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Kidney and heart failure outcomes associated with SGLT2 inhibitor use

Annemarie B. van der Aart-van der Beek[1,2], *Rudolf A. de Boer*[3] and *Hiddo J. L. Heerspink*[1,4]✉

Abstract | Chronic kidney disease (CKD) and heart failure affect many people worldwide. Despite the availability of pharmacological treatments, both diseases remain associated with considerable morbidity and mortality. After observations that sodium–glucose co-transporter 2 (SGLT2) inhibitors — originally developed as glucose-lowering agents — improved cardiovascular and renal outcomes in patients with type 2 diabetes, dedicated trials were initiated to evaluate the cardiovascular and kidney protective effects in patients with CKD or heart failure. The results of these clinical trials and subsequent detailed analyses have shown that the benefits of SGLT2 inhibitors are consistent across many patient subgroups, including those with and without type 2 diabetes, at different stages of CKD, and in patients with heart failure with preserved or reduced ejection fraction. In addition, post-hoc analyses revealed that SGLT2 inhibitors reduce the risk of anaemia and hyperkalaemia in patients with CKD. With respect to their safety, SGLT2 inhibitors are generally well tolerated. More specifically, no increased risk of hypoglycaemia has been observed in patients with CKD or heart failure without diabetes and they do not increase the risk of acute kidney injury. SGLT2 inhibitors therefore provide clinicians with an exciting new treatment option for patients with CKD and heart failure.

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The flavonoid phlorizin was isolated from the bark of apple trees about 200 years ago. Its bitter taste — similar to that of known malaria drugs — suggested it may be an effective treatment for malaria. However, phlorizin was soon demonstrated to cause glucosuria and concomitant lowering of blood glucose levels and, in the decades that followed, phlorizin was mainly used as a tool for studying diabetes and kidney physiology[1]. The first human clinical trial with phlorizin dates back to 1933 (REF.[2]). In that study, phlorizin increased glycosuria as expected. However, an apparent reduction in kidney function was observed in a number of participants, which is a striking finding given current knowledge of the effects of sodium–glucose co-transporter 2 (SGLT2) inhibitors on renal haemodynamics[3,4]. It was not until the early 1990s that sodium–glucose co-transporters were identified as the site of action of phlorizin and as a potential pharmacological target for the treatment of diabetes[5–7]. Elegant micropuncture studies demonstrated that phlorizin reversed the increased tubular reabsorption of severely diabetic rats[8]. However, the poor absorption of phlorizin following oral administration and adverse gastrointestinal effects limited the pharmacological use of this agent as an antidiabetic medication, prompting the development of phlorizin analogues that are highly specific for the SGLT2 transporter.

Regulatory requirements to demonstrate the cardiovascular safety of new anti-hyperglycaemic drugs led to the initiation of large cardiovascular outcome trials with newly developed SGLT2 inhibitors. In 2015, the results of the first cardiovascular outcome trial — Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) — were published, demonstrating a reduction in the risk of major adverse cardiovascular events (MACE; a composite outcome of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) and hospitalization for heart failure with empagliflozin[9]. Subsequent cardiovascular outcome trials with other SGLT2 inhibitors reported similar decreases in the relative risks of hospitalization for heart failure. Moreover, these trials also demonstrated the ability of SGLT2 inhibitors to consistently improve major kidney outcomes[10–13].

Currently, four SGLT2 inhibitors are approved for clinical use in the European Union and the United States: dapagliflozin, empagliflozin, canagliflozin and ertugliflozin. Chronic kidney disease (CKD) and heart failure share common pathological pathways[14,15] (FIG. 1). The mechanisms by which SGLT2 inhibitors protect against the progression of kidney disease and heart failure have been reviewed elsewhere[16]. Here, we summarize findings from recent clinical trials of SGLT2 inhibitors. We focus

Key points

- Individuals with chronic kidney disease (CKD) are at an increased risk of heart failure; conversely, kidney function decline is common in individuals with heart failure.
- Sodium–glucose co-transporter 2 (SGLT2) inhibitors reduce the risk of kidney disease progression and hospitalization for heart failure, both in patients with CKD and in patients with heart failure.
- The beneficial effects of SGLT2 inhibitors on kidney function and heart failure are consistent across stages of CKD and independent of the severity of heart failure.
- SGLT2 inhibitors reduce the risk of anaemia and hyperkalaemia, which are common complications in patients with CKD or heart failure.
- The characteristic decline in estimated glomerular filtration rate after initiation of SGLT2 inhibitors reflects their renal haemodynamic effects and is not associated with an increased risk of acute kidney injury or accelerated loss of kidney function.

on the effects of these agents in patients with CKD and heart failure, and describe how potential mechanisms of action may translate into clinical benefit.

Effects of SGLT2 inhibitors in patients with CKD

The first three cardiovascular outcome trials of SGLT2 inhibitors — EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 — included mainly participants with preserved kidney function, and few participants reached renal end points. However, subgroup analyses suggested that the effects of the SGLT2 inhibitors on cardiovascular and renal end points were consistent across different estimated glomerular filtration rates (eGFRs) and urine albumin:creatinine ratios (UACRs)[17–23]. This finding led to the suggestion that SGLT2 inhibitors could be effective treatments for CKD. To date, three trials that assessed this hypothesis have been completed. The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was the first to specifically evaluate the efficacy and safety of an SGLT2 inhibitor in patients with type 2 diabetes (T2D) and CKD[24]. The trial included 4,401 patients with T2D, with mean eGFR 56 ml/min/1.73 m^2 and median UACR 923 mg/g, all of whom received a renin–angiotensin–aldosterone system (RAAS) inhibitor. Canagliflozin reduced the risk of kidney failure, doubling of serum creatinine level or death from renal or cardiovascular causes by 30% compared with placebo. These benefits were observed despite only modest effects on glycated haemoglobin, systolic blood pressure (SBP) and body weight. Further evidence of the beneficial effects of SGLT2 inhibitors in individuals with CKD was provided by the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial, which included a broader population of 4,304 participants with CKD — both with and without T2D — on a stable dose of RAAS inhibition[25], and slightly lower eGFR (mean 43 ml/min/1.73 m^2) than participants in CREDENCE. In DAPA-CKD, dapagliflozin reduced the primary composite outcome of a sustained decline in eGFR of at least 50%, kidney failure or death from renal or cardiovascular causes by 39% compared with placebo. Notably, the effects of dapagliflozin were consistent in patients with and without diabetes[26]. The third completed trial to assess effects of SGLT2 inhibitors in patients with T2D and CKD was the Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial[27], in which 10,584 participants with T2D, CKD (median eGFR 44 ml/min/1.73 m^2) and additional cardiovascular risk were treated with the dual SGLT1 and SGLT2 inhibitor sotagliflozin. Unlike CREDENCE and DAPA-CKD, the SCORED trial had a composite cardiovascular primary outcome of cardiovascular death, hospitalization for heart failure and urgent visits for heart failure; the secondary outcomes included a composite renal end point. The trial was terminated early for commercial reasons; however, the final analysis demonstrated that sotagliflozin reduced the primary cardiovascular outcome by 26%. By contrast, results for the secondary composite renal outcome did not differ significantly from placebo, likely because of the early termination of the trial and inadequate power to assess secondary end points. Of relevance to clinical practice, it is worth noting that all three trials continued SGLT2 inhibitor use if during the trial the eGFR fell below the inclusion criteria of the respective trial. The three trials also demonstrated the SGLT2 inhibitors to be generally well tolerated. Diabetic ketoacidosis was more frequently observed with canagliflozin or sotagliflozin than placebo in the CREDENCE and SCORED trials but was not reported in dapagliflozin-treated patients in the DAPA-CKD trial.

Together, the large SGLT2 trials completed to date demonstrate that these agents reduce the relative risk of major kidney outcomes across levels of kidney function (FIG. 2; Supplementary Table 1). As summarized below, additional subgroup analyses from these three clinical trials have provided new insights relating to the efficacy and safety of SGLT2 inhibitors in patients with CKD.

Consistency of SGLT2 inhibitor effects across CKD stages

Subgroup analyses of data from the CREDENCE trial showed that the cardiovascular and renal risk reductions achieved with canagliflozin were similar in subgroups defined by eGFR (30 to <45 ml/min/1.73 m^2, 45 to <60 ml/min/1.73 m^2 and 60 to <90 ml/min/1.73 m^2) and baseline UACR (≤1,000 mg/g, >1,000 to <3,000 mg/g and ≥3,000 mg/g)[24,28,29]. Although the relative benefits were consistent across eGFR categories, the absolute benefits were greater in subgroups with lower eGFR, who are at a greater risk of adverse cardiovascular and kidney effects. A similar analysis of DAPA-CKD reported consistent effects of dapagliflozin in subgroups with eGFR <45 ml/min/1.73 m^2 and ≥45 ml/min/1.73 m^2, and in subgroups with UACR ≤1,000 mg/g and >1,000 mg/g[25]. Despite these reassuring results, data regarding the safety and efficacy of SGLT2 inhibitors in patients with stage 4 CKD (eGFR <30 ml/min/1.73 m^2) have, until more recently, been limited.

The CREDENCE trial included participants with eGFR >30 ml/min/1.73 m^2 at the time of screening. Nevertheless, a small number of participants (n = 174; 4%) had an eGFR <30 ml/min/1.73 m^2 (mean 26 ml/min/1.73 m^2) at the time of randomization. A post hoc analysis indicated that the effects of canagliflozin on kidney, cardiovascular and mortality outcomes were

similar in these participants to those of participants with eGFR >30 ml/min/1.73 m^2, with no increase in adverse events, including acute kidney injury (AKI)[30]. However, these results should be interpreted with caution, given that they are based on a post hoc analysis of a small sample size. DAPA-CKD enrolled participants with an eGFR >25 ml/min/1.73 m^2, and consequently, a significantly larger proportion of the trial population (n = 624; 14%) had stage 4 CKD at baseline compared with patients in CREDENCE. A prespecified analysis of dapagliflozin in these participants demonstrated a reduction in the primary composite outcome of a sustained decline in eGFR of at least 50%, kidney failure or death from renal or cardiovascular causes by 27% (95% CI −2 to 47%) relative to placebo[31]. The magnitude of the benefit of dapagliflozin versus placebo for patients with CKD stage 4 was similar to that of patients with stage 2 or 3 CKD, with nearly identical hazard ratios for all end points and no significant interactions by CKD stage. In patients with stage 4 CKD, the rate of eGFR decline was −2.15 ml/min/1.73 m^2 per year in participants treated with dapagliflozin compared with −3.38 ml/min/1.73 m^2 per year in participants receiving placebo (P = 0.005). The incidence of serious adverse events and adverse events of interest were similar in both treatment groups.

Both CREDENCE and DAPA-CKD included participants with severe albuminuria. Whether the benefits of SGLT2 inhibitors extend to patients with CKD and normal or mildly increased albuminuria has not been studied in a dedicated clinical trial. However, meta-analyses from the SGLT2 inhibitor outcome trials suggest that the benefits of these agents are consistent across the spectrum of eGFR and UACR levels and therefore regulatory agents such as the FDA and EMA have approved dapagliflozin for the treatment of CKD across a wide spectrum of eGFR and UACR levels. Nevertheless, more data on the kidney effects of SGLT2 inhibitors in patients with low eGFR and normoalbuminuria remain highly desirable. The ongoing EMPA-Kidney trial[32] includes participants with CKD with and without diabetes who are eligible if their eGFR is between ≥20 ml/min/1.73 m^2 and <45 ml/min/1.73 m^2 or between ≥45 ml/min/1.73 m^2 and <90 ml/min/1.73 m^2 in combination with macroalbuminuria (UACR ≥200 mg/g)[33]. The EMPA-Kidney trial will provide additional insights into the effects of SGLT2 inhibitors in patients with advanced CKD. Examining the efficacy and safety of SGLT2 inhibition in this population is especially relevant given that RAAS inhibitors have mainly been studied in patients with macroalbuminuria and few proven effective

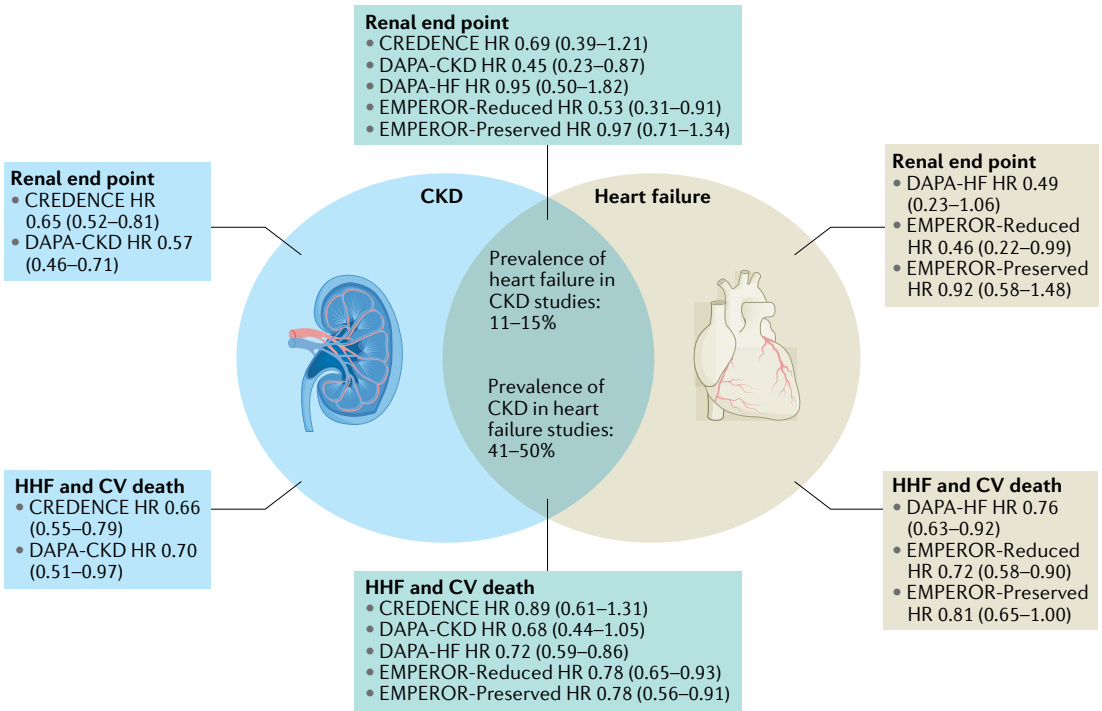

Fig. 1 | **Association between CKD and heart failure.** Chronic kidney disease (CKD) and heart failure share traditional risk factors including age, hypertension and diabetes. In addition, biological changes that occur as kidney function deteriorates (for example, inflammation and haemodynamic changes) increase the onset and progression of heart failure and vice versa. Consequently, CKD and heart failure often coexist, and adequate treatment may positively affect the prognosis of both conditions. Hazard ratios for composite kidney outcomes (defined as kidney failure, a sustained doubling of serum creatinine level or death due to kidney conditions in the CREDENCE trial; as estimated glomerular filtration rate decline ≥50%, kidney failure or death due to kidney conditions in the DAPA-CKD and DAPA-HF trials; and as kidney failure or sustained estimated glomerular filtration rate decline ≥40% in the EMPEROR-Reduced and EMPEROR-Preserved trials) and for the composite of cardiovascular (CV) death and hospitalization for heart failure (HHF) in the major sodium–glucose co-transporter 2 (SGLT2) inhibitor CKD and heart failure trials, across subgroups defined by baseline CKD and heart failure status, demonstrate beneficial effects of SGLT2 inhibitors across levels of kidney function and in patients with and without heart failure[92,94–96,115]. Data are from REFS[20,24,25,92,94–96,105,115–118].

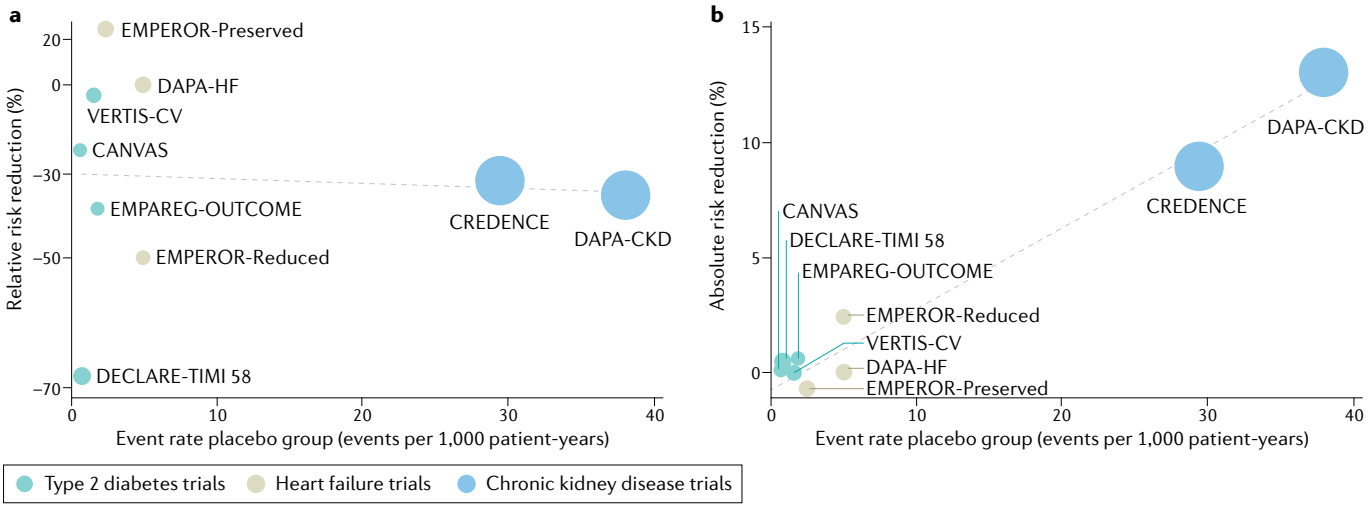

Fig. 2 | **Effect of SGLT2 inhibitors on kidney failure. a** | Findings from the major cardiovascular and renal outcome trials demonstrate that relative risk reductions in kidney failure are independent of the baseline risk. **b** | The absolute reduction in risk of kidney failure is higher in clinical trials such as CREDENCE and DAPA-CKD that enrolled patients with established chronic kidney disease, and who are at a higher risk of kidney failure. Kidney failure was defined as sustained estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2, sustained initiation of continuous kidney replacement therapy and transplantation in all trials, except for VERTIS CV, in which kidney failure was defined as the sustained initiation of continuous kidney replacement therapy and transplantation. The size of the circles reflects the number of participants in the study. Data are from REFS[19,119]. SGLT2, sodium–glucose co-transporter 2.

therapies for patients with low eGFR and normal or mildly increased albuminuria are available.

Thus, data from CREDENCE and DAPA-CKD provide a basis for the use of SGLT2 inhibitors to reduce kidney events and attenuate loss of kidney function across the spectrum of eGFR values, and support the initiation of dapagliflozin in patients with stage 4 CKD.

Consistency of SGLT2 inhibitors in patients with and without type 2 diabetes

SGLT2 inhibitors were initially developed as antidiabetic drugs on the basis of their glucose-lowering effects; their long-term cardiovascular efficacy and safety were subsequently established in patients with T2D. However, even in the early stages of their development, the pharmacodynamic properties of these agents were shown to be preserved in patients without diabetes. As an example, a large study in obese individuals without diabetes demonstrated that canagliflozin significantly reduced body weight compared with placebo[34]. An analysis from another clinical trial that compared canagliflozin with the sulfonylurea derivative glimepiride showed superior effects of canagliflozin in stabilizing eGFR decline despite equivalent glycaemic control, suggesting that the kidney protective effects of this agent may be independent of its glucose-lowering effect[35]. As reviewed elsewhere, mechanistic studies indicated that the SGLT2 inhibitors may afford kidney protection through reductions in intra-glomerular pressure and glomerular hyperfiltration[16,36]. Glomerular hyperfiltration is a common pathological pathway in different types of CKD, suggesting that the kidney protective effects of SGLT2 inhibitors could potentially extend to various non-diabetic kidney diseases. This hypothesis was tested in the DIAMOND and DAPA-CKD trials. The DIAMOND trial was a cross-over trial in 53 patients with CKD without diabetes (24-h protein excretion >500 mg and ≤3,500 mg; eGFR ≥25 ml/min/1.73 m^2)[37]. Participants were randomly assigned to 6-week treatment periods of placebo followed by dapagliflozin 10 mg once daily or vice versa, separated by a 6-week wash-out period. One of the secondary outcomes was change in measured (m)GFR as assessed by plasma disappearance of iohexol. After 6 weeks of treatment, dapagliflozin induced a decline in mGFR of 6.6 ml/min/1.73 m^2 (−9.0 ml/min/1.73 m^2 to −4.2 ml/min/1.73 m^2) compared with that induced by placebo. This decline reversed completely after discontinuation of dapagliflozin with mGFR values returning to baseline within 6 weeks, indicating a haemodynamic effect consistent with that observed in patients with diabetes. In the DAPA-CKD trial, 32% of participants had non-diabetic kidney disease. Hazard ratios for the primary composite outcome of sustained decline in eGFR of at least 50%, kidney failure, renal death or cardiovascular death were similar in participants with and without diabetes, confirming that the cardiorenal benefits of SGLT2 inhibitors extend to patients with non-diabetic kidney disease[25].

A prespecified subgroup analysis of the DAPA-CKD trial specifically evaluated the effect of dapagliflozin according to baseline glycaemic status[38]. The findings demonstrated consistent effects of dapagliflozin in patients with normoglycaemia (HbA_{1c} < 5.7%), prediabetes (HbA_{1c} 5.7–6.5%) and T2D (HbA_{1c} ≥ 6.5%), with risk reductions for the primary composite outcome of 38%, 63% and 36%, respectively (*P* value for interaction 0.19). These results were achieved despite only a modest reduction in HbA_{1c} in participants with T2D (−0.1%; 95% CI −0.2 to 0.0) and the absence of an effect on HbA_{1c} in participants with prediabetes or normoglycaemia, and

support the notion that the renoprotective effects of SGLT2 inhibitors are unlikely mediated by glycaemic control[35].

Although diabetic kidney disease was the most frequent cause of CKD in DAPA-CKD (58%), the trial also included participants with chronic glomerulonephritis (16%), ischaemic or hypertensive chronic kidney disease (16%) and CKD of other or uncertain cause (10%). A prespecified analysis of DAPA-CKD found consistent effects of dapagliflozin across all of these aetiological subgroups for both primary and secondary outcomes[26]. A separate analysis of DAPA-CKD data investigated the effects of dapagliflozin in patients with immunoglobulin A (IgA) nephropathy[39]. This disease is the most common form of glomerulonephritis; however, current treatment options are limited and approximately one-third of all patients progress to kidney failure. The analysis demonstrated that dapagliflozin reduced the risk of the primary composite outcome by 71% (HR 0.29; 95% CI 0.0.12–0.0.73; $P = 0.005$), and the secondary kidney outcome by 79% (HR 0.0.24; 95% CI 0.09–0.65; $P = 0.002$) in DAPA-CKD participants with IgA nephropathy. Despite the usual dip in eGFR after starting dapagliflozin, the mean annual rate of eGFR decline was smaller with dapagliflozin than with placebo (between-group difference of 2.4 ml/min/1.73 m^2; 95% CI 1.1–3.7). Another analysis showed similar beneficial kidney effects of dapagliflozin in DAPA-CKD participants with focal segmental glomerulosclerosis (FSGS)[40].

The finding that SGLT2 inhibitors reduced kidney outcomes in patients with CKD, irrespective of diabetic status or underlying cause of kidney disease is important for clinical practice, as patients without diabetes and CKD constitute at least 50% of all patients requiring dialysis and are often excluded from large clinical trials with new therapies.

SGLT2 inhibitors in patients with and without cardiovascular disease

The initial cardiovascular outcome trials with SGLT2 inhibitors mainly included participants with preserved kidney function. Subgroup analyses of these trials suggested that the beneficial effects of SGLT2 inhibitors on cardiovascular death, myocardial infarction or stroke were more pronounced in participants with established cardiovascular disease at baseline[10,11]. A meta-analysis of EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI 58 showed that SGLT2 inhibition reduced the risk of MACE by a modest 11% (HR 0.89; 95% CI 0.83–0.96; $P = 0.0014$) overall. However, this effect was restricted to participants with a history of cardiovascular disease at baseline (HR 0.86; 95% CI 0.80–0.93); in participants without established cardiovascular disease no risk reduction was observed (HR 1.00; 95% CI 0.87–1.16; P for interaction = 0.0501)[41]. Similar effects were observed with respect to heart failure in both the primary and secondary prevention groups.

The CREDENCE trial included participants with CKD — 50% of whom had cardiovascular disease at baseline. In contrast to findings from the cardiovascular outcome trials, an analysis of cardiovascular outcomes in CREDENCE showed that canagliflozin consistently reduced the risk of MACE in both primary and secondary prevention groups (HR 0.68; 95% CI 0.49–0.94 and HR 0.85; 95% CI, 0.69–1.06, respectively; P for interaction = 0.25)[42]. Similar effects were also observed for the individual components of the composite outcome, and for the composite of cardiovascular death or hospitalization for heart failure. The robust and consistent reductions in MACE and renal outcomes in participants with and without known cardiovascular disease at baseline suggest that patients with low GFR and significant proteinuria carry a cardiovascular risk similar to that imparted by the presence of cardiovascular disease. That patients with low eGFR and high albuminuria carry a risk that is at least equivalent to other cardiovascular risk factors has been observed in large observational studies as well, but the CREDENCE trial highlights the clinical implication of this finding with respect to initiation of canagliflozin treatment[43].

Clinical implications of an acute decline in eGFR

As mentioned earlier, SGLT2 inhibitors cause an acute, transient decline in eGFR of −3 to −5 ml/min/1.73 m^2 over 2–4 weeks[11,12,24,25]. Larger decreases of about 6–10 ml/min/1.73 m^2 are observed for mGFR[37,44,45]. The initial 'dip' in GFR is similar to that observed after initiation of RAAS inhibitors, and is most likely a consequence of the haemodynamic effects of SGLT2 inhibitors in the kidney[16,36]. Inhibition of SGLT2 increases delivery of sodium to the distal tubule — an effect that augments tubuloglomerular feedback, which in turn, leads to a reduction in glomerular hyperfiltration. The clinical implications of the acute decline in eGFR were unknown and when first reported, raised concerns about the safety and long-term efficacy of SGLT2 inhibitors in clinical practice. It was important to resolve these concerns to avoid clinical inertia with these agents.

Two new analyses shed light on the incidence and clinical implications of the acute eGFR decline. A post hoc analysis of data from the EMPA-REG OUTCOME trial demonstrated that an eGFR decline of >10% occurred in 28.3% of participants versus 13.4% of placebo-treated participants (OR 2.7; 95% CI 2.3–3.0) 4 weeks after initiation of empagliflozin[46]. A more pronounced eGFR decline of >30% occurred infrequently. Use of diuretics and higher KDIGO risk category at baseline, as defined by Kidney Disease: Improving Global Outcomes (KDIGO) criteria, were independently associated with an increased incidence of an initial eGFR dip with empagliflozin. Importantly, eGFR stabilized in all participants treated with empagliflozin after 12 weeks, even in those who experienced an eGFR decline >10% or >30% at week 4. By contrast, mean eGFR continued to decline over time in the placebo-treated patients. After treatment discontinuation, mean eGFR increased in those who had received empagliflozin, but remained stable in those who had received placebo. Safety outcomes, including AKI, were similar in the empagliflozin-treated participants, regardless of the initial eGFR decline.

Another post hoc analysis characterized the initial eGFR dip and its association with long-term outcomes in participants with T2D and CKD from the CREDENCE trial[47]. After 3 weeks, 45% of participants treated with

canagliflozin experienced an eGFR decline of >10%, versus 21% of participants treated with placebo (OR 3.07; 95% CI 2.73–3.5). An eGFR decline of >30% was a rare event in patients treated with canagliflozin, although it occurred slightly more frequently in CREDENCE than in patients treated with empagliflozin in the EMPA-REG OUTCOME trial (4.2% and 1.4% for canagliflozin and empagliflozin, respectively). From week 13 onwards, the magnitude of the initial dip in eGFR after canagliflozin initiation did not influence the long-term eGFR trajectory, such that regardless of the acute decline in eGFR, long-term eGFR trajectories were similar and importantly, remained less steep than those of patients on placebo. In addition, the overall and renal safety profiles were similar regardless of the initial eGFR dip, except for the small group of participants who experienced an acute decrease in eGFR >30%, in whom the risk of kidney-related adverse effects was slightly increased.

Of note, the acute effects of SGLT2 inhibition on eGFR were attenuated in patients with more severe CKD. For example, in the DAPA-CKD trial, the eGFR dip was less pronounced in participants with stage 4 CKD compared with that of participants with stages 2 or 3 CKD (1.42 ml/min/1.73 m^2 versus 2.56 ml/min/1.73 m^2 over 2 weeks)[31].

Thus, the acute decline in eGFR that is observed after initiation of SGLT2 inhibitors reflects their renal haemodynamic effects. The reassuring data from analyses of EMPA-REG OUTCOME and CREDENCE data confirm that the acute decline in eGFR is not associated with an increased risk of adverse events, including AKI or accelerated progressive loss of kidney function.

SGLT2 inhibitors reduce the risk of acute kidney injury

The eGFR decline that is frequently observed after initiation of SGLT2 inhibitor treatment also raised concern that SGLT2 inhibition could increase the risk of AKI, similar to the effects of RAAS inhibitors in patients who are hypovolaemic or septic. These concerns were strengthened following post-marketing surveillance reports of AKI in patients with T2D and preserved kidney function following SGLT2 inhibitor initiation. Data from clinical trials and 'real-world' data from registries, however, do not support this notion. A meta-analysis of the effects of SGLT2 inhibitors on major kidney outcomes in patients with T2D found that SGLT2 inhibitors reduced the risk of AKI by 25%, with consistent effects across studies[48]. These results were confirmed in other meta-analyses that specifically evaluated safety[49,50], in which SGLT2 inhibitors reduced the risk of serious AKI by 36–41%, with no heterogeneity detectable across studies, and a magnitude of protection against AKI that was comparable for the different SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin). Observational studies have compared the risk of AKI associated with SGLT2 inhibitor use with that associated with the use of DPP4 inhibitors and other glucose-lowering drugs[51–53], demonstrating that initiation of an SGLT2 inhibitor is associated with a relative risk reduction of 21–53% compared with that of other glucose-lowering agents, similar to results observed in clinical trials.

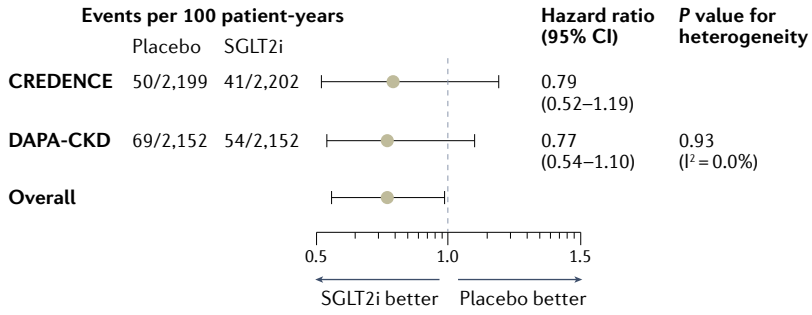

Fig. 3 | **Risk of acute kidney injury with SGLT2i use.** Post hoc analyses of investigator-reported incidences of acute kidney injury in the DAPA-CKD and CREDENCE trials demonstrate a trend towards a reduced risk of acute kidney injury with sodium–glucose co-transporter 2 inhibitor (SGLT2i) use. Data are from REFS[54,55].

Two dedicated analyses of the CREDENCE and DAPA-CKD trials published in 2021 provide additional evidence that SGLT2 inhibitors can be used safely and that their use decreases the risk of renal adverse events and abrupt declines in kidney function, even in patients at a high risk of AKI[54,55]. In a post hoc analysis of CREDENCE trial data, canagliflozin was associated with a reduced incidence of renal-related adverse events (HR 0.71; 95% CI 0.61–0.82), serious renal-related adverse events (HR 0.72; 95% CI 0.51–1.00) and AKI (HR 0.85; 95% CI 0.64–1.13)[54]. A similar analysis of DAPA-CKD data further substantiated the renal safety profile of SGLT2 inhibitors, demonstrating a reduced risk of abruptly declining kidney function, defined as a doubling in serum creatinine level between two subsequent study visits (HR 0.68; 95% CI 0.49–0.94) and investigator-reported, AKI-related serious adverse events (HR 0.77; 95% CI 0.54–1.10)[55]. Combined, these two studies show that SGLT2 inhibition reduces the risk of AKI-related serious adverse events with clinically relevant risk reductions (FIG. 3). These reassuring data raise the question as to how and when to monitor kidney function after initiation of SGLT2 inhibitors. As SGLT2 inhibitors do not increase the risk of AKI and because the acute decline in eGFR is not associated with an increased risk of adverse events or progressive kidney function loss, it has been suggested that in the majority of patients there is no need to monitor eGFR or electrolytes after SGLT2 inhibitor initiation, unless there is clinical concern about volume depletion, for example, orthostatic hypotension, or in patients using high-dose diuretics or in the elderly[56].

SGLT2 inhibitors improve blood pressure control in CKD

High blood pressure is a major risk factor for the development of CKD and cardiovascular disease. Likewise, progression of kidney disease is frequently accompanied by increased blood pressure[57]. In patients with CKD, high blood pressure is difficult to control, and despite an arsenal of antihypertensive drugs, many patients do not meet guideline recommended blood pressure targets. Resistant hypertension — often defined as SBP ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg while receiving three or more classes of blood pressure-lowering drugs — is common in patients with stage 4–5 CKD[57]. SGLT2 inhibitors lower SBP

and DBP. An early meta-analysis of 43 SGLT2 inhibitor trials in participants with T2D demonstrated that SGLT2 inhibitors reduce SBP and DBP by 2.5 mmHg (95% CI 2.9–2.1) and 1.5 mmHg (95% CI 1.1–1.8), respectively[58]. A more recent analysis of the CREDENCE trial — in which 76% of participants had hypertension (defined as baseline SBP ≥130 mmHg) and 31% had resistant hypertension — demonstrated that canagliflozin reduced SBP by 3.5 mmHg compared with placebo within 3 weeks. This effect was independent of baseline SBP, number of blood-pressure-lowering drugs and history of treatment-resistant hypertension, and was maintained throughout the study[59].

The mechanism of action that is responsible for the blood pressure-lowering properties of SGLT2 inhibitors is not fully elucidated and likely multifactorial. Glycosuria and its associated natriuresis and osmotic diuresis have traditionally been thought to be important factors. However, the observation that the glycosuric effect of SGLT2 inhibitors disappears in patients with impaired kidney function while the effect on blood pressure is preserved, challenges this proposal. The DAPASALT trial was specifically aimed at evaluating the effects of dapagliflozin on natriuresis, intra- and extracellular volume, and 24-h blood pressure[60]. The trial included 14 participants with T2D and preserved kidney function, who were subjected to a controlled, standardized sodium diet, with measurements performed at the start of the treatment (days 2–4), at the end of the treatment (days 12–14) and at follow-up (days 15–18). The study investigators reported a significant reduction in blood pressure after 2–4 days (−6.1 mmHg; 95% CI −9.1 to −3.1) and after 12–14 days (−7.2 mmHg; 95% CI −10.0 to −4.3). However, dapagliflozin did not significantly change mean 24-h sodium excretion, with a baseline value of 150 (SD 32) mmol/24 h and changes of −7.0 mmol/24 h (95% CI −22.4 to 8.4) and 2.1 mmol/24 h (95% CI −28.8 to 33.0) after 2–4 and 12–14 days, respectively. Extracellular volume was significantly reduced after 2–4 days (−0.7 l; 95% CI −1.3 to −0.1) but not after 12–14 days. Plasma volume and intracellular volume did not significantly change during treatment with dapagliflozin. The lack of an increase in natriuresis in the presence of a profound blood pressure-lowering effect suggests that blood pressure reduction by SGLT2 inhibitors may be independent of sodium excretion and that other factors may explain the blood pressure-lowering effects of these agents.

A separate 2021 study investigated the effects of dapagliflozin on SBP, urinary glucose and sodium excretion, and a vast array of vasoactive factors including components of the RAAS, atrial natriuretic peptide (ANP), cyclic guanosine monophosphate (cGMP) and neprilysin[61] in 52 obese participants with T2D and eGFR ≥60 ml/min/1.73 m^2. In that trial, dapagliflozin also significantly reduced SBP compared with placebo, both after the first dose (−7 ± 3 mmHg) and after 12 weeks (−7 ± 2 mmHg). Although glucosuria was clearly detectable after the first dapagliflozin dose, no acute changes in natriuresis were observed. In fact, after 12 weeks, urinary sodium excretion was significantly decreased, suggesting that it is unlikely that natriuresis contributed to the blood pressure-lowering effect of dapagliflozin. Treatment with dapagliflozin resulted in a reduction in the plasma concentration of the vasoconstrictors angiotensin II (−23 ± 5%) and angiotensinogen (−15 ± 6%), and an increase in the plasma concentration of the vasodilators ANP (49 ± 24%) and cGMP (81 ± 21%). Levels of other vasoactive mediators did not change significantly. These data suggest that vasoactive mediators may be involved in the blood pressure-lowering effects of SGLT2 inhibitors, although no association was observed between the change in plasma concentrations of relevant vasoactive mediators and the change in blood pressure during SGLT2 inhibition. This lack of association may simply represent the absence of a direct relationship but could also be because blood pressure regulation is a complex process in which many factors interact, making a direct relationship difficult to demonstrate. Finally, SGLT2 inhibitors have been proposed to reduce renal stress and renal afferent nervous activity, resulting in suppression of central sympathetic activity and reduced blood pressure[62]. Whatever the underlying mechanism by which SGLT2 inhibitors lower blood pressure in patients with CKD, they are a welcome addition to the therapeutic options for hypertension, in particular for a population in whom blood pressure is difficult to control.

SGLT2 inhibitors reduce the risk of anaemia

Anaemia is a common complication in patients with T2D and CKD[63]. The prevalence of anaemia increases with progression of kidney disease, and affects nearly all patients with kidney failure. Renal anaemia is associated with an increased risk of adverse cardiovascular and kidney outcomes, and a reduced quality of life. Treatment with erythropoiesis-stimulating agents (ESAs) and intravenous iron supplementation are the current mainstays of anaemia management[64]. However, although ESAs improve quality of life and the need for blood transfusion, they do not improve cardiovascular outcomes or progression of kidney disease[65]. In addition, ESA resistance is a common problem in patients with anaemia and CKD[64]. The availability of additional treatment options for the treatment of anaemia in patients with CKD is therefore much needed.

In patients with T2D, increased reabsorption of glucose via SGLT2 in the proximal tubule is accompanied by increased consumption of ATP by the Na^+/K^+ pump, and increased oxygen consumption by mitochondria to meet the increased demand for ATP. The metabolic stress and tubulointerstitial hypoxia that result from excessive glucose reabsorption induce the transformation of erythropoietin-producing fibroblasts into myofibroblasts, decreasing their ability to produce erythropoietin[66]. Hepcidin — a key hormone that is involved in the regulation of iron storage by macrophages and the intestinal absorption of iron — may also influence the development of anaemia in patients with CKD. Hepcidin levels are elevated patients with CKD, owing to its reduced renal clearance and as a consequence of inflammation, resulting in a functional iron deficiency and potentially contributing to ESA resistance.

SGLT2 inhibitors have been associated with increases in haematocrit and haemoglobin in patients with T2D. A 2013 study that compared the diuretic and haematopoietic effects of dapagliflozin, hydrochlorothiazide and placebo in patients with T2D and preserved kidney function, found that 12 weeks of dapagliflozin treatment increased haematocrit by 2.2% (95% CI 1.3–3.0), compared with changes of −0.9% (−2.3 to 0.6) and −0.2% (−1.0 to 0.6) for hydrochlorothiazide and placebo, respectively[44]. A similar effect on haemoglobin was seen, with an increase of 6 g/l (95% CI 3–9 g/l) in patients treated with dapagliflozin, compared with changes of −3 g/l (95% CI −8 to 2 g/l) and −1 g/l (95% CI −3 to 2 g/l) with hydrochlorothiazide and placebo, respectively. These findings were confirmed by other studies[9,67]. A 2020 post-hoc analysis of anaemia-related clinical events in CREDENCE[68] reported that canagliflozin reduced the primary composite outcome of investigator-reported anaemia or the initiation of treatments for anaemia by 35% (HR 0.65; 95% CI 0.55–0.77; $P < 0.0001$). Moreover, canagliflozin lowered the risk of new-onset anaemia (HR 0.48; 95% CI 0.41–0.55; $P < 0.001$) and severe anaemia (HR 0.50; 95% CI 0.39–0.64; $P < 0.001$). Finally, in individuals with anaemia at baseline, correction of anaemia was more frequently observed with canagliflozin (HR 2.59; 95% CI 2.18–3.08; $P < 0.001$). Canagliflozin also achieved a mean increase in haemoglobin of 7 g/l (95% CI 6–8 g/l) and a mean increase in haematocrit of 2.4% (95% CI 2.2–2.6%) compared with that achieved with placebo. This effect was consistent across subgroups defined by baseline haemoglobin, haematocrit and estimated plasma volume. Similarly, a substudy of the EMPA-HEART (Effects of Empagliflozin on Cardiac Structure in Patients With Type 2 Diabetes) CardioLink-6 trial found that administration of 10 mg empagliflozin once daily induced an early rise in erythropoietin levels and significantly higher haemoglobin and haematocrit values after 6 months of treatment than that achieved with placebo[69].

The increase in haemoglobin and haematocrit observed with SGLT2 inhibitors can be partly explained by the decrease in plasma volume due to the mild diuretic effects of these agents. However, diuresis peaks within hours to days and then decreases again, whereas the effect of SGLT2 inhibitors on haemoglobin and haematocrit persists over time. Of note, hydrochlorothiazide has stronger diuretic effects than SGLT2 inhibitors, but does not improve haemoglobin or haematocrit, suggesting a direct effect of SGLT2 inhibition on erythropoiesis. Transient increases in reticulocyte count and erythropoietin concentrations have been observed 2–4 weeks after initiation of SGLT2 inhibition[44]. By blocking the SGLT2 transporter, SGLT2 inhibitors decrease the demand for ATP in mitochondria of the proximal tubules, thereby reducing oxidative stress and tubulointerstitial hypoxia and reversing the transformation of erythropoietin-producing fibroblasts into myofibroblasts[66]. SGLT2 inhibitors also suppress hepcidin levels, resulting in increased absorption of dietary iron and the release of iron from macrophages, further stimulating erythropoiesis[70].

In conclusion, SGLT2 inhibitors seem to inhibit the onset of anaemia and reduce existing anaemia in patients with T2D. More data are needed to confirm these observations and to elucidate the mechanism of action that underlies these beneficial effects.

SGLT2 inhibitors reduce the risk of hyperkalaemia

Patients with T2D are at increased risk of hyperkalaemia, as are those with CKD. Treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, which is the standard of care for patients with T2D and CKD, further increases the risk of hyperkalaemia. Early evidence that suggested a transient stimulatory effect of some SGLT2 inhibitors on potassium levels[71] prompted concerns regarding the effect of SGLT2 inhibitors on hyperkalaemia risk, potentially limiting their use in clinical practice. However, these concerns seem unjustified. In a pooled analysis of 13 phase IIb and III trials of dapagliflozin in patients with T2D, dapagliflozin use did not increase serum potassium levels over a treatment period up to 24 weeks (mean change −0.05 mmol/l; 95% CI −0.07 to −0.03 mmol/l and −0.02 mmol/l; 95% CI −0.04 to 0.00 mmol/l in the dapagliflozin and placebo group, respectively)[72]. A similar analysis evaluated the effects of canagliflozin on serum potassium levels in the CANVAS program[73]. Over the course of the study, the mean change in serum potassium levels from baseline was −0.02 mmol/l (95% CI −0.04 to −0.01 mmol/l) for canagliflozin versus placebo, with no differences in subgroups defined by baseline eGFR (≥60 ml/min/1.73 m^2, 45 to <60 ml/min/1.73 m^2 and <45 ml/min/1.73 m^2), canagliflozin dose, or RAAS inhibitor use. However, these studies included patients with relatively normal kidney function who are at a lower risk of hyperkalaemia than patients with CKD. Moreover, the short follow-ups did not enable investigation of the long-term effects of SGLT2 inhibitor use on potassium levels or the incidence of hyperkalaemia. However, a 2021 analysis of the CREDENCE trial has provided new insights into the effects of SGLT2 inhibitors on hyperkalaemia in patients with diabetic kidney disease[74]. The study demonstrated that, compared with placebo, canagliflozin significantly reduced the risk of the composite outcome (of investigator-reported hyperkalaemia and initiation of potassium-sparing medication) by 22% and reduced the risk of laboratory-defined hyperkalaemia (that is, potassium ≥6.0 mmol/l) by 23%, with no effect on the risk of hypokalaemia. Initiation of a potassium binder occurred less frequently with canagliflozin (HR 0.66; 95% CI 0.46–0.93), which is clinically relevant as the most frequently used potassium binder, sodium polystyrene sulfonate, is poorly tolerated and newer potassium binders are generally expensive. It is also important to note that despite the more frequent initiation of potassium binders in the placebo group in this study, hyperkalaemia occurred less frequently over time with canagliflozin. The lower risk of hyperkalaemia with canagliflozin is in contrast to that associated with RAAS inhibitor use. Specifically, the FIDELIO DKD trial demonstrated that the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone reduced the risk of a composite kidney outcome by 18%[75].

However, finerenone increases potassium levels and the risk of hyperkalaemia. The findings from this analysis of CREDENCE trial data raise the question as to whether SGLT2 inhibitors and MRAs might be combined in the future to augment kidney protection and reduce hyperkalaemia. Various short-term studies are ongoing to explore this possibility, including ROTATE-3, which combines eplerenone and dapagliflozin; and MIRACLE[76], which combines the MRA AZD9977 and dapagliflozin[77].

Effects of SGLT2 inhibitors in patients with heart failure

Heart failure is a major public health problem; it has an estimated prevalence of 1–2% in the overall population, but increases with age to affect >10% in individuals over 65 years of age[78]. Patients with heart failure often have comorbidities, including CKD. In fact, 40–50% of patients with heart failure have CKD; conversely, patients with CKD are at a higher risk of developing heart failure[79] (FIG. 1). Specifically, observational data show that hospitalization for heart failure is associated with an acceleration of kidney function decline (change in eGFR slope of −1.1 ml/min/1.73 m^2; 95% CI −1.2 to −1.0, post-event compared with pre-event)[80].

Despite pharmacological treatment with RAAS inhibitors, beta-blockers and MRAs, heart failure remains associated with significant morbidity, and a mortality rate of approximately 60% within 5 years of diagnosis[81]. In large cardiovascular and kidney outcome trials in patients with T2D, SGLT2 inhibitors have consistently reduced the risk of hospitalization for heart failure by 30–35%[9–11,24]. The precise mechanism underlying the beneficial effects of SGLT2 inhibitors on heart failure remains incompletely understood. Improved glycaemic control, blood-pressure lowering and weight reduction have been suggested to explain these striking effects. Osmotic diuresis — resulting in a reduction in interstitial fluid volume rather than a reduction in circulating volume — has also been proposed to contribute to the observed improvements in clinical outcomes[82]. More recent data suggest that SGLT2 inhibitors may exert direct cardioprotective effects, including improvements in cardiomyocyte calcium handling and cardiac energy metabolism, increased autophagy and decreases in epicardial fat mass[83,84].

Approximately 10–15% of all patients in EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 and VERTIS had heart failure at baseline. The observed reductions in heart failure hospitalization in these trials among individuals with prevalent heart failure and in those free of heart failure at baseline led to the conclusion that the reduced hospitalization events largely reflected a lower risk of developing new onset heart failure. This conclusion is a very relevant outcome for the cardiovascular field, as few agents can effectively reduce the risk of new-onset heart failure[85,86], and the prevention of heart failure is a very important outcome in at-risk patients, particularly those with T2D.

The proposed mechanisms of action combined with the striking effects of SGLT2 inhibitors on heart failure outcomes in patients with T2D suggested that these agents may also be of benefit to patients with prevalent heart failure, independent of diabetic status.

SGLT2 inhibitors and heart failure with reduced ejection fraction

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial evaluated the effects of dapagliflozin in 4,744 patients with prevalent heart failure with reduced ejection fraction (HFrEF; defined as chronic heart failure (New York Heart Association classes II–IV) with a left ventricular ejection fraction ≤40%, and elevated natriuretic peptides, with or without T2D)[87]. Patients were randomized to receive either dapagliflozin 10 mg once daily or placebo, which was given on top of recommended heart failure medications. Over a median follow-up of 18.2 months, dapagliflozin reduced the incidence of the primary composite outcome — a worsening heart failure event (either a hospitalization or an urgent visit requiring intravenous diuretic therapy) or cardiovascular death — by 26% compared with placebo (HR 0.74; 95% CI 0.65–0.85; $P<0.001$), with a number needed to treat of 21. Event rates were substantially and significantly lower for each of the two components of the composite outcome. In addition, treatment with dapagliflozin resulted in a significant improvement in the Kansas City Cardiomyopathy Questionnaire, indicating fewer symptoms. Strikingly, the effects of dapagliflozin were independent of the presence or absence of T2D and HbA_{1c} level[88]; moreover, the 55% of DAPA-HF participants who did not have prevalent T2D at entry into the trial had a lower likelihood of developing incident T2D during the trial when allocated to dapagliflozin[89]. Corroborative data regarding the efficacy and safety of SGLT2 inhibitors for the treatment of HFrEF were provided by the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced)[90]. Despite the enrolment of patients with more severe heart failure — characterized by lower left ventricular rejection fraction and higher NT-proBNP than DAPA-HF — the results were largely consistent. Over a median follow-up of 16 months, empagliflozin lowered the risk of the primary outcome of cardiovascular death or hospitalization for heart failure by 25% (HR 0.75; 95% CI 0.65–0.86; $P<0.001$). This benefit was mainly driven by a 31% risk reduction in hospitalization for heart failure, and was observed both in the presence (50%) and absence (50%) of diabetes. In contrast to DAPA-HF, empagliflozin had no significant effect on cardiovascular death in EMPEROR-Reduced. However, a meta-analysis of the aggregate data of EMPEROR-Reduced and DAPA-HF revealed a reduction in cardiovascular mortality (HR 0.86; 95% CI 0.76–0.98) and all-cause mortality (HR 0.87; 95% CI 0.77–0.98)[91].

There has been speculation as to why the effects of empagliflozin on mortality were less striking in EMPEROR-Reduced than the effects of dapagliflozin in DAPA-HF. First, EMPEROR-Reduced had a shorter follow-up and accrued fewer end points, possibly resulting in a lack of power. Furthermore, EMPEROR-Reduced enrolled patients with more severe heart failure than did DAPA-HF, and it has been suggested that SGLT2

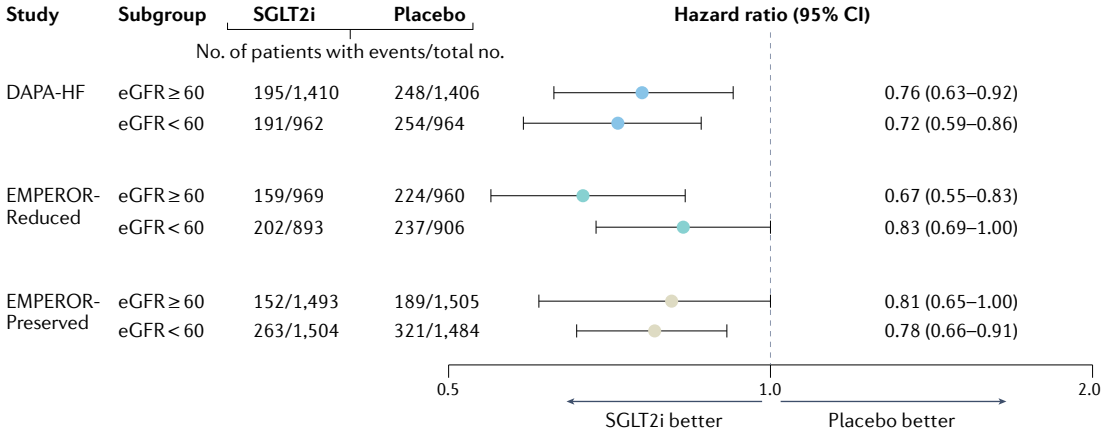

Fig. 4 | **Effect of SGLT2i on heart failure end points according to baseline kidney function.** Subgroup analyses of DAPA-HF, EMPEROR-Reduced and EMPEROR-Preserved demonstrate that effects are consistent in participants with and without chronic kidney disease (defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2) at baseline. Data are from REFS[87,90,92]. SGLT2i, sodium glucose cotransporter 2 inhibitor.

inhibitors might be more efficacious in patients with less severe heart failure who might be more amenable to disease-modifying drugs[91]. On the other hand, the effects of empagliflozin on cardiovascular mortality in the EMPEROR-Reduced trial were almost identical to those observed in the EMPEROR-Preserved trial[92]; thus, this finding may in fact reflect the real effect size of empagliflozin on cardiovascular mortality in patients with prevalent heart failure.

Additional data regarding the effects of SGLT2 inhibition in patients with heart failure were provided by the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial, which investigated whether the dual SGLT1/2 inhibitor sotagliflozin reduced cardiovascular and renal end points in patients with T2D and acutely decompensated heart failure[93]. Although the trial was prematurely terminated owing to loss of funding by the sponsor, available data demonstrate that sotagliflozin effectively and significantly reduced the number of primary outcome events (deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure); HR 0.67; 95% CI 0.52–0.85). The effects on eGFR were negligible. These data provide further support for the salutary effects of SGLT2 inhibitors in patients with prevalent heart failure, as well as in patients with recent decompensated heart failure — a vulnerable group for whom few therapies are available.

Consistency of SGLT2 inhibitor effects across levels of baseline kidney function. The DAPA-HF trial enrolled participants with an eGFR ≥30 ml/min/1.73 m^2, 41% of whom had an eGFR <60 ml/min/1.73 m^2 at baseline. A subgroup analysis of DAPA-HF demonstrated the effects of dapagliflozin on the incidence of cardiovascular death or worsening heart failure to be consistent in participants with CKD (defined as <60 ml/min/1.73 m^2) compared with that of participants with eGFR ≥60 ml/min/1.73 m^2 (HR 0.72; 95% CI 0.59–0.86 and HR 0.76; 95% CI 0.63–0.92, respectively)[94]. In EMPEROR-Reduced, 53% of enrolled participants had CKD (defined as baseline eGFR <60 ml/min/1.73 m^2 or UACR >300 mg/g), and participants with an eGFR as low as 20 ml/min/1.73 m^2 were included. A prespecified analysis of EMPEROR-Reduced demonstrated similar reductions in the primary outcome of cardiovascular death or hospitalization for heart failure regardless of the presence or absence of CKD (HR 0.78; 95% CI 0.65–0.93 and HR 0.72; 95% CI 0.58–0.90, respectively)[95] (FIG. 4). Consistent effects were also observed in subgroups defined by baseline eGFR and albuminuria.

SGLT2 inhibitors reduce the progression of kidney disease in patients with HFrEF. Both the DAPA-HF and EMPEROR-Reduced trials evaluated the effects of SGLT2 inhibitor treatment on the progression of kidney disease as secondary outcomes. In DAPA-HF, the risk of reaching the composite outcome of a sustained decline in eGFR of ≥50%, kidney failure or kidney death was lower with dapagliflozin than with placebo, although this difference was not statistically significant (HR 0.71; 95% CI 0.44–1.16)[87]. A subanalysis demonstrated that the rate of eGFR decline was attenuated with dapagliflozin compared with placebo (−1.09 ml/min/1.73 m^2 per year; 95% CI −1.40 to −0.77 versus −2.85 ml/min/1.73 m^2 per year; 95% CI −3.17 to −2.53; P < 0.001), regardless of diabetes status[94]. A pooled analysis of DAPA-HF and EMPEROR-Reduced validated the renoprotective effects of SGLT2 inhibitors in HFrEF and demonstrated a reduction in the risk of the composite renal end point of a sustained decline in eGFR of 50% or higher, kidney failure or renal death (HR 0.62; 95% CI 0.43–0.90; P = 0·013), without signs of heterogeneity[91].

In EMPEROR-Reduced, the prespecified composite renal outcome (of chronic dialysis or kidney transplantation or a profound, sustained reduction in eGFR) occurred in 30 patients (1.6%) in the empagliflozin group and in 58 patients (3.1%) in the placebo group (HR 0.50; 95% CI 0.32–0.77). The annual eGFR decline was also lower in the empagliflozin group compared with placebo (−0.55 ± 0.23 ml/min/1.73 m^2 per year

versus −2.28 ± 0.23 ml/min/1.73 m^2 per year, respectively; between-group difference 1.73 ml/min/1.73 m^2 per year; 95% CI 1.10–2.37; $P < 0.001$)[90]. Serious renal adverse events were reported less frequently in the active treatment groups in both trials. These observations complement the results of subgroup analyses of CREDENCE and DAPA-CKD, in which the benefits were consistent in participants with and without heart failure[24,96].

Patients with HFrEF are frequently treated with (loop) diuretics. An interesting subgroup analysis from DAPA-HF explored the efficacy and safety of dapagliflozin according to baseline diuretic use[97]. Compared with placebo, dapagliflozin reduced the risk of the primary composite end point in all participants, regardless of background diuretic use and across the range of diuretic dosages (P for interaction = 0.61). Other subgroup analyses of the DAPA-HF and EMPEROR-Reduce trials that have compared the efficacy and safety of dapagliflozin and empagliflozin in participants receiving MRAs or sacubitril/valsartan[98–102] have consistently demonstrated efficacy of SGLT2 inhibitors, regardless of concomitant MRA or neprilysin inhibitor use, supporting the combined use of SGLT2 inhibitors with these drugs.

SGLT2 inhibitors and heart failure with preserved ejection fraction

About half of all patients with heart failure have preserved ejection fraction (HFpEF). HFpEF is a distinctly different syndrome from HFrEF; whereas HFrEF is characterized by impaired left ventricular contraction, HFpEF is characterized by impaired left ventricular filling, resulting in insufficient stroke volume during exercise or other situations in which the heart rate is increased[103]. The pathophysiology of HFpEF is not completely understood, but systemic inflammation and endothelial dysfunction are thought to have important roles[104]. As with HFrEF, many patients with HFpEF have CKD, and CKD is an independent risk factor for all-cause mortality, cardiovascular death and hospitalization for heart failure in patients with HFpEF[104]. The pharmacological treatment of HFpEF is challenging. Medications that are used in the treatment of HFrEF (RAAS inhibitors and beta-blockers) have failed to demonstrate an effect on mortality in patients with HFpEF, limiting treatment options to loop diuretics for the symptomatic control of fluid overload.

The underlying rationale for the use of SGLT2 inhibitors in HFpEF includes their antihypertensive effects, their ability to lower body weight, and induce cardiometabolic improvements and renoprotection. Cardiovascular outcome trials in T2DM (that is, EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58 and VERTIS) likely included a proportion of patients with HFpEF; however, the type of heart failure was not consistently reported. The first trials to specifically report the effects of SGLT2 inhibitors in HFpEF were SOLOIST and SCORED[27,105]. In SCORED, sotagliflozin reduced the primary outcome of cardiovascular death, hospitalization for heart failure and urgent visits for heart failure in both participants with an ejection fraction of 40 to <50% and in those with an ejection fraction ≥50% (HR 0.50; 95% CI 0.32–0.77 and HR 0.72; 95% CI 0.52–0.99, respectively)[27]. In SOLOIST, the risk of reaching the same end point was also reduced, although this difference was not statistically significant (HR 0.74; CI 0.40–1.39 for participants with an ejection fraction of 40–49% and HR 0.66; 95% CI 0.38–1.15 for those with an ejection fraction ≥50%)[105]. Meta-analyses further strengthened the hypothesis that SGLT2 inhibitors may be beneficial in HFpEF[106,107]. The first trial to specifically evaluate the effects of SGLT2 inhibitors in HFpEF was the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved), in which empagliflozin reduced the primary combined end point of cardiovascular death and heart failure hospitalization in almost 5,988 patients with HFpEF. Over a median follow-up of 26 months, the primary outcome event occurred in 13.8% of patients in the empagliflozin group and in 17.1% in the placebo group (HR 0.79; 95% CI 0.69–0.90; $P < 0.001$)[92]. Further analyses demonstrated a strong reduction in heart failure hospitalization, whereas mortality was not significantly reduced. The effects of empagliflozin were consistent in patients with or without diabetes. The results of DELIVER — the second trial designed to test the effects of an SGLT2 inhibitor (in this case dapagliflozin) on mortality in patients with HFpEF are expected in early 2022 (REF.[108]).

Conclusions

A growing number of clinical trials have demonstrated SGLT2 inhibitors to be safe and effective drugs that improve kidney outcomes in patients with and without diabetes. Relative risk reductions are consistent across levels of kidney function and in patients with and without heart failure, with greatest absolute benefit in patients at highest risk of progressive kidney disease. In addition, SGLT2 inhibitors improve heart failure outcomes for patients with HFrEF or HFpEF, and thus form a much-needed addition to the therapeutic arsenal. SGLT2 inhibitors are now making their way into guidelines for the treatment of CKD and heart failure[109–111], and it is likely that the indications for SGLT2 inhibitor use will expand even further in the future. Interesting trials are underway that will evaluate the combined use of SGLT2 inhibitors with other medications such as endothelin receptor antagonists and MRAs to determine whether combined therapies can have synergistic beneficial effects. Furthermore, future trials may identify additional patient groups that may benefit from treatment with SGLT2 inhibitors. For example, limited data suggest that SGLT2 inhibitors could be of added value after transplantation and in dialysis patients with residual diuresis[112–114]. Future research will help to establish the definitive place for SGLT2 inhibitors in clinical practice; however, based on available evidence we call on clinicians to incorporate these exciting new treatment options for CKD and heart failure into daily practice.

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Author contributions
The authors contributed equally to all aspects of the article.

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