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REVIEW

Potential Underlying Mechanisms Explaining the Cardiorenal Benefits of Sodium–Glucose Cotransporter 2 Inhibitors

Subodh Verma ⓘ · Sunder Mudaliar ⓘ · Peter J. Greasley ⓘ

ABSTRACT

There is a bidirectional pathophysiological interaction between the heart and the kidneys, and prolonged physiological stress to the heart and/or the kidneys can cause adverse cardiorenal complications, including but not limited to subclinical cardiomyopathy, heart failure and chronic kidney disease. Whilst more common in individuals with Type 2 diabetes, cardiorenal complications also occur in the absence of diabetes. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were initially approved to reduce hyperglycaemia in patients with Type 2 diabetes. Recently, these agents have been shown to significantly improve cardiovascular and renal outcomes in patients with and without Type 2 diabetes, demonstrating a robust reduction in hospitalisation for heart failure and reduced risk of progression of chronic kidney disease, thus gaining approval for use in treatment of heart failure and chronic kidney disease. Numerous potential mechanisms have been proposed to explain the cardiorenal effects of SGLT2i. This review provides a simplified summary of key potential cardiac and renal mechanisms underlying the cardiorenal benefits of SGT2i and explains these mechanisms in the clinical context. Key mechanisms related to the clinical effects of SGLT2i on the heart and kidneys explained in this publication include their impact on (1) tissue oxygen delivery, hypoxia and resultant ischaemic injury, (2) vascular health and function, (3) substrate utilisation and metabolic health and (4) cardiac remodelling. Knowing the mechanisms responsible for SGLT2i-imparted cardiorenal benefits in the clinical outcomes will help

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healthcare practitioners to identify more patients that can benefit from the use of SGLT2i.

Key Summary Points

There is a bidirectional pathophysiological interaction between the heart and the kidneys, with heart failure and chronic kidney disease often causing or worsening the other

Sodium-glucose cotransporter 2 inhibitors were initially approved for treatment of Type 2 diabetes but have since demonstrated significant cardiorenal benefits to patients with and without Type 2 diabetes; however, the mechanisms via which these benefits are imparted are largely unknown

We present three key SGLT2i mechanisms via which this class of therapeutics imparts its cardiorenal benefits; these include improvement in kidney function and tissue oxygen delivery, vascular health and function and metabolic health

The use of SGLT2i therapy in treating HF and CKD in individuals with and without T2D has a marked impact, reducing the risk associated with worsening of these conditions

DIGITAL FEATURES

This article is published with digital features, including an infographic to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.23968659.

INTRODUCTION

Heart failure (HF) and chronic kidney disease (CKD) are major health problems worldwide. Globally, approximately 64 million people are estimated to have HF, with the disease having a 5-year mortality rate of nearly 50% and predicted to rise significantly by 2030 (24% increase [1, 2]). Similarly, CKD-related mortality and rates of treatment requiring kidney replacement have been rising globally over the last few decades (Fig. 1) [3, 4]. Notably, despite this, a substantial number of patients with HF and CKD remain undiagnosed, especially in the early disease stages [5, 6].

HF and CKD form a vicious circle, in which one disease causes or worsens the other, leading to cardiorenal syndrome [7]. There is an interdependent relationship between the heart and kidneys, wherein the crosstalk is done via various haemodynamic, neurohormonal, inflammatory and metabolic processes [8]. The pathophysiological interaction between these organs is bidirectional, and prolonged physiological stress to either organ can ultimately lead to adverse cardiorenal complications, including but not limited to subclinical cardiomyopathy, advanced HF or CKD (Fig. 2) [9].

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) were initially approved for treatment of Type 2 diabetes—and act by selectively inhibiting SGLT2-mediated glucose and sodium reabsorption in the proximal tubule of the kidneys, leading to their increased excretion in the urine (known as glycosuria and natriuresis, respectively) and lowering of blood glucose levels in patients with diabetes. This mechanism of action is insulin independent, thus minimising the risk of hypoglycaemia [10].

SGLT2i have also been shown to reduce hospitalisations due to HF and death from cardiovascular (CV) causes in patients with and without T2D [11–16]. The EMPA-REG Outcome trial was the first SGLT2i study showing that patients with T2D at high risk for CV events receiving empagliflozin had a lower rate of death from CV causes, nonfatal myocardial infarction or nonfatal stroke and death from any cause [13]. Subsequently, DECLARE-TIMI
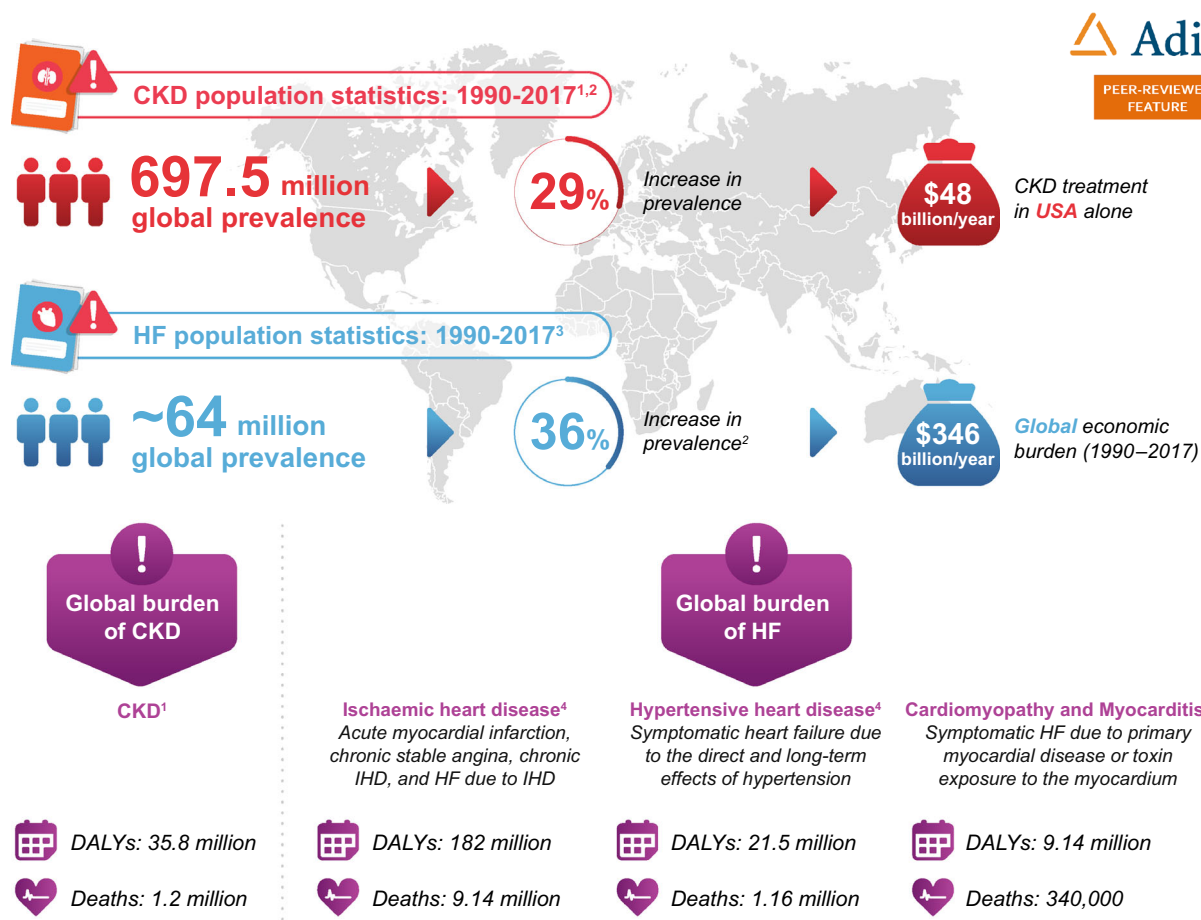
Fig. 1 Epidemiology and global burden of CKD and HF. Calculation of disease burden using DALYs: one DALY represents the loss of the equivalent of 1 year of full health. DALYs for a disease or health condition are the sum of the years of life lost to the condition because of premature mortality. *CKD* chronic kidney disease, *DALY*, disability-adjusted life year, *HF* heart failure, *IHD* ischaemic heart disease. 1. GDB collaboration. Lancet. 2020;395(10225):709–733; 2. National Kidney Foundation. https://www.kidney.org/kidneydisease/global-facts-about-kidney-disease; 3. Lippi et al. AME Med J. 2020;5:15; 4. Roth et al. J Am Coll Cardiol. 2020;76(25)2982–3021

58 and CANVAS showed that in patients with T2D with a history of atherosclerotic CV disease (CVD) or with high risk for CVD, both dapagliflozin and canagliflozin reduced the rate of CV death or hospitalisation for HF (hHF) [14]. A post hoc analysis of the DECLARE-TIMI 58 study showed that participants achieved cardiorenal benefits with dapagliflozin treatment, irrespective of their baseline HbA1c level [17]. Another large meta-analysis showed SGLT2i to have robust benefits on reducing hHF and progression of kidney disease regardless of existing atherosclerotic CVD or history of HF [18].

DAPA-HF was the first study to demonstrate the CV benefits of SGLT2i in patients with established HF and reduced ejection fraction, regardless of the presence of T2D [11]. The EMPEROR-preserved and -reduced trials and the CHIEF-HF trial replicated these results with empagliflozin and canagliflozin, respectively [16, 19, 20]. Recently, the DELIVER study showed that in patients with HF and a mildly reduced or preserved ejection fraction, dapagliflozin reduced the combined risk of worsening HF or CV death, with lowered symptom burden and without excess adverse events [21]. Results
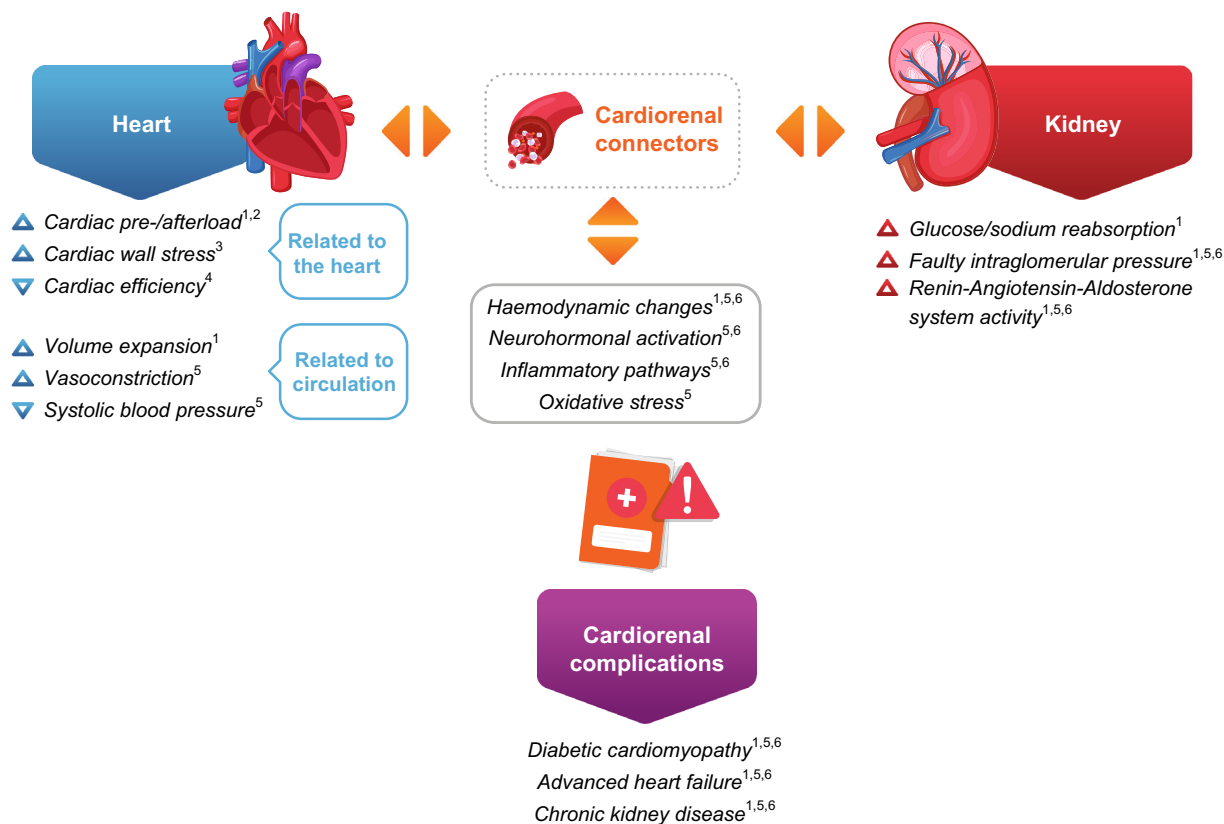
Fig. 2 Bidirectional pathophysiological interaction between the heart and the kidneys. 1. Sattar N, McGuire DK. Circulation. 2018;138(1):7–9; 2. Verma S, et al. Diabetes Care. 2016;39(12):e212-e3; 3. Kang S, et al. Can J Cardiol. 2020;36(4):543–53; 4. Santos-Gallego CG, et al. J Am Coll Cardiol. 2019;73(15):1931–4; 5. Ronco C, et al. J Am Coll Cardiol. 2008;52(19):1527–39; 6. Rangaswami J, et al. Circulation. 2019;139(16):e840–e78

of a patient-level, pooled meta-analysis of the DAPA-HF and DELIVER trials indicated that in patients with HF, dapagliflozin significantly reduced the risk of death from CV causes, any-cause death and major adverse CV events, irrespective of left ventricular ejection fraction; furthermore, there was a larger reduction in total hHF than in death, indicating that most patients with HF, regardless of ejection fraction, are likely to benefit from SGLT2 treatment [22]. Results of another meta-analysis, including five major randomised controlled trials, namely, DELIVER, DAPA-HF, EMPEROR-Preserved, EMPEROR-Reduced and SOLOIST-WHF, were also aligned to the abovementioned studies. Together, these data provide a strong case for the use of SGLT2i for the treatment of HF, irrespective of the presence of left ventricular ejection fraction or the care setting [23].

In addition to demonstrating the CV benefits of canagliflozin, the CANVAS program also showed a possible benefit of canagliflozin in slowing the progression of albuminuria, implying at the possibility of renal benefits of SGLT2i in patients with T2D [12]. Subsequently, the DAPA-CKD study showed that in patients with CKD, regardless of the presence of T2D, dapagliflozin significantly lowered progression of kidney disease and reduced the risk of death from renal or CV causes [24–26]. Similar results were seen in the EMPA-REG trial using empagliflozin in patients with and without diabetes and in the CREDENCE trial with canagliflozin in T2D patients [27, 28] (Table 1). Thus, selected SGLT2i have received approval for use in the treatment of HF and CKD in the USA, Europe and many other countries [29–31].

Table 1 Key cardiovascular and renal studies demonstrating SGLT2i-imparted cardiorenal benefits

Study	Population	Key result	References
DAPA-HF	Participants with HF, EF $\leq$ 40%, elevated NT-proBNP, with and without T2D	The risk of worsening HF or death from CV causes was lower in those receiving dapagliflozin compared with placebo, regardless of the presence or absence of diabetes	McMurray et al. New Engld J Med. 2019;381(21):1995–2008
CANVAS program	Participants with T2D and high CV risk	Participants treated with canagliflozin had a lower risk of CV events than those who received placebo	Neal et al. N Engl J Med. 2017;377(7):644–57
		Although the renal outcomes are not viewed as statistically significant, results showed a possible benefit of canagliflozin with respect to the progression of albuminuria and composite outcome of a sustained 40% reduction in eGFR, need for renal-replacement therapy or death from renal causes	
EMPA-Reg outcome	Participants with T2D and high CV risk	Compared with placebo added to standard care, participants receiving empagliflozin added to standard care had a lower rate of the primary composite CV outcome and of death from any cause	Zinman et al. N Engl J Med. 2015;373(22):2117–28
DECLARE-TIMI	Participants with T2D who had or were at risk for atherosclerotic cardiovascular disease	In participants with T2D who had or were at risk for atherosclerotic CV disease, dapagliflozin treatment did not affect MACE compared with the placebo group, but it did result in a lower rate of CV death and hHF	Wiviott et al. N Engl J Med. 2019;380(4):347–57

Table 1 continued

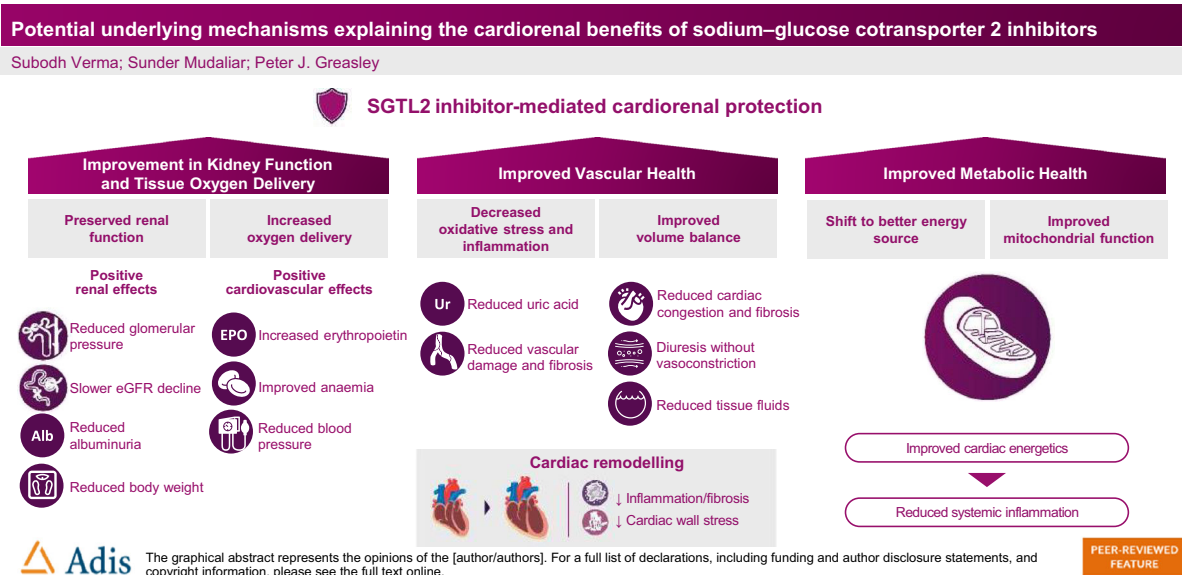| Study	Population	Key result	References
EMPEROR-Preserved	Participants with chronic HF and LVEF > 40%, with or without T2D	Empagliflozin reduced the combined risk of CV death or hHF in participants with HF and a preserved ejection fraction, regardless of the presence or absence of diabetes	Anker et al. N Engl J Med. 2021;385(16):1451–61
CHIEF-HF	Participants with HF, regardless of EF or diabetes status	Canagliflozin significantly improves symptom burden in HF	Spertus et al. Nat Med. 2022;28(4):809–813
EMPEROR-Reduced	Participants with HF and reduced EF, with or without T2D	Compared with placebo, empagliflozin reduced the composite risk of CV death or hHF, and improved health status and functional class; however, study results did not support a dominant role of diuresis in mediating the physiological changes or clinical benefits of SGLT2 inhibitors on the course of HF in participants with reduced EF	Packer et al. J Am Coll Cardiol. 2021;77(11):1381–92
DELIVER	Participants with HF or structural heart disease, LVEF > 40%, elevated NT-proBNP, with or without T2D	Dapagliflozin reduced the combined risk of worsening HF or CV in participants with HF and a mildly reduced or preserved EF	Solomon et al. N Engl J Med. 2022;387(12):1089–98
DAPA-CKD	Participants with CKD, with and without diabetes	The risk of a composite of a sustained decline in eGFR of at least 50%, end-stage kidney disease or death from renal or CV causes was significantly lower in participants receiving dapagliflozin versus those receiving placebo	Heerspink et al. New Engld J Med. 2020;383(15):1436–46

Table 1 continued

Study	Population	Key result	References
CREDENCE	Participants with T2D and albuminuric CKD	The risk of kidney failure and CV events was lower in the canagliflozin group than in the placebo group	Perkovic et al. N Engl J Med. 2019;380(24):2295–306
EMPA-KIDNEY	Participants with a range of CKD	Empagliflozin therapy led to lower risk of progression of kidney disease or death from CV causes than placebo	Herrington et al. N Engl J Med. 2023; 388:117–127
DAPA-HF and DELIVER pooled meta-analysis	Participants with HF, EF ≤40%, elevated NT-proBNP, with and without T2D (DAPA-HF) Participants with HF or structural heart disease, LVEF > 40%, elevated NT-proBNP, with or without T2D (DELIVER)	Dapagliflozin reduced the risk of death from CV causes, death from any cause and total hHF. There was no evidence that the effect of dapagliflozin differed by EF	Jhund et al. Nat Med. 2022;28:1956–64
DELIVER, DAPA-HF, EMPEROR-Preserved, EMPEROR-Reduced and SOLOIST-WHF meta-analysis	Participants with reduced EF (DAPA-HF and EMPEROR-Reduced), and those admitted to hospital with worsening HF, irrespective of ejection fraction (SOLOIST-WHF)	SGLT2i reduced the risk of CV death and hHF in a broad range of patients with HF	Vaduganathan et al. Lancet. 2022;400(10354):757–67

CKD chronic kidney disease, *CV* cardiovascular, *EF* ejection fraction, *eGFR* estimated glomerular filtration rate, *hHF* hospitalisation for heart failure, *HF* heart failure, *LVEF* left ventricular ejection fraction, *MACE* major adverse cardiovascular events, *NT-proBNP* N-terminal pro-brain natriuretic peptide, *SGLT2i* sodium–glucose cotransporter 2 inhibitors, *T2D* Type 2 diabetes

Various potential mechanisms have been proposed to explain how SGLT2i impart cardiorenal benefits. This review provides a simplified summary of key potential cardiac and renal mechanisms underlying the cardiorenal benefits of SGLT2i, which can assist in identifying more patients that can benefit from the use of these agents (Fig. 3).

Infographic

Potential underlying mechanisms explaining the cardiorenal benefits of sodium–glucose cotransporter 2 inhibitors

Subodh Verma; Sunder Mudaliar; Peter J. Greasley

SGTL2 inhibitor-mediated cardiorenal protection

The graphical abstract represents the opinions of the [author/authors]. For a full list of declarations, including funding and author disclosure statements, and copyright information, please see the full text online.

Improvement in Kidney Function and Tissue Oxygen Delivery

Glomerular filtration and solute reabsorption via the proximal tubules are critical aspects of kidney function. These critical processes appear to be altered in several kidney diseases [32–34]. SGLT2i act by selectively inhibiting SGLT2-mediated glucose and sodium reabsorption in the proximal tubule of the kidneys, leading to glycosuria, natriuresis and osmotic diuresis. The metabolic and natriuretic effects of SGLT2i are in themselves potentially beneficial for kidney function. In patients with kidney-related conditions, like diabetes and CKD, decreased sodium delivery to the macula densa in the kidneys causes glomerular vasodilation and hyperfiltration (GFR above normal). SGLT2i reduce sodium reabsorption in the proximal tubule and increase its delivery to the macula densa, thus increasing tubuloglomerular feedback and reducing hyperfiltration. This action of SGLT2i is complementary to angiotensin-converting enzyme inhibitors, which reduce intraglomerular pressure and hyperfiltration by dilating the efferent renal arterioles.

The rate of urinary albumin excretion is a clinical marker highlighting the severity of kidney disease, with albuminuria-improving treatments being associated with a reduction in the progression of CKD [35]. Use of SGLT2i showed a marked reduction in excretion of urinary albumin (as indicated by the improved urinary albumin-to-creatinine ratio [UACR]), an initial decrease in estimated glomerular filtration rate (eGFR) and a longer-term slowing of the rate of eGFR decline [26, 32, 36, 37]. A secondary analysis of the DECLARE-TIMI 58 study showed that dapagliflozin not only reduced the rate of new-onset micro- or macroalbuminuria relatively early during the trial but also showed statistically significant reduction of urinary albumin excretion in patients in all UACR categories (UACR ≤ 15, 15 < UACR < 30, 30 ≤ UACR ≤ 300 and 300 < UACR mg/g) [38]. In patients with vascular disease, changes in albuminuria have been shown to predict mortality and cardiovascular and renal outcomes, independent of baseline albuminuria, implying the presence of an underlying albuminuria-associated mechanism playing a role in the cardiorenal benefits of SGLT2i [39]. It has been postulated that SGLT2i may exert these benefits by favourably affecting glomerular hydrostatic pressure, plasma volume, arterial stiffness and tissue (interstitial) fluid [13, 40–44].
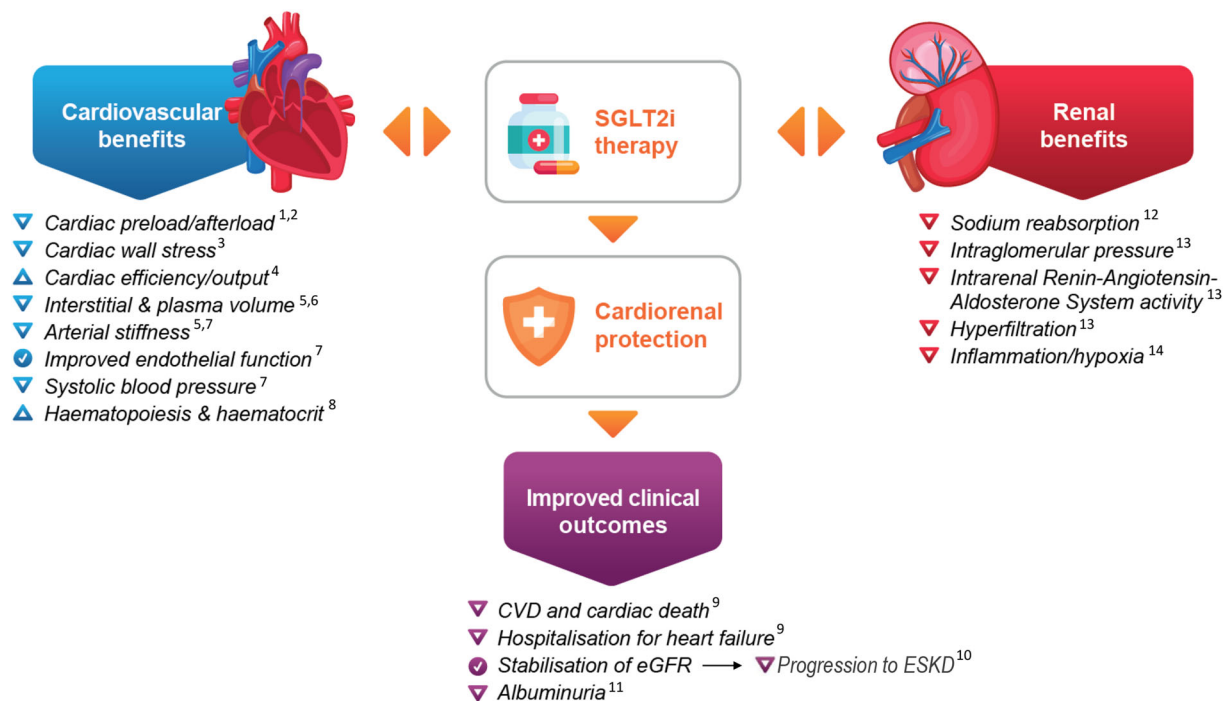
Fig. 3 Clinical effects of SGLT2i-mediated cardiorenal protection. *CVD* cardiovascular disease, eGFR, estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *SGLT2i* sodium–glucose cotransporter 2 inhibitor. 1. Sattar N, McGuire DK. Circulation. 2018;138(1):7–9; 2. Verma S, et al. Diabetes Care. 2016;39(12):e212-e3; 3. Kang S, et al. Can J Cardiol. 2020;36(4):543–53; 4. Santos-Gallego CG, et al. J Am Coll Cardiol. 2019;73(15):1931–4; 5. Staels B. Am J Med. 2017;130(6 s):S30-s9; 6. Hallow KM, et al. Diabetes Obes Metab. 2018;20(3):479–87; 7. Solini A, et al. Cardiovasc Diabetol. 2017;16(1):138; 8. Maruyama T, et al. Diabetes Technol Ther. 2019;21(12):713–720; 9. Heerspink HJL, et al. N Engl J Med. 2020;383(15):1436–1446; 10. Heerspink HJL, et al. Lancet Diabetes Endocrinol. 2021;9(11):743–754; 11. Mosenzon O, et al. Diabetes Care. 2021;44(8):1805–15; 12. Hallow KM, et al. Am J Physiol Renal Physiol. 2018;315(5):F1295-F1306; 13. Heerspink HJL, et al. Kidney Int. 2018;94(1):26–39; 14. Packer M. Diabetes Care. 2020;43(3):508–11

The DIAMOND study was the first investigation evaluating the renal haemodynamic and albuminuria-lowering effects of dapagliflozin treatment in 53 subjects with non-diabetic proteinuric CKD. Results showed that compared with placebo, dapagliflozin did not significantly affect proteinuria while causing an acute but reversible decline in GFR and reduction in bodyweight and blood pressure, though subsequent randomised controlled trials demonstrated that SGLT2i did indeed reduce proteinuria and delay progression of kidney disease in patients with albuminuria [45–47]. The DIAMOND study also demonstrated that whilst conferring these benefits, dapagliflozin did not reduce HbA1c or fasting plasma glucose in subjects without diabetes, nor were kidney haemodynamics adversely affected in this population. This implies that dapagliflozin treatment has ubiquitous positive effects on kidney function irrespective of glycaemic status [48]. These positive effects may be mediated via tubuloglomerular feedback in individuals without T2D as they have lower glucose filtration than individuals with diabetes. It is possible that the activation of tubuloglomerular feedback, and/or another autoregulatory system, by SGLT2i, may not affect proteinuria in individuals without diabetes, thus offering renoprotection [48].

Increased Erythropoietin Production

Erythropoietin (EPO) is produced by interstitial fibroblasts in the kidneys in a process involving oxygen sensing. In patients with diabetes, excessive glucose reabsorption overtaxes the proximal tubules, increasing oxygen requirement and causing tubulointerstitial hypoxia. As a consequence, damaged renal tubules undergo transformation, losing their function, thus impairing EPO production. SGLT2 inhibitors reduce the workload of the proximal tubules and improve tubulointerstitial hypoxia, allowing fibroblasts to resume EPO production, thereby leading to an increase in erythropoiesis and an increase in haemoglobin/haematocrit levels. Thus, increased haematocrit could indicate reduced renal stress in diabetic patients [49]. This mechanism has been demonstrated in patients with T2D using dapagliflozin and canagliflozin [50, 51]. Dapagliflozin has also been associated with a modest increase (2–4%) in haematocrit [52]. The resulting increase in haematocrit leads to increased oxygen delivery to tissues, particularly to the heart, which may account for some of the beneficial CV effects of SGLT2i. An exploratory analysis of a phase 3 trial of empagliflozin showed that increases in haemoglobin and haematocrit were the most important mediators of the reduction in risk of CV mortality [53, 54]. This may have implications in individuals with worsening heart conditions or obesity, wherein oxygen delivery by the heart is ineffective due to the increased need for oxygen [55]. However, more research is required to investigate this aspect.

Improvements in Anaemia

As explained above, treatment with SGLT2i showed increase in levels of haemoglobin, haematocrit and EPO, thus assisting with correcting and/or preventing anaemia [50–53, 56]. SGLT2i may also alleviate renal hypoxia and prevent resulting kidney injury by improving oxygen supply to the kidneys through improved cardiac function and by reducing renal oxygen requirements in the proximal tubules [32, 36, 57, 58]. Both dapagliflozin and empagliflozin were shown to assist with correcting and/or preventing anaemia in patients with HF irrespective of the presence of diabetes [59, 60]. Increase in haematocrit and haemoglobin could also indicate changes in natriuresis and effective circulating volume contraction. This small increase in haemo-concentration may be linked with improved cardiovascular prognosis in cardiovascular outcome trials involving SGLT2is in individuals with T2D [61].

IMPROVED CARDIOVASCULAR HEALTH

Improved Endothelial Function

The endothelium maintains vascular homeostasis through several complex physiological functions, including release of vasoactive factors that regulate vascular tone, blood fluidity and coagulation, while limiting smooth muscle cell proliferation and inflammation. Endothelial dysfunction is a consistent finding in individuals with T2D and can independently predict risk of CV disease [62]. SGLT2i have been shown to improve endothelial function, thus positively affecting vascular function [43]. It has been proposed that this improvement may be related to reduced exposure of the endothelium to sodium and glucose [43, 63, 64]. In vitro observations indicate that SGLT2i may confer cardioprotection partly through their ability to preserve and restore the structural integrity of the endothelial glycocalyx—a protective matrix-like barrier of macromolecules that helps to maintain vascular health by promoting the anti-inflammatory action of the endothelium [65]. Indeed, a preliminary study showed improved systemic endothelial function after 48 h of treatment with dapagliflozin [43]. The randomised, open-label DEFENCE study showed a similar effect, with dapagliflozin improving endothelial function when used in combination with metformin in patients with T2D—an effect that was observed alongside a significant reduction in oxidative stress [66].

Decreased Vascular Stiffness and Inflammation

Increased ventricular mass is associated with an increased risk of CVD. SGLT2i have been shown to improve arterial stiffness and prompt regression towards a normal ventricular mass, thus conferring protection against HF and arrhythmias [67, 68]. A pilot study reported a significant improvement in systemic endothelial function and arterial stiffness 48 h after treatment with dapagliflozin. This was independent of changes in blood pressure and was observed with stable urinary excretion of sodium, suggesting a fast and beneficial effect on the blood vessels, possibly mediated by a reduction in oxidative stress [43]. A recent meta-analysis of a double-blind placebo-controlled randomised trial evaluating left ventricular remodelling by cMRI observed that SGLT2i significantly and consistently reduced left ventricular mass in individuals with HF, with and without diabetes, proposing this as a potential mechanism responsible for positive CV effects of SGLT2i [69].

SGLT2i may also be able to confer cardioprotection via a range of anti-inflammatory actions at the tissue and organ levels [70]. For example, hyperuricaemia is common in individuals with heart and kidney diseases, which appears to promote CV pathophysiology by proliferating vascular smooth muscle cells and increasing production of pro-inflammatory, pro-oxidative and vasoconstrictive mediators [71–73]. Having demonstrated activity in reducing uric acid levels [74–76], it is possible that SGLT2i may be able to ameliorate this pathological pathway. SGLT2i reduce uric acid levels by increasing its excretion in urine. Unabsorbed glucose is thought to compete with uric acid for a glucose transporter in the renal tubules, a major regulator of uric acid homeostasis, explaining why reduction in uric acid levels was greater in individuals without T2D and in those with lower HbA1c in the DAPA-HF study [77].

Another potential mechanism is related to epicardial adipose tissue (EAT), which supplies free fatty acids for energy production by cardiac muscle cells and has been associated with coronary atherosclerosis and insulin resistance [78, 79]. In individuals with T2D and HF, EAT is also known to produce large quantities of activin A, an inflammation-enhancing cytokine [80]. Dapagliflozin and canagliflozin have been shown to decrease EAT in individuals with T2D [81, 82], thus reducing vascular inflammation and fibrosis, possibly by improving the balance between inflammation-promoting and -reducing cytokines secreted by the adipose tissue [42].

Improved Balance of Intra and Extravascular Fluid Volume

SGLT2i reduce volume overload as a result of osmotic diuresis in patients with T2D due to glycosuria resulting in a decrease in intravascular volume [83]. This helps to lessen the strain/stretch on the heart, known as myocardial preload [84]. These actions may also contribute to reduction in ventricular mass. Individuals with HF also suffer from congestion, wherein fluid accumulates both inside and outside the blood vessels. SGLT2i have been shown to reduce the volume of tissue fluid to a greater extent than blood volume, thus increasing fluid clearance and reducing congestion, with minimal impact on circulation, arterial filling, activation of the renin-angiotensin-aldosterone system (RAAS) in response to a drop in blood pressure and blood supply to organs. Consequently, vasoconstriction in response to a fall in blood volume is prevented—an aggravating effect seen with other diuretic treatments [43, 85].

Beneficial effects of SGLT2i on blood volume have also been demonstrated in individuals without T2D [86, 87]. Empagliflozin decreases 24-h systolic blood pressure by 5 mmHg with significant renal tubular effects in individuals with normal blood pressure; mechanisms involved in this decrease were independent of weight control but may be related to volume contraction [86]. Empagliflozin has also been shown to reduce pulmonary pressure in patients with HF, possibly via modulation of sympathetic activity [87, 88]. Furthermore, in individuals without T2D, it has been hypothesized that SGLT2i-induced osmotic diuresis results in

greater electrolyte-free water clearance and thus in greater fluid clearance from the interstitial fluid (IF) space than from the circulation. This alleviates cardiac congestion with minimal impact on blood volume, arterial filling and organ perfusion. Using a mathematical model, this hypothesis was tested using data from a study in healthy subjects receiving dapagliflozin or bumetanide; the model predicted that dapagliflozin produces a twofold greater reduction in IF volume compared to blood volume, while the reduction in IF volume with bumetanide is only 78% of the reduction in blood volume. Excess fluid accumulation in the vascular compartment and IF space is a typical characteristic of HF. Thus, by causing a greater reduction in IF volume compared with that in blood volume, SGLT2i may provide better cardiorenal protection in individuals without T2D [85, 89].

Regulation of sodium ion channels in the heart and kidneys may also be a way in which SGLT2i produce their cardiorenal benefits. For example, evidence suggests that dapagliflozin may help to reduce blood pressure by improving the sodium balance [90]. The sodium-hydrogen exchanger-3 (NHE3) in kidneys mediates sodium reabsorption following renal glomerular filtration [91–93]. Reduced NHE3 activity in the proximal tubule following treatment with SGLT2i leads to decreased sodium reabsorption followed by lowering of glomerular pressure, and reduction of blood and tissue fluid volume. Sodium-hydrogen exchanger-1 (NHE1) is also thought to play an important role in the pathogenesis of HF [91]. NHE1 activity is raised in HF, and its inhibition decreases susceptibility to severe ventricular arrhythmia, reduces contractile dysfunction and limits tissue death/damage both when blood supply to the heart muscle is insufficient (ischaemia), and when it subsequently returns (reperfuses) [94]. Benefits of SGLT2i on HF have been suggested to be mediated by inhibition of sodium-hydrogen exchange in the heart via NHE1, thus resulting in reduced sodium concentration [14, 42, 95–97]. It is possible that SGLT2i may favourably induce cardiac remodelling by these mechanisms, thus reducing the risk of arrhythmias and sudden death [42, 97]. However, a recent study found that empagliflozin and other SGLT2i had no effect on cardiac NHE1 activity over a range of concentrations, including the therapeutic dose, warranting further research on this hypothesis [98].

Suppressed Collagen Synthesis/Fibrosis

Cardiac fibrosis is widely regarded as a pathway leading to HF [42]. The fibrosis results from remodelling of the heart, making the ventricles less compliant to expansion and thus accelerating development of HF. In individuals with diabetes, remodelling of the extracellular matrix leads to accumulation of collagen, subsequent cross-linking of the collagen and activation of signalling pathways promoting fibrosis [99]. These structural changes contribute to the cardiac stiffness and diastolic dysfunction seen in individuals with diabetes, which ultimately produce stress on the heart wall, chamber enlargement and contractile dysfunction [100]. Dapagliflozin and empagliflozin have been shown to prevent cardiac fibrosis in studies with murine myocytes [101, 102]. Similarly, preliminary data using human myofibroblasts have shown that empagliflozin may have a direct effect on restructuring of the extracellular matrix via attenuation of myofibroblast activity and cell-mediated collagen remodelling. This may be a potential mechanism for SGLT2i-mediated CV benefits in individuals without T2D [103].

IMPROVED METABOLIC HEALTH

Shift in Substrate Utilisation

The constant high-energy demand of the heart is primarily met by the oxidation of lipid-derived long-chain fatty acids [104]. However, it can also derive energy from several other substrates, including glucose, pyruvate and lactate; a proportional amount of ketones may also be used to generate energy. Under conditions of a mild persistent elevation of ketones in the blood (hyperketonaemia), as is seen in T2D and HF, larger-than-usual amounts of the ketone,

beta-hydroxybutyrate, are taken up by the heart for energy utilisation instead of fatty acids [67, 105]. It is proposed that this improves transduction of oxygen consumption into work efficiency at the mitochondrial level. Furthermore, SGLT2i-induced haemoconcentration enhances oxygen release. Thus, aligned with other SGLT2i benefits, such a metabolic substrate shift is capable of conferring cardioprotection in diabetic and non-diabetic patients.

Based on studies involving dapagliflozin and empagliflozin, it has been hypothesised that SGLT2i shift metabolism towards the oxidation of free fatty acids and stimulate ketone production (ketogenesis) [106, 107]. This shift results in increased levels of beta hydroxybutyrate in circulation, which offers significant cardioprotection to individuals with diabetes [67, 108, 109]. The shift in substrate utilisation can also be explained as follows. In individuals with prolonged diabetes, there is altered insulin sensitivity and a decrease in insulin-stimulated glucose disposal. Dapagliflozin treatment induces glucosuria, lowers plasma glucose and increases insulin-stimulated glucose disposal. This increase in glucose uptake is mainly reflected in an increase in non-oxidative glucose disposal (glycogen synthesis), while glucose oxidation is decreased. To meet the energy demand of the cell, there is a switch from glucose to fat oxidation for energy production [106], accompanied by increased ketone production. These changes in fuel utilisation may lead to improvements in the function and efficiency of the heart [107, 110]. Stimulation of ketogenesis also imparts benefits such as reductions in inflammatory responses and blood pressure [111, 112].

Improved Mitochondrial Function

Autophagy is a cellular degradation and recycling process [113]. The process involves the recycling of unwanted cellular components, degrading the glycogen and lipids present in the components to generate adenosine triphosphate (ATP), the most basic form of cellular fuel. Autophagy also serves to remove damaged mitochondria and other organelles from the cytosol, thereby reducing oxidative stress and inflammation [114]. On detection of low energy levels by the mitochondria, the enzymes sirtuin 1 (SIRT1) and 5' adenosine monophosphate-activated protein kinase (AMPK) function stimulate autophagy [115]. Suppression of SIRT1-AMPK signalling pathway results in impaired autophagy, which may play a role in the pathogenesis of heart and kidney diseases in individuals with T2D [115]. Impaired autophagy has also been linked to dysfunction of cardiac muscle cells, increased inflammation and appearance of renal lesions in diabetic nephropathy [115]. By assessing changes in circulating protein levels in patients with HF, Zannad et al. explored the effect of empagliflozin on the circulating levels of intracellular proteins by using large-scale proteomics in 1134 patients with HF from the EMPEROR-Reduced and EMPEROR-Preserved studies. They showed that empagliflozin altered heart proteins, promoting autophagic flux. Other treatment effects of empagliflozin, including reduced oxidative stress, inhibition of inflammation and fibrosis, enhanced energy stores and increased regenerative capacity of the heart, also contributed in imparting positive cardiac changes. Changes in circulating protein levels in patients with HF seen in this study are consistent with the findings of other experimental studies showing that the effects of SGLT2i are likely related to actions on the heart and kidney to promote autophagic flux, nutrient deprivation signalling and transmembrane sodium transport [116].

Hyperglycaemia may increase mitochondrial oxygen consumption, causing cellular hypoxia [117, 118]. Thus, by reducing blood glucose levels, anti-hyperglycaemic drugs may be capable of promoting autophagy by inducing activation of various low-energy sensors, such as SIRT1 and AMPK. Indeed anti-hyperglycaemic drugs, such as incretins and thiazolidinediones, have been shown to induce autophagy [119–121]. However, the magnitude of this effect may be offset by other actions. It has been proposed that SGLT2i activate SIRT1-AMPK signalling, thus promoting autophagy [115]. It is possible that the magnitude of autophagy induced by SGLT2i is more prominent compared to other anti-hyperglycaemic drugs

because of several other SGLT2i-associated mechanisms involved in the manifestation of the cardiorenal benefits shown by this drug class. Increased autophagy leads to reduced oxidative stress, normalised mitochondrial structure and function, suppressed inflammation, reduced injury to coronary vessels, enhanced cardiac performance and lowered risk of cardiomyopathy [115]. Kidney cells, including podocytes and proximal tubular cells, strongly express AMPK, and metabolic-related renal diseases—like obesity-related and diabetic chronic kidney disease—are associated with dysregulated AMPK in the kidneys. Conversely, activating AMPK ameliorates the pathological and phenotypical features in such renal diseases [122]. Mimicking the cellular response to starvation by indirectly activating low-energy sensor AMPK, SGLT2i hinder the development of nephropathy [115].

Figure 3 details the various mechanisms that may be involved in cardiorenal protection by SGLT2i.

OTHER: CARDIAC REMODELLING

In addition to improved cardio-energetics (see 'Shift in substrate utilisation') and positive effects on ventricular mass (see 'Decreased vascular stiffness and inflammation'), SGLT2i have also been indicated to play a decisive role in cardiac remodelling. Individuals with T2D may have decreased ability to revascularise ischaemic tissues due to low levels of circulating perivascular progenitor cells. Recent data suggest SGLT2i stimulate vascular repair via increased trafficking of bone marrow—derived haematopoietic stem/progenitor cells (HSPCs)—known to be essential for regeneration of cardiac vessels in individuals without T2D [123, 124]. Dapagliflozin improved endothelial repair through enhanced HSPCs at the site of vessel injury for repair, thus facilitating cardiac regenerative and remodelling processes [125]. Restoration of vascular regenerative cell production, by reducing glucotoxicity and systemic inflammation post bariatric surgery or by modulating HSPC functions, may provide unique approaches for treating ischaemic

disease using SGLT2i [126]. Dapagliflozin has also demonstrated enhanced healing of carotid artery wounds, wherein the vascular repair was stimulated, in part, through distinct alterations in systemic metabolism, including improved glucose control and induction of ketogenesis [125, 127]. Preventing adverse cardiac remodelling and/or preventing ischaemia/reperfusion injury is another way in which SGLT2i are associated with cardiac remodelling. Empagliflozin has been shown to prevent adverse left ventricular remodelling in nondiabetic pigs with HF, possibly by enhancing myocardial energetics [128]. A preliminary study in humans showed that empagliflozin improves 'cardiac energy-deficient' and hinders unwanted myocardial cellular remodelling, thus improving cardiac function and offering therapeutic opportunities to prevent or modulate HF in individuals with T2D [128].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

ADVERSE EFFECTS OF SGLT2I-ASSOCIATED MECHANISMS IMPARTING CARDIORENAL BENEFITS

Under specific circumstances, some of the above-listed mechanisms activated by SGLT2i can produce undesirable effects. One such undesirable effect is normoglycaemic ketosis (blood glucose < 250 mg/dl; arterial pH < 7.3, serum bicarbonate < 18 mEq/l [severe metabolic acidosis] and presence of ketone bodies) [129]. This can have serious clinical consequences and may need professional intervention for resolution, which may require reducing SGLT2i dose or stopping SGLT2i treatment [130–132]. However, since these are known adverse events related to SGLT2i treatment; evidence and guidance are available for the

clinical management of these conditions when patients are on SGLT2i therapy [132–137].

CONCLUSION

There is a bidirectional pathophysiological interaction between the heart and the kidneys. SGLT2i produce cardiorenal benefits that are not solely dependent on their effects to improve glycaemia and are not limited to individuals with T2D. In addition to the effects of SGLT2i on the heart and kidneys, other mechanisms involving alteration and regulation of metabolism, energy sources, sodium ion channels, haematocrit and EPO levels and anti-inflammatory effects may underlie their ability to confer cardiorenal protection to individuals with and without diabetes. The use of SGLT2i therapy in treating HF and CKD in individuals with and without T2D has a marked impact, reducing the risk associated with worsening of these conditions and decreasing complications in T2D. Notably, the use of SGLT2i therapy may be beneficial in managing multiple comorbidities and protecting the heart and the kidney from developing cardiorenal disease.

Declaration

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