SGLT2 inhibitor side-by-side comparison

March 2024

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Executive Summary

Introduction

The first sodium-glucose cotransporter-2 (SGLT2) inhibitor, canagliflozin (Invokana), was approved in 2013 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). Since that time, 5 other SGLT2 inhibitors – dapagliflozin (Farxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro), bexagliflozin (Brenzavvy), and sotagliflozin (Inpefa) – have been approved in the US. Sotagliflozin additionally inhibits SGLT1, making it the only agent in this class marketed as an SGLT1/2 inhibitor; however, some data indicate that canagliflozin also exhibits SGLT1 inhibition at approved doses. All approved SGLT2 inhibitors, with the exception of sotagliflozin, share the indication specific to glycemic control in adults with T2DM. Empagliflozin is also approved for this indication in pediatric patients ≥ 10 years of age. As a class, SGLT2 inhibitors provide an intermediate reduction in hemoglobin A1c (HbA1c), around 0.5-1%, depending on background therapy. The SGLT2 inhibitors vary with regard to the FDA-approved indications related to cardiorenal outcomes, which is the focus of this review.

Guidelines

The table below summarizes recent practice guidelines that include recommendations for the use of SGLT2 inhibitors.

Guideline	Recommendation
ADA 2024	• A patient-centered, shared decision-making approach should guide the selection of pharmacologic agents for patients with T2DM; consider effects of pharmacologic agents on CV and renal comorbidities. SGLT2 inhibitors are recommended in patients with T2DM with, or at risk of, ASCVD, HF, or CKD. Select SGLT2 inhibitors with proven benefit based on patient comorbidities. • For patients with T2DM hospitalized with HF, an SGLT2 inhibitor is recommended to be initiated or continued during hospitalization and upon discharge (in the absence of contraindications and following recovery from acute illness). • SGLT2 inhibitors with proven benefit per ADA include: o ASCVD: canagliflozin and empagliflozin o HF: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (sotagliflozin's effects on HF outcomes are discussed in text, but it is not specially listed as an agent with benefit) o CKD: canagliflozin, dapagliflozin, and empagliflozin
AACE 2023	• SGLT2 inhibitors with proven benefit may be used as an alternative to GLP1-RA with proven benefit as first-line therapy in patients with ASCVD or high CV risk. • SGLT2 inhibitors with proven efficacy should be initiated as first-line therapy in patients with HF or CKD. • SGLT2 inhibitors with proven benefit per AACE/ACE include: o ASCVD: canagliflozin and empagliflozin o HF: not specified o CKD: not specified
AHA/ACC/HFSA 2022	SGLT2 inhibitors are recommended as a class 1a recommendation in patients with HFrEF and a class 2a recommendation in patients with HFpEF. Empagliflozin and dapagliflozin are the primary agents discussed within the guideline. Canagliflozin and sotagliflozin are mentioned as well within text discussion.
KDIGO 2022	SGLT2 inhibitors are recommended in patients with T2DM, CKD, and an eGFR ≥ 20 mL/min/1.73m^2. SGLT2 inhibitors listed as having a proven benefit in this patient population include canagliflozin, dapagliflozin, and empagliflozin.

Abbreviations: AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; ACC = American College of Cardiology; ADA = American Diabetes Association; ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; GLP1-RA = glucagon-like peptide 1 receptor agonist; HbA1c = hemoglobin A1c; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction (LVEF ≤ 40%); KDIGO = Kidney Disease: Improving Global Outcomes; NYHA = New York Heart Association; SGLT-2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus

Efficacy

The efficacy data reviewed are focused specifically on cardiorenal outcomes. The CANVAS and CREDENCE studies provide evidence of a reduction in major adverse cardiac events (MACE) and composite renal outcomes with canagliflozin in patients with T2DM and high cardiovascular (CV) risk or chronic kidney disease (CKD), respectively. DECLARE-TIMI 58 provides evidence for a reduction in risk of hospitalization for heart failure (HF) in patients with T2DM and high CV risk who receive dapagliflozin. DAPA-HF, DELIVER, and DAPA-CKD support the use of dapagliflozin in patients with HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and CKD, respectively, with or without diabetes. EMPA-REG OUTCOME demonstrated a benefit for MACE, including CV death in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) given empagliflozin. EMPEROR-Reduced and EMPEROR-Preserved demonstrated a benefit in reducing the collective risk of CV death and hospitalization for HF in patients with HFrEF and HFpEF, respectively. EMPA-KIDNEY demonstrated a reduction in a renal composite outcome with empagliflozin in patients with CKD. VERTIS-CV evaluated ertugliflozin in patients with T2DM and ASCVD, but did not find a significant difference in MACE compared with placebo. Hospitalization for HF, a secondary outcome, appeared to be reduced by ertugliflozin. Studies evaluating cardiorenal outcomes as the primary endpoint with bexagliflozin are not available. The BEST trial evaluated a composite of CV death and hospitalization for HF as well as a MACE composite outcome as secondary outcomes, but neither outcome was statistically different when compared with placebo. A reduction in albuminuria, evaluated as a secondary endpoint, was observed with bexagliflozin in patients with T2DM and CKD in the C-448 trial. SOLOIST-WHF evaluated the use of sotagliflozin in patients with T2DM recently hospitalized for HF and demonstrated a reduction in the composite HF outcome of CV death, hospitalization for HF, or urgent HF visit. SCORED evaluated the use of sotagliflozin in patients with T2DM and CKD with increased CV risk. The same primary outcome as in the SOLIST-WHF trial was reduced with sotagliflozin compared with placebo. The table below provides a summary of the evidence of cardiorenal outcomes demonstrated in clinical trials for the different SGLT2 inhibitors. See Appendix A for study details and summary of evidence for further discussion of clinical trials evaluating cardiorenal outcomes.

Summary of evidence of cardiorenal outcomes by SGLT2 inhibitor

Cardiorenal outcome	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin	Bexagliflozin	Sotagliflozin
MACE	++	-	++	-	-	+
HF	+	+++	+++	+	-	+++
Renal	+++	+++	+++	-	+	-

Outcome definitions
MACE = some variability across studies, but most commonly defined as a composite of CV death, nonfatal MI, or nonfatal stroke
HF = generally consistent across studies; most commonly defined as a composite of CV death or hospitalization (or urgent visit) due to HF
Renal = some variability across studies but most commonly defined as a composite of a sustained reduction in eGFR, RRT, eGFR < 15 mL/min/1.73m2, or death from renal or CV disease

Key
+++ = benefit demonstrated in ≥ 1 RCT evaluating as a primary endpoint; consistent findings in other trials and/or individual components of primary endpoint related to this outcome were also significantly different
++ = benefit demonstrated in ≥ 1 RCT evaluating as a primary endpoint, but may not be consistent across trials or individual component of composite endpoint for this endpoint did not consistently demonstrate a significant difference
+ = some data (eg, secondary endpoint) suggest possible benefit, trials evaluating as a primary outcome not available
- = no significant difference demonstrated in clinical trials or clinical trials not available to assess this outcome

Some data are available for the use of SGLT2 inhibitors in hospitalized patients. The SOLOIST-WHF trial evaluated patients recently hospitalized for HF. Treatment with sotagliflozin was started either before or within 3 days of hospital discharge. Dapagliflozin and empagliflozin have both been studied in hospitalized patients with acute decompensated HF (ADHF). These trials suggested potential benefit, but further study is needed. Use of SGLT2 inhibitors in ADHF is off-label.

Comparative efficacy

The question of whether SGLT2 inhibitors have a class effect for cardiorenal outcomes is of interest. While these drugs share a similar mechanism of action, there may be differences in their physiological effects. Some SGLT2 inhibitors also inhibit SGLT1, which could have additional cardioprotective effects. Head-to-head trials comparing these drugs are not available, but meta-analyses have been conducted to indirectly compare the effect of individual SGLT2 inhibitors on cardiorenal outcomes. These analyses suggest that different SGLT2 inhibitors may have varying effects on outcomes such as cardiovascular death, hospitalization for heart failure, and renal outcomes. However, the results are not consistent across studies, and limitations with these indirect comparisons, such as differences in patient characteristics and risk factors, varying definitions of outcomes, and unequal representation of data across each of the SGLT2 inhibitors, preclude the ability to make definitive conclusions. Overall, the current body of evidence is insufficient regarding the comparative efficacy of the drugs in this class for cardiorenal outcomes. See the comparative efficacy section within the summary of evidence in the side-by-side comparison for the full discussion on this topic.

Safety

The most common adverse reactions with SGLT2 inhibitors include female genital mycotic infections and urinary tract infections. Diarrhea is also common with sotagliflozin, possibly due to the mechanism of action of SGLT1 inhibition. The SGLT2 inhibitors all share the following warnings in their product labeling: risk of ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant insulin and insulin secretagogues, necrotizing fasciitis of the perineum, and genital mycotic infections. Canagliflozin, empagliflozin, ertugliflozin, and bexagliflozin also carry warnings for lower limb amputations. Significantly more patients receiving canagliflozin had lower limb amputations compared with placebo in the CANVAS trial. This finding led to the addition of a boxed warning for limb amputations to canagliflozin product labeling in 2017; however, this boxed warning was later removed by FDA in 2020 based on the review of additional data that indicated the risk was lower than previously described. Numerically more patients in clinical studies with empagliflozin, including the EMPA-KIDNEY trial; the VERTIS-CV trial with ertugliflozin; and the BEST trial with bexagliflozin had lower limb amputations compared with placebo. Canagliflozin also carries a warning for an increased risk of bone fracture based on data from the CANVAS trial; this warning is not included in the product labeling for the other SGLT2 inhibitors. Limb amputations have also been reported with dapagliflozin and sotagliflozin, but a warning is not included in the product labeling for either agent. All SGLT2 inhibitors require consideration of renal function prior to initiating therapy but vary in the eGFR thresholds for dosing recommendations. Canagliflozin is the only SGLT2 inhibitor that also includes dosage adjustment recommendations for concomitant use with UGT inducers.

Summary

As a class, SGLT2 inhibitors provide an intermediate reduction in HbA1c, around 0.5-1%, depending on background therapy. Canagliflozin, dapagliflozin, empagliflozin, and sotagliflozin all have indications for cardiorenal outcomes. Dapagliflozin and empagliflozin are the only SGLT2 inhibitors indicated for use in patients with CKD with or without diabetes. Dapagliflozin, empagliflozin, and sotagliflozin are approved for use in HF, with or without diabetes. Ertugliflozin and bexagliflozin are only indicated for glycemic control in T2DM. With regard to the question of class effect, no definitive conclusions can be made based on the current body of evidence as to whether or not identical cardiorenal outcomes can be expected across all the SGLT2 inhibitors.

Looking forward

An authorized generic dapagliflozin product was approved in January 2024. None of the other SGLT2 inhibitors are available in generic presentations. The authorized generic version of dapagliflozin is priced at approximately a 35% reduction off wholesale acquisition cost (WAC) compared with brand Farxiga. However, due to the significant rebates available for brand Farxiga (up to 60%), the authorized generic dapagliflozin may not offer a cost advantage to payers or pharmacies. Multiple abbreviated new drug applications for dapagliflozin have been filed with FDA, and these products are expected to enter the market in the second half of 2025. When this happens, it is expected that these generics will be available at 70 to 90% off the WAC of Farxiga. Loss of exclusivity dates for other SGLT2 inhibitors range from another 3 to 10 years out from 2024.

SGLT2 inhibitor side-by-side comparison

	Generic name (brand name)					
	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
Manufacturer	Janssen	AstraZeneca, Prasco	Boehringer Ingelheim / Eli Lilly	Merck	TheracosBio	Lexicon
Approval date	2013	2014	2014	2017	2023	2023
FDA-approved indications (adults)						
T2DM-related	• Adjunct to diet and exercise to improve glycemic control in adults *with T2DM* • To reduce the risk of MACE in adults *with T2DM* and established CV disease • To reduce the risk of ESRD, doubling of Scr, CV death, and hospitalization for HF in adults *with T2DM* and diabetic nephropathy with albuminuria	• Adjunct to diet and exercise to improve glycemic control in adults *with T2DM* • To reduce the risk of hospitalization for HF in adults *with T2DM* and either established CV disease or multiple CV risk factors	• Adjunct to diet and exercise to improve glycemic control in adults *with T2DM* • To reduce the risk of CV death in adults *with T2DM* and established CV disease	Adjunct to diet and exercise to improve glycemic control in adults *with T2DM*	Adjunct to diet and exercise to improve glycemic control in adults *with T2DM*	To reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults *with T2DM*, CKD, and other CV risk factors
HF-specific	--	To reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults *with HF (includes HFrEF and HFpEF)*	To reduce the risk of CV death plus hospitalization for HF in adults *with HF (includes HFrEF and HFpEF*)	--	--	To reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults *with HF** **Note: The labeled indication is not specific to ejection fraction; however data from the SOLOIST-WHF study*

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						were insufficient to separately evaluate patients with HFpEF. The majority of patients in this study had HFrEF.
CKD-specific	--	To reduce the risk of sustained eGFR decline, ESRD, CV death, and hospitalization for HF in adults *with CKD* at risk of progression	To reduce the risk of sustained eGFR decline, ESRD, CV death, and hospitalization in adults *with CKD* at risk of progression	--	--	--
FDA-approved indications (pediatric patients)	--	--	Adjunct to diet and exercise to improve glycemic control in patients ≥ 10 y *with T2DM*	--	--	--
Limitations of use	• Not recommended for patients with T1DM • Not recommended for use to improve glycemic control in adults *with T2DM* with an eGFR < **30 mL/min/1.73m^2**	• Not recommended for patients with T1DM • Not recommended for use to improve glycemic control in adults *with T2DM* with an eGFR **< 45 mL/min/1.73m^2** • Not recommended for the treatment of CKD in patients with polycystic kidney disease or patients requiring, or with a recent history, of immunosuppressive	• Not recommended for patients with T1DM • Not recommended for use to improve glycemic control in adults *with T2DM* with an eGFR **< 30 mL/min/1.73m^2** • Not recommended in the treatment of CKD with PKD or patients requiring or with a recent history of IV immunosuppressive therapy or > 45 mg of prednisone or	• Not recommended for patients with T1DM • Not recommended for use to improve glycemic control in adults *with T2DM* with an eGFR **< 45 mL/min/1.73m^2**	• Not recommended for patients with T1DM • Not recommended for use to improve glycemic control in adults *with T2DM* with an eGFR **< 30 mL/min/1.73m^2**	--

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		therapy for kidney disease	equivalent for kidney disease			
Pharmacology						
Target	SGLT1 and SGLT2[7]	SGLT2	SGLT2	SGLT2	SGLT2	SGLT1 and SGLT2
Mechanism of action	SGLT2 is the predominant transporter responsible for the majority of reabsorption of glucose from glomerular filtrate back into circulation. Inhibition of SGLT2 results in reduced renal reabsorption of glucose, a lower renal threshold for glucose, and an increase in urinary glucose excretion. Sodium reabsorption is also reduced, leading to increased delivery of sodium to the distal tubule, which may influence the following physiological functions: decreased intraglomerular pressure, lowering of preload and afterload of the heart, and down regulation of sympathetic activity.					See column to left regarding effect of SGLT2 inhibition. Inhibiting SGLT1 reduces *intestinal* absorption of glucose and sodium (likely contributes to diarrhea). The mechanism for sotagliflozin's CV benefits has not been established.
Pharmacokinetics						
Absorption	• Oral bioavailability is ~65% • Tmax ~ 1-2 h • High-fat meals have no effect; administer with or without food	• Oral bioavailability is ~78% • Tmax ~ 2 h • High-fat meals decrease Cmax and prolong Tmax, but do not affect AUC; administer with or without food	• Oral bioavailability not provided • Tmax ~ 1.5 h • High-fat meals slightly reduce AUC; administer with or without food	• Oral bioavailability is ~100% • Tmax ~ 1 h • High-fat meals decrease Cmax and prolong Tmax, but do not affect AUC; administer with or without food	• Oral bioavailability not provided • Tmax ~ 2-4 h • High-fat meals increase Cmax AUC; administer with or without food	• Oral bioavailability is ~25% • Tmax ~ 1-3 h • High-caloric meals increase Cmax AUC; administer not more than 1 h prior to the first meal of the day
Distribution	Protein binding ~ 99%	Protein binding ~ 91%	Protein binding ~ 86%	Protein binding ~ 94%	Protein binding ~ 93%	Protein binding ~ > 93%
Metabolism	• Primarily via *O*-glucuronidation (UGT1A9 and UGT2B4) to	• Primarily via *O*-glucuronidation (UGT1A9) to an inactive metabolite	• Primarily via *O*-glucuronidation (UGT2B7, UGT1A3, UGT1A8,	• Primarily via *O*-glucuronidation (UGT1A9 and UGT2B7) to	• Primarily via *O*-glucuronidation, (UGT1A9), and	• Primarily via *O*-glucuronidation, (UGT1A9), and

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	inactive metabolites • CYP3A4-mediated metabolism is a minor clearance pathway (7%)	• CYP-mediated metabolism is a minor clearance pathway	UGT1A9) to minor metabolite	inactive metabolites • CYP-mediated metabolism is a minor clearance pathway (12%)	CYP3A to a lesser extent	CYP3A to a lesser extent
Excretion	• 41.5% recovered in feces as canagliflozin; 10.2% recovered as metabolites • 33% excreted in urine (predominantly as inactive metabolites	• 15% recovered in feces as dapagliflozin; 6% recovered as metabolites • 75% excreted in urine (predominantly as inactive metabolites	• 41.2% recovered in feces (predominantly as empagliflozin) • 54.4% excreted in urine (predominantly as empagliflozin)	• 33.8% recovered in feces as ertugliflozin; 7.1% recovered as metabolites • 50.2% excreted in urine (predominantly as inactive metabolites	• 51.1% recovered in feces (predominantly as bexagliflozin) • 40.5% excreted in urine (as the 3'-O-glucuronide inactive metabolite)	• 37% recovered in feces (predominantly as sotagliflozin) • 57%% excreted in urine (as the 3'-O-glucuronide inactive metabolite)
Terminal half-life	10.6-13.1 h	12.9 h	12.4 h	16.6 h	12 h	21-35 h
Dosage and administration						
Prior to initiation	• Assess renal function • Assess volume status and correct volume depletion if needed					
Dosage (adults)	• **eGFR ≥ 60 mL/min/1.73m²**: 100 mg once daily; may increase to 300 mg once daily • **eGFR 30 to < 60 mL/min/1.73m²**: 100 mg once daily	• **eGFR ≥ 45 mL/min/1.73m²**: *For glycemic control in T2DM:* Initiate therapy at 5 mg once daily; increase to 10 mg once daily if needed for additional glycemic control	• **eGFR ≥ 30 mL/min/1.73m²**: *For glycemic control in T2DM:* 10 mg once daily; may increase to 25 mg daily for additional glycemic control *For all other indications:* 10 mg once daily	• **eGFR ≥ 45 mL/min/1.73m²**: Initiate therapy at 5 mg once daily; may increase to 15 mg once daily if additional glycemic control is needed	• **eGFR ≥ 30 mL/min/1.73m²**: 20 mg once daily • **eGFR < 30 mL/min/1.73m²**: Use is not recommended	• **eGFR ≥ 25 mL/min/1.73m²**: *All indications:* Initiate therapy at 200 mg once daily. Titrate dose to 400 mg daily as tolerated at least 2 wks after initiation.

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	• **eGFR < 30 mL/min/1.73m²**: Initiation not recommended; however, patients with albuminuria > 300 mg/d may continue 100 mg daily to reduce the risk of ESRD, doubling of Scr, CV death, and hospitalization for HF	*For all other indications:* 10 mg once daily • **eGFR 25 to < 45 mL/min/1.73m²**: *For glycemic control in T2DM:* Not recommended *For all other indications:* 10 mg once daily • **eGFR < 25 mL/min/1.73m²**: Initiation not recommended; however, patients may continue 10 mg once daily to reduce risk of eGFR decline, ESRD, CV death, and hospitalization for HF	• **eGFR < 30 mL/min/1.73m²**: *For glycemic control in T2DM:* Not recommended *Other indications:* Data are insufficient for initiating therapy in patients: ○ with *T2DM* and established CV disease with an eGFR < 30 mL/min/1.73m² ○ who have *HF* with an eGFR < 20 mL/min/1.73m² ○ *Note: Adult patients in the EMPA-REG-OUTCOME, EMPEROR-Preserved, EMPEROR-Reduced, and EMPA-KIDNEY trials were not required to discontinue therapy for worsening eGFR to < 20 mL/min/1.73m²*	• **eGFR < 45 mL/min/1.73m²**: Use is not recommended		• **eGFR < 25 mL/min/1.73m²**: No dosage adjustments are provided in product labeling. *Note: therapy was stopped in clinical studies in patients whose eGFR fell below 15 mL/min/1.73m² or who were initiated on chronic dialysis.*

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			or initiation of dialysis			
Dosage (pediatric patients)	NA	NA	• **eGFR ≥ 30 mL/min/1.73m²**: *For glycemic control in T2DM:* 10 mg once daily; may increase to 25 mg daily for additional glycemic control • **eGFR < 30 mL/min/1.73m²**: *For glycemic control in T2DM:* Not recommended *Note: patients with eGFR < 60 mL/min/1.73m² were not included in pediatric trials.*	NA	NA	NA
Dosage adjustments with concomitant UGT inducers (*eg, rifampin, phenytoin, phenobarbital, ritonavir*)	• **eGFR ≥ 60 mL/min/1.73m²**: Increase dosage to 200 mg once daily if patient tolerates 100 mg. Dosage may be increased to 300 mg once daily. • **eGFR < 60 mL/min/1.73m²**: Increase dosage to 200 mg once	--	--	--	--	--

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	daily if patient tolerates 100 mg.					
Route of administration	Oral					
Preferred time of administration	Prior to first meal of the day	Daily, with or without food	Morning, with or without food	Morning, with or without food	Morning, with or without food	Morning, not > 1 h before first meal of the day
Temporary interruption prior to surgery	3d	3 d	3 d	4 d	3 d	3d
HbA1c reduction[8-12]	SGLT2 inhibitors, as a class, offer a moderate / intermediate reduction in HbA1c, generally around 0.5-1%.					
Effect on weight[8,10-12]	SGLT2 inhibitors, as a class, typically contribute to a mild degree of weight loss, typically around 2 to 3 kg.					
Effect on blood pressure[10-12]	SGLT2 inhibitors, as a class, typically provide a slight reduction in systolic blood pressure, around 3 to 5 mmHg.					
Efficacy – cardiorenal outcomes[13-29]	**Outcome definitions** **MACE** = some variability across studies, but most commonly defined as a composite of CV death, nonfatal MI, or nonfatal stroke **HF** = generally consistent across studies; most commonly defined as a composite of CV death or hospitalization (or urgent visit) due to HF **Renal** = some variability across studies but most commonly defined as a composite of a sustained reduction in eGFR, RRT, eGFR < 15 mL/min/1.73m^2, or death from renal or CV disease **Key** **+++** = benefit demonstrated in ≥ 1 RCT evaluating as a primary endpoint; consistent findings in other trials and/or individual components of primary endpoint related to this outcome were also significantly different **++** = benefit demonstrated in ≥ 1 RCT evaluating as a primary endpoint, but may not be consistent across trials or individual component of composite endpoint for this endpoint did not consistently demonstrate a significant difference **+** = some data (eg, secondary endpoint) suggest possible benefit, trials evaluating as a primary outcome not available **-** = no significant difference demonstrated in clinical trials or clinical trials not available to assess this outcome *See Appendix A for study details and summary of evidence for further discussion of clinical trials evaluating cardiorenal outcomes, including a discussion on comparative efficacy*					
MACE	++	-	++	-	-	+
HF	+	+++	+++	+	-	+++
Renal	+++	+++	+++	-	+	-

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Safety						
Boxed warning	As individual agents, none of the SGLT2 inhibitors carry a boxed warning; however, canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are available in combination products containing metformin, which carries a boxed warning for lactic acidosis.[30]				None; bexagliflozin is not available in combination products containing metformin.	None; sotagliflozin is not available in combination products containing metformin.
Contraindications	• Hypersensitivity reaction (eg, anaphylaxis, angioedema) to the respective SGLT2 inhibitor or an excipient in the product					
Precautions	• **Volume depletion:** SGLT2 inhibitors may cause intravascular volume contraction. Patients with eGFR < 60 mL/min/1.73m^2, elderly, and patients on loop diuretics may be at increased risk. • **Ketoacidosis:** Reports of ketoacidosis have been identified in clinical trials and postmarketing surveillance in patients receiving SGLT2 inhibitors. Assess patients with signs and symptoms consistent with severe metabolic acidosis for ketoacidosis; ketoacidosis with SGLT2 inhibitors may be present even when blood glucose levels are < 250 mg/dL. Consider temporarily discontinuing SGLT2 inhibitors at least 3 d prior to surgery (at least 4 d prior for ertugliflozin). • **Urosepsis and pyelonephritis:** Treatment with SGLT2 inhibitors increases the risk for UTIs; serious UTIs including urosepsis and pyelonephritis have been reported in postmarketing reports. • **Hypoglycemia with concomitant use of insulin and insulin secretagogues:** SGLTs may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. • **Fournier's gangrene:** Necrotizing fasciitis of the perineum (Fournier's gangrene) has been reported in postmarketing surveillance in patients with DM receiving SGLT2 inhibitors. • **Genital mycotic infections:** SGLT2 inhibitors increase the risk of genital mycotic infections; uncircumcised males and patients with a history of genital mycotic infections may be at a higher risk.					
	• **Hypersensitivity reaction**: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported in patients on canagliflozin. These reactions generally occurred within hours to days following	--	• **Hypersensitivity reaction**: Hypersensitivity reactions, including angioedema, have been reported in patients on empagliflozin. • **Lower limb amputation**: An imbalance in the incidence of lower limb amputations has been observed	• **Lower limb amputation:** An increased risk of lower limb amputation was observed compared with placebo in the VERTIS-CV study for the 5 mg dose (5.7 vs. 4.7 events per 1000 patient-years) and 15 mg dose (6 vs.	• **Lower limb amputation:** An increased risk of lower limb amputation was observed compared with placebo in the BEST study (8.3 vs. 5.1 events per 1000 patient-years). Consider risk factors for amputation prior to initiating	--

	Generic name (brand name)					
	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
	initiation of therapy. • **Lower limb amputation:** An increased risk of lower limb amputation was observed compared with placebo in the CANVAS (5.9 vs. 2.8 events per 1,000 patient-years) and CANVAS-R (7.5 vs. 4.2 events per 1000 patient years) studies. The risk of amputation was greatest for patients with a history of prior amputation, PVD, neuropathy, and diabetic foot ulcers. A boxed warning for limb amputation was added to canagliflozin product labeling in 2017; however, this boxed warning was subsequently removed by FDA in 2020 after reviewing additional data. FDA concluded		in clinical studies with SGLT2 inhibitors. Across 4 clinical studies with empagliflozin the event rate of lower limb amputation was 5 event per 1000 patient-years compared with 4.3 event per 1000 patient-years in the placebo group. An increased risk of lower limb amputation was observed with empagliflozin compared with placebo in the EMPA-KIDNEY trial (4.3 vs 2.0 events per 1000 patient-years). Ensure preventative foot care and monitoring plans are in place for patients on empagliflozin.	4.7 events per 1000 patient years). The risk of lower limb amputation was 0.2% in patients receiving the 5 mg dose, 0.5% in patients receiving the 15 mg dose, and 0.1% in patients in the placebo group across 7 clinical trials evaluating the use of ertugliflozin. The risk of amputation may be higher in patients with a history of prior amputation, PVD, neuropathy, and diabetic foot ulcers.	therapy. Ensure preventative foot care and monitoring plans are in place for patients on bexagliflozin.	

	Generic name (brand name)					
	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
	that while the risk is still increased, it is lower than what was previously described.[31] Ensure preventative foot care and monitoring plans are in place for patients on canagliflozin. • **Bone fracture**: An increased risk of bone fracture was observed in the CANVAS trial, starting as early as 12 wks after initiation of therapy.					
Adverse reactions	Most common (incidence ≥ 5%) are female genital mycotic infections, urinary tract infection, and increased urination.	Most common (incidence ≥ 5%) are female genital mycotic infections, nasopharyngitis, and urinary tract infections.	Most common (incidence ≥ 5%) are female genital mycotic infections, and urinary tract infections.	Most common (incidence ≥ 5%) is female genital mycotic infections.	Most common (incidence > 5%) are female genital mycotic infections, urinary tract infection, and increased urination.	Most common (incidence ≥ 5%) are urinary tract infections, volume depletion, diarrhea, and hypoglycemia.
Drug-drug interactions (as reported in product labeling)	• **UGT inducers:** Reduce AUC of canagliflozin. Dose adjustment may be needed. • **Insulin or insulin secretagogues:** Increased risk of	• **Insulin or insulin secretagogues:** Increased risk of hypoglycemia with coadministration. • **Lithium:** Use with SGLT2 inhibitors may decrease	• **Diuretics:** Coadministration with empagliflozin may increase urine volume and frequency of voids, which might increase the risk for volume depletion.	• **Insulin or insulin secretagogues:** Increased risk of hypoglycemia with coadministration.	• **UGT inducers:** May significantly reduce exposure to bexagliflozin and lead to decreased efficacy.	• **UGT inducers:** May reduce exposure to sotagliflozin and lead to decreased efficacy. • **Digoxin:** Digoxin exposure may be increased with

	Generic name (brand name)					
	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
	hypoglycemia with coadministration. • **Digoxin:** Digoxin exposure may be increased with concomitant canagliflozin. Monitor digoxin levels. • **Lithium:** Use with SGLT2 inhibitors may decrease serum lithium concentrations.	serum lithium concentrations.	• **Insulin or insulin secretagogues:** Increased risk of hypoglycemia with coadministration. • **Lithium:** Use with SGLT2 inhibitors may decrease serum lithium concentrations.	• **Lithium:** Use with SGLT2 inhibitors may decrease serum lithium concentrations.	• **Insulin or insulin secretagogues:** Increased risk of hypoglycemia with coadministration. • **Lithium:** Use with SGLT2 inhibitors may decrease serum lithium concentrations.	concomitant sotagliflozin. Monitor digoxin levels. • **Lithium:** Use with SGLT2 inhibitors may decrease serum lithium concentrations.
Drug-lab interactions	• **Urine glucose test:** SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests; monitoring glycemic control with urine glucose tests is not recommended in patients receiving SGLT2 inhibitors. • **1,5-anhydroglucitol (1,5-AG) assay:** Monitoring glycemic control with 1,5-AG assay is not recommended in patients receiving SGLT2 inhibitors, as measurements will be unreliable while on therapy.					
Special populations						
Pregnancy and lactation	**Pregnancy** • Data are insufficient to determine the risk associated with using any of the SGLT2 inhibitors during pregnancy. • Based on animal data, use of SGLT2 inhibitors is not recommended during the second and third trimesters of pregnancy. Studies in rats with each of the SGLT2 inhibitors found increased kidney weights and renal and pelvic dilatations when the drugs were administered during a period of renal development corresponding to second and third trimesters in human pregnancy. **Lactation** Human data for lactation are not available for SGLT2 inhibitors. SGLT2 inhibitors are not recommended in women who are breastfeeding due to the potential for serious adverse reactions in the breastfed infant.					
Pediatric population	Safety and efficacy have not been established in patients < 18 y.	Safety and efficacy have not been established in patients < 18 y.	Empagliflozin is approved for use in patients ≥ 10 y to improve glycemic control in T2DM. Safety and efficacy have not been established in patients < 10 y.	Safety and efficacy have not been established in patients < 18 y.	Safety and efficacy have not been established in patients < 18 y.	Safety and efficacy have not been established in patients < 18 y.

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	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
Geriatric population	• Patients ≥ 65 y may be more likely to experience an AE related to reduced intravascular volume • Patients ≥ 65 y may also have smaller reductions in HbA1c compared with younger adults	• Patients ≥ 65 y receiving dapagliflozin for glycemic control experience more hypotension compared with younger patients in clinical studies • Safety and efficacy were similar in patients ≥ 65 y in the DAPA-HF, DAPA-CKD, and DELIVER studies	• Patients ≥ 75 y may be more likely to experience an AE related to reduced intravascular volume or a UTI • Patients ≥ 65 y with renal impairment receiving empagliflozin for glycemic control are expected to experience reduced glycemic efficacy • Safety and efficacy were similar in patients ≥ 65 y in EMPEROR-Reduced, EMPEROR-Preserved, and EMPA-KIDNEY studies	• Patients ≥ 65 y may be more likely to experience an AE related to reduced intravascular volume • Safety and efficacy were similar in patients ≥ 65 y in VERTIS-CV study	• No overall differences in efficacy were observed in patients ≥ 65 in clinical studies. Elderly patients may be at increased risk of adverse reactions related to volume depletion	• No overall differences in efficacy were observed in patients ≥ 65 in clinical studies. Elderly patients may be at increased risk of adverse reactions related to volume depletion.
Renal impairment	• Initiation is not recommended in patients with an eGFR < 30 mL/min/1.73m^2 • Patients with renal impairment may be at increased risk for hypotension and AKI • Efficacy and safety have not been evaluated in patients on	• Use for glycemic control in patients without CV disease or CV risk factors is not recommended in patients with an eGFR < 45 mL/min/1.73m^2 • Not studied in patients with an eGFR < 25 mL/min/1.73m^2 for any indication • Efficacy and safety have not been	• Use for glycemic control in patients without CV disease or CV risk factors is not recommended in patients with an eGFR < 30 mL/min/1.73m^2 • Not studied in patients with an eGFR < 20 mL/min/1.73m^2 for any indication • Efficacy and safety of initiating therapy	• Use is not recommended in patients with an eGFR < 45 mL/min/1.73m^2 • Efficacy and safety have not been evaluated in patients on dialysis. Avoid use.	• Use is not recommended in patients with an eGFR < 30 mL/min/1.73m^2 • Efficacy and safety have not been evaluated in patients on dialysis. Avoid use.	• Efficacy and safety have not been evaluated in patients with eGFR < 25 mL/min/1.73m^2 • Efficacy and safety have not been evaluated in patients on dialysis. Avoid use.

	Generic name (brand name)					
	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
	dialysis. Avoid use.	evaluated in patients on dialysis. Avoid use.	(for any indication) has not been evaluated in patients on dialysis. Avoid use. *Note: Adult patients in the EMPA-REG-OUTCOME, EMPEROR-Preserved, EMPEROR-Reduced, and EMPA-KIDNEY trials were not required to discontinue therapy for worsening eGFR to < 20 mL/min/1.73m^2 or initiation of dialysis.*			
Hepatic impairment	• Dosage adjustment is not necessary in *mild to moderate* hepatic impairment • Canagliflozin has not been evaluated in patients with *severe* hepatic impairment and is not recommended in this population	• Dosage adjustment is not necessary in hepatic impairment; however, dapagliflozin has not been studied in patients with *severe* hepatic impairment – assess benefit-risk in this population	• Dosage adjustment is not necessary in hepatic impairment	• Dosage adjustment is not necessary in *mild to moderate* hepatic impairment • Ertugliflozin has not been evaluated in patients with *severe* hepatic impairment and is not recommended in this population	• Dosage adjustment is not necessary in *mild to moderate* hepatic impairment • Bexagliflozin has not been evaluated in patients with *severe* hepatic impairment and is not recommended in this population	• Dosage adjustment is not necessary in *mild* hepatic impairment • Sotagliflozin has not been evaluated in patients with *moderate to severe* hepatic impairment and is not recommended in this population

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	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
How supplied						
Dosage form	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Strength	• 100 mg • 300 mg	• 5 mg • 10 mg	• 10 mg • 25 mg	• 5 mg • 15 mg	• 20 mg	• 200 mg • 400 mg
Storage	20˚C to 25˚C	20˚C to 25˚C	20˚C to 25˚C	20˚C to 25˚C	20˚C to 25˚C	20˚C to 25˚C
Combination products[32-41]	In combination with: • **Metformin:** Invokamet, Invokamet XR	In combination with: • **Metformin:** Xigduo XR • **Saxagliptin:** Qtern • **Saxagliptin and metformin:** Qternmet XR	In combination with: • **Metformin:** Synjardy, Synjardy XR • **Linagliptin:** Glyxambi • **Linagliptin and metformin:** Trijardy XR	In combination with: • **Metformin:** Segluromet • **Sitagliptin:** Steglujan	NA	NA
Financial information						
WAC (per tablet)[42]	• 100 mg: $20 • 300 mg: $20	**Brand Farxiga** • 5 mg: $19 • 10 mg: $19 **Authorized generic** • 5 mg: $13 • 10 mg: $13	• 10 mg: $20 • 25 mg: $20	• 5 mg: $12 • 15 mg: $12	• 20 mg: $4	• 200 mg: $20 • 400 mg: $20
Brand manufacturer participates in 340B Drug Pricing Program	Yes	Yes	Yes	Yes	No	Yes
Vizient contract	Yes	Yes	Yes	Yes	No	Yes
Generic availability	No	Yes (as authorized generic)	No	No	No	No
Anticipated LOE[43]	2027-28	2025	2034	2031	2034	2033

