

## Review

# The role of sodium-glucose co-transporter (SGLT)-2 inhibitors in heart failure management and implications for the kidneys

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## Abstract

Sodium-glucose co-transporter (SGLT)-2 inhibitors were initially developed for management of type 2 diabetes but have been shown to offer improved outcomes in heart failure, a condition in which concomitant chronic kidney disease (CKD) is common. Randomised controlled trials initially demonstrated prognostic cardiovascular and renal benefits of SGLT2 inhibitors in high cardiovascular risk individuals with type 2 diabetes particularly in relation to heart failure. Improved outcomes have been replicated in cohorts with established heart failure and/or CKD and appear to extend in those without diabetes. Several specific agents have been considered, with evidence of a class effect, and dapagliflozin and empagliflozin are now incorporated into major international cardiovascular guidelines for management of heart failure with reduced ejection fraction. Beyond glucose lowering effects the mechanisms mediating SGLT2 inhibitors favourable actions are not fully elucidated. Haemodynamic alterations, natriuresis, osmotic diuresis, and weight loss likely contribute to improved outcomes, along with an enhanced cardiometabolic profile. The functional drop in estimated glomerular filtration rate (eGFR) which accompanies SGLT2 inhibitor initiation, before eGFR stabilisation, is likely central in the observed renal benefits. In this review we discuss in detail the evidence for SGLT2 inhibitors in heart failure, particularly with regard to kidney health.

**Keywords:** sodium-glucose co-transporter (SGLT)-2 inhibitors; heart failure; chronic kidney disease (CKD)

## 1. Introduction

Heart failure remains a condition with substantial unmet needs in management and associated burden for both patients and healthcare resources [1] and is more common among people with diabetes and/or chronic kidney disease (CKD) [2]. Heart failure and CKD frequently co-exist because the two share common risk factors and pathophysiological mechanisms which affect one another [3]. The introduction of sodium-glucose co-transporter (SGLT)-2 inhibitors in the management of type 2 diabetes was accompanied by the emergence of unexpected benefits beyond their glucose-lowering action. Their prognostic benefit in heart failure first emerged in EMPA-REG trial, a trial aimed to assess the effects of empagliflozin on cardiovascular health of high-risk individuals with type 2 diabetes [4]. Thereafter, a series of randomised clinical trials (RCTs) have demonstrated their efficacy across the spectrum of heart and renal disease, which appear to be also present in non-diabetic populations raising enthusiasm across the scientific community. In the present review, we will discuss the evidence regarding the SGLT2 inhibitors action in heart failure and the relevant implications on kidney health.

## 2. Randomised controlled trials

### 2.1 High cardiovascular risk and CKD studies (Table 1)

The EMPA-REG trial was the first study to suggest a beneficial effect of a SGLT2 inhibitor, empagliflozin on cardiovascular outcomes in individuals with type 2 diabetes. More specifically, EMPA-REG aimed to assess the cardiovascular effects of empagliflozin on patients with diabetes and at high risk for a cardiovascular event (total  $n = 7020$ ) compared to placebo [4]. Of the study population, 17.8% had an estimated glomerular filtration rate (eGFR), between 45–59 and 7.7% between 30 to 44 mL/min/1.73 m<sup>2</sup>. The study was designed to assess a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke, as the primary outcome with a key secondary outcome being a composite of the primary outcome plus hospitalisation for unstable angina. It was shown that the empagliflozin group had a significantly lower risk for the primary outcome, which was mainly driven by a reduction in the risk of cardiovascular death [hazard ratio (HR) 0.86, 95% confidence interval (CI), 0.74–0.99;  $p < 0.001$ ], with the risk of death from any cause also lower (HR 0.68, 95% CI 0.57–0.82;  $p < 0.001$ ). While the risk for hospitalisation for unstable angina did not appear to differ, it was noted that the empagliflozin treated patients were less likely to be hos-



pitalised for heart failure (HR 0.65, 95% CI 0.50–0.85;  $p = 0.002$ ). The publication of these findings was soon followed by those with regards to renal outcomes of the same trial population. Empagliflozin reduced the risk of incident or worsening nephropathy by 39% versus placebo with the findings being consistent independent of the presence of CKD at recruitment, while it was also associated with a lower relative risk for initiation of renal replacement therapy and doubling of serum creatinine [5]. These encouraging results were noted in a population that was already optimally managed in terms of their cardiovascular and CKD risk suggesting that empagliflozin was to offer additional benefits to traditional management. Furthermore, only approximately 10% of the EMPA-REG study population had pre-existing heart failure, which is indicative that empagliflozin treatment in this context reduced incident heart failure.

The Canagliflozin Cardiovascular Assessment Study (CANVAS), then, followed to suggest what the scientific community had already hoped for, that the EMPA-REG findings were not drug-specific but rather class-specific [6]. Among 10,142 high cardiovascular risk individuals with type 2 diabetes and a mean eGFR of 76.7 mL/min/1.73 m<sup>2</sup>, canagliflozin reduced the risk of the occurrence of the primary outcome (i.e., the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) versus placebo. The risk of hospitalisation for heart failure was also lower in the canagliflozin group, with a history of heart failure present in 14.4% of the population at recruitment. Similarly, to EMPA-REG, it appeared that canagliflozin benefits possibly extend to CKD with a reduction noted in the progression of albuminuria and the composite outcome of a sustained 40% reduction in the eGFR the need for renal-replacement therapy, or death from renal causes, though on the basis of the prespecified hypothesis testing sequence, these were not considered statistically significant. Renal effects of canagliflozin were more elaborately assessed in CREDENCE, that randomized 4401 individuals with type 2 diabetes and established CKD, defined by an eGFR between 30 to <90 mL/min/1.73 m<sup>2</sup> and albuminuria (albumin-to-creatinine ratio >300 to 5000 mg/g) to receive canagliflozin or placebo [7]. The positive results in the canagliflozin group led to the early discontinuation of the trial following a planned interim analysis which showed that the risk for the primary outcome (a composite of end-stage kidney disease, doubling of the serum creatinine level, or death from renal or cardiovascular causes) was lower by 30%. Looking at the renal-specific outcomes, the composite of end-stage kidney disease, doubling of the creatinine level, or death from renal causes was also lower, while once again the protective effect against hospitalisation for heart failure was present. Most importantly, the renoprotective effect of canagliflozin was evident on a background of optimal management with renin-aldosterone-angiotensin-system (RAAS) inhibitors, the only drugs until then proven

to change the natural history of CKD and confer a prognostic benefit in heart failure [8].

Despite failing to achieve significance in primary endpoints, the DECLARE-TIMI trial demonstrated that dapagliflozin also had a protective action against hospitalisation for heart failure in individuals (total  $n = 17,160$ ) with type 2 diabetes and high cardiovascular risk similarly to empagliflozin and canagliflozin in EMPA-REG and CANVAS, respectively [9]. This patient cohort had mean and nadir eGFR of 45.4 and 60 mL/min/1.73 m<sup>2</sup>, respectively, i.e., and overall better renal function at baseline as opposed to most other studies (minimum eGFR between 20–30 mL/min/1.73 m<sup>2</sup>). The risk for the renal composite outcome (a sustained decrease of 40% or more in eGFR to less than 60 mL/min/1.73 m<sup>2</sup>, new end-stage renal disease, or death from renal or cardiovascular causes) was also lower with dapagliflozin. Along the same lines, ertugliflozin in VERTIS-CV [10] was not associated with any protective effect from major adverse cardiovascular events (MACE), but there was a 30% lower hospitalisation risk for heart failure in the treatment group versus placebo.

The DAPA-CKD [11] that followed, though focusing on renal effects, suggested that dapagliflozin benefit extends to non-diabetic populations. It enrolled 4304 individuals with an eGFR between 25 and 75 mL/min/1.73 m<sup>2</sup> and albuminuria as defined by an albumin-to-creatinine ratio between 200 to 5000 mg/g. The observed treatment efficacy led to earlier termination of the trial with the primary outcome of a composite of sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes occurring in fewer people in the dapagliflozin group over a median follow-up period of 2.4 years. On reviewing the cardiac and renal effects separately, dapagliflozin was associated with a reduced HR for the renal composite of a sustained decline in the eGFR of at least 50%, end-stage kidney disease, or renal death at 0.56 (95% CI 0.45–0.68), and also a lower risk for the composite of death from cardiovascular causes or hospitalisation for heart failure. In a subgroup analysis according to heart failure status, dapagliflozin was equally effective in reducing the primary composite endpoint in both patients with known and without history of heart failure (HR 0.58, 95% CI 0.37–0.91 and HR 0.62, 95% CI 0.51–0.75, respectively;  $p$  interaction = 0.59). The effects on cardiovascular death/heart failure hospitalisation (HR 0.68, 95% CI 0.44–1.05 vs HR 0.70, 95% CI 0.51–0.97, respectively;  $p$  interaction = 0.90), and all-cause death (HR 0.56, 95% CI 0.34–0.93 vs HR 0.73, 95% CI 0.54–0.97, respectively;  $p$  interaction = 0.39), were also comparable between the two groups. Overall, dapagliflozin appeared to have consistent benefits in patients with CKD independent of their cardiac status [12]. The EMPA-KIDNEY study which is ongoing aims to clarify the effects of empagliflozin in a CKD population with an eGFR as low as 20 mL/min/1.73 m<sup>2</sup> and albuminuria with or without diabetes [13].

**Table 1. Heart failure and renal effects of SGLT2 inhibitors in randomised controlled trials.**

study	N	Inclusion eGFR (mL/min/1.73 m <sup>2</sup> )	mean eGFR (mL/ min/1.73 m <sup>2</sup> )	Diabetes (%)	HF (%)	Primary endpoint	Hazard Ratio (95% CI) for primary endpoint	Hazard Ratio (95% CI) for HF hospitalisation
EMPEROR-REDUCED pagliflozin 10 mg)	(em- 3730	>20	61.8	49.8	100	CV death or hospitalisation for worsening HF	0.75 (0.65–0.86)	0.69 (0.59–0.81)
DAPA-HF (dapagliflozin 10 mg)	4744	>30	66	41.8	100	CV death or worsening HF (hospitalisation or urgent visit for intravenous therapy)	0.74 (0.65–0.85)	0.70 (0.59–0.83)
SOLOIST-WHF (sotagliflozin 200– 400 mg)	1222	>30	Median 49.2	100%	100	CV death or total number of worsening HF events (hospitalisation or urgent visit)	0.67 (0.52–0.85)	0.64 (0.49–0.83)
EMPEROR-PRESERVED (empagliflozin 10 mg)	5988	>30	60.6	49	100	CV death or hospitalisation for HF	0.79 (0.69–0.90)	0.73 (0.61–0.88)
CREDENCE (canagliflozin 100 mg)	4401	30–90	56.3	100	14.8	Sustained doubling of creatinine, sustained eGFR <15, ESRD, or death from renal or CV causes	0.70 (0.59–0.82)	0.61 (0.47–0.80)
DAPA-CKD (dapagliflozin 10 mg)	4304	25–75	43.2	67.5	10.8	Sustained ≥50% decline in eGFR, sustained eGFR <15, ESRD, or death from renal or CV cause	0.61 (0.51–0.72)	0.71 (0.55–0.92)*
SCORED (sotagliflozin 200–400 mg)	10584	25–60	Median 44.4	100	30	CV death or total number of HF events (hospitalisation or urgent visit)	0.74 (0.63–0.88)	0.67 (0.55–0.82)
CANVAS (canagliflozin 100–300 mg)	10142	>30	76.7	100	14.4	CV death, non-fatal myocardial infarction, non-fatal stroke	0.86 (0.75–0.97)	0.67 (0.52–0.87)
DECLARE-TIMI		>60	85.4	100	10	CV death, myocardial infarction or ischaemic stroke CV death or hospitalisation for worsening HF	0.93 (0.84–1.03) And 0.83 (0.73–0.95)	0.73 (0.61–0.88)
VERTIS (ertugliflozin 5 or 15 mg)	8246	>30	76	100	24	CV death, non-fatal myocardial infarction or non-fatal stroke	0.97 (0.85–1.11)	0.70 (0.54–0.90)
EMPA-REG (empagliflozin 10 mg or 25 mg)	7020	>30	74	100	10.1	CV death, non-fatal myocardial infarction, non-fatal stroke	0.86 (0.74–0.99)	0.65 (0.50–0.85)

HF, heart failure; eGFR, estimated glomerular filtration rate; CV, cardiovascular; ESRD, end-stage renal disease. \*composite of CV death or HF hospitalization.

The SCORED study [14] aimed to assess whether sotagliflozin, a dual SGLT1 (in the gastrointestinal tract) and 2 inhibitor, would have any comparable effects in a population with diabetes, high cardiovascular risk and CKD (eGFR 25–60 mL/min/1.73 m<sup>2</sup>) and any level of albuminuria. As in some other studies, it appeared that the principal effect on reduction of the primary endpoint of cardiovascular death, hospitalisation and urgent visits for heart failure (HR 0.74, 95% CI 0.63–0.88;  $p < 0.001$ ), is driven by an effect on heart failure rather than death. The secondary renal endpoint of first occurrence of a sustained decrease of  $\geq 50\%$  in the eGFR from baseline for  $\geq 30$  days, long-term dialysis, renal transplantation, or sustained eGFR of  $< 15$  mL/min/1.73 m<sup>2</sup> for  $\geq 30$  days did not differ between treatment groups.

## 2.2 Heart failure studies (Table 1)

The observed benefits in the aforementioned trials reflected a preventative action of SGLT2 inhibitors from incident heart failure in individuals with type 2 diabetes and high cardiovascular risk. The answer as to whether they could claim a role in the management of established heart failure and whether their benefits may extend to non-diabetic individuals, derived from the studies that followed and focused on populations with known heart failure. The DAPA-HF trial [15] assessed 4744 patients with known heart failure [New York Heart Association (NYHA) class II–IV and an ejection fraction (EF) of 40% or lower], who were randomised to receive dapagliflozin (at a dose of 10 mg once daily) or placebo on top of standard therapy. Of note, only 41.8% of the trial population had known type 2 diabetes, and the cut-off eGFR 30 mL/min/1.73 m<sup>2</sup> with a mean eGFR at 66 mL/min/1.73 m<sup>2</sup>. After 18.2 months of follow up, patients on dapagliflozin demonstrated a lower risk for the primary outcome (i.e., a composite of worsening heart failure defined as hospitalisation or an urgent visit resulting in intravenous therapy for heart failure or cardiovascular death) with a HR of 0.74 (95% CI 0.65–0.85;  $p < 0.001$ ), and the risk for each component of the primary outcome examined individually, was significantly lower in the dapagliflozin group. Most importantly, it appeared that these findings did not differ between people with and without diabetes, suggesting, what had already been speculated, that the pleiotropic beneficial effects of SGLT2 inhibitors, are mediated by mechanisms other than their glucose-lowering actions. In this trial, the pre-specified renal outcome of sustained  $\geq 50\%$  decline in eGFR, sustained eGFR  $< 15$  mL/min/1.73 m<sup>2</sup>, end-stage renal disease, or renal death did not differ between the groups. Of note, when Jackson *et al.* [16] assessed the efficacy and tolerability of dapagliflozin according to the background diuretic dose, it appeared that treatment benefits were consistent across the range of furosemide doses.

The publication of EMPEROR-REDUCED trial [17] followed a few months later to demonstrate comparable ef-

fects of empagliflozin in addition to standard therapy in a population ( $n = 3730$ ) with heart failure NYHA class II–IV and EF of or below 40%, enriched with patients with markedly low EF; diabetes was present in 49.8%, while the nadir eGFR was 20 mL/min/1.73 m<sup>2</sup>, i.e., lower than that in DAPA-HF with a mean value of 61.4 mL/min/1.73 m<sup>2</sup>. Over a median follow up of 16 months, the primary outcome (a composite of cardiovascular death or hospitalisation for worsening heart failure) was less likely to occur within the empagliflozin group with a HR of 0.75 (95% CI 0.65–0.86;  $p < 0.001$ ) versus placebo, but this was principally driven by a reduction in hospitalisation for heart failure as there was no significant change in the risk of cardiovascular death per se; the empagliflozin effect did not differ according to the presence of diabetes or not. The trial also reported on patients' renal function suggesting that the annual rate of decline in eGFR was slower with empagliflozin than with placebo group ( $-0.55$  vs  $-2.28$  mL/min/1.73 m<sup>2</sup>/year,  $p < 0.001$ ) and there was a 50% lower risk for the composite renal outcome of chronic dialysis or renal transplantation or a profound, sustained reduction in the eGFR. The beneficial effects of empagliflozin treatment were significant and similar in both patients with known CKD at baseline and those without (renal impairment defined as eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>) [18].

A meta-analysis [19] of the two trials DAPA-HF and EMPEROR-REDUCED confirmed the lower hospitalisation risk with treatment with either agent and suggested that though relatively small, there is a significant reduction in cardiovascular death (pooled HR 0.86, 95% CI 0.76–0.98;  $p = 0.027$ ) and all-cause mortality (pooled HR 0.87, 95% CI 0.77–0.98;  $p = 0.018$ ) associated with SGLT2 inhibition in pooled data analysis, implying that the individual trials may have not been sufficiently powered to demonstrate a robust effect on death. Also, a combined renoprotective effect was demonstrated in this population with a reduction in the risk for the renal endpoint of chronic dialysis, renal transplantation, or a  $\geq 50\%$  sustained reduction of eGFR by 38% (HR 0.62, 95% CI 0.43–0.90;  $p = 0.013$ ). When the pooled treatment effect on the composite of first hospitalisation for heart failure or cardiovascular death was analysed in subgroups of patients divided by age, presence of diabetes, renal function, body mass index (BMI), use of angiotensin receptor-neprilysin inhibitor (ARNI), race, geographical region and NYHA class, it was shown that the effects were consistent across subgroups except for different NYHA categories, geographic region and race. More specifically, there was no risk reduction of the composite of heart failure hospitalisation or cardiovascular death in patients with advanced stages of heart failure.

With these trials focusing on heart failure with reduced EF, the question whether there are beneficial effects of SGLT2 inhibitor treatment in relation to heart failure with preserved EF was raised. Two trials, DELIVER and EMPEROR PRESERVED were designed to answer this ques-



tion. Though, DELIVER is still on going [20], the findings from EMPEROR PRESERVED have recently been published [21] making empagliflozin the first pharmacological agent ever reported to confer a prognostic benefit in heart failure with preserved EF. This study enrolled 5988 patients with NYHA class II–IV heart failure and an EF of more than 40%, assigned to receive empagliflozin or placebo on top of standard therapy. The empagliflozin group had a lower risk of the primary outcome of cardiovascular death or hospitalisation for heart failure with a HR of 0.79 (95% CI 0.69–0.90;  $p < 0.001$ ) compared to placebo, which, however, was principally driven by a reduction in the risk for hospitalisation for heart failure and was evident in both patients with diabetes and without. It is worth noting that on subgroup analysis, the risk reduction for the primary outcome retained statistical significance for the subgroups of EF <50% and EF ≥50% to <60% but was not significant for LVEF ≥60%; this might indicate that within the heart failure with preserved EF patient group, those with mid-range EF likely benefit most from empagliflozin treatment. The eGFR decline was slower in the empagliflozin group (−1.25 vs −2.62 mL/min/1.73 m<sup>2</sup>,  $p < 0.001$ ), however, there was no difference in the composite renal outcome between the two groups. The DELIVER trial findings are awaited to report whether dapagliflozin might also have a similar beneficial effect in a comparable patient population.

The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial [22] aimed to review the dual SGLT1 and 2 inhibitor effects on heart failure from a slightly different angle. In SOLOIST-WHF the investigators assessed the effects of sotagliflozin, in a patient population ( $n = 1222$ ) with diabetes and end-stage heart failure but not limited to reduced EF, but also recently discharged after a heart failure decompensation hospitalisation. It appeared that early initiation of sotagliflozin following a heart failure worsening event, led to significant reduction of risk for the primary outcome (composite of cardiovascular death and hospitalisation and urgent visits for heart failure versus) placebo over a 9-month follow-up period. However, this was principally driven by a reduction in the events of worsening heart failure.

In addition, a meta-analysis of 7 large RCTs (DAPA-HF, EMPEROR-Reduced, SOLOIST-WHF CANVAS, EMPA-REG OUTCOME, DECLARE-TIMI 58 and VERTIS-CV) [23] focused on patients with known heart failure ( $n = 16,820$ ) and reported that SGLT2 inhibition reduced the composite endpoint of first heart failure hospitalisation or cardiovascular death (HR 0.77, 95% CI 0.72–0.83,  $p < 0.001$ ;  $I^2 = 0\%$  with individual component risk also reduced (for first heart failure hospitalisation HR 0.71, 95% CI 0.64–0.78;  $p < 0.001$ ;  $I^2 = 0\%$  and for cardiovascular death HR 0.87, 95% CI 0.79–0.96;  $p = 0.005$ ;  $I^2 = 0\%$ ). These findings were consistent across heart failure and cardiovascular outcome trials and independent of the presence

of diabetes.

Further to the large outcome trials, the EMPERIAL (Effect of EMPagliflozin on ExeRcise ability and HF symptoms In patients with chronic heart faiLure) [24], EMBRACE-HF (Empagliflozin Evaluation by Measuring Impact on Hemodynamics in Patients With Heart Failure) [25] and EMPA-RESPONSE-AHF, were smaller studies which aimed to assess other aspects of empagliflozin action in heart failure.

The EMPERIAL trial [24] evaluated measures in relation to symptoms and patient-reported outcomes, rather than crude events of hospitalisation or death with empagliflozin treatment. The study included patients with heart failure with both reduced ( $n = 312$ ) and preserved ( $n = 315$ ) EF with or without diabetes, who were randomised to empagliflozin versus placebo. However, at 12 weeks of treatment there was no significant difference in the primary endpoint of 6-minute walk test distance (6MWT), or in the symptom-assessment questionnaires used [Kansas City Cardiomyopathy Questionnaire Total Symptom Score (KCCQ-TSS) and Chronic Heart Failure Questionnaire Self-Administered Standardized format (CHQ-SAS)] compared to placebo.

With an aim to review the effect of SGLT2 inhibition in the context of acute heart failure, the EMPA-RESPONSE-AHF recruited patients within 24 hours of an acute heart failure admission and randomised them to either empagliflozin ( $n = 40$ ) or placebo ( $n = 39$ ) for 30 days. Treatment with empagliflozin did not cause any significant difference from placebo in the primary endpoint of dyspnoea score, diuretic response (weight change per 40 mg furosemide), change in N-terminal pro brain natriuretic peptide (NT-proBNP), and length of hospital stay; nevertheless, it was associated with a reduced rate of the secondary combined endpoint of in-hospital worsening heart failure, re-admission or death at 60 days compared with placebo [4 (10%) vs 13 (33%);  $p = 0.014$ ]. This patient group also showed a significantly higher urinary output up until day 4 compared to placebo, but net fluid loss difference at day 4 did not reach statistical significance [26]. In contrast to what was expected based on SGLT2 inhibitors principal mechanism of action, the fractional urinary sodium excretion did not change and it appeared that the most relevant action in that context is osmotic diuresis via enhanced glucosuria, which also led to an increase in plasma osmolality [27].

The EMBRACE-HF trial [25] randomised 65 patients with heart failure independent of their EF and diabetes status to receive empagliflozin versus placebo for 12 weeks in order to assess the effects on pulmonary artery diastolic pressure (PADP) from baseline to end of treatment (average PADP weeks 8–12, which was the primary end point) on equivalent doses of loop diuretics between the two groups. Significant reductions in PADP were noted as early as at week 1 and became more prominent with time reaching a

1.7 mm Hg difference (95% CI 0.3–3.2;  $p = 0.02$ ) versus placebo at week 12. However, empagliflozin treatment did not result in any significant differences in KCCQ-TSS, NT-proBNP and 6MWD.

Overall, these smaller studies though demonstrating miscellaneous—mainly haemodynamic—effects, failed to demonstrate an improvement from a symptom perspective, not at least with the measures utilised.

As a result of the robust evidence from the large RCTs, US Food and Drug Administration (FDA) approved dapagliflozin for use in heart failure with reduced EF in May 2020 to reduce the risk of cardiovascular death and hospitalisation [28], for empagliflozin to follow in August 2021, with the two agents being included in an update on existing Guidelines for Heart Failure by the American Heart Association [29]. Around the same time, the European Society of Cardiology (ESC) published their new guidelines on heart failure which endorsed dapagliflozin and empagliflozin for the treatment of heart failure with reduced EF with a class I recommendation [30].

### 3. Real world data

Further to evidence from RCTs, real world data are consistent with a beneficial effect on heart failure. Data on patients with type 2 diabetes and heart failure enrolled in the Swedish heart failure Registry between 2016 and 2018 were assessed in relation to the initiation of SGLT2 inhibitors and potential cardiovascular effects [31]. The percentage of people initiated on the treatment increased over time from 5.5% to 12% (total  $n = 6805$ ) at the end of 2018. SGLT2 inhibitor treatment was associated with a reduced risk for cardiovascular death or first heart failure hospitalisation (HR 0.70, 95% CI 0.52–0.95), which was evident at median follow-up of 256 days and was independent of the EF, metformin use and renal function. SGLT2 inhibitor use was also associated with a lower risk of all-cause and cardiovascular death, heart failure or cardiovascular hospitalisation, and cardiovascular death or myocardial infarction or stroke.

The OBSERVE-4D study [32] compared the effects of canagliflozin ( $n = 142,800$ ) versus other SGLT2 inhibitors ( $n = 110,897$ ) and other antihyperglycaemic agents ( $n = 460,885$ ) using data from four US administrative databases. Canagliflozin was associated with a marked reduction in hospitalisation for heart failure when compared with other non-SGLT2 inhibitors (meta-analytic HR 0.39, 95% CI 0.26–0.60), while the effect of canagliflozin was similar with that of other SGLT2 inhibitors. Moreover, data from an Italian real-world study [33], suggested SGLT2 inhibitors were superior to dipeptidyl peptidase-4 (DPP4) inhibitors in all cardiovascular outcomes examined. More specifically, SGLT2 inhibitors were associated with reduced risk of 3-point major cardiovascular events (myocardial infarction, stroke, or all-cause death; HR 0.74, 95% CI 0.58–0.94), heart failure (HR 0.44, 95% CI 0.25–0.95)

or other cardiovascular admission (HR 0.72, 95% CI 0.60–0.87), myocardial infarction (HR 0.75, 95% CI 0.56–1.00), and all-cause death (HR 0.49, 95% CI 0.25–0.95).

A propensity score matched analysis from CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) ( $n = 153,078$  in each cohort) showed that SGLT2 inhibitor use was associated with a lower risk of heart failure and the composite of heart failure or death compared to other glucose lowering agents in both patients with and without baseline cardiovascular disease [10,34]. A lower risk of heart failure hospitalisation, as well as all-cause mortality and major cardiovascular events was also noted in association with SGLT2 inhibitor treatment as compared to other antidiabetic medications in EASEL (Evidence for Cardiovascular Outcomes With Sodium Glucose Cotransporter 2 Inhibitors in the Real World) population-based cohort study ( $n = 25,258$ ) [35]. Consistently, canagliflozin initiation was associated with reduced heart failure hospitalisation and death rates versus other non-SGLT2 inhibitor agents in a US based cohort [36].

Nevertheless, in a Danish nationwide registry-based cohort study there was no difference in the heart failure hospitalisation risk between new users of SGLT2 inhibitors and GLP1 receptor antagonists [37].

### 4. Biomarkers

NT-proBNP is the most widely used biomarker in patients with heart failure, the prognostic value of which is more definitive in heart failure with significantly reduced EF, but overall appears to have a role in guiding the management [38]. Troponin, which is also used in clinical practice, was not reported in any of the RCTs.

Findings so far have been conflicting with regards to a “biochemical” response in heart failure to SGLT2 inhibition. All three large RCTs on heart failure (DAPA-HF, EMPEROR-REDUCED and EMPEROR-PRESERVED) have demonstrated significant reductions in NT-proBNP with SGLT2 inhibition treatment, while several smaller ones have not showed similar findings. The CANDLE study aimed to assess the NT-proBNP response to treatment with canagliflozin versus glimepiride, in patients with type 2 diabetes and stable chronic heart failure. However, it had to be discontinued, since canagliflozin failed to reach the non-inferiority endpoint (i.e., failed to achieve a significant and at least equal to glimepiride reduction in NT-proBNP levels at 24 weeks) [39,40]. On a similar note, the (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction) DEFINE-HF study [41] which compared dapagliflozin to placebo in 263 patients, dapagliflozin did not seem to be associated with a more pronounced reduction in NT-proBNP levels than placebo; however, it did result in a higher proportion of patients within the group to report an improvement in symptoms (as assessed by KCCQ-TSS)

and achieve a meaningful reduction in NT-proBNP levels. These findings were consistent independently of the presence of diabetes. Empagliflozin in EMPBRACE-HF did not lead to a significant reduction in NT-proBNP levels either, compared to placebo [25]. Overall the effect of SGLT2 inhibition is less definitively described. However, the clinical significance of the changes or absence of them, appears less relevant in the context of improved clinical outcomes; it does though provide a hint, that the mechanisms involved are likely complex.

## 5. Mechanisms

A series of mechanisms have been proposed, through which SGLT2 inhibitors might exert their favorable actions on the heart and the kidneys and cannot but be perceived as a continuum. The cardiovascular system and the kidneys are physiologically interrelated through haemodynamic, hormonal and molecular mechanisms. The pathophysiological façade of this interconnection is the cardiorenal syndrome. The effects of SGLT2 inhibitors on more than one point of this intersection should be considered. Their glucose-lowering action can only minimally account for, especially given that the beneficial effects of treatment appear evident in impaired renal function that the glucose treatment effect is limited, and even in the absence of diabetes. Moreover, the cardiovascular benefit appears to emerge early on during treatment at approximately 12 weeks [42], suggesting that more acute effects than merely the amelioration of the cardiometabolic profile, must be principally involved, with haemodynamic alterations possibly playing a key role.

Inherent to their mode of action, natriuresis and osmotic diuresis have no wonder been believed to at least partly mediate SGLT2 inhibitors beneficial effects in heart failure. A small but consistent reduction in blood pressure appears to occur early after initiation of treatment and not to be related to baseline blood pressure levels or any changes in heart rate or body weight [43,44]. In the longer term, weight loss is likely to contribute [45]. Nevertheless, evidence especially with regards to absolute sodium excretion has been inconsistent. Empagliflozin was shown to increase natriuresis and reduce plasma volume in a small study of 20 patients with type 2 diabetes and stable heart failure [46], though in the RECEDE-CHF trial (SGLT2 Inhibition in Combination With Diuretics in Heart Failure), it did not result in similar effects [47]. The DAPASALT study [48] was an open-label, non-randomised study which assessed the volume effects of dapagliflozin treatment in patients with type 2 diabetes and normal renal function on a controlled salt intake. A significant reduction was noted in blood pressure and extracellular fluid levels, without however, any significant change in plasma volume or fractional sodium excretion. Of note, this population did not have known heart failure. As mentioned earlier, the EMPA-RESPONSE-AHF pointed more towards the osmotic diuresis effect in acute heart failure, while the EMBRACE HF showed an improve-

ment in filling pressures but not in NT-proBNP. Though interpretation is difficult, there is suggestion that the mechanistic effects of SGLT2 inhibitors might be more complex than initially presumed, and sodium intake might play a role [49]. Direct intracellular sodium regulating effects in cardiomyocytes have also been proposed as potential mediating factors of cardioprotection [50].

So far, there is not an abundance of data to shed light on the mechanisms involved specifically in heart failure associated SGLT2 inhibitors benefits. Other actions of SGLT2 inhibitors such as weight loss, reduction of visceral adiposity, amelioration of lipid profile and effects on endothelial function and arterial stiffness are parameters that contribute to an enhanced cardiometabolic profile [51], though they might be less relevant in the context of advanced heart failure. A role for increased ketone body production [52,53] and ameliorated oxidative stress and inflammation has also been suggested to contribute to reduced cardiovascular risk. The SGLT2 inhibitors renoprotective effect per se is key for the benefits observed in relation to both prevention of incident heart failure and hospitalisation. This is also likely mediated by several mechanisms rather than a single one such as some of those mentioned above (lower blood pressure, natriuresis, body weight reduction) [54], though the increased tubuloglomerular feedback and resultant reduced intraglomerular hypertension and hyperfiltration, and, therefore, albuminuria are core [55].

Overall, there seems to be a protective effect from both incident heart failure and decompensation of established heart failure. To what extent each of the above mechanisms contributes to the variable benefits of SGLT2 inhibition might well vary according to patient characteristics, i.e., cardiac and renal function, diabetes status, fluid status and total sodium content. It is likely that there are longer-, medium- and shorter-term effects, as a significant change in PADP was noted as early as week 1 [25] of empagliflozin treatment, and improved clinical outcomes are noted within weeks after treatment initiation [22,42].

## 6. Early effects on renal function

With the introduction of SGLT2 inhibitors in clinical practice as hypoglycaemic drugs, concerns were raised regarding the likelihood that their use may be associated with an increased risk of acute kidney injury (AKI) and volume depletion. This was largely driven by specific features of their mechanism of action, including the fact that initiation of SGLT2 inhibitors is accompanied by an initial reduction in eGFR, which is, then, followed by stabilisation of eGFR slope and improved renal outcomes. Alongside induced osmotic diuresis and natriuresis, these are rather mechanistic features of their action than side-effects. On those early days, this initial eGFR drop led to some post-marketing reports of “AKI events” following their initiation. Of note, more than half of these reported “AKI events”, occurred within the first 4 weeks of initiation, which is indicative of their known early effect.

As a result, the FDA advised caution to health care professionals with regards to their use, especially in the context of other factors that increase AKI risk such as CKD, heart failure and certain pharmacological agents such as RAAS inhibitors and diuretics. However, none of the RCTs which have included populations traditionally considered at “high AKI risk”, have demonstrated any relevant risk associated with their use. The heart failure trials, DAPA-HF and EMPEROR-REDUCED [15,17] showed that the AKI rate was similar between the treatment and placebo groups in populations with varying stages of heart failure severity and established renal impairment at baseline (eGFR <60 mL/min/1.73 m<sup>2</sup>) present in a substantial proportion (>40%). Interestingly, in EMPA-REG [5], there were significantly fewer AKI events with empagliflozin compared to placebo, while the AKI rate was similar for either eGFR categories (eGFR <60 mL/min/1.73 m<sup>2</sup> and eGFR >60 mL/min/1.73 m<sup>2</sup>). CREDENCE and DAPA-CKD [7,11] which included CKD populations to explore renal outcomes with SGLT2 inhibition, demonstrated comparable AKI event rates between canagliflozin or dapagliflozin, respectively, and placebo. Some of the cardiovascular outcomes trials [6,9,10] have also showed similar or even lower AKI risk associated with SGLT2 inhibitor treatment, while a meta-analysis of the four major cardio-vascular outcome trials (CANVAS, CREDENCE, EMPA-REG OUTCOME and DECLARE-TIMI 58) [56,57], demonstrated a 25% lower AKI risk associated with SGLT2 inhibitor treatment suggesting a protective effect. In line with the above, real-world data from large observational cohorts have not indicated a higher risk for AKI, associated with SGLT2 inhibitor treatment when compared with other glucose lower drugs, mainly glucagon-like peptide 1 (GLP1) receptor agonists or DPP4 inhibitors [6,58–60] with a meta-analysis [61] of 112 trials (n = 96,722) and 5 observational cohorts (n = 83,934) suggesting a protective effect of SGLT2 inhibitors against AKI. The initial eGFR drop that accompanies initiation of SGLT2 inhibitors [5,7,11,62–64] is followed by stabilisation of the eGFR slope within weeks and is fully reversible upon discontinuation of treatment.

## 7. Adverse events

Overall, trial data have shown that SGLT2 inhibitors are safe and well tolerated drugs. Mycotic genital infections can be associated with their use, while an increased risk for urinary tract infections has been shown in VERTIS CV [10] and EMPEROR-PRESERVED [21] trials but not in any other. Though an increased risk for Fournier’s gangrene has not been demonstrated in any trial data, due to the severity of the condition formal drug authorities have issued warning and advised vigilance [65,66].

Regarding volume related adverse events, findings have varied across trials with some suggesting a higher hypovolaemia risk [11,14,56] while others not [4,5,7,9] and without a demonstrable link with a specific agent or con-

dition. The large heart failure trials showed that hypovolaemia rate was similar between the treatment and the placebo groups despite most patients also on simultaneous diuretic treatment [15,17]. A subgroup analysis of DAPA-HF, volume related adverse events were more common with dapagliflozin, than placebo, in patients on higher diuretic doses [16]. Furthermore, a higher risk for diabetic ketoacidosis has been noted in some trials which included patients with type 2 diabetes only [7,9,10,22] but not in others [4,5] and has not been noted in any non-diabetic populations. Certain factors appear to exacerbate this risk such as ketogenic diet, pregnancy, alcohol consumption etc., hence caution may be advisable in certain populations and circumstances. Therefore, US Food and Drug Administration (FDA), European Medicines Agency (EMA) and UK Medicines & Healthcare products Regulatory Agency (MHRA) have issued relevant warnings and guidance that recommend temporary discontinuation of the drug during acute illness or scheduled surgery [67,68].

Other unexpected adverse events of significance are a possible toe amputation and fracture risk, both having emerged in CANVAS in association with canagliflozin [56]. More specifically, an increased fracture rate was noted with canagliflozin versus placebo in CANVAS but not CANVAS-R arm of the CANVAS Program [6] or CREDENCE [7]. Other large RCTs have not confirmed such risk linked with the use of other SGLT2 inhibitors either, including in heart failure populations. The increased amputation signal which emerged in association with canagliflozin in an interim safety analysis of CANVAS raised concerns, and caution has been advised in high risk populations [69,70] even though these findings were not reproduced in other canagliflozin or other SGLT2 inhibitors RCTs.

## 8. Conclusions

The abundance of high-quality evidence demonstrating a prognostic benefit from SGLT2 inhibitor treatment in heart failure, has led to the incorporation of two class representatives, dapagliflozin and empagliflozin, in the pharmacological management of heart failure with reduced EF as dictated by the guidelines published by major international cardiovascular organizations. Though reductions in cardiovascular mortality have been recorded, the most consistent effect in all RCTs appears to be in relation to preventing hospitalisation for heart failure. Treatment benefits affect both patients with diabetes and those without, are independent of the level of glycaemia [71] and present at all levels of kidney function tested (minimum eGFR in RCTs 30 mL/min/1.73 m<sup>2</sup>). Moreover, so far evidence suggests that at least for empagliflozin, positive effects extend to patients with heart failure with preserved EF as well. Overall, there is likelihood that especially survival benefits are more relevant in patients with less advanced heart failure [19]. Alongside direct cardioprotection, there appears to be a robust renoprotective effect for both individuals at high



risk and those with established renal impairment. Limited studies conducted examining other aspects of heart failure, such as symptom scoring systems.

It is the first time in years following RAAS inhibitors that pharmacological agents appear to confer prognostic benefit in heart failure and renal disease. In all large RCTs, SGLT2 inhibitors have been given on top of standard therapy with 80 to 99.9% of each study cohort already on RAAS inhibitors. Moreover, the two drug categories have very distinct mechanisms of actions and likely complementary in their overall cardiac and renal benefits; therefore, it is reasonable that SGLT2 inhibition is recommended as an add-on to RAAS and that the two treatments are not considered interchangeable. Heart failure is associated with progressive renal impairment with eGFR decline of 2–3 mL/min/1.73 m<sup>2</sup>/year versus 1 mL/min/1.73 m<sup>2</sup>/year in people with normal renal function [72] and a 2-fold increase in risk to develop CKD in patients with normal renal function [73], while CKD affects as many as 39–60% of patients with chronic heart failure [74]. Therefore, the cardio- and reno-protective effects of SGLT2 inhibitors are likely interconnected and affect more than one aspect of the cardiorenal continuum. The main mechanisms involved are most likely those inherent to the drugs' primary mechanism of action; however what other parameters might influence their effects (e.g., sodium intake) or whether they differ according to specific patient characteristics, requires further clarification, so that targeted treatment can be applied.

### Author contributions

EL, EA—conceived of the presented topic, wrote the manuscript, edited and reviewed the final version of the manuscript. JRJ, ET—wrote part of the manuscript. All the authors read and approved the final manuscript.

### Ethics approval and consent to participate

Not applicable.

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### Conflict of interest

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