OPTUMRx

Therapeutic Class Overview
Sodium-Glucose Cotransporter-2 Inhibitors

INTRODUCTION

- In the United States, diabetes mellitus affects more than 30 million people and is the 7th leading cause of death (*Centers for Disease Control and Prevention [CDC] 2019*).
- 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] 2020a)*. 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 2020b)*.
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy *(ADA 2020a)*.
- 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 2020)*.
- 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 2020)*.
- 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)	-
Qternmet XR (dapagliflozin/saxagliptin/metformin)	-
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)	-

Drug	Generic Availability
Trijardy XR (empagliflozin/linagliptin/metformin ER)	-
Ertugliflozin products	
Steglatro (ertugliflozin)	-
Segluromet (ertugliflozin/metformin)	-
Steglujan (ertugliflozin/sitagliptin)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration (FDA) Approved Indications for Single-Entity Products

Indications	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)
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		✓		
To reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and HHF in adults with T2DM and diabetic nephropathy with albuminuria		✓		
To reduce the risk of HHF in adults with T2DM and established CVD or multiple CV risk factors	✓			

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; T2DM = type 2 diabetes mellitus

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).

(*Prescribing information: Farxiga 2020, Invokana 2020, Jardiance 2020, Steglatro 2020*)

Table 3. FDA Approved Indications for Combination Products

Indications	Invokamet, Invokamet XR* (canagliflozin/metformin)	Synjardy, Synjardy XR* (empagliflozin/metformin)	Xigduo XR* (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/metformin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Qternmet XR* (dapagliflozin/ saxagliptin/metformin)	Steglujan (ertugliflozin/sitagliptin)	Trijardy XR* (empagliflozin/linagliptin/ metformin)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM			✓		✓	✓	✓		✓
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 ertugliflozin and/or metformin				✓					

Abbreviations: T2DM = type 2 diabetes mellitus
* These combination products contain metformin ER.

Limitations of use: Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are not recommended in patients with T1DM or for the treatment of DKA. Glyxambi and Steglujan have not been studied in patients with a history of pancreatitis. Qternmet XR should be started only in patients currently taking metformin.

(Prescribing information: Glyxambi 2020, Invokamet/Invokamet XR 2020, Qtern 2020, Qternmet XR 2020, Segluromet 2020, Steglujan 2020, Synjardy 2020, Synjardy XR 2020, Trijardy XR 2020, Xigduo XR 2020)

- 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

Type 2 diabetes mellitus (T2DM)

- The safety and efficacy of the SGLT2 inhibitors for T2DM 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 2015a)*
  - 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 2015a, Schernthaner et al 2013)*
  - As add-on therapy to insulin *(Neal et al 2015, Rosenstock et al 2014, Rosenstock et al 2015b, 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, Synjardy XR, and Trijardy XR to their individual components in healthy subjects was used to support the 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 2015b)* 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 2015a, Rosenstock et al 2019)*. 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)*.

  - Qternmet XR (dapagliflozin/metformin/saxagliptin) was approved in May 2019; the dapagliflozin/saxagliptin/metformin combination improved glycemic control at week 24 compared to dapagliflozin plus metformin or saxagliptin plus metformin *(Rosenstock et al 2019, Matthaei et al 2015b)*.
  - 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 (CKD) *(Barnett et al 2014, Fioretto et al 2018, Grunberger et al 2018, Kohan et al 2014, Perkovic et al 2019, 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 *(Feng et al 2019, 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) and renal 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 2020b, Das et al 2018, Davies et al 2018, Garber et al 2020)*.
  - 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 2020b, Das et al 2018, Davies et al 2018, Garber et al 2020)*.
- 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. This study was completed in December 2019; results are not yet available *(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.
- The double-blind CREDENCE trial (N = 4401) evaluated renal outcomes in patients with T2DM and albuminuric chronic kidney disease. Patients with an estimated glomerular filtration rate (eGFR) ≥ 30 and < 90 mL/min/1.73 m^2, albuminuria, and treated with renin–angiotensin system blockade were randomized to receive canagliflozin 100 mg or placebo for a median follow-up of 2.6 years *(Perkovic et al 2019).*
  - A primary outcome event (composite of end-stage kidney disease [dialysis, transplantation, or a sustained eGFR of < 15 mL/min/1.73 m^2], a doubling of the serum creatinine level, or death from renal or CV causes) was observed in fewer patients treated with canagliflozin vs placebo (43.2 vs 61.2 per 1000 patient-years, respectively; HR, 0.70; 95% CI, 0.59 to 0.82; p = 0.00001).
  - Results also favored canagliflozin for the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes (HR, 0.66; 95% CI, 0.53 to 0.81; p < 0.001), end-stage kidney disease (HR, 0.68; 95% CI, 0.54 to 0.86; p = 0.002)., composite of CV death, MI, or stroke (HR, 0.80; 95% CI, 0.67 to 0.95; p = 0.01), and HHF (HR, 0.61; 95% CI, 0.47 to 0.80; p < 0.001).
  - No significant differences were observed in the rates of amputation or fracture with canagliflozin vs placebo.

Heart failure (HF)

- DAPA-HF (N = 4744) was a Phase 3, event-driven, international, multicenter, double-blind, placebo-controlled RCT that evaluated dapagliflozin vs placebo added to standard of care in patients with established HF and a reduced ejection fraction (≤ 40%), with or without T2DM *(McMurray et al 2019)*.
  - After a median follow-up of 18.2 months, a primary outcome event (composite of worsening HF [ie, hospitalization or an urgent visit resulting in intravenous therapy for HF] or CV death) occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and 502 of 2371 patients (21.2%) in the placebo group (HR, 0.74; 95% CI, 0.65 to 0.85; p < 0.001).
  - Findings in patients with diabetes were similar to those in patients without diabetes.

- The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

CLINICAL GUIDELINES

Overview

- Professional society guidelines emphasize individualized therapy based upon patient- and drug-specific factors such as comorbidities, weight, hypoglycemia risk, propensity for AEs, drug interactions, and patient preferences *(ADA 2020b, Copeland et al 2013, Davies et al 2018, Garber et al 2020)*.
- Metformin is recommended for first-line pharmacologic therapy in treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with established atherosclerotic CV disease (ASCVD), high ASCVD risk, HF, or CKD, independent of HbA1c. Metformin is considered the drug of choice for children with T2DM *(ADA 2020b, Copeland et al 2013, Garber et al 2020)*.

- **ADA: Standards of Medical Care in Diabetes – 2020** *(ADA 2020b)*
  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A; refer to guideline for description of levels of evidence).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
    - Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure (level A).
    - 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 or indicators of high risk, established kidney disease, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen, independent of HbA1c (level A).
    - In patients with T2DM who need greater glucose lowering than can be obtained with oral agents, GLP-1 receptor agonists are preferred to insulin when possible (level B).
    - Intensification of treatment for patients with T2DM not meeting treatment goals should not be delayed (level B).
    - The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate specific factors that impact treatment choice (level E).
  - For patients with indicators of high-risk or established ASCVD, CKD, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with proven benefit should be considered independently of baseline HbA1c or individualized HbA1c target.
    - If ASCVD predominates, a GLP-1 receptor agonist with proven CVD benefit is preferred. Alternatively, an SGLT2 inhibitor with proven CVD benefit is recommended if eGFR is adequate.
    - If HF or CKD predominates, an SGLT2 inhibitor with evidence of reducing HF and/or CKD in CV outcome trials is preferred if eGFR is adequate. If SGLT2 inhibitors are contraindicated, not tolerated, or if eGFR Is not adequate, a GLP-1 receptor agonist with proven CVD benefit should be added.

Table 4. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD Progression
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral
SGLT2i	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin
GLP-1ra	High	No	Loss	Benefit: See labeled indication	Neutral	SQ, oral	Benefit: liraglutide

				Neutral: lixisenatide			
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	Oral	Neutral
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; 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.

† FDA approved for CVD benefit

‡ FDA approved for HF indication

§ FDA approved for CKD indication

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2020)*
  - 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 HbA1c, duration of T2DM, 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.
    - The therapeutic regimen should be as simple as possible to optimize adherence.
  - For patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended.
    - For patients with established or high ASCVD risk, stage 3 CKD, or HF with reduced ejection fraction, an SGLT2 inhibitor or long-acting GLP-1 receptor agonist with proven efficacy is recommended independent of glycemic control.
    - Other acceptable alternatives to metformin as initial therapy include DPP-4 inhibitors and TZDs. Alpha-glucosidase inhibitors, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
  - 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 MACE risk, as well as a lower risk for HHF. Canagliflozin was also associated with an increased risk of amputation in the CANVAS trial.
      - The CREDENCE trial specifically assessed kidney benefits in patients with stage 3 CKD and albuminuria. Canagliflozin significantly reduced the risk of a composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), a doubling of the serum creatinine level, or death from renal or CV causes by 30%. HHF was also reduced by 39%.
    - 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 MACE.
      - The DAPA-HF trial involved patients who had HF with reduced ejection fraction (58% of whom did not have diabetes). Dapagliflozin was associated with a 26% reduction in risk of worsening HF or CV death
    - HF-related endpoints appear to account for most of the observed benefits in the published studies.
    - In their respective CV outcomes trials, canagliflozin, dapagliflozin, and empagliflozin reduced progression of kidney disease.
    - Safety concerns with treatment include increased risks of mycotic genital infections, slightly increased LDL-C levels, limited efficacy in patients with an eGFR < 45 mL/min/1.73 m^2, and dehydration due to increased diuresis leading to initial renal impairment, hypotension, syncope, and falls. Postmarketing reports of SGLT2 inhibitor-associated DKA are still being investigated. The class is also associated with an increased risk of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious genital infection.