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	Canagliflozin (Invokana)[1]	**Dapagliflozin (Farxiga)[2]**	**Empagliflozin (Jardiance)[3]**	**Ertugliflozin (Steglatro)[4]**	**Bexagliflozin (Brenzavvy)[5]**	**Sotagliflozin (Inpefa)[6]**
Coverage considerations[44-49]						
Coverage	• Variable by payer • If covered, will likely require step therapy or prior authorization	• Generally, a preferred agent • Most insurance companies require step therapy depending on indication; some require prior authorization	• Generally, a preferred agent • Most insurance companies require step therapy depending on indication; some require prior authorization	• Generally, nonformulary / not listed • If covered, will likely require step therapy or prior authorization	• Generally, nonformulary / not listed • If covered, will likely require step therapy or prior authorization	• Generally, nonformulary / not listed • If covered, will likely require step therapy or prior authorization
Copay card	Yes	Yes	Yes	No	No	Yes
Free trial offer	Yes	Yes	No	No	No	Yes
Patient assistance program	Yes	Yes	Yes	No	No	Yes
Other	Available through Cost Plus Drug Company; estimated cost $8 per tablet (plus shipping and handling)	Generic product available through Cost Plus Drug Company; estimated cost of $13 per tablet (plus shipping and handling)	--	--	Available through Cost Plus Drug Company; estimated cost $2 per tablet (plus shipping and handling)	--
US percent market share in 2023[50]						
SGLT2 inhibitor alone	2.21%	33.25%	55.86%	1.4%	Data not available	0.1%
Combination products	0.31%	2.38%	4.43%	0.15%	NA	NA
Total market share	2.52%	35.63%	60.29%	1.55%	Data not available	0.1%* **approved May 2023*
Vizient CDBRM inpatient utilization in 2023	1100 cases	119 000 cases	178 000 cases	2 cases	Data not available	Data not available

Summary of evidence

Introduction

The first SGLT2 inhibitor, canagliflozin (Invokana), was approved in 2013 as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[1] Since that time, 5 other SGLT2 inhibitors – dapagliflozin (Farxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro), bexagliflozin (Brenzavvy), and sotagliflozin (Inpefa) – have been approved in the US. Sotagliflozin additionally inhibits SGLT1, and is the only agent in this class marketed as an SGLT1/2 inhibitor; however, some data indicate that canagliflozin also exhibits SGLT1 inhibition at approved doses.[6,7] All SGLT2 inhibitors, with the exception of sotagliflozin, share the indication specific to glycemic control in T2DM.[1-6] For patients with T2DM, sotagliflozin is indicated to reduce the risk of CV death, hospitalization for HF, and urgent HF visit in adults patients with CKD and other CV risk factors; sotagliflozin is not indicated for glycemic control alone.[6] As a class, SGLT2 inhibitors provide an intermediate reduction in HbA1c, around 0.5-1%, depending on background therapy.[8-12] Several meta-analyses[10,11] have found that at its highest dose of 300 mg, canagliflozin may offer a slightly greater reduction in HbA1c compared with other SGLT2 inhibitors; however, it is likely that other factors, such as cardiorenal outcomes data / indications, will guide SGLT2 inhibitor selection. SGLT2 inhibitors also typically result in a slight reduction in body weight (ie, 2-3 kg) and systolic blood pressure (ie, 3-5 mmHg). The SGLT2 inhibitors vary with regard to the FDA-approved indications related to cardiorenal outcomes. The proposed mechanism of actions for SGLT2 inhibitors for cardiorenal benefits are discussed in the comparative efficacy section below. The cardiorenal indications for the different SGLT2 inhibitors are driven by the results from pivotal studies for each of the respective agents; the outcomes of these trials are the focus of this review.

With the exception of an authorized generic version for dapagliflozin, none of the SGLT2 inhibitors are available in generic presentations. The authorized generic version of dapagliflozin is priced at approximately a 35% reduction off WAC compared with brand Farxiga. However, due to the significant rebates available for brand Farxiga (up to 60%), the authorized generic dapagliflozin may not offer a cost advantage to payers or pharmacies. Multiple abbreviated new drug applications for dapagliflozin have been filed with FDA, and these products are expected to enter the market in the second half of 2025. When this happens, it is expected that these generics will be available at 70 to 90% off the WAC of Farxiga. LOE dates for other SGLT2 inhibitors range from another 3 to 10 years out from 2024.[12]

Canagliflozin

CANVAS[13] and CREDENCE[14] are the pivotal trials evaluating cardiorenal outcomes data with canagliflozin. Both trials were specific to patients with T2DM. Data on cardiorenal outcomes with canagliflozin in patients without T2DM are lacking. The CANVAS program was compromised of 2 trials, CANVAS and CANVAS-R. Collectively, these trials included 10142 patients with T2DM and ASCVD or ≥ 2 CV risk factors. Patients with an eGFR < 30 mL/min/1.73m^2 and NYHA class IV HF were excluded. The primary outcome, a composite of CV death, nonfatal MI, and nonfatal stroke, was significantly reduced in patients who received canagliflozin compared with placebo. The individual components of the primary composite outcome were not significantly different, however. Other key secondary outcomes of interest included hospitalization for HF and a composite of CV death and hospitalization for HF, both of which were significantly reduced with canagliflozin compared with placebo. A secondary composite renal outcome was also evaluated, which included a sustained reduction in eGFR of ≥ 40%, RRT, or death from renal disease. Both the composite renal outcome and progression to albuminuria were reduced with canagliflozin compared with placebo.[13] The CREDENCE trial evaluated the use of canagliflozin in patients with T2DM and CKD. Patients with an eGFR < 30 mL/min/1.73m^2 and NYHA class IV HF were also excluded in this trial. The primary outcome was a composite renal outcome that included ESRD (RRT or eGFR < 15 mL/min/1.73m^2), doubling of Scr, or death from a renal or CV cause. Canagliflozin significantly reduced the risk of the primary composite renal outcome compared with placebo. For the individual components of the primary outcome, doubling of Scr and ESRD were significantly reduced with canagliflozin. CV death was not significantly different, and an insufficient number of patients died from renal causes in order to evaluate this outcome separately. Secondary CV outcomes reduced by canagliflozin included hospitalization for heart failure, a composite of CV death or hospitalization for HF, and a composite of CV death, MI, or stroke.[14]

Dapagliflozin

The pivotal trials evaluating cardiorenal outcomes with dapagliflozin include DECLARE-TIMI 58[15], DAPA-HF[16], DELIVER[17], and DAPA-CKD.[18] DECLARE-TIMI 58 evaluated 17160 patients with T2DM and ASCVD or ≥ 2 CV risk factors. Patients were excluded with an eGFR < 60 mL/min/1.73m^2. The trial had 2 coprimary endpoints, a composite of CV death, MI, or stroke and a composite of CV death or hospitalization for HF. The first coprimary endpoint did not reach statistical significance, but dapagliflozin reduced the risk of CV death or hospitalization due to HF compared with placebo. This appears to be driven by the reduction in hospitalization due to HF, which was significantly lower when evaluated separately, while no difference was observed for the risk of CV death alone. A composite renal outcome was evaluated as a secondary endpoint, which included a ≥ 40% sustained reduction in eGFR, ESRD, or death from renal or CV cause, and was significantly lower with dapagliflozin

compared with placebo.[15] DAPA-HF, DELIVER, and DAPA-CKD enrolled patients with or without diabetes. DAPA-HF evaluated the use of dapagliflozin in 4744 patients with HFrEF and NYHA class II-IV on standard therapy; the majority of patients were classified as NYHA class II (~67%). Patients were required to have an NT-proBNP ≥ 600 pg/mL (or ≥ 400 pg/mL in patients with a hospitalization due to HF in the past 12 mos and ≥ 900 pg/mL in patients with atrial fibrillation or atrial flutter). Approximately 42% of patients had T2DM. Patients with an eGFR < 30 mL/min/1.73m^2 and ADHF were excluded. The primary outcome, a composite of worsening HF or CV death, was significantly reduced with dapagliflozin compared with placebo. Additionally, both components of the primary composite outcome were significantly lower with dapagliflozin when evaluated individually. All-cause mortality was also significantly lower with dapagliflozin. A renal composite endpoint was evaluated, but was not significantly different between dapagliflozin and placebo.[16] DELIVER evaluated the use of dapagliflozin in 6263 patients with HFpEF and NYHA II-IV requiring at least intermittent diuretic therapy; the majority of patients were classified as NYHA class II (~75%). The mean LVEF was approximately 54%. Patients were required to have an NT-proBNP ≥ 300 pg/mL (or ≥ 600 pg/mL in patients with atrial fibrillation or atrial flutter). Approximately 45% of patients had T2DM. Patients with an eGFR < 25 mL/min/1.73m^2 were excluded. Patients were eligible for enrollment either as outpatients or during hospitalization of HF treatment. The primary outcome was a composite of worsening HF (hospitalization for HF or urgent HF) and CV death and was significantly lower in patients who received dapagliflozin compared with those who received placebo. This appears to be driven by a reduction in hospitalization for HF, given that the HR for urgent visit for HF and CV death both crossed 1. The change from baseline to month 8 in the KCCQ total symptom score was evaluated as a key secondary outcome and demonstrated a benefit in favor of the dapagliflozin group.[17] DAPA-CKD evaluated 4304 patients with CKD. Approximately 67% of patients had T2DM. Patients with an eGFR < 25 mL/min/1.73m^2 and NYHA class IV HF were excluded. The primary outcome was a composite renal outcome including a ≥ 50% sustained reduction in eGFR, ESRD, or death from renal or CV disease. Significantly fewer patients receiving dapagliflozin compared with placebo experienced the primary outcome. When the components of the composite outcome were evaluated individually, fewer patients receiving dapagliflozin experienced a sustained reduction in eGFR or ESRD. CV death was not significantly different and the number of deaths due to renal disease was insufficient to evaluate separately. Key secondary outcomes included a composite of CV death or hospitalization for HF and all-cause mortality.[18] Both outcomes were lower with dapagliflozin compared with placebo. Primary outcomes in DAPA-HF, DELIVER, and DAPA-CKD were consistent in pre-specified subgroups with and without diabetes.[16-18]

Dapagliflozin is also being evaluated for use in ADHF; use in this setting is off-label. DICTATE-AHF[51] and DAPA-RESPONSE-AHF[52] are both completed. Results for DAPA-RESPONSE-AHF are published, while available data for DICTATE-AHF was presented at the European Society of Cardiology Congress in August 2023. DICTATE-AHF evaluated diuretic efficiency, which factors in weight change and diuretic dose, as the primary outcome. The odds of achieving this outcome were in favor of the dapagliflozin group, but a significant difference was not demonstrated. DAPA-RESPONSE-AHF evaluated dyspnea score as the primary outcome and demonstrated a significant difference in favor of dapagliflozin compared with placebo. Rehospitalization rates were also lower in the dapagliflozin group. One notable limitation of both of these studies are the relatively small sample sizes (238 in DICTATE-AHF and 87 in DAPA-RESPONS-AHF). Further study is needed to better understand the use of dapagliflozin in the ADHF setting. DAPA ACT HF-TIMI 68[53] (NCT04363697), a large RCT targeting 2400 patients, is also evaluating ADHF, but results are not yet available.

Empagliflozin

EMPA-REG-OUTCOME[19] evaluated the use of empagliflozin in 7020 patients with T2DM and ASVCD. Patients were excluded with an eGFR < 30 mL/min/1.73m^2. The primary outcome, a composite of CV death, nonfatal MI, or nonfatal stroke, was significantly reduced in patients who received empagliflozin compared with placebo. CV death alone was lower with empagliflozin, but no difference was observed for nonfatal MI or stroke when evaluated separately. Key secondary outcomes included hospitalization for HF, a composite of CV death or hospitalization for HF, and all-cause mortality, all of which were lower with empagliflozin compared with placebo.[19] A pre-specified analysis of renal outcomes was published separately. Empagliflozin reduced the risk of the composite renal outcome – doubling of Scr, RRT, or death from renal disease – as well as progression to macroalbuminuria compared with placebo.[20] EMPEROR-Reduced[21] and EMPEROR-Preserved[22] evaluated the use of empagliflozin in heart failure patients, with or without diabetes. EMPEROR-Reduced evaluated 3730 patients with HFrEF and NYHA class II-IV; the majority of patients were classified as NYHA class II (~75%). Patients were required to have a NT-proBNP ≥ 600 with LVEF ≤ 30%; patients with higher LVEF had higher NT-proBNP requirements, up to 2,500 pg/mL for LVEF 36-40%. This criteria was established in order to enroll patients at increased risk of a HF event. NT-proBNP requirements in the EMPEROR-Reduced trial were the highest among the key studies evaluating SGLT2 inhibitors in a HF population. T2DM was present in approximately 50% of patients at baseline. Patients with an eGFR < 20 mL/min/1.73m^2 and ADHF were excluded. Empagliflozin reduced the risk of the primary composite outcome of CV death or hospitalization due to HF compared with placebo. This was largely driven by the reduction in hospitalization for HF; no difference was found for CV death or all-cause mortality when evaluated as individual outcomes. A secondary composite renal outcome was also evaluated. Patients receiving empagliflozin were less likely to require RRT or experience a sustained reduction in eGFR (defined as a sustained reduction in eGFR of ≥ 40% or sustained eGFR < 15 mL/min/1.73m^2 with a baseline eGFR ≥

30 mL/min/1.73m^2 or < 10 mL mL/min/1.73m^2 with a baseline eGFR < 20 mL/min/1.73m^2).[21] EMPEROR-Preserved evaluated 5988 patients with HFpEF and NYHA class II-IV; the majority of patients were classified as NYHA class II (~82%). Overall, two-thirds of patients had a LVEF > 50%; the median LVEF was 54%. Patients were required to have a NT-proBNP ≥ 300 pg/mL (or ≥ 900 pg/mL in patients with atrial fibrillation). T2DM was also present in approximately 50% of patients at baseline in EMPEROR-Preserved. Patients with an eGFR < 20 mL/min/1.73m^2 and ADHF were excluded. Significantly fewer patients receiving empagliflozin experienced the primary composite outcome of CV death or hospitalization due to HF compared with placebo. Similar to the findings in EMPEROR-Reduced, this outcome appears to be driven by the reduction in hospitalization due to HF; CV death and all-cause mortality were not significantly different compared with placebo. The same composite renal outcome evaluated in EMPEROR-Reduced was also evaluated in EMPEROR-Preserved, but a significant difference was not observed.[22] The findings for the primary outcomes in both EMPEROR-Reduced and EMPEROR-Preserved were consistent regardless of whether patients had T2DM.[21,22,54] EMPA-KIDNEY evaluated 6609 patients with CKD. Patients were required to either have an eGFR between 20 and 44 mL/min/1.73m^2 or an eGFR between 45 and 89 mL/min/1.73m^2 with an UACR ≥ 200 mg/g. Overall, the mean eGFR of patients enrolled in the trial was ~37 mL/min/1.73m^2. T2DM and CV disease were present in approximately 46% and 26% of patients at baseline, respectively. The trial was stopped early following an interim analysis in which conditions for stopping were met (ie, HR and p-values were below the prespecified thresholds). The primary outcome was a composite renal outcome including a ≥ 40% sustained reduction in eGFR from baseline, a sustained decrease in eGFR to <10 mL/min/1.73m^2, ESRD, or death from renal or CV disease. Significantly fewer patients receiving empagliflozin compared with placebo experienced the primary outcome. When the components of the composite outcome were evaluated individually, kidney disease progression was significantly reduced with empagliflozin compared with placebo; ESRD, eGFR parameters, and death from renal causes were evaluated together within the kidney disease progression outcome that was reported. Death from CV causes was not significantly different between groups. The results for the primary composite outcome were consistent among patients with and without T2DM.[23]

Empagliflozin has also been evaluated for use in ADHF; use in this setting is off-label. EMPULSE[55] and EMPAG-HF[56] are published trials evaluating the use of empagliflozin for ADHF. EMPULSE evaluated the use of empagliflozin in 530 patients admitted for acute HF following clinical stabilization (median time 3 days from hospitalization). More patients treated with empagliflozin, compared with placebo, achieved the primary outcome of clinical benefit, a composite outcome which included death, number of HF events, time to first HF event, and change in KCCQ score.[55] EMPAG-HF was a smaller study in 60 patients randomized to empagliflozin or placebo in addition to standard medical care within 12 hours of hospitalization for ADHF. The addition of empagliflozin increased median urine output by 25% over 5 days without significantly affecting renal function.[56] EMPA-HF[57] will evaluate the use of empagliflozin in acute HF before clinical stabilization; study rationale and design are published.

Ertugliflozin

VERTIS-CV[24] is the key study evaluating cardiorenal outcomes with ertugliflozin. VERTIS-CV included 8246 patients with T2DM and ASCVD. Patients with an eGFR < 30 mL/min/1.73m^2 and NYHA class IV HF were excluded. The original primary objective was to demonstrate noninferiority with placebo for a composite outcome of CV death, nonfatal MI, or nonfatal stroke.[58] Following the publication of EMPA-REG OUTCOME, the protocol for VERTIS-CV was amended to include a superiority analysis for the cardiorenal outcomes and to double the sample size.[24] EMPA-REG OUTCOME[19] as well as CANVAS[13] and DECLARE-TIMI 58[15] were also designed as noninferiority studies with prespecified criteria for evaluating superiority. Ertugliflozin failed to demonstrate superiority vs placebo for the primary composite endpoint, as well as the first key secondary composite outcome of CV death or hospitalization due to HF. As a result of the prespecified hierarchical testing procedure, further statistical analysis of outcomes was not performed; however, HRs are provided for other secondary outcomes. The confidence interval for hospitalization due to HF did not cross 1 when ertugliflozin was compared with placebo. Other outcomes, including a renal composite outcome were not different with ertugliflozin compared with placebo. The reason for the results in VERTIS-CV not reaching significance are unclear. The baseline characteristics of patients in VERTIS-CV were similar to trials with other SGLT2 inhibitors that evaluated similar outcomes. Additionally, the rate of MACE seen in VERTIS-CV is also similar to what has been observed in other trials.[24]

Bexagliflozin

Studies evaluating cardiorenal outcomes as the primary efficacy endpoint for bexagliflozin are not available. Available clinical studies evaluated glycemic control via HbA1c reduction as the primary outcome. However, the BEST[25,26] trial evaluated the use of bexagliflozin for glycemic control in patients with increased CV risk and the C-448[27] trial evaluated the use of bexagliflozin for glycemic control in patients with renal impairment. Cardiorenal outcomes were evaluated as secondary endpoints in these trials and are discussed here. BEST included 1701 patients with T2DM and either an established history of CVD (ie, ASCVD or HF) or multiple (≥ 2) risk factors for CVD (ie ≥ 55 y with T2DM ≥ 10 y, controlled HTN, smoker, reduce kidney function, dyslipidemia). ASCVD was present in 63% of patients, HF was present in 15% of patients, and 23% of patients had ≥ 2 CV risk factors. The BEST trial is not published; however some results are available in a published abstract and are posted on ClinicalTrials.gov. MACE (including CV death, MI, stroke, and unstable angina) as well as a composite of CV death and hospitalization for HF were reported as secondary

outcomes. Neither outcome demonstrated a significant difference compared with placebo.[25,26] This study was not powered to evaluate cardiorenal outcomes, so definitive conclusions on the effect of bexagliflozin on these outcomes cannot be drawn. C-448 evaluated the use of bexagliflozin in 312 patients with T2DM and an eGFR of 30 to 59 mL/min/1.73m^2; the average eGFR was 45 mL/min/1.73m^2. Approximately 38% of patients had a UACR of 30 to <300 mg/g and 25% of patients had macroalbuminuria (UACR ≥ 300 mg/g). Albuminuria was evaluated as a secondary outcome as the geometric mean reduction in UACR. Treatment with bexagliflozin demonstrated a significant reduction in UACR at 24 weeks.[27]

Sotagliflozin

SOLOIST-WHF[28] evaluated the use of sotagliflozin in 1222 patients with T2DM recently hospitalized for HF. There was no requirement for a specific cut-off of LVEF to be eligible for the trial; however, the majority of the patients in the study had HFrEF. The median LVEF was 35% and 79% of patients had an LVEF <50%. Patients were required to be clinically stable prior to randomization. Study treatment was started either before or within 3 days of hospital discharge. The trial was ended early due to loss of funding from the sponsor. The initial estimated sample size target for enrollment was 4000 patients. The original primary endpoint was first occurrence of CV death or hospitalization for HF. However, due to the trial ending early, the primary endpoint was changed to a composite of CV death, hospitalization for HF, or urgent visit for HF in order to increase the power of the trial. Sotagliflozin demonstrated a significant difference for the primary composite outcome compared with placebo. When evaluated individually, hospitalizations and urgent visits for HF were significantly lower with sotagliflozin, but no significant difference was found for CV death. Additionally, a combined MACE and HF outcome that included CV death, nonfatal MI, nonfatal stroke, and hospitalization for HF was significantly lower in favor of sotagliflozin compared with placebo. Results for MI and stroke are not reported separately. SCORED[29] evaluated the use of sotagliflozin 10584 patients with T2DM with CKD at increased CV risk. The median eGFR of patients was ~45 mL/min/1.73m^2; patients were excluded if they had an eGFR <25 mL/min/1.73m^2. Approximately 89% of patients had ≥ 1 major CV risk factor and 31% of patients had a history of HF. This trial was also stopped early due to loss of funding from the sponsor. The study originally had 2 co-primary endpoints, which were first occurrence of MACE (CV death, nonfatal MI, or nonfatal stroke) and first occurrence of CV death or hospitalization for HF. Due to the trial ending early, the primary endpoint was adjusted since the number of events was less than the planned number of events determined during trial design. The primary endpoint was changed to a composite of the total number of CV deaths, hospitalizations for HF, and urgent visits for HF. Compared with placebo, sotagliflozin significantly reduced the incidence of the primary endpoint. Hazard ratios for the initial co-primary endpoints also did not cross 1, but formal statistical analysis was not performed due to a nonsignificant finding in a secondary outcome in a preceding analysis in the hierarchical structure. When the components of the adjusted primary outcome were evaluated individually, hospitalizations or urgent visits for HF were significantly reduced with sotagliflozin compared with placebo, while no statistical difference was found for the incidence of CV death. A composite renal endpoint was also evaluated as a secondary outcome. No difference (ie, HR crossed 1) was found in the first occurrence of ≥ 50% decrease in eGFR from baseline, long-term dialysis, renal transplantation, or sustained eGFR < 15 mL/min/1.73m^2 between sotagliflozin and placebo; however, formal statistical analysis of this outcome was not performed due to hierarchical testing. Both SOLOIST-WHF and SCORED required patients to have T2DM. In contrast, trials evaluating HF and renal outcomes as primary endpoints with dapagliflozin and empagliflozin did not require patients to have T2DM. However, sotagliflozin is approved for use in HF without the requirement of having T2DM. Use in patients with CKD is approved for use in patients with T2DM and other CV risk factors only.

Comparative efficacy

The question of whether or not SGLT2 inhibitors can be viewed as having a class effect for cardiorenal outcomes is of interest. While the drugs in this class all share a similar mechanism of action, this does not necessarily guarantee each drug will exert identical physiological effects. For example, statins differ in degree of potency for lipid lowering effects, despite sharing the same mechanism of action. To explore the question of class effect for SGLT2 inhibitors with regard to cardiorenal outcomes, both the pharmacology of the individual agents and comparative literature need to be considered.

All 6 agents in this drug class inhibit SGLT2, which is the predominant transporter responsible for the reabsorption of glucose from glomerular filtrate back into circulation. SGLT2 inhibition also results in a reduction in sodium reabsorption which contributes to decreased intraglomerular pressure, a reduction in preload and afterload of the heart, and down regulation of sympathetic activity.[1-6] Other potential mechanisms of action and effects of SGLT2 inhibition include, but are not limited to, reductions in blood pressure, weight loss, alterations in cardiac metabolism, interactions with the Na+/H+ ion exchanger in the heart, reduced arterial stiffness, improvement in oxygen supply through increased red-cell mass, decreased uric acid, and a reduction in inflammation and oxidative stress.[29,59,60] Sotagliflozin is the only drug in this class marketed in the US as an SGLT1/SGLT2 inhibitor. However, canagliflozin has also been shown to inhibit SGLT1 as well.[7] Canagliflozin and sotagliflozin have been collectively referred to as non-selective for SGLT2, while other agents in this class are considered to be selective for SGLT2.[60] SGLT1 receptors are present in the intestines and heart.[61] Inhibition of SGLT1 may contribute to further reductions in sodium and glucose uptake which could positively affect cardiac preload and afterload

resulting in enhanced cardioprotective effects.[60] Mendelian randomization data have suggested a possible association with SGLT1 inhibition and decreased rates of CV events.[29] There is therefore at least a theoretical basis for potential differences between the agents in this drug class based on the differences in SGLT receptor selectivity.

Head-to-head trials comparing cardiorenal outcomes for the SGLT2 inhibitors are not available. There are hundreds of published meta-analyses evaluating the effect of SGLT2 inhibitors which pool data across individual agents to assess the impact of the agents as a class on various outcomes, including cardiorenal endpoints. This indicates that there is some assumption that these agents may exert a class effect to a degree. However, a limitation of this approach is that only agents for which data exists (ie, RCTs evaluating a given outcome have been conducted) can be used for pooled estimates. Therefore, SGLT2 inhibitors without such data (eg, bexagliflozin) will not be represented. Unsurprisingly, pooled analyses of agents that have demonstrated benefit for a given cardiorenal outcome individually have also demonstrated benefit in the pooled analyses. For example, a meta-analysis[62] published in the *Lancet* in 2022 pooled data from DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF and found that SGLT2s reduced the risk for CV death or hospitalization due to HF. This finding is expected given that each these individual trials evaluated this outcome as the primary endpoint and found a significant difference compared with placebo for the respective SGLT2 inhibitor assessed. However, the absence of data for canagliflozin and bexagliflozin in this analysis makes it difficult to definitely conclude this is a benefit that extends to all agents in this drug class. Additionally, this type of analysis does not allow for determination of whether or not there is a difference in efficacy within a given outcome across the individual SGLT2 inhibitors.

Several meta-analyses have attempted to indirectly compared SGLT2 inhibitors across cardiorenal outcomes. For the purpose of this discussion, meta-analyses published prior to 2023 are not considered since they would be less likely to have been able to include the most current body of published evidence for cardiorenal outcomes in SGLT2 inhibitors. A PubMed search identified 5 articles that met the criteria of including an indirect comparison of at least 2 or more SGLT2 inhibitors for cardiorenal outcomes. The meta-analyses must also have included data from the respective pivotal cardiorenal outcomes trials for the individual SGLT2 inhibitors assessed. Most of the analyses focused on MACE or HF outcomes; however, one paper specifically compared renal outcomes.[63] Indirect head-to-head comparisons were performed in addition to ranking the SGLT2 inhibitors by treatment effect across outcomes of interest. Most commonly, treatment effects were ranked by calculating the surface under the cumulative ranking curve (SUCRA); however, 1 article[64] used a Markov chain Monte Carlo method. SUCRA is a Bayesian summary of rank which represents the estimated proportion of treatments expected to be worse relative to the treatment of interest. The SUCRA value is the ratio of the area under the cumulative ranking curve to the entire area in the plot in which a higher value corresponds with a higher rank.[65] Chen, HB et al[64] conducted an analysis of 5 pivotal trials for dapagliflozin, empagliflozin, or sotagliflozin assessing patients with HF. Sotagliflozin was ranked the highest for the composite outcome of CV death or hospitalization for HF, and dapagliflozin was ranked the highest for all-cause and CV mortality based on a Markov chain Monte Carlo model. However, the authors concluded that no overall significant differences in major efficacy outcomes were found between dapagliflozin, empagliflozin, and sotagliflozin. Kongmalai et al[66] evaluated 11 trials and indirectly compared canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin across MACE and HF outcomes. Based on SUCRA rankings, the authors concluded that canagliflozin may be preferred in patients with T2DM and HF, while analysis of HF-specific trials suggested that sotagliflozin may be preferred. Ghosal et al[67] and Chen, JY et al[60] are the most comprehensive meta-analyses identified which provide indirect comparisons across the SGLT2 inhibitors for cardiorenal outcomes. Ghosal et al included all 13 pivotal trials evaluating canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, and sotagliflozin for cardiorenal outcomes (see Appendix A). Chen, JY et al includes the same 13 pivotal trials in addition to the EMPULSE trial evaluating empagliflozin in acute HF. Ghosal et al focused specifically on the outcome of CV death and found that in patients with ASCVD or multiple CV risk factors empagliflozin was favored. In patients with HF, dapagliflozin was favored in the SUCRA analysis.[67] Chen, JY et al evaluated various MACE and HF outcomes and found that the SGLT2 inhibitor favored varied across outcomes and subgroups evaluated. Empagliflozin was favored over dapagliflozin for all-cause mortality in patients with T2DM. Sotagliflozin was favored for the outcome of CV death or hospitalization for HF in the subgroup of patients with HF, while canagliflozin was favored for this outcome in the subgroup without HF. Sotagliflozin was favored in the SUCRA ranking when MACE outcomes were assessed. Chen, JY et al also evaluated MACE outcomes based on SGLT2 selectivity. Canagliflozin and sotagliflozin were considered nonselective while empagliflozin, dapagliflozin, and ertugliflozin were classified as SGLT2 selective inhibitors. Nonselective SGLT2 inhibitors lowered the risk of MACE in HF patients significantly more than selective SGLT2 inhibitors.[60] This is consistent with a previous meta-analysis by Täger et al[68] that evaluated SGLT2 inhibitors based on degree of SGLT2 selectivity in patients with HF. Finally, Ma et al[63] conducted a meta-analysis of 30 trials to indirectly compare canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and tofogliflozin – the latter 2 SGLT2 inhibitors are not approved in the US – for renal outcomes in patients with T2DM. Canagliflozin, followed by empagliflozin, were ranked the highest via the SUCRA method. However, given the requirement for patients to have T2DM in the studies included in this meta-analysis, DAPA-CKD and EMPA-KIDNEY were not included, both of which are pivotal trial for renal outcomes with dapagliflozin and empagliflozin, respectively.

Across the most recent indirect comparisons of SGLT2 inhibitors, the specific agent favored varied between studies and outcomes evaluated. Sotagliflozin was most commonly, but not unanimously, favored for outcomes related to HF. This may be explained by the inclusion of the SOLOIST-WHF trial, which had the largest ARR in a composite HF outcome of any of the SGLT2 agents (all patients in this trial were recently hospitalized for HF, so it is possible that baseline risk in these patients could have been different compared with HF trials evaluating other SGLT2 inhibitors).[28] Additionally, the finding by Chen, JY et al[60] that nonselective SGLT2 inhibitors (ie, SGLT1/2 inhibition) demonstrated improved MACE outcomes in HF patients aligns with the potential added theoretical benefits of SGLT1 inhibition. In the 2 most comprehensive meta-analyses, empagliflozin was favored in outcomes related to death, including all-cause mortality in patients with T2DM and CV death in patients with high CV risk. EMPA-REG-OUTCOME[19] was the only cardiorenal outcomes trial of an SGLT2 inhibitor to evaluate MACE as a primary outcome which demonstrated a significant difference in the primary outcome as well as both CV death and all-cause mortality alone. However, compared with other studies, EMPA-REG-OUTCOME may have included patients at greater CV risk given that the inclusion criteria required patients to have established ASCVD, while other similar studies required either ASCVD or CV risk factors. This could suggest a potential for greater benefit in secondary vs primary prevention. The single analysis which evaluated renal outcomes favored canagliflozin in patients with T2DM.

Indirect comparisons have important limitations that need to be considered. While some analyses included subgroup comparisons, the underlying assumption is that the SGLT2 inhibitor agent is the primary variable that would explain any differences observed. However, there are many other potential covariates, such as biochemical parameters and differences in patient risk factors that could explain variance in outcomes found across trials. For example, some trials required patients to have T2DM, while others did not. Trials also varied with regard to CV risk and presence and/or type of HF. Since these analyses used study level data rather than individual patient data, they were unable to adequately explore potential differences in baseline factors that could confound the results. Additionally, not all trials used the same definitions for the composite outcomes. While composite HF outcomes were generally similar across trials, MACE and renal composite endpoints were more variable. The individual SGLT2 inhibitors were also not all equally represented due to the availability of published literature for the different agents. For example, ertugliflozin only had 1 trial included when it was part of these analyses, and bexagliflozin was not included in any of the analyses. As a result, individual analyses for specific outcomes in these indirect comparisons were only possible for studies in which those outcomes were reported. Therefore, SGLT2 inhibitors that lack studies with those particular outcomes are either not represented or underrepresented. Large, head-to-head studies are needed in order to truly determine if there are meaningful differences in outcomes between the SGLT2 inhibitors.

Overall, no definitive conclusions can be made with regard to whether or not identical cardiorenal outcomes can be expected across all the SGLT2 inhibitors. There is at least a theoretical basis as to why these agents may differ in their physiological effects based on differences in selectivity for SGLT2. Due to the variable findings across individual cardiorenal outcomes studies, the lack of or limited data for ertugliflozin and bexagliflozin, and the limitations of the indirect comparisons discussed above, no absolute conclusions can be made with regard to comparative effectiveness of these agents for cardiorenal outcomes based on the current body of evidence. Accordingly, published guidelines, summarized below, advocate for the use of SGLT2 inhibitors with proven benefit for the respective disease state.

Guideline recommendations

The 2024 ADA Standards of Medical Care in Diabetes recommend a patient-centered, shared clinical decision-making approach to the selection of pharmacologic agents for patients with T2DM. ADA recommends that the effects of treatment options on CV and renal comorbidities be considered. SGLT2 inhibitors are recommended in patients with T2DM, with, or at risk of, ASCVD, HF, or CKD. For each of these disease states, ADA recommends selecting an SGLT2 with proven benefit. For ASCVD, canagliflozin and empagliflozin are the SGLT2s identified by ADA as having a proven benefit. Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are listed as SGLT2 inhibitors benefit in HF. Previously, canagliflozin and ertugliflozin were not included on this list for HF. Neither canagliflozin nor ertugliflozin has a HF-specific, FDA-labeled indication (ie, irrespective of T2DM); however, clinical trials did suggest a potential benefit in HF with each agent when HF outcomes were evaluated as secondary endpoints. A discussion of HF outcomes with sotagliflozin is included in the text, but it is not specifically listed in Table 9.2 as an SGLT2 with benefit for HF; however, sotagliflozin does have data to support benefit in HF. For CKD, canagliflozin, dapagliflozin, and empagliflozin are the agents listed by ADA as having a proven benefit.[8] The AACE 2023 guidelines provide similar recommendations to the ADA 2024 guidelines, with the exception of a preference for GLP1-RA in patients with T2DM and ASCVD or a high CV risk. SGLT2 inhibitors with proven benefit may be used as an alternative to GLP1-RA with proven benefit as first-line therapy in patients with ASCVD or high CV risk. SGLT2 inhibitors with proven benefit are recommended as first-line therapy in patients with HF or CKD. SGLT2 inhibitors with proven benefit in ASCVD identified by AACE 2023 include canagliflozin and empagliflozin. Individual SGLT2 agents with proven benefit are not specifically mentioned for HF and CKD.[69]

Other guidelines, not specific to T2DM, have addressed the use of SGLT2 inhibitors. SGLT2 inhibitors are addressed in the 2022 AHA/ACC/HFSA guideline for the management of HF. AHA/ACC/HFSA recommends the use of SGLT2 inhibitors as a class 1a recommendation in patients with HFrEF, a class 2a recommendation in patients with HF with mildly reduced ejection fraction, and a class 2a recommendation in patients with HFpEF; these recommendations are made regardless of whether or not a patient has T2DM. Empagliflozin and dapagliflozin are the primary agents discussed within the guideline. Canagliflozin and sotagliflozin are also mentioned in text, but this guideline was published prior to the FDA-approval of sotagliflozin.[59] KDIGO 2022 guidelines for diabetes management in patients with CKD recommend the use of an SGLT2 inhibitor in patients with T2DM, CKD, and an eGFR ≥ 20 mL/min/1.73m^2. Once an SGLT2 inhibitor is initiated, the guidelines note that therapy may be continued if eGFR falls below the recommended threshold as long as treatment is tolerated or the patient undergoes a renal transplant. SGLT2 inhibitors listed as having a proven benefit in this patient population the KDIGO 2022 guidelines include canagliflozin, dapagliflozin, and empagliflzoin.[70] Bexagliflozin is not discussed in any of the above guidelines.

Summary

The SGLT2 inhibitors as a class provide an intermediate reduction in HbA1c of approximately 0.5-1%. Canagliflozin, dapagliflozin, and empagliflozin are FDA approved for different cardiorenal indications based on the results of pivotal trials evaluating cardiorenal outcomes. Ertugliflozin and bexagliflozin are not approved for use outside of glycemic control in patients with diabetes. Across trials, cardiorenal outcomes evaluated can be classified as MACE-, HF-, or renal-related outcomes. Evidence for benefit in cardiorenal outcomes appears to be the greatest for HF- and renal-related outcomes when evaluating the primary outcomes across trials. A renal composite outcome was the primary outcome in the CREDENCE trial with canagliflozin, the DAPA-CKD trial with dapagliflozin, and the EMPA-KIDNEY trial with empagliflozin. The estimated ARR for the renal composite outcome was 4.3%, 5.3%, and 3.8% respectively. A HF-related outcome was the primary outcome in the EMPEROR-Reduced (HFrEF) and EMPEROR-Preserved (HFpEF) trials with empagliflozin, the DAPA-HF (HFrEF) and DELIVER (HFpEF) trials with dapagliflozin, and the SOLOSIT-WHF (predominantly HFrEF) and SCORED (not predominantly a HF population; 31% of patients had HF) trials with sotagliflozin. The estimated ARR for the primary HF-related outcome was 5.4% in EMPEROR-Reduced, 3.2% in EMPEROR-Preserved, 5% in DAPA-HF, 3.1% in DELIVER, 17.5% in SOLOIST-WHF, and 2.5% in SCORED. There were 4 key trials which evaluated a composite MACE outcome as a primary outcome. The CANVAS trial with canagliflozin and the EMPA-REG OUTCOME trial with empagliflozin demonstrated statistically significant differences in this outcome; however, the estimated ARR for this outcome was 1.1% and 1.6%, respectively. Additionally, the individual components of the MACE outcome were not significantly different in the CANVAS trial, and only 1 out of 3 components (ie, CV death) of the primary outcome was significantly different in the EMPA-REG OUTCOME trial. The other 2 trials which included MACE as a primary outcome did not demonstrate a significant difference with the respective SGLT2 inhibitors compared with placebo. These trials include DECLARE-TIMI 58 with dapagliflozin, which included a composite MACE outcome as a co-primary outcome, and VERTIS-CV with ertugliflozin. While these studies are not head-to-head, the EMPA-REG OUTCOME trial demonstrated the largest ARR in a primary composite MACE outcome. Patients in this trial were included if they had established ASCVD, while patients in the CANVAS and DECLARE-TIMI 58 trials were included with ASCVD or if they had ≥ 2 risk factors for ASCVD, indicating a possible difference in CV risk across the trial populations. VERTIS-CV, however, also limited enrollment to patients with established ASCVD, similar to EMPA-REG OUTCOME, but did not find a statistical difference for a primary composite MACE outcome. The SCORED trial with sotagliflozin was originally designed to evaluate a MACE outcome as a co-primary endpoint; however the primary outcome was revised following a loss of funding from the study sponsor. When evaluated as a secondary endpoint, MACE events were reduced with sotagliflozin compared with placebo. Clinical trials evaluating cardiorenal outcomes as a primary endpoint are not available for bexagliflozin. Dapagliflozin, empagliflozin, and sotagliflozin are approved for use in HF in patients with or without diabetes; all 3 agents are approved in this population without regard to ejection fraction. However, it is important to note that the majority of HF patients evaluated in clinical studies with sotagliflozin had HFrEF. Dapagliflozin and empagliflozin are the only SGLT2 inhibitors with stand-alone indications for use in CKD. Empagliflozin is the only SGLT2 inhibitor approve for use in pediatric patients; however, use in this population is for glycemia control only. Head-to-head trials comparing the SGLT2 inhibitors are lacking, and meta-analyses providing indirect comparisons of the SGLT2 inhibitors have produced differing results. With regard to the question of class effect, no definitive conclusions can be made based on the current body of evidence as to whether or not identical cardiorenal outcomes can be expected across all the SGLT2 inhibitors.SGLT2 inhibitors are first-line treatment options across various clinical practice guidelines for T2DM, CKD, and HF. ADA guidelines recommend the use of SGLT2 inhibitors with proven benefit for cardiorenal indications depending on patient-specific risk factors and comorbidities. AACE guidelines offer similar guidance for the use of SGLT2 inhibitors patients with T2DM and relevant risk factors. ACC/AHA/HFSA guidelines recommend the use of SGLT2 inhibitors in patients with HFrEF and HFpEF.

Abbreviations: AACE = American Association of Clinical Endocrinologists; ACE = American College of Endocrinology; ACC = American College of Cardiology; ACEi = angiotensin-converting enzyme inhibitor; ADA = American Diabetes Association; ADHF = acute decompensated heart failure; AE = adverse event; AHA = American Heart Association; AKI = acute kidney injury; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; AUC = area under the curve; CABG = coronary artery bypass graft surgery; CI = confidence interval; CKD = chronic kidney disease; Cmax = maximum concentration; CrCl = creatinine clearance (estimate via Cockroft-Gault equation); CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; DB = double-blind; DKA = diabetic ketoacidosis; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GLP-1 = glucagon-like peptide-1; HF =

heart failure; HFpEF = heart failure with preserved ejection fraction (LVEF > 40%); HFrEF = heart failure with reduced ejection fraction (LVEF ≤ 40%); HFSA = Heart Failure Society of America; HR = hazard ratio; KCCQ = Kansas City cardiomyopathy questionnaire; KDIGO = Kidney Disease: Improving Global Outcomes; LFT = liver function test; LOE = loss of exclusivity; LVEF = left ventricular ejection fraction; MACE = major cardiovascular adverse events; MI = myocardial infarction; mmHG = millimeters of mercury; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NNT = number needed to treat; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PC = placebo-controlled; PKD = polycystic kidney disease; PMH = past medical history; PVD = peripheral vascular disease; RCT = randomized controlled trial; RRT= renal replacement therapy (includes dialysis and renal transplantation); Scr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; Tmax = time to maximum concentration; UACR = urinary albumin-to-creatinine ratio; UGT = uridine 5'-diphospho-glucuronosyltransferase; ULN = upper limit of normal; UTI = urinary tract infection; WAC = wholesale acquisition cost

Appendix A – SGLT2 inhibitor cardiorenal efficacy study summaries

Canagliflozin (Invokana) studies		
Pivotal trial(s)	CANVAS[13]	CREDENCE[14]
N	10,412	4,401
Design	DB, PC, RCT	DB, PC, RCT
Median follow-up	2.4 y	2.6 y
Key inclusion criteria	• T2DM (HbA1c 7-10.5%) • ASCVD or ≥ 2 CV risk factors	• T2DM (HbA1c 6.5-12%) • CKD (eGFR 30 to < 90 mL/min/1.73m^2 and UACR > 300-5,000 mg/g) • On stable ACEi/ARB
Key exclusion criteria	• eGFR < 30 mL/min/1.73m^2 • LFT ≥ 2 x ULN • NYHA class IV • ACS, re-vascularization, stroke, TIA in past 3 mos	• eGFR < 30 mL/min/1.73m^2 • LFT ≥ 2 x ULN • NYHA class IV • ACS, re-vascularization, or CVA in past 12 wks
Primary efficacy outcome (vs placebo)		
Outcome type	MACE	Renal
Outcome definition	CV death, nonfatal MI, or nonfatal stroke	RRT, eGFR < 15 mL/min/1.73m^2, doubling of Scr, or death from renal or CV cause
Result, HR (95% CI)	**0.86 (0.75-0.97)**	**0.70 (0.59-0.82)**
Result, ARR (NNT) *(values reported are calculated estimates)*	1.1% (90)	4.3% (24)
Secondary outcomes of interest (vs placebo)		
CV death, HR (95% CI)	0.87 (0.72-1.06)	0.78 (0.61-1.00)
Nonfatal MI, HR (95% CI)	0.85 (0.69-1.05)	--
Nonfatal stroke, HR (95% CI)	0.90 (0.71-1.15)	--

Canagliflozin (Invokana) studies		
Hospitalization for HF, HR (95% CI)	**0.67 (0.52-0.87)**	**0.61 (0.47-0.80)**
CV death or hospitalization for HF, HR (95% CI)	**0.78 (0.67-0.91)**	**0.69 (0.57-0.83)**
CV death, nonfatal MI, or nonfatal stroke, HR (95% CI)	*see primary outcome*	**0.80 (0.67-0.95)**
All-cause mortality, HR (95% CI)	0.87 (0.74-1.01)	0.83 (0.68-1.02)
Composite renal outcome definition	Sustained reduction in eGFR, RRT, or death from renal disease	*see primary outcome*
Composite renal outcome, HR (95% CI)	**0.60 (0.47-0.77)**	*see primary outcome*
Progression to albuminuria definition	> 30% increase in albuminuria, or new micro- or macroalbuminuria	--
Progression to albuminuria, HR (95% CI)	**0.73 (0.67-0.79)**	--

Dapagliflozin (Farxiga) studies				
Pivotal trial(s)	DECLARE-TIMI 58[15]	DAPA-HF[16]	DAPA-CKD[18]	DELIVER[17]
N	17160	4744	4304	6263
Design	DB, PC, RCT	DB, PC, RCT	DB, PC, RCT	DB, PC, RCT
Median follow-up	4.2 y	1.5 y	2.4 y	2.3 y
Key inclusion criteria	• T2DM (HbA1c 6.5-12%) • ASCVD or ≥ 2 risk factors for ASCVD	• HFrEF (LVEF ≤ 40%) • NYHA class II, III, IV on standard therapy • NT-pro-BNP ≥ 600 pg/mL (variable by PMH)	• eGFR 25-75 mL/min/ 1.73m^2 • UACR 200-5,000 mg/g • On stable ACEi/ ARB	• HFpEF (LVEF ≥ 40%) • NYHA class II, III, IV with at least intermittent need for diuretic therapy • NT-pro-BNP ≥ 300 pg/mL; ≥ 600 pg/mL if atrial fibrillation/flutter) present
Key exclusion criteria	• CrCl < 60 mL/min • LFT ≥ 3 x ULN • Acute CV event in past 8 wks	• eGFR < 30 mL/min/ 1.73m^2 • LFT ≥ 3 x ULN • ADHF • ACS or CVA in past 12 wks	• eGFR < 25 mL/min/ 1.73m^2 • PKD • LFT ≥ 3 x ULN • NYHA class IV • ACS or CVA in past 12 wks	• eGFR < 25 mL/min/ 1.73m^2 • Severe hepatic impairment • ACS or CVA in past 12 wks
Primary efficacy outcome (vs placebo)				
Outcome type	MACE / HF	HF	Renal	HF
Outcome definition	Co-primary 1) CV death, MI, stroke 2) CV death or hospitalization for HF	Worsening HF (hospitalization or visit with IV therapy) or CV death	Sustained reduction in eGFR, RRT, eGFR < 15 mL/min/ 1.73m^2, or death from renal or CV disease	Worsening HF (unplanned hospitalization for HF or urgent visit for HF) or CV death
Result, HR (95% CI)	1) 0.93 (0.84-1.03) 2) **0.83 (0.73-0.95)**	**0.74 (0.65-0.85)**	**0.61 (0.51-0.72)**	**0.82 (0.73-0.92)**
Result, ARR (NNT) *(values reported are calculated estimates)*	1) NA 2) 0.9% (109)	5% (21)	5.3% (19)	3.1% (33)
Secondary outcomes of interest (vs placebo)				
CV death, HR (95% CI)	0.98 (0.82-1.17)	**0.82 (0.69-0.98)**	0.81 (0.58-1.12)	0.88 (0.74-1.05)

Dapagliflozin (Farxiga) studies				
Nonfatal MI, HR (95% CI)	0.89 (0.77-1.01)	--	--	--
Nonfatal stroke, HR (95% CI)	1.01 (0.84-1.21)	--	--	--
Hospitalization for HF, HR (95% CI)	**0.73 (0.61-0.88)**	**0.70 (0.59-0.83)**	--	**0.77 (0.67-0.89)**
CV death or hospitalization for HF, HR (95% CI)	*see co-primary outcome*	**0.75 (0.65-0.85)**	**0.71 (0.55-0.92)**	--
CV death, nonfatal MI, or nonfatal stroke, HR (95% CI)	*see co-primary outcome*	--	--	--
All-cause mortality, HR (95% CI)	0.93 (0.82-1.04)	**0.83 (0.71-0.97)**	**0.69 (0.53-0.88)**	0.94 (0.83-1.07)
Composite renal outcome definition	Sustained reduction in eGFR, RRT, eGFR <15 mL/min/ 1.73m^2, or death from renal or CV disease	Sustained reduction in eGFR, RRT, eGFR <15 mL/min/ 1.73m^2, or death from renal disease	*see primary outcome*	--
Composite renal outcome, HR (95% CI)	**0.76 (0.67-0.87)**	0.71 (0.44-1.16)	*see primary outcome*	--
Progression to albuminuria definition	--	--	--	--
Progression to albuminuria, HR (95% CI)	--	--	--	--

