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REVIEW ARTICLE

Cardiorenal effects of SGLT2 inhibitors: who might benefit?

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Sodium glucose co-transporter-2 inhibitors have been shown to have multiple cardiovascular and renal benefits in patients with type 2 diabetes. In large randomised controlled trials they reduced major cardiovascular outcomes, hospitalisation for heart failure and adverse kidney outcomes, independently of their glucose-lowering effects. They are simple to prescribe and do not require dose titration. Compelling indications for this class of medications in patients with type 2 diabetes include those at high or very high risk of cardiovascular events and those with established atherosclerotic cardiovascular disease. They are also indicated for patients with heart failure and chronic kidney disease, regardless of diabetic status.

Keywords: cardiovascular disease, high risk, renal disease, secondary prevention, SGLT2 inhibitors

Introduction

In South Africa, even in tertiary specialist clinics, fewer than one out of every four patients with type 2 diabetes mellitus achieves HbA1c < 7%, the recommended target to reduce microvascular complications.[1,2] South Africa is not unusual in this regard and, worldwide, glycaemic control among people with type 2 diabetes is notoriously poor.[3] Especially if uncontrolled, type 2 diabetes is an important cause of both cardiovascular disease (CVD) and kidney disease and, in comparison with the general population, people with diabetes have a higher prevalence of CVD, heart failure and chronic kidney disease (CKD).[4–7]

Approximately one-third of the global population with type 2 diabetes has CVD and one in five will develop heart failure.[4] Patients with type 2 diabetes and heart failure have more severe symptoms, worse health-related quality of life outcomes, and higher risk of hospitalisation for heart failure compared with those who have heart failure without type 2 diabetes. Mortality is high and similar to that in non-diabetic patients with established coronary heart disease.[8]

Approximately two out of five people with type 2 diabetes will develop diabetic kidney disease, and, in these patients, the risk of end-stage kidney disease is considerably increased.[5,7] The risk of CVD death also increases with worsening kidney function, and CVD is the leading cause of death in patients with type 2 diabetes and CKD.[7]

Although glycaemic control is a cornerstone of treatment in early type 2 diabetes, complications continue to increase with duration of diabetes. In patients with long-standing type 2 diabetes and complications, with the exception of nephropathy, intensive glucose control has not consistently improved cardiovascular or microvascular outcomes.[9,10]

Recently, however, the large outcomes studies using sodium glucose co-transporter-2 (SGLT2) inhibitors have shown that they can significantly reduce the risk of both CVD and diabetic kidney disease in patients with long-standing diabetes. Therefore, identifying patients at high risk for cardiorenal complications is extremely important.[1,11,12]

In this article, we describe the glucose-independent benefits of SGLT2 inhibitors, and the profile of patients who are most likely to benefit from them.

Methods

Clinical guidelines, review articles, randomised controlled studies and observational studies were sourced by performing a literature search on PubMed and Google using terms including 'sodium glucose co-transporter type 2', 'cardiorenal syndrome', 'complications', 'diabetes mellitus', 'heart failure', and 'kidney/renal impairment/failure'. The review article was written based on the available literature.

Benefits of SGLT2 inhibitors

SGLT2 inhibitors have multiple effects that help to reduce cardiorenal risk

The pathophysiological mechanisms that are common to CVD, heart failure and CKD in type 2 diabetes are multiple and complex. They include sympathetic stimulation and renin-angiotensin-aldosterone system (RAAS) activation, chronic inflammation, endothelial dysfunction, accelerated atherosclerosis, fibrosis, volume overload and oxidative stress.[13–15]

In patients with type 2 diabetes, SGLT2 inhibitors reduce glucose reabsorption in the proximal convoluted tubule

independently of insulin, resulting in glucosuria and HbA1c reductions of approximately 0.6–1.0% depending on the initial glucose level.[16,17] They are also associated with modest reductions in blood pressure and bodyweight. In addition, they have been shown to have multiple cardiovascular and renal benefits in type 2 diabetes, which are detailed in Table 1. A full description of these mechanisms is beyond the scope of this article and readers are referred to reviews by Fathi et al.[18] and Bailey et al.[16] for more information.

SGLT2 inhibitors have significant clinical benefits beyond glycaemic control

In large landmark cardiovascular outcome studies conducted in patients with type 2 diabetes, SGLT2 inhibitors were consistently associated with clinically important reductions in hospitalisation for heart failure (by approximately 35%) and adverse kidney outcomes (between 30% and 50% reduction). However, probably related to differences in the prior cardiovascular risk, reduction in major adverse cardiovascular events (MACE) differed across the studies (Table 2).[20–29] Although specific differences between the SGLT2 inhibitors with regard to individual outcomes cannot be excluded, heterogeneity between the patient populations and designs of the outcome studies preclude direct comparisons between them.[30] No head-to-head trials have been performed. Numerous reviews and meta-analyses of these studies in patients with type 2 diabetes have been published and can be referred to for more detail.[13,18,19,30–42]

Table 1: Putative mechanisms of cardiorenal protection associated with SGLT2 inhibitors[16,18,19]

Heart
- Improved energy metabolism due to increased ketones
- Improved cardiac remodelling, improved autophagy and lysosomal degradation
- Inhibition of the Na^+/H^+ exchange
- Reduced inflammation
- Reduced ischaemic reperfusion injury
- Reduced oxidative stress
- Reduced epicardial fat mass

Kidney
- Increased diuresis and natriuresis
- Glucosuria
- Initial reduction in plasma volume
- Restoration of tubuloglomerular feedback and glomerular afferent arteriolar autoregulation
- Improvement of tubular oxygenation
- Reduction of reactive oxygen species
- Reduction in uric acid
- Inhibition of the Na^+/H^+ exchange
- Improved energy metabolism
- Reduced inflammation and fibrosis

Vasculature
- Reduced inflammation
- Reduced blood pressure
- Increased provascular progenitor cells
- Improved vascular function

Body
- Reduced blood glucose
- Weight loss
- Inhibition of sympathetic nervous system
- Increased erythropoietin and haematocrit

In all of these studies, it is important to note that the patients had long-standing type 2 diabetes, already with complications, or were at high risk for atherosclerotic cardiovascular disease (ASCVD), with mean and/or median times since diagnosis of longer than 10 years.

Protective benefits of SGLT2 inhibitors are independent of glycaemia, kidney function and ejection fraction

In patients with type 2 diabetes, the cardio- and renoprotective effects of SGLT2 inhibitors are independent of their glucose-lowering effects, and are consistent regardless of baseline HbA1c and background metformin use.[32–34] In the landmark studies (initially designed as FDA-mandated, non-inferiority cardiovascular safety outcome studies), the benefits in terms of progression of kidney disease or hospitalisation for heart failure were similar in patients with and without ASCVD or a history of heart failure, and regardless of baseline kidney function.[25,34,35]

SGLT2 inhibitors do not require dose titration

Almost all of the guideline-recommended pharmacotherapies for type 2 diabetes, heart failure and CKD require dose titration from a low starting dose to evidence-based doses, or, if that is not possible, to the maximal tolerated dose.[1,12,43,44] Especially in the absence of a reliable biomarker that would help to guide and motivate dose increases, doctors are often reluctant to up-titrate because of concern over poor tolerability and side effects.[45] The inconvenience of dose titration and frequent clinic visits associated with this can affect patients' adherence to the treatment regimen, leading to underdosing (failure to increase the dose), overdosing (starting too high, or increasing too rapidly), and/or missed doses.[46] The complexities of drug titration are further complicated by the polypharmacy and complex treatment regimens required for underlying comorbidities.

Considering these challenges, it is not surprising that most patients with type 2 diabetes, heart failure and/or kidney disease do not receive target or maximal tolerated doses, or optimal drug combinations stipulated by treatment guidelines.[47–52] The consequent failure to achieve and maintain optimal treatment has significant implications in terms of disease progression, reduced quality of life and increased morbidity and mortality.[51,53,54] This, in turn, increases the burden on the healthcare system and associated costs of healthcare.[55]

Unlike other medications for diabetes and CVD or kidney disease, the starting dose of SGLT2 inhibitors is also the maintenance dose and dose titration is not required.

Compelling indications for SGLT2 inhibitors in patients with type 2 diabetes

Based on the results of the cardiovascular outcome studies and recommendations of international guidelines, in order to prevent cardiorenal complications, compelling indications for SGLT2 inhibitors in patients with type 2 diabetes include high or very high risk of cardiovascular events and established ASCVD (Table 3).[1,11,12,43] These recommendations apply to

Table 2: Cardiovascular and kidney outcomes in CV outcome studies

Study	Baseline characteristics[a]	SGLT2 inhibitor and follow-up duration	CV outcomes Hazard ratio (95% CI)[b]	Kidney outcomes Hazard ratio (95% CI)
Patients with type 2 diabetes and high CV risk (established ASCVD)				
EMPA-REG OUTCOME[20,21]	T2D and ASCVD *N* = 7 020 Mean age 63 BMI 31 kg/m^2 DOD > 10 years 52% eGFR 60–90 ml/min 26% eGFR < 60 ml/min 76% CAD 47% previous MI 23% previous stoke 21% PAD 10% HF	Empagliflozin 10 mg or 25 mg (pooled) versus placebo, once daily 3.1 years (median)	• MACE (PEP): HR 0.86 (0.74–0.99) • CV death or HHF: HR 0.66 (0.55–0.79) • HHF: HR 0.65 (0.50–0.85) • CV death: HR 0.62 (0.49–0.77) • All cause death: HR 0.68 (0.57–0.82)	• Incident or worsening nephropathy (progression to macroalbuminuria; doubling of the serum creatinine with eGFR ≤ 45 ml/min; initiation of renal-replacement therapy; or death from kidney disease): HR 0.61 (0.53–0.70) Progression to macroalbuminuria: HR 0.62 (0.54–0.72) • Doubling of the serum creatinine with eGFR ≤45 ml/min: HR 0.54 (0.40–0.75) • Annual rate of decline in eGFR: slower in the empagliflozin group (−0.19 versus −1.67 ml/min/year; $p < 0.001$)
CANVAS[22]	T2D and high CV risk *N* = 10 142 Mean age 63 BMI 32 kg/m^2 DOD 13.5 years eGFR 76.5 ml/min 72% ASCVD 66% CAD 19% cerebrovascular disease 21% PAD 90% hypertension 23% microalbuminuria 8% macroalbuminuria	Canagliflozin 100 mg with optional increase to 300 mg at week 13 (pooled) versus placebo, once daily 2.4 years (median)	• MACE (PEP): HR 0.86 (0.75–0.97) • CV death or HHF: HR 0.78 (0.67–0.91) • HHF: HR 0.67 (0.52–0.87)	• Progression of albuminuria (> 30% increase in albuminuria and change from either normoalbuminuria to microalbuminuria or macroalbuminuria or from microalbuminuria to macroalbuminuria): HR 0.73 (0.67–0.79) • 40% reduction in eGFR, renal-replacement therapy, or renal death: HR 0.60 (0.47–0.77)
VERTIS-CV[26]	T2D and ASCVD *N* = 8 246 Mean age 64 BMI 32 kg/m^2 DOD 13 years eGFR 76 ml/min 22% CAD 23% cerebrovascular disease 19% PAD 23% HF 48% previous MI	Ertagluflozin 5 mg or 15 mg (pooled) versus placebo, once daily 3.5 years (median)	• HHF: HR 0.70 (0.54–0.90)	
Patients with type 2 diabetes and primary or secondary CV prevention				
DECLARE-TIMI 58[24]	T2D *N* = 17 160 Mean age 64 BMI 32 kg/m^2 DOD 11 years eGFR 85.2 ml/min 41% secondary prevention cohort with established ASCVD 59% primary prevention cohort with multiple risk factors	Dapagliflozin 10 mg versus placebo, once daily 4.2 years (median)	• CV death or HHF Overall: HR 0.83 (0.73–0.95) ASCVD subgroup: HR 0.83 (0.71–0.98) • HHF Overall: HR 0.73 (0.61–0.88) ASCVD subgroup: HR 0.78 (0.63–0.97) Multiple risk factor subgroup: HR 0.64 (0.46–0.88)	• Worsening kidney function (≥ 40% decrease in eGFR, ESKD, or death from renal cause): Overall: HR 0.53 (0.43–0.66) ASCVD subgroup: HR 0.55 (0.41–0.75) Multiple risk factor subgroup: HR 0.51 (0.37–0.69)

[a]Baseline characteristics approximated for active treatment group. [b]Risk reduction can be calculated by subtracting HR from 1; e.g. for HR 0.65, risk reduction is 0.35 = 35%.
ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CAD: coronary artery disease; CI: confidence interval; CVD: cardiovascular disease; DOD: duration of diabetes (median); eGFR: estimated glomerular filtration rate (ml/min/1.72 m^2); ESKD: end-stage kidney disease; HHF: hospitalisation for heart failure; HF: heart failure; HR: hazard ratio; MACE: major adverse cardiovascular events (CV death, myocardial infarction or ischaemic stroke); MI: myocardial infarction; PAD: peripheral artery disease; PEP: primary endpoint; T2D: type 2 diabetes.

patients with type 2 diabetes irrespective of whether they are treatment naive or already receiving metformin, and regardless of HbA1c, even if it is normal.[11]

Patient selection and risk assessment

While it is straightforward to identify patients with established ASCVD (and cardiovascular risk scoring is unnecessary in these

Table 3: Compelling indications for SGLT2 inhibitors in patients with type 2 diabetes

Indication	Potential benefits
At high or very high risk of cardiovascular events[11,43]	To reduce hospitalisations for heart failure and prevent or reduce progression of kidney disease
With established ASCVD[1,11]	To reduce hospitalisations for heart failure, major cardiovascular events, and cardiovascular death; to prevent or reduce progression of kidney disease

Table 4: Patients with type 2 diabetes who are at risk of ASCVD[11]

Very high risk	• Target organ damage: left ventricular hypertrophy, proteinuria or eGFR < 30 ml/min/1.72 m^2, or retinopathy • 3 or more major risk factors: age, hypertension, dyslipidaemia, smoking, obesity
High risk	• Duration of diabetes 10 years or more without target organ damage, plus any additional risk factor (age, hypertension, dyslipidaemia, smoking, obesity)
Moderate risk	• Young patients (aged < 50 years) with diabetes duration less than 10 years and without other risk factors (hypertension, dyslipidaemia, smoking, obesity)

eGRF: estimated glomerular filtration rate.

patients), a careful history and examination is required to identify those who are at high risk of ASCVD (Table 4). These include people older than 60 years, male gender, family history of cardiovascular or kidney disease, uncontrolled HbA1c, current smoking, uncontrolled hypertension and dyslipidaemias.[56,57] Importantly, the Framingham risk score has not been validated in people with pre-diabetes or diabetes and should not be used.[58]

All patients with type 2 diabetes should be screened for CKD at least annually, regardless of treatment. This should include an eGFR and spot urine albumin/creatinine ratio (ACR), preferably on an early morning urine sample. At any eGFR, the degree of albuminuria is associated with risk of CVD, CKD progression and mortality. Therefore, classification of kidney disease, assessment of associated risks and treatment decisions should be based on a combination of eGFR and ACR (Table 5).[59]

Precautions when prescribing SGLT2 inhibitors to patients with type 2 diabetes

Adverse events with SGLT2 inhibitors are uncommon.[60] Nevertheless, as with all drugs for type 2 diabetes, one should be vigilant for potential adverse effects that might cause concern, reduce adherence, lead to discontinuation of therapy or threaten health.

Genital infection and urinary tract infection

SGLT2 inhibitors cause glucosuria. Consequently, patients taking SGLT2 inhibitors are at risk of genital mycotic infections. These are easily treated with topical antifungal agents or a single oral dose of fluconazole, and the SGLT2 inhibitor need not be stopped.[61] Patients should be advised to maintain good genital hygiene and consult their doctor or clinic sister if they develop any new symptoms, such as redness or pruritus.

In a population-based cohort study including more than 335 000 patients, the incidence rate of severe urinary tract infection was 1.76 per 1 000 patient years, which was similar to that in patients initiating other second-line antidiabetic treatments (dipeptidyl peptidase [DDP]−4 inhibitors and GLP-1 receptor agonists).[62] Nevertheless, patients should be advised to contact their doctor if they develop symptoms suggesting infection, including flank or back pain; fever; nausea/vomiting; cloudy, dark or foul-smelling urine; frequency; and/or dysuria. Urinary tract infections are treated with the usual antibiotics, with antimicrobial sensitivity testing (before initiating an antibiotic) as necessary.

Transient fall in eGFR

A small and reversible decline in estimated glomerular filtration rate (eGFR) is expected after starting an SGLT2 inhibitor and does not require dose reduction or discontinuation of the drug. Kidney function should be evaluated before starting an SGLT2 inhibitor and re-evaluated at four weeks and three months. Thereafter, kidney function should be monitored at intervals determined by the grade of CKD.[43,63]

Dehydration and hypotension

Initiation of an SGLT2 inhibitor may be associated with increased fluid loss, with potential for dehydration and hypotension. Concomitant use of thiazides, loop diuretics and neprilysin/angiotensin receptor blockers increase risk of excessive diuresis, dehydration and symptomatic hypotension.

In clinical trials, SGLT2 inhibitors were associated with improvements in kidney outcomes, and acute kidney injury was not observed.[23,29,32,40,64–66] Nevertheless, dehydration potentially could increase risk of acute kidney failure, especially in patients receiving concomitant treatment with diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or non-steroidal anti-inflammatory drugs. Elderly or frail patients may be especially at risk. Therefore, fluid balance should be monitored regularly, and patients should be advised about symptoms of dehydration. SGLT2 inhibitors should be discontinued in patients who develop fever, vomiting or diarrhoea.[67]

Severe hypoglycaemia

In none of the landmark trials of SGLT2 inhibitors was the incidence of hypoglycaemia greater than with placebo. However, in patients with type 2 diabetes, care should be taken when prescribing an SGLT2 inhibitor with concomitant insulin and also where an SGLT2 inhibitor is added to a pre-existing sulphonylurea, especially one that is rapid-acting.[67] Consideration should be given to reducing the dose of these agents before starting an SGLT2 inhibitor (in patients at, or close to target HbA1c), and blood glucose should be monitored carefully.

Ketoacidosis

In the landmark trials, the risk of ketoacidosis was very low. It was observed only in patients with diabetes and was generally less frequent than 0.5%.[21,22,24–26,29] Factors that can increase risk of ketoacidosis in patients with type 2 diabetes include reduced basal insulin dose or omission of insulin, reduced or inconsistent carbohydrate intake, surgery, excessive alcohol use, use of illicit drugs, dehydration, acute viral or bacterial illness, acute myocardial infarction and vomiting. Symptoms of fatigue, nausea/vomiting or abdominal pain, even when glucose levels are within or near normal limits (i.e. euglycaemic

Table 5: KDIGO classification of chronic kidney disease: prognosis of CKD by GFR and albuminuria categories[59]

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	Low risk 1 if CKD	Moderate risk 1	High risk 2
	G2	Mildly decreased	60-89	Low risk 1 if CKD	Moderate risk 1	High risk 2
	G3a	Mildly to moderately decreased	45-59	Moderate risk 1	High risk 2	Very high risk 3
	G3b	Moderately to severely decreased	30-44	High risk 2	Very high risk 3	Very high risk 3
	G4	Severely decreased	15-29	Very high risk 3	Very high risk 3	Very high risk 4+
	G5	Kidney failure	<15	Very high risk 4+	Very high risk 4+	Very high risk 4+

Colours show the risk of progression, morbidity and mortality. Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk. Numbers indicate a guide to the frequency of visits (number of times per year).[59]

ketoacidosis), should raise suspicion of ketoacidosis and prompt blood and/or urine tests for presence of ketones.[61,67–69]

To avoid potential risk of diabetic ketoacidosis, SGLT2 inhibitors should be discontinued before scheduled surgery, or during critical medical illness, fasting or insufficient meal intake due to loss of appetite. Patients should be advised to avoid low carbohydrate and ketogenic diets.

Bone fractures and amputation

In the CANVAS trial, canagliflozin was associated with a statistically significant increase in bone fractures and lower extremity amputations.[22] However, this has not been observed in subsequent studies, including large randomised controlled trials and meta-analyses.[60,70]

Additional indications for SGLT2 inhibitors in patients with or without type 2 diabetes

Studies including patients with and/or without type 2 diabetes show that SGLT2 inhibitors are of benefit in patients with heart failure and CKD with albuminuria (Table 6). The DAPA-heart failure, DELIVER, EMPEROR, DAPA-CKD and EMPA-KIDNEY studies enrolled patients both with and without type 2 diabetes, and subgroup analyses showed that the benefits were similar regardless of the presence of type 2 diabetes. Both the DAPA-CKD and EMPA-KIDNEY studies were discontinued prematurely because of positive results in the SGLT2 inhibitor arms.

Several studies have indicated that cardiovascular outcomes, including hospitalisation for heart failure, may be better in patients with lower baseline estimated glomerular filtration rate (eGFR).[34,36,71] In one meta-analysis, hazard ratios (HRs) for 3-point MACE were 0.94, 0.90, 0.84 and 0.71 for baseline eGFR > 90, 60–90, 45–60 and < 45 ml/min/1.72 m^2, respectively.[34] Kidney outcomes were fairly consistent across eGFR at < 45–90 ml/min/1.72 m^2. Although the glucose-lowering effects of SGLT2 inhibitors require adequate GFR, cardio-renal benefits have been demonstrated in patients with GFRs as low as 25 ml/min/1.72 m^2.[29]

In patients with heart failure, clinically meaningful improvements were observed regardless of ejection fraction ≤ 65%, and in patients taking standard therapies for heart failure (including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or sacubitril/valsartan plus a beta-blocker, with or without a mineralocorticoid receptor antagonist) and with device therapy (an implantable cardioverter-defibrillator, cardiac resynchronisation therapy, or both).[25,27,28,72]

Based on these studies, SGLT2 inhibitors are recommended for treatment of patients with heart failure with reduced ejection

Table 6: Outcomes in SGLT2 inhibitor studies of patients with heart failure or CKD

Study	Baseline characteristics[a]	SGLT2 inhibitor and follow-up duration	CV outcomes Hazard ratio (95% CI)[b]	Kidney outcomes Hazard ratio (95% CI)
Patients with heart failure (including patients with and without T2D)				
DAPA-HF[25]	HFrEF; NYHA class II, III or IV *N* = 4 744 Mean age 66 BMI 28 kg/m^2 42% T2D 38% AF eGFR 66.0 ml/min 48% HHF in preceding 12 months	Dapagliflozin 10 mg versus placebo, once daily 18.2 months (median)	• CV death, HF hospitalisation or urgent HF visit (PEP): HR 0.74 (0.65–0.85) T2D: HR 0.75 (0.63–0.90) No T2D: HR 0.73 (0.60–0.88) • Worsening HF (HHF or urgent visit for HF): HR 0.70 (0.59–0.83) • CV death: HR 0.82 (0.69–0.98) • CV death or HF hospitalisation: HR 0.75 (0.65–0.85)	
EMPEROR-Reduced[27]	HFrEF; NYHA class II, III or IV *N* = 3 730 Mean age 67 BMI 28 kg/m^2 50% T2D 36% AF eGFR 62 ml/min 72% hypertension 31% HHF in preceding 12 months	Empagliflozin 10 mg versus placebo, once daily 16 months (median)	• CV death or HHF (PEP): HR 0.75 (0.65–0.86) T2D: HR 0.72 (0.60–0.87) No T2D: HR 0.78 (0.64–0.97) • HHF: HR 0.70 (0.58–0.85)	• Annual rate of decline in eGFR: slower in the empagliflozin group (−0.55 versus −2.28 ml/min/year; $p < 0.001$) • Composite renal outcome (chronic dialysis or kidney transplantation, or sustained reduction of eGFR ≥ 40%, or sustained estimated GFR < 15 ml/min in patients with a baseline eGFR ≥ 30 ml/min, or sustained eGFR < 10 ml/min in patients with a baseline eGFR < 30 ml/min): HR 0.50 (0.32–0.77)
EMPEROR-Preserved[28]	HFpEF; NYHA class II, III or IV *N* = 5 988 Mean age 72 BMI 29.8 kg/m^2 49% T2D 51% AF eGFR 61 ml/min 91% hypertension 23% HHF in preceding 12 months	Empagliflozin 10 mg versus placebo, once daily 26.2 months (median)	• CV death or HHF (PEP): HR 0.79 (0.69–0.90) T2D: HR 0.79 (0.67–0.94) No T2D: HR 0.78 (0.64–0.95) • HHF: HR 0.73 (0.61–0.88)	• Annual rate of decline in eGFR: slower in the empagliflozin group (−1.25 versus −2.62 ml/min/year; $p < 0.001$)
DELIVER[74]	HFpEF; NYHA class II, III or IV *N* = 6 263 Mean age 72 BMI 29.8 kg/m^2 45% T2D 56% AF/flutter eGFR 61.0 ml/min 41% prior HHF	Dapagliflozin 10 mg versus placebo, once daily 2.3 years (median)	• CV death, HF hospitalisation or urgent HF visit (PEP): 0.82 (0.73–0.92) T2D: HR 0.83 (0.70–0.97) No T2D: HR 0.81 (0.68–0.96) • Worsening HF (HHF or urgent visit for HF): HR 0.79 (0.69–0.91) • HHF: HR 0.77 (0.67–0.89) • Worsening HF or CV death: HR 0.77 (0.67–0.89)	No predefined renal endpoints
Patients with CKD and T2D				
CREDENCE[23]	T2D and CKD *N* = 4 401 Mean age 63 BMI 31 kg/m^2 DOD 15.8 years Mean eGFR 56.2 ml/min	Canagliflozin 100 mg versus placebo, once daily 2.62 years (median)	• CV death, MI or stroke: HR 0.80 (0.67–0.95) • CV death or HHF: HR 0.69 (0.57–0.83) • HHF: 0.61 (0.47–0.80) • CV death, MI, stroke, or HHF or hospitalisation for angina: HR 0.74 (0.63–0.86)	• Composite of ESKD (dialysis, transplantation, or a sustained eGFR of < 15 ml/min), a doubling of the serum creatinine level, or death from renal or CV causes (PEP): HR 0.70 (0.59–0.82) • ESKD: HR 0.68 (0.54–0.86) • Doubling of the serum creatinine level: HR 0.60 (0.48–0.76)

(*Continued*)

Table 6: Continued.

Study	Baseline characteristics[a]	SGLT2 inhibitor and follow-up duration	CV outcomes Hazard ratio (95% CI)[b]	Kidney outcomes Hazard ratio (95% CI)
	50% CVD 97% hypertension 15% HF			• Dialysis, kidney transplantation, or renal death: HR 0.72 (0.54–0.97)
Patients with CKD (including patients with and without T2D)				
DAPA-CKD[29]	CKD eGFR ≥ 25 to ≤ 75 ml/min; mean 43 ml/min; 59% < 45 ml/min; 14% < 30 ml/min) *N* = 4 304 Mean age 61 BMI 29.4 kg/m^2 67% T2D 38% CVD 11% HF	Dapagliflozin 10 mg versus placebo, once daily 2.4 years (median)	• CV death or HHF: HR 0.71 (0.55–0.92) • All-cause death: HR 0.69 (0.53–0.88)	• Worsening kidney function (sustained decline in the eGFR of ≥ 50%, ESKD, or renal death): HR 0.56 (0.45–0.68) • Worsening kidney function or CV death (PEP): Overall: HR 0.61 (0.51–0.72) T2D: HR 0.64 (0.52–0.79) No T2D: HR 0.50 (0.35–0.72) • ESKD: HR 0.64 (0.50–0.82)
EMPA-KIDNEY[65,75]	CKD at risk of progressive disease eGFR ≥ 20 to < 45 ml/min or eGFR ≥ 45 to < 90 ml/min with uACR ≥200 mg/g Mean eGFR 37.5 ml/min; 34% < 30; 44% ≥ 30–< 45; 21% ≥ 45 ml/min KDIGO risk category: 26% low, moderate or high; 74% very high *N* = 6 609 Mean age 63.9 BMI 29.7 kg/m^2 46% diabetes 44% T2D 26% CVD 10% HF 7% PAD	Empagliflozin 10 mg versus placebo, once daily	• Composite outcome of kidney disease progression or cardiovascular death (PEP) (kidney disease progression is defined as ESKD, renal death, a sustained decline in eGFR to < 10 ml/min or a ≥ 40% eGFR decline): HR 0.72 (0.64–0.82) • Hospitalisation for any cause: HR 0.86 (0.78–0.95)	• Progression of kidney disease: HR 0.71 (0.62–0.81) • ESKD or CV death: HR 0.73 (0.59–0.89)

[a]Baseline characteristics approximated for active treatment group. [b]Risk reduction can be calculated by subtracting HR from 1; e.g. for HR 0.65, risk reduction is 0.35 = 35%.

AF: atrial fibrillation; BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; CVD: cardiovascular disease; DOD: duration of diabetes (median); eGFR: estimated glomerular filtration rate (ml/min/1.72 m^2); ESKD: end-stage kidney disease; HHF: hospitalisation for heart failure; HFpEF: heart failure with preserved ejection fraction (> 40%); HFrEF: heart failure with reduced ejection fraction (< 40%); HR: hazard ratio; KDIGO: Kidney Disease: Improving Global Outcomes; NYHA: New York Heart Association heart failure classification; PAD: peripheral artery disease; PEP: primary endpoint; T2D: type 2 diabetes; uACR: urinary albumin:creatinine ratio.

fraction (HFrEF), those with ejection fraction up to approximately 55% and those with CKD (eGFR > 25 ml/min) with albuminuria, regardless of whether or not they have diabetes.[43,44,63,73]

Conclusion

In large-scale randomised controlled trials, the SGLT2 inhibitors reduced the risk of adverse cardiovascular and renal outcomes in patients with type 2 diabetes. They also improved outcomes in patients with heart failure with reduced ejection fraction and CKD, regardless of diabetic status. Data from more recent trials suggest that SGLT2 inhibitors may also reduce cardiovascular and kidney morbidity across a wider range of patients, including those with type 2 diabetes regardless of ASCVD risk, and patients with heart failure with preserved ejection fraction.[24,28,73] It is important for clinicians to be aware which patients are likely to gain the most benefit from these agents. In those patients, timeous initiation of treatment has the potential to reduce morbidity and mortality.

Key points

- In large randomised controlled trials, the SGLT2 inhibitors reduced major cardiovascular outcomes, hospitalisation for heart failure and adverse kidney outcomes, independently of their glucose-lowering effects.
- Compelling indications for SGLT2 inhibitors in patients with type 2 diabetes include those at high or very high risk of cardiovascular events and those with established atherosclerotic cardiovascular disease.
- SGLT2 inhibitors are also indicated for patients with heart failure and chronic kidney disease, regardless of diabetic status.

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