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

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See the end of the article for CE details.
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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. 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 glycated hemoglobin (A1c) < 7% for most patients with diabetes. According to the U.S. National Health and Nutrition Examination Survey, only 52.5% of individuals reported achieving this goal from 2007-2010. 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.

**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™). All agents are dosed once daily and use is contraindicated when estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73 m²; 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.\(^4\)

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 SGLT2 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.” 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. In contrast, the AACE/ACE guidelines recommend a lower threshold of an A1c ≥7.5% for initiation of dual therapy. 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 subgroup 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).\(^47\)\(^-\)\(^53\) 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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{55,63,64} Patients at greatest risk of this
complication are those with a history of
recurrent UTIs and women.\textsuperscript{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.\textsuperscript{61} Meta-analyses
have shown a wide range of risk for GMIs
related to individual agents.\textsuperscript{55,63,64} These
infections can occur regardless of infection
history.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{42} Patients should also
be counseled to maintain adequate hydration
when initiating treatment.\textsuperscript{58}

The FDA revised labeling in December
2015 to include a warning regarding these
agents causing ketoacidosis.\textsuperscript{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.\textsuperscript{64} Burke and
colleagues completed a systematic review of
reported cases of ketoacidosis related to
SGLT2 inhibitors.\textsuperscript{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.\textsuperscript{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 SGLT2 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.
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<sup>8-11</sup>

<table>
<thead>
<tr>
<th></th>
<th>Canagliflozin (Invokana®)</th>
<th>Dapagliflozin (Farxiga®)</th>
<th>Empagliflozin (Jardiance®)</th>
<th>Ertugliflozin (Steglatro™)</th>
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<tbody>
<tr>
<td><strong>Starting Dose</strong></td>
<td>100 mg daily</td>
<td>5 mg daily</td>
<td>10 mg daily</td>
<td>5 mg daily</td>
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<tr>
<td><strong>Max Dose</strong></td>
<td>300 mg daily</td>
<td>10 mg daily</td>
<td>25 mg daily</td>
<td>15 mg daily</td>
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<tr>
<td><strong>Renal Impairment</strong></td>
<td>eGFR 45 to &lt;65 mL/min/1.73 m²: 100 mg daily</td>
<td>eGFR &lt;60 mL/min/1.73 m²: do not initiate, discontinue if persistent</td>
<td>eGFR 45 to &lt;60 mL/min/1.73 m²: no dosage adjustment necessary</td>
<td>eGFR &lt;60 mL/min/1.73 m²: do not initiate, discontinue if persistent</td>
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<tr>
<td></td>
<td>eGFR &lt;45 mL/min/1.73 m²: do not initiate, discontinue if persistent</td>
<td>eGFR &lt;45 mL/min/1.73 m²: do not initiate, discontinue if persistent</td>
<td>eGFR &lt;45 mL/min/1.73 m²: do not initiate, discontinue if persistent</td>
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<tr>
<td></td>
<td>eGFR &lt;30 mL/min/1.73 m²: use is contraindicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Available Strengths</strong></td>
<td>100 mg</td>
<td>5 mg</td>
<td>10 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td>10 mg</td>
<td>25 mg</td>
<td>15 mg</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Not affected by food but recommended to administer before the first meal of the day</td>
<td>Not affected by food but recommended to administer in the morning</td>
<td>Not affected by food but recommended to administer in the morning</td>
<td>Not affected by food but recommended to administer in the morning</td>
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</table>

*<sup>eGFR</sup> = estimated glomerular filtration rate
Table 2: Efficacy of SGTL2 inhibitors

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Medications evaluated</th>
<th>Primary endpoint: change in baseline A1c (%)</th>
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<tr>
<td>Stenlof K et al. Diabetes Obes Metab. 2013;15:372-82.19</td>
<td>canagliflozin 100 mg canagliflozin 300 mg vs. placebo</td>
<td>-0.77* -1.03* 0.14</td>
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<tr>
<td>Ferrannini E. et al. Diabetes Care. 2010;33(10):2217-24.20</td>
<td>dapagliflozin 2.5 mg dapagliflozin 5 mg dapagliflozin 10 mg vs. placebo</td>
<td>-0.58 -0.77* -0.89* -0.23</td>
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<tr>
<td>Roden M et al. Lancet Diabetes Endocrinol. 2013;1:208-219.21</td>
<td>empagliflozin 10 mg empagliflozin 25 mg sitagliptin 100 mg vs. placebo</td>
<td>-0.74* -0.85* -0.73* (placebo-subtracted changes)</td>
</tr>
<tr>
<td>Aronson R et al. Diabetes Obes Metab. 2018;1-8. doi: 10.1111/dom.1325122</td>
<td>ertugliflozin 5 mg ertugliflozin 15 mg vs. placebo/metformin</td>
<td>-0.9 -1.0 -1.0</td>
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**Dual therapy: metformin**

<table>
<thead>
<tr>
<th>Medications evaluated</th>
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<tbody>
<tr>
<td>canagliflozin 100 mg canagliflozin 300 mg sitagliptin 100 mg vs. placebo</td>
<td>-0.79* -0.94* -0.73* -0.17</td>
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<tr>
<td>canagliflozin 100 mg canagliflozin 300 mg vs. glimepiride 6-8 mg/day</td>
<td>-0.01; non-inferior -0.12*; superior (mean difference)</td>
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<tr>
<td>canagliflozin 100 mg canagliflozin 300 mg vs. placebo ± sulfonylurea</td>
<td>-0.97* -1.06* -0.47</td>
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<tr>
<td>dapagliflozin 2.5 mg dapagliflozin 5 mg</td>
<td>-0.67* -0.70*</td>
</tr>
<tr>
<td>Study and Treatment Details</td>
<td>Change in Hemoglobin A1C (placebo-subtracted)</td>
</tr>
<tr>
<td>-----------------------------</td>
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<tr>
<td>Nauck et al. Diabetes Care. 2011;34:2015-22.</td>
<td>0.84* vs. placebo</td>
</tr>
<tr>
<td>Haring HU et al. Diabetes Care. 2014;37:1650-59.</td>
<td>0.70* vs. placebo</td>
</tr>
<tr>
<td>Ridderstrale M et al. Lancet Diabetes Endocrinol. 2014;2:691-700.</td>
<td>0.11* vs. glimepiride 1-4 mg</td>
</tr>
<tr>
<td>Rosenstock J et al. Diabetes Obes Metab. 2018;20(3):520-529.</td>
<td>0.11* vs. glimepiride 1-4 mg</td>
</tr>
<tr>
<td>Hollander P et al. Diabetes Ther. 2018;9(1):193-207.</td>
<td>0.11* vs. glimepiride 1-4 mg</td>
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**Dual therapy: sulfonylurea**

<table>
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<tr>
<th>Study and Treatment Details</th>
<th>Change in Hemoglobin A1C (placebo-subtracted)</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Fulcher G et al. Diabetes Ther. 2015;6(3):289-302.</td>
<td>0.7* vs. placebo</td>
<td>0.83*</td>
</tr>
<tr>
<td>Strojek K e al. Diabetes, Obes Metab. 2011;13(10):928-38.</td>
<td>0.58* vs. placebo</td>
<td>0.63*</td>
</tr>
</tbody>
</table>

**Dual therapy: DPP4 inhibitor**

<table>
<thead>
<tr>
<th>Study and Treatment Details</th>
<th>Change in Hemoglobin A1C (placebo-subtracted)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jabbour S et al. Diabetes Care. 2014;37:740–50.</td>
<td>0.5* vs. placebo ± metformin 1,500 mg/day</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Miller S et al. Diabetes Ther. 2018;9(1):253-268. 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. 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. 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. 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. 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. 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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Inclusion</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Secondary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>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 ≤ 45kg/m² Established CVD* eGFR &gt; 30ml/min/1.73m²</td>
<td>Composite: death from CVD, nonfatal MI, nonfatal stroke</td>
<td>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&lt;0.001 for noninferiority, p=0.04 for superiority)</td>
<td>Composite of primary outcome plus hospitalization for unstable angina</td>
<td>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&lt;0.001 for noninferiority, p=0.08 for superiority)</td>
</tr>
<tr>
<td>Canagliflozin (CANVAS Program)**</td>
<td>Adult T2DM with baseline A1c 7-10.5%</td>
<td>Composite: death from CVD, nonfatal MI, nonfatal stroke</td>
<td>Patient events per 1000 patient-years</td>
<td>Death from any cause, CVD death, progression of albuminuria, composite: CVD death and hospitalization for heart failure</td>
<td>Patient events per 1000 patient-years</td>
</tr>
<tr>
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<td>---</td>
</tr>
<tr>
<td>≥ 30 years of age with established CVD</td>
<td>≥ 50 years of age with two or more risk factors for CVD**</td>
<td>eGFR &gt; 30 ml/min/1.73 m²</td>
<td>26.9 canagliflozin vs. 31.5 placebo (HR 0.86, CI 0.75 - 0.97; p&lt;0.001 noninferiority, p=0.02 superiority)</td>
<td>16.3 canagliflozin vs. 20.8 placebo (HR 0.78, CI 0.67-0.91)</td>
<td></td>
</tr>
</tbody>
</table>

* 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>
<thead>
<tr>
<th><strong>Table 4: ADA treatment recommendations</strong>&lt;sup&gt;47&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foundation of treatment</strong></td>
</tr>
<tr>
<td><strong>Mono-therapy</strong></td>
</tr>
<tr>
<td><strong>Dual therapy</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfonylurea</td>
</tr>
<tr>
<td><strong>Triple therapy</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfonylurea</td>
</tr>
<tr>
<td><strong>Combination injectable therapy</strong></td>
</tr>
</tbody>
</table>

<sup>†</sup>If patient does not tolerate or has a contraindication to metformin, choose an agent from a different class (Table 7)  
<sup>*</sup>If patient has atherosclerotic cardiovascular disease, add an agent that has proven cardiovascular benefit (Table 7)  
<sup>#</sup>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

<table>
<thead>
<tr>
<th>Monotherapy*</th>
<th>Dual therapy: first-line agent plus one of the following*</th>
<th>Triple therapy: first- and second-line agent plus one of the following*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>GLP1 receptor agonant</td>
<td>GLP1 receptor agonant</td>
</tr>
<tr>
<td>GLP1 receptor agonist</td>
<td>SGLT2 inhibitors</td>
<td>SGLT2 inhibitors</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>DPP4 inhibitors</td>
<td>TZDs</td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>TZDs</td>
<td>Basal insulin</td>
</tr>
<tr>
<td>TZDs</td>
<td>Basal insulin</td>
<td>DPP4 inhibitors</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Colesevelam</td>
<td>Colesevelam</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Bromocriptine</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td></td>
<td>Alpha-glucosidase inhibitors</td>
<td>Alpha-glucosidase inhibitors</td>
</tr>
<tr>
<td></td>
<td>Sulfonylurea</td>
<td>Sulfonylurea</td>
</tr>
</tbody>
</table>

*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

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

*empagliflozin, *canagliflozin, †dapagliflozin
Table 7: Comparison of available antidiabetics\(^{47,51-53}\)

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

\(^*\)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
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B.</td>
<td>Empagliflozin 10 mg once daily</td>
</tr>
<tr>
<td>C.</td>
<td>Canagliflozin 100 mg once daily</td>
</tr>
<tr>
<td>D.</td>
<td>All of the above are appropriate</td>
</tr>
</tbody>
</table>

**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.
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References:


