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DRUG NEWS

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Recent Arrivals On The Diabetes Front: SGLT2 Inhibitors
Canagliflozin, Dapagliflozin, Empagliflozin

OVERVIEW

- **Agents:** Sodium-glucose cotransporter 2 (SGLT2) inhibitors interfere with the reabsorption of glucose and decrease the glucose threshold in the kidneys. This leads to an increase in urinary glucose excretion, and a reduction in blood glucose.[1] Three agents are marketed in Canada: canagliflozin (Invokana™), dapagliflozine (Forxiga™), and empagliflozin (Jardiance™)
- **Therapeutic use:** Oral antihyperglycemic agents for the treatment of type 2 diabetes mellitus (T2DM).[2]
- **Dosing[3-5]:**
  - canagliflozin 100 - 300mg PO once daily
  - dapagliflozin 5-10 mg PO once daily
  - empagliflozin 10-25 mg PO once daily
- **Benefits:** SGLT2 inhibitors decrease $HbA1_c$, reduce weight, and lower blood pressure.[6] Cardiovascular benefits have recently been reported with empagliflozin.[7] When used as monotherapy, risk of hypoglycemia is small.[8]
- **Disadvantages / Risks:** SGLT2 inhibitors are expensive (~$3 per tablet),[9] have limited use in patients with renal dysfunction, increase the risk of genital mycotic infections, and their long term effects are unknown.[2,8]

INDICATIONS

- Canagliflozin, dapagliflozin and empagliflozin are indicated as monotherapy alongside diet and exercise when the patient cannot take metformin as well as part of various combinations (see Table 1).[3-5]

Table 1: Approved Combinations of SGLT2 Inhibitors with other Antihyperglycemic Agents[3-5]

	Canagliflozin	Dapagliflozin	Empagliflozin
Metformin	√	√	√
Sulfonylurea	√	√	
Metformin + Sulfonylurea	√	√	√
Metformin + Pioglitazone	√		√
Metformin + Sitagliptin*		√	
Insulin +/- Metformin	√	√	√

- SGLT2 inhibitors have not been studied for safety and efficacy in individuals <18 years old, and therefore are not recommended for this population.[3-5] While animal studies have not indicated any risk of malformation from any of the SGLT2 inhibitors, human data are not available in pregnancy or lactation.10 A theoretical concern has been raised that renal tubule and pelvic dilatation may increase risks of use in $2^{nd}/3^{rd}$ trimesters and lactation.[10]
- SGLT2 inhibitors are less effective in patients with renal impairment. Initiating therapy with these agents is not recommended if the estimated glomerular filtration rate (eGFR) is less than 60 ml/minute and ongoing therapy should be discontinued if eGFR falls below 45 ml/minute.[3-5]

EFFICACY

- Dual therapy with metformin and an SGLT2 inhibitor is more effective in achieving glycated hemoglobin ($HbA1_c$) < 7%, reducing $HbA1_c$, weight, and systolic blood pressure than placebo.[6]
- No head-to-head trials have been conducted to compare the efficacy of the three agents. A systematic review published in February of 2016 reviewed 13 randomized controlled trials with more than 6000 participants and analyzed the effectiveness of SGLT2 inhibitors.[6] The authors reviewed data from patients with T2DM and inadequate glucose control, treated with either SGLT2 inhibitor monotherapy or dual therapy in combination with metformin; both arms included diet and exercise. With dual therapy:
    - the greatest reduction in HbA1c (-0.77%) was seen with canagliflozin 300mg; canagliflozin 100mg and dapagliflozin 10mg produced similar results
    - more patients achieved $HbA1_c$ of < 7% with empagliflozin 10mg and 25mg, and canagliflozin 300mg
    - the greatest weight loss (-2.5 kg) was with canagliflozin 300mg
    - the greatest reduction of systolic blood pressure (SBP) was by dapagliflozin 10mg; canagliflozin 300mg and empagliflozin 25mg were both more effective than empagliflozin 10mg at reducing SBP

