Hypoglycemics, SGLT2 Inhibitors
Therapeutic Class Review (TCR)

September 4, 2019

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indications
canagliflozin (Invokana®)[1]	Janssen	▪ Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) ▪ To reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM and established cardiovascular disease (CVD) ▪ To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults T2DM and diabetic nephropathy with albuminuria > 300 mg/day
canagliflozin/ metformin (Invokamet®)[2]	Janssen	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate ▪ To reduce the risk of MACE in adults with T2DM and established CVD*
canagliflozin/ metformin (Invokamet® XR)[3]	Janssen	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both canagliflozin and metformin is appropriate ▪ To reduce the risk of MACE in adults with T2DM and established CVD*
dapagliflozin (Farxiga®)[4]	AstraZeneca	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM ▪ To reduce the risk of hospitalization for heart failure in adults with T2DM and established CVD or multiple cardiovascular (CV) risk factors
dapagliflozin/ metformin ER (Xigduo® XR)[5]	AstraZeneca	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both dapagliflozin and metformin is appropriate ▪ Dapagliflozin is indicated to reduce the risk of hospitalization for heart failure in adults with T2DM and established CVD or multiple CV risk factors.
empagliflozin (Jardiance®)[6]	Boehringer Ingelheim	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM ▪ To reduce the risk of cardiovascular death in adults with T2DM and established CVD
empagliflozin/ metformin (Synjardy®)[7]	Boehringer Ingelheim	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both empagliflozin and metformin is appropriate ▪ To reduce the risk of cardiovascular death in adults with T2DM and established CVD*
empagliflozin/ metformin ER (Synjardy® XR)[8]	Boehringer Ingelheim	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM when both empagliflozin and metformin is appropriate ▪ To reduce the risk of cardiovascular death in adults with T2DM and established CVD*
ertugliflozin (Steglatro™)[9]	Merck, Sharp & Dohme	▪ Adjunct to diet and exercise to improve glycemic control in adults T2DM
ertugliflozin/ metformin (Segluromet™)[10]	Merck, Sharp & Dohme	▪ Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are not adequately controlled on a regimen containing ertugliflozin or metformin, or in patients who are already treated with both ertugliflozin and metformin

Agents in this review are not indicated for the treatment of type 1 diabetes or diabetic ketoacidosis.

* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with canagliflozin/metformin (Invokamet), canagliflozin/metformin ER (Invokamet XR), empagliflozin/metformin (Synjardy) or empagliflozin/metformin ER (Synjardy XR).

OVERVIEW

It is estimated that over 30 million people in the United States (US) have diabetes.[11] Type 2 diabetes (T2DM) accounts for about 90% to 95% of all diagnosed cases of diabetes in adults.[12] Improved glycemic control benefits patients with either type 1 or type 2 diabetes. In general, for every 1% reduction in hemoglobin A1c (HbA1c), the risk of developing microvascular diabetic complications (nephropathy, neuropathy, and retinopathy) is reduced by 40%.[13]

In addition to exogenous insulin, there are several pathways by which blood glucose may be regulated in diabetic patients. The sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion. Studies evaluating the impact of SGLT2 inhibitors on macrovascular complications, (e.g., cardiovascular [CV] outcomes) include the EMPA-REG OUTCOME and CANVAS/CANVAS-R. The EMPA-REG OUTCOME trial reported approximately a one-third relative risk reduction for cardiovascular death, hospitalization due to heart failure, and all-cause death with use of empagliflozin (Jardiance) as compared to placebo, while the CANVAS and CANVAS-R trials demonstrated a 14% risk reduction (hazard ratio [HR], 0.86 [95% CI, 0.75 to 0.97]) in first occurrence of major adverse cardiovascular event (MACE) in patients with T2DM treated with canagliflozin (Invokana).[14,15] Cardiovascular benefit of dapagliflozin was not demonstrated in clinical trials.[16] Based on the DECLARE–TIMI 58 trial, dapagliflozin did not result in a lower rate of MACE compared to placebo; however, it did lead to a lower incidence of HF-related hospitalizations.

In 2019, the American Diabetes Association (ADA) Standards of Medical Care in Diabetes continued to include the sodium-glucose cotransporter 2 (SGLT2) inhibitors in the management algorithm for T2DM.[17] The position statement recommends HbA1c < 7% as a reasonable target for most nonpregnant adult patients. A target HbA1c of 6% to 6.5% is recommended in most pregnant women. Relaxed HbA1c goals are recommended in some older patients (≥ 65 years) to reduce the risk of hypoglycemia, particularly in those with chronic comorbidities, cognitive impairment, or functional dependence. Based on a diabetes care decision cycle designed to prevent complications and optimize quality of life, therapy should be individualized based on HbA1c target, impact on weight and hypoglycemia, side effects, the frequency and mode of administration, patient adherence, patient preference, and cost. Metformin is recommended as initial therapy for the treatment of T2DM, along with lifestyle interventions at the time of diagnosis, unless metformin is contraindicated. If metformin fails to produce the target HbA1c after 3 months of therapy, a thiazolidinedione (TZD), sulfonylurea (SU), dipeptidyl peptidase-4 (DPP-4) inhibitor, SGLT2 inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin should be added in patients *without* atherosclerotic cardiovascular disease (ASCVD). In patients newly diagnosed with T2DM with markedly symptomatic and/or elevated blood glucose levels or HbA1c (≥ 10%), basal insulin therapy should be considered, typically with metformin with or without another noninsulin agent. If target HbA1c is still not achieved after 3 months, then the addition of rapid-acting mealtime insulin or a GLP-1 agonist or a change to twice daily premixed insulin should be considered. If there is a compelling need to minimize weight gain or promote weight loss, a GLP-1 agonist or SGLT2 inhibitor are recommended. Patients with T2DM are at increased risk of cardiovascular (CV) morbidity and mortality; therefore, aggressive management of CV risk factors (e.g., blood pressure and lipid therapy, antiplatelet treatment, and smoking cessation) should be part of a multifactorial risk reduction approach.[18] The ADA prefers medications with proven CV and renal benefit in patients with CV and/or renal disease, respectively. In patients with ASCVD, the addition of empagliflozin, canagliflozin, dapagliflozin, or liraglutide is preferred (Class A recommendations).[19,20] In

patients with heart failure (HF) or chronic kidney disease (CKD), empagliflozin, canagliflozin, or dapagliflozin is preferred. In general, the ADA advises that prescribers use SGLT2 inhibitors with caution in patients at risk for bone fracture.[21]

The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2019 diabetes management algorithm and 2015 clinical practice guidelines for developing a diabetes care plan emphasize a comprehensive approach including individualized targets for weight loss, glucose, lipid, and hypertension management.[22,23] AACE/ACE supports an HbA1c target of ≤ 6.5% if it can be reached without substantial hypoglycemia or other adverse effect. The algorithm stratifies choice of therapy based on the patient's initial HbA1c level: < 7.5%, ≥ 7.5%, and > 9%. The guidelines suggest patients with an HbA1c < 7.5% start with lifestyle therapy and antihyperglycemic monotherapy, whereas patients with an HbA1c ≥ 7.5% begin with dual therapy. Patients with an HbA1c > 9% and no symptoms may start on maximum doses of 2 antihyperglycemic agents; patients with an HbA1c > 9% with symptoms should begin insulin therapy, with or without other agents. The patient's HbA1c should be reassessed every 3 months, failure to improve may warrant additional complementary therapy for optimal glycemic control. Within each therapy group (monotherapy, dual therapy, and triple therapy), the guidelines provide a hierarchical order of use for the drugs where, like the ADA guidelines, metformin is the preferred treatment of choice for monotherapy and first-line agent for dual and triple therapy. The AACE/ACE guidelines include the use of SGLT2 inhibitors as an alternative to metformin for monotherapy and as an appropriate add-on to metformin in dual therapy and triple therapy; agents for monotherapy are recommended in the following order (highest to lowest recommendation): metformin, GLP-1 receptor agonists, SGLT2 inhibitors, DPP-4 inhibitors, TZDs, alpha-glucosidase inhibitors, and sulfonylureas/secretagogue glinides. Notably, TZDs, basal insulin, and sulfonylureas/secretagogue glinides should be used with caution. AACE/ACE recognizes that empagliflozin and canagliflozin are associated with significantly reduced cardiac mortality, hospitalization for heart failure, as well as secondary renal endpoints. Additionally, dapagliflozin demonstrated reduced all-cause mortality and the composite of CV death and HF hospitalization; however, it did not significantly lower the combined risk of CV death and nonfatal MI and stroke. AACE/ACE also acknowledges the risk of initial renal impairment, hypotension, syncope, and falls due to dehydration related to increased diuresis with SGLT2 inhibitors, and in clinical trials, canagliflozin and dapagliflozin were associated with increased incidence of bone fracture. They recommend stopping SGLT2 inhibitor therapy 24 hours before scheduled surgeries and expected metabolically stressful activities, such as extreme sports. Avoid therapy with SGLT2 inhibitors with insulin in patients on a very low carbohydrate diet or with excess alcohol intake.

The American College of Physicians (ACP) revised their guidelines for T2DM in 2017.[24] They recommend metformin as first-line therapy and state a sulfonylurea, TZD, SGLT-2 inhibitor, or a DPP-4 inhibitor are preferred second-line treatments. These guidelines are also endorsed by the American Academy of Family Physicians (AAFP). In 2018, the ACP developed a statement to guide clinicians in selecting targets for pharmacologic treatment of T2DM, including recommending a goal HbA1c level between 7% and 8% in most patients.[25] In addition, they state that clinicians should consider de-intensifying pharmacologic therapy in patients who achieve HbA1c < 6.5%, treat patients to minimize symptoms related to hyperglycemia, and avoid targeting an HbA1c level in patients with a life expectancy < 10 years due to advanced age because the harms outweigh the benefits in this population.

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In 2018, the World Health Organization (WHO) released guidelines for treatment intensification in patients with T2DM.[26] They recommend addition of a DPP-4 inhibitor, a SGLT2 inhibitor, or a TZD if insulin is unsuitable in patients with T2DM who do not achieve glycemic control with metformin and/or a sulfonylurea. In addition, in 2019, the WHO updated their classification of diabetes mellitus based on clinical parameters to identify diabetes subtypes and includes T1DM, T2DM, hybrid forms of diabetes (e.g., slowly evolving immune-mediated, ketosis-prone T2DM), other specific types (e.g., monogenic, drug- or chemical-induced, infection-related), unclassified diabetes, and hyperglycemia first detected during pregnancy.[27]

The Endocrine Society issued 2019 guideline recommendations for diabetes in patients aged ≥ 65 years.[28] They recommend simplified outpatient medication regimens and glycemic targets tailored to improve compliance and prevent complications, such as hypoglycemia and falls, particularly in patients with cognitive impairment. First-line treatment for ambulatory patients is lifestyle modification. When pharmacological therapy is indicated, metformin, in addition to lifestyle management, is recommended first-line. If glycemic targets are not attained with metformin and lifestyle management, oral and injectable therapies with low risk for hypoglycemia are suggested. The guidelines also have recommendations for management of common comorbidities in this population including hypertension, hyperlipidemia, congestive heart failure, retinopathy, neuropathy, and chronic kidney disease. Additionally, SGLT2 inhibitors have been shown to reduce major adverse cardiovascular events (MACE), heart failure, and progression of CKD. Consequently, these should be prescribed early in treatment. Due to adverse effects related to volume depletion with canagliflozin, dosages should be limited to 100 mg/day in susceptible patients (e.g. elderly).

The products dapagliflozin/saxagliptin (Qtern®), empagliflozin/linagliptin (Glyxambi®) and ertugliflozin/sitagliptin (Steglujan™), which combine an SGLT2 inhibitor and a DPP-4 inhibitor, are not included in this clinical review.

PHARMACOLOGY[29,30,31,32,33,34,35,36,37,38]

Canagliflozin (Invokana, Invokamet, Invokamet XR), dapagliflozin (Farxiga, Xigduo XR), empagliflozin (Jardiance, Synjardy, Synjardy XR), and ertugliflozin (Steglatro, Segluromet) are sodium-glucose cotransporter 2 (SGLT2) inhibitors. Sodium-glucose cotransporter 2, which is expressed in the proximal renal tubules, is the transporter responsible for the majority of the reabsorption of filtered glucose from the tubular lumen in the kidney. By inhibiting SGLT2, these agents reduce reabsorption of filtered glucose and lower the renal threshold for glucose (RTG), thereby increasing urinary glucose excretion and improving blood glucose control.

Metformin (Invokamet, Invokamet XR, Segluromet, Synjardy, Synjardy XR, Xigduo XR), a biguanide, decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

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PHARMACOKINETICS[39,40,41,42,43,44,45,46,47,48]

Drug	Bioavailability (%)	Tmax (hr)	Half-life (hr)	Metabolism	Excretion (%)
canagliflozin (Invokana)	65	1–2	10.6–13.1	hepatic (O-glucuronidation via UGT1A9 and 2B4; 2 inactive metabolites)	feces: 60 urine: 33
dapagliflozin (Farxiga)	78	< 2	12.9	hepatic (UGT1A9; 1 inactive metabolite)	feces: 21 urine: 75
empagliflozin (Jardiance)	nr	1.5	12.4	hepatic (O-glucuronidation via UGT1A3, 2B7,1A8, and 1A9)	feces: 41.2 urine: 54.4
ertugliflozin (Steglatro)	100	1	16.6	hepatic (O-glucuronidation via UGT1A9 and 2B7); minimal (12%) CYP-mediated oxidation	feces: 40.9 urine: 50.2
metformin	50–60	nr	6.2	no metabolites have been identified in humans	feces: nr urine: 90

Tmax = time to maximum serum concentration

The bioequivalence of canagliflozin/metformin (Invokamet/XR), dapagliflozin/metformin ER (Xigduo XR), empagliflozin/metformin (Synjardy), and empagliflozin/metformin ER (Synjardy XR) combinations are bioequivalent to co-administration of corresponding doses of their individual components under fed conditions. A comparison of the bioequivalence of ertugliflozin/metformin (Segluromet) co-formulated product and its individual components is not described in the product label.

CONTRAINDICATIONS/WARNINGS[49,50,51,52,53,54,55,56,57,58]

Canagliflozin (Invokana, Invokamet, Invokamet XR), dapagliflozin (Farxiga, Xigduo XR), empagliflozin (Jardiance, Synjardy, Synjardy XR), and ertugliflozin (Steglatro, Segluromet) are contraindicated in patients with a history of serious hypersensitivity reactions to the active ingredient.

All SGLT2 inhibitors are contraindicated in patients with end stage renal disease (ESRD) and in patients receiving dialysis. The single SGLT2 inhibitor component products are contraindicated in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 for canagliflozin, dapagliflozin, and ertugliflozin, and eGFR < 45 mL/min/1.73 m^2 for empagliflozin; initiation of ertugliflozin is not recommended in patients with and eGFR of 30 to < 60 mL/min/1.73 m^2. The combination products, canagliflozin/metformin (IR and ER) and empagliflozin/metformin (IR and ER), are contraindicated in patients with eGFR < 45 mL/min/1.73 m^2; dapagliflozin/metformin ER (Xigduo XR) and ertugliflozin/metformin are contraindicated in patients with eGFR < 30 mL/minute/1.73 m^2.

In May 2017, the Food and Drug Administration (FDA) released a safety communication based on final safety data from the CANVAS and CANVAS-R studies, which revealed approximately a 2-fold increase in leg and foot amputations (primarily toes) in patients with T2DM who were treated with canagliflozin compared to placebo (5.9 versus 2.8 events per 1000 patient-years and 7.5 versus 4.2 events per 1000 patient-years, respectively).[59] Patients in the studies had either established cardiovascular disease or were at risk for cardiovascular disease. Patients were followed for an average of 5.7 years in CANVAS and 2.1 years in CANVAS-R. The FDA required new warnings, including a boxed warning, to the labeling for canagliflozin-containing products (Invokana, Invokamet, Invokamet XR) to describe the increased risk of lower limb amputations. Clinicians should consider predisposing patient factors (prior

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amputation, peripheral vascular disease, neuropathy, diabetic foot ulcers) before prescribing canagliflozin. Patient taking canagliflozin should be monitored for signs and symptoms such as new pain or tenderness, sores, or infections in the legs or feet.

In August 2018, the FDA issued another safety communication regarding the risk of Fournier's gangrene with the use of the SGLT2 inhibitors.[60] Cases of this necrotizing fasciitis of the perineum have been reported with SGLT2 inhibitors based on results of a case series. Between March 2013 and May 2018, 12 cases of Fournier's gangrene were found in patients taking an SGLT2 inhibitor, resulting in significant medical care needed and 1 death. As a result, the FDA is requiring a new warning to be added to the labeling of all SGLT2 inhibitors and SGLT2 inhibitor-containing medications regarding this risk. Healthcare providers should assess patients for Fournier's gangrene if they present with symptoms consistent with this diagnosis and patients should be treated accordingly immediately.

Hypersensitivity reactions, including anaphylaxis and angioedema, have occurred when using canagliflozin, dapagliflozin, and empagliflozin. If hypersensitivity reactions occur, canagliflozin, dapagliflozin, and empagliflozin should be discontinued and the patient should be treated as per standards of care and monitored until signs and symptoms resolve.

Metformin-containing products (Invokamet, Invokamet XR, Synjardy, Synjardy XR, Xigduo XR, Segluromet) are contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis (DKA). The labels carry a boxed warning that, although rare, potentially fatal lactic acidosis can occur due to metformin therapy. This risk increases with renal or hepatic impairment, sepsis, dehydration, excessive alcohol intake, and acute congestive heart failure.

In 2015, the Food and Drug Administration (FDA) issued a warning that use of SGLT2 inhibitors may lead to ketoacidosis.[61] Twenty cases of DKA, ketoacidosis, or ketosis were reported to the FDA in patients treated with SGLT2 inhibitors from March 2013 to June 6, 2014; all required emergency department visits or hospitalization. Diabetic ketoacidosis can occur in patients with diabetes, most commonly in patients with type 1 diabetes, and is usually accompanied by high serum glucose levels. The cases reported to the FDA were unusual because most of the patients had T2DM and their serum glucose levels, when reported, were only slightly increased unlike typical cases of DKA. Healthcare providers and patients should monitor closely for signs of ketoacidosis, including difficulty breathing, nausea, vomiting, abdominal pain, confusion, and unusual fatigue or sleepiness; if any occur, medical attention should be sought immediately. In December 2015, the FDA released a safety communication expanding their recommendation, advising that patients should stop taking their SGLT2 inhibitor and seek immediate medical attention if symptoms consistent with ketoacidosis occur.[62] In addition, fatal cases of ketoacidosis have been reported with use of SGLT2 inhibitors.

Combination agents containing metformin (Invokamet, Invokamet XR, Synjardy, Synjardy XR, Xigduo XR, Segluromet) carry boxed warnings regarding the risk of lactic acidosis which can occur with metformin accumulation. The risk increases with age ≥ 65 years, concomitant use of select drugs, radiologic studies using contrast, surgical procedures, hypoxia, excessive alcohol intake, hepatic impairment, renal impairment, and acute congestive heart failure. Treatment including metformin should be discontinued and the patient hospitalized immediately if lactic acidosis is suspected.

Long-term use of metformin may lead to vitamin B12 deficiency, which may be reversed with discontinuation of metformin or vitamin B12 supplementation. Monitor serum vitamin B12 every 2 to 3 years.

Patients with a history of genital mycotic infections and uncircumcised males are more likely to develop mycotic infections when using SGLT2 inhibitors and should be monitored closely. Patients treated with SGLT2 inhibitors are also at increased risk for urinary tract infections, including urosepsis and pyelonephritis, and should be monitored closely. As part of the December 2015 FDA safety communication, patients are advised they should be aware of signs and symptoms of urinary tract infection and contact their healthcare professional if experienced.[63]

SGLT2 inhibitors cause intravascular volume contraction and can lead to renal impairment. There have been reports of acute kidney injury, some requiring hospitalization and dialysis in patients treated with use of canagliflozin-, dapagliflozin-, and empagliflozin-containing agents. SGLT2 inhibitors can decrease the eGFR and increase serum creatinine. Patients with hypovolemia, particularly the elderly and those with moderate renal impairment, may be at increased risk for these changes. Renal function should be evaluated prior to initiation of therapy and monitored periodically thereafter. Other factors that may make patients more susceptible to acute kidney injury should also be considered (e.g., concomitant medications, reduced oral intake, fluid losses).

Canagliflozin can cause hyperkalemia in patients with moderate renal impairment (eGFR 45 to < 60 mL/min/1.73 m^2). Potassium levels should be monitored regularly after beginning canagliflozin in patients with impaired renal function and in patients who are predisposed to increased potassium levels due to mediations or other medical conditions.

Symptomatic hypotension can occur after starting SGLT2 inhibitors as they cause osmotic diuresis leading to intravascular volume contraction. Symptomatic hypotension occurs particularly in patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2), elderly patients, patients with low systolic blood pressure, and patients on diuretics or drugs which interfere with the renin-angiotensin-aldosterone system. The patient's volume status should be assessed and corrected prior to starting SGLT2 inhibitor therapy and monitored thereafter.

SGLT2 inhibitors can increase the risk of hypoglycemia when combined with insulin or insulin secretagogues; therefore, a lower dose of insulin or insulin secretagogue may be required when given in combination with a SGLT2 inhibitor.

SGLT2 inhibitors may cause dose-related increases in low-density-lipoprotein cholesterol (LDL-C); therefore, monitoring is warranted to determine the need for treatment intervention. Historically, this has been a classwide warning, but the most recent updates to the canagliflozin (Invokana), dapagliflozin (Farxiga), and dapagliflozin/metformin (Xigduo XR) product labeling no longer contain this warning.

Temporarily discontinue canagliflozin/metformin, canagliflozin/metformin XR, dapagliflozin/metformin ER, empagliflozin/metformin, empagliflozin/metformin ER, and ertugliflozin/metformin (Segluromet) in patients undergoing radiologic procedures who receive intravenous iodinated contrast agents and in patients undergoing any surgical procedure associated with restricted intake of food and fluids. Caution should be used with metformin-containing products in patients experiencing hypoxic states.

In September 2015, the FDA issued a safety communication regarding decreased bone mineral density and increased risk of bone fracture associated with canagliflozin use.[64] Fractures have been reported as early as 12 weeks after starting canagliflozin therapy. Pooled clinical trial data report an incidence of bone fracture of 17.7 for canagliflozin 300 mg compared to 14.2 for comparator per 1,000 patient years of exposure; mean duration of exposure was 68 weeks.[65] Prescribers should consider all factors

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that may contribute to fracture risk before initiating canagliflozin. The FDA is evaluating this risk with dapagliflozin- and empagliflozin-containing products. In clinical studies, 13 patients with moderate renal impairment who were treated with dapagliflozin experienced bone fracture, the majority of which were reported within the first 52 weeks of therapy, compared to zero patients treated with placebo.

DRUG INTERACTIONS[66,67,68,69,70,71,72,73,74,75]

When administered with UDP-glucuronosyltransferase (UGT) enzyme inducers (e.g., rifampin, phenytoin, ritonavir, phenobarbital), the exposure of canagliflozin (Invokana, Invokamet, Invokamet XR) is reduced, which may decrease the efficacy of canagliflozin. If co-administration is needed and the patient has an eGFR ≥ 60 mL/min/1.73 m^2, prescribers should consider increasing the dose from 100 mg to 200 mg once daily; if tolerated, it can be further increased to 300 mg if additional glycemic control is needed. If co-administration is needed and the patient has an eGFR < 60 mL/min/1.73 m^2, the dose can be increased to 200 mg once daily; other antihyperglycemic therapy should be considered in patients taking 200 mg daily who require additional glycemic control. If coadministration of a UGT inducer is required in patients on canagliflozin/metformin (IR or ER) a total daily dose of canagliflozin of 300 mg may be considered in patients already tolerating total daily doses of canagliflozin 100 mg, have an eGFR > 60 mL/min/1.73 m^2, and require additional glycemic control; other antihyperglycemic therapy should be considered in patients with an eGFR 45 to < 60 mL/min/1.73 m^2. Empagliflozin (Jardiance, Synjardy, Synjardy XR) does not inhibit UGT1A1; therefore, no drug interaction is expected when co-administered with substrates of this enzyme. Although metabolism of dapagliflozin (Farxiga, Xigduo XR) and ertugliflozin (Steglatro, Segluromet) involve UGT enzymes, current labeling of these products do not report drug interactions with concurrent use of UGT enzyme inducers.

Co-administration of digoxin and canagliflozin may increase the exposure to digoxin and, therefore, close monitoring and dose adjustment of either agent, if needed, is warranted.

Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and the dapagliflozin 3-0-glucoronide metabolite is a substrate for the OAT3 active transporter. Dapagliflozin has not been shown to induce nor inhibit any of the cytochrome isoenzymes or P-gp, OCT2, OAT1, or OAT3 active transporters. None of the co-administered drugs that were studied (including other classes of oral antidiabetic medications or rifampin) have demonstrated the need for dosage adjustment when given concomitantly with dapagliflozin. Empagliflozin is a substrate for uptake transporters P-gp, OAT3, OATP1B1, and OATP1B3, but does not inhibit these transporters at clinically relevant plasma concentrations; therefore, no relevant drug interactions are expected.

Cationic drugs, such as amiloride, digoxin, dolutegravir, morphine, procainamide, quinidine, quinine, ranolazine, ranitidine, triamterene, trimethoprim, vancomycin, and vandetanib that are eliminated by renal tubular secretion have a theoretical potential interaction with metformin by competing for common renal tubular transport systems. No specific dosing changes are recommended. Increased metformin plasma concentrations are seen with concurrent administration of cimetidine, furosemide, and nifedipine. No specific dosing changes are recommended. Contrast agents increase the risk of metformin-induced lactic acidosis. Concomitant use of topiramate or other carbonic anhydrase inhibitors may increase the risk of lactic acidosis. Monitor for signs and symptoms of acidosis when these drugs are used concomitantly with metformin-containing agents (Invokamet, Invokamet XR, Segluromet, Synjardy, Synjardy XR, Xigduo XR).

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ADVERSE EFFECTS[76,77,78,79,80,81,82,83,84,85]

Adverse Effects	Drug			
	canagliflozin (Invokana)	dapagliflozin (Farxiga)	empagliflozin (Jardiance)	ertugliflozin (Steglatro)
Genital mycosis, female	10.6-11.6 (2.8)	6.9-8.4 (1.5)	5.4-6.4 (1.5)	9.1-12.2 (3)
Genital mycosis, male	3.8-4.2 (0.7)	2.7-2.8 (0.3)	1.6-3.1 (0.4)	3.7-4.2 (0.4)
Urinary tract infection	4.4- 5.9 (3.8)	4.3-5.7 (3.7)	7.6-9.3 (7.6)	4-4.1 (3.9)
Increased urination	4.6-5.1 (0.7)	2.9-3.8 (1.7)	3.2-3.4 (1)	2.4-2.7 (1)
Vulvovaginal pruritus	1.6-3.2 (0)	nr	nr	reported
Thirst	2.4-2.8 (0.1)	nr	1.5-1.7 (0)	1.4-2.7 (0.6)
Constipation	1.8-2.4 (0.9)	1.9-2.2 (1.5)	nr	nr
Nausea	2.1-2.3 (1.6)	2.5-2.8 (2.4)	1.1-2.3 (1.4)	nr
Nasopharyngitis	nr	6.3-6.6 (6.2)	nr (Jardiance); reported (Synjardy, Synjardy XR)	2-2.5 (2.3)
Back Pain	nr	3.1-4.2 (3.2)	reported	1.7-2.5 (2.3)
Influenza	nr	2.3-2.7 (2.3)	nr	nr
Dyslipidemia	nr	2.1-2.5 (1.5)	2.9-3.9 (3.4)	reported
Discomfort with urination	nr	1.6 -2.1 (0.7)	nr	nr
Pain in extremity	nr	1.7-2 (1.4)	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

When used alone, SGLT2 inhibitors do not appear to cause hypoglycemia. Use of SGLT2 inhibitors results in modest weight loss.

Urine glucose tests should not be used to monitor glycemic control in patients that are on SGLT2 inhibitors. Sodium-glucose cotransporter 2 inhibitors increase urinary glucose excretion and will result in positive urine glucose tests. In addition, measurement of 1,5-anhydroglucitol (1,5-AG), a glucose analog that competes with glucose for renal reabsorption, is an unreliable method to assess glycemic control.

Initiation of metformin therapy is commonly associated with gastrointestinal adverse effects. As described above, long-term use of metformin may lead to vitamin B12 deficiency.

SPECIAL POPULATIONS[86,87,88,89,90,91,92,93,94,95]

Pediatrics

The safety and efficacy of SLGT2 inhibitors have not been determined in patients under 18 years old.

Geriatrics

No dosage adjustment is recommended for canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin based on age.

Patients 65 years and older may be at increased risk of experiencing intravascular volume-depletion adverse reactions compared to younger patients while on SGLT2 inhibitor therapy; for canagliflozin, this may occur particularly with the 300 mg dose and a more prominent increase in incidence was seen in patients who were 75 years and older. Studies with empagliflozin reported increased risk of urinary tract infections in those 75 years of age and older. When comparing younger patients to older patients, the older patients experienced smaller reductions in HbA1c relative to placebo.

Although differences in responses between elderly and younger patients are not expected, controlled studies of metformin did not include sufficient numbers of elderly patients. Due to the age-related decline of renal function, initiation and maintenance dosing of metformin should be based on a conservative approach in patients with advanced age.

Pregnancy

Canagliflozin (Invokana), canagliflozin/metformin (Invokamet), dapagliflozin (Farxiga), dapagliflozin/metformin ER (Xigduo XR), empagliflozin (Jardiance), and empagliflozin/metformin (Synjardy/XR) were previously assigned Pregnancy Category C, but their labeling has been updated to descriptive information based on the Pregnancy and Lactation Labeling Rule (PLLR) and advises that there are no adequate and well-controlled studies of in pregnant women. Labeling for ertugliflozin (Steglatro) and ertugliflozin/metformin (Segluromet) are also in formatted based on the PLLR and contain descriptive text. In general, labeling of all SGLT2 inhibitors recommend against their use during the second and third trimester of pregnancy.

The potential for unintended pregnancy should be discussed with premenopausal women since metformin may result in ovulation in some anovulatory women.

Renal Impairment

The safety and efficacy of SGLT2 inhibitors have not been studied in patients with severe renal impairment, end stage renal disease (ESRD), or in patients on dialysis. These agents are not expected to be effective in these patient populations. Clinical studies have shown that the glucose lowering benefit of SGLT2 inhibitors decreases in patients with worsening renal function. Also, the risks of renal impairment, volume depletion adverse reactions, and urinary tract infection-related adverse reactions may increase with worsening renal function.

The risk of metformin accumulation and lactic acidosis also increases with worsening renal impairment. However, in April 2016, the FDA published an alert stating that based on evaluation of various safety

studies regarding metformin, they have concluded that metformin may be safely used in patients with mild renal impairment and some patients with moderate renal impairment.[96]

Canagliflozin (Invokana) is contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 who are being treated for glycemic control and those on dialysis, and its use should be discontinued if eGFR persistently falls below 45 mL/min/1.73m^2. Data are insufficient to recommend dosing of canagliflozin (Invokana) in patients with an eGFR < 30 mL/min/1.73 m^2 with albuminuria > 300 mg/day or with an eGFR < 45 mL/min/1.73 m^2 with albuminuria ≤ 300 mg/day; for those meeting the former requirement (eGFR < 30 mL/min/1.73 m^2 with albuminuria > 300 mg/day), treatment of canagliflozin can be continued at 100 mg daily. Key clinical trials of canagliflozin did not include patients with end-stage renal disease (ESRD) on dialysis. Dapagliflozin (Farxiga) and is contraindicated in with eGFR < 30 mL/min/1.73 m^2 and is not recommended with eGFR 30 to < 45 mL/min/1.73 m^2. No dosage adjustment is needed in patients with an eGFR ≥ 45 mL/min/1.73 m^2.

Empagliflozin (Jardiance) is not recommended in patients with eGFR < 45 mL/min/1.73 m^2, and its use should be discontinued if eGFR persistently falls below 45 mL/min/1.73m^2.

Ertugliflozin (Steglatro) and ertugliflozin/metformin (Segluromet) are contraindicated in with eGFR < 30 mL/min/1.73 m^2 and should be discontinued if eGFR is persistently falls between 30 and < 60 mL/min/1.73 m^2. Canagliflozin/metformin (Invokamet, Invokamet XR) and empagliflozin/metformin (IR and ER) (Synjardy, Synjardy XR) are contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. The dose of canagliflozin should be limited to 100 mg/day (50 mg twice daily for canagliflozin/metformin XR) in those with eGFR 45 to < 60 mL/min/1.73 m^2. Dapagliflozin/metformin ER (Xigduo XR) is contraindicated in patients with eGFR < 30 mL/min/1.73 m^2; its use is not recommended with eGFR < 45 mL/min/1.73 m^2.

Hepatic Impairment

Canagliflozin (Invokana) is not recommended for use in patients with severe hepatic impairment. No dosage adjustments are recommended for those with mild or moderate hepatic impairment. Use of canagliflozin/metformin (Invokamet, Invokamet XR) is not recommended in patients with hepatic impairment.

No dose adjustment is recommended for dapagliflozin, empagliflozin, and ertugliflozin for patients with hepatic impairment. However, the safety and efficacy of these agents have not been specifically studied in patients with severe hepatic impairment.

In general, the metformin-containing products canagliflozin/metformin, dapagliflozin/metformin ER, empagliflozin/metformin, empagliflozin/metformin XR, and ertugliflozin/metformin are not recommended in patients with hepatic impairment due to increased risk of lactic acidosis.

DOSAGES[97,98,99,100,101,102,103,104,105,106]

Drug	Parameters	Dosage	Availability
canagliflozin (Invokana)	Recommended starting dose	100 mg once daily taken before the first meal	100 mg, 300 mg tablet
	Patients tolerating canagliflozin 100 mg daily, requiring additional glycemic control, and have an eGFR ≥ 60 mL/min/1.73 m^2	300 mg once daily	
	Moderate renal impairment (eGFR 45 to 59 mL/min/1.73 m^2)	100 mg once daily	
canagliflozin/ metformin (Invokamet)	Recommended starting dose (Base initial dose on patient's current regimen)	For patients not on either metformin or canagliflozin: one 50/500 mg tablet twice daily For patients on metformin: switch to Invokamet containing canagliflozin 50 mg with a similar total daily dose of metformin taken twice daily with meals; For patients on canagliflozin: switch to Invokamet containing metformin 500 mg with a similar total daily dose of canagliflozin taken twice daily with meals; For patients on canagliflozin and metformin: switch to Invokamet containing the same total daily doses of each component taken twice daily with meals	50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg immediate-release tablet
	Moderate renal impairment (eGFR 45 to 59 mL/min/1.73 m^2)	50 mg twice daily of the canagliflozin component	
canagliflozin/ metformin ER (Invokamet XR)	Recommended starting dose (Base initial dose on patient's current regimen)	For patients not on either metformin or canagliflozin: two 50/500 mg tablets once daily with the morning meal For patients on metformin: switch to 2 tablets of Invokamet XR containing a total of canagliflozin 100 mg with a similar total daily dose of metformin taken once daily with the morning meal; For patients on canagliflozin: switch to 2 tablets of Invokamet XR containing a total of metformin 1,000 mg with the current total daily dose of canagliflozin taken once daily with the morning meal; For patients on canagliflozin and metformin: switch to 2 tablets of Invokamet XR containing the same total daily doses of each component taken once daily with the morning meal	50/500 mg, 50/1,000 mg, 150/500 mg, 150/1,000 mg extended-release tablet
	Moderate renal impairment (eGFR 45 to 59 mL/min/1.73 m2)	100 mg/day of the canagliflozin component	

eGFR = estimated glomerular filtrate rate

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Dosages (continued)

Drug	Parameters	Dosage	Availability
dapagliflozin (Farxiga)	Recommended starting dose to improve glycemic control	5 mg once daily, taken in the morning, with or without food	5 mg, 10 mg tablet
	Patients tolerating dapagliflozin 5 mg once daily who require additional glycemic control	10 mg once daily	
	To reduce the risk of hospitalization for heart failure	10 mg once daily	
dapagliflozin/ metformin ER (Xigduo XR)	Recommended starting dose to improve glycemic control	5 mg once daily (if not already taking dapagliflozin), taken in the morning with food; Gradually escalate dosage to reduce gastrointestinal side effects due to metformin; Do not exceed 10 mg dapagliflozin/2,000 mg metformin per day; Swallow whole; do not crush, cut, or chew For patients needing a dose of Xigduo XR 5/2,000 mg, use two 2.5/1,000 mg ER tablets.	2.5/1,000 mg 5/500 mg, 5/1,000 mg, 10/500 mg, 10/1,000 mg extended-release tablet
	To reduce the risk of hospitalization for heart failure	10 mg of the dapagliflozin component once daily	
empagliflozin (Jardiance)	Recommended starting dose	10 mg once daily in the morning, with or without food	10 mg, 25 mg tablet
	Patients tolerating empagliflozin 10 mg once daily who require additional glycemic control	25 mg once daily	
empagliflozin/ metformin (Synjardy)	Recommended starting dose (Base initial dose on patient's current regimen)	For patients on metformin: switch to empagliflozin 5 mg with similar total daily dose of metformin; administer twice daily with meals; For patients on empagliflozin: switch to metformin 500 mg with a similar total daily dose of empagliflozin; administer twice daily with meals; Gradually escalate dosage to reduce gastrointestinal side effects due to metformin; Do not exceed 25 mg empagliflozin and 2,000 mg metformin per day	5/500 mg, 5/1,000 mg, 12.5/500 mg, 12.5/1,000 mg immediate-release tablet

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Drug	Parameters	Dosage	Availability
empagliflozin/ metformin ER (Synjardy XR)	Recommended starting dose (Base initial dose on patient's current regimen)	Base initial dose on patient's current regimen For patients on metformin: switch Synjardy XR containing a total of empagliflozin 10 mg with a similar total daily dose of metformin taken once daily with the morning meal; For patients on empagliflozin: switch to 2 tablets of Synjardy XR containing a total of metformin ER 1,000 mg with the current total daily dose of empagliflozin taken once daily with the morning meal; For patients on canagliflozin and metformin: switch Synjardy XR containing the same total daily doses of each component taken once daily with the morning meal Synjardy XR 5/1,000 mg and 12.5/1,000 mg tablets should be taken as 2 tablets together once daily Synjardy XR 10/1,000 mg and 25/1,000 mg tablets should be taken as a single tablet once daily	5/1,000 mg, 10/1,000 mg, 12.5/1,000 mg, 25/1,000 mg extended-release tablet
ertugliflozin (Steglatro)	Recommended starting dose	5 mg once daily in the morning, with or without food	5 mg, 15 mg tablet
	Patients tolerating ertugliflozin 5 mg once daily who require additional glycemic control	15 mg once daily	
ertugliflozin/ metformin (Segluromet)	Recommended starting dose (Base initial dose on patient's current regimen)	Administer twice daily with meals Do not exceed ertugliflozin 15 mg and metformin 2,000 mg daily For patients on metformin, switch to Segluromet containing 2.5 mg ertugliflozin, with a similar total daily dose of metformin. For patients on ertugliflozin, switch to Segluromet containing 500 mg metformin, with a similar total daily dose of ertugliflozin. For patients already treated with ertugliflozin and metformin, switch to Segluromet containing the same total daily dose of ertugliflozin and a similar daily dose of metformin.	2.5/500 mg, 2.5/1,000 mg, 7.5/500 mg, 7.5/1,000 mg tablet

Renal function should be assessed prior to starting SGLT-2 inhibitor therapy. Do not initiate canagliflozin if eGFR < 30 mL/min/1.73m^2; canagliflozin/metformin (IR and ER), empagliflozin or empagliflozin/metformin (IR or ER) if eGFR < 45 mL/min/1.73 m^2; and dapagliflozin, dapagliflozin/metformin, ertugliflozin, or ertugliflozin/metformin if eGFR < 60 mL/min/1.73 m^2. Discontinue SGLT2 inhibitor therapy if eGFR persistently falls below these respective eGFR levels.

If canagliflozin and a UGT inducer are co-administered and the patient has an eGFR > 60 mL/min/1.73 m^2, prescribers may consider increasing the daily dose of canagliflozin to 200 mg if additional glycemic control is needed, a dose of 300 mg may be considered.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in US, single-blind or open-label design, or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to a paucity of double-blind, direct comparator trials, studies with a placebo comparator were included in the absence of comparative trials.

There have been no clinical efficacy studies conducted with the combination products canagliflozin/metformin (Invokamet, Invokamet XR), dapagliflozin/metformin ER (Xigduo XR), and empagliflozin/metformin (Synjardy), empagliflozin/metformin ER (Synjardy XR), or ertugliflozin/metformin (Segluromet). With the exception of ertugliflozin/metformin (Segluromet), bioequivalence of the combination products, to the respective SGLT2 inhibitor and metformin co-administered as individual tablets has been demonstrated in healthy subjects.

Since 2008, the FDA requires large studies that assess the cardiovascular risk of new antidiabetic agents.[107] These studies (1) should use an upper bound of 95% confidence interval of < 1.3 for the risk ratio of important CV events; (2) must include patients with relatively advanced disease, elderly, and those with renal impairment; (3) must include a minimum of 2 years safety data; (4) must include prospective data with independent adjudication of CV events in all phase 2 and 3 studies; and (5) may include meta-analyses of CV events. Cardiovascular outcomes studied will be included in this review when available for the drugs in this class.

canagliflozin (Invokana) monotherapy

A 26-week double-blind, placebo-controlled study was performed in 584 patients with T2DM who were not controlled by diet and exercise in order to determine the safety and efficacy of canagliflozin.[108,109] Patients who were taking other antihyperglycemics (n=281) discontinued the medication and entered an 8-week washout period followed by a 2-week, single-blind, placebo run-in period. Patients who were not taking oral antihyperglycemics (n=303) were allowed to enter the 2-week, single-blind, placebo run-in period immediately. After the placebo run-in period, patients were then randomized to receive canagliflozin 100 mg, canagliflozin 300 mg, or placebo once daily. Primary endpoint was the

change from baseline in HbA1c. At week 26, HbA1c was significantly reduced from baseline with canagliflozin 100 and 300 mg compared with placebo (-0.77%, -1.03% and 0.14%, respectively; p<0.001 for both dosages). The percent of patients achieving an HbA1c < 7% was 45%, 62%, and 21% for patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and placebo once daily, respectively (p<0.001). Canagliflozin 100 mg and 300 mg once daily also improved fasting plasma glucose (FPG) compared to placebo (-27, -35, and 8 mg/dL, respectively). Patients treated with canagliflozin 100 mg and 300 mg once daily also had greater reductions in the 2-hour postprandial glucose (PPG) compared to placebo (-43, -59, and 5 mg/dL, respectively) and significant reductions in body weight compared to placebo (-2.8%, -3.9%, and -0.6%, respectively; p<0.001 for both). Statistically significant changes in systolic blood pressure were also observed for 100 mg and 300 mg dosages (-3.7 mmHg and -5.4 mmHg, respectively; p<0.001).

canagliflozin (Invokana) versus metformin

In a 26-week, double-blind, phase 3 trial, 1,186 patients were randomized (1:1:1:1:1) to fixed-dose combination of canagliflozin 100 mg/metformin ER (CANA100/MET), canagliflozin 300 mg/metformin ER (CANA300/MET), or monotherapy with canagliflozin 100 mg (CANA100) or 300 mg (CANA300), or metformin ER (MET).[110] Metformin doses were titrated per protocol; doses of canagliflozin were not titrated. Primary end point was change in HbA1c at week 26 for combinations versus monotherapies. The HbA1c reduction at week 26 was statistically significantly greater in the combination therapies groups compared to the monotherapy groups from a mean baseline of 8.8%; reduction for CANA100/MET, CANA300/MET, CANA100, CANA300, and MET were -1.77%, -1.78%, -1.37%, -1.42%, and -1.3%, respectively and resulted in final mean HbA1c's of 7%, 7%, 7.4%, 7.3%, and 7.4%, respectively. Reductions in body weight were significantly more for all canagliflozin-treated groups versus MET (-3.2, -3.9, -2.8, -3.7, and -1.9 kg, respectively). Incidence of hypoglycemia was between 3% and 3.5% for canagliflozin arms and 4.6% with MET.

canagliflozin (Invokamet XR) as add-on therapy to metformin

A double-blind, placebo- and active-controlled study was performed in 1,284 patients with T2DM who were inadequately controlled on metformin monotherapy (≥ 2,000 mg/day, or ≥ 1,500 mg/day if higher dose not tolerated) to assess the safety and efficacy of canagliflozin when combined with metformin.[111,112] If patients were taking less than the required metformin dose or were taking metformin plus another antihyperglycemic (n=275), they were switched to metformin monotherapy for at least 8 weeks before they were allowed to enter the 2-week, single-blind, placebo run-in. Patients who were already taking the required metformin dose (n=1,009) were immediately allowed to enter a 2-week, single-blind, placebo run-in period. After completing the placebo run-in phase, patients were randomized to receive canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or placebo once daily with metformin for 26 weeks (Period I). Patients who completed Period I then entered Period II for an additional 26 weeks during which those who were initially received placebo switched to sitagliptin 100 mg in a blinded fashion, while the other patients in the study continued their original study drug. Comparisons were performed for canagliflozin versus placebo at week 26 and canagliflozin versus sitagliptin at week 52. At week 26, the study indicated that the addition of canagliflozin 100 mg and 300 mg resulted in statistically significant improvements in HbA1c compared to placebo with metformin (-0.79%, -0.94% and -0.17%, respectively; p<0.001 for both dosages). The percent of patients achieving an HbA1c < 7% was 58%, 46%, and 30% with the addition of canagliflozin 300 mg and 100 mg, and placebo, respectively. A larger reduction in FPG occurred with canagliflozin 100 mg (-

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27 mg/dL) and canagliflozin 300 mg (-38 mg/dL) compared to placebo (2 mg/dL). A reduction in PPG was also greater with canagliflozin 100 mg (-48 mg/dL) and canagliflozin 300 mg (-57 mg/dL) compared to placebo (-10 mg/dL). Patients treated with canagliflozin 100 mg and 300 mg once daily also had greater reductions in body weight compared to placebo (-3.7%, -4.2%, and -1.2%, respectively; p<0.001 for both dosages). At week 52, canagliflozin 100 mg and 300 mg demonstrated non-inferiority, and canagliflozin 300 mg demonstrated statistical superiority, to sitagliptin in lowering HbA1c (−0.73%, −0.88%,−0.73%, respectively). Canagliflozin 100 mg and 300 mg reduced body weight compared to sitagliptin at week-52 (-3.8%, -4.2%, and -1.3%, respectively; p<0.001). Incidence of hypoglycemia was higher with canagliflozin; 6.8% with both canagliflozin doses compared to 4.1% with sitagliptin and 2.7% with placebo/sitagliptin at 52 weeks. Statistically significant mean changes in systolic blood pressure relative to placebo were observed with canagliflozin 100 mg and 300 mg (-5.4 mmHg and -6.6 mmHg, respectively; p<0.001 for both doses).

The safety and efficacy of canagliflozin in combination with metformin were studied in 1,450 patients with T2DM who were inadequately controlled on metformin monotherapy (≥ 2,000 mg/day, or ≥ 1,500 mg/day, if higher dose not tolerated) in a 52-week, double-blind, active-controlled study.[113] After a 2-week, single-blind, placebo run-in period, patients who were already taking the maximum required metformin dose (n=928) were randomized. Other patients (n=522) were switched to metformin monotherapy for 10 weeks and then entered the 2-week single-blind run-in period. After the 2-week run-in period, patients were randomized to receive canagliflozin 100 mg or 300 mg, or glimepiride (titration up to 6 mg or 8 mg) given once daily with metformin. The study concluded that addition of canagliflozin 100 mg and glimepiride had similar reductions in HbA1c; only canagliflozin 300 mg plus metformin provided a greater reduction from baseline in the HbA1c level when compared to glimepiride plus metformin (difference -0.12%; 95% confidence interval [CI], -0.22 to -0.02). The percent of patients reaching an HbA1c < 7% was 54%, 60%, and 56% for patients treated with canagliflozin 100 mg, canagliflozin 300 mg, and glimepiride, respectively. A larger reduction in FPG occurred in the canagliflozin 100 mg (-24 mg/dL) and canagliflozin 300 mg (-28 mg/dL) compared to glimepiride (-18 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to the glimepiride group (-4.2%, -4.7%, and +1%, respectively; p<0.001 for both).

canagliflozin (Invokamet XR) as add-on therapy to metformin and sitagliptin

A 26-week, double-blind, placebo-controlled trial included 217 patients with T2DM who were inadequately controlled on metformin (≥ 1,500 mg/day) plus sitagliptin (100 mg/day).[114] Mean baseline eGFR was 90 ml/min/1.73m^2. After a 2-week single-blind, placebo run-in period, patients were randomly assigned to canagliflozin 100 mg or placebo as add on to background therapy (metformin plus sitagliptin). Baseline HbA1c was 8.5% and 8.4% in the canagliflozin and placebo groups, respectively. Adjusted mean change in HbA1c from baseline to week 26 was -0.03% and -0.83%, respectively. Change in FPG was -3 mg/dL and -28 mg/dL, respectively.

canagliflozin (Invokana) as add-on therapy to sulfonylurea

An 18-week, double-blind, placebo-controlled sub-study was performed in 127 patients with T2DM who were inadequately controlled on sulfonylurea monotherapy in order to assess the safety and efficacy of canagliflozin combined with sulfonylurea.[115] Patients taking sulfonylurea monotherapy and who were stable on a protocol specified dose (≥ 50% maximum dose) for at least 10 weeks completed

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a 2-week, single-blind, placebo run-in phase. Upon completion of the run-in phase, patients with poor glycemic control were randomized to add-on therapy with canagliflozin 100 mg, canagliflozin 300 mg, or placebo once daily. The study concluded that canagliflozin 100 mg and 300 mg daily resulted in statistically significant improvements in HbA1c compared to placebo when combined with a sulfonylurea (p<0.001). Canagliflozin 300 mg daily compared to placebo also resulted in higher rates of achieving an HbA1c < 7% (33% versus 5%) and larger reductions in FPG (-36 mg/dL versus +12 mg/dL).

canagliflozin (Invokana) as add-on therapy to metformin and sulfonylurea

The efficacy and safety of canagliflozin in combination with metformin and a sulfonylurea were studied in 469 patients with T2DM who were inadequately controlled on combined metformin (≥ 2,000 mg/day, or ≥ 1,500 mg/day if higher dose not tolerated) and sulfonylurea (maximum or near maximum dose) therapy in a 26-week, double-blind, placebo-controlled study.[116] Patients who were on protocol-specified doses of metformin and sulfonylurea (n=372) were allowed to directly enter a 2-week, single-blind, placebo run-in period. Other patients (n=97) were required to be on a stable protocol dose of metformin and sulfonylurea for 8 weeks or more before entering the 2-week run-in phase. After the run-in period, patients were randomized to receive canagliflozin 100 mg or 300 mg, or placebo taken once daily added to metformin and sulfonylurea. The study resulted in canagliflozin 100 mg and 300 mg having statistically significant improvements in HbA1c compared to placebo when combined with metformin and sulfonylurea (p<0.001). More patients treated with canagliflozin 100 mg or 300 mg obtained an HbA1c < 7% (43% and 57%, respectively) compared to placebo (18%) (p<0.001). Canagliflozin 100 mg and 300 mg lowered FPG (-18 mg/dL and -31 mg/dL, respectively) more than placebo (4 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to the placebo group (-2.1%, -2.6%, and -0.7%, respectively; p<0.001 for both).

A 52-week, double blind, active-controlled study enrolled 755 patients with T2DM who were uncontrolled on a combination of metformin (≥ 2,000 mg/day, or ≥ 1,500 mg/day, if higher dose not tolerated) and sulfonylurea (maximum or near maximum dose) was performed to compare the efficacy and safety of the addition of canagliflozin 300 mg versus sitagliptin 100 mg to metformin and sulfonylurea.[117,118] Patients already on the protocol-specified doses of metformin and sulfonylurea (n=716) were allowed to enter a 2-week single-blind, placebo run-in phase. Other patients (n=39) had to be stabilized on the protocol-specified dose of metformin and sulfonylurea for at least 8 weeks before entering the 2-week run-in period. All patients were then randomized to canagliflozin 300 mg or sitagliptin 100 mg plus metformin and sulfonylurea. A total of 464 patients completed the 52-week treatment period. At the conclusion of the study, it was determined that canagliflozin 300 mg resulted in a greater HbA1c reduction compared to sitagliptin 100 mg when added to metformin and sulfonylurea (p<0.05). The rate of patients achieving an HbA1c < 7% was higher in the canagliflozin 300 mg treatment group (48%) versus the sitagliptin 100 mg treatment group (35%). The addition of canagliflozin 300 mg also lowered FPG more than sitagliptin 100 mg (-30 and -6 mg/dL, respectively). Patients in the canagliflozin 300 mg group also had greater reductions in body weight compared to the sitagliptin group (-2.5% and -0.3%, respectively; p<0.001). A decrease in systolic blood pressure was seen with canagliflozin 300 mg, while a small increase was reported with sitagliptin 100 mg (-5.06 mmHg versus +0.85 mmHg).

canagliflozin (Invokana) as add-on therapy to metformin and pioglitazone

A 26-week, double-blind, placebo-controlled study was performed in 342 patients with T2DM who were poorly controlled on metformin (≥ 2,000 mg/day, or ≥ 1,500 mg/day, if higher dose not tolerated) and pioglitazone (30 or 45 mg/day) to evaluate the efficacy and safety of canagliflozin plus metformin and pioglitazone.[119] Patients (n=163) who were already on protocol-specific doses of metformin and pioglitazone entered a 2-week, single-blind, placebo run-in period. Other patients (n=181) were required to be on metformin and pioglitazone at protocol-specific stable doses for at least 8 weeks before entering the 2-week run-in period. After the run-in phase, patients were then randomized to canagliflozin 100 mg or 300 mg, or placebo given once daily with metformin and pioglitazone. The study resulted in the addition of canagliflozin 100 mg and 300 mg having statistically significant improvements in HbA1c compared to placebo (p<0.001). Canagliflozin 100 mg and 300 mg resulted in a greater percentage of patients achieving an HbA1c < 7% compared to placebo (47, 64, and 33%, respectively) (p<0.001). Canagliflozin 100 mg and 300 mg had larger reductions in FPG (-27 and -33 mg/dL, respectively) compared to placebo (3 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to placebo when add to metformin and pioglitazone (-2.8%, -3.8% and -0.1%, respectively; p<0.001). In addition, statistically significant mean changes from baseline in systolic blood pressure relative to placebo were -4.1 mmHg and -3.5 mmHg with canagliflozin 100 mg and 300 mg, respectively (p<0.05 for both doses).

canagliflozin (Invokana) as add-on therapy to insulin

An 18-week, double-blind, placebo-controlled substudy of a cardiovascular study was performed to assess the efficacy and safety of canagliflozin in combination with insulin.[120] The study included 1,718 patients with T2DM who were uncontrolled on insulin at doses of at least 30 units/day or who were on insulin in combination with other antihyperglycemic agents. Patients entered a 2-week, single-blind, placebo run-in period after at least 10 weeks of basal, bolus, or basal/bolus insulin therapy. After the run-in period, patients were randomized to receive canagliflozin 100 mg or 300 mg, or placebo once daily plus insulin. The study concluded that canagliflozin-treated patients experienced a statistically significant improvement in their HbA1c levels (p<0.001) compared to placebo treated patients when added to insulin. The percent of patients' achieving an HbA1c < 7% was 20%, 25%, and 8% for canagliflozin 100 mg, canagliflozin 300 mg, and placebo, respectively. Canagliflozin 100 mg and 300 mg also resulted in a larger decrease in FPG (-19 and -25 mg/dL, respectively) compared to placebo (4 mg/dL). Patients in the canagliflozin 100 mg and 300 mg groups also had greater reductions in body weight compared to the placebo group (-1.8%, -2.8%, and -0.1%, respectively; p<0.001). Statistically significant mean change in systolic blood pressure relative to placebo was reported with both doses of canagliflozin; -3.5 mmHg for the 100 mg dose (p=0.023) and -6 mmHg for the 300 mg dose (p<0.001).

canagliflozin (Invokana) as add-on to standard of care, cardiovascular outcomes

CANVAS/CANVAS-R: The CANVAS Program included 2 similarly designed double-blind, parallel-group, placebo-controlled studies (CANVAS, n=4,330, CANVAS-R, n=5,812) that investigated the effects of canagliflozin on cardiovascular safety outcomes in adults with T2DM and high risk of cardiovascular disease (CVD).[121] CANVAS-R also assessed the effects on albuminuria. All patients had an eGFR > 30 mL/min/1.73m^2. In CANVAS, patients were randomized (1:1:1) to canagliflozin 100 mg, canagliflozin 300 mg, or placebo; in CANVAS-R, patients were randomized (1:1) to canagliflozin 100 mg, with an option to increase to 300 mg after week 12, or placebo. The mean age was 63.3 years, 35% were

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women, mean duration of T2DM was 13.5 years, mean eGFR was 76.5 mL/min/1.73m^2, and 65.6% had a history of CVD. The primary outcome was a composite of cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke). A total of 9,734 (96%) patients completed the trials. The mean follow-up was 188.2 weeks (295.9 weeks in CANVAS, 108 weeks in CANVAS-R). There were significantly fewer primary outcome events reported with canagliflozin than with placebo (26.9 versus 31.5 participants per 1000 patient-years; HR, 0.86; 95% CI, 0.75 to 0.97; p<0.001 for noninferiority; p=0.02 for superiority). Although, benefit was seen for all 3 components of the primary outcome measure with canagliflozin, no difference in any individual component reached significance. Less patients treated with canagliflozin experienced albuminuria than those treated with placebo (89.4 versus 128.7 patients per 1,000 patient-years; HR, 0.73 [95% CI, 0.67 to 0.79]). However, the demonstrated renal effect was greater in CANVAS-R (HR of 0.64 versus HR of 0.8 in CANVAS). In addition, regression of albuminuria was seen in more patients treated with canagliflozin (293.4 versus 187.5 per 1,000 patient-years). The composite outcome of sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes occurred less often with canagliflozin than placebo (5.5 versus 9 per 1,000 patient-years; HR 0.6; 95% CI, 0.47 to 0.77); this was similar in CANVAS and CANVAS-R. The CANVAS Program also revealed a higher risk of lower limb amputation (toes, feet, legs) with canagliflozin than with placebo (6.3 versus 3.4 patients per 1,000 patient-years; HR, 1.97; 95% CI, 1.41 to 2.75), the majority (71%) being at the level of the toe or metatarsal.

canagliflozin (Invokana) in patients with renal impairment and cardiovascular outcomes

CREDENCE: A double-blind, randomized clinical trial evaluated canagliflozin in patients (n=4,401) with T2DM and albuminuric chronic kidney disease (eGFR, 30 to < 60 mL/min/1.73 m^2 and albuminuria, [ratio of albumin (mg) to creatinine (g), > 300 to 5,000]).[122] Patients were required to be receiving a stable maximum dose of an angiotensin converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) for 4 weeks before randomization. Patients were randomized 1:1 to canagliflozin 100 mg once daily or placebo. Per the recommendation of the data and safety committee, the trial was stopped early. The median follow-up time was 2.62 years. The primary composite endpoint measure included end-stage kidney disease (dialysis, transplantation, or sustained eGFR of < 15 mL/min/1.73 m^2), doubling of serum creatinine (SCr) level, or death from renal or CV causes. The relative risk of the primary endpoint in the canagliflozin group was 30% lower compared to the placebo group, with event rates 43.2 and 61.2 per 1,000 patient-years, respectively (hazard ratio [HR], 0.7; 95% CI, 0.59 to 0.82; p=0.00001). The canagliflozin arm had a lower relative risk of SCr level doubling or death from renal cause by 34% compared to the placebo arm (HR, 0.66; 95% CI, 0.53 to 0.81; p<0.001) and a 32% lower relative risk of end-stage kidney disease compared to the placebo arm (HR, 0.68; 95% CI, 0.54 to 0.86, p=0.002). The risk of CV death, MI, or stroke (HR, 0.8; 95 CI, 0.67 to 0.95, p=0.01) and hospitalization for heart failure (HR, 0.61; 95 CI, 0.47 to 0.8, p<0.001) were also lower with canagliflozin.

dapagliflozin (Farxiga) monotherapy

Dapagliflozin was studied as monotherapy in treatment-naïve patients with T2DM. A 24-week randomized, double-blind, placebo-controlled phase 3 trial (n=485) randomly assigned patients to 1 of 7 arms to receive once-daily placebo or dapagliflozin 2.5 mg, 5 mg, or 10 mg once daily in the morning (main cohort) or evening (exploratory cohort).[123] The primary endpoint was change in baseline from HbA1c in the main cohort. At 24 weeks, the adjusted mean HbA1c reductions from baseline were -0.58

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for dapagliflozin 2.5 mg, -0.77 for dapagliflozin 5 mg, and -0.89 for dapagliflozin 10 mg compared to -0.2 for placebo. These reductions were statistically significant with 5 mg and 10 mg dapagliflozin (p=0.0005 and p<0.0001, respectively). An increased incidence in signs and symptoms and other reports suggestive of urinary tract infections (UTIs) and genital infections were noted with dapagliflozin treatment.

dapagliflozin initial combination therapy with metformin extended-release (Xigduo XR)

A total of 1,241 treatment-naïve patients with inadequately controlled T2DM (HbA1c >7.5 % and <12%) participated in 2 active-controlled studies of 24-week duration to evaluate the safety and efficacy of initial therapy with dapagliflozin, metformin extended-release, or the combination.[124] Patients were randomized in a double-blind fashion to 1 of 3 treatment arms: a combination of dapagliflozin and metformin ER or monotherapy with either dapagliflozin or metformin ER. In the first trial, dapagliflozin was dosed at 5 mg daily and, in the second trial, dapagliflozin was dosed at 10 mg daily. Metformin ER in combination and as monotherapy was titrated to 2,000 mg per day. The primary endpoint was HbA1c change from baseline; secondary endpoints included change in fasting plasma glucose (FPG) and weight. In both trials, combination therapy led to significantly greater reductions in HbA1c compared with either monotherapy. In study 1, HbA1c reductions were -2.05 for dapagliflozin plus metformin ER, -1.19 for dapagliflozin, and -1.35 for metformin ER (p<0.0001). In study 2, HbA1c reductions were -1.98 for dapagliflozin + metformin ER, -1.45 for dapagliflozin, and -1.44 for metformin ER (p<0.0001). Single agent dapagliflozin 10 mg was non-inferior to single agent metformin ER for reducing HgA1c in this study. Combination therapy was also statistically superior to monotherapy with either agent in reduction of FPG (p<0.0001 for both studies); combination therapy was more effective than metformin ER for weight reduction (p<0.0001). Events suggestive of genital infection were reported in 6.7%, 6.9%, and 2% (study 1) and 8.5%, 12.8%, and 2.4% (study 2) of patients in combination, dapagliflozin, and metformin ER groups, respectively; events suggestive of UTIs were reported in 7.7%, 7.9%, and 7.5% (study 1) and 7.6%, 11%, and 4.3% (study 2) of patients, respectively.

dapagliflozin (Farxiga) versus placebo as add-on to metformin

Patients with inadequate glycemic control (HbA1c $\geq$ 7% and $\leq$ 10%) receiving a dose of at least 1,500 mg/day of metformin (n=546) were randomized to add-on either dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo for 24 weeks.[125] Patients receiving dapagliflozin 5 mg or 10 mg achieved statistically significant improvements in HbA1c and FPG, as well as statistically significant reduction in body weight compared with placebo at week 24 (p<0.0001 for all 3 parameters versus placebo plus metformin).

dapagliflozin (Farxiga) versus glipizide as add-on to metformin

A 52-week, double-blind, multicenter, active-controlled, noninferiority trial randomized patients receiving metformin monotherapy (minimum dose 1,500 mg/day) and inadequate glycemic control (HbA1c $\geq$ 6.5% and $\leq$ 10%) to add-on dapagliflozin or glipizide.[126] Initial doses were dapagliflozin 2.5 mg or glipizide 5 mg. Glipizide and dapagliflozin were up-titrated over 18 weeks to optimal glycemic effect (FPG < 110 mg/dL) or to the highest dose level (up to a maximum of 20 mg of glipizide or 10 mg of dapagliflozin) as tolerated by the patients. At the end of the titration period, 87% of patients with dapagliflozin had been titrated to the maximum study dose (10 mg) while only 73% of glipizide patients were receiving the maximum dose (20 mg). The primary endpoint, adjusted mean HbA1c reduction with dapagliflozin compared with glipizide, was statistically non-inferior at 52 weeks. Secondary

endpoints included adjusted mean weight loss and proportion of patients experiencing hypoglycemia. Dapagliflozin produced significant adjusted mean weight loss (-3.2 kg) versus weight gain (1.2 kg) with glipizide (p<0.001). The proportion of patients experiencing hypoglycemia was 3.4% for dapagliflozin and 39.7% for glipizide (p<0.001).

dapagliflozin (Farxiga) add-on to a sulfonylurea

A 24-week placebo-controlled study evaluated dapagliflozin when added-on to glimepiride monotherapy (minimum dose 4 mg) in patients with inadequate glycemic control (HbA1c $\geq$ 7% and $\leq$ 10%).[127] Patients (n=597) were randomized to dapagliflozin 5mg, 10 mg, or placebo, in addition to glimepiride 4 mg per day. In combination with glimepiride, dapagliflozin 10 mg provided statistically significant improvement in HbA1c, FPG, 2-hour post prandial glucose (PPG), and statistically significant reduction in body weight compared with placebo plus glimepiride at week 24.

dapagliflozin (Farxiga) add-on to a thiazolidinedione

Patients (n=420) on a stable dose of pioglitazone (either 30 mg or 45 mg per day) who had inadequate glycemic control (HbA1c $\geq$ 7% and $\leq$ 10.5%) for 12 weeks were randomized to dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo, in addition to their current dose of pioglitazone.[128] In combination with pioglitazone, treatment with dapagliflozin 10 mg provided statistically significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving HbA1c < 7%, and a statistically significant reduction in body weight compared with placebo plus pioglitazone.

dapagliflozin (Farxiga) add-on to a DPP-4 Inhibitor with or without metformin

A total of 452 patients who were either drug naïve or who were treated at baseline with metformin or a dipeptidyl peptidase 4 (DPP-4) inhibitor alone or in combination and who had inadequate glycemic control (HbA1c $\geq$ 7% and $\leq$ 10%) participated in a 24-week placebo-controlled study to evaluate dapagliflozin in combination with the DPP-4 inhibitor, sitagliptin, with or without metformin.[129] Patients were stratified based on the presence or absence of background metformin (minimum 1,500 mg per day) and, within each stratum, were randomized to dapagliflozin 10 mg plus sitagliptin 100 mg once daily or placebo plus sitagliptin 100 mg once daily. Prior to randomization, 37% of patients were drug naïve, 32% were on metformin alone, 13% were on a DPP4 inhibitor alone, and 18% were on a DPP4 inhibitor plus metformin. In combination with sitagliptin (with or without metformin), dapagliflozin provided statistically significant improvements in HbA1c, FPG, and a statistically significant reduction in body weight compared with placebo plus sitagliptin (with or without metformin) at 24 weeks.

dapagliflozin (Farxiga) add-on combination therapy with insulin

A double-blind, placebo-controlled, multicenter trial randomized a total of 71 patients to placebo, dapagliflozin 10 mg or dapagliflozin 20 mg in patients who were on a stable dose regimen of insulin and at least 1 oral antidiabetic agent, such as a metformin with or without a thiazolidinedione.[130] Upon initiation of dapagliflozin, patients were changed to an open-label therapy with 50% of their usual daily insulin dose. Both doses of dapagliflozin decreased HbA1c, FPG, and PPG compared to placebo and overall adverse events were balanced across all groups.

A 24-week, placebo-controlled, multicenter study examined 808 patients with inadequate glycemic control (HbA1c between 7.5% and 10.5%) who were on a stable insulin regimen (mean dose of at least

30 units/day) and a maximum of 2 oral antidiabetic medications, including metformin.[131] After the initial 24 weeks, a 24-week extension was allowed, as well as an additional 56-week extension period for a total of 104 weeks. In this study, 50% of patients were on insulin monotherapy and 50% were on 1 or 2 oral antidiabetic agents in addition to insulin. Patients were randomized to dapagliflozin 2.5 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, or placebo and stratified according to the presence or absence of background oral antidiabetic agents. The primary endpoint was change in HbA1c from baseline after 24 weeks. Secondary outcomes included changes in body weight, insulin dose, and FPG at 24 weeks. No dose modifications of study medication or other oral antidiabetic medications were allowed during the treatment phase except to decrease the dose of oral antidiabetic medications if hypoglycemia became a concern in patients who had already discontinued insulin. Insulin was down-titrated if 2 or more self-monitored blood glucose readings were 80 mg/dL or less in the first 7 days or < 70 mg/dL after the first 7 days. At week 24, all doses of dapagliflozin once daily resulted in a statistically significant reduction in HbA1c levels compared to placebo. These differences were maintained at 48 weeks. The effect of dapagliflozin on HbA1c was similar in patients treated with insulin alone and patients treated with insulin plus oral antidiabetic agents. Significantly greater decreases in body weight occurred in all the dapagliflozin groups compared to placebo (p<0.001) and these differences were maintained at 48 weeks, as well. Mean daily insulin doses were decreased in all dapagliflozin groups compared to placebo at both 24 and 48 weeks (p<0.001). Higher incidences of urinary tract infections, genital infections, and hypoglycemic events were observed in the dapagliflozin groups compared to placebo. At week 104, 513 patients (63.6%) completed the study. Mean HbA1c changes from baseline at 104 weeks were -0.4% in the placebo group and -0.6 to -0.8% in the dapagliflozin groups.[132] In the placebo group, mean insulin dose increased by 18.3 units/day and weight increased by 1.8 kg at 104 weeks, whereas in the dapagliflozin groups, insulin dose was stable and weight decreased by 0.9 to 1.4 kg. Adverse events, including hypoglycemia, were similar between all groups. Proportions of patients with events suggestive of genital infection and of UTI were higher with dapagliflozin versus placebo (genital infection 7.4% to 14.3% versus 3%; UTI 8.4 to 13.8% versus 5.6%) but most occurred in the first 24 weeks and most were single episodes that responded to routine management.

dapagliflozin (Farxiga) as add-on to usual therapy

A randomized, double-blind, 24-week clinical trial with a 28-week extension was performed to assess the efficacy of dapagliflozin in 964 patients with T2DM and documented CVD.[133,134] The study was stratified by age (< 65 and ≥ 65 years). Patients were randomized to dapagliflozin 10 mg or placebo once daily added to their usual care. Total daily insulin doses were reduced by 25% at the start of the study. Primary endpoints were change from baseline in HbA1c and proportion of participants achieving a 3-item endpoint of reduction HbA1c ≥ 0.5%, decrease in body weight of at least 3%, and reduction of systolic blood pressure ≥ 3 mmHg at 24 weeks. Forty-seven percent were aged 65 years and older and 7.7% were 75 years and older, mean duration of T2DM was 13 years, mean baseline HbA1c was 8.1%, and approximately 60% of patients on insulin therapy. The placebo-corrected change in HbA1c with dapagliflozin was -0.4% at week 24. The difference in adjusted mean change in body weight was -2.07 kg (p<0.0001) and the difference in change in mean seated systolic blood pressure was -3.76 mmHg (p=0.025). Significantly more participants achieved the 3-item endpoint with dapagliflozin than with placebo (10 versus 1.9%, respectively). Similar results were reported in both groups. Hypoglycemia was reported in 28.2% of patients who received dapagliflozin compared to 25.3% who received placebo.

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dapagliflozin (Farxiga) and cardiovascular outcomes

DECLARE–TIMI 58:[135] A total of 17,160 patients with T2DM who had or were at risk for ASCVD were randomized to dapagliflozin or placebo. The primary efficacy outcomes were major adverse CV events (including CV death, MI, or ischemic stroke) and a composite of CV death or hospitalization for heart failure. After a median of 4.2 years, while there was no significant difference in the rate of MACE with dapagliflozin compared to placebo (dapagliflozin, 8.8%; placebo, 9.4%; HR, 0.93 [95% CI, 0.84 to 1.03]; p=0.17), a significantly lower rate of CV death or hospitalization for heart failure was demonstrated with dapagliflozin (4.9% versus 5.8%; HR, 0.83 [95% CI, 0.73 to 0.95]; p=0.005). This was almost entirely due to a lower rate of hospitalization for heart failure (HR, 0.73; 95% CI, 0.61 to 0.88). A renal event was reported in 4.3% of patients treated with dapagliflozin compared to 5.6% with placebo (HR, 0.76; 95% CI, 0.67 to 0.87).

dapagliflozin (Farxiga) in patients with renal impairment

DERIVE:[136] A double-blind, parallel-group study evaluated dapagliflozin in patients (n=321) with inadequately controlled T2DM and moderate renal impairment (eGFR, 45 to < 60 mL/min/1.73 m^2). Patients were randomized (1:1) to dapagliflozin 10 mg once daily or placebo. At 24 weeks, dapagliflozin significantly decreased HbA1c (primary endpoint) compared with placebo (difference, -0.34%; 95 CI, -0.53 to -0.15; p<0.001). Decrease in eGFR from baseline to week 24 was greater with dapagliflozin than placebo (-2.49 mL/min/1.73 m^2); however, at the end of the 3-week post-treatment follow-up period, eGFR returned to baseline (0.61 mL/min/1.73 m2 [95 CI, -1.59 to 2.81]).

empagliflozin (Jardiance) monotherapy

A randomized, double-blind, placebo-controlled, parallel group study evaluated the efficacy and safety of empagliflozin monotherapy in 986 treatment-naïve adults with T2DM who were inadequately controlled with diet and exercise.[137,138] After a 2-week open-label placebo run-in phase, 986 patients who remained inadequately controlled and had an HbA1c between 7% and 10% were randomized to 24 weeks of daily oral empagliflozin 10 mg or 25 mg, placebo, or sitagliptin 100 mg as a comparator. Patients with HbA1c > 10% in the open-label phase received empagliflozin 25 mg. Primary endpoint was the change in HbA1c from baseline. At Week 24, treatment with empagliflozin 10 mg and 25 mg and sitagliptin provided statistically significant reductions in HbA1c compared to placebo (-0.74, -0.85, -0.73, respectively; p <0.0001 for all). Significant reductions were also reported with secondary endpoints of fasting plasma glucose (FPG). Patients on empagliflozin (-1.93 kg for 10 mg, -2.15 kg for 25 mg, p<0.001 for both) experienced significantly greater weight loss than those assigned to sitagliptin (+0.52 kg) and placebo. The incidence of reported hypoglycemic events was low in all groups, and was of mild intensity. Changes in eGFR were small and were similar across all groups. At Week 24, the placebo-adjusted reduction in systolic blood pressure was statistically significant for empagliflozin 10mg (-2.6 mmHg; p=0.0231) and empagliflozin 25 mg (-3.4 mmHg; p=0.0028).

empagliflozin (Jardiance) add-on to metformin (Synjardy)

In a double-blind, placebo-controlled trial, a total of 637 patients with T2DM who were inadequately controlled on metformin (≥ 1,500 mg/day or maximum tolerated dose) were randomized to add-on therapy with empagliflozin 10 mg or 25 mg daily or placebo.[139,140] At Week 24, add-on treatment with either dose of empagliflozin resulted in statistically significant reductions compared to placebo in HbA1c (-0.7%, -0.8%, and -0.1%, respectively p<0.0001), FPG (-20, -22, and +6 mg/dL), and body weight

(-2.5%, -2.9%, and -0.5%; respectively). In addition, treatment with empagliflozin led to a significant reduction in systolic blood pressure compared to placebo (placebo-corrected -4.1 mmHg for empagliflozin 10 mg and -4.8 mmHg for empagliflozin 25 mg; p<0.0001 for both strengths).

empagliflozin (Jardiance) plus metformin (Synjardy) versus glimepiride plus metformin

In a double-blind study, 1,545 patients with inadequately controlled T2DM with metformin (≥ 1,500 mg/day or maximum tolerated dose) were randomized to add-on with empagliflozin 25 mg daily or glimepiride 1 to 4 mg daily.[141,142,143] At 52 weeks, empagliflozin 25 mg and glimepiride produced similar reductions in HbA1c. Each agent resulted in reductions in FPG (-19 and -9 mg/dL, respectively). Reported changes in body weight were -3.9% for empagliflozin and +2% for glimepiride. The mean daily dose of glimepiride was 2.7 mg (maximal approved dose in the US is 8 mg/day). There was a significant difference in the adjusted mean change in systolic blood pressure between the 2 groups (-3.6 mmHg for empagliflozin versus 2.2 mmHg for glimepiride; p<0.0001). In addition, at 104 weeks, empagliflozin was shown to be non-inferior to glimepiride.[144] The incidence of adverse reactions, including serious reactions, was similar between treatment groups.

empagliflozin (Jardiance) add-on to metformin (Synjardy) and sulfonylurea

In a 24-week double-blind, placebo-controlled study, 666 patients with T2DM who were inadequately controlled (HbA1c 7% to 10%) on metformin (≥ 1,500 mg/day or maximum tolerated dose) plus a sulfonylurea (at least half the recommended dose or maximum tolerated dose) were randomized to receive add-on therapy with empagliflozin 10 mg or 25 mg daily, or placebo.[145,146,147] Treatment with either dose of empagliflozin provided statistically significant reductions compared with placebo in HbA1c (-0.8%, -0.8%, and -0.2%; respectively; p<0.0001 for both), FPG (-23, -23, and +6 mg/dL, respectively), and body weight (-2.9%, -3.2%, and -0.5%, respectively).

empagliflozin (Jardiance) add-on to pioglitazone with or without metformin

In a 24-week double-blind, placebo-controlled study, patients with T2DM inadequately controlled on metformin (≥ 1,500 mg/day) and pioglitazone (≥30 mg/day) entered an open-label 2-week placebo run-in phase.[148,149] After which, 498 patients with inadequate glycemic control (HbA1c 7% to 10%) were randomized to daily empagliflozin 10 mg or 25 mg or placebo, in combination with pioglitazone, with or without metformin. Of the patients treated, 75.5% were on background therapy with pioglitazone plus metformin, while the remaining 24.5% were on background pioglitazone alone. Both doses of empagliflozin compared with placebo resulted in statistically significant reductions in HbA1c (-0.6%, -0.7%, and -0.1%, respectively; p<0.0001), FPG (-17, -22, and +7 mg/dL, respectively), and body weight (-2%, -1.8%, and -0.6%, respectively). Empagliflozin reduced HbA1c in patients on background pioglitazone plus metformin and pioglitazone alone. Adverse events experienced were mild or moderate in intensity. A 52-week extension trial is also underway.

empagliflozin (Jardiance) add-on to insulin with or without metformin and/or sulfonylureas

A 78-week double-blind, placebo-controlled study included 494 patients with T2DM inadequately controlled on insulin, with or without oral agents, to evaluate the efficacy of empagliflozin as add-on therapy to insulin.[150] Patients entered a 2-week placebo run-in period on basal insulin (e.g., insulin glargine, insulin detemir, or NPH insulin) with or without metformin and/or sulfonylurea background

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therapy. Patients with inadequate glycemic control were then randomized to the addition of empagliflozin 10 mg or 25 mg, or placebo. Patients were maintained on a stable dose of insulin during the run-in period, and during the first 18 weeks of treatment. For the remaining 60 weeks, insulin could be adjusted. The mean total daily insulin dose at baseline for empagliflozin 10 mg, 25 mg, and placebo was 45, 48, and 48 units, respectively. Empagliflozin in combination with insulin, with or without metformin and/or sulfonylurea, resulted in statistically significant reductions in HbA1c and FPG and body weight compared to placebo.

empagliflozin (Jardiance) as add-on to standard of care

The effect of empagliflozin on cardiovascular morbidity and mortality in patients with T2DM was evaluated when added to standard of care in a randomized, placebo-controlled trial.[151] A total of 7,020 patients were randomized to empagliflozin 10 mg or 25 mg or placebo once daily. The primary outcome was composite of death due to cardiovascular causes, or nonfatal MI or stroke. The key secondary outcome included the primary outcome plus hospitalization for unstable angina. The primary outcome occurred in 10.5% of patients in the pooled empagliflozin group (10 mg and 25 mg) and 12.1% of the placebo group (HR], 0.86; 95% CI, 0.74 to 0.99; p=0.04 for superiority). A significantly lower rate of CV death (3.7% versus 5.9%), hospitalization for heart failure (2.7% versus 4.1%), and death from any cause (5.7% versus 8.3%) were reported with empagliflozin compared to placebo. No significant differences in the occurrence of MI or stroke of in key secondary outcomes were reported.

ertugliflozin (Steglatro) versus placebo

A 26-week, double-blind, placebo-controlled trial was performed in 461 patients with T2DM who were not controlled by diet and exercise (HbA1C, 7% to 10.5%).[152] Patients were either treatment-naïve or were ≥ 8 weeks without antihyperglycemic treatment. After a 2-week, single-blind, placebo run-in period, patients were randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily. The primary endpoint, change from baseline HbA1C at week 26, was significantly higher in the ertugliflozin groups compared to the placebo group. The mean reduction in HbA1C relative to the placebo group was -0.99% (95% CI, -1.22 to -0.76; p<0.001) in the ertugliflozin 5 mg group and   -1.16% (95% CI, -1.39 to -0.93; p<0.001) in the ertugliflozin 15 mg group. Compared to the placebo group, patients in the ertugliflozin 5 mg and 15 mg groups were 3.6 and 6.8 times as likely to achieve a HbA1C < 7%, respectively (ertugliflozin 5 mg: 95% CI, 1.85 to 6.95; ertugliflozin 15 mg: 95% CI, 3.46 to 13.24; p<0.001 for both). Patients treated with ertugliflozin 5 mg and 15 mg also had greater reductions in body weight compared to placebo with a difference of -1.76 kg (95% CI, -2.57 to -0.95; p<0.001) in patients taking ertugliflozin 5 mg and -2.16 kg (95% CI, -2.98 to -1.64; p<0.001) in patients taking ertugliflozin 15 mg.

ertugliflozin (Steglatro) versus placebo as add-on to metformin

VERTIS MET:[153,154] A 26-week, double-blind, placebo-controlled study was conducted in 621 patients with T2DM inadequately controlled (HbA1C, 7% to 10.5%) on metformin monotherapy (≥ 1,500 mg/day for ≥ 8 weeks). Following a 2-week, single-blind, placebo run-in period, participants were randomized to ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily as add on to metformin. Change from baseline HbA1C at week 26 was significantly higher in the ertugliflozin 5 mg and 15 mg groups compared to the placebo group (mean difference from placebo, -0.5% [95% CI, -0.7 to -0.4; p<0.001] and -0.7% [95% CI, -0.9 to -0.5; p<0.001], respectively). The percent of patients achieving a HbA1C < 7% was 74% in patients taking ertugliflozin 5 mg, 87% in patients taking ertugliflozin 15 mg,

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and 38% in patients taking placebo. Ertugliflozin 5 mg and 15 mg once daily also improved FPG compared to placebo (-30.3 mg/dL and -40.9 mg/dL versus -8.7 mg/dL, respectively). Patients treated with ertugliflozin 5 mg and 15 mg also had greater reductions in body weight compared to placebo (-3.2 kg and -3 kg versus -1.4 kg, respectively).

ertugliflozin (Steglatro) versus glimepiride as add-on to metformin

VERTIS SU:[155] A 52-week, double-blind, placebo-controlled study was performed in 1,326 patients with T2DM who were not adequately controlled (HbA1C, 7% to 9%) on metformin (≥ 1,500 mg/day for ≥ 8 weeks). Following a 2-week, single-blind, placebo run-in period participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or glimepiride 1 mg/day titrated up to the maximum approved dose (6 or 8 mg/day depending on country) once daily with concurrent metformin background therapy. Glimepiride 3 mg was the mean daily dose. The primary efficacy endpoint was change in baseline in HbA1c at week 52, with a noninferiority margin of 0.3%. Ertugliflozin 15 mg was found to be noninferior to glimepiride with a least mean difference of 0.1% (95% CI, 0 to 0.2). However, ertugliflozin 5 mg did not demonstrate noninferiority to glimepiride with a mean difference of 0.2% (95% CI, 0.1 to 0.3). Patients treated with ertugliflozin 5 mg and 15 mg once daily had greater reductions in body weight compared to glimepiride (-2.6 kg and -3 kg versus 0.6 kg, respectively).

ertugliflozin (Steglatro) versus sitagliptin as add-on to metformin

VERTIS FACTORIAL:[156] A 26-week, double-blind, active-controlled study was performed in 1,233 patients with T2DM who were not adequately controlled (HbA1C, 7.5% to 11%) on metformin monotherapy (≥ 1,500 mg/day). Participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, sitagliptin 100 mg, or coadministration of ertugliflozin/sitagliptin 5/100 mg or ertugliflozin/sitagliptin 15/100 mg once daily. The primary endpoint, change from baseline HbA1c at week 26, was significantly higher in the combination products. A -1.5% mean reduction of HbA1c was observed in patients taking ertugliflozin/sitagliptin 5/100 mg and 15/100 mg daily as compared to the individual agents ertugliflozin 5 mg (-1%), ertugliflozin 15 mg (-1.1%), and sitagliptin 100 mg (-1.1%) (p<0.001 for all comparisons). The percent of patients achieving a HbA1c < 7% was 26.4% in the ertugliflozin 5 mg group, 31.9% in the ertugliflozin 15 mg group, 32.8% in the sitagliptin 100 mg group, 52.3% in the ertugliflozin/sitagliptin 5/100 mg group, and 49.2% in ertugliflozin/sitagliptin 15/100 mg group.

ertugliflozin (Steglatro) plus sitagliptin versus placebo plus sitagliptin

VERTIS SITA:[157] A 26-week, double-blind, placebo-controlled study was performed in 291 patients hyperglycemic treatment-naïve patients with T2DM who were not adequately controlled by diet and exercise (HbA1C, 8% to 10.5%). Patients entered a 2-week, single-blind, placebo run-in period. After the placebo run-in period, patients were then randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo in combination with sitagliptin 100 mg once daily. The primary endpoint, change from baseline HbA1c at week 26, was significantly higher in the active combination treatment groups compared to the placebo group. The mean reduction of HbA1c relative to the placebo group was -1.2% (95% CI, -1.5 to -0.8; p<0.001) in the ertugliflozin 5 mg plus sitagliptin 100 mg group and -1.2% (95% CI, -1.6 to -0.9; p<0.001) in the ertugliflozin 15 mg plus sitagliptin 100 mg group. Patients in the ertugliflozin 5 mg plus sitagliptin 100 mg group were 6.9 times as likely to achieve a HbA1c < 7% than patients in the placebo group (95% CI, 2.8 to 16.8; p<0.001) and patients in the ertugliflozin 15 mg plus sitagliptin 100 mg group were 7.4 times as likely to achieve a HbA1c < 7% than patients in the placebo

group (95% CI, 3 to 18.3; p<0.001). Patients treated with ertugliflozin 5 mg and 15 mg in combination with sitagliptin 100 mg once daily also had greater reductions in body weight compared to placebo with a difference in means of -2 kg (95% CI, -2.99 to -1.01; p<0.001) in patients taking ertugliflozin 5 mg + sitagliptin 100 mg and -2.1 kg (95% CI, -3.1 to -1.11; p<0.001) in patients taking ertugliflozin 15 mg plus sitagliptin 100 mg.

ertugliflozin (Steglatro) as add-on to metformin and sitagliptin

VERTIS SITA2:[158] A 26-week, double-blind, placebo-controlled study was performed in 464 patients with T2DM who were not adequately controlled (HbA1c, 7% to 10.5%) on metformin (≥ 1,500 mg/day for ≥ 8 weeks) and sitagliptin 100 mg once daily. Following a 2-week, single-blind, placebo run-in period participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo once daily. The primary endpoint, change from baseline HbA1c at week 26, was significantly higher in the ertugliflozin groups compared to the placebo group. The mean reduction of HbA1c relative to the placebo group was -0.7% (95% CI, -0.9 to -0.5; p<0.001) in the ertugliflozin 5 mg group and -0.8% (95% CI, -0.9 to -0.6; p<0.001) in the ertugliflozin 15 mg group. The percent of patients achieving a HbA1c < 7% was 32.1% in patients taking ertugliflozin 5 mg, 39.9% in patients taking ertugliflozin 15 mg, and 17% in patients taking placebo. Patients treated with ertugliflozin 5 mg and 15 mg once daily also had greater reductions in body weight compared to placebo (-3.4 kg, -3 kg, and -1.3 kg, respectively).

META-ANALYSES

The efficacy and safety of canagliflozin, dapagliflozin, and empagliflozin use in adults with T2DM was compared in a meta-analysis of 38 randomized controlled trials of 24 weeks or longer (n=23,997).[159] Compared to placebo, all 3 agents reduced HbA1c, FPG, and body weight. Canagliflozin 300 mg reduced HbA1c and FPG to a greater extent compared to any dose of the other agents. When each was compared to placebo at their highest doses, canagliflozin 300 mg reduced HbA1c by 0.9% and empagliflozin 25 mg and dapagliflozin 10 mg each reduced HbA1c by 0.7%; FPG was reduced by 1.9 mmol/L, 1.5 mmol/L, and 1.4 mmol/L with canagliflozin, empagliflozin, and dapagliflozin, respectively. Canagliflozin 300 mg and 100 mg increased the risk of hypoglycemia compared to dapagliflozin 10 mg and empagliflozin 10 mg (odds ratios [ORs], 1.4 to 1.6). All inhibitors similarly increased the risk of genital infection (balanitis, prostatitis, or vulvovaginitis). Dapagliflozin 10 mg increased the risk of urinary tract infection compared to empagliflozin 25 mg (OR, 1.4). Similar reductions in body weight were reported for the highest doses of all 3 agents. In addition, canagliflozin 300 mg reduced systolic BP and increased LDL-cholesterol to a greater extent compared to dapagliflozin and empagliflozin at any dose.

A meta-analysis of randomized controlled trials conducted from January 2005 to January 2015 indirectly compared the efficacy of SGLT2 inhibitors in patients with inadequately controlled T2DM with diet and exercise alone or metformin monotherapy.[160] All studies were at least 24 weeks in duration. A greater percentage of patients on monotherapy achieved an HbA1c < 7% on canagliflozin 300 mg than on canagliflozin 100 mg (RR, 0.72%; 95% CI, 0.59 to 0.87) and dapagliflozin 10 mg (RR, 0.63; 95% CI, 0.48 to 0.85); however, there were no significant differences compared with either dose of empagliflozin. A greater reduction in HbA1c was reported with canagliflozin 300 mg compared to the other SGLT-2 inhibitors (mean difference ranged from 0.2% to 0.64%). There were no significant differences in weight reduction. Decreases in systolic blood pressure ranged from 6 mmHg with canagliflozin 300 to 2.6 mmHg with empagliflozin 10 mg. Similar proportions of patients on dual

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therapy with metformin achieved HbA1c < 7% for all SGLT2 inhibitors. Canagliflozin 300 mg reduced HbA1c more than the other drugs, but statistical significance was only reported versus canagliflozin 100 mg.

Earlier meta-analyses have confirmed efficacy of SGLT2 inhibitors as a class compared to placebo as either monotherapy or add-on therapy, but meta-analyses of high-quality evidence estimating comparative efficacy between these agents are limited.[161,162,163]

A meta-analysis evaluated the effects of SGLT2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with T2DM.[164] Prospective randomized trials of greater than 7 days duration in databases prior to September 30, 2015 comparing an SGLT2 inhibitor with placebo or another active control were included (6 regulatory submissions, n=37,525; 57 studies, n=33,385). Trials evaluating 3 other SGLT2 inhibitors not available in the US were included in addition to the trials with canagliflozin, dapagliflozin, empagliflozin. However, results related to canagliflozin, dapagliflozin, empagliflozin were also presented when available and many of the cardiovascular and mortality outcomes assessed were primarily sourced from trials of canagliflozin, dapagliflozin, empagliflozin. SGLT2 inhibitors were associated with a decrease in major adverse cardiovascular events (RR, 0.84; 95% CI, 0.75 to 0.95; p=0.006), cardiovascular death (RR, 0.63; 95% CI, 0.51 to 0.77; p<0.0001), heart failure (RR, 0.65; 95% CI, 0.5 to 0.85; p=0.002), and death from any cause (RR, 0.71; 95% CI, 0.61 to 0.83; p<0.001). No statistically significant differences were found in non-fatal MI or angina (p=0.18 and p=0.7, respectively), although a trend toward an increase in non-fatal stroke (RR, 1.3; 95% CI, 1 to 1.68; p=0.049) was found as well as an increased risk of genital infections (RR, 2.88; 95% CI, 2.48 to 3.34; p<0.05). The authors noted that much of the data demonstrating cardiovascular improvement was related to a large outcomes study with empagliflozin driving the meta-analysis results, but they also stated that findings with the other agents also supported their results. The cause of the potential protection associated with these agents is unknown as they have been associated with blood pressure and weight lowering effects in addition to their antihyperglycemic effects, all of which may contribute to a potential mortality benefit. While this meta-analysis is promising, future outcomes trials and meta-analyses are needed to confirm these findings as confidence with each individual agent is limited due to overall limited information on these outcomes.

A total of 71 trials were found with a MEDLINE search of the following SGLT-2 inhibitors: dapagliflozin, empagliflozin, canagliflozin, ipragliflozin, ertugliflozin, and luseogliflozin (ipragliflozin and luseogliflozin are not approved in the US).[165,166] Randomized trials in patients with T2DM and a treatment duration ≥ 12 weeks were collected up to November 16, 2015. Comparison to placebo or other comparators were included. The principal outcome was the effect of SGLT2 inhibitor on all-cause and cardiovascular mortality. Secondary endpoints were MI and stroke. A total of 31,199 patients were treated with SGLT2 inhibitors and 16,088 with comparator. Mantel-Haenszel odds ratio with 95% confidence interval (MH-OR) was calculated. Treatment with SGLT2 inhibitors was associated with a significant reduction in all-cause mortality (MH-OR, 0.7; 95% CI, 0.59 to 0.83; p<0.001), cardiovascular mortality (MH-OR, 0.43; 95% CI, 0.36 to 0.53; p<0.001), and MI (MH-OR, 0.77; 95% CI, 0.63 to 0.94; p<0.01) but not stroke (MH-OR, 1.09; 95% CI, 0.86 to 1.38; p=0.5). There was no apparent difference across SGLT2 inhibitors after excluding cardiovascular outcome trials. Researchers concluded that the cardiovascular benefits observed with empagliflozin in the EMPAREG OUTCOME study is a class effect.

Thirty-eight trials (n=23,997) of at least 24 weeks in duration were included in a network meta-analysis that assessed the cardiometabolic and safety outcomes of canagliflozin, dapagliflozin, or

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empagliflozin.[167] When compared to placebo, all SGLT2 inhibitors reduced HbA1c at all dosages. Among the SGLT2 inhibitors, greater HbA1c reductions were seen with canagliflozin 300 mg compared with all other agents (differences ranging from −0.3% versus dapagliflozin 5 mg to −0.1% versus canagliflozin 100 mg). No significant differences between dapagliflozin and empagliflozin at different doses were found. In addition, compared to placebo, all SGLT2 inhibitors reduced body weight (1.6 kg to 2.5 kg), systolic (2.8 to 4.9 mmHg) and diastolic (1.5 to 2 mmHg) blood pressure. A modest increase in high density lipoprotein cholesterol (HDL-C) (up to 0.07 mmol/L) was seen with all SGLT2 inhibitors, but due to limited data their effects on total cholesterol could not be ascertained. Lastly, the risk of urinary tract and genital infection was similar between the agents.

A meta-analysis of the cardiovascular events from 21 phase 2b/3 trials for dapagliflozin assessed the cardiovascular risk of dapagliflozin compared to placebo or comparator treatment.[168] A total of 9,339 patients were included. All phase 3 studies were up to 208 weeks in duration (16 studies). Dapagliflozin doses included were 2.5 mg to 10 mg. The analysis demonstrated that there was no increased risk of cardiovascular event with dapagliflozin when used as monotherapy or added to background antidiabetic treatment in patients with T2DM and may result in a potential benefit, including in patients with a history of cardiovascular disease (overall: HR, 0.77 [95% CI, 0.54 to 1.1]; with CVD: HR 0.8 [95% CI, 0.53 to 1.22]).

A systematic review and meta-analysis based on data from a MEDLINE, Embase, the Cochrane Library, and websites of US, European, and Japanese regulatory included nearly 71,000 patients in 6 regulatory submissions and 57 published prospective randomized trials assessed the effect of SGLT2 inhibitors on risk of major adverse cardiovascular events as compared with controls.[169] SGLT2 inhibitors included canagliflozin, dapagliflozin, empagliflozin, and ipragliflozin (ipragliflozin is not available in the US). A protective effect was demonstrated on major cardiovascular event (RR, 0.84; 95% CI, 0.75 to 0.95; p=0.006), cardiovascular death (RR, 0.63; 95% CI, 0.51 to 0.77; p<0.0001), heart failure (RR 0.65 [95% CI, 0.5 to 0.85]; p=0.002), and death from any cause (RR 0.71; 95% CI, 0.61 to 0.83; p<0.0001). An adverse effect on non-fatal stroke was found (RR, 1.3; 95% CI, 1 to 1.68; p=0.049). There was no significant effect seen on risk of non-fatal MI or angina. Similar effects on cardiovascular outcomes or death was seen among the difference SGLT2 inhibitor agents and incidence of genital infections. This analysis was funded by the National Health and Medical Research Council of Australia.

In the CVD-REAL study data were collected from medical claims, primary care/hospital records and national registries from the US, Norway, Denmark, Sweden, Germany, and the United Kingdom (UK) in an effort to find the benefit seen in real-world use of SLGT2 inhibitors for T2DM treatment.170 Investigators compared hospitalization for heart failure (HHF) and death in patients (n=309,056) newly prescribed any SGLT2 inhibitor compared to other antidiabetic agents. Baseline characteristics were balanced between the 2 groups. Canagliflozin, dapagliflozin, and empagliflozin represented 53%, 42% and 5% of the total exposure time in the SGLT2 inhibitor class, respectively. SGLT2 inhibitor therapy, compared to other antidiabetic agents, was associated with lower rates of HHF (HR, 0.61; 95% CI, 0.51 to 0.73; p<0.001), death (HR, 0.49; 95% CI, 0.41 to 0.57; p<0.001); and HHF or death (HR, 0.54; 95% CI, 0.48 to 0.6; p<0.001) with no significant difference seen by country.

A total of 301 trials were included in a meta-analysis to assess the relative efficacy and safety associated with glucose-lowering drugs including SGLT2 inhibitors in treating T2DM.[171] Trials included triple therapy (add-on to metformin and sulfonylurea), dual therapy (add-on to metformin). No significant differences were seen between any drug class as monotherapy, or for dual- or triple-

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therapy. Sulfonylurea (odds ratio [OR], 3.13 [95% CI, 2.39 to 4.12]) and basal insulin (OR, 17.9 [95% CI, 1.97 to 162]) were associated with greatest odds of hypoglycemia. Dual therapy that included an SGLT2 inhibitor was associated with the lowest risk of hypoglycemia (OR, 0.12 [95% CI, 0.08 to 0.18]), while triple therapy that included a GLP1 agonist was associated with the lowest risk (OR, 0.6 [95% CI, 0.39 to 0.94]).

SUMMARY

The 2019 American Diabetes Association (ADA) Standards of Medical Care in Diabetes the selection of medications should be patient-centric and prescribers should consider potential issues such as HbA1c target, impact on weight and hypoglycemia, side effects, the frequency and mode of administration, patient adherence, patient preference, and cost. If no contraindication exists, and if well tolerated, metformin is the preferred initial treatment for T2DM. In patients *without* atherosclerotic cardiovascular disease (ASCVD), if monotherapy with metformin at the maximum tolerated dose does not achieve or maintain the desired HbA1c level over 3 months, either a thiazolidinedione (TZD), sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, SGLT2 inhibitor, glucagon-like peptide-1 (GLP-1) receptor agonist, or basal insulin should be added. In patients with ASCVD, the addition of empagliflozin, liraglutide, canagliflozin, or dapagliflozin is preferred (Class A recommendations). In patients with heart failure (HF) or chronic kidney disease (CKD), empagliflozin, canagliflozin, and dapagliflozin are preferred. If target HbA1c is still not achieved after an additional 3 months, then an agent from a different group listed should be added.

The 2019 American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) algorithm also recommends metformin as first-line therapy. These guidelines recommend SGLT2 inhibitors as one of the alternatives to metformin for monotherapy and an appropriate add-on to metformin in dual and triple therapy for glycemic control. The SGLT2 drugs may be used as add-on therapy to 2 or 3 other agents, including insulin, in patients who would benefit from weight loss as well. AACE/ACE also recognizes proven cardiovascular benefit of empagliflozin and canagliflozin.

The SGLT2 inhibitors are efficacious agents in reducing HbA1c, postprandial glucose, and fasting plasma glucose, as well as reducing systolic blood pressure and weight. Since these agents exert their glycemic effects in the kidney, they have limited benefit in patients with chronic kidney disease (CKD). However, in April 2016, based on several safety studies, the FDA concluded that metformin may be safely used in patients with mild renal impairment and some patients with moderate renal impairment. Patients receiving SLGT2 inhibitor therapy are at increased risk of urinary and genital tract infections due to its glycosuria effect. The FDA recently alerted prescribers of an increased risk of bone fracture in patients treated with canagliflozin (Invokana, Invokamet, Invokamet XR). Prescribers should consider all factors that can increase the risk of bone fracture before prescribing canagliflozin. The agency is evaluating the potential for this risk as it relates to dapagliflozin (Farxiga, Xigduo XR) and empagliflozin (Jardiance, Synjardy, Synjardy XR). Similarly, an increased risk of leg and foot amputations with canagliflozin compared to placebo was found recently; a boxed warning regarding this finding was added to the drug label of canagliflozin-containing products. The long-term safety of SGLT2 inhibitors remains to be established.

Clinical studies have been published that evaluated the cardiovascular outcomes associated with SGLT2 inhibitor therapy. The EMPA-REG-OUTCOMES trial reported approximately a one-third relative risk reduction for cardiovascular death, hospitalization due to heart failure, and all-cause death with use of empagliflozin (Jardiance) as compared to placebo. CANVAS and CANVAS-R trials reported significantly

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fewer primary outcome events with canagliflozin than with placebo overall; although, no difference in any individual component (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) reached significance. Also, fewer patients treated with canagliflozin experienced albuminuria as compared to those treated with placebo. In addition, the CREDENCE trial reported a 30% reduction in the composite of end-stage kidney disease (ESRD), doubling of serum creatinine (SCr) level, or death from renal or cardiovascular causes with canagliflozin compared to placebo in patients with renal impairment and T2DM. Conversely, the DECLARE–TIMI 58 trial revealed that dapagliflozin did not result in a lower rate of major adverse cardiovascular events (MACE) compared to placebo; however, its use lead to a lower incidence of HF-related hospitalizations.

Available SGLT2 inhibitors include canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro). All 4 products also are available in combination with metformin: canagliflozin/metformin (Invokamet, Invokamet XR), dapagliflozin/metformin ER (Xigduo XR), empagliflozin/metformin (Synjardy), empagliflozin/metformin ER (Synjardy XR), and ertugliflozin/metformin (Segluromet). Warnings and adverse effects of single-component metformin agents also apply to these combination products.

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