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REVIEW
Diabetes and metabolic syndrome

Protective effects of SGLT-2 inhibitors across the cardiorenal continuum: two faces of the same coin

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The cardiovascular and renal systems are closely interconnected in health and disease. Disorders affecting one of these systems frequently involve the other. Both diseases progress through a continuous chain of events, defined as the 'cardiorenal continuum', which is initiated by risk factors that lead to subclinical disease, clinical events, and ultimately to heart failure and end-stage kidney disease. Previous studies have shown that interventions anywhere along this chain of events can interrupt the pathophysiological cascade and provide cardiovascular and/or kidney 'protection'. More recently, clinical trials with SGLT-2 inhibitors (SGLT2i) have shown a significant reduction in cardiovascular and kidney outcomes. Evidence from EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58, VERTIS-CV, CREDENCE, and more recently DAPA-HF, EMPEROR-Reduced, and DAPA-CKD show that the beneficial effects of SGLT2i are observed across all stages of the cardiorenal continuum, ranging from patients with diabetes and multiple risk factors to those with established cardiovascular disease and even independently of diabetes status. This review provides a critical appraisal of the efficacy and safety of SGLT2i, demonstrating that this is a novel way to disrupt the chain of pathological events in the cardiorenal continuum and prevent cardiovascular and kidney disease in patients with and without diabetes.

Keywords Sodium-glucose transporter 2 inhibitors • Heart failure • Atherosclerosis • Renal insufficiency • Diabetes mellitus • Type 2

The interplay between the cardiovascular and renal systems

There is long-standing evidence of an important crosstalk between the cardiovascular system and the kidney. Historically, the Egyptian 'Book of the Dead' (1600–1240 BC) is one of the first known texts mentioning that the heart and the kidneys were the only organs left inside the body during the process of mummification to assist the deceased in the afterlife.[1] Physiologically, we know that these two systems are interconnected through the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, natriuretic peptides, vasopressin, among several other mechanisms and that this intersection occurs both in health and disease. It is known that major cardiac events are the cause of almost half of the mortality in patients with chronic kidney disease (CKD)[2] and also that cardiovascular disease (CVD) is the most common cause of death among stage 3–5 CKD patients.[3] Cardiovascular mortality continuously increases as estimated glomerular filtration rate (eGFR) decreases, starting at eGFR levels of 75 mL/min/1.73 m^2.[4] Even subclinical kidney disease is associated with a significant increase in major adverse cardiovascular events (MACE) and heart failure hospitalization (hHF), with studies showing a progressive increase in risk of those events when urine albumin/creatinine ratio (UACR) is above 10 mg/g, a level which is still considered to be in the normal range.[5] Chronic heart failure (HF) is the most common cardiovascular complication in patients with CKD,

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especially HF with preserved ejection fraction (EF).[6] On the other hand, in large samples of patients with both types of HF, CKD G3a or higher was present in about 55% and there is a stepwise increase in mortality risk according to the stage of CKD.[7] The convergence of heart–kidney interaction is particularly evident in the increasing clinical relevance of the cardiorenal syndrome and its several phenotypes, as recently described.[8]

The cardiorenal continuum

About 30 years ago, Dzau *et al.*[9] postulated the seminal concept of the cardiovascular continuum. This revolutionary idea framed CVD as a continuous chain of events that is initiated by a cornucopia of risk factors and continuously progresses through several physiological pathways until the development of end-stage heart disease (*Figure 1*). The concept is clinically relevant, because an intervention anywhere along this chain of events can disrupt the pathophysiological processes thus providing 'cardioprotection'. Several clinical trials, especially those with RAAS blockers, beta-blockers, and statins, have provided consistent evidence for this proof of concept. In addition, over the last decades, we also began to understand that events leading to disease progression can overlap and intertwine, and do not always occur as a sequence of discrete, tandem incidents.[9] Subsequently, the concept of cardiovascular continuum has expanded to other areas, with a focus on kidney disease, particularly in the diabetic subset. Indeed, nephropathy ranges from a subclinical phase (microalbuminuria), followed by a later phase of macroalbuminuria, CKD, and end-stage kidney disease (ESKD)[10] (*Figure 1*). Similarly, several clinical outcome trials have demonstrated that the RAAS blockade reduces the progression of kidney disease, providing nephroprotection and delay, or even interrupt, the chain of events that lead to ESKD.[10]

Type-2 diabetes mellitus (T2DM) is one of the most relevant risk factors for both HF and ESKD, being an important 'trigger' of the cardiorenal continuum. In fact, T2DM increases the risk of HF by 2.5-fold[11] and HF is one of the two most frequent cardiovascular complications in T2DM.[12] T2DM can compromise the heart through several mechanisms, ultimately leading to HF. First, diabetic macroangiopathy leads to coronary artery disease (CAD), myocardial ischaemia, and ischaemic cardiomyopathy. In addition, T2DM can directly injury myocardial structure, function, and metabolism, leading to HF (especially HF with preserved EF) independently of other factors, a process described as 'diabetic cardiomyopathy'[13,14] (*Figure 1*). Simultaneously, diabetes is an important contributor for nephropathy, accounting for 30–50% of all CKD.[15] Although the paradigm of the natural history of diabetic nephropathy is still evolving, this process usually starts at a subclinical level with microalbuminuria, which later evolves to CKD[16] (*Figure 1*). Nevertheless, although ESKD may be the most recognizable consequence of diabetic kidney disease, most patients actually die from CVD. Another example of the interplay between cardiovascular and renal systems in these patients comes from recent data from the SAVOR-TIMI 53 and DECLARE-TIMI 58 trials showing that abnormal eGFR (<60 mL/min/1.73 m^2)

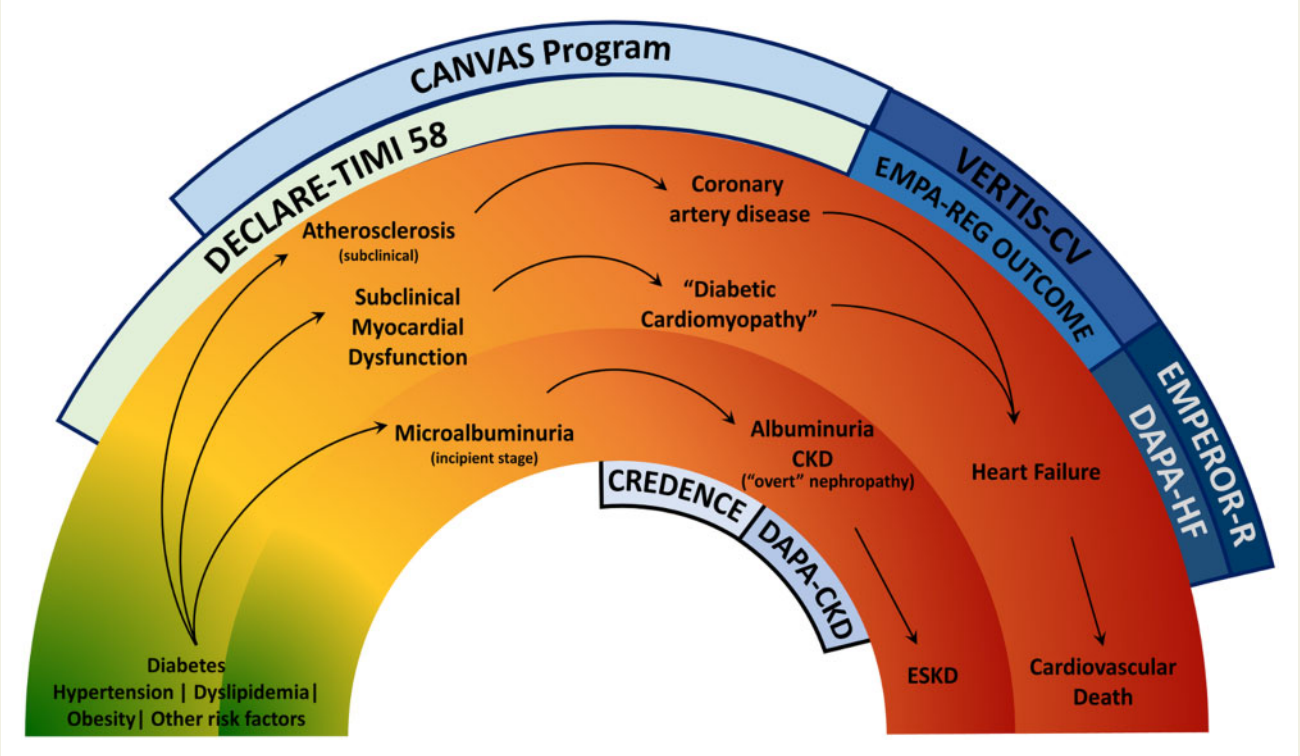


Figure 1 Clinical trials of SGLT2 inhibitors across the cardiorenal continuum.

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and UACR (>30 mg/g) are 2 of the 5 most important independent risk predictors of hHF in T2DM.[17]

SGLT-2 inhibitors have been studied in patients across different stages of the cardiovascular continuum showing a consistent reduction in the risk of hHF. The EMPA-REG OUCOME and VERTIS-CV trials included only patients with previous history of atherosclerotic cardiovascular disease (ASCVD) and showed a 35% and 30% reduction in hHF, respectively. The CANVAS Program and the DECLARE-TIMI 58 trial have also included patients with T2DM and multiple risk factors in primary prevention (34% and 59%, respectively), demonstrating a 33% and 27% reduction in hHF, respectively. Both DAPA-HF and EMPEROR-Reduced trials included patients with HF reduced ejection fraction (EF < 40%), which represent patients in the right end of the cardiovascular continuum, and also showed a ~30% reduction in hHF, independently of the diabetes status. Finally, in the two trials that focused on patients with different stages of chronic kidney disease, there was also a significant reduction in hHF. The CREDENCE trial included diabetic patients with kidney disease and demonstrated a 39% reduction in hHF, whereas the DAPA-CKD which included patients with CKD (with and without diabetes) showed a 29% reduction in the combined endpoint of hHF and CV death.

SGLT2 inhibitors: cardiovascular outcomes across the cardiorenal continuum

Four different SGLT2i have been evaluated in cardiovascular outcomes trials and included patients with T2DM across different stages of the cardiovascular continuum (*Figure 1*). The EMPA-REG OUTCOME trial evaluated the effect of empagliflozin in patients with established atherosclerotic cardiovascular disease (ASCVD, 99%),[18] and VERTIS-CV trial tested the role of ertugliflozin in a similar population.[19] On the contrary, the CANVAS Program[20] tested the effect of canagliflozin in a setting of secondary and primary prevention (34% had no previous ASCVD), and the DECLARE-TIMI 58[21] included mainly 'primary prevention' patients (59%).

Effect on heart failure hospitalization

All these four trials showed a consistent and similar ~30% reduction in hHF (*Table 1*), as demonstrated in recent meta-analysis [hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.61–0.76].[22]

This 'preventive effect' in the risk of hHF was observed irrespective of the presence of previous HF and with relatively similar risk reductions across different HF risk scores.[17] It was also evident both in patients with and without previous cardiovascular events. While DECLARE-TIMI 58 only included patients with a creatinine clearance ≥60 mL/min/1.73 m^2, EMPA-REG OUTCOME, CANVAS Program, and VERTIS-CV studied individuals with eGFR >30 mL/min/1.73 m^2. Regarding the influence of kidney function on hHF, meta-analyses have shown a consistent reduction in hHF [relative risk (RR) 0.61; 95% CI 0.48–0.78] also in patients with CKD (eGFR <60 mL/min/1.73 m^2).[23] Additionally, there was a reduction in hHF across the different albuminuria subgroups, as shown in CANVAS Program,[24] suggesting that the reduction in hHF is observed across all stages of nephropathy, as illustrated in *Figure 2*. Outside the clinical trials, data from several 'real-world' studies in unselected populations of patients with T2DM have confirmed a 30–50% reduction in hHF.[25]

Effect on major adverse cardiovascular events

Regarding the risk of MACE, both EMPA-REG OUTCOME and CANVAS Program showed a statistically significant reduction in MACE, which was not observed in DECLARE-TIMI 58 (*Table 1*). Additionally, empagliflozin led to a lower total and cardiovascular mortality (HR 0.68; 95% CI 0.57–0.82 and HR 0.62; 95% CI 0.49–0.77, respectively).[18] A meta-analysis of these three cardiovascular outcomes trials showed that SGLT2i were associated with an 11% reduction in MACE (HR 0.89; 95% CI 0.80–0.98)[26]; an effect that was only observed in patients with previous ASCVD (HR 0.86; 95% CI 0.80–0.93), but not in patients without a previous event (HR 1.00, 95% CI 0.87–1.16, *P* for interaction = 0.0501). Surprisingly, in the VERTIS-CV trial,[19] a significant reduction in MACE was not demonstrated (HR 0.97; 95% CI 0.85–1.11) although this trial included patients with established ASCVD, which contrast with the effect on hHF, which was consistent within the class and was previously detailed.

Regarding the influence of renal function on the risk of MACE, there was a trend towards a greater reduction of MACE as eGFR decreases, which did not reach statistical significance.[26] In patients with eGFR <60 mL/min/1.73 m^2, there was a 19% reduction in MACE (RR 0.81; 95% CI 0.70–0.94), which was mainly derived from a 23% reduction in myocardial infarction (MI), without a significant reduction in stroke, cardiovascular, or total mortality.[23] There was no interaction between MACE reduction and different albuminuria levels.[24]

Cardiovascular benefits of SGLT2i in patients with HFrEF (with and without diabetes)

Given the significant and consistent results of SGLT2i in the reduction of hHF in patients with diabetes, the latest trials aimed to evaluate its effects in patients at the right extreme of the cardiovascular continuum (*Figure 1*), specifically in patients with HF with reduced ejection fraction (EF < 40%), irrespective of diabetes status. In the DAPA-HF trial,[27] dapagliflozin reduced the combined primary endpoint of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death by 26% (HR 0.74; 95% CI 0.65–0.85), with a 30% reduction in hHF (HR 0.70; 95% CI 0.59–0.83), and an 18% reduction in cardiovascular mortality (HR 0.82; 95% CI 0.69–0.98). This trial enrolled patients with eGFR ≥30 mL/min/1.73 m^2, and the effect on the primary endpoint was observed irrespective of baseline kidney function. No detailed subanalysis has been published to date regarding the influence of different stages of kidney function or albuminuria levels. The reduction in the risk of worsening HF or cardiovascular death occurred independently of diabetes status or baseline HbA1c level.[28] More recently, the EMPEROR-Reduced also showed that in patients with EF < 40% empagliflozin can reduce hHF by 31% (HR 0.69; 95% CI 0.59–0.81), irrespective of diabetes status.[29] A recent meta-analysis of these two

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Table 1 Characteristics and outcomes of SGLT2i clinical trials

	CV outcomes trials in T2DM				Trials in CKD patients		Trials in HF-reduced EF (EF < 40%)	
	EMPA-REG OUTCOME	**VERTIS-CV**	**CANVAS Program**	**DECLARE-TIMI 58**	**CREDENCE**	**DAPA-CKD**	**DAPA-HF**	**EMPEROR-Reduced**
Drug (dose)	Empagliflozin (10 or 25 mg)	Ertugliflozin (5 or 15 mg)	Canagliflozin (100 or 300 mg)	Dapagliflozin (10 mg)	Canagliflozin (100 mg)	Dapagliflozin (10 mg)	Dapagliflozin (10 mg)	Empagliflozin (10 mg)
Inclusion criteria								
T2DM	Yes	Yes	Yes	Yes	Yes	—	—	–
Cardiovascular	CVD	CVD	CVD or RF	CVD or RF	—	No	HFrEF NYHA II–IV High NT-proBNP	HFrEF NYHA II–IV High NT-proBNP
Renal	eGFR >30	eGFR ≥30	eGFR >30	eGFR >60	eGFR 30–90 UACR 300–5000	eGFR 25–75 UACR 200–5000	eGFR ≥30	eGFR ≥20
Patient characteristics								
n	7020	8246	10 142	17 160	4401	4304	4744	3730
Follow-up (years)	3.1	3.5	2.4	4.2	2.62	2.4	1.52	1.33
Age	63	64	63	64	63	62	66	67
Male	72%	70%	64%	63%	66%	67%	76%	76%
Previous CVD	99%	100%	66%	41%	50%	37%	56%	52%
Previous HF	10%	23%	14%	10%	15%	11%	100%	100%
RAAS-blocker	81%	81%	80%	81%	100%	98%	94%	89%
Baseline eGFR (mL/min/1.73 m^2)	74	76	77	85	56	43	66	62
Urine A/C ratio (mg/g)	31% ≥30	39% ≥30	30% ≥30	NA	927	949	NA	NA
T2DM	100%	100%	100%	100%	100%	68%	42%	50%
HbA1c	8.1%	8.3%	8.2%	8.3%	8.3%	7.1%	5.8% | 7.4%	NA
Years of T2DM	57% >10 years	12.9	13.5	11.8	15.8	15	7.4	NA
Cardiovascular outcomes								
MACE	0.86 (0.74–0.99)	0.97 (0.85–1.11)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.80 (0.67–0.95)	NA	NA	NA
Death (any cause)	0.68 (0.57–0.82)	NA	0.87 (0.74–1.01)	0.93 (0.82–1.04)	0.83 (0.68–1.02)	0.69 (0.53–0.88)	0.83 (0.71–0.97)	0.92 (0.77–1.10)
Death (CV)	0.62 (0.49–0.77)	0.92 (0.77–1.11)	0.87 (0.72–1.06)	0.98 (0.82–1.17)	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.82 (0.69–0.98)	0.92 (0.75–1.12)
HHF	0.65 (0.50–0.85)	0.70 (0.54–0.90)	0.67 (0.52–0.87)	0.73 (0.61–0.88)	0.61 (0.47–0.80)	0.71 (0.55–0.92)[a]	0.70 (0.59–0.83)	0.69 (0.59–0.81)
Renal outcomes								
Composite renal[b]	0.54 (0.40–0.75)	0.81 (0.63–1.04)	0.60 (0.47–0.77)	0.53 (0.43–0.66)	0.66 (0.53–0.81)	0.56 (0.45–0.68)	0.71 (0.44–1.16)	0.50 (0.32–0.77)
Loss of renal function	0.56 (0.39–0.79)[c]	NA	0.50 (0.30–0.84)[c]	0.54 (0.43–0.67)[d]	0.60 (0.48–0.76)[c]	0.53 (0.42–0.67)	NA	NA
ESKD	0.45 (0.21–0.97)	NA	0.77 (0.30–1.97)	0.31 (0.13–0.79)	0.68 (0.54–0.86)	0.64 (0.50–0.82)	NA	NA
Acute kidney injury	0.76 (0.62–0.93)	NA	0.66 (0.39–1.11)	0.69 (0.55–0.87)	0.85 (0.64–1.13)	NA	NA	NA

Cardiovascular and renal outcomes are presented as HR (95% CI).

A/C, albumin/creatinine; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HbA1c, glycated haemoglobin; HF, heart failure; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events (composite cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); NA, not available; RAAS, renin-angiotensin-aldosterone system; T2DM, type-2 diabetes mellitus.

[a]Composite endpoint hospitalization for heart failure or cardiovascular death.

[b]Composite renal outcomes defined as substantial loss of kidney function (doubling serum creatinine or 40% decrease in eGFR), ESKD (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), or renal death.

[c]Doubling serum creatinine.

[d]Forty percent of eGFR reduction.

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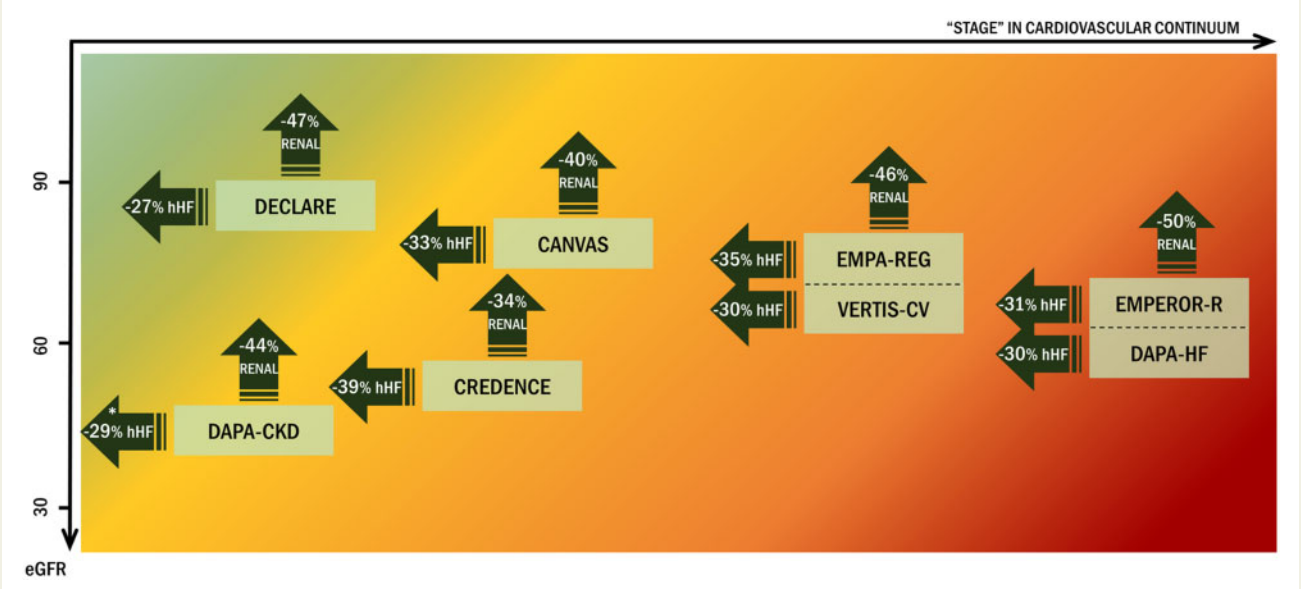


Figure 2 Summary of the effects of SGLT2i on heart failure hospitalization and renal outcomes (RENAL) in different trials, stratified according to the stage of the cardiorenal continuum. *DAPA-CKD only reported the combined endpoint of hHF + CV mortality.

studies[30] demonstrated a combined reduction of 31% of first hHF (HR 0.69; 95% CI 0.62–0.78), and a statistically significant reduction of 13% and 14% in all-cause death and cardiovascular death, respectively.

Cardiovascular effects of SGLT2i in patients with chronic kidney disease

Finally, it is relevant to observe the effect of SGLT2i on hHF in studies which focused primarily on patients with CKD. The CREDENCE trial[31] studied the effect of canagliflozin in T2DM patients with albuminuric CKD defined as an eGFR of 30–89 mL/min/1.73 m^2 and UACR >300 mg/g. The primary outcome was not cardiovascular events, but a composite endpoint of ESKD (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), doubling serum creatinine level, or death from renal or cardiovascular causes. It included patients with and without previous cardiovascular disease in an approximate 50:50 ratio. Although this study evaluated a different population (patients with diabetes and CKD), hHF was reduced in the same magnitude, with a 39% reduction in hHF (HR 0.61; 95% CI 0.47–0.80), and there was also a reduction in MACE (HR 0.80; 95% CI 0.67–0.95). A subsequent sub-analysis showed that the reduction in hHF was essentially the same irrespective of the presence of previous cardiovascular disease.[32] Regarding the risk of MACE, in contrast to previous studies that suggested that MACE reduction was only evident in patients with previous cardiovascular disease, in CREDENCE the reduction in MACE was observed both in the primary (HR 0.68; 95% CI 0.49–0.94) and secondary prevention group (HR 0.85; 95% CI 0.69–1.06; *P* for interaction = 0.25).[32] Since CREDENCE included patients with higher rates of known cardiovascular disease (50%) and a significant amount of patients with eGFR < 60 mL/min/1.73 m^2 (60%), the event rates of cardiovascular outcomes were generally higher compared with the other trials even in the subgroup of patients with previous cardiovascular disease.[32] This high baseline risk may explain, in part, the benefits in the primary prevention group seen in CREDENCE compared with the other studies. In the CREDENCE trial, the reduction in MACE was independent of basal eGFR or UACR.[32] More recently, the DAPA-CKD studied the effect of dapagliflozin in patients with kidney dysfunction (eGFR ≥25 to ≤75 mL/min/1.73 m^2 and UACR 200–5000 mg/g), with and without diabetes, and showed a 29% reduction in the combined endpoint of hHF and CV death.[33]

Summary point

In summary, the combination of the available data suggests that SGLT2i can prevent, delay, and reduce the risk of hHF across the different stages of the cardiovascular continuum, and that this effect is observed irrespective of baseline kidney function and existence of albuminuria. On the contrary, the reduction in MACE is modest and was not consistent across trials.

SGLT2 inhibitors: renal effects across the cardiorenal continuum

Although EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58, and VERTIS-CV trials where initially designed to evaluate the cardiovascular safety of SGLT2i, extensive data are now available regarding the renal effects of these agents because all these trials included secondary, and prespecified, kidney outcomes that have been reported in several sub-analysis.[34–36] It should be noted that there was some heterogeneity across the different trials regarding the way how kidney function was assessed.[37] eGFR was estimated using MDRD equation in EMPA-REG OUTCOME and CANVAS Program, whereas DECLARE-TIMI 58 monitored kidney function

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using the CKD-EPI formula and used the Cockroft–Gault equation for renal inclusion criterion. Other studies have shown that the CKD-EPI equation is superior in estimating GFR, while the MDRD formula underestimates GFR at higher levels. Regarding the definition of renal outcomes, there was also significant variation between trials. Substantial loss of kidney function was considered in EMPA-REG OUTCOME as doubling of serum creatinine, which was different from DECLARE-TIMI 58 that defined it as 40% decrease in eGFR; CANVAS Program used both definitions. In addition, the loss of kidney function was required to be sustained (i.e. persisting for at least 4 weeks) in CANVAS Program and DECLARE-TIMI 58, while EMPA-REG OUTCOME included progression to macroalbuminuria in its prespecified renal outcome, which is a softer endpoint.[31,34,36,37]

Renal outcomes of SGLT2i in patients with patients with T2DM

However, when combined, these trials show a consistent 45% reduction of composite endpoint of substantial loss of kidney function, ESKD, or renal death (HR 0.55, 95% CI 0.48–0.64).[26] There was no significant heterogeneity in renal outcomes between agents and the benefits in renal outcomes were observed irrespective of previous cardiovascular disease or baseline kidney function,[26] though there was a trend towards an attenuation of the magnitude of these benefits with progressively lower eGFR.[38] 'Real world' data from large databases have confirmed the information obtained from clinical trials, showing a large reduction in the composite renal outcome of substantial loss of eGFR and ESKD with SGLT2i (HR 0.49; 95% CI 0.35–0.67).[39] The effects of ertugliflozin on renal outcomes were also evaluated in the VERTIS-CV trial as a secondary outcome, showing a trend for a reduction of the composite renal endpoint of renal death, dialysis/transplant, or doubling serum creatinine (HR 0.81; 95% CI 0.64–1.03) which did not reach statistical significance.

Renal outcomes of SGLT2i in patients with patients with established chronic kidney disease (with and without T2DM)

CREDENCE trial was specifically designed to primarily evaluate the effects of SGLT2i on renal outcomes. It included patients with T2DM and CKD, with an eGFR of 30–89 mL/min/1.73 m^2 and UACR >300 mg/g, already receiving RAAS blocker.[31] Canagliflozin preserved kidney function, showing a 34% reduction of the primary composite renal outcome (doubling serum creatinine, ESKD, or renal death—HR 0.66; 95% CI 0.53–0.81), with a number needed to treat of 28 over 2.5 years. There was no interaction of the effect according to basal eGFR, basal UACR, or previous cardiovascular disease. More recently, the DAPA-CKD, another landmark clinical trial, evaluated the effect of dapagliflozin 10 mg in patients with albuminuric CKD (eGFR 25–75 mL/min/1.73 m^2), with or without diabetes.[33] The study was prematurely stopped due to 'overwhelming efficacy' of the drug, showing a 39% reduction in the composite primary outcome of sustained decline in eGFR of at least 50%, ESKD, or death from renal or cardiovascular causes (HR 0.61; 95% CI 0.51–0.72). Each of the components of the composite outcome occurred less frequently in the dapagliflozin group. Therefore, CREDENCE and DAPA-CKD demonstrate that renal protective effects of SGLT2i extend to a broad population of patients with CKD across different stages of kidney disease (*Figure 1*), independently of diabetes status, and that these agents should be used as an add-on therapy to RAAS blockers in CKD patients to reduce simultaneously the risk of kidney and cardiovascular outcomes.

Renal benefits of SGLT2i in patients with 'subclinical' chronic kidney disease

Across different stages of kidney disease, there is an early subclinical phase of nephropathy characterized by micro- and macroalbuminuria. Regarding the effects of SGLT2i in this subclinical phase, both EMPA-REG OUTCOME and CANVAS Program[34,35] showed a 40% lower progression to macroalbuminuria, with the latter also showing a 20% lower risk of new-onset of microalbuminuria, a 70% higher likelihood of regression of albuminuria, and an overall 18% albuminuria reduction.[35] A subanalysis of DECLARE-TIMI 58 confirmed this trend, as the use of dapagliflozin increased the likelihood of improvement from macro- to normo/micro- or micro- to normoalbuminuria by 54%, alongside a lower 27% chance of deterioration from normo- to micro/macro- or micro- to macroalbuminuria.[40] UACR was also lowered by 31% in the CREDENCE trial.[31] Dapagliflozin demonstrated to be capable of reducing albuminuria by 33% in hypertensive-T2DM patients already under RAAS-blockers.[41] Additional studies have confirmed regression of these earlier markers of nephropathy, being particularly more evident in those with basal kidney impairment. Macroalbuminuric patients benefit the most from SGLT2 inhibition regarding reduction of albuminuria, annual loss of kidney function, and renal composite outcome with a higher absolute benefit in lower all-cause mortality,[24] though kidney benefits were consistent across different UACR.[24]

Renal outcomes of SGLT2i in patients with patients HFrEF

It is also important to address the renal outcomes observed in HF trials, namely in DAPA-HF[27] and EMPEROR-Reduced,[29] which had as inclusion criteria an eGFR ≥30 and ≥20 mL/min/1.73 m^2, respectively. Nevertheless, both studies included patients with relatively preserved kidney function, with a mean eGFR of 64 mL/min/1.73 m^2 and a proportion of 44% with CKD (eGFR <60 mL/min/1.73 m^2) in DAPA-HF and a mean eGFR of 62 mL/min/1.73 m^2 in EMPEROR-Reduced. First, the reduction in the primary endpoint of worsening HF and cardiovascular mortality was observed in patients with and without CKD. Regarding the risk of having the composite renal endpoint of chronic dialysis, kidney transplantation, or a ≥50% sustained reduction of eGFR, a recent meta-analysis of the two trials reported a 38% reduction (HR 0.62; 95% CI 0.43–0.90) in this population.[30] The changes in eGFR over time were similar in both trials with a mean difference of eGFR slope of 1.8 mL/min/1.73 m^2 between dapagliflozin and placebo in DAPA-HF and of 1.73 (95% CI 1.10–2.37) mL/min/1.73 m^2 between empagliflozin and placebo in EMPEROR-Reduced (both $P < 0.0001$).

Acute vs. long-term effects of SGLT-2 inhibitors on kidney function

Finally, it should be further detailed the acute vs. chronic effects of SGLT2i on kidney function. Different trials have shown that when patients initiate SGLT2i there is an initial reduction of eGFR of about

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2.4–4.7 mL/min/1.73 m^2.[31,34–36] This effect is reversible after discontinuation of the drug, thus probably reflecting a hemodynamic adaptation to the treatment.[34,35] Of note, trials did not show an increase in acute kidney injury events with SGLT2i that, on the contrary, were reduced by 25%.[38] However, in the long-term, as the rate of eGFR decline is lower after this initial stabilization, there is a global chronic preservation of kidney function (1.18–2.74 mL/min/1.73 m^2 per year), with the eGFR crossing at about 1–2 years post-randomization.[34–36] Even in the VERTIS-CV trial, which did not reach a statistically significant reduction in the predefined composite renal endpoint, a lower degree of eGFR decline over time was observed, with differences after 60 months of 3.01 mL/min/1.73 m^2 (95% CI 1.63–4.39) for the ertugliflozin 5 mg dose and of 3.05 (95% CI 1.67–4.43) for the 15 mg dose ($P < 0.001$ for both). In general, trials have shown that this attenuation in eGFR decline was evident across all levels of basal eGFR and UACR.[38] In CANVAS Program, the rate of eGFR decline after 13 weeks was greatest in those with baseline macroalbuminuria (3.0 mL/min/1.73 m^2 per year, 95% CI 2.0–4.0) compared with those with microalbuminuria (1.0 mL/min/1.73 m^2 per year, 95% CI 0.6–1.4) or normoalbuminuria (1.1 mL/min/1.73 m^2 per year, 95% CI 0.9–1.2).[35] Beyond clinical trials, registry data also showed that SGLT2i initiation was associated with an attenuation of the natural eGFR decline by 1.53 mL/min/1.73 m^2/year (95% CI 1.34–1.72), despite the initial acute decrease in eGFR after treatment initiation, with the curves crossing at about 6–12 months.[39]

Summary point

In summary, this detailed analysis of the renal outcomes suggests that SGLT2i can delay and prevent the rate of kidney function decline across different stages of nephropathy, over large ranges of eGFR levels independently of diabetes status. Studies also suggest that SGLT2i can regress earlier markers of dysfunction such as albuminuria. This effect was observed independently, and beyond, the use of RAAS inhibitors.[38]

As the renal and cardiovascular systems intersect, nephroprotection is combined with a significant reduction of cardiovascular events (especially hHF) which occurs independently of baseline kidney function, as detailed in *Figure 2*.

SGLT2 inhibitors have been extensively studied in different patient populations. In general, all these trials showed a significant reduction in heart failure hospitalization (hHF) and a reduction in composite renal outcome (RENAL), as shown in this figure. The renal outcome reported in this figure is the combination of substantial loss of kidney function (doubling serum creatinine or 40% decrease in eGFR), ESKD (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), or renal death. In the VERTIS-CV and DAPA-HF, the reduction in the renal endpoint did not reach statistical significance and therefore it is not reported in the figure.

In the figure, trials are presented stratified according to the stage of the cardiovascular and renal continuum. The *y*-axis reports the mean basal eGFR in these trials, showing for example, that the CREDENCE trial (which evaluated patients with kidney dysfunction) has the lowest eGFR at study entry (more details in *Table 1*). The *x*-axis reflects the 'stage' in cardiovascular continuum, depicting the DAPA-HF and EMPEROR-Reduced at the right extreme because it included patients suffering from HF with reduced ejection fraction and, on the opposite side, the DECLARE-TIMI 58 trial which included the largest number of patients in primary atherosclerotic prevention, followed by CREDENCE and CANVAS Program. As detailed in *Table 1*, EMPA-REG OUTCOME and VERTIS-CV only included patients with established ASCVD.

Proposed mechanisms for the cardiorenal benefits of SGLT2 inhibition

This remarkable story of SGLT-2i clinical benefits has led to an unprecedent movement of 'reverse translational science', which has moved from bedside to bench to unravel the mechanisms behind these clinical effects. More than 20 hypothetical pathophysiological mechanisms have been proposed to explain the cardiorenal benefits of SGLT2 inhibition.[13,42] Despite the obvious hypoglycaemic effect of SGLT2i, is it highly unlikely that this could be the explanation for these cardiorenal benefits because all these trials have shown that they occur independently of T2DM status or effect on HbA1c reduction, and because a similar benefit was not observed with other more powerful antihyperglycaemic drugs. Moreover, it is known that with lower eGFR there is a reduction of its glucose-lowering effect, but the cardiovascular and renal benefits persist even in the lower ranges of kidney function, as previously discussed.

Regarding the mechanisms responsible for the ~30% consistent reduction in hHF, two most likely explanations have emerged. The first is based on a possible beneficial haemodynamic impact of SGLT-2 inhibition related with a 'smart diuresis' effect, with greater electrolyte-free water clearance, especially regarding the interstitial fluid space.[42] This theory could be supported by the observation in clinical trials that the reduction in hHF occurs very early after SGLT2i initiation. For example, in EMPEROR-HF the first statistical reduction in hHF was observed just 12 days after drug initiation. Another likely explanation is the 'metabolic hypothesis', which postulates that after SGLT-2i initiation there a shift towards a more ketogenic metabolism which could be associated with an energetic advantage and responsible for cardiovascular benefits.[13,43] More recently, a new view of this metabolic hypothesis was proposed. These new data suggest that the ketonaemia observed after SGLT-2 inhibition is not the source of an efficient fuel but instead a marker of a 'fasting mimicry effect'. This induces the activation of the SIRT-1 and AMPK signalling pathways which have well-known effects in the reduction of oxidative stress, improvement of mitochondrial structure and function, inflammation suppression, and enhanced contractile performance that can explain, in part, both the cardiovascular and renal benefits of these drugs.[44]

New studies are demonstrating that through the combination of several of these pleiotropic mechanisms, SGLT2i can improve myocardial structure and induce 'reverse cardiac remodelling', by reducing left ventricular mass and left ventricular dimensions, and improving diastolic function (*E*/e').[45,46]

Finally, regarding the mechanisms involved in kidney function protection, the main mechanism seems to be related with the enhanced tubuloglomerular feedback, secondary to increased sodium delivery to the macula densa, which subsequently causes afferent artery

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vasoconstriction. This effect is responsible for the acute (initial dip), temporary and reversible reduction in eGFR when SGLT2i is initiated (as previously described), and can also be responsible on the mid-term for the reduction in intraglomerular hypertension and hyperfiltration, which can attenuate the decline in eGFR and albuminuria progression.[42] However, because the kidney and the heart intersect at several levels, other explanations that integrate these two systems should be considered. One is the demonstration that SGLT-2 inhibition in the kidney leads to the inhibition of the central sympathetic nervous system, which is one of the most important determinants in the pathophysiology of HF and kidney disease and can explain some of the cardiorenal benefits observed in clinical trials.[47] Another important link is the well demonstrated effect of SGLT-2i in the production of erythropoietin and an increase in the haematocrit.[48] In fact, a previous mediation analysis suggested that an increase in haematocrit (which can also result from haemoconcentration) could account for more than half of the mortality benefit observed in EMPA-REG OUTCOME.[49] This increased kidney EPO production can lead to systemic organ protection by virtue of its capacity of acting as a circulating pleiotropic cytokine with favourable effects on cardiomyocyte mitochondrial function, angiogenesis, cell proliferation, and anti-inflammatory effect.[48]

In summary, despite all the studies and pathophysiological explanations, it is not clear which mechanism is primarily responsible for the cardiorenal benefits of SGLT2i, as mostly likely they are the result of the intersection of several multifactorial and interrelated mechanisms that connect the heart and the kidney.

Conclusion

Evidence from EMPA-REG OUTCOME, CANVAS Program, DECLARE-TIMI 58, VERTIS-CV, CREDENCE, DAPA-HF, and EMPEROR-Reduced trials show that the SGLT2i can prevent and reduce the risk of hHF across the different stages of the cardiovascular continuum, ranging from patients with risk factors only to the most advanced stages of disease. This benefit is independent of baseline kidney function or the stage of kidney dysfunction. At the same time, SGLT2i can delay the rate of kidney function decline, albuminuria, and the risk of ESKD, across the different stages of the renal continuum and irrespective of diabetes status.

A new paradigm has emerged in the clinical use of SGLT2i. Current evidence shows that this pharmacological class can disrupt the chain of pathological events both in the cardiovascular and renal continuum, simultaneously providing cardio- and nephroprotection, which should be viewed as the two faces of the same coin.

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