Therapeutic Class Overview
Sodium-Glucose Cotransporter-2 Inhibitors

INTRODUCTION

- In the United States (US), diabetes mellitus affects more than 30 million people and is the 7th leading cause of death (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations *(American Diabetes Association [ADA] 2019[a])*. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications *(ADA 2019[b])*.
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy *(ADA 2019[a])*.
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy *(Garber et al 2019)*.
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing the rate of hepatic glucose production, decreasing the rate of glucagon secretion, and blocking glucose reabsorption by the kidney *(Garber et al 2019)*.
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The SGLT2 inhibitor class consists of 4 unique molecular entities, canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, and their combination products with metformin or a DPP-4 inhibitor.
  - SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Inhibition of SGLT2 reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.
- Medispan class: Antidiabetics, Sodium-glucose cotransporter 2 inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Dapagliflozin products	
Farxiga (dapagliflozin)	-
Xigduo XR (dapagliflozin/metformin hydrochloride extended-release [ER])	-
Qtern (dapagliflozin/saxagliptin)	-
Canagliflozin products	
Invokana (canagliflozin)	-
Invokamet (canagliflozin/metformin hydrochloride)	-
Invokamet XR (canagliflozin/metformin ER)	-
Empagliflozin products	
Jardiance (empagliflozin)	-
Glyxambi (empagliflozin/linagliptin)	-
Synjardy (empagliflozin/metformin)	-
Synjardy XR (empagliflozin/metformin ER)	-
Ertugliflozin products	
Steglatro (ertugliflozin)	-
Segluromet (ertugliflozin/metformin)	-

Drug	Generic Availability
Steglujan (ertugliflozin/sitagliptin)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	Single-Entity				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR* (canagliflozin/ metformin)	Synjardy, Synjardy XR* (empagliflozin/ metformin)	Xigduo XR* (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✓	✓	✓	✓							
To reduce the risk of CV death in adult patients with T2DM and established CVD			✓								
To reduce the risk of MACE (CV death, nonfatal myocardial infarction and nonfatal stroke) in adults with T2DM and established CVD		✓									
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both components is appropriate.					✓†		✓†	✓†	✓		✓
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin						✓					
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with ertugliflozin and/or metformin										✓	

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; MACE = major adverse cardiovascular events; T2DM = type 2 diabetes mellitus

* These combination products contain metformin ER.

† Labeling for combination products containing empagliflozin and canagliflozin state that the single-entity products are additionally indicated to reduce CV risk; however, the effectiveness of the combination products for CV risk reduction has not been established.

Limitations of use: Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are not recommended in patients with type 1 diabetes mellitus (T1DM) or for the treatment of diabetic ketoacidosis (DKA). Glyxambi and Steglujan have not been studied in patients with a history of pancreatitis. Qtern should only be used in patients who tolerate 10 mg dapagliflozin.

(*Prescribing information: Farxiga 2019, Glyxambi 2018, Invokana 2018, Invokamet/Invokamet XR 2018, Jardiance 2018, Qtern 2018, Segluromet 2018, Steglatro 2018, Steglujan 2018, Synjardy 2018, Synjardy XR 2018, Xigduo XR 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of the SGLT2 inhibitors were evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. SGLT2 inhibitors have demonstrated efficacy in lowering glycosylated hemoglobin (HbA1c) levels by ~0.5% to 1.5% *(Davies et al 2018)*. They have been studied as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, fasting plasma glucose (FPG), weight gain, post-prandial glucose (PPG), and blood pressure when used as monotherapy or in combination therapy:
  - As monotherapy *(Bailey et al 2012, Ferrannini et al 2010, Ferrannini et al 2013, Inagaki et al 2014, Stenlöf et al 2013, Terra et al 2017)*
  - With metformin *(Bailey et al 2010, Haring et al 2014, Henry et al 2012, Leiter et al 2015, Rosenstock et al 2013, Rosenstock et al 2016, Rosenstock et al 2018, Ross et al 2015)*
  - With an SFU *(Fulcher et al 2015, Strojek et al 2011, Strojek et al 2014, Wilding et al 2013)*
  - With metformin and an SFU *(Dagogo-Jack et al 2018, Haring et al 2013, Matthaei et al 2015)*
  - As add-on therapy to TZDs *(Forst et al 2014, Kovacs et al 2014, Rosenstock et al 2012)*
  - As add-on therapy or compared to DPP-4 inhibitors *(Jabbour et al 2014, Lavalle-Gonzalez et al 2013, Roden et al 2013, Rosenstock et al 2015[a], Schernthaner et al 2013)*
  - As add-on therapy to insulin *(Neal et al 2015, Rosenstock et al 2014, Rosenstock et al 2015[b], Wilding et al 2012)*
- The combination of SGLT2 inhibitors with metformin lowers HbA1c compared to placebo. These studies use the coadministration of the two components instead of fixed-dose combination tablets for Invokamet, Segluromet, Synjardy, and Xigduo XR. The bioequivalency of Invokamet XR and Synjardy XR to the immediate release combination products in healthy subjects was used to support the Food and Drug Administration (FDA) approval of these extended-release combination products.
- Glyxambi (empagliflozin/linagliptin) was the first FDA-approved SGLT2-inhibitor/DPP-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized controlled trial (RCT) in patients with T2DM demonstrated reductions in HbA1c with Glyxambi that were superior to those of empagliflozin or linagliptin alone as add-on to metformin *(DeFronzo et al 2015)*. Qtern (dapagliflozin/saxagliptin) was approved in February 2017; efficacy and safety were observed as add-on therapy with saxagliptin in patients on dapagliflozin plus metformin at 24 weeks *(Matthaei et al 2015)* and at 52 weeks *(Matthaei et al 2016)*; with dapagliflozin added to saxagliptin plus metformin at 24 weeks *(Mathieu et al 2015)* and 52 weeks *(Mathieu et al 2016)*; and with saxagliptin plus dapagliflozin addition vs the single addition of saxagliptin or dapagliflozin to metformin at 24 weeks *(Rosenstock et al 2015[a])*. Additionally, the add-on combination of dapagliflozin and saxagliptin resulted in improved glycemic control compared to glimepiride in patients on metformin monotherapy (*Muller-Wieland et al 2018)*. Steglujan (ertugliflozin/sitagliptin) was approved in December 2017; efficacy and safety of co-initiation of ertugliflozin and sitagliptin were observed at 26 weeks in patients inadequately controlled on diet and exercise (*Miller et al 2018*). In patients inadequately controlled with metformin, ertugliflozin plus sitagliptin was more effective in glycemic control at weeks 26 and 52 as compared to individual components alone (*Pratley et al 2018*).
- The SGLT2 inhibitors have also shown noninferiority in decreasing HbA1c in direct comparisons when compared to SFUs:
  - Dapagliflozin vs glipizide, both in combination with metformin *(Nauck et al 2011)*
  - Canagliflozin vs glimepiride *(Cefalu et al 2013)*
  - Empagliflozin vs glimepiride *(Ridderstrale et al 2014, Ridderstrale et al 2018)*
  - Ertugliflozin vs glimepiride (*Hollander et al 2018*)

- Additional studies have demonstrated the safety and efficacy of SGLT2 inhibitors in special populations:
  - Patients with T2DM and chronic kidney disease *(Barnett et al 2014, Fioretto et al 2018, Grunberger et al 2018, Kohan et al 2014, Yale et al 2014, Yale et al 2013)*
  - Patients with T2DM and CV disease (CVD) *(Leiter et al 2014)*
  - Patients with T2DM and nonalcoholic fatty liver disease *(Kuchay et al 2018)*
  - Elderly patients *(Bode et al 1995, Bode et al 2015, Sinclair et al 2014, Sinclair et al 2016)*
    - A pooled analysis of six phase 3, double-blind, placebo-controlled, RCTs compared the efficacy and safety of canagliflozin in patients < 75 years and ≥ 75 years of age. Canagliflozin 100 mg and 300 mg were associated with placebo-subtracted mean reductions in HbA1c in patients < 75 years (-0.69% and -0.85%, respectively) and ≥ 75 years (-0.65% and -0.55%, respectively). Dose-related reductions in FPG, body weight, and blood pressure were also seen with canagliflozin 100 mg and 300 mg in patients in both age groups. Overall adverse event incidences were 67.1% with canagliflozin 100 mg, 68.6% with canagliflozin 300 mg, and 65.9% with non-canagliflozin (pooled group of comparators in all studies) in patients < 75 years, and 72.4%, 79.1%, and 72.3%, respectively, in patients ≥ 75 years, with a similar safety profile in both groups *(Sinclair et al 2016).*
- Various long-term studies have been conducted that provide data on the safety and efficacy after at least one year of treatment with the SGLT2 inhibitors *(Araki et al 2015, Aronson et al 2018, Bailey et al 2015, Bode et al 2015, Del Prato et al 2015, Kovacs et al 2015, Nauck et al 2014, Yale et al 2017)*.
- Other post-hoc analyses of pooled data from RCTs have further evaluated the effects of SGLT2 inhibitors on parameters such as blood pressure, weight gain, and adverse events *(Davies et al 2015, Ptaszynska et al 2014, Weir et al 2014)*.
- Furthermore, various meta-analyses have been conducted that have demonstrated the individual efficacy of the SGLT2 inhibitors *(Liakos et al 2014, Orme et al 2014, Sun et al 2014, Yang et al 2014, Zhang et al 2018)*.

Comparative efficacy

- While there are no head-to-head studies comparing the efficacy and safety of the SGLT2 inhibitors, a 2016 systematic review and network meta-analysis found that canagliflozin 300 mg reduced HbA1c, FPG, and systolic blood pressure, while increasing low-density lipoprotein cholesterol (LDL-C) to a greater extent compared with other inhibitors (dapagliflozin and empagliflozin) at any dose *(Zaccardi et al 2016)*.
- Another systematic review and network meta-analysis found similar results *(Shyangdan et al 2016)*. When used as monotherapy, a greater proportion of patients achieved a HbA1c <7% on canagliflozin 300 mg than on canagliflozin 100 mg and dapagliflozin 10 mg, but there were no significant differences compared with either dose of empagliflozin. Canagliflozin 300 mg reduced HbA1c more than other SGLT2 inhibitors, with the mean difference ranging from 0.20% to 0.64%. There were no significant differences between the SGLT2 inhibitors with respect to weight reduction.
- Another systematic review and network meta-analysis found that ertugliflozin 15 mg reduced HbA1c more than dapagliflozin 10 mg and empagliflozin 25 mg, both as monotherapy and in combination with metformin (*McNeill et al 2019*).
- The Agency for Healthcare Research and Quality (AHRQ) updated its review of the diabetes medications for adults with T2DM to include the results from an additional eight studies *(Bolen et al 2016)*. Findings related to the SGLT2 inhibitors included some of the following:
  - Body weight was maintained or reduced by metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.
  - Systolic blood pressure was reduced by 3 to 5 mm Hg by SGLT2 inhibitors and GLP-1 agonists compared to metformin.
  - Some adverse events were higher with specific classes of drugs including gastrointestinal (GI) events (metformin and GLP-1 agonists) and risk of genital mycotic infection (SGLT2 inhibitors).

Cardiovascular (CV) outcome studies

- EMPA-REG OUTCOME was the first study to demonstrate a positive benefit on CV outcomes due to glucose lowering with empagliflozin as add-on to standard of care in T2DM patients with high CV risk *(Zinman et al 2015)*. Empagliflozin significantly reduced the risk of the composite MACE endpoint (CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) by 14% vs placebo ($p < 0.001$ for noninferiority; $p = 0.04$ for superiority). In addition, there was a 38% reduction in CV death, 35% reduction in hospitalization for heart failure (HHF), and 32% reduction in death from any cause associated with its use; however, there were no significant between-group differences in the rates of MI or stroke. The underlying mechanism of empagliflozin and its effect on CV outcomes are not clearly understood. Recently updated guidelines acknowledge the established CV benefit with empagliflozin *(ADA 2019, Das et al 2018, Davies et al 2018, Garber et al 2019)*.

- A recently published follow-up to the EMPA-REG OUTCOME study examined the pre-specified secondary objective of the effect of empagliflozin on microvascular outcomes, and in particular, progression of kidney disease in patients with T2DM at high risk for CV events. In this new analysis, incident or worsening nephropathy occurred in 525 of 4124 patients taking empagliflozin and 388 of 2061 in the placebo group (12.7% vs 18.8%; hazard ratio [HR]: 0.61; 95% confidence interval [CI], 0.53 to 0.70; p < 0.001). This renal end point consisted of a combination of progression to macroalbuminuria, a doubling of serum creatinine, the start of renal-replacement therapy, or renal death. A relative risk reduction of 38% was seen with the endpoint of progression to macroalbuminuria, which occurred in 459 of 4091 patients taking empagliflozin compared with 330 of 2033 patients on placebo (11.2% vs 16.2%; HR, 0.62; 95% CI, 0.54 to 0.72; p < 0.001) *(Wanner et al 2016)*.

- The CANVAS Program was comprised of 2 trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), that included a total of 10,142 patients with T2DM and high CV risk *(Neal et al 2017)*. The studies were designed to assess the CV safety and efficacy of canagliflozin, as well as to evaluate the balance between potential benefits of the drug and its associated risks (eg, genitourinary infection, DKA, fracture). Significantly fewer participants in the canagliflozin group had a primary outcome event (composite of CV death, nonfatal MI, or nonfatal stroke) vs placebo: 26.9 vs 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; p < 0.001 for noninferiority; p = 0.02 for superiority). Recently updated guidelines acknowledge the established CV benefit with canagliflozin, but also note the increased risk of amputation (*ADA 2019, Das et al 2018, Davies et al 2018, Garber et al 2019*).
- The DECLARE-TIMI 58 study (N = 17,160) evaluated CV outcomes with dapagliflozin in patients with established CVD or multiple risk factors. After a median follow up of 4.2 years, dapagliflozin demonstrated noninferiority to placebo for the primary outcome of MACE (upper boundary of the 95% CI < 1.3; p < 0.001 for noninferiority); however, dapagliflozin was not statistically significantly superior to placebo with respect to MACE (8.8% vs 9.4%; HR, 0.93; 95% CI, 0.84 to 1.03; p = 0.17) (*Wiviott et al 2019*).
  - Dapagliflozin significantly reduced a composite outcome of CV death and HHF (4.9% vs 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; p = 0.0005). The significant result was driven by reductions in HHF (HR, 0.73; 95% CI, 0.61 to 0.88), as there was no difference between groups in the rate of CV death (HR, 0.98; 95% CI, 0.82 to 1.17).
  - Patients who received dapagliflozin were associated with a higher risk of DKA (p = 0.02) and serious genital infections vs placebo (p < 0.001).
- The VERTIS CV study (N = 8237) will evaluate CV outcomes with ertugliflozin in patients with established CVD. Estimated study completion is in the second half of 2019 (*ClinicalTrials.gov*).
- A meta-analysis of the 3 published CV outcome trials (N = 34,322) evaluated the CV and renal benefits of the SGLT2 inhibitor class. SGLT2 inhibitors were associated with an 11% reduction in MACE vs placebo (HR, 0.89; 95% CI, 0.83 to 0.96; p = 0.0014). MACE risk reduction was statistically significant in the subgroup of patients with established CVD (HR, 0.86; 95% CI, 0.80 to 0.93), but not in the subgroup of patients with only risk factors for CVD (HR, 1.00; 95% CI, 0.87 to 1.16; p for interaction = 0.0501). SGLT2 inhibitors significantly reduced the risk for a composite outcome of HHF or CV death (HR, 0.77; 95% CI, 0.71 to 0.84; p < 0.0001) and progression to renal disease (HR, 0.55; 95% CI, 0.48 to 0.64; p < 0.0001), with consistent results across the subgroups of patients with and without established CVD (*Zelniker et al 2019*).
- A meta-analysis evaluating the CV effects of SGLT2 inhibitors in patients with T2DM pooled 35 studies that reported at least 1 CV outcome (*Usman et al 2018*). As compared to placebo, the pooled analysis found that SGLT2 inhibitors were associated with a reduction in all-cause mortality (odds ratio [OR], 0.79; 95% CI, 0.70 to 0.89), (MACE (OR, 0.8; 95% CI 0.76 to 0.92), non-fatal MI (OR, 0.85; 95% CI, 0.73 to 0.98) and HHF (OR, 0.67; 95% CI, 0.59 to 0.76).
- A network meta-analysis evaluated the CV effects of empagliflozin compared to DPP-4 inhibitors in patients with T2DM with established CVD or at high risk for CV outcomes (*Balijepalli et al 2018)*. The analysis pooled 4 studies and found that empagliflozin was superior to saxagliptin (HR, 0.60; 95% credible interval [CrI], 0.46 to 0.80) and sitagliptin (HR, 0.60; 95% CrI, 0.46 to 0.79) in reducing the risk of CV mortality. Similar results were found for all-cause mortality (empagliflozin vs saxagliptin: HR, 0.61; 95% CrI, 0.49 to 0.76; and vs sitagliptin: HR, 0.67; 95% CrI, 0.54 to 0.83).
- The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors (CVD-REAL) study is the first large real-world study of > 300,000 patients with T2DM, both with and without established CVD that evaluated outcomes of HHF and all-cause death in patients with T2DM treated with SGLT2 inhibitors vs other glucose-lowering drugs. Data were collected from patients living in 6 countries (United States, Germany, Sweden, Norway, Denmark, and the United Kingdom) *(Kosiborod et al 2017)*. Overall, treatment with SGLT2 inhibitors vs other agents was associated with a 39% relative risk reduction in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite.

- An additional observational analysis from the CVD-REAL investigators evaluated the risk of CVD and CV mortality in patients initiating SGLT2 inhibitors compared to other glucose-lowering drugs in the CVD-REAL Nordic study (*Birkeland et al 2017*). Approximately 90,000 patients were identified from registries in Denmark, Norway, and Sweden. The baseline prevalence of CVD was 25%. Use of SGLT2 inhibitors was found to be associated with a reduced risk of CV events, HHF, and CV mortality compared to other glucose-lowering drugs, with relative risk reductions of 22%, 30%, and 47%, respectively.
  - The CVD-REAL Nordic study also evaluated MACE in approximately 40,000 patients with T2DM, both with and without CVD, who were new users of dapagliflozin or DPP-4 inhibitors (*Persson et al 2018)*. Dapagliflozin use was associated with a 21% relative reduction in MACE, 38% relative reduction in HHF, and a 41% relative reduction in all-cause mortality as compared to DDP-4 inhibitor use.
- The EASEL cohort study evaluated patients with T2DM and established CVD and compared those who were initiated on SGLT2 inhibitors versus other glucose-lowering drugs (*Udell et al 2018*). The propensity-matched population included 25,258 patients. Initiation of a SGLT2 inhibitor, as compared to a non-SGLT2 inhibitor, was associated with a relative risk reduction of 43% for the combined endpoint of all-cause mortality and HHF, and a 33% relative risk reduction for MACE. However, SGLT2 inhibitor use was also associated with a higher risk of below-knee amputation (HR, 1.99; 95% CI, 1.12 to 3.51), mainly driven by patients exposed to canagliflozin.

CLINICAL GUIDELINES

Overview

- Professional society guidelines are consistent in recommending metformin as the optimal first-line pharmacologic therapy for treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SGLT2 inhibitors are among the second-line options for subsequent therapy. All guidelines emphasize individualized therapy based upon patient-specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes *(ADA 2019, Copeland et al 2013, Davies et al 2018, Garber et al 2019)*. Metformin is considered the drug of choice for children with T2DM *(Copeland et al 2013)*.
- A 2018 American College of Cardiology expert consensus decision pathway on CV risk reduction in patients with T2DM and atherosclerotic CV disease (ASCVD) suggests adding an SGLT2 inhibitor or GLP-1 receptor agonist that has demonstrated beneficial CV outcomes to other guideline-directed therapy for diabetes (specifically, metformin). Among the SGLT2 inhibitors with CV outcome data at the time that the pathway was written (canagliflozin and empagliflozin), empagliflozin was the preferred SGLT2 inhibitor based on the available evidence and overall risk to benefit ratio *(Das et al 2018)*.

- **ADA/European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes, 2018** *(Davies et al 2018)*
  - The goals of T2DM therapy are to prevent or delay complications and maintain quality of life, which requires glycemic control, CV risk factor management, regular follow-up, and a patient-centered approach to enhance patient engagement in self-care activities. Careful consideration of patient-specific factors and preferences must inform the process of individualizing treatment goals and strategies.
  - Due to new evidence of benefit with specific agents in the reduction of mortality, heart failure (HF), and progression of renal disease, the overall approach to glucose-lowering medication in T2DM for the ADA/EASD consensus report was updated in 2018. A history of CVD, CKD, and HF should be taken into consideration early in the process of treatment selection. Additionally, the guideline recommends early consideration of weight, hypoglycemic risk, treatment cost, and other patient-related factors that may influence the choice of drug therapy.
    - Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven CV benefit are recommended as part of glycemic management.
    - For patients with ASCVD with concomitant HF, SGLT2 inhibitors are recommended.
    - For patients with T2DM and CKD (with or without ASCVD), an SGLT2 inhibitor shown to reduce CKD progression should be considered. If SGLT2 inhibitors are contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression should be considered.
  - Initial monotherapy: Metformin remains the preferred drug for initial monotherapy based on its efficacy, safety, tolerability, low cost, and extensive clinical experience.

- Add-on to metformin: The selection of a second agent added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific AEs, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost.
- Intensification beyond 2 medications: Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
- Addition of injectable medications: For patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.
- Beyond basal insulin: Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.

- **ADA: Standards of Medical Care in Diabetes – 2019** *(ADA 2019)*
  - SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in T2DM. None of the available 4 agents are FDA-approved for the treatment of patients with T1DM.

  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
    - Dual therapy should be considered in patients with newly diagnosed T2DM who have HbA1c ≥ 1.5% above their glycemic target (level E).
    - Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (> 10%) or blood glucose levels (> 300 mg/dL) are very high (level E).
    - A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
    - In patients with T2DM and established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen (level A).
    - In patients with T2DM and established ASCVD with a high risk of or existing HF, SGLT2 inhibitors are preferred (level C).
    - In patients with T2DM and CKD, use of SGLT2 inhibitors or GLP-1 receptor agonists shown to reduce the risk of CKD progression, CV events, or both should be considered (level C).
    - In most patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin (level B).
    - The medication regimen should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate new patient factors (level E).
  - Initial therapy
    - Metformin should be initiated at the time T2DM is diagnosed if there are no contraindications.
    - For patients with contraindications or intolerance to metformin, initial therapy with an SGLT2 inhibitor, GLP-1 receptor agonist, DPP-4 inhibitor, TZD, SFU (2nd generation), or insulin should be considered based on patient factors.
  - Combination therapy
    - Dual therapy is recommended for patients who do not achieve their HbA1c goal after 3 months of monotherapy.
    - For patients without ASCVD or CKD, an agent from any of the 6 preferred classes (SFU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin) can be added to metformin, with the choice of agent based on drug-specific effects (ie, avoidance of adverse effects such as hypoglycemia and weight gain) and patient factors (ie, cost and personal preference).
    - For patients with ASCVD, HF, or CKD, the best choice for add-on therapy is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated benefit.
    - Similar considerations are applied in patients who require a third agent to achieve glycemic goals.

Table 3. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD	Additional considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral	GI AEs common B12 deficiency
SGLT2i	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin	Oral	Benefit: canagliflozin, empagliflozin	Boxed warning for amputation: canagliflozin Genitourinary infections
GLP-1ra	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide > semaglutide > exenatide ER	Neutral	SQ	Benefit: liraglutide	Boxed warning for thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide ER)
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	Oral	Neutral	Potential risk of acute pancreatitis Joint pain
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral	Boxed warning for CHF (pioglitazone, rosiglitazone)
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral	FDA special warning on increased risk of CV mortality based on studies of an older SFU (tolbutamide)
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral	Injection site reactions

Abbreviations: AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CV = cardiovascular; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; ER = extended-release; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones

* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2019)*
  - Founding principles of the Comprehensive Type 2 Diabetes Management Algorithm:
    - Lifestyle optimization is essential for all patients with diabetes.
    - Minimizing the risk of both severe and non-severe hypoglycemia is a priority. Minimizing risk of weight gain is also a priority.
    - The HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. A target HbA1c ≤ 6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
    - Glycemic control targets include fasting and post-prandial glucose as determined by self-monitoring of blood glucose.
    - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial A1C, duration of T2D, and obesity status.
      - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status. Combination therapy is usually required and should involve agents with complementary mechanisms of action.

- Therapy must be evaluated frequently (eg, every 3 months) until the patient is stable, using multiple criteria (eg, HbA1c, self-monitoring of blood glucose records, lipid and blood pressure levels, hypoglycemia events, AEs).

○ Glycemic control algorithm for T2DM:

- In patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. For patients with ASCVD or CKD, GLP-1 receptor agonists and SGLT2 inhibitors with proven benefits may be preferred.
  - Other acceptable alternatives to metformin include DPP-4 inhibitors and TZDs; AGIs, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
- In patients who do not achieve their HbA1c goal after 3 months of monotherapy or patients who present with HbA1c ≥ 7.5%, dual therapy should be started by adding 1 of the following agents to metformin (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, colesevelam, bromocriptine quick release (QR), AGI, SFU, or meglitinide.
- If dual therapy does not achieve the HbA1c goal in 3 months, triple therapy should be started by adding 1 of the following agents to metformin plus a second-line agent (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, colesevelam, bromocriptine QR, AGI, SFU, or meglitinide.
- If triple therapy fails to achieve the HbA1c goal in 3 months, then the patient should proceed to or intensify insulin therapy.
- In patients with entry HbA1c > 9.0%, dual therapy or triple therapy is recommended if the patient is asymptomatic. If the patient is symptomatic, insulin therapy alone or in combination with other agents is recommended.

○ SGLT2 inhibitor-specific information:

- SGLT2 inhibitors have a glucosuric effect that results in decreased HbA1c, weight, and systolic blood pressure.
- Empagliflozin was associated with significantly lower rates of all-cause and CV death and lower risk of HHF in the EMPA-REG OUTCOME trial.
- Canagliflozin was associated with a reduction in risk for the combined CV outcome of CV death, MI, or nonfatal stroke, as well as a lower risk for HHF. Canagliflozin was also associated with an increased risk of amputation in the CANVAS trial.
- Dapagliflozin was associated with a reduction in the composite outcome of CV death and HHF in the DECLARE-TIMI 58 trial; however, dapagliflozin did not significantly decrease the risk for the composite outcome of CV death, nonfatal MI, and stroke.
- Safety concerns with treatment include increased risks of mycotic genital infections, slightly increased LDL-C levels, limited efficacy in patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2, and hypotension due to increased diuresis. Postmarketing reports of SGLT2 inhibitor-associated DKA are still being investigated. Reports were primarily in T1DM and T2DM patients with less than expected hyperglycemia (euglycemic DKA).

Table 4. AACE/ACE Profiles of Antidiabetic Medications

	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
Metformin	Neutral	Slight loss	eGFR < 30: contraindicated	Moderate	Neutral	Neutral	Neutral
GLP-1ra	Neutral	Loss	Possible benefit: liraglutide Exenatide not indicated CrCl < 30	Moderate	Liraglutide FDA approved for prevention of MACE	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45 Possible CKD benefit	Neutral	Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Alogliptin, saxagliptin: Possible increased HHF	Neutral	Neutral
AGI	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
TZD	Neutral	Gain	Neutral	Neutral	Moderate CHF risk May reduce stroke risk	Moderate fracture risk	Neutral

SFU	Moderate/severe	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	ASCVD benefit	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance; CV = cardiovascular; DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

SAFETY SUMMARY

- Contraindications:
  - History of serious hypersensitivity reaction to canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin.
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
  - Metformin-containing products have the following contraindications:
    - Severe renal impairment (Segluromet: eGFR < 30 mL/min/1.73 m^2; Invokamet, Invokamet XR, Synjardy, Synjardy XR: eGFR < 45 mL/min/1.73 m^2; Xigduo XR: eGFR < 60 mL/min/1.73 m^2), end-stage renal disease, or dialysis
    - Known hypersensitivity to metformin hydrochloride
    - Acute or chronic metabolic acidosis, including DKA, with or without coma. DKA should be treated with insulin.
  - Linagliptin-containing products have the following contraindications:
    - History of hypersensitivity reactions to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticarial, or bronchial hyperreactivity.
  - Saxagliptin-containing products have the following contraindications:
    - History of a serious hypersensitivity reaction to dapagliflozin or to saxagliptin, including anaphylaxis, angioedema or exfoliative skin conditions.
    - Moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
  - Sitagliptin-containing products have the following contraindications:
    - History of hypersensitivity reactions to sitagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.
- Boxed Warnings:
  - Canagliflozin-containing products carry a Boxed Warning for lower limb amputation. An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin use was observed in the CANVAS and CANVAS-R trials in patients with T2DM who had established CVD or were at risk for CVD. Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving canagliflozin for infections or ulcers of the lower limbs, and discontinue if these occur.
  - Metformin-containing products carry a Boxed Warning for lactic acidosis. Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as concomitant use of certain drugs, age > 65 years, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and abdominal pain. Laboratory abnormalities include increased lactate/pyruvate ratio, anion gap acidosis, metformin plasma levels generally > 5 mcg/mL, and elevated blood lactate. If acidosis is suspected, discontinue treatment and hospitalize the patient immediately.
- Warnings and Precautions
  - Several FDA drug safety communications have been issued for canagliflozin.
    - The FDA published a drug safety communication in June 2016 stating that the existing warning about the risk of acute kidney injury for canagliflozin (Invokana, Invokamet, Invokamet XR) and dapagliflozin (Farxiga, Xigduo XR)

has been strengthened. Based on recent confirmed cases of acute kidney injury, the warning in the drug label has been revised to include more specific parameters regarding the monitoring of renal function and discontinuation in cases of renal impairment *(FDA Drug Safety Communication 2016[b])*.

- The drug safety communication issued in May 2016 with interim safety results from the CANVAS and CANVAS-R studies has since culminated in a formal boxed warning on all canagliflozin-containing agents for the risk of lower limb amputation *(FDA Drug Safety Communication 2016[a] and 2017)*.
- The FDA issued a drug safety communication regarding the risk of fracture and bone density in 2016.
  - The FDA evaluated the incidence of bone fractures based on a pooled analysis of nine clinical trials (n = 10,194) with patients ages 55 to 80 who had a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of bone fractures were greater with canagliflozin 100 mg and 300 mg vs placebo or an active comparator (1.4 and 1.5 vs 1.1 per 100 patient-years of exposure, respectively). Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (eg, fall from no more than standing height), and affect the upper extremities *(Watts et al 2016)*.
  - Based on an FDA-required post-marketing trial, canagliflozin caused greater loss of bone mineral density at the hip and lower spine than placebo over two years in elderly individuals (55 to 80 years of age) with poorly controlled T2DM. Placebo-corrected declines in bone mineral density at the total hip were 0.9% and 1.2%, respectively for canagliflozin 100 mg and 300 mg, and were 0.1% at the femoral neck for both canagliflozin doses. Placebo-adjusted bone mineral density decline at the distal forearm was 0.4% with canagliflozin 300 mg and 0% with canagliflozin 100 mg *(Bilezikian et al 2016, FDA Drug Safety Communication 2015)*.
  - A pooled analysis of data from clinical trials did not find an increased risk of fracture with empagliflozin vs placebo or glimepiride *(Kohler et al 2018)*.
- The FDA issued a drug safety communication regarding rare occurrences of necrotizing fasciitis of the perineum (also referred to as Fournier's gangrene) in 2018 (*FDA Drug Safety Communication 2018*).
  - From March 2013 to May 2018, the FDA identified 12 cases (7 males and 5 females) of Fournier's gangrene in patients taking an SGLT2 inhibitor. The infection developed within several months of starting an SGLT2 inhibitor, and all 12 patients were hospitalized and required surgery.
  - In comparison, only 6 cases of Fournier's gangrene (all in men) were identified in review of other antidiabetic drug classes over a period of more than 30 years.

Table 5. Warnings and Precautions

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
Hypotension: Before initiating therapy, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Ketoacidosis: Assess patients who present with signs/symptoms of metabolic acidosis regardless of blood	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
glucose level.											
Acute kidney injury: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Impairment in renal function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR < 60 mL/min/1.73 m^2. Avoid initiation of dapagliflozin and ertugliflozin when eGFR < 60 mL/min/1.73 m^2.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Macrovascular outcomes: No clinical studies have established conclusive evidence of macrovascular risk reduction.	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔
Necrotizing fasciitis of the perineum (Fournier's Gangrene): Cases, which may be life-threatening, have been reported. Evaluate patients with pain, tenderness, erythema, or swelling of the genital or perineal area who also have accompanying fever or malaise. Broad spectrum antibiotics and surgical debridement are likely needed.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypersensitivity reactions: Monitor for anaphylaxis and		✔	✔		✔	✔	✔	✔			✔

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
angioedema. Discontinue use and treat and monitor until signs and symptoms resolve.											
Genital mycotic infections: Monitor and treat if indicated.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Increased LDL-C: Monitor LDL-C and treat per standard of care.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Bladder cancer: An imbalance in bladder cancers was observed in clinical trials. Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.	✔					✔			✔		
Lower limb amputation: An approximately 2-fold increased risk of lower limb amputations was observed with canagliflozin in patients with T2DM who had either established CVD or were at risk for CVD.		✔		✔ †			✔			✔ †	✔ †
Urosepsis and Pyelonephritis: Evaluate for signs/symptoms of UTI and treat promptly, if indicated.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Bone fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed. Consider factors that contribute to fracture risk before initiating canagliflozin		✔					✔				
Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.							✔	✔	✔	✔	
Pancreatitis: There have been post marketing reports of acute					✔	✔					✔

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
pancreatitis, including fatal pancreatitis. Discontinue if suspected.											
Arthralgia: Severe and debilitating arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate.					✔	✔					✔
Bullous pemphigoid: Patients taking DPP-4 inhibitors have required hospitalization due to bullous pemphigoid. Patients should report development of blisters or erosions. Discontinue if suspected.					✔	✔					✔
HF: In a CV outcomes trial enrolling participants with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8280, 3.5%) were hospitalized for HF compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of HHF was higher in the saxagliptin group (estimated HR, 1.27; 95% CI, 1.07 to 1.51). Subjects with a prior history of HF and subjects with renal impairment had a higher risk for HHF, irrespective of treatment assignment; monitor, observe, and advise patients of this risk and consider discontinuation in any patients that develop signs of HF.					✔ †	✔					✔ †
Radiologic studies with intravascular iodinated contrast							✔	✔	✔	✔	

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
materials: metformin can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Metformin-containing agents should be withheld at the time of or prior to the procedure (and withheld for 48 hours subsequent to the procedure). They should be reinstituted only after renal function is normal or mildly impaired.											

† Warning refers to data with another agent in the class.

- Adverse effects:
  - The most common adverse effects seen with the SGLT2 inhibitors are genital mycotic infections and urinary tract infections.
  - Most common adverse reactions associated with metformin (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
- Drug Interactions:

  All SGLT2 Inhibitors:
  - Positive urine glucose test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
  - Interference with 1,5-anhydroglucitol (1,5-AG) assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

  Canagliflozin:
  - Co-administration of canagliflozin with inducers of uridine diphosphate glucuronosyltransferase (UGT) enzymes such as rifampin, phenytoin, phenobarbital, and ritonavir may result in decreased canagliflozin area under the concentration curve (AUC); consider increasing canagliflozin dosage to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or more and require additional glycemic control. Consider another antihyperglycemic agent in patients with eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.
  - Co-administration of canagliflozin 300 mg with digoxin have been reported to increase the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively).

  Dapagliflozin:
  - When dapagliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

  Empagliflozin:

- Diuretics: Co-administration of diuretics with increased urine volume and frequency of voids may increase the potential for volume depletion.
- When empagliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

Ertugliflozin:
- When ertugliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

Linagliptin-containing products:
- Efficacy of linagliptin may be reduced when used in combination with a strong inducer of cytochrome P450 (CYP) 3A4 or P-glycoprotein. Consider alternative treatments.

Saxagliptin-containing products:
- Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors; do not co-administer Qtern with strong CYP3A4/5 inhibitors.

Sitagliptin-containing products:
- Sitagliptin slightly increases serum concentration levels of digoxin. Digoxin therapy should be monitored, but no dosage adjustment is recommended.

Metformin-containing products:
- Cationic drugs such as cimetidine may reduce metformin elimination and may increase the risk for lactic acidosis. Other drugs which may increase exposure to metformin include ranolazine, vandetanib, and dolutegravir.
- Alcohol may potentiate the effect of metformin on lactate metabolism. Advise against excessive alcohol intake.
- Topiramate or other carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis.
- Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving a metformin-containing drug, monitor for hypoglycemia.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Farxiga (dapagliflozin)	Tablets	Oral	Daily	Initiation is not recommended if eGFR is < 45 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 30 mL/min/1.73 m^2.
Invokana (canagliflozin)	Tablets	Oral	Daily	Limit dose to 100 mg once daily in patients who have an eGFR of 45 to < 60 mL/min/1.73 m^2. Not recommended if eGFR persistently falls below 45 mL/min/1.73 m^2. Not recommended in cases of severe hepatic impairment.
Jardiance (empagliflozin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 45 mL/min/1.73 m^2. Discontinue therapy if eGFR persistently falls below 45 mL/min/1.73 m^2.
Steglatro (ertugliflozin)	Tablets	Oral	Daily	Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 30 mL/min/1.73 m^2.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Not recommended in cases of severe hepatic impairment.
Combination products				
Invokamet (canagliflozin/ metformin)	Tablets	Oral	Two times daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Invokamet XR (canagliflozin/ metformin ER)	Tablets	Oral	Daily	Limit canagliflozin to 100 mg (two 50 mg tablets) daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Xigduo XR (dapagliflozin/ metformin ER)	Tablets	Oral	Daily	Not recommended in patients with eGFR < 45 mL/min/1.73 m^2. Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Not recommended in hepatic impairment.
Qtern (dapagliflozin/ saxagliptin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 60 mL/min/1.73 m^2. Discontinue if eGFR falls persistently below 60 mL/min/1.73 m^2.
Glyxambi (empagliflozin/ linagliptin)	Tablets	Oral	Daily	Do not initiate or continue if eGFR < 45 mL/min/1.73 m^2. Discontinue if eGFR is persistently < 45 mL/min/1.73 m^2.
Synjardy (empagliflozin/ metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy. Use should generally be avoided in patients with hepatic disease
Synjardy XR (empagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy. Use should generally be avoided in patients with hepatic disease
Segluromet (ertugliflozin/ metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy. Not recommended in hepatic impairment.
Steglujan (ertugliflozin/ sitagliptin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2. Not recommended in cases of severe hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are inhibitors of SGLT2, the co-transporter responsible for the majority of reabsorption of glucose filtered by the kidney. By inhibiting SGLT2, these agents reduce reabsorption of filtered glucose, lower the renal threshold for glucose, and thereby increase urinary glucose excretion.
- Similar to other currently available oral antidiabetic agents, SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by ~0.5% to 1.5%. They have been studied as monotherapy and in combination with metformin and other antidiabetic agents.
- The SGLT2 inhibitor/metformin combinations include Invokamet/Invokamet XR (canagliflozin/metformin), Synjardy/Synjardy XR (empagliflozin/metformin), Segluromet (ertugliflozin/metformin), and Xigduo XR (dapagliflozin/metformin). Glyxambi (empagliflozin/linagliptin), Qtern (dapagliflozin/saxagliptin), and Steglujan (ertugliflozin/sitagliptin) are SGLT2 inhibitor/DPP-4 inhibitor combination products.
- In clinical trials, the SGLT2 inhibitors have been evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. They have demonstrated effectiveness when used as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, FPG, weight, PPG, and blood pressure when used as monotherapy or in combination therapy.
- All 4 single-entity SGLT2 inhibitors are dosed once daily. Initiation of dapagliflozin and ertugliflozin are not recommended in patients with an eGFR < 60 mL/min/1.73 m^2. Empagliflozin and canagliflozin are not recommended in patients with an eGFR < 45 mL/min/1.73 m^2. Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including increased LDL-C levels, increased serum creatinine and a concomitant decrease in eGFR, volume depletion, and genital mycotic infections. Warnings for bone fractures and lower limb amputation were added for canagliflozin-containing products. Warnings for DKA, urosepsis and pyelonephritis, and necrotizing fasciitis of the perineum were also added to the labeling of SGLT2 inhibitors after increased incidences were reported post-marketing.
- Consensus guidelines generally recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated doses. SGLT2 inhibitors are preferred add-on agents for dual therapy in patients with established ASCVD, CKD, or HF. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes.
- Large CV outcome trials have demonstrated a CV benefit with certain SGLT2 inhibitors. The EMPA-REG OUTCOME trial was a long-term, placebo-controlled study involving 7020 patients with T2DM at high risk for CV events. When added to standard of care, empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal MI, or nonfatal stroke) by 14% vs placebo ($p < 0.001$ for noninferiority; $p = 0.04$ for superiority). In the CANVAS Program, significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs placebo: 26.9 vs 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority). In the DECLARE-TIMI 58 study, dapagliflozin was noninferior to placebo with respect to MACE ($p < 0.001$ for noninferiority; $p = 0.17$ for superiority) and significantly reduced a composite outcome of CV death and HHF (HR, 0.83; 95% CI, 0.73 to 0.95; $p = 0.0005$) in patients with established CVD or multiple risk factors for CVD.
- The SGLT2 inhibitors provide another treatment option for glycemic control in patients unable to tolerate first-line treatment with metformin or other oral antidiabetic therapies due to adverse effects or risk for hypoglycemia. Positive CV outcomes have been demonstrated with empagliflozin, canagliflozin, and dapagliflozin, suggesting that SGLT2 inhibitors may play a significant role in T2DM patients at high risk for CV events.

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