According to the results of a survey of participants at a Midday Symposium and Webinar about SGLT2 inhibitors held during the 49th ASHP Midyear Clinical Meeting and Exhibitio, the answer is yes. Conducted about two months after the symposium and webinar, the survey indicated that over a third of practicing pharmacists have made or still intend to make the following practice changes:

- Review updated diabetes guidelines for treatment goals and monitoring parameters
- Educate the team on the unique mechanism of action with SGLT-2 inhibitors
- Consider which patients might benefit from SGLT-2 inhibitors
- Consult with colleagues on appropriate combination therapy with SGLT-2 inhibitors
- Consult with colleagues on where they are seeing patient challenges with SGLT-2 inhibitors

Lack of experience with newer treatment options was the most frequently reported barrier to making practice changes, indicating that pharmacists are still learning about this new class of medications. Reported equally as a challenge to practice change was a lack of time or resources, a common concern among pharmacists in many practice settings. Formulary restrictions were also mentioned which may explain why lack of opportunity was often reported as a barrier to practice changes. Encouragingly, pharmacists did report sharing information from this activity with others in their institution. If you missed the Midyear symposium, a free on-demand version of the activity is available. It is approved for 1.5 hours of continuing pharmacy education. Eighty-nine percent of the survey respondents indicated that they would recommend the activity for other pharmacists who are interested in learning more about this topic. Plus you can take advantage of the other learning activities that are a part of this educational initiative.

Additional ASHP Advantage Educational Activities and Other Free CE
Visit the ASHP eLearning site to browse listings of convenient on-demand continuing education (CE) activities, as well as publications and live webinars. More than 50 hours of free on-demand CE programming are available.
REFERENCES


For complete information about educational activities that are part of this initiative, visit www.ashpadvantage.com/sglt2. There is no charge for the activities, and ASHP membership is not required.

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