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**SGLT2 inhibitors in heart failure with reduced ejection fraction:
a paradigm shift towards dual cardio-renal protection**

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Synopsis: Sodium-glucose transport inhibitors (SGLT2i) have been found to be effective in preventing heart failure in patients with diabetes or chronic kidney disease with or without cardiovascular disease. Recent evidence suggests that SGLT2i substantially, improve cardiovascular and renal outcomes in patients with heart failure with reduced ejection fraction (HFrEF). In this review, we discuss the combined cardio-renal benefits of SGLT2i in patients with HFrEF. In addition, we discuss the impact of reno-protection in the mid-term management of HFrEF and possible implementation strategies for initiating SGLT2i in routine care of HFrEF. **(88 words)**

Key words: SGLT2i; HFrEF; cardiovascular outcomes; renal outcomes

Key points:

- SGLT2i substantially improve cardiovascular and renal outcomes in HFrEF.
- Mid-term reno-protective effects of SGLT2i may facilitate the continuation of recommended doses of ACE inhibitors or neprilysin inhibitor and mineralocorticoid antagonists.
- Current evidence suggests a likely benefit in initiating all HFrEF drugs concomitantly (or within a very short timeframe) at low dose and subsequently up-titrate.

Background

Heart failure (HF) remains one of the leading causes of morbidity and mortality worldwide. Despite considerable advances in therapy, prognosis remains poor in heart failure with reduced ejection fraction (HFrEF). Current guidelines recommend foundational therapy consisting of angiotensin converting enzyme inhibitors (ACEi) / angiotensin-neprilysin inhibitor (ARNi), mineralocorticoid antagonists (MRAs) and β -blockers to prevent adverse outcomes. Recently, sodium-glucose transport inhibitors (SGLT2i) have been approved for treatment and prevention of HFrEF in conjunction with foundational therapy^{1,2}.

Cardiovascular, metabolic and renal diseases are interlinked with one another due to the commonality of risk factors. HF and chronic kidney disease (CKD) can moreover be regarded as a cardio-renal continuum given that they share several common risk factors and disease pathways that interact with each other³, such that the presence of one worsens the prognosis of the other and vice versa.

Originally developed for the treatment of type 2 diabetes, SGLT2i lower the risk of both cardiovascular and renal outcomes in patients with HFrEF, CKD and/or at high risk of HF⁴⁻⁸. In the present article, we review the cardiovascular and renal benefits of SGLT2i in HFrEF, as well as their preventive potential against progression to HF.

I/ Evidence of the benefits of SGLT2i on cardiovascular outcomes in patients with HFrEF

Cardiovascular outcome trials performed in type 2 diabetes indicated that SGLT2i prevent adverse cardiovascular outcomes in patients with diabetes and high cardiovascular risk⁷⁻⁹. These findings generated the hypothesis that SGLT2i may have similar beneficial effects in HFrEF irrespective of diabetes status.

SGLT2i in chronic stable HFrEF

Two large pivotal clinical trials, DAPA-HF and EMPEROR-Reduced, provided convincing evidence that SGLT2i reduce adverse cardiovascular outcomes in HFrEF^{4,5}. Based on these results, SGLT2i were approved as initial treatment in HFrEF, in combination with foundational therapy.

Both DAPA-HF and EMPEROR-Reduced trials included patients with chronic stable HFrEF irrespective of diabetes status – and eventually included approximately 50% of patients with diabetes (Table 1). DAPA-HF was conducted in relatively low risk patients whereas the EMPEROR-Reduced trial used risk enrichment strategies by enrolling patients with markedly reduced left ventricular ejection fraction (LVEF) or patients with reduced LVEF (30-40%) with increased levels of NT-pro-BNP (depending on the range of LVEF and heart rhythm). Given these differences in inclusion criteria, these two trials investigated the effects of SGLT2i over a wide range of disease states and risk factors. Patients were approximately 65 years old and one fifth of the trial population in both trials were women. In EMPEROR-Reduced, mean LVEF (27%) and eGFR (62 ml/min/1.73m²) were numerically lower compared to DAPA-HF (mean LVEF 31% and eGFR 66 ml/min/1.73m²). The primary composite outcome was similar in both trials and consisted of cardiovascular mortality and hospitalisation for HF. In DAPA-HF, the primary composite outcome also included an urgent visit resulting in intravenous therapy for HF as a component of primary outcome, which has been shown to be strongly associated with subsequent outcome⁴. This latter component of the composite outcome is likely to become standard with the emergence of ambulatory approaches for managing worsening HF.

In both trials, the primary outcome was significantly reduced and the magnitude of effect was in fact nearly identical (DAPA-HF: 0.74 [0.65-0.85], EMPEROR-Reduced: 0.75 [0.65-0.86]) (Figure: Graphical Abstract). In DAPA-HF, all components of the primary composite outcome were significantly reduced. However, in EMPEROR-Reduced, the reduction in primary outcome was driven by a reduction in hospitalisation for HF. This difference was perhaps due to differences in participants' baseline characteristics or trial duration¹⁰. Statistical power issues may also be at play since EMPEROR-Reduced had a smaller sample size (n= 3730 vs. 4744) and a shorter follow-up (16 vs. 18.2 months) compared to DAPA-HF. A meta-analysis of the two trials using pooled study-level data (DAPA-HF) and patient-level

data (EMPEROR-Reduced) showed that SGLT2i reduced all-cause mortality by 13% in patients with different clinical profiles, without significant evidence of heterogeneity across the trials¹¹.

SGLT2i in acute HF

A pilot randomised controlled trial (EMPA-RESPONSE-AHF) explored the effects of empagliflozin on symptoms, diuretic response and change in NT-pro-BNP level from baseline to day 4 and on the combined endpoint of in-hospital worsening of HF, all-cause mortality and/or HF readmission at day 60 in patients with acute HF (n=80)¹². Empagliflozin increased urinary output during the initial 4 days of treatment and significantly reduced the combined endpoints compared to placebo over 60 days.

In the SOLOIST-WHF trial, the effects of SGLT2i were studied irrespective of LVEF (although median LVEF was eventually 35%) in worsening HF¹³. Sotagliflozin was associated with a lower total number of deaths from cardiovascular causes, hospitalisations and urgent visits for HF compared to placebo (HR: 0.67 [0.52 -0.85]). Over a median follow-up of 9 months, sotagliflozin reduced cardiovascular death and first hospitalisation for worsening HF by 29% (HR: 0.71 [0.56-0.89]). The hazard ratios in SOLOIST-WHF were almost identical to the results of clinical trials in chronic stable HFrEF.

In the EMPULSE trial, the effect of early initiation of SGLT2i in acute HF was assessed using a Win-ratio approach. Four events were hierarchically considered: death, number of HF events (e.g. hospitalisations for HF, urgent HF visits, and unplanned outpatient visits), time to first HF event, and change from baseline in Kansas City Cardiomyopathy Questionnaire - Total Symptom Score (KCCQ-TSS)¹⁴. Empagliflozin was associated with a significant improvement in the above conditions (Win Ratio 1.36 [1.09-1.68], p=0.0054). Of note, empagliflozin was associated with fewer deaths compared to placebo (4.2% vs. 8.3%)¹⁴. Taken together, the results of the three aforementioned trials suggest that an early initiation of SGLT2i in hospitalised patients with acute HF can sizeably reduce subsequent hospitalisation and mortality.

SGLT2i in HFrEF according to comorbidities (details in Table 1)

The numerous, post-hoc and sub-group analyses of the DAPA-HF and EMPEROR-Reduced trials reported that SGLT2i were associated with similar risk reductions in patients with HFrEF irrespective of older age, aetiology and duration of HF, or the presence of chronic obstructive pulmonary disease, diabetes and impaired renal function¹⁵⁻²². Overall, no sizeable differences in treatment response have been identified.

SGLT2i in HFrEF according to background medication

SGLT2i are well-tolerated in the presence of background therapy (diuretics, ACEi/ARNi, β -blockers and MRAs) and reduce the risk of adverse cardiovascular outcome irrespective of background therapy²³⁻²⁶.

Co-administration of ARNi with SGLT2i may have additional benefits over treatment with ARNi due to their differing mechanisms in HFrEF^{23,27}. Aside from this pharmacological reasoning, the pooled subgroup analysis of the DAPA-HF and EMPEROR-Reduced trials showed that SGLT2i are equally effective in reducing hospitalisation for HF and cardiovascular mortality irrespective of background ARNi treatment¹¹. Similarly, SGLT2i were equally effective in MRA users and non-users (HR: 0.75 [0.63-0.88] and 0.76 [0.59-0.97], respectively) in EMPEROR-Reduced²⁵.

SGLT2i may furthermore facilitate the use of other HF drugs. A secondary analysis of EMPEROR-Reduced showed that SGLT2i were associated with lower rates of discontinuation of MRAs [0.78 (0.64–0.96)] in MRA users during follow-up²⁵. In this analysis, empagliflozin was also associated with a lower risk of severe hyperkalaemia (>6 mmol/l) (HR: 0.70 [0.47-1.04]). Overall, the lower risk of hyperkalaemia and fewer MRA discontinuations in patients treated with empagliflozin underscore that SGLT2i may favour MRA use.

II / Evidence of SGLT2i benefit on renal outcomes in patients with HFrEF

Much of the evidence on the efficacy of SGLT2i on renal outcomes in HFrEF is based on the subsequent analyses of the pre-specified secondary outcomes in the DAPA-HF and EMPEROR-Reduced trials. Approximately half of the patients enrolled in DAPA-HF and EMPEROR-Reduced had CKD (41%

and 48%, respectively). Of note, renal outcomes were defined slightly differently in the 2 trials. In DAPA-HF, the composite renal outcome was defined as $\geq 50\%$ sustained decline in eGFR, end-stage kidney disease and renal death. In EMPEROR-Reduced, the composite renal outcome was rather defined as time to first occurrence of chronic dialysis, kidney transplant, sustained reduction of $\geq 40\%$ eGFR, or sustained eGFR < 15 ml/min/1.73 m² if eGFR was > 30 ml/min/1.73 m² or < 10 ml/min/1.73 m² for patients with baseline eGFR ≤ 30 ml/min/1.73 m².

The secondary analyses of both trials assessed the benefits of dapagliflozin and empagliflozin depending on baseline renal function and whether dapagliflozin and empagliflozin had an effect on renal function^{18,28}. In DAPA-HF, dapagliflozin was not associated with a significant reduction in composite renal outcome (HR=0.71 [0.44–1.16], P=0.17)^{4,28} whereas empagliflozin significantly reduced composite renal outcome (HR=0.50 [0.32–0.77])⁵. The favourable effects of empagliflozin remained similar even when the definition of CKD in DAPA-HF was applied in EMPEROR-Reduced¹¹. The lack of significant association of dapagliflozin with renal outcomes in DAPA-HF is likely due to lower statistical power since patients included in DAPA-HF were at a relatively lower risk of outcome at baseline. It should be emphasised that the association of SGLT2i with renal outcomes, even if not significant, appeared sizeable in DAPA-HF (HR=0.71, i.e. 29% reduction in renal outcomes) and that the association of dapagliflozin with eGFR slope, a more insightful outcome in a relatively low risk population, was significant (see below). In fact, when the treatment effects of the two trials were assessed in the meta-analysis, SGLT2i were associated with a significant reduction in primary renal outcome (using the DAPA-HF definition) (HR: 0.62 [0.43-0.90]) with no significant heterogeneity¹¹.

It should also be emphasised, that both dapagliflozin and empagliflozin reduced the slope of eGFR decline in a very homogenous manner in patients with HFrEF. Dapagliflozin significantly reduced the rate of decline in eGFR between day 14 and 720: -1.09 (-1.40 to -0.77) vs. placebo -2.85 (-3.17 to -2.53) mL/min/1.73m²/year²⁸. Similarly, empagliflozin was associated with a slower annual rate of eGFR decline compared to the placebo group (-0.55 vs. -2.28 ml/min/1.73 m²/year, HR: 1.73 (1.10-2.37); P<0.001) even though EMPEROR-Reduced enrolled patients with a lower eGFR at baseline⁵.

Of note, the EMPIRE-HF renal trial specifically assessed the short-term effect of empagliflozin on both congestion (using estimated plasma volume) and renal function in HFrEF. In this trial, empagliflozin was associated with a decline in measured GFR within 12 weeks of initiation along with a significant decline in estimated plasma volume and extracellular volume²⁹. The early decline in measured GFR was expected due to hemodynamic effects, partly through the decongesting effect of SGLT2i. A similar initial decline in eGFR was noted within weeks of SGLT2i initiation in DAPA-HF and EMPEROR-Reduced. This early drop was reversible after cessation of SGLT2i³⁰. This drop was followed by a sustained improvement in eGFR slope in the SGLT2i group (compared to placebo) throughout the study period in both EMPEROR-Reduced and DAPA-HF, likely related to non-hemodynamic effects.

Trials assessing renal outcomes in patients with CKD and diabetes also conclusively show that SGLT2i are nephro-protective^{6,31}: SGLT2i significantly reduced the risk of worsening renal function, end-stage kidney disease and renal death^{6,31}. Furthermore, a post-hoc analysis of DAPA-CKD in patients with baseline HF (n=436) found that dapagliflozin reduced the composite of cardio-renal outcome by 42% (HR: 0.58 [0.37-0.91])³².

The above overall data underscore that SGLT2i reduce adverse renal outcomes and have substantial beneficial effects on preserving mid-term renal function in HFrEF (Figure: Graphical Abstract).

Other clinically meaningful outcomes

Quality of Life: Short-term effects on quality of life were assessed in a moderately sized clinical trial (DEFINE-HF n= 263): a greater number of patients receiving dapagliflozin had a meaningful improvement (≥ 5 points) in the KCCQ - Overall Symptom Score (KCCQ-OSS) compared to patients receiving placebo (43% vs. 33%) after 12 weeks of therapy³³. Similarly, improvements in KCCQ-Total Symptom Score were reported in the EMPULSE trial (mean difference 4.45 [0.32-8.59], p=0.034). In the EMPERIAL-Reduced trial, there was no significant difference in KCCQ-TSS score between placebo and empagliflozin at the end of the 12 weeks. However, the median improvement in KCCQ-TSS was numerically higher by 3.13 (0.00-7.29) points in the empagliflozin group compared to placebo (change

from baseline: 7.29 [-2.60 - 18.75] and 3.65 [-6.25 - 13.54], respectively) in patients with HFrEF³⁴, which is within the same range of effect observed in the EMPULSE trial.

A mid-term benefit in quality of life has been reported in both DAPA-HF and EMPEROR-Reduced trials, with SGLT2i being associated with better odds of meaningful improvement in KCCQ score (all components) (≥ 5 -point-OSS OR: 1.13[1.07-1.21] and 1.20 [1.05-1.37]) and lower odds of deterioration (≥ 5 -point OSS OR 0.85 [0.80-0.91] and 0.75 [0.64-0.87], respectively)^{35,36}. In DAPA-HF, KCCQ-TSS score was 2.8 points higher in dapagliflozin vs. placebo after 8 months of follow-up³⁶. As point of reference, the improvement in KCCQ-OSS score was 1.1 after 8 months of treatment with sacubitril/valsartan³⁷. Although no direct comparison on improvement of quality of life between ARNi and SGLT2i has been performed, SGLT2i appear to provide a similar or greater overall improvement in quality of life.

Exercise tolerance: In two moderately-sized, randomised double-blind trials, SUGAR-DM-HF and EMPIRE-HF, there was no significant difference in distance walked or physical activity between the SGLT2i and placebo group^{38,39}. However, these neutral results could be due to relatively small sample size, relatively short-term outcome assessment, or presence of comorbid conditions on which HF treatment has no effect. Exploratory studies have shown that SGLT2i may have a beneficial impact on exercise tolerance and cardiac oxygen consumption during exercise^{40,41}. More evidence is needed to better understand the effect of SGLT2i on exercise tolerance.

Congestion: Adding SGLT2i to standard care significantly reduced congestion within a week in acutely decompensated HF⁴². SGLT2i reduced NT-pro-BNP levels in long-duration clinical trials (mean difference in pooled analysis: -194.0 [-249.9 to -138.0], I^2 :61%)⁴³. In DEFINE-HF, dapagliflozin was not associated with a significant decline in NT-pro-BNP levels (1133 pg/dL [1036–1238] vs. 1191 pg/dL [1089–1304], $P=0.43$) at 12 weeks; however, more patients receiving SGLT2 had a meaningful reduction ($\geq 20\%$) in NT-pro-BNP levels (OR: 1.9 [1.1-3.3])³³. Even if decongestion effects exist, this did not translate into a significant decrease in loop diuretic dose in patients randomised to SGLT2i in DAPA-HF

(mean furosemide-equivalent dose: 59.8 ± 109 vs. 65.6 ± 104 mg at 12 months)²⁴. However, fewer patients receiving SGLT2i needed intensification of diuretic dose in both DAPA-HF (10.2% vs. 14.2%, $p < 0.001$) and EMPEROR-Reduced trials (15.9% vs. 22.2%) compared to placebo^{24,44}.

Systolic function and ventricular remodelling: SGLT2i has been shown to improve some of the echocardiographic markers of left ventricular function³⁸. In patients with HFrEF with diabetes/prediabetes, empagliflozin was associated with a decrease in left ventricular end-systolic (mean difference: -6.0 (-10.8 to -1.2) mL/m²; $P=0.015$) and end-diastolic volume index (mean difference: -8.2 (-13.7 to -2.6) mL/m²; $P=0.004$) in comparison to placebo after 36 weeks of treatment³⁸. There was no significant change in LVEF (mean difference: 0.3 [-1.7 to 2.3])³⁸.

III/ Prevention of HF onset in high-risk patients

SGLT2i appear to have pleiotropic effects on cardiovascular, metabolic and renal systems⁴⁵. A meta-analysis by Bhatia et al. estimated the relative and absolute effects of SGLT2i in preventing HF events in a broad spectrum of patients with cardiovascular or renal disease or diabetes⁴⁶. Overall, SGLT2i reduced the risk of hospitalisation for HF by 31% (HR 0.69 [0.64–0.74]). The absolute benefit from SGLT2i, however, was dependent on baseline risk: the number needed to treat to prevent one hospitalisation for HF ranged from approximately 100 in CKD to 200-400 in high-risk diabetes. Given the high prevalence of diabetes and CKD, SGLT2i may have a large impact on the incidence of HF at the population level.

Diabetes: Trials performed in diabetes reported a significant and highly consistent reduction in hospitalisation for HF with SGLT2i (EMPA-REG-Outcome HR: 0.65 (0.50-0.85), DECLARE-TIMI HR: 0.73 (0.61-0.88), CANVAS HR: 0.67 (0.52- 0.87), VERTIS-CV HR: 0.70 (0.54-0.90))^{7-9,47} (Table 2). A meta-analysis in patients with diabetes with or without atherosclerotic cardiovascular disease showed that hospitalisation for HF was significantly reduced by SGLT2i but not by glucagon-like peptide-1 receptor agonists⁴⁸.

A considerable amount of data on the efficacy of SGLT2i has emerged from large observational studies and population registries. The CVD-REAL and CVD-REAL2 multi-national observational studies enrolled participants (n= 153,078/group and n= 235,064/group, respectively after propensity score matching) who were newly initiated on SGLT2i and other glucose lowering drugs^{49,50}. In CVD-REAL2, SGLT2i (vs. other glucose lowering treatment) were associated with a significantly lower risk of hospitalisation for HF (HR: 0.64 [0.50 to 0.82]). Similar findings were reported from CVD-REAL and the EASEL Population-Based Cohort Study^{50,51}.

CKD: In patients with CKD, SGLT2i are associated with a reduced risk of cardiovascular outcomes. In a large, multi-centre, randomised, double-blind trial (DAPA-CKD), dapagliflozin reduced the risk of cardiovascular death and hospitalisation for HF by 29% (HR: 0.71 [0.55 - 0.92]) over a follow-up of 2.4 years⁶. Moreover, SGLT2i were seemingly equally effective in preventing hospitalisations for HF and urgent visits for HF in patients with both diabetes and CKD (HR=0.67 [0.55–0.82]) in the SCORED trial in which only 20% of patients had a history of HF⁵².

Myocardial infarction: Patients with MI constitute a specific subgroup of interest in the setting of HF. Evidence regarding the efficacy of SGLT2i in patients with MI is relatively sparse. For the time being, SGLT2i have been evaluated in patients with acute MI in small-moderate sized trials to assess whether they improve cardiac nerve activity⁵³.

IV/ Safety profile of SGLT2i in HFrEF

SGLT2i appear to have an excellent safety profile in HFrEF. In most studies, the rate of adverse effects such as volume depletion, hypotension and serious renal events with SGLT2i was similar to placebo in patients with HFrEF. However, the rate of genital tract infection may be higher with SGLT2i⁵⁴. The risk of urinary tract infection appears to be higher in patients with diabetes in comparison to patients with HFrEF (i.e. without diabetes)^{4,7}. In patients with acute HF with diabetes, sotagliflozin (which has a combined SGLT2i and SGLT1i effect) was associated with an increased risk of diarrhoea and severe hypoglycaemia¹³.

SGLT2i have relatively neutral effects on blood pressure and lack association with hypotension⁵⁵: In patients with persistent low blood pressure, SGLT2i can consequently be continued⁵⁵. In fact, when adjusted for placebo use, SGLT2i were associated with a slight early increase in SBP in patients with blood pressure below 110 mmHg⁵⁵.

Initiation of SGLT2i has been associated with an “eGFR dip” in the first few weeks of therapy, particularly in patients with advanced renal disease^{56,57}. This initial dip in eGFR is expected and is similar to ACEi/ARBs⁵⁸. This does not indicate AKI nor warrants discontinuation of therapy unless the dip is substantial (i.e., >30% of eGFR and/or eGFR<25 ml/min). This initial change is reversible and, following this dip, SGLT2i have been found significantly associated with reduced cardiovascular and renal outcomes³⁰. Findings from large clinical trials actually suggest that SGLT2i have mid-term reno-protective effects in HF, which ultimately is what matters most from a clinical perspective.

Additionally, a systematic review of observational studies identified that SGLT2i exposure was not associated with increased risk of AKI, urinary tract infection or fractures, albeit a possible risk of diabetic ketoacidosis in diabetes⁵⁴.

V/ Potential impact of reno-protective properties of SGLT2i in HFrEF

Nearly half of all patients with HFrEF have CKD. As CKD progresses, volume overload/congestion becomes increasingly difficult to manage. The development of CKD is a known clinical variable associated with worse prognosis in HFrEF. In addition, worsening renal function and/or hyperkalaemia is a major hurdle in maintaining HFrEF treatments⁵⁸⁻⁶⁰. Nevertheless, decreasing the dose of HFrEF drugs (for example: due to progressively declining renal function) is associated with poorer outcome⁶¹. ACEi and SGLT2i both have nephro-protective properties. However, with progressive renal failure, ACEi/ARNi are often withheld, which further exacerbates heart failure (Figure1). In contrast, SGLT2i can be prescribed to patients with eGFR as low as 20 ml/min/1.73m². More importantly, SGLT2i slow the progression of CKD in HFrEF, thereby facilitating the maintenance of optimal doses of HF drugs³. The continued prescription of these drugs at optimal dose is highly likely to translate into long-term clinical benefits. As mentioned above, among patients receiving MRA at baseline, SGLT2i were

associated with a lower frequency of MRA discontinuation compared to placebo in the EMPEROR-Reduced trial²⁵. In turn, maintaining MRA will also further enhance the impact of SGLT2i since it has been estimated that a comprehensive treatment with all 4 drugs (ARNi + β -blocker + MRA + SGLT2i) reduces cardiovascular death or hospitalisation for HF by 62% in comparison to limited conventional therapy (ACEi/ARBs + β -blocker)⁶², the latter being more likely to be used in patients with impaired renal function. Yet, this long-term benefit cannot be derived from trials (since having a relatively short follow-up).

Figure 1 schematically illustrates the impact of SGLT2 reno-protective effects on drug prescription and subsequent prognosis in HFrEF.

VI/ Implementation of SGLT2i in HFrEF

The present guidelines recommend SGLT2i in all patients with HFrEF combined with the foundational therapy consisting of ACEi/ARNi, β -blocker and MRAs^{1,2}. However, the guidelines do not suggest any specific sequence of drug initiation and/or up-titration. In the ESC 2016 guidelines for heart failure, a sequential approach for HF drug optimisation was recommended⁶³, which could lead to a substantial delay in the initiation of life-saving therapies. Several HF experts propose a more fast-track approach which allows early initiation of SGLT2i to reduce the subsequent risk of CV death and/or hospitalisation and for better tolerability of MRAs and ACEi^{64,65}. From a pharmacological standpoint, different classes of HFrEF treatments are more likely to have additive benefits as opposed to maximising one particular drug class. In addition, evidence of benefits appeared very early and were significant within 30 days in the DAPA-HF trial (HR: 0.51[0.28- 0.94] at 28 days of treatment)^{4,66}. McMurray et al. and Greene et al. accordingly suggest that it may be more beneficial to initiate all drugs at low dose concomitantly (or within a short time-frame) rather than a “sequential” sequence (up-titrating one and then adding the next drug^{64,65}). In addition, given the excellent safety profile of SGLT2i, their initiation may actually be better tolerated than up-titration of another class (for example, in a patient with borderline BP and heart rate, it would be actually easier to add SGLT2i than increase beta-blockers).

VII/ Knowledge gaps

SGLT2i may have a class effect with no substantial difference in efficacy across drugs. However, a recent network meta-analysis indicates that empagliflozin, canagliflozin and dapagliflozin are equally effective in improving worsening HF whereas empagliflozin was superior to other SGLT2i in reducing all-cause and cardiovascular death⁶⁷. However, these results may emerge from differences in the trials per se rather than differences in actual SGLT2i effects. More direct comparison studies will be needed to determine whether a specific SGLT2 inhibitor should be used in a given patient to maximise its benefit.

Several mechanisms mediating SGLT2i activity have been suggested such as osmotic diuresis and natriuresis leading to decongestion, improved cardiac metabolism, improved myocardial efficiency, reduced sympathetic overdrive, and reduced oxidative stress and inflammation⁶⁸. However, key mechanisms underlying SGLT2i efficacy have yet to be clearly elucidated.

SGLT2i are effective in reducing adverse outcomes regardless of background therapy. However, the best implementation strategy for prescribing SGLT2i in HFrEF needs to be outlined. A fundamental question that remains is “should SGLT2 inhibitors be initiated at very early stages of HFrEF?”. Dedicated trials should test whether a fast-track implementation strategy of SGLT2i provides additional benefits to a conventional approach of initiating and up-titrating the foundational therapy of ACEi/ARBs, β -blocker and MRAs and subsequently adding SGLT2i^{64,65}. Current guidelines leave the decision, to physicians on how SGLT2 inhibitor should be initiated in *de novo* HF, especially in the setting of acute HF.

Additional data is moreover needed on whether SGLT2i are equally effective in preventing HF onset in post-MI patients. The ongoing DAPA-MI (NCT04564742) and EMPACT-MI (NCT04509674) trials should clarify the effect of SGLT2i in patients with acute MI.

Conclusion

SGLT2i have a homogeneous/pleiotropic benefit in cardiovascular medicine, including HFrEF. The cardio-renal protective effect of SGLT2i is a major evolution in the treatment of HFrEF. How to best implement this important therapeutic breakthrough is to be better determined. However, given the very

rapid impact of SGLT2i on outcome and their good safety profile, an early introduction of these drugs in most patients with HFrEF appears to be advisable.

Clinical care points

1. SGLT2i are safe and effective in HFrEF with or without diabetes and/or with or without CKD.
2. Given the rapid efficacy of SGLT2i, physicians should target an early initiation of these drugs to reduce the risk of adverse cardiovascular and renal outcome.
3. At SGLT2 inhibitors initiation, patients must be informed on the risk of urinary tract/genital infection and advised on perineal hygiene.
4. At SGLT2 inhibitors initiation in patients with diabetes, dose reduction of insulin and sulfonylureas should be considered to avoid the risk of hypoglycaemia.
5. Before initiating SGLT2 inhibitors in patients with impaired renal function/CKD, renal function and volume status must be assessed. If hypovolemia is present, then it must be corrected before initiating SGLT2i.
6. Renal function monitoring after SGLT2i initiation may be required in patients with CKD because of initial eGFR dip. Dose adjustments/temporary cessation of SGLT2i may be considered if eGFR dip is substantial ($\geq 30\%$ decline of eGFR).

Expansions of trial names presented in this paper:

Trial name	Expansion
CANVAS	Canagliflozin Cardiovascular Assessment Study
CREDESCENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CVD-REAL	Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors
DAPA-HF	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DECLARE-TIMI	Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction
DEFINE-HF	Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction
EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction
SCORED	Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk
SOLOIST-WHF	Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure
SUGAR-DM-HF	Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects in Patients With Diabetes Mellitus, or Prediabetes, and Heart Failure
VERTIS CV	Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial

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Table 1: Cardiovascular and renal outcomes in pivotal trials and subgroup analyses of SGLT2i in HFrEF[#].

Trial name	Patient population and subgroups in post- hoc trials	Objective	Primary endpoint	Results	Author	Year
DAPA-HF Duration: 18.2 months N= 4744	HFrEF with or without diabetes	To assess the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with HFrEF	The primary CV outcome: a composite of WHF (hospitalisation or an urgent visit resulting in IV therapy for HF) or CV death	HR: 0.74 (0.65 to 0.85)	McMurray	2019
			Renal composite outcome	HR: 0.71 (0.44–1.16)		
	Patients with ischemic and non-ischemic aetiology	Efficacy according to ischaemic and non-ischaemic aetiology	The primary CV outcome	Patients with ischaemia: HR 0.77, (0.65-0.92), Patients without ischaemia HR 0.71, (0.58-0.87), P-interaction = 0.55)	Butt	2021
	Duration since diagnosis of HF	Efficacy in relation to time from diagnosis of HF	The primary CV outcome	≥2 to ≤12 months: HR: 0.86 (0.63-1.18), >1 to 2 years: HR: 0.95 (0.64-1.42), >2 to 5 years: HR: 0.74 (0.57-0.96), >5 years: HR: 0.64 (0.53-0.78) P- interaction=0.26	Yeoh	2020
	Patients with and without COPD	Outcomes related to COPD	The primary CV outcome	Patients with COPD: HR 0.67 (0.48–0.93) Without COPD: HR 0.76 (0.65–0.87); P-interaction=0.47	Dewan	2021
	Age group of participants: <55, 55-64, 65-74, ≥ 75 years	The efficacy and safety of therapies in the elderly	The primary CV outcome	<55: HR: 0.87 (0.60-1.28), 55- 64: HR: 0.71 (0.55-0.93), 65 -74: HR: 0.76 (0.61-0.95), ≥75 years: HR: 0.68 (0.53-0.88). P-interaction: =0.76	Martinez	2020
	KCCQ-TSS score tertiles ≤65.6, 65.7-87.5, ≥87.5	The effects of dapagliflozin on a broad range of health status outcomes KCCQ	The primary CV outcome	KCCQ-TSS tertiles <65.6: HR 0.70 (0.57-0.86); 65.7-87.5: HR 0.77 (0.61-0.98), ≥87.5: HR 0.62 (0.46-0.83)	Kosiborod	2020
	Treated with or without ARNi at baseline	Efficacy of dapagliflozin in patients depending on sacubitril/valsartan use at baseline	The primary CV outcome	Taking ARNi HR: 0.75(0.50 - 1.13) Not taking ARNi HR: 0.74 (0.65 – 0.86)	Solomon	2020
With and without diabetes	Assess the effects of dapagliflozin in patients with HFrEF with and without diabetes	The primary CV outcome	With diabetes HR: 0.75 (0.63-0.90) Without diabetes HR: 0.73 (0.60-0.88) p-interaction: 0.8	Petrie	2020	
EMPEROR-Reduced Duration = 16 months N= 3730	Preferential enrolment of patients with HFrEF with a greater severity of LVSD.	The effects of empagliflozin in patients across the broad spectrum of HFrEF	The primary outcome was a composite of CV death or HHF, analysed as the time to first event.	HR: 0.75(0.65 -0.86)	Packer	2020
			Renal composite outcome	HR: 0.50 (0.32-0.77)		

	Patients receiving and not receiving ARNi	Influence of ARNi on the efficacy and safety of empagliflozin	Primary outcome	Patients receiving ARNi: HR: 0.64 (0.45-0.89) Patients not receiving ARNi: HR: 0.77 (0.66-0.90), P = 0.0008, interaction P = 0.31	Packer	2021
	Patients receiving and not receiving MRAs	To study the mutual influence of empagliflozin and MRAs in EMPEROR-Reduced	Primary outcome	In MRA nonusers: empagliflozin vs. placebo: 0.76 (0.59–0.97); Receiving an MRA: empagliflozin vs. placebo: 0.75 (0.63–0.88) (p-interaction: 0.93).	Ferreira	2021
	KCCQ-CSS tertiles at 3, 8 and 12 months	Assess whether the benefits of empagliflozin varied by baseline health status and impact of empagliflozin on patient-reported outcomes	Primary outcome	KCCQ-CSS tertiles <62.5: HR 0.83 (0.68-1.02); 62.6-85.4: HR 0.74 (0.58-0.94), ≥85.4: HR 0.61 (0.46-0.82) P-trend = 0.10	Butler	2021
	Groups according to SBP at baseline (<110; 110-130; >130 mm Hg).	Assess the interplay of SBP and the effects of empagliflozin	Primary outcome	SBP >130: HR 0.82 (0.62-1.09); 110-130: 0.71 (0.58-0.87); <110: 0.78 (0.61-1.00)	Bohm	2021
SOLOIST-WHF Duration = 9 months N= 1222 (EF<50% = 966)	Patients with type 2 DM and AHF	Safety and efficacy of SGLT2i when initiated soon after an acute HF episode	Total number of deaths from CV causes and hospitalisations and urgent visits for heart failure (first and subsequent events)	HR: 0.67 (0.52 - 0.85)	Bhatt	2021
EMPA-RESPONSE-AHF	AHF	Safety and clinical efficacy of SGLT2i in patients with AHF	Change in VAS dyspnoea score: Diuretic response at day 4 Length of stay Percentage change in NT-pro-BNP at day 4	No difference was observed in VAS dyspnoea score, diuretic response, length of stay, or change in NT-pro-BNP between empagliflozin and placebo.	Damman	2020
EMPULSE-HF Duration = 90 days N= 530	Patients hospitalised for acute HF		Composite of death. Number of HF events, urgent/unplanned visits using Win-ratio approach	HR: 1.36 (1.09-1.68), p=0.0054)	Bavry	2021
EMPIRE-HF Duration = 12 weeks N= 190	Patients with HF rEF	To investigate the effect of empagliflozin on NT-pro-BNP in HF rEF	Primary endpoint was the between-group difference in the change of NT-pro-BNP from baseline to 12 weeks	Adjusted ratio of change empagliflozin/placebo 0.98 (0.82-1.11)	Jensen	2020

Empire-HF renal Duration = 12 weeks N= 120	Patients with HFrEF	To investigate the effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured GFR	The between-group difference in the changes in estimated extracellular volume, estimated plasma volume, and measured GFR from baseline to 12 weeks.	Empagliflozin resulted in reductions in estimated extracellular volume (-0.12 L (-0.18 to -0.05); p=0.00056), estimated plasma volume (-7.3%, -10.3 to -4.3; p<0.0001), and measured GFR (-7.5 ml/min, -11.2 to -3.8; p=0.00010)	Jensen	2021
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HFrEF: heart failure with reduced ejection fraction; AHF: acute heart failure; CV: cardiovascular; HF: heart failure; HR: hazard ratio; COPD: chronic obstructive pulmonary disease; KCCQ: Kansas City Cardiomyopathy Questionnaire; ARNi: angiotensin receptor/neprilysin inhibitor; MRA: mineralocorticoid receptor antagonists; SBP: systolic blood pressure; DM: diabetes mellitus; OR: odds ratio; VAS: visual analogue scale

First line in bold presents the results of the primary outcome in the trial and subsequent lines present the results of secondary analyses.

Table 2: Cardiovascular outcomes in patients receiving SGLT2i with Type 2 diabetes and CKD.

Trial name	Patient population and sub-population	Duration	N	HF at baseline (n)	Objective	endpoint	Results	Author	Year
EMPA-REG OUTCOME	Type 2 diabetes at high CV risk	3.1 y	7020	706	Examined the effects of empagliflozin, as compared with placebo, on CV morbidity and mortality in patients with type 2 diabetes at high risk for CV events receiving standard care.	The primary composite outