Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors and Their Place in Therapy

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Goal:
Provide pharmacists with the knowledge to effectively utilize or recommend sodium-glucose co-transporter 2 (SGLT2) inhibitors in the treatment of type 2 diabetes mellitus (T2DM) and recognize when dose adjustments and drug monitoring are warranted.

Learning Objectives:
Upon completion of this article the learner should be able to:

1. Recall the mechanism of action of SGLT2 inhibitors
2. Recognize available SGLT2 inhibitors and appropriate dosing
3. Identify at least 3 potential benefits and concerns of SGLT2 inhibitors
4. Compare/contrast ADA and AACE/ACE guideline recommendations and landmark trials such as EMPA-REG and CANVAS

Summary: SGLT2 inhibitors are a novel class of oral antidiabetic agents that moderately improve glycemic control by lowering glycosylated hemoglobin approximately 1%. These agents work by increasing urinary glucose excretion and are indicated as adjunct to diet and exercise to improve glycemic control in adults with T2DM. Empagliflozin and canagliflozin also have the advantage of cardiovascular benefit. Additional favorable effects compared to other antidiabetic classes include weight loss, low risk of hypoglycemia, and decreases in blood pressure. Adverse effects associated with SGLT2 inhibitors include genital mycotic infections, urinary tract infections, dehydration, increased urination, hyperkalemia, and ketoacidosis. American Association of Clinical Endocrinologists and American College of Endocrinology recommend SGLT2 inhibitors as the third antidiabetic class in its hierarchy. After metformin, the American Diabetes

Association recommends consideration of drug-specific and patient factors for combination therapy. Specifically, if a patient has atherosclerotic cardiovascular disease**,** then combination therapy should include an antidiabetic agent with evidence of cardiovascular risk reduction.

Conclusion: SGLT2 inhibitors provide a unique mechanism of action that results in a low risk of hypoglycemia and offers a treatment option in the beta-cell-centric model. SGLT2 inhibitors may be appropriate in combination with additional antidiabetic classes. The benefits of these agents should be weighed against potential risks**,** and patient-specific factors must be taken into consideration.

Background:

In 2017, the Centers for Disease Control and Prevention (CDC) reported 30.3 million people, or 9.4% of the United States population**,** have diabetes.[1] Complications of uncontrolled diabetes include both microvascular and macrovascular complications; controlling diabetes is important to prevent these complications. The American Diabetes Association (ADA) recommends a goal glycosylated hemoglobin (A1c) < 7% for most patients with diabetes.[2] According to the U.S. National Health and Nutrition Examination Survey, only 52.5% of individuals reported achieving this goal from 2007-2010.[3] Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the newest class of oral antidiabetic agents. They have a unique mechanism of action that has never previously been targeted. Four SGLT2 inhibitors have been approved by the U.S. Food and Drug Administration (FDA) since 2013 and more are in clinical studies. As a pharmacist, understanding place in therapy, landmark trials, and national guideline recommendations regarding use of SGLT2 inhibitors is important.

Mechanism of Action:

Two of many components affecting glycemic control are glucose absorption in the intestines and glucose reabsorption in the kidneys.[4] Sodium-glucose co-transporters are located throughout the body, not just in the kidneys. SGLT2 is primarily found in the kidneys and is responsible for approximately 90% of the reabsorption of glucose. Sodium-glucose co-transporter 1 (SGLT1) is primarily located in the intestines and is responsible for glucose absorption into the blood. Within the kidneys, SGLT1 is only responsible for approximately 10% of glucose reabsorption. Normally, up to 180 g of sugar can be reabsorbed through the kidneys each day without glucose spilling into the urine. SGLT2 inhibitors block approximately 30-50% of glucose reabsorption in the kidneys by lowering the renal threshold for glucose resulting in excess glucose excretion in the urine. This mechanism of action is independent of the presence of insulin.[5-7]

Available Agents:

Currently, there are four FDA approved oral SGLT2 inhibitors available in the United States: canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®), and ertugliflozin (Steglatro™).[8-11] All agents are dosed once daily and use is contraindicated when estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73 m^2; however, there are variations for when use should be discontinued or not initiated based on eGFR (Table 1). Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin all come as

combination products with metformin**:** Invokamet®**,** Xigduo XR®, Synjardy®, and Segluromet™ respectively.[12-15] Dapagliflozin, empagliflozin, and ertugliflozin are available as combination products with dipeptidyl peptidase-4 (DPP4) inhibitors**:** Qtern®, Glyxambi®, and Steglujan™ respectively.[16-18]

Indications:

SGLT2 inhibitors are approved for adults 18 years and older with type 2 diabetes mellitus (T2DM).[8-11] These agents are approved for use as an adjunct to diet and exercise to improve glycemic control. They are not approved for use in children or those with type 1 diabetes mellitus (T1DM). Recently, empagliflozin expanded its indication to include decreased risk of cardiovascular death in adults with T2DM and a history of cardiovascular disease.[10]

Supporting Evidence for Use:

SGLT2 inhibitors primarily impact fasting blood glucose levels and decrease A1c approximately 0.7-1.1%.[19-40] The available agents have similar A1c lowering potential; however, there currently are no head-to-head studies comparing SGLT2 inhibitors. Based on available data, the A1c lowering of each agent is similar when used as monotherapy or in combination with other oral antidiabetic agents or insulin (Table 2). This is because the mechanism of action is independent of the presence of insulin.[41] The potential for A1c reduction is based on baseline glucose levels; therefore, patients with a greater degree of hyperglycemia may have more A1c lowering with SGLT2 inhibitors than those with more mild hyperglycemia.