Empagliflozin (Jardiance) studies				
Pivotal trial(s)	EMPA-REG-OUT-COME[19]	EMPEROR-Reduced[21]	EMPEROR-Preserved[22]	EMPA-KIDNEY[23]
N	7020	3730	5988	6609
Design	DB, PC, RCT	DB, PC, RCT	DB, PC, RCT	DB, PC, RCT
Median follow-up	3.1 y	1.3 y	2.2 y	2 y
Key inclusion criteria	• T2DM (HbA1c 7-10%) • ASCVD	• HFrEF (LVEF ≤ 40%) • NYHA class II, III, IV on standard therapy • NT-pro-BNP ≥ 600 pg/mL (variable by EF)	• HFpEF (LVEF > 40%) • NYHA class II, III, IV • NT-pro-BNP ≥ 300 pg/mL (variable by PMH)	• eGFR 20-44 mL/min/1.73m^2 or eGFR 45-89 mL/min/1.73m^2 with a UACR ≥ 200 mg/g • On RAS inhibitor, unless considered not indicated or patient could not tolerate
Key exclusion criteria	• eGFR < 30 mL/min/ 1.73m^2 • LFT ≥ 3 x ULN • BMI > 45 kg/m^2 • ACS, stroke or TIA in past 2 mos	• eGFR < 20 mL/min/ 1.73m^2 • LFT ≥ 3 x ULN • BMI > 45 kg/m^2 • ADHF • Significant chronic pulmonary disease • MI, CABG, stroke, TIA in past 90 d		• eGFR < 20 mL/min/ 1.73m^2 • PKD • Receipt of kidney transplant • LFT ≥ 3 x ULN
Primary efficacy outcome (vs placebo)				
Outcome type	MACE	HF	HF	Renal
Outcome definition	CV death, nonfatal MI, or nonfatal stroke	CV death or hospitalization for HF	CV death or hospitalization for HF	RRT, sustained reduced in eGFR, or death from renal or CV disease
Result, HR (95% CI)	**0.86 (0.74-0.99)**	**0.75 (0.65-0.86)**	**0.79 (0.69-0.90)**	**0.72 (0.64-0.82)**
Result, ARR (NNT) *(values reported are calculated estimates)*	1.6% (62)	5.4% (19)	3.2% (31)	3.8% (27)
Secondary outcomes of interest (vs placebo)				
CV death, HR (95% CI)	**0.62 (0.49-0.77)**	0.92 (0.75-1.12)	0.91 (0.76-1.09)	0.84 (0.60-1.19)
Nonfatal MI, HR (95% CI)	0.87 (0.70-1.09)	--	--	--

Empagliflozin (Jardiance) studies				
Nonfatal stroke, HR (95% CI)	1.24 (0.92-1.67)	--	--	--
Hospitalization for HF, HR (95% CI)	**0.65 (0.50-0.85)**	**0.69 (0.59-0.81)**	**0.71 (0.60-0.83)**	--
CV death or hospitalization for HF, HR (95% CI)	**0.66 (0.55-0.79)**	*see primary outcome*	*see primary outcome*	0.84 (0.67-1.07)
CV death, nonfatal MI, or nonfatal stroke, HR (95% CI)	*see primary outcome*	--	--	--
All-cause mortality, HR (95% CI)	**0.68 (0.57-0.82)**	0.92 (0.77-1.10)	1.00 (0.87-1.15)	0.87 (0.70-1.08)
Composite renal outcome definition	Doubling of Scr, RRT, or death from renal disease[20]	RRT or sustained reduction in eGFR	RRT or sustained reduction in eGFR	*see primary outcome*
Composite renal outcome, HR (95% CI)	**0.54 (0.40-0.75)**[20]	**0.50 (0.32-0.77)**	0.95 (0.73-1.24)	*see primary outcome*
Progression to albuminuria definition	Progression to macro-albuminuria[20]	--	--	--
Progression to albuminuria, HR (95% CI)	**0.62 (0.54-0.72)**[20]	--	--	--

Ertugliflozin (Steglatro) studies	
Pivotal trial(s)	VERTIS-CV[24]
N	8,246
Design	DB, PC, RCT
Median follow-up	3 y
Key inclusion criteria	• T2DM (HbA1c 7-10.5%) • ASCVD
Key exclusion criteria	• eGFR < 30 mL/min/1.73m^2 • LFT ≥ 2 x ULN • NYHA class IV • CV event or CVA between screening and randomization
Primary efficacy outcome (vs placebo)	
Outcome type	MACE
Outcome definition	CV death, nonfatal MI, or nonfatal stroke
Result, HR (95% CI)	0.97 (0.85-1.11)
Result, ARR (NNT) *(values reported are calculated estimates)*	NA
Secondary outcomes of interest (vs placebo)	
CV death, HR (95% CI)	0.92 (0.77-1.11)
Nonfatal MI, HR (95% CI)	1.04 (0.86-1.26)
Nonfatal stroke, HR (95% CI)	1.06 (0.82-1.37)
Hospitalization for HF, HR (95% CI)	**0.70 (0.54-0.90)**
CV death or hospitalization for HF, HR (95% CI)	0.88 (0.75-1.03)

CV death, nonfatal MI, or nonfatal stroke, HR (95% CI)	*see primary outcome*
All-cause mortality, HR (95% CI)	0.93 (0.80-1.08)
Composite renal outcome definition	Doubling of Scr, RRT, or death from renal disease
Composite renal outcome, HR (95% CI)	0.81 (0.63-1.04)
Progression to albuminuria definition	--
Progression to albuminuria, HR (95% CI)	--

Bexagliflozin (Brenzavvy) studies *Note: clinical trials with cardiorenal outcomes as the primary endpoint are not available for bexagliflozin; data for secondary endpoints evaluating cardiorenal outcomes are provided in the table below*		
Pivotal trial(s)	BEST[25,26]	C-448[27]
N	1701	312
Design	DB, PC, RCT	DB, PC, RCT
Median follow-up	2.4 y	Not specified (trial duration was 24 wks)
Key inclusion criteria	• T2DM (HbA1c 7-11%) • Established history of CVD (ie, ASCVD or HF) or multiple (≥ 2) risk factors for CVD (ie ≥ 55 y with T2DM ≥ 10 y, controlled HTN, smoker, reduce kidney function, dyslipidemia)	• T2DM on stable regimen • eGFR 30-59 mL/min/1.73m^2
Key exclusion criteria	• eGFR < 45 mL/min/1.73m^2 • Abnormal liver function • History of MI, stroke, or hospitalization for HF in last 3 mo	• eGFR < 30 mL/min/ 1.73m^2 • Receipt of kidney transplant • History of MI, stroke, or hospitalization for HF in last 3 mo
Primary efficacy outcome (vs placebo)		
Outcome type	Glycemic control	Glycemic control
Outcome definition	HbA1c at wk 24	HbA1c at wk 24
Result, HR (95% CI)	NA	NA
Result, ARR (NNT) *(values reported are calculated estimates)*	NA	NA
Secondary outcomes of interest (vs placebo)		
CV death, HR (95% CI)	--	--
Nonfatal MI, HR (95% CI)	--	--
Nonfatal stroke, HR (95% CI)	--	--
Hospitalization for HF, HR (95% CI)	--	--

CV death or hospitalization for HF, HR (95% CI)	0.74 (0.47-1.17)	--
CV death, nonfatal MI, or nonfatal stroke, HR (95% CI)	0.79 (0.56-1.09)* **also includes unstable angina in MACE definition in addition to CV death, MI, and stroke*	--
All-cause mortality, HR (95% CI)	--	--
Composite renal outcome definition	--	--
Composite renal outcome, HR (95% CI)	--	--
Progression to albuminuria definition	--	NA – outcome reported related to albuminuria is for geometric mean reduction in UACR at 24 wks
Progression to albuminuria, % (95% CI)	--	*Reduction in UACR at 24 wks with bexagliflozin:* 20.1% (95% CI, 2.52-34.56%; *P* = .03)

Sotagliflozin (Inpefa) studies		
Pivotal trial(s)	SOLOIST-WHF[28]	SCORED[29]
N	1222	10584
Design	DB, PC, RCT	DB, PC, RCT
Median follow-up	9.2 mo	
Key inclusion criteria	• T2DM • Hospitalized for HF and required IV diuretics • Clinically stable prior to randomization • NT-pro-BNP ≥ 600 pg/mL; ≥ 1800 pg/mL if atrial fibrillation/flutter present	• T2DM with HbA1c ≥ 7% • eGFR 25-60 mL/min/1.73m^2 • ≥18 y with ≥ 1 major CV risk factor or ≥ 55 y with ≥ 2 minor CV risk factors
Key exclusion criteria	• eGFR < 30 mL/min/ 1.73m^2 • End-stage HF • LFT ≥ 3 x ULN • ACS or CVA in past 12 wks	• eGFR < 25 mL/min/ 1.73m^2 • End-stage HF • Receipt of solid organ transplant • LFT ≥ 3 x ULN
Primary efficacy outcome (vs placebo)		
Outcome type	HF	HF* **originally had co-primary endpoints related to HF and MACE*
Outcome definition	CV death, hospitalization for HF, or urgent visit for HF	CV death, hospitalization for HF, or urgent visit for HF
Result, HR (95% CI)	**0.67 (0.52-0.85)**	**0.74 (0.63-0.88)**
Result, ARR (NNT) *(values reported are calculated estimates)*	17.5% (6)	2.5% (41)
Secondary outcomes of interest (vs placebo)		
CV death, HR (95% CI)	0.84 (0.58-1.22)	0.90 (0.73-1.12)
Nonfatal MI, HR (95% CI)	--	**0.68 (0.52-0.89)*** **includes fatal and nonfatal MI*
Nonfatal stroke, HR (95% CI)	--	**0.66 (0.48-0.91)*** **includes fatal and nonfatal stroke*
Hospitalization for HF, HR (95% CI)	**0.64 (0.49-0.83)**	**0.67 (0.55-0.82)**

CV death or hospitalization for HF, HR (95% CI)	--	**0.77 (0.66-0.91)*** **original co-primary endpoint*
CV death, nonfatal MI, or nonfatal stroke, HR (95% CI)	**0.72 (0.56-0.92)*** **also includes hospitalizations for HF in composite*	**0.84 (0.72-0.99)*** **original co-primary endpoint*
All-cause mortality, HR (95% CI)	0.82 (0.59-1.14)	0.99 (0.83-1.18)
Composite renal outcome definition	--	First occurrence of ≥ 50% decrease in eGFR from baseline, long-term dialysis, renal transplantation, or sustained eGFR < 15 mL/min/1.73m^2
Composite renal outcome, HR (95% CI)	--	0.71 (0.46-1.08)
Progression to albuminuria definition	--	--
Progression to albuminuria, HR (95% CI)	--	--

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ADHF = acute decompensated heart failure; AKI = acute kidney injury; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft surgery; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance (estimate via Cockroft-Gault equation); CV = cardiovascular; CVA = cerebrovascular accident; CVD = cardiovascular disease; DB = double-blind; DKA = diabetic ketoacidosis; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GLP-1 = glucagon-like peptide-1; HF = heart failure; HFpEF = heart failure with preserved ejection fraction (LVEF > 40%); HFrEF = heart failure with reduced ejection fraction (LVEF ≤ 40%); HR = hazard ratio; LFT = liver function test; LVEF = left ventricular ejection fraction; MACE = major cardiovascular adverse events; MI = myocardial infarction; mmHG = millimeters of mercury; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NNT = number needed to treat; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PC = placebo-controlled; PKD = polycystic kidney disease; PMH = past medical history; PVD = peripheral vascular disease; RAS = renin-angiotensin system; RCT = randomized controlled trial; RRT= renal replacement therapy (includes dialysis and renal transplantation); Scr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; UACR = urinary albumin-to-creatinine ratio; ULN = upper limit of normal

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