Wyoming Drug Utilization Review

Type 2 Diabetes Mellitus: SGLT2 Inhibitor Therapy

Written by Meghan O'Brien, PharmD candidate, 2021

In new-onset type 2 diabetes mellitus (T2DM), metformin is the preferred first-line therapy with lifestyle modifications(1). If metformin is contraindicated or intolerable due to adverse effects of gastrointestinal reactions (diarrhea) or lactic acidosis, then alternatives are available. If after a three-month period of using metformin monotherapy plus lifestyle modifications and the HbA1c is not at goal, a preferred agent with clinical criteria such as a sodium glucose cotransporter 2 (SGLT2) inhibitor can be used. New studies on dapagliflozin suggest that it can be used in heart failure with reduced ejection fraction (HFrEF) and T2DM or in HFrEF alone (2). Wyoming Medicaid includes dapagliflozin and empagliflozin as preferred secondary medications with required clinical criteria for T2DM (3).

SGLT2 inhibitors increase glucose secretion by reducing filtered renal glucose reabsorption (1,4). This results in decreased blood glucose. This mechanism also leads to increased urination with the possibility of a urinary tract infection (UTI) due to concentrated sugar in the urine (4). Dehydration can also occur and can lead to dizziness, lightheadedness, or thirst (4). Other side effects of SGLT2 inhibitors include weight loss, yeast infection, hyperkalemia, risk of amputation, risk of bladder cancer (dapagliflozin), and rare ketoacidosis (4). The American Diabetes Association (ADA)(2) guidelines recommend to make careful decisions in using this class if the patient has a history of "traumatic amputation within 12 months of screening, or an active foot ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening." If these events do occur, then the medication should be discontinued until the event has ended, and later the medication can be restarted (4). SGLT2 inhibitors are not recommended in patients with eGFR <45 mL/min and should be avoided in patients with eGFR <30 mL/min (4). Advantages of SGLT2 inhibitors include weight loss, reduced chronic kidney disease (CKD), reduced blood pressure (3 to 5 mmHg) and less acute kidney injury (4,5). Patients with HFrEF may have reduced hospitalizations for heart failure (hHF), reduced major adverse cardiovascular events (MACE) and reduced cardiovascular death (2). The four SGLT2 inhibitors approved by the FDA in T2DM are dapagliflozin (Farxiga), empagliflozin (Jardiance), canagliflozin (Invokana), and ertugliflozin (Steglatro) (6). Dapagliflozin is currently the only one FDA approved for HFrEF (2). While doses of SGLT2 inhibitors differ, they are all dosed once daily and reduce HbA1c by 0.5-0.7% (4).

SGLT2 inhibitors are recommended for dual therapy in patients with high-risk atherosclerotic cardiovascular disease (ASCVD), CKD and/or heart failure (HF) (2). The combination of SGLT2 inhibitors and GLP-1 receptor agonists has shown benefits in HbA1c-lowering and weight-reduction efficacy independent of baseline or individual HbA1c (2). The cardiorenal benefit in diabetes for these two classes together has not been fully established (2). Meta-analysis on SGLT2 inhibitors reveals this class is effective in CKD, hHF, and all risk group levels of cardiovascular disease (CVD) with no significance in preventing MACE alone (2). SGLT2 inhibitors have the highest level of benefit with CKD, HF, and/or HFrEF in T2DM (2).

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Dapagliflozin has benefits in patients with HFrEF with T2DM or without T2DM (7). Dapagliflozin lowers the risk of cardiovascular death when the patient has HFrEF more than a patient without HFrEF (7). The mechanism in reducing HF in patients with diabetes is not fully understood. Kato et al (7) suggests that the mechanism may not only be because of intravascular volume loss. Wiviott et al (5) tested a primary outcome of safety between dapagliflozin and placebo with respect to MACE. Dapagliflozin does not benefit patients in reducing MACE outcomes alone, however, it is safe to use in patients with a history of cardiovascular events (5). The DECLARE-TIMI 588 trial found benefits in MACE with patients who had established CV disease when using dapagliflozin. MACE benefits were not found in patients with only a few risk factors (8). GLP-1 receptor agonists remain the most beneficial for MACE outcomes in T2DM. Empagliflozin has also shown benefits in decreasing cardiovascular death and hHF (9). Empagliflozin and dapagliflozin have similar outcomes, advantages and adverse effects.

SGLT2 inhibitors are an appropriate add-on therapy for patients with T2DM if HbA1c is not goal after 3 months of metformin and lifestyle modifications. There are limited medications for HFrEF and dapagliflozin is an FDA approved drug that can reduce symptoms and mortality of HFrEF. Dapagliflozin may be preferred in patients with HF and T2DM.

References:

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The P&T Committee met for its quarterly business meeting on August 12, 2021

Highlights of this meeting include:

- Exservan, Myfembree, and Kerendia will be limited to indication.
- Kloxxado will require prior authorization.
- Medications used for gender transition therapy were discussed. A psychiatric evaluation will be required for both temporary (puberty blocking) agents as well as permanent (hormonal) gender transition treatments. Clinical chart notes discussing the results of a psychiatric evaluation of the client are required in order to be granted approval for gender dysphoria drug treatments.

The proposed prior authorization criteria are open for public comment. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board
Dept. 3375, 1000 E. University Avenue
Laramie, WY 82071.

Comments should be received prior to September 15, 2021.

The next P&T Committee meeting will be held November 11, 2021 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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