SGLT2 inhibitors exhibit most of their glucose-lowering effect at lower doses.[23,26,28] When the dose of these agents is titrated up, additional A1c lowering may not be substantial. These agents should be started at a lower dose and increased as indicated.[8-11] SGLT2 inhibitors are less efficacious in patients with renal impairment as the kidneys are not able to filter as much glucose.[42] Also, patients with renal impairment are at increased risk of side effects.

Two pivotal trials have been published demonstrating the cardiovascular benefits of empagliflozin and canagliflozin in patients with T2DM.[43,44] The Empagliflozin Cardiovascular Outcomes and Mortality Study (EMPA-REG) focused on patients with established cardiovascular disease (CVD), while the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program included both patients with symptomatic atherosclerotic CVD and patients at high risk for CVD. These studies had multiple similarities: baseline characteristics of both trials included primarily white males over the age of 60 with an A1c of 8-8.2%. These studies both demonstrated improvements in the treatment group with regards to A1c reduction, weight loss, and a reduction in both systolic and diastolic blood pressure. Cardiovascular outcomes of dapagliflozin and ertugliflozin are being evaluated.[45,46]

EMPA-REG:[43]
The EMPA-REG study examined the impact of empagliflozin on cardiovascular morbidity and mortality. This multinational study included 7020 patients. Patients received empagliflozin 10 mg, empagliflozin 25 mg**,** or placebo in a 1:1:1 ratio. Use of additional agents for glycemic control remained unchanged for 12 weeks

following randomization with exceptions for predefined hyperglycemia or medical necessity. After 12 weeks, use of additional glucose lowering agents was guided by best practice and local guidelines. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke.

Patients treated with empagliflozin had a lower rate of the primary composite outcome compared to placebo (Table 3). Further review of this composite outcome demonstrates that death from cardiovascular causes occurred at a statistically significant lower rate in the empagliflozin treated group; however, the rates of nonfatal MI or nonfatal stroke failed to achieve significance. There was no difference in the key secondary outcome as both treatment groups had similar rates of hospitalization for unstable angina. Additional cardiovascular outcomes evaluated revealed that patients treated with empagliflozin had fewer hospitalizations for heart failure (2.7%) compared to placebo (4.1%) (HR 0.65, CI 0.50-0.85, p=0.002).

With regards to safety, the only adverse event reported more frequently in empagliflozin treated patients was genital mycotic infections. This is consistent with previous studies of SGLT2 inhibitors.

CANVAS Program:[44]
The CANVAS Program is the integrated analysis of the CANVAS and CANVAS-Renal (CANVAS-R) trials evaluating cardiovascular, renal**,** and safety outcomes of canagliflozin. Over 10,000 patients participated in the multinational CANVAS Program, 4330 in CANVAS and 5812 in CANVAS-R. Inclusion criteria (Table 3) were identical for each study. Patients received canagliflozin 100 mg, canagliflozin 300 mg, or placebo in a 1:1:1 ratio in the CANVAS study. In the CANVAS-R study, patients received canagliflozin 100 mg or placebo in a 1:1 ratio with the option to increase to canagliflozin 300 mg at week 13 if needed. Use of additional agents for glycemic control and to control other risk factors was guided by best practice and local guidelines. The primary outcome was a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke which is identical to EMPA-REG.

Fewer patients treated with canagliflozin experienced the primary composite outcome (Table 3). While the individual components of this outcome failed to achieve significance, the data suggested benefit. Exploratory prespecified cardiovascular and renal outcomes were also evaluated and demonstrated beneficial effects of canagliflozin on the rate of hospitalizations for heart failure, rate of progression of albuminuria**,** and a renal composite outcome.

The majority of adverse effects were similar in the canagliflozin and placebo groups with notable exceptions. Infections of male or female genitalia, volume depletion, and osmotic diuresis were observed more frequently in canagliflozin treated patients, which is consistent with previous SLGT2 inhibitor studies. There was a higher risk of amputation of toes, feet**,** and legs in the canagliflozin treated patients compared to placebo (6.3 vs. 4.3 participants per 1000 patient-years, HR 1.97; CI 1.41 to 2.75) with the highest risk occurring in patients with a history of amputations or peripheral vascular disease.

Place in Therapy for SGLT2 Inhibitors:

SGLT2 inhibitors are considered one of six potential pharmacologic classes for use with 2-drug or 3-drug combination therapy using a patient-centered approach for T2DM management per the ADA "Standards of Medical Care in Diabetes."[47] In 2018, the ADA recommended combination therapy include metformin and an antidiabetic agent proven to reduce major cardiovascular events and cardiovascular mortality (i.e. empagliflozin and liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist) specifically in patients with established atherosclerotic CVD. Additionally, canagliflozin may be considered as combination therapy with metformin to reduce major cardiovascular events in this patient population. If the patient does not have atherosclerotic CVD, the ADA recommends one of six treatment options in combination with metformin (Table 4) based on drug-specific and patient factors. Consideration should be given to initiating dual therapy when the A1c is ≥9% to achieve A1c goals faster according to the ADA.

The ADA 2018 guidelines and The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2018 guidelines both recommend combination therapy if the A1c goal is not achieved after 3 months of metformin monotherapy treatment.[47,48] In contrast, the AACE/ACE guidelines recommend a lower threshold of an A1c ≥7.5% for initiation of dual therapy.[48] AACE/ACE guidelines also recommend a specific hierarchy for both monotherapy and dual therapy (Table 5) which differs from ADA. According to ACCE/ACE, SGLT2 inhibitors are considered third-line for T2DM management following metformin and GLP-1 receptor agonists. SGLT2 inhibitors can be considered as monotherapy in patients who have a contraindication or intolerance to the first-line therapy, metformin.[47,48]

Patient characteristics, results, and sub-group analyses from the EMPA-REG and CANVAS trials may be helpful in determining utility for specific patients.[43,44] While both studies demonstrated fewer composite cardiovascular primary outcome events, only EMPA-REG specifically demonstrated a reduction in cardiovascular deaths. Both studies demonstrated fewer heart failure hospitalizations in the treatment group. CANVAS demonstrated a benefit with prespecified renal outcomes as previously described. While not reported with the cardiovascular outcome results of EMPA-REG, prespecified renal outcomes were identified and reported in a separate publication and demonstrate slower progression of kidney disease, assessed by multiple markers, in patients treated with empagliflozin.[49]

The current antidiabetic treatment approach from clinical guidelines may be challenged based on the newly proposed beta-cell-centric model.[50] The focus of this model is beta-cell dysfunction in diabetes of all types. It is proposed that there are 11 pathways contributing to hyperglycemia, described as the "egregious eleven." The primary goal of therapy with this model is stabilizing and preserving beta-cell function. Medications should be selected that target as many "egregious eleven" pathways as needed with the least number of antidiabetic agents possible to decrease the patient's blood sugar without causing hypoglycemia or weight gain. Individualized patient care is emphasized along with a combination of antidiabetic agents that act synergistically.

SGLT2 inhibitors are recommended in the beta-cell-centric model as a target that does not pose risk to the function of the beta-cells in addition to reducing weight and posing minimal hypoglycemic risk.

Due to the mechanism of action independent of insulin, SGLT2 inhibitors may be utilized in patients who have developed insulin resistance. A patient centered approach is important when deciding appropriate use of an SGLT2 inhibitor. Providers must weigh advantages and disadvantages of these agents as well as other antidiabetic medications (Tables 6 and 7).[47,51-53] Drug choice should be based on patient preferences as well as various patient, disease, and drug characteristics, with the goal of reducing blood glucose levels while minimizing side effects, especially hypoglycemia and weight gain, and avoiding further impairment of beta-cell function.[47,50,54]

Advantages:

SGLT2 inhibitors possess a unique set of advantages. Understanding these advantages will help clinicians determine the optimal treatment for their patients. As previously discussed, empagliflozin and canagliflozin provide unique cardiovascular and renal benefits in specified high-risk patient populations; however, it is unknown if these benefits will occur in lower-risk patients or with all SGLT2 inhibitors.[43,44]

An advantage of SGLT2 inhibitors is weight loss. The initial reduction in total body weight is related to fluid loss. Subsequent weight reduction is due to loss of fat mass from caloric loss with increased urinary glucose excretion.[55] While SGLT2 inhibitors can cause a decrease in weight due to excess glucose excretion; they are not approved for weight loss. Maximum weight loss is estimated to be 2-3 kg occurring at approximately 6 months; however, a meta-analysis by Berhan and colleagues showed a mean difference in weight of only -0.59 kg.[20,26,33,37,56] Weight loss, which is mainly visceral fat, is generally sustained over time.[38,55,57]

