Sodium–glucose Cotransporter 2 Inhibitors in Heart Failure: Potential Mechanisms of Action, Adverse Effects and Future Developments

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Abstract

Heart failure is a common complication in patients with diabetes, and people with both conditions present a worse prognosis. Sodium–glucose cotransporter 2 inhibitors (SGLT2Is) increase urinary glucose excretion, improving glycaemic control. In type 2 diabetes (T2D), some SGLT2Is reduce major cardiovascular events, heart failure hospitalisations and worsening of kidney function independent of glycaemic control. Multiple mechanisms (haemodynamic, metabolic, hormonal and direct cardiac/renal effects) have been proposed to explain these cardiorenal benefits. SGLT2Is are generally well tolerated, but can produce rare serious adverse effects, and the benefit/risk ratio differs between SGLT2Is. This article analyses the mechanisms underlying the cardiorenal benefits and adverse effects of SGLT2Is in patients with T2D and heart failure and outlines some questions to be answered in the near future.

Keywords

Type 2 diabetes, heart failure, sodium–glucose cotransporter, sodium-glucose cotransporter inhibitors, cardiovascular outcome trials, safety profile

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Type 2 diabetes (T2D) remains a major cardiovascular (CV) risk factor[1–5] and it confers an approximately two- to threefold fold excess risk for coronary heart disease, including MI, stroke and heart failure (HF) in patients with and in patients without established cardiovascular disease (CVD).[1,6–8] The prevalence of T2D among patients with HF is as high as 40–45% and that of HF in patients with T2D is reported to be 10–23%.[8] Patients with both conditions – regardless of ejection fraction – present a higher risk of hospitalisation for HF (HHF), all-cause and CV mortality, irrespective of ischaemic/non-ischaemic aetiology.[8–10] The risk is further increased in the presence of diabetic nephropathy. Therefore, new therapeutic strategies that improve symptoms and reduce mortality and hospitalisations are needed for patients with T2D, HF and renal impairment.

For decades, it was hypothesised that glucose-lowering drugs (using HbA_{1c} as a surrogate marker) might improve CV outcomes. However, this glucocentric approach was proved incorrect because firstly, some glucose-lowering drugs (muraglitazar, rosiglitazone) decreased HbA_{1c} levels but worsened CV outcomes, and secondly, the results of the post-trial follow-up of the UK Prospective Diabetes Study (UKPDS),and of a meta-analysis of large glucose-lowering outcome trials,suggested an approximately 15% cardiovascular risk reduction (RR) per 1% decrement in HbA_{1c}.[11,12] The UKPDS recruited low-risk patients with newly diagnosed T2D (only 7.5% had CVD at baseline). During the interventional phase of the study, intensive glucose control using metformin and sulphonylurea-insulin reduced HbA_{1c} by 0.9% for a median of 10 years, but not the risk of death, MI, HF, stroke, or amputations.[11] However, in the 10-year post-trial follow-up, patients originally randomised to intensive therapy achieved a significant reduction in MI (15%) and all-cause mortality (13%) despite an early loss of glycaemic differences between the intensive and conventional therapy groups.[13]

These findings suggested that early and intensive glucose control in newly diagnosed T2D patients could have long-term benefits ('legacy effect'), irrespective of treatment modality. However, the meta-analysis of randomised controlled trials (RCTs) of more- versus less-intensive glycaemic control in patients with long-standing T2D (8–12 years) and either known CV disease or other risk factors showed that more-intensive glycaemic control (difference in HbA_{1c} 0.9%) was associated with a significant 9% RR for the composite of major adverse cardiovascular events (MACE; CV death, nonfatal stroke or nonfatal MI) during an average follow-up of 4.4 years. This reduction was driven primarily by a 15% RR in MI. However, intensive glucose lowering did not reduce the risk of fatal/nonfatal stroke, peripheral artery disease, hospitalised or fatal HF or CV and all-cause mortality, but increased the risk of severe hypoglycaemia.[12,14]

The differences in outcomes among these studies and the long-term 'legacy effect' observed in the UKPDS could be related to important

differences in the study populations, HbA_{1c} reduction from baseline, speed of HbA_{1c} lowering, duration of follow-up and background therapies.

Because of the concerns regarding adverse cardiovascular outcomes with antidiabetic agents, in 2008 the US Food and Drug Administration (FDA) mandated sponsors to conduct long-term cardiovascular outcome trials (CVOTs) for ensuring the cardiovascular safety of all new glucose-lowering drugs, with a focus on MACE.[15] Surprisingly, HF was not included as a component of composite endpoints.

Recent CVOTs performed with three sodium–glucose cotransporter 2 inhibitors (SGLT2Is; canagliflozin, empagliflozin and dapagliflozin) demonstrated noninferiority compared with placebo in the MACE primary composite end point and that they reduced the risk of HHF and of progression of renal disease, regardless of the presence of atherosclerotic CVD or HF at baseline.[16] These findings represent a clinical breakthrough in treating T2D as compared with classical glucose-lowering drugs. This article analyses the effects of SGLT2Is in CVOTs, the mechanisms underlying their cardiorenal benefits and their safety profile, together with questions that should be answered in the near future.

SGLT2 Inhibitors

Sodium-dependent glucose cotransporters (SGLTs) are responsible for tissular glucose translocation. SGLT1 is widely expressed in numerous organs (the distal S3 segment of the proximal renal tubule, intestines, heart and skeletal muscles), while SGLT2 is expressed in the luminal surface of the S1 segment of the proximal tubule and alfa-pancreatic cells.[17–19] The active transport of glucose via SGLT2 is linked to Na^+ transport maintained by its active extrusion via the Na^+/K^+ ATPase of the basolateral membrane into the intracellular fluid. Under normal conditions, glucose is freely filtered into the urine at the glomerulus (180 g/day) and reabsorbed in the proximal tubuli by SGLT2 (90%) and SGLT1 (10%).[20]

The plasma glucose concentration above which urinary glucose excretion occurs is approximately 180–200 mg/dl, but under diabetic conditions increases up to 300 mg/dl because of the increased activity of SGLT2. SGLT2Is (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin) shift the renal tubular threshold for glycosuria to 50 mg/dl, reduce the reabsorption of filtered glucose (30–50%) and increase glycosuria, decreasing plasma glucose and HbA_{1c} levels independent of insulin.[17] Because glycosuria occurs only in the presence of hyperglycaemia, the risk of hypoglycaemia with SGLT2Is is low. Additionally, because Na^+ is co-transported with glucose, SGLT2Is cause an osmotic diuresis (increased urine output 107–450 ml/day) and a small natriuresis.[21]

Cardiovascular Outcomes Trials with SGLT2Is

Cardioprotective Effects

The effects of empagliflozin, canagliflozin and dapagliflozin were analysed in three CVOTs: EMPAgliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients – Removing Excess Glucose (EMPA-REG OUTCOME), the CANagliflozin cardioVascular Assessment Study (CANVAS) Program and Dapagliflozin Effect on CardiovascuLAR Events – Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) respectively (*Table 1*).[22–24]

The EMPA-REG OUTCOME trial recruited patients with T2D and established CVD (secondary prevention).[22] Empagliflozin (pooled data of 10 and 25 mg doses) reduced the primary MACE outcome, an effect driven by a marked risk reduction in CV death (38%), without significant effects on atherosclerotic ischaemic events (nonfatal MI and nonfatal stroke). Additionally, empagliflozin significantly reduced all-cause, sudden and HHF. The reduction in HHF was observed in patients with and without documented HF at baseline and was associated to a reduction in the introduction of loop diuretics.[22,25] The benefits were consistent among subgroups defined by baseline characteristics, including age, HbA_{1c} levels, BMI, estimated glomerular filtration rate (eGFR) or patients with versus without HF and across categories of medications to treat diabetes and/or HF.[22,25–27]

The CANVAS Program integrated 2 trials (CANVAS and CANVAS-Renal) recruiting participants with T2D and established CVD (65.6%) or at risk for CV events (primary prevention).[23] Canagliflozin significantly decreased MACE and HHF to a similar extent to empagliflozin. However, none of the three individual components of MACE, nor all-cause mortality, were significantly reduced by canagliflozin.[23] Thus, it is difficult to understand what drives the superiority of canagliflozin for MACE over placebo. The benefit for the primary outcome was abrogated in patients without established CVD, suggesting that the benefit may be mostly in secondary prevention, while the point estimate for HHF was similar in both cohorts, suggesting that this cardiac benefit may extended to diabetic individuals without overt CVD. Interestingly, the benefit on CV death or HHF may be greater in patients with a history of HF at baseline.[28,29]

The DECLARE-TIMI 58 trial recruited patients (40.6%) with established atherosclerotic CVD and with multiple risk factors for atherosclerotic CVD (59.4%).[24] Dapagliflozin met the pre-specified primary safety endpoint of noninferiority for MACE, but in the two primary efficacy analyses, it did not result in a significantly lower rate of MACE than placebo. However, dapagliflozin resulted in a lower rate of the other pre-specified primary efficacy outcome (the composite of CV death or HHF), which reflected a lower rate oh HHF, regardless of a history of atherosclerotic cardiovascular disease or HF.

Thus, SGLT2Is reduce HHF and exert cardioprotective effects in T2D patients, but there were important differences between the CVOTs (*Table 1*). First, almost all patients in the EMPA-REG OUTCOME trial received secondary prevention of CVD, while the CANVAS Program and DECLARE-TIMI 58 trial included patients who had or were at risk for atherosclerotic CVD (i.e. both primary and secondary prevention). Second, HHF and mortality outcome curves begin to separate within the first 3 months in the EMPA-REG study but later in other CVOTs, i.e. earlier than would be expected from any decrease in atherothrombotic events.[22-24,30,31] Third, only empagliflozin reduced both CV and all-cause mortality, probably because EMPA-REG OUTCOME was a secondary prevention trial and it is presumed that the higher the baseline risk for CV events the better the CV protection, while patients without CVD might require longer drug exposure to observe the benefits.[22] Finally, canagliflozin reduced the risk of nonfatal stroke, while a trend for an increased risk of stroke was observed with empagliflozin, which might be related to the higher CV risk of the population enrolled in EMPA-REG, including more patients with prior stroke (23% versus 19.3%).[32] In a *post hoc* analysis, this difference was attributed to events occurring >90 days after the last intake of study drug and driven by nonfatal ischaemic stroke, but there were no differences in the risk of recurrent, fatal, or disabling strokes, or transient ischaemic attacks, between empagliflozin and placebo.[32]

Renoprotective Effects

Chronic kidney disease (CKD) affects up to 40% of patients with T2D and increases mortality and morbidity.[33,34] In the CVOTs, mean baseline eGFR

Table 1: Characteristics of Cardiovascular Outcomes Trials Completed with Sodium–glucose Cotransporter 2 Inhibitors

Parameters	EMPA-REG OUTCOME[22]	CANVAS Program[23 †]	DECLARE-TIMI 58[24]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Number of patients/mean age (years)	7,020/63.1	10,142/63.3	17,160/63.9
Women (%)	28.5	35.8	37.4
White/Asian/black	72.6/21.5/5.1	78.3/12.7/3.3	79.4/13.5/3.6
Diabetes duration (years)	57% >10	13.5	10.5
HbA_{1c} (%)	8.0	8.2	8.3
BMI (kg/m^2)	30.7	32	32
Established CV disease (%)	99.5	65.6	40.6
Coronary artery disease (%) MI (%) Stroke (%) Heart failure (%) Peripheral artery disease (%)	76 47 23.5 10.1 21	57 – 19.3 14.4 20.8	33.0 – 7.6 10.0 6.0
Median follow-up time (years)	3.1	2.4	4.2
eGFR (ml/min/1.73 m^2)	83.1	76.5	85.2
eGFR <60 ml/min/1.73 m^2 (%)	25.9	20.1	7.4
Microalbuminuria (%)	10.9	22.6	
Macroalbuminuria (%)	28.5	7.6	
Prior history of amputations (%)	–	2.3	–
Primary endpoint	MACE (1)	MACE (1)	MACE (2); a composite of CVD or HHF
Three-point MACE: CV death, nonfatal MI, or nonfatal stroke	0.86 (0.74–0.99) NI, p<0.001 Superiority, p=0.04	0.86 (0.75–0.97) NI, p<0.001 Superiority, p=0.02	0.93 (0.84–1.03) NI, p<0.001 Superiority, p=0.17
CV death	0.62 (0.49–0.77)*	0.87 (0.72–1.06)	0.98 (0.81–1.17)
CV death or hospitalisation for HF	0.66 (0.55–0.79)*	0.78 (0.67–0.91)*	0.83 (0.73–0.95)*
All-cause mortality	0.68 (0.57–0.82)*	0.87 (0.74–1.01)	0.93 (0.82–1.04)
Hospitalisation for HF	0.65 (0.50–0.85)*	0.67 (0.52–0.87)*	0.73 (0.61–0.88)*
MI (fatal or nonfatal)	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)
Stroke (fatal or nonfatal)	1.18 (0.89–1.56)	0.87 (0.69–1.09)	1.01 (0.84–1.21)
Fatal or hospitalisation for HF	0.65 (0.50–0.85)*	0.67 (0.52–0.87)*	0.83 (0.73–0.95)*
Worsening of nephropathy[‡]	0.61 (0.53–0.70)*	0.60 (0.47–0.77)*	0.76 (0.67–0.87)*
Progression of albuminuria	0.62 (0.54–0.72)*	0.73 (0.67–0.79)*	
Dose (mg)	10 and 25	100 and 300	10
Approved clinical indication	As an adjunct to diet and exercise to improve glycaemic control in adults with T2D		
	Reduce the risk of CV death in adult patients with T2D and established CVD	Reduce the risk of MACE in adults with T2D and established CVD	

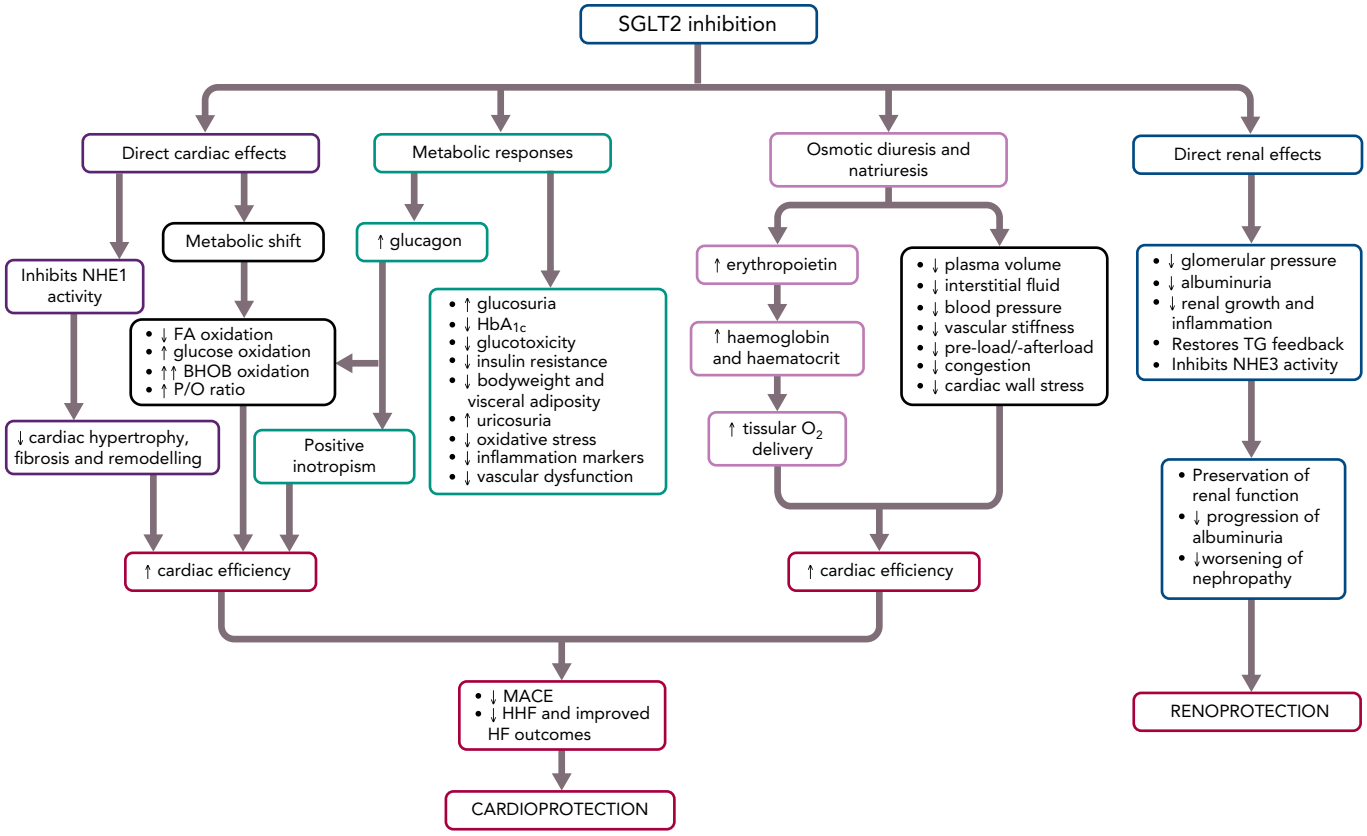
*Outcomes reported as HR (95% CI). * Significant. †Pooled data from CANVAS and CANVAS-R. MACE(1): death from cardiovascular causes, nonfatal MI, or nonfatal stroke. MACE(2): CV death, MI, or ischaemic stroke. ‡Worsening nephropathy was defined as doubling of the serum creatinine level and an eGFR of ≤45 ml/min/1.73m^2, the need for continuous renal-replacement therapy, or death due to renal events in EMPA-REG OUTCOME; 40% reduction in eGFR, renal-replacement therapy, or death from renal causes in CANVAS; sustained decrease of ≥40% in eGFR to <60 ml/min/1.73m^2, new end-stage renal disease, or death from any cause in DECLARE-TIMI 58. CANVAS = CANagliflozin cardioVascular Assessment Study; CV = cardiovascular; CVD = cardiovascular disease; DECLARE-TIMI 58 = Dapagliflozin Effect on CardiovascuLAR Events – Thrombolysis in Myocardial Infarction 58; eGFR = estimated glomerular filtration rate; EMPA-REG = EMPAgliflozin cardiovascular outcome event trial in type 2 diabetes mellitus patients – Removing Excess Glucose; HF = heart failure; MACE = major adverse cardiovascular events; NI = noninferiority; SGLT2I = sodium–glucose cotransporter 2 inhibitor; T2D = type 2 diabetes.*

ranged between 76 and 85 ml/min/1.73m^2 but there were important differences in the percentage of patients with an eGFR <60 ml/min/1.73 m^2 or with macro/microalbuminuria (*Table 1*). Canagliflozin, dapagliflozin and empagliflozin showed a favourable effect on renal outcomes and slowed the progression of albuminuria and new onset or worsening nephropathy, even when the components of renal outcomes differ between CVOTs (*Table 1*).[16,22–24,30,31]

In the EMPA-REG OUTCOME trial, where 25.9% of the population had CKD, the relative reductions in the risk of MACE, CV death, all-cause mortality, and HHF were independent of eGFR down to 30 ml/min/1.73m^2 or albuminuria status at baseline and similar across the two doses of empagliflozin versus placebo.[27] Similarly, in the CANVAS Program (20.1% of patients had CKD), the effects of canagliflozin on MACE, HHF and progression of kidney disease appeared similar across different levels of kidney function down to eGFR levels of 30 ml/min/1.73m^2.[35] These findings require further confirmation in specific, powered trials in patients with diabetic kidney disease.

Interestingly, the curves of renal outcomes start to separate within the first months and were maintained for >3 years, and the renal benefits were observed in patients on renin–angiotensin–aldosterone system (RAAS) inhibitors and with an eGFR >30 ml/min/1.73 m^2, despite the attenuated HbA_{1c}-lowering effects in this setting.[22-24,30,31,36]

Figure 1: Potential Mechanisms Involved in the Cardioprotective and Renoprotective Effects of Sodium–glucose Cotransporter 2 Inhibitors



BHOB = 3-beta-hydroxybutyrate; FA = fatty acid; HHF = hospitalisations for HF; MACE = major adverse cardiovascular events; NHE = Na+-H+ exchanger; P/O = ATP yield per oxygen atom consumed of oxidative phosphorylation; SGLT2 = sodium-glucose cotransporter 2; TG = tubuloglomerular.

Because patients with lower eGFR at baseline are at an increased risk of HHF, the renoprotective effects of SGLT2Is may contribute to improved HF outcomes.[30,31,36,37]

Mechanisms of Action

Multiple mechanisms are proposed to explain the early cardiorenal benefits of SGLT2Is[17–20,22,36–73] (*Figure 1 and Table 2*). The early benefits observed in EMPA-REG OUTCOME and CANVAS Program cannot be explained by the modest changes in HbA_{1c}, blood pressure (BP), weight, visceral adiposity, uricaemia or haematocrit, alone or in combination, suggesting that other glucose-independent mechanisms may contribute to the cardiorenal protective effects of SGLT2Is.[19,30,36,37,41,55] In fact, the reduction in CV events related to glucose control appears only after many years of follow-up[17,37] and in T2D patients antihypertensive therapy takes years to reduce major CV events, including nonfatal stroke and MI which remain unaltered with SGLT2Is.[17,43,44,74]

Three hypotheses have been proposed to explain the beneficial CV effects of SGLT2Is – the diuretic hypotheses, the thrifty substrate hypothesis and the NHE (Na^+-H^+ exchanger) hypothesis.

The Diuretic Hypotheses

The early (<3 months) and significant reduction in HHF and CV mortality produced by empagliflozin in the absence of significant changes in the incidence of MI or stroke suggests that the predominant mechanism may relate to its haemodynamic effects. It has been hypothesised that the reduction in Na^+ and water retention, leading to reduced ventricular filling pressure and cardiac workload, could be an important mechanism.[30,75–77] Indeed, an exploratory analysis of the EMPA-REG OUTCOME trial showed that changes in markers of plasma volume were the most important mediators of the reduction in the risk of CV death with empagliflozin versus placebo.[75] However, the diuretic effects of SGLT2Is are quite different from those observed with thiazide or loop diuretics.[77]

The first reason for this is that SGLT2Is act in the proximal tubule, where they inhibit glucose and Na^+ reabsorption resulting in osmotic diuresis. However, compared with osmotic diuretics, SGLT2Is do not affect plasma osmolarity.

Second, because SGLT2Is work in the proximal tubule, they increase delivery of fluid and electrolytes to the macula densa, thereby activating tubuloglomerular feedback, an effect that is not achieved by loop and thiazide diuretics because they reduce Na^+ flux to the macula densa.[17,69] Third, compared with loop diuretics, SGLT2Is produce a greater fluid clearance from the interstitial fluid space than from the circulation, potentially resulting in better congestion relief with minimal impact on BP, arterial filling and organ perfusion or inducing a neurohumoral activation.[78]

Furthermore, SGLT2Is produce greater electrolyte-free water clearance than loop or thiazide diuretics acting at different sites of the nephron and producing more potent diuresis and natriuresis.[17,20] Finally, loop diuretics reduce HHF but not CV mortality[69] and their long-term use reduces the risk of stroke but can worsen renal function renal function – effects that are not observed with SGLT2Is.[33,69,70,77] Because

Table 2: Mechanisms of Action Underlying the Beneficial Effects of Sodium–glucose Cotransporter 2 Inhibitors on Cardiovascular and Renal Outcomes

Pharmacological Effect	Cardiovascular and Renal Benefits of SGLT2Is
Glycosuria[17–19,36–38]	• Reduce glucose and Na^+ reabsorption in the proximal tubule • Urinary glucose excretion (60–100 g/day) decreases fasting plasma glucose (–0.73 mmol/l) and HbA_{1c} levels (0.4–1.1%) • Increase loss of calories and decrease body weight • Decrease serum uric acid levels • Reduce the cardiac effects of glucotoxicity
Osmotic diuresis and natriuresis[17–19,22,39–41]	• Decrease plasma volume (cardiac preload) and total Na^+ tissue content • SGLT2Is produce a greater fluid clearance from the interstitial space than from the circulation, resulting in better control of congestion without reducing arterial filling and tissue perfusion • Decrease ventricular preload and wall tension and elevated filling pressures • Counteract insulin-related fluid retention • These effects would reduce congestion, clinical decompensation and the risk of HHF
BP reduction[19,39,42–44]	• Due to osmotic diuresis and natriuresis and a reduction in intravascular volume and vascular stiffness, reduce BP (3.4–5.4/1.5–2.2 mmHg). • Reduce afterload, intracardiac filling pressures and wall stress and may prevent clinical decompensation • Do not produce a reflex sympathetic activation
Decrease arterial stiffness and PVR[40,42,45]	• Arterial stiffness is a well-recognised predictor of CV morbidity and mortality • Due to weight loss, circulating volume contraction and vascular smooth muscle relaxation through a negative Na^+ balance • Reduce PVR, BP and afterload, improve subendocardial blood flow and may contribute to reduce HHF
Decrease body weight and visceral adiposity[17–19,36,37,46]	• Glycosuria results in caloric loss (240–400 Kcal/day) and body weight reduction (1.8–2.7 kg) • Visceral adiposity is associated with adverse left ventricular remodelling, lower cardiac output and increased PVR
Increase in haemoglobin and haematocrit levels[19,39,47]	• Due to due osmotic diuresis and a transient increase in erythropoietin secretion • Improve myocardial/tissular oxygen delivery
Anti-inflammatory and antioxidant effects[48,49]	• Reduce oxidative stress, pro-inflammatory and pro-oxidant biomarkers, decrease the formation of advanced glycation end products and improve endothelial function
A shift in cardiac and renal fuel energetics[41,50–55]	• Shift fuel energetics from FFA and glucose toward ketone bodies - Produce ATP energy more efficiently - Decrease myocardial and renal O_2 consumption - Reduce hypoxic stress on the diabetic heart and kidney - Increase cardiac work efficiency and function
Metabolic effects[19,36,37,54–56]	• Decrease excess glucose uptake by the heart • Release glucagon which increases hepatic ketogenesis and exerts positive cardiac inotropic and chronotropic effects • Produce an uricosuric effect via the glucose transporter member 9 (GLUT9) and decrease uric acid levels • Increase LDL-/HDL-cholesterol and reduce triglyceride plasma levels
Cardioprotective effects [19,36,37,41,50,55–66]	• Inhibit NHE3 • Reduce intracellular Na^+ and Ca^{2+} load and increase mitochondrial Ca^{2+} levels in failing cardiac myocytes and in the diabetic kidney • Restore mitochondrial function, activate ATP production and improve systolic function in the failing heart • Slow the progression of LV hypertrophy in diabetic patients • In animal models, reduce myocardial fibrosis, hypertrophy and remodelling, decrease cardiac macrophage infiltration and improve systolic/diastolic function
Renoprotective effects[18–20,67–71]	• Decrease hyperglycaemia and BP • Inhibit NHE1 and 3 • Restore tubuloglomerular feedback, produce afferent vasoconstriction and decrease intraglomerular pressure and hyperfiltration • Reduce the progression of renal disease • Renoprotective effects may contribute to the reduction in HHF

BP = blood pressure; FFA = free fatty acids; HHF = hospitalisation for heart failure; LV = left ventricular; NHE = Na^+-H^+ exchanger; PVR = peripheral vascular resistances; SBP/DBP = systolic/diastolic BP; SGLT2I = sodium-glucose cotransporter 2 inhibitor.

of these important differences, it is unlikely that SGLT2Is prevent HHF by acting simply as diuretics.[20,37,39]

The Thrifty Substrate Hypothesis

A shift in cardiorenal fuel energetics (the 'thrifty substrate' hypothesis). Under physiological conditions, nearly 95% of cardiac energy is derived from mitochondrial oxidative metabolism and fuel is derived from free fatty acids (FAs; 60–70%), glucose (30%) and – to a lesser degree – lactate, ketones and amino acids.[79] In T2D, glucose utilisation decreases while oxidation of FAs markedly increases because of peripheral insulin resistance and inability of insulin to suppress lipolysis.[37,80,81] These changes decrease cardiac efficiency/function because excessive FA oxidation is energetically less efficient, increases oxidative stress and cardiac lipotoxicity and impairs LVF.[37,50,80,81] SGLT2Is increase the hepatic synthesis and decrease the urinary excretion of ketones producing a mild,

but persistent, hyperketonaemia.[51] Under these conditions beta-hydroxybutyrate (BHOB) is freely taken up by the heart and kidney and oxidised in preference to FAs and glucose, producing ATP more efficiently. In fact, ATP production/O_2 consumption ratio (P/O) favours BHOB (2.50) over FA (2.33), and even when the P/O ratio of BHOD and pyruvate are similar, the combustion of BHOB liberates 31% more calories.[50–53,82]

In rat hearts, BHOB increases external cardiac work and reduces oxygen consumption, thereby improving cardiac efficiency in the diabetic heart.[48–53,82] Thus, it has been hypothesised that the cardiorenal benefits of SGLT2Is might be related to a shift in cardiorenal metabolism away from FAs and glucose oxidation toward ketone bodies, a more energy-efficient fuel, which improves cardiac and renal work efficiency/function, reduces oxygen consumption and exhibits antioxidative and antiarrhythmic properties.[41,50–53] The utilisation of ketones together with an increased oxygen delivery from SGLT2I-induced haemoconcentration and a reduced cardiac load resulting from decreases in intravascular volume and BP could be involved in the early benefits observed in CVOTs.

The NHE Hypothesis

A reduction in intracellular sodium ($[Na^+]_i$) by inhibiting the sarcolemmal Na^+-H^+ exchanger (NHE; the NHE hypothesis).[19,50,55,72] NHE1 is the predominant isoform in the heart and vasculature, while NHE3 is expressed at the apical surface of renal epithelial cells where it co-localises and functionally interacts with SGLT2.[55] In patients with T2D and HF, the activity of NHE1/3 is markedly enhanced. This increase facilitates the accumulation of intracellular Na^+ ($[Na^+]_i$), which stimulates the reverse activity of the Na^+/Ca^{2+} exchanger (NCX) leading to an increase in $[Ca^{2+}]_i$ and cardiomyocyte injury, facilitates mitochondrial Ca^{2+} extrusion to the cytoplasm and decreases mitochondrial Ca^{2+} ($[Ca^{2+}]_m$).[55,58–62,83] The reduction in $[Ca^{2+}]_m$ impairs Ca^{2+}-induced stimulation of Krebs cycle dehydrogenases and reduces ATP production and mitochondrial antioxidative capacity.[54,55,58,60–63,71]

Even when SGLT2 is not expressed in the heart, SGLT2Is can inhibit cardiac NHE1, possibly through a binding site for SGLT2 on NHE1.[55] The inhibition of NHE1 reduces intracellular Na^+ and Ca^{2+} concentrations and increases $[Ca^{2+}]_m$, which restores mitochondrial function and redox state, activates ATP production in the failing heart and improves systolic function.[55,62] In animal models, SGLT2Is via the inhibition of NHE1 reduce cardiac hypertrophy and fibrosis and ventricular arrhythmias, slow the progression of left ventricular (LV) remodelling and diabetic cardiomyopathy and improve systolic/diastolic function.[55,57–68] In normotensive patients with T2D and established coronary artery disease, but without HF, empagliflozin significantly reduces LV mass and slows the progression of LV hypertrophy versus placebo.[84] This finding suggests that empagliflozin promotes a reverse remodelling, which may contribute to the early cardiovascular and HF benefits observed in the EMPA-REG OUTCOME trial.

However, several questions remain unanswered, including the mechanism underlying the increase in BHOB, the time course of the hyperketonaemia, the relationship between the dose, hyperketonaemia and improvement in cardiac function, or whether hyperketonaemia might increase the risk of diabetic ketoacidosis (DKA).[59,79,83,84] Additionally, an increase in metabolic efficiency and/or NHE inhibition should prove beneficial in myocardial ischaemia and HHF, but in CVOTs these two endpoints were differentially affected by SGLT2Is.[50,79] Thus, at the present time, the 'thrifty substrate' hypothesis needs to be demonstrated.[83]

Renal Effects

In patients with T2D, glucose and Na^+ reabsorption increases in the proximal tubule via SGLT2 and Na^+ delivery to the macula densa decreases, which stimulates renin release by the juxtaglomerular cells and activates the RAAS. This causes, via tubuloglomerular feedback, an afferent arteriolar vasodilation that increases the GFR ('hyperfiltration') and contributes to diabetic nephropathy. SGLT2Is reduce Na^+ reabsorption in the proximal tubule and increase its delivery to the macula densa.[19,20,69,73,85] This inhibits renin release, activates tubuloglomerular feedback, produces an afferent arteriolar vasoconstriction, normalises the GFR and reduces intraglomerular pressure counteracting hyperglycaemia-induced hyperfiltration – an effect that would be expected to slow the progression of diabetic nephropathy.[17–20,69,70,73,85] However, afferent arteriolar vasoconstriction is present in patients with HF and an enhancement of such vasoconstriction would not be expected to produce favourable renal effects in non-diabetic patients with HF.[55] SGLTIs initially reduce eGFR (~5 ml/min/1.73m^2) and albuminuria (30–40%), but eGFR recovers baseline values after 6–12 months, reflecting a haemodynamic alteration rather than a glomerular damage.[31,84] Additionally, the renoprotective effects of SGLT2Is have been related to a decrease in hyperglycaemia, BP, glomerular capillary pressure and glomerular hyperfiltration, and direct effects on mesangial expansion, tubular growth, and inflammation.[18–20,69,70,85]

Adverse Events

SGLT2Is are generally well tolerated and adverse events (AEs) are considered mild-to-moderate in severity.[18–20,22-24,36,37,83,86–101] However, some serious AEs have been reported in postmarketing surveillance programs (*Table 3*). In the CANVAS Program, canagliflozin significantly increased the risk of fractures and below-knee lower extremity amputations.[23,95] In the EMPA-REG trial, amputations and fractures were not mentioned in the study protocol, but a *post-hoc* analysis reported a similar rate of both AEs with empagliflozin or placebo.[26,55] However, EMPA-REG and CANVAS were not powerful enough to detect significant differences in either amputation or fracture among the studied population. Recently, several real-world studies have led to contradictory conclusions on the risk of amputations[90–92,94] and a meta-analysis failed to demonstrate an increase in fracture events with SGLT2Is.[96] Therefore, it remains unclear whether the risk of these AEs extends across the drug class. Early trials raised the concern that SGLT2Is may increase the risk of bladder and breast cancer, and a meta-analysis suggested an increased risk of bladder cancer with empagliflozin.[100] However, given the short-term follow-up and uncertainty of evidence, future long-term prospective studies and postmarketing surveillance studies are warranted.

Unresolved Issues

Many questions remain to answered in future preclinical studies and carefully designed controlled trials (*Table 4*).

What are the mechanisms underlying the early cardiorenal benefits of SGLT2Is? CVOTs were designed to test the safety of SGLT2Is but not the mechanism of action. Therefore, the mechanisms underlying the early separation of the curves of CV mortality, HHF and progression of renal disease and the long-term sustained benefits of SGLT2Is are yet to be elucidated. It is possible that haemodynamic, metabolic,

Table 3. Adverse Effects of Sodium–glucose Cotransporter 2 Inhibitors

Adverse Effect	Risk Factors and Recommendations*
Infections[22–24,36,37,83,86]	• Related to glycosuria • Genital mycotic infections: balanitis and vulvovaginitis • UTIs: rare cases of pyelonephritis and urosepsis, sometimes requiring hospitalisation • Necrotising fasciitis of the perineum (Fournier's gangrene). Discontinue SGLT2Is and start treatment immediately with broad-spectrum antibiotics and surgical debridement if necessary • Risk factors: women, previous genital fungal infections, uncircumcised males • Monitor and treat infections as appropriate • Avoid SGLT2Is in patients with previous history of complicated UTIs, indwelling urinary catheter and recurrent genital mycotic infections • SGLT2Is may decrease quality of life in men with prostatic hypertrophy and women with urinary incontinence
Volume depletion	• Risk factors: elderly, patients with dehydration, hypovolaemia, renal impairment, low BP or taking diuretics or nephrotoxic drugs • Assess volume status and BP before initiating treatment - SGLT2Is should be used with caution or discontinued in the presence of hypovolaemia to avoid worsening of renal function - Delay SGLT2I therapy in hypovolaemic or hypotensive individuals until fluid status and BP are corrected • When SGLT2Is are combined with vasodilators or thiazide diuretics it may be necessary to reduce dose by 50%
Hypoglycaemia	• Glucose is not being filtered in the glomerulus when glycaemia is normal; thus, the risk of hypoglycaemia with SGLT2Is is low • Risk of hypoglycaemia when combined with insulin or sulfonylureas
Hypotension	• In combination with hypovolaemia can cause dizziness and orthostatic hypotension and may increase the risk of falls and fractures • The risk of symptomatic hypotension increases in the elderly, patients with renal impairment, low BP or treated with antihypertensives, diuretics or vasodilators • Monitor for signs and symptoms of hypotension
Acute kidney injury[17,36,37,101]	• Appears within 1 month of starting therapy with canagliflozin and dapagliflozin • Risk factors: volume depletion, hypotension, diuretics, ACE inhibitors, ARBs, NSAIDs, or nephrotoxic drugs • Monitor for signs and symptoms of acute kidney injury • SGLT2Is are contraindicated in patients with eGFR <45 ml/min/1.73 m^2 (dapagliflozin when <60 ml/min/1.73 m^2), severe renal impairment, end-stage renal disease, or dialysis
Diabetic ketoacidosis[19,36,37,87–89]	• Appears with mildly elevated glucose levels (<13.9 mmol/L) which can delay diagnosis and therapy • Osmotic diuresis may worsen the hypovolaemic state of DKA, particularly in patients with nausea and decreased oral intake • Risk factors: hypovolaemia, acute illness or surgery, alcohol abuse, carbohydrate restriction, low insulin secretory capacity, increased glucagon secretion, previous episodes of ketosis, latent autoimmune diabetes in adults and T1D (SGLT2 are not approved for use) • SGLT2Is should be stopped during acute illness and at least 48 h before any planned surgical procedure • SGLT2Is are contraindicated in patients with DKA
Lower-limb amputations[23,28,29,90–94]	• Canagliflozin may increase the risk of lower limb (toe or metatarsal) amputations. • SGLT2Is produce haemoconcentration and volume depletion and decrease in BP, effects that may reduce limb perfusion and produce tissue ischaemia. Canagliflozin activates AMP kinase, which inhibits complex I of the respiratory chain and favours tissue ischaemia • Risk factors: men, prior history of lower-limb amputation, advanced peripheral vascular disease, peripheral neuropathy, and diabetic foot ulcers. • EMA recommends careful monitoring of all patients receiving SGLT2Is, emphasising foot care. Consider stopping treatment if patients develop lower-extremity infections, new pain or tenderness, sores, ulcers, infection, osteomyelitis, or gangrene. • Avoid canagliflozin (all SGLT2Is) in patients at the highest amputation risk until more safety data are accumulated
Bone fractures[95–99]	• Canagliflozin (not empagliflozin or dapagliflozin) increases the rate of all-bone and low-trauma fractures within the first weeks of treatment • Independent of changes in bone mineral density or alterations in calcium homeostasis • Fractures possibly related to: increased parathyroid hormone and FGF23 excretion and orthostatic hypotension and postural falls due to volume depletion • Canagliflozin (possibly all SGLT2Is) should be used with caution in patients with fragility fractures or established osteoporosis, or at risk of falling
Increase of LDL cholesterol levels[54,57]	• The clinical meaning is uncertain. Monitor and treat as appropriate T2D and established CVD
Cancer[100]	• Avoid dapagliflozin in patients with active bladder cancer (and empagliflozin)?

**Recommendations according to the FDA and/or EMA.*
ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; BP = blood pressure; CVD = cardiovascular disease; DKA = diabetic ketoacidosis; eGFR = estimated glomerular filtration rate; EMA = European Medicines Agency; FDA = Food and Drug Administration; FGF = fibroblast growth factor; NSAIDs = non-steroidal anti-inflammatory drugs; SGLT2I = sodium–glucose cotransporter 2 inhibitor; T1D = type 1 diabetes; T2D = type 2 diabetes; UTI = urinary tract infection.

hormonal and direct cardiac and renal mechanisms, possibly unrelated to SGLT2 inhibition, and with different roles over time and in different populations might be involved. So, are the same mechanisms involved in the cardiovascular and renal benefits? A better understanding of the mechanisms of action is the first step to identify the patients who could benefit most from the use of SGLT2Is.

Table 4: Questions to Address in Future Preclinical and Clinical Research with SGLT2Is

1. What are the mechanisms underlying the early and long-term sustained benefits of SGLT2Is on cardiorenal outcomes? • Are the same mechanisms involved in the beneficial effects on cardiovascular and renal outcomes? • Where is SGLT2 expressed in the heart, vessels, kidney and peripheral and central nervous system controlling cardiovascular functions? • The putative mechanisms of action of SGLT2Is should be validated in *in vivo* models and patients with and without T2D, and in those with HF with reduced or preserved ejection fraction. • Are the mechanisms of action comparable across SGLT2Is or specific to individual compounds? • Are there ethnic variations in the response to SGLT2Is?
2. Is the cardiovascular and renal benefit a class effect? • Head-to-head comparisons among SGLT2Is are needed, but they will probably never be performed.
3. How can the marked differences observed in CVOTs among SGLT2Is be explained?
4. What is the benefit of SGLT2Is in patients with HF? • Can the benefits on HF be extended across the left ventricular ejection fraction spectrum in patients with and without T2D? • Can SGLT2Is improve cardiovascular and renal outcomes in patients with T2D but without established CVD? • Can SGLT2Is improve cardiovascular and renal outcomes in patients with CVD but without T2D? • Can the cardiovascular and renal benefits be extended to patients without established CVD or T2D? • What is the beneficial effect of SGLT2Is observed in individuals with newly diagnosed T2D without CVD or nephropathy? • Can SGLT2Is reduce the likelihood of developing CVD in lower-risk patients who have not yet manifested CVD?
5. Can the cardiovascular and renal protection observed in CVOTs be extrapolated to the real world? • Can the results be extrapolated to patients with T2D with or without established CVD?
6. What is the risk:benefit ratio of SGLT2Is in HF patients without T2D in the real world? • Can peripheral hypoperfusion present in HF patients increase the amputation risk? • Are lower-limb extremity amputations and fractures a class effect? • It is critical to clarify the association between SGLT2Is and risk of cancer.

CVD = cardiovascular disease; CVOT = cardiovascular outcome trials; HF = heart failure; SGLT2I = sodium-glucose cotransporter 2 inhibitor; T2D = type 2 diabetes.

Is the cardiorenal benefit a class effect? A class effect would not be expected if the underlying mechanisms are unrelated to SGLT2 inhibition. There are differences among SGLT2Is in their SGLT2/SGLT1 selectivity (>2,500 for empagliflozin, 1,116 for dapagliflozin, 250 for canagliflozin), pharmacokinetic properties and – possibly – pharmacodynamic off-target properties[17–19,36,37,102] Thus, there is no evidence that the benefits can be a 'class effect'. Indeed, the FDA and European Medicines Agency approved all SGLT2Is for glycaemic control in adults with T2D. Additionally, empagliflozin is also approved to reduce the risk of CV death in adults with T2D and established CVD, and canagliflozin to reduce the risk of MACE in adults with T2D and established CVD.

How can the marked differences observed in CVOTs among SGLT2Is be explained? *Table 1* shows that there are important differences between CVOTs in clinical outcomes related to differences in the recruited population, trial design, concurrent use of cardioprotective drugs, adjudication of CV events or statistical analysis.[20–22] In a recent meta-analysis of 13 clinical trials recruiting 34,533 diabetic patients (60.2% with established atherosclerotic CVD), the most consistent effect of SGLT2Is was to reduce HHF (31%) and progression of renal disease (45%), with a modest reduction in MACE (11%).[14] The reduction in MACE was apparent only in patients with established atherosclerotic CVD, while the reduction in HHF or progression of renal disease was observed regardless of the presence of atherosclerotic CVD, a previous a history of HF and across different levels of kidney function down to eGFR levels of 30 ml/min/1.73 m^2. Are ethnic differences implicated in the response to SGLT2Is? Asian participants (who account for almost half of the world's population with diabetes)[1] and white participants had better CV benefits than black participants in the EMPA-REG study, whereas canagliflozin was superior in black and white participants.[22,23] These findings suggest that the benefits of SGLT2Is may depend on the population in which they are used.

What is the real benefit of SGLT2Is in patients with HF? CVOTs were not designed to assess the efficacy of SGLT2Is in patients with HF. Indeed, <15% of the patients had HF at baseline, HF phenotyping – including echocardiography or biomarkers (B-type natriuretic peptide, troponin T) – was not performed, and effects of SGLT2Is on LV structure and function or haemodynamics remain to be determined. The significant reduction in HHF observed even in patients without atherosclerotic CVD or a history of HF raises the possibility of using SGLT2Is not only in the primary prevention but also for the treatment of HF patients with reduced and/or preserved ejection fraction.

Can the cardiovascular and renal protection observed in CVOTs be extrapolated to the real world? The observational Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) and CVD-REAL Nordic trials suggested that initiation of SGLT2Is versus other glucose-lowering drugs was associated with a lower risk of HHF and death regardless of pre-existing CVD, and with reduced CV mortality in patients with T2D and a broad cardiovascular risk profile.[103–106]

Therefore, the benefits observed with empagliflozin and canagliflozin may be a class effect applicable to a broad population of patients with T2D in real-world practice, including in primary prevention. However, because of the observational design, short follow-up and immortal time and time-lag biases, the >50% lower rates of all-cause mortality associated with the use of SGLT2Is in these trials are more likely exaggerated.[107] Additionally, in these trials only 25% of patients presented established CVD, most were treated with canagliflozin and dapagliflozin (not with empagliflozin) and drug safety was not reported. Thus, at the present time there is not enough evidence to extrapolate the data from the CVOTs to the real-world setting.[107]

What is the risk/benefit ratio of SGLT2Is in the real world? Optimal prescription of SGLT2Is requires the understanding of their risk/benefit ratio, but AEs should not overshadow their cardiorenal protective effects. Some serious AEs were not observed in CVOTs, possibly because of the short follow-up and the selection and strict supervision

of patients, but they were reported in postmarketing surveillance studies and some of these AEs were unexpected. Are bone fractures and amputations a class effect? What are the mechanisms involved in bone fractures and amputations? What is the clinical meaning of the trend in stroke in the EMPA-REG OUTCOME trial? Further research is needed to identify the risk factors for the development of serious AEs, including infections, Fournier's gangrene, acute kidney injury, DKA, amputations and bone factures in patients treated with the different SGLT2Is in daily clinical practice. Furthermore, there is little information on drug interactions between SGLT2Is and other treatments prescribed in patients with T2D and HF. In the EMPA-REG OUTCOME trial, the effect of empagliflozin on HHF was reduced by mineralocorticoid receptor antagonists, which only represented 6% of patients in this trial, but are used in >60% of HF patients. Drug–drug interactions should be analysed in long-term RCTs recruiting diabetic and non-diabetic patients with CVD.

The results of several on-going long-term randomised trials should provide key information on the cardiorenal protective effects of SGLT2Is in different patient populations, their safety profile, which patients are at greatest risk for serious AEs, and possible differences in the efficacy/safety profile between drugs of this pharmacological class. ■

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