Table 5. AACE/ACE Profiles of Antidiabetic Medications

Drug Class	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: long-acting GLP-1ra Exenatide not indicated CrCl < 30	Moderate	Potential benefit of long-acting GLP-1ra in ASCVD Neutral for HF	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45* Potential CKD benefit*	Neutral	Prevent HHF; Manage HFrEF† Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur in various stress settings
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Possible increased HHF with alogliptin and saxagliptin	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 for HF	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	Lowers LDL-C	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe in ASCVD	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk Neutral for ASCVD	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CKD = chronic kidney disease; 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; HFrEF = heart failure reduced ejection fraction; HHF = hospitalization for heart failure; LDL-C = low density lipoprotein-cholesterol; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

* Canagliflozin indicated for eGFR ≥ 30 mL/min/1.73 m^2 in patients with CKD 3 and albuminuria.

† Dapagliflozin has a potential benefit in primary prevention of HHF and demonstrated efficacy in HFrEF.

- **Endocrine Society: Guideline for Treatment of Diabetes in Older Adults** (*LeRoith et al 2019*)
  - Glycemic management strategies must be adjusted to the individual needs of older patients. Specific factors regarding certain drug classes are particularly important for older patients with diabetes, especially those with CKD and heart disease.
    - In T2DM patients ≥ 65 years of age, metformin is recommended as the initial oral medication chosen for glycemic management in addition to lifestyle management (unless the patient has significantly impaired kidney function or gastrointestinal intolerance).
    - Patients who are not able to achieve glycemic targets with metformin and lifestyle changes can receive add-on therapy with oral or injectable agents and/or insulin.
      - GLP-1 receptor agonists and SGLT2 inhibitors should be prescribed early, given their beneficial CV outcomes.
      - SFUs and meglitinides should be avoided and insulin should be used sparingly to reduce the risk of hypoglycemia.
      - Glycemic treatment regimens should be kept as simple as possible.
  - SGLT2 inhibitors reduce HbA1c by approximately 0.8%, can reduce weight, and do not cause hypoglycemia.
    - Empagliflozin and canagliflozin have been shown to decrease MACE, HF, and the progression of CKD.
    - SGLT2 inhibitors cause an obligate increase in urine volume and an increase in urogenital candida infections.
    - Canagliflozin has also been shown to be associated with a decrease in bone mineral density at the hip, but not the femoral neck, lumbar spine, or distal radius, with a significant increase in fractures of arms and legs but not the spine.

- **American College of Cardiology (ACC)/American Heart Association (AHA): Guideline on the Primary Prevention of CV Disease** *(Arnett et al 2019)*
  - For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
  - For adults with T2DM and additional ASCVD risk factors who require glucose lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate an SGLT2 inhibitor or GLP-1 receptor agonist to improve glycemic control and reduce CVD risk.
    - SGLT2i act in the proximal tubule to increase urinary excretion of glucose and sodium, leading to a reduction in HbA1c, body weight, and blood pressure. Three RCTs have shown a significant reduction in ASCVD events and HF with use of an SGLT2i. Although most patients studied had established CVD at baseline, the reduction in HF has been shown to extend to primary prevention populations.
    - The GLP-1RAs increase insulin and glucagon production in the liver, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. Three GLP-1RAs have been found to significantly reduce the risk of ASCVD in adults with T2DM who are at high ASCVD risk.

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, Xigduo XR, Trijardy XR: eGFR < 30 mL/min/1.73 m^2; Invokamet, Invokamet XR, Qtern, Qternmet XR, Synjardy, Synjardy XR: eGFR < 45 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 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 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 2016b)*.

- 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 2016a 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 6. 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)	Qternmet XR (dapagliflozin/ saxagliptin/metformin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin)	Trijardy XR (empagliflozin/linagliptn /metformin ER)
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 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.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
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 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. Do not use in patients with active bladder cancer and use 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 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.													
Lactic acidosis/radiologic studies with intravascular iodinated contrast materials: metformin can lead to acute alteration of renal function and has been associated with lactic acidosis. Metformin-containing agents should be withheld at the time of or prior to a radiological study with contrast (and withheld for 48 hours subsequent to the procedure) in certain patients. Metformin-containing products should be reinstituted only after renal function is stable.							✔	✔	✔	✔	✔		✔

† 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.
- When 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.

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 200 mg and then 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. For patients with an eGFR < 60 mL/min/1.73 m^2, if an inducer of UGT is co-administered, increase the canagliflozin dose to 200 mg once daily in patients currently tolerating 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- Co-administration of canagliflozin 300 mg with digoxin has been reported to increase the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively).

Empagliflozin:

- Diuretics: Co-administration results in an increased urine volume and frequency of voids, which may increase the potential for volume depletion.

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.

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 7. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Farxiga (dapagliflozin)	Tablets	Oral	Daily	Use is not recommended if eGFR is < 45 mL/min/1.73 m^2.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Contraindicated in patients with eGFR below 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis.
Invokana (canagliflozin)	Tablets	Oral	Daily	Limit dose to 100 mg once daily in patients who have an eGFR of 30 to < 60 mL/min/1.73 m^2. Contraindicated in patients with eGFR below 30 mL/min/1.73 m^2 who are being treated for glycemic control and on dialysis. 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 m2, end-stage renal disease, or on dialysis.
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. Contraindicated in patients with eGFR below 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. 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. Avoid use 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. Avoid use 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, end-stage renal disease, or on dialysis. Avoid use in hepatic impairment.
Qtern (dapagliflozin/ saxagliptin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, end-stage renal disease, or on dialysis.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Qternmet XR (dapagliflozin/saxagliptin/ metformin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. Avoid use in hepatic impairment.
Glyxambi (empagliflozin/ linagliptin)	Tablets	Oral	Daily	Contraindicated in patients with severe renal impairment, end-stage renal disease, or on dialysis. Do not initiate 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 m2, end-stage renal disease, or on dialysis. Advise premenopausal females of the potential for an unintended pregnancy. Avoid use in hepatic impairment.
Synjardy XR (empagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. Advise premenopausal females of the potential for an unintended pregnancy. Avoid use in hepatic impairment.
Trijardy XR (empagliflozin/linagliptin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. Do not initiate or continue in patients with an eGFR < 45 mL/min/1.73 m^2. Not recommended in patients with hepatic impairment.
Segluromet (ertugliflozin/metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. 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. Avoid use in hepatic impairment.
Steglujan (ertugliflozin/sitagliptin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. 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. Qternmet XR (dapagliflozin/saxagliptin/metformin) and Trijardy XR (empagliflozin/linagliptin/metformin ER) are SGLT2 inhibitor/DDP-4 inhibitor/metformin combinations.
- 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 and renal function should be monitored prior to and during therapy for all agents. Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including 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.
- 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.
- According to current clinical guidelines for the management of T2DM, metformin is recommended first-line for the initial pharmacologic treatment of T2DM, and SGLT2 inhibitors are among the second-line options. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with established ASCVD, high ASCVD risk, HF, or CKD, independent of HbA1c *(ADA 2020b, Garber et al 2020).*

REFERENCES

- American Diabetes Association (ADA). Diabetes Basics: Type 2. ADA Web site. http://www.diabetes.org/diabetes-basics/type-2. Accessed January 21, 2020[a].
- American Diabetes Association. Standards of Medical Care in Diabetes−2020. *Diabetes Care.* 2020[b];43(Suppl 1):S1-S212. https://care.diabetesjournals.org/content/43/Supplement_1. Accessed January 21, 2020.
- Araki E, Tanizawa Y, Tanaka Y, et al. Long-term treatment with empagliflozin as add-on to oral anti-diabetes therapy in Japanese patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2015;17(7):665-74.
- Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease. A report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2109;74(10):1376-1414. doi: 10.1016/j.jacc.2019.03.009.
- Aronson R, Frias J, Goldman A, et al. Long-term efficacy and safety of ertugliflozin monotherapy in patients with inadequately controlled T2DM despite diet and exercise: VERTIS MONO extension study. *Diabetes Obes Metab.* 2018 Jun;20(6):1453-1460. doi: 10.1111/dom.13251.

- Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, double-blind, placebo-controlled trial. *Lancet.* 2010;375:2223-2233.
- Bailey CJ, Iqbal N, T'Joen C, et al. Dapagliflozin monotherapy in drug-naive patients with diabetes: a randomized-controlled trial of low-dose range. *Diabetes Obes Metab.* 2012;14(10):951-959.
- Bailey CJ, Morales-Villegas EC, Woo, V, et al. Efficacy and safety of dapagliflozin monotherapy in people with type 2 diabetes: a randomized double-blind placebo-controlled 102-week trial. *Diabet Med.* 2015;32:531-41.
- Balijepalli C, Shirali R, Kandaswamy P, et al. Cardiovascular Safety of Empagliflozin Versus Dipeptidyl Peptidase-4 (DPP-4) Inhibitors in Type 2 Diabetes: Systematic Literature Review and Indirect Comparisons. *Diabetes Ther.* 2018 Aug;9(4):1491-1500. doi: 10.1007/s13300-018-0456-7.
- Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomize, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 2014;2(5):369-84.
- Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with Type 2 diabetes treated with canagliflozin. *J Clin Endocrinol Metab*. 2016;101(1):44-51.
- Birkeland KI, Jorgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. *Lancet Diabetes Endocrinol.* 2017 Sep;5(9):709-717. doi: 10.1016/S2213-8587(17)30258-9.
- Bode B, Stenlof K, Harris S, et al. Long-term efficacy and safety of canagliflozin over 104 weeks in patients aged 55-80 years with type 2 diabetes. *Diabetes Obes Metab.* 2015;17:294-303.
- Bode B, Stenlof K, Sullivan D, Fung A, Usiskin K. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. *Hosp Pract.* 1995;41:72-84.
- Bolen S, Tseng E, Hutfless S, et al. Diabetes Medications for Adults With Type 2 Diabetes: An Update. Comparative Effectiveness Review No. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2012-00007-I.) AHRQ Publication No. 16-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2016. https://www.ncbi.nlm.nih.gov/sites/books/NBK362863/. Accessed January 21, 2020.
  Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation.* 2017 Jul 18;136(3):249-259.
- Cefalu W, Leiter L, Yoon KH L, et al. Efficacy and safety of canagliflozin vs glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 noninferiority trial. *Lancet.* 2013;182-941-950.
- Centers for Disease Control and Prevention (CDC). Diabetes quick facts. Updated August 6, 2019. Available at: https://www.cdc.gov/diabetes/basics/quick-facts.html. Accessed January 21, 2020.
- ClinicalTrials.gov Web site. http://clinicaltrials.gov/. Accessed January 21, 2020.
- Copeland KC, Silverstein J, Moore KR, et al. Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics*. 2013;131:364-382.
- Dagogo-Jack S, Liu J, Eldor R, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin: The VERTIS SITA2 placebo-controlled randomized study. *Diabetes Obes Metab.* 2018;20(3):530-540. doi: 10.1111/dom.13116.
- Das SR, Everett BM, Birtcher KK, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol.* 2018;72(24):3200-3223. doi: 10.1016/j.jacc.2018.09.020.
- Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2018;41(12):2669-2701. doi: 10.2337/dci18-0033.
- Davies MJ, Trujillo A, Vijapurkar U, et al. Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus. *Diabetes Obes Metab.* 2015;17:426-429.
- DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care.* 2015;38:384-393.
- Del Prato S, Nauck M, Duran-Garcia S, et al. Long-term glycaemic response and tolerability of dapagliflozin vs a sulphonylurea as add-on therapy to metformin in type 2 diabetes patients: 4-year data. *Diabetes Obes Metab.* 2015;17(6):581-90.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 21, 2020.
- Farxiga prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. January 2020.
- FDA Drug Safety Communications. Canagliflozin (Invokana, Invokamet): Drug Safety Communication – Clinical Trial Results Find Increased Risk of Leg and Foot Amputations. May 18, 2016[a]. https://www.fda.gov/Drugs/DrugSafety/ucm500965.htm. Accessed January 21, 2020.
- FDA Drug Safety Communications. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). Updated July 13, 2017. https://www.fda.gov/Drugs/DrugSafety/ucm557507.htm. Accessed January 21, 2020.
- FDA Drug Safety Communications. FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. Updated January 15, 2016. https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm . Accessed January 21, 2020.
- FDA Drug Safety Communications. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. Updated September 7, 2018. https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Accessed January 21, 2020.
- FDA Drug Safety Communications. FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR).Updated June 17, 2016[b]. http://www.fda.gov/drugs/drugsafety/ucm505860.htm. Accessed January 21, 2020.
- Feng M, Lv H, Xu X, Wang J, Lyu W, Fu S. Efficacy and safety of dapagliflozin as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2019;98(30):e16575. doi: 10.1097/MD.0000000000016575.
- Ferrannini E, Berk A, Hantel S, et al. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. *Diabetes Care.* 2013;36(12):4015-21.
- Ferrannini E, Jimenez Ramos S, Salsali A, Tang W, List J. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise. *Diabetes Care.* 2010;33:2217-2214.

- Fioretto P, Del Prato S, Buse JB, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study. *Diabetes Obes Metab.* 2018;20(11):2532-2540. doi: 10.1111/dom.13413.
- Forst T, Guthrie R, Goldenberg R, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes on background metformin and pioglitazone. *Diabetes Obes Metab.* 2014;16(5):467-77.
- Fulcher G, Matthews DR, Perkovic V, et al. Efficacy and safety of canagliflozin used in conjunction with sulfonylurea in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Diabetes Ther.* 2015 Sep;6(3):289-302.
- Garber AJ, Handelsman Y, Grunberger G, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2020 Executive Summary. *Endocr Pract.* 2020;26(1):107-139.
- Glyxambi prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. January 2020.
- Grunberger G, Camp S, Johnson J, et al. Ertugliflozin in Patients with Stage 3 Chronic Kidney Disease and Type 2 Diabetes Mellitus: The VERTIS RENAL Randomized Study. *Diabetes Ther.* 2018;9(1):49-66. doi: 10.1007/s13300-017-0337-5.
- Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care.* 2014;37:1650-9.
- Haring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care.* 2013;36:3396-3404.
- Henry RR, Murray AV, Marmolejo MH, Hennicken D, et al. Dapagliflozin, metformin XR, or both: initial pharmacotherapy for type 2 diabetes, a randomized controlled trial. *Int J Clin Pract.* 2012;66:446-456.
- Hollander P, Liu J, Hill J, et al. Ertugliflozin Compared with Glimepiride in Patients with Type 2 Diabetes Mellitus Inadequately Controlled on Metformin: The VERTIS SU Randomized Study. *Diabetes Ther.* 2018;9(1):193-207. doi: 10.1007/s13300-017-0354-4.
- Inagaki N, Kondo K, Yoshinari T, et al. Japanese patients with type 2 diabetes inadequately controlled with diet and exercise: a 24-week, randomized, double-blind, placebo-controlled, Phase III study. *Expert Opin Pharmacother*. 2014;15:1501-1515.
- Invokamet and Invokamet XR prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. January 2020.
- Invokana prescribing information. Janssen Pharmaceuticals, Inc. Titusville, NJ. January 2020.
- Jabbour A, Hardy E, Sugg J, Parikh S. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. *Diabetes Care.* 2014;37(3):740-50.
- Jardiance prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. January 2020.
- Kohan DE, Fioretto P, Tang W, et al. Long-term study of patients with type 2 diabetes and moderate renal impairment shows that dapagliflozin reduces weight and blood pressure but does not improve glycemic control. *Kidney Int.* 2014 Apr;85(4):962-71.
- Kohler S, Kaspers S, Salsali A, Zeller C, Woerle HJ. Analysis of fractures in patients with type 2 diabetes treated with empagliflozin in pooled data from placebo-controlled trials and a head-to-head study versus glimepiride. *Diabetes Care.* 2018;41(8):1809-1816. doi: 10.2337/dc17-1525
- Kosiborod M, Cavender MA, Fu AZ, et al.; CVD-REAL Investigators and Study Group*. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of
- Kovacs CS, Seshiah V, Merker L, et al. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. *Clin Ther.* 2015 Aug;37(8):1773-88.
- Kovacs CS, Seshiah V, Swallow R, et al. Empagliflozin improves glycemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab.* 2014;16:147-58.
- Kuchay MS, Krishan S, Mishra SK, et al. Effect of empagliflozin on liver fat in patients with type 2 diabetes and nonalcoholic fatty liver disease: a randomized controlled trial (E-LIFT Trial). *Diabetes Care.* 2018;41(8):1801-1808. doi: 10.2337/dc18-0165
- Lavalle-Gonzalez, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomized trial. *Diabetologia*. 2013;56:2582-2592.
- Leiter LA, Cefalu WT, Tjerk W, et al. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. *J Am Geriatr Soc*. 2014;62:1252-62.
- Leiter, LA, Yoon HK, Arias P et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. *Diabetes Care.* 2015;38(3):355-64.
- LeRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of diabetes in older adults: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2019;104(5):1520-1574. doi: 10.1210/jc.2019-00198.
- Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab.* 2014;16:984-993.
- Mathieu C, Herrera Marmolejo M, González JG, et al. Efficacy and safety of triple therapy with dapagliflozin add-on to saxagliptin plus metformin over 52 weeks in patients with type 2 diabetes. *Diabetes Obes Metab.* 2016;18(11):1134-1137.
- Mathieu C, Ranetti AE, Li D, et al. Randomized, double-blind, phase 3 trial of triple therapy with dapagliflozin add-on to saxagliptin plus metformin in type 2 diabetes. *Diabetes Care.* 2015;38(11):2009-17.
- Matthaei S, Aggarwal N, Garcia-Hernandez P, et al. One-year efficacy and safety of saxagliptin add-on in patients receiving dapagliflozin and metformin. *Diabetes Obes Metab.* 2016;18(11):1128-1133.
- Matthaei S, Bowering K, Rohwedder K, et al. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. *Diabetes Care.* 2015[a];38:365-372.
- Matthaei S, Catrinoiu D, Celiński A, et al. Randomized, double-blind trial of triple therapy with saxagliptin add-on to dapagliflozin plus metformin in patients with type 2 diabetes. *Diabetes Care.* 2015[b];38(11):2018-24.
- McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019 Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print]
- McNeill AM, Davies G, Kruger E, et al. Ertugliflozin compared to other anti-hyperglycemic agents as monotherapy and add-on therapy in type 2 diabetes: a systematic literature review and network meta-analysis. *Diabetes Ther.* 2019 Jan 28. doi: 10.1007/s13300-019-0566-x meta-analysis. *BMJ Open*. 2016 Feb 24;6(2):e009417.
- Miller S, Krumins T, Zhou H, et al. Ertugliflozin and Sitagliptin Co-initiation in Patients with Type 2 Diabetes: The VERTIS SITA Randomized Study. *Diabetes Ther.* 2018;9(1):253-268. doi: 10.1007/s13300-017-0358-0.

- Muller-Wieland D, Kellerer M, Cypryk K, et al. Efficacy and safety of dapagliflozin or dapagliflozin plus saxagliptin versus glimepiride as add-on to metformin in patients with type 2 diabetes. *Diabetes Obes Metab.* 2018 Jun 27. doi: 10.1111/dom.13437. [Epub ahead of print]
- Nauck MA, Del Prato S, Duran-Garcia A, et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. *Diabetes Obes Metab.* 2014;16(11):1111-20.
- Nauck MA, Del Prato S, Meier JJ, et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. *Diabetes Care.* 2011;34:2015-2022.
- Neal B, Perkovic V, de Zeeuw D et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes Care.* 2015;38:403-411.
- Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-657. doi: 10.1056/NEJMoa1611925.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 21, 2020.
- Orme M, Fenici P, Duprat-Lomon I, et al. A systematic review and mixed-treatment comparison of dapagliflozin with existing anti-diabetes treatments for those with type 2 diabetes mellitus inadequately controlled by sulfonylurea monotherapy. *Diabetol Metab Syndr*. 2014 Jun 11;6:73.
- Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. doi: 10.1056/NEJMoa1811744.
- Persson F, Nystrom T, Jorgensen ME, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study. *Diabetes Obes Metab.* 2018 Feb;20(2):344-351. doi: 10.1111/dom.13077.
- Pratley R, Eldor R, Raji A, et al. Ertugliflozin plus sitagliptin versus either individual agent over 52 weeks in patients with type 2 diabetes mellitus inadequately controlled with metformin: The VERTIS FACTORIAL randomized trial. *Diabetes Obes Metab.* 2018;20(5):1111-1120. doi: 10.1111/dom.13194.
- Ptaszynska A, Johnsson KM, Parikh SJ, et al. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. *Drug Saf.* 2014;37(10):815-29.
- Qtern prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. January 2020.
- Qternmet XR prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. January 2020.
- Ridderstrale M, Andersen KR, Zeller C, et al. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomized, active-controlled, double-blind, phase 3 trial. *Lancet Diabetes Endrocrinol*. 2014;2:691-700.
- Ridderstrale M, Rosenstock J, Andersen KR, et al. Empagliflozin compared with glimepiride in metformin-treated patients with type 2 diabetes: 208-week data from a masked randomized controlled trial. *Diabetes Obes Metab.* 2018 Jul 2. doi: 10.1111/dom.13457. [Epub ahead of print]
- Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol.* 2013;1(3):208-19.
- Rosenstock J, Frias J, Pall D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy (VERTIS MET). *Diabetes Obes Metab.* 2018;20(3):520-529. doi: 10.1111/dom.13103.
- Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. *Diabetes Care.* 2015[a];38:376-83.
- Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care.* 2014;37:1815-23.
- Rosenstock J, Jelaska A, Zeller C, et al for the EMPA-REG BASALTM trial investigators. Impact of empagliflozin added on to basal insulin in type 2 diabetes inadequately controlled on basal insulin: a 78-week randomized, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2015[b] Oct;17(10):936-48.
- Rosenstock J, Perl S, Johnsson E, Garcia-Sanchez R, Jacob S. Triple therapy with low-dose dapagliflozin plus saxagliptin versus dual therapy with each monocomponent, all added to metformin, in uncontrolled type 2 diabetes. *Diabetes Obes Metab*. 2019;21(9):2152-2162.
- Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. *Diabetes Obes Metab.* 2013;15:1154-60.
- Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, an SGLT2 inhibitor, on HbA1c, body weight, and hypoglycemia risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. *Diabetes Care.* 2012;35:1473-1478.
- Ross S, Thamer C, Cescutti J, et al. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. *Diabetes Obes Metab.* 2015;17:699-702.
- Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G. Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea: A 52-week randomized trial. *Diabetes Care.* 2013;36:2508-2515.
- Segluromet prescribing information. Merck Sharp & Dohme. Whitehouse Station, NJ. January 2020.
- Shyangdan DS, Uthman OA, Waugh N. SGLT2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network
- Sinclair A, Bode B, Harris S, et al. Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. *BMC Endocrine Disorders*. 2014;14:37.
- Sinclair AJ, Bode B, Harris S, et al. Efficacy and safety of canagliflozin in individuals aged 75 and older with Type 2 Diabetes Mellitus: A pooled analysis. *J Am Geriatr Soc*. 2016;64:543-552.
- Steglatro prescribing information. Merck Sharp & Dohme. Whitehouse Station, NJ. January 2020.
- Steglujan prescribing information. Merck Sharp & Dohme. Whitehouse Station, NJ. January 2020.
- Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab.* 2013;15(4):372-82.
- Strojek K, Yoon KH, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. *Diabetes Obes Metab.* 2011;13:928-938.

- Strojek K, Yoon KH, Hruba V, et al. Dapagliflozin added to glimepiride in patients with type 2 diabetes mellitus sustains glycemic control and weight loss over 48 weeks: a randomized, double-blind, parallel-group, placebo-controlled trial. *Diabetes Ther.* 2014;5:267-83.
- Sun Y, Zhou Y, Chen X et al. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *BMJ Open*. 2014 Apr 7;4(4):e004619.
- Supplement to: Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. DOI: 10.1056/NEJMoa1611925.
- Synjardy prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. January 2020.
- Synjardy XR prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. January 2020.
- Terra SG, Focht K, Davies M, et al. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. *Diabetes Obes Metab.* 2017 May;19(5):721-728. doi: 10.1111/dom.12888.
- Trijardy XR prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT: January 2020.
- Udell JA, Yuan Z, Rush T, et al. Cardiovascular Outcomes and Risks After Initiation of a Sodium Glucose Co-Transporter 2 Inhibitor: Results From the EASEL Population-Based Cohort Study. *Circulation.* 2018;137(14):1450-1459. doi: 10.1161/CIRCULATIONAHA.117.031227.
- Usman MS, Siddiqi TJ, Memon MM, et al. Sodium-glucose co-transporter 2 inhibitors and cardiovascular outcomes: A systematic review and meta-analysis. *Eur J Prev Cardiol*. 2018 Mar;25(5):495-502. doi: 10.1177/2047487318755531.
- Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med*. 2016;375(4):323-334.
- Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab*. 2016;101(1):157-166.
- Weir MR, Januszewicz A, Gilbert RE et al. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. *J Clin Hypertens*. 2014;16:875-882.
- Wilding J, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea. *Int J Clin Pract.* 2013;67:1267-1282.
- Wilding JP, Woo V, Soler N, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin. *Ann Intern Med*. 2012;156:405-415.
- Wiviott SD, Raz I, Bonica MP, et al; DECLARE-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357. doi: 10.1056/NEJMoa1812389
- Xigduo XR prescribing information. AstraZeneca Pharmaceuticals LP. Wilmington, DE. January 2020.
- Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab.* 2013;14:463-479.
- Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes and chronic kidney disease. *Diabetes Obes Metab.* 2014;16:1016-1027.
- Yale JF, Xie J, Sherman SE, Garceau C. Canagliflozin in Conjunction With Sulfonylurea Maintains Glycemic Control and Weight Loss Over 52 Weeks: A Randomized, Controlled Trial in Patients With Type 2 Diabetes Mellitus. *Clin Ther.* 2017 Nov;39(11):2230-2242. doi: 10.1016/j.clinthera.2017.10.003.
- Yang XP, Lai D, Zhong XY, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2014;70:1149-1158.
- Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab.* 2016 Aug;18(8):783-94.
- Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019 Jan 5;393(10166):31-39. doi: 10.1016/S0140-6736(18)32590-X.
- Zhang YJ, Han SL, Sun XF, et al. Efficacy and safety of empagliflozin for type 2 diabetes mellitus: Meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2018;97(43):e12843. doi: 10.1097/MD.0000000000012843
- Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.

Publication Date: April 1, 2020