Another advantage of SGLT2 inhibitors is the decrease in both systolic and diastolic blood pressure. Studies reveal an average decrease of approximately 3-5 mmHg systolic and 2 mmHg diastolic.[58] The mechanism is not fully understood but is likely due to a dose-related osmotic diuresis. In addition to blood pressure reductions without effects on heart rate, empagliflozin has been shown to have favorable effects on arterial stiffness and vascular resistance.[59] Patients should be cautioned that orthostatic changes may occur when the medication is initiated or the dose is increased. Due to an increased risk of hypotension, use SGLT2 inhibitors cautiously in combination with diuretics and other blood pressuring lowering agents.[8-11,58]

Lastly, due to the unique mechanism of action, the risk of hypoglycemia is low.[58] Unlike insulin and insulin secretagogues, SGLT2 inhibitors do not independently have a risk of hypoglycemia.[51,52] However, in combination with insulin or insulin secretagogues, SGLT2 inhibitors may increase the risk of hypoglycemia.[8-11]

Disadvantages:

As with any drug class, there are important disadvantages to consider that may be significant enough to impede use. Since these agents are brand name only, one key disadvantage is the significant cost with an out-of-pocket expense over $300 for a one-

month supply.[60] Other disadvantages related to adverse effects are discussed below in more detail.

SGLT2 inhibitors are associated with increased incidence of urinary tract infections (UTIs).[61] Although these are mainly mild to moderate, the FDA Adverse Event Reporting System (FAERS) database identified 19 cases of urosepsis and pyelonephritis from March 2013 to October 2014.[62] The overall frequency of UTIs in patients taking SGLT2 inhibitors is highly variable from 4%-12%; however, there is only an approximate 1% increase in risk of UTIs with all SGLT2 inhibitors compared to placebo.[61] Meta-analyses have shown a wide range of risk for UTIs related to individual agents, with lower doses of SGLT2 inhibitors demonstrating a higher incidence of UTIs.[55,63,64] Patients at greatest risk of this complication are those with a history of recurrent UTIs and women.[61]

Genital mycotic infections (GMIs) are another concern with these agents. There is an approximate risk of 6-12% in women and 3-4% in men for GMIs.[61] Meta-analyses have shown a wide range of risk for GMIs related to individual agents.[55,63,64] These infections can occur regardless of infection history.[61] However, patients at higher risk are women with a prior history of GMIs and uncircumcised men.

SGLT2 inhibitors can cause dehydration and osmotic diuresis of approximately 350 mL daily, which is equivalent to one extra void per day.[58] FAERS database has identified 101 cases of acute kidney injury (AKI) occurring over a 2 year period with canagliflozin and dapagliflozin; 98 of these cases required hospitalization and 15 patients required dialysis.[65] Most patients who discontinued the SGLT2 inhibitor fully recovered. In over half of the cases reported, the AKI occurred within the first month of initiation. Patient characteristics that may increase risk of AKI include hypovolemia, chronic renal insufficiency, congestive heart failure, and use of diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs. The impact of SGLT2 inhibitors on kidney function is not known; pooled data from eight trials of canagliflozin showed an initial decrease in eGFR which resolved with continued SGLT2 inhibitor use.[66] The incidence of renal-related adverse events for canagliflozin was similar to those not taking canagliflozin. More frequent renal function monitoring is recommended in patients at higher risk.[42] Patients should also be counseled to maintain adequate hydration when initiating treatment.[58]

The FDA revised labeling in December 2015 to include a warning regarding these agents causing ketoacidosis.[62] The mechanism for this effect is not clear, and ketoacidosis occurred when patients were euglycemic or had mildly elevated glycaemia. A post-hoc analysis did not show increased incidence of ketoacidosis with canagliflozin compared to non-canagliflozin users over 104 weeks.[64] Burke and colleagues completed a systematic review of reported cases of ketoacidosis related to SGLT2 inhibitors.[67] The review identified patient-specific factors likely contributing to the incidence of ketoacidosis. These factors included latent autoimmune diabetes of adulthood (LADA), recent major surgery, and decreased or discontinued insulin. Use should be cautioned in patients with LADA or T1DM, and patients undergoing major surgery should stop these agents at least 24-48 hours prior to surgery.[48,67] If ketoacidosis occurs, SGLT2 inhibitors should be discontinued and should not be restarted.

Common symptoms of ketoacidosis include increased urination, excessive thirst, blurred vision, rapid breathing, confusion, and weight loss.[68]

SGLT2 inhibitors are also associated with increased low-density lipoprotein (LDL), increased urination, dehydration, and dose-dependent hyperkalemia.[39,58] The adverse event profile of this drug class may not be fully realized. For example, an imbalance in bladder cancers was observed in clinical trials with dapagliflozin but not with other SGLT2 inhibitors.[9] Canagliflozin has been associated with an increased risk of leg and foot amputations as well as increased risk of bone fractures and decreased bone mineral density.[44,69,70] Pharmacists must recognize the potential for unknown risks when prescribing or dispensing these relatively new agents.

Future Use:

Additional SGLT2 inhibitors are in development and a combination SGLT1/SGLT2 inhibitor (i.e. sotagliflozin) is in clinical studies. As mentioned previously, SGLT1 is the primary transporter responsible for absorption of glucose in the intestines and is thought to be overexpressed in the GI tract of patients with T2DM.[71] The combination SGLT1/SGLT2 inhibitor works by blocking glucose absorption from the diet as well as causing excess glucose to be excreted in the urine. Sotagliflozin has demonstrated significant reductions in postprandial glucose compared to placebo ($p = 0.005$). Sotagliflozin may cause significant gastrointestinal adverse events such as diarrhea and nausea.

SGLT2 inhibitors are also being studied for use in the treatment of T1DM due to a mechanism of action independent of the presence of insulin.[72] Currently, insulin therapy is the mainstay for T1DM management.[47] Short-term human studies have suggested that SGLT2 inhibitors may be useful as an adjunct-to-insulin in T1DM.[72,73] A systematic review by Chen and colleagues included 10 studies evaluating the safety and efficacy of these agents in T1DM.[74] The systematic review found SGTL2 inhibitor use in T1DM resulted in significant reductions in fasting glucose, A1c, weight, and total daily insulin dose.

Due to concerns for ketoacidosis, use of SGLT2 inhibitors in T1DM should be cautioned until further studies have been conducted.[67] The systematic review by Chen and colleagues mentioned above found an increased risk of ketoacidosis in the SGLT2 inhibitor group compared to placebo in T1DM.[74] Ketoacidosis was reported in 3 of the 10 studies reviewed with a total of 16 events. Surprisingly, Burke and colleagues found one-third of ketoacidosis cases related to SGLT2 inhibitors were in patients with T1DM but the majority occurred in patients with T2DM.[67] Of the cases in T1DM, some individuals had precipitating factors such as illness, pump failure, or alcohol use. Six of the thirteen (67%) reviewed cases of ketoacidosis in T1DM were related to reductions in insulin doses. If SGLT2 inhibitors are used along with insulin, AACE/ACE recommends avoiding discontinuation of insulin or drastically decreasing the dose of insulin as well as avoiding very low carbohydrate diets and excessive alcohol intake.[48,75]

Conclusion:

SGLT2 inhibitors offer a unique mechanism of action not previously targeted. The

mechanism of action is independent of the presence of insulin resulting in a low risk of hypoglycemia. These agents may be a good option as they do not pose risk to the function of the beta-cells in addition to reducing weight. Recent cardiovascular data showing the beneficial effects of empagliflozin and canagliflozin may lead to increased use of these agents. Based on results of the EMPA-REG trial, empagliflozin expanded its FDA approved indication to include decreased risk of cardiovascular death in adults with T2DM and a history of cardiovascular disease. When considering an SGLT2 inhibitor the benefits should be weighed against potential risks. SGLT2 inhibitors may be appropriate second-line therapy in combination with additional agents, oral and/or insulin, using a patient centered approach.

Table 1: Summary of available SGLT2 inhibitors[8-11]

	Canagliflozin (*Invokana*®)	**Dapagliflozin (*Farxiga*®)**	**Empagliflozin (*Jardiance*®)**	**Ertugliflozin (*Steglatro*™)**
Starting Dose	100 mg daily	5 mg daily	10 mg daily	5 mg daily
Max Dose	300 mg daily	10 mg daily	25 mg daily	15 mg daily
Renal Impairment	eGFR 45 to <65 mL/min/1.73 m^2: 100mg daily	eGFR <60 mL/min/1.73 m^2: do not initiate, discontinue if persistent	eGFR 45 to <60 mL/min/1.73 m^2: no dosage adjustment necessary	eGFR <60 mL/min/1.73 m^2: do not initiate, discontinue if persistent
	eGFR <45 mL/min/1.73 m^2: do not initiate, discontinue if persistent		eGFR <45 mL/min/1.73 m^2: do not initiate, discontinue if persistent	
	eGFR <30 mL/min/1.73 m^2: use is contraindicated			
Available Strengths	100 mg 300 mg	5 mg 10 mg	10 mg 25 mg	5 mg 15 mg
Administration	Not affected by food but recommended to administer before the first meal of the day	Not affected by food but recommended to administer in the morning	Not affected by food but recommended to administer in the morning	Not affected by food but recommended to administer in the morning

**eGFR = estimated glomerular filtration rate*

Table 2: Efficacy of SGTL2 inhibitors[19-40]

Monotherapy	**Medications evaluated**	**Primary endpoint: change in baseline A1c (%)**
Stenlof K et al. Diabetes Obes Metab. 2013;15:372-82.[19]	canagliflozin 100 mg canagliflozin 300 mg vs. placebo	-0.77* -1.03* 0.14
Ferrannini E. et al. Diabetes Care. 2010;33(10):2217-24.[20]	dapagliflozin 2.5 mg dapagliflozin 5 mg dapagliflozin 10 mg vs. placebo	-0.58 -0.77* -0.89* -0.23
Roden M et al. Lancet Diabetes Endocrinol. 2013;1:208-219.[21]	empagliflozin 10 mg empagliflozin 25 mg sitagliptin 100 mg vs. placebo	-0.74* -0.85* -0.73* (placebo-subtracted changes)
Aronson R et al. Diabetes Obes Metab. 2018;1-8. doi: 10.1111/dom.13251[22]	ertugliflozin 5 mg ertugliflozin 15 mg vs. placebo/metformin	-0.9 -1.0 -1.0
Dual therapy: metformin		
Lavalle-Gonzalez FJ et al. Diabetologia. 2013;56:2582-92.[23]	canagliflozin 100 mg canagliflozin 300 mg sitagliptin 100 mg vs. placebo	-0.79* -0.94* -0.73* -0.17
Cefalu W et al. Lancet. 2013;382:941-50.[24]	canagliflozin 100 mg canagliflozin 300 mg vs. glimepiride 6-8 mg/day	-0.01; non-inferior -0.12*; superior (mean difference)
Ji L et al. Diabetes Obes Metab. 2015;17(1):23-31.[25]	canagliflozin 100 mg canagliflozin 300 mg vs. placebo ± sulfonylurea	-0.97* -1.06* -0.47
Bailey CJ et al. Lancet. 2010;375:2223-33.[26]	dapagliflozin 2.5 mg dapagliflozin 5 mg	-0.67* -0.70*

	dapagliflozin 10 mg vs. placebo	-0.84* -0.30%
Nauck et al. Diabetes Care. 2011;34:2015-22.[27]	dapagliflozin 2.5-10 mg glipizide 5-20 mg	-0.52; non-inferior -0.52
Haring HU et al. Diabetes Care. 2014;37:1650-59.[28]	empagliflozin 10 mg empagliflozin 25 mg vs. placebo	-0.70* -0.77* -0.13
Ridderstrale M et al. Lancet Diabetes Endocrinol. 2014;2:691-700.[29]	empagliflozin 25 mg vs. glimepiride 1-4 mg	-0.11*; superior (mean difference)
Rosenstock J et al. Diabetes Obes Metab. 2018;20(3):520-529.[30]	ertugliflozin 5 mg ertugliflozin 15 mg vs. placebo	-0.7* -0.9* (placebo-subtracted changes)
Hollander P et al. Diabetes Ther. 2018;9(1):193-207.[31]	ertugliflozin 5 mg ertugliflozin 15 mg vs. glimepiride	-0.6; non-inferior -0.6; non-inferior -0.7

Dual therapy: sulfonylurea		
Fulcher G et al. Diabetes Ther. 2015;6(3):289-302.[32]	canagliflozin 100 mg canagliflozin 300 mg vs. placebo	-0.7* -0.83* (placebo-subtracted changes)
Strojek K e al. Diabetes, Obes Metab. 2011;13(10):928-38.[33]	dapagliflozin 2.5 mg dapagliflozin 5 mg dapagliflozin 10 mg vs. placebo	-0.58* -0.63* -0.82* -0.13
Dual therapy: DPP4 inhibitor		
Jabbour S et al. Diabetes Care. 2014;37:740–50.[34]	dapagliflozin 10 mg vs. placebo ± metformin 1,500 mg/day	-0.5* 0.0

Miller S et al. Diabetes Ther. 2018;9(1):253-268.[35]	ertugliflozin 5 mg ertugliflozin 15 mg vs. placebo	-1.6* -1.7* -0.4
Dual therapy: TZD		
Rosenstock J et al. Diabetes Care. 2012;35:1473-78.[36]	dapagliflozin 5 mg dapagliflozin 10 mg vs. placebo	-0.82* -0.97* -0.42
Dual therapy: insulin		
Wilding J et al. Ann Intern Med. 2012;156(6):405-15.[37]	dapagliflozin 2.5 dapagliflozin 5 mg dapagliflozin 10 mg vs. placebo	-0.40* -0.49* -0.59* (mean difference)
Rosenstock J et al. Diabetes Care. 2014;37:1815-23.[38]	empagliflozin 10 mg empagliflozin 25 mg vs. placebo ± metformin	-0.94* -1.02* -0.50
Triple therapy: metformin + sulfonylurea		
Schernthaner G et al. Diabetes Care. 2013;36:2508-15.[39]	canagliflozin 300 mg vs. sitagliptin 100 mg	-1.03*; superior -0.66
Triple therapy: metformin + DPP4 inhibitor		
Softeland E et al. Diabetes Care. 2017;40(2):201-209.[40]	empagliflozin 10 mg empagliflozin 25 mg vs. placebo	-0.79* -0.70* (placebo-subtracted changes)

**statistically significant; abbreviations: thiazolidinedione (TZD), dipeptidyl peptidase-4 (DPP4)*

Table 3: SGLT2 cardiovascular outcome studies

Medication	Inclusion	Primary Outcome	Results	Secondary Outcome	Results
Empagliflozin (EMPA-REG)[43]	Adult T2DM - A1c 7-9% with no glucose lowering treatment for 12 weeks prior to randomization - A1c 7-10% with stable glucose lowering treatment for 12 weeks prior to randomization BMI $\leq$ 45kg/m^2 Established CVD* eGFR > 30ml/min/1.73m^2	Composite: death from CVD, nonfatal MI, nonfatal stroke	Percentage of patients based on rate/1000 patient-years 10.5% empagliflozin vs. 12.1% placebo (HR 0.86, CI 0.74 -0.99; p<0.001 for noninferiority, p=0.04 for superiority)	Composite of primary outcome plus hospitalization for unstable angina	Percentage of patients based on rate/1000 patient-years 12.8% empagliflozin vs. 14.3% placebo (HR 0.89, CI 0.78-1.01; p<0.001 for noninferiority, p=0.08 for superiority)

Canagliflozin (CANVAS Program)[44]	Adult T2DM with baseline A1c 7-10.5% ≥ 30 years of age with established CVD Or ≥ 50 years of age with two or more risk factors for CVD** eGFR > 30 ml/min/1.73 m^2	Composite: death from CVD, nonfatal MI, nonfatal stroke	Patient events per 1000 patient-years 26.9 canagliflozin vs. 31.5 placebo (HR 0.86, CI 0.75 - 0.97; p<0.001 noninferiority, p=0.02 superiority)	Death from any cause, CVD death, progression of albuminuria, composite: CVD death and hospitalization for heart failure	Patient events per 1000 patient-years Death from any cause: 17.3 canagliflozin vs. 19.5 placebo (HR 0.87, CI 0.74-1.01) Progression of albuminuria: 89.4 canagliflozin vs. 128.7 placebo (HR 0.73, CI 0.67- 0.79) Death from CVD and hospitalization for heart failure: 16.3 canagliflozin vs. 20.8 placebo (HR 0.78, CI 0.67-0.91)

** CVD: > 1 of the following: > 2 months since myocardial infarction (MI), stroke, unstable angina with evidence of coronary artery disease (CAD); multivessel CAD, single vessel CAD with positive stress test or unstable angina hospitalization < 1 year; occlusive peripheral arterial disease (PAD)*

***CVD risk factors: T2DM duration > 10 years, systolic blood pressure > 140mmHg while receiving 1 or more antihypertensive, current smoker, micro- or macroalbuminuria or HDL < 38.7mg/dl.*

Table 4: ADA treatment recommendations[47]

Foundation of treatment	Healthy eating, weight control, increased physical activity, and diabetes education					
Mono-therapy	Metformin[+]					
Dual therapy*	Metformin plus add second agent after considering drug-specific and patient-specific factors					
	Sulfonylurea	TZD	DPP4 inhibitor	SGLT2 inhibitor	GLP1 receptor agonist	Basal insulin
Triple therapy*	Metformin and second agent plus add third agent after considering drug-specific and patient-specific factors[#]					
	Sulfonylurea	TZD	DPP4 inhibitor	SGLT2 inhibitor	GLP1 receptor agonist	Basal insulin
Combination injectable therapy	Basal insulin + mealtime insulin or Basal insulin + GLP1 receptor agonist or change to premixed insulin twice daily					

[+]*If patient does not tolerate or has a contraindication to metformin, choose an agent from a different class (Table 7)*
**If patient has atherosclerotic cardiovascular disease, add an agent that has proven cardiovascular benefit (Table 7)*
[#] *GLP1 receptor agonists and DPP4 inhibitors should not be prescribed in combination*

Table adapted from the ADA 2018 "Standards of Medical Care in Diabetes." Abbreviations: thiazolidinedione (TZD), glucagon-like peptide-1 (GLP1), dipeptidyl peptidase-4 (DPP4), sodium-glucose cotransporter-2 (SGLT2)

Table 5: AACE/ACE treatment recommendations[48]

Monotherapy*	**Dual therapy: first-line agent plus one of the following***	**Triple therapy: first- and second-line agent plus one of the following***
Metformin	GLP1 receptor agonist	GLP1 receptor agonist
GLP1 receptor agonist	SGLT2 inhibitors	SGLT2 inhibitors
SGLT2 inhibitors	DPP4 inhibitors	TZDs
DPP4 inhibitors	TZDs	Basal insulin
TZDs	Basal insulin	DPP4 inhibitors
Alpha-glucosidase inhibitors	Colesevelam	Colesevelam
Sulfonylurea	Bromocriptine	Bromocriptine
	Alpha-glucosidase inhibitors	Alpha-glucosidase inhibitors
	Sulfonylurea	Sulfonylurea

**Listed in order of suggested hierarchy according to AACE/ACE*

Table adapted for the 2018 consensus statement by AACE/ACE. Abbreviations: thiazolidinedione (TZD), glucagon-like peptide-1 (GLP1), dipeptidyl peptidase-4 (DPP4), sodium-glucose cotransporter-2 (SGLT2)