Table 2: SGLT2 Inhibitor Dual Therapy with Metformin: Outcomes[6]

	Canagliflozin		Empagliflozin		Dapagliflozin
	100 mg	300 mg	10 mg	25 mg	10mg
Decrease in HbA1c	✓✓	✓✓	✓	✓	✓✓
Patients HbA1c < 7%	✓	✓✓	✓✓	✓✓	✓
Decrease in weight	✓✓	✓✓	✓	✓	✓
Decrease in blood pressure	✓✓	✓✓	✓	✓✓	✓✓✓

CARDIOVASCULAR BENEFITS

In 2016, the Canadian Diabetes Association (CDA) updated their recommendations for pharmacotherapy of T2DM to include the addition of an SGLT2 inhibitor for individuals with uncontrolled T2DM and clinical cardiovascular disease.[11] This recommendation stems from the publication of a randomized, double-blind, placebo-controlled trial (EMPA-REG) analyzing cardiovascular outcomes of empagliflozin with over 7,000 participants treated for 3.1 years.[7] EMPA-REG demonstrated that empagliflozin has more benefits than decreasing blood glucose, blood pressure, and weight. Most patients included in the study had cardiovascular disease (99%), and the majority had T2DM for more than 10 years (57.2%). Participants were assigned to empagliflozin 10mg, 25mg, or placebo, added to standard care. Overall, patients on empagliflozin had a significantly lower risk of cardiovascular death, death from any cause, and hospitalization from heart failure compared to placebo. Rates for severe and serious adverse effects, and adverse effects leading to the discontinuation of empagliflozin were all lower than placebo.

Since the SGLT2 inhibitors are relatively new, it will take time to better understand their long term effects, whether the entire class demonstrates cardiovascular benefits, and if the same benefit would be seen in T2DM patients without established cardiovascular disease.[12] Currently, the EMPA-REG trial is the only one to demonstrate cardiovascular benefits with an SGLT2 inhibitor; however trials are currently underway for canagliflozin (CANVAS), and dapagliflozin (DECLARE) which may shed light on whether the benefits are class-wide.[13]

ADVERSE EFFECTS

- **Hypoglycemia:** The risk of SGLT2 inhibitors causing hypoglycemia when used as monotherapy is low as their mechanism of action is independent of insulin secretion to reduce blood glucose. The incidence of hypoglycemia with canagliflozin, empagliflozin, and dapagliflozin is higher when used with a sulfonylurea or insulin.[8]
    - If HbA1c is not highly elevated or the patient has other risk factors for hypoglycemia, consider reducing the dose of sulfonylurea or insulin when initiating an SGLT2 inhibitor, then titrate as needed to maintain glycemic control.
    - Withhold SGLT2 inhibitors on sick days.
- **Genital infections**: The risk of genital infections is increased with SGLT2 inhibitors since there is an increase in excretion of glucose through the urine. This can affect 5-10% of users, and has been more common in women (mostly vulvovaginitis) than men (mostly mycotic balanitis). However, most cases are easily diagnosed and are successfully treated.[8]
    - Counsel patients to monitor for symptoms. Over-the-counter antifungals are usually effective. Unless the patient experiences multiple episodes, it is not necessary to discontinue the SGLT2 inhibitor.
- **Urinary Tract Infections (UTIs):** The incidence of UTIs with canagliflozin and dapagliflozin is only slightly higher than placebo, and empagliflozin has not been shown to cause an increased incidence compared to placebo.[14] Risk factors leading to a higher incidence of UTIs with SGLT2 inhibitors include: age > 65 years old, female sex and a history of recurrent UTIs.
    - The majority of cases are diagnosed based on usual symptoms and can be successfully treated with antibiotics without discontinuing the SGLT2 inhibitor.[8]
- **Volume Depletion/Low Blood Pressure:** SGLT2 inhibitors can cause hypotension, dizziness and dehydration. This is an uncommon occurence but is more likely to occur in individuals > 75 years old, with a creatinine clearance <60mL/min, and who are also taking loop diuretics.[8]
    - If a concern, counsel on maintaining adequate hydration and consider reducing the dose of concommitant diurects or other antihypertensive drugs.
- **Lipoproteins:** SGLT2 inhibitors may increase low- and high-density lipoproteins, but lower triglycerides.[8]
- **Cancer:** There have been cases reported of breast and bladder cancer associated with dapagliflozin; currently there is no evidence that supports a causal relationship between dapagliflozin use and cancer.[15] The DECLARE trial has been modified to adequately evaluate for an association between cancer and dapagliflozin.
- **Ketoacidosis:** Ketoacidosis has been reported as a rare adverse effect. The diagnosis can be delayed as glucose levels are usually lower than expected with a ketoacidosis event. The EMPA-REG trial with empagliflozin demonstrated that ketoacidosis rates were similar to placebo. More data are needed to determine if certain patient factors increase susceptibility to ketoacidosis.[14]
    - Counsel patients on symptoms of possible ketoacidosis (difficulty breathing, nausea, vomiting, abdominal pain, confusion, unusual fatigue) and the need to seek medical attention immedicately if these occur.
- **Others:** There may be an association of an increase in lower limb amputation (mostly toe) with canagliflozin compared to placebo.[16] Currently in the CANVAS trial, 7 out of 1000 patients, and 5 out of 1000 patients taking canagliflozin 100mg and 300mg ,respectively, have required amputation. This is compared to 3 of 1000 patients in the placebo arm; follow-up has been ongoing for 4.5 years.

The FDA is currently evaluating the need for regulatory action for possible acute renal injury, thromboembolisms, and stroke in association with use of SGLT2 inhibitors.[17] Overall, there are special populations that seem to be more susceptible to some adverse effects (females, older patients, or those with decreased renal function). Long term safety data are still unknown for the SGLT2 inhibitors.[2]

PLACE IN THERAPY

- In clinical practice SGLT2 inhibitors will mostly be added to therapy as either a 2nd or 3rd line option.
- The CDA Clinical Practice Guidelines consider SGLT2 inhibitors a 2nd line therapy option when metformin, along with diet and exercise, have not achieved glycemic targets. Also, if $HbA1_c \geq 8.5\%$ at the time of diagnosis of T2DM, metformin and an additional agent can be started immediately, which includes an SGLT2 inhibitor.[11]

THIRD PARTY COVERAGE

- The Canadian Drug Expert Committee (CDEC) has recommended canagliflozin and empagliflozin be included on drug formularies when glycemic targets are not achieved with metformin combined with a sulfonylurea and insulin is not an option. The recommended criteria for dapagliflozin are a little more flexible[18]:
    - in combination with metformin when it alone is not adequate and sulfonylureas and insulin are not options;
    - in combination with a sulfonylurea when it alone is not adequate and metformin and insulin are not options;
    - in combination with metformin and insulin when they do not adequately control hyperglycemia; and
    - in combination with insulin when it alone is not adequate and metformin is not an option
    - the combination with metformin and sulfonylurea is currently under review.
- Canagliflozin and empaglifozin are covered under the Saskatchewan Drug Plan & Extended Benefits Branch (SDPEBB) if the patient meets the exception drug status (EDS) criteria, i.e.: the patient must already have had prescriptions for metformin and/or a sulfonylurea in which adequate control was not achieved or to which the patient was intolerant.[19] Currently dapagliflozin is not covered by SDPEBB.
- Currently canagliflozin is the only SGLT2 inhibitor listed in the Non-Insured Health Benefits (NIHB) Drug Benefits List. It is a limited use benefit in which patients will qualify only if adequate glycemic control has not been achieved or an intolerance exists with metformin and a sulfonylurea.[20]

CONCLUSION

The SGLT2 inhibitors represent a novel class of antihyperglycemic agents that offer promising results in terms of cardiovascular effects, weight loss (or neutrality), and glycemic control. However, as wth all new drugs, enthusiasm needs to be tempered until longer-term safety data are available.

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