Table 6: Summary of advantages and disadvantages of SGLT2 inhibitors

Advantages	Disadvantages
Decreased risk of cardiovascular death in patients with T2DM with history of cardiovascular disease[#]	Increased risk of leg/foot amputations*
	Adequate renal function required
	Increased urinary frequency
Cardiovascular and renal benefits in high risk patients[#,*]	Increased risk of genital mycotic infections
Low risk of hypoglycemia	Increased LDL
Small amount of weight loss	Dehydration and AKI
Small decrease in blood pressure	Ketoacidosis
Effectiveness independent of insulin	Electrolyte disturbances (hyperkalemia)
Moderate efficacy (~1% A1c lowering)	Increased risk of bone fractures*
Safe to combine with other oral antidiabetics and insulin	Increased risk of UTIs infections including pyelonephritis and urosepsis
Unique mechanism of action	Increased risk of bladder cancer[+]

[#]*empagliflozin, *canagliflozin, [+]dapagliflozin*

Table 7: Comparison of available antidiabetics[47,51-53]

Drug/Drug Class	A1c lowering potential (%)	Blood glucose target	Weight effect	Risk of hypoglycemia	Cardiovascular effects	Renal effects
Metformin	1.5	Fasting	Neutral or loss	Low	Potential benefit	Neutral
Sulfonylurea	1.5-2	Fasting/ Post-prandial	Gain	High	Neutral	Neutral
GLP1 agonist	0.8-1.5	Post-prandial	Loss	Low	Benefit[+]	Benefit[+]
DPP4 inhibitor	0.5-0.7	Post-prandial	Neutral	Low	Neutral	Neutral
TZD	1-1.5	Fasting	Gain	Low	Potential benefit[#]	Neutral
SGLT2 inhibitor	0.7-1.1	Fasting	Loss	Low	Benefit[*]	Benefit[*]
Basal insulin	Unlimited	Fasting	Gain or neutral	Possible	Neutral	Neutral

[*]*canagliflozin and empagliflozin,* [+] *liraglutide and semaglutide,* [#]*pioglitazon*

Patient Case: 46-year-old white female comes in for her 6-month follow-up appointment with her primary care physician. She has a past medical history significant for obesity, hypertension, dyslipidemia, myocardial infarction, and lifestyle-controlled diabetes. Her A1c today is 8.2% and her renal function is normal. Her current medications include lisinopril 20 mg daily, metoprolol tartrate 50 mg twice daily, atorvastatin 40 mg daily, and aspirin 81 mg daily. She reports worsening diet and non-adherence with evening medications.

1. What is the patient's goal A1c according to the ADA?

A. <6.5%

B. <7%

C. <7.5%

D. <8%

Answer: B

Explanation: For most patients, the ADA recommends an A1c goal of <7%.

2. What is the best first-line agent to start in this patient?

A. Canagliflozin

B. Glipizide

C. Liraglutide

D. Metformin

Answer: D

Explanation: At this point it is best to emphasize adherence to a diabetic diet as well as start metformin. Metformin is recommended first-line by both AACE/ACE and ADA.

The patient comes back for her 3 month follow-up appointment. She is now taking metformin 1000 mg BID and reports adherence with diet and exercise. Her A1c today is now 7.4%.

3. Should an SGLT2 inhibitor be considered for this patient?

A. Yes due to history of myocardial infarction

B. No due to history of dyslipidemia

Answer: A

Explanation: SGLT2 inhibitors may be appropriate at this time especially due to cardiovascular benefits. ADA recommends weighing risks vs. benefits of SGLT2 inhibitors compared to other second-line options. AACE/ACE would prioritize GLP1 agonists prior to initiation of SGLT2 inhibitors. However, patient preference may be to avoid injectable medications. Although SGLT2 inhibitors can increase LDL, this is not a reason to avoid use.

4. The physician decides to initiate an SGLT2 inhibitor. What SGLT2 inhibitor is the most appropriate to initiate?

A. Dapagliflozin 5 mg once daily

B. Empagliflozin 10 mg once daily

C. Canagliflozin 100 mg once daily

D. All of the above are appropriate

Answer: B

Explanation: Although canagliflozin has cardiovascular benefits, empagliflozin is the only SGLT2 inhibitor that has an approved indication to decrease risk of cardiovascular death in patients with established cardiovascular disease.

The Indiana Pharmacists Alliance (IPA) is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. To receive continuing pharmacy education (CPE) pharmacists MUST COMPLETE THE ONLINE QUIZ AND EVALUATION FORM. A score of 70% or above is required to receive CPE credit. The link to the quiz can be accessed from the home study section in the CE Portal of the IPA website, www.indianapharmacists.org. This is a free service of IPA members in 2018. Initial release date: 05/01/2018. Expiration Date: 05/01/2021. Questions: Call IPA office at 317-634-4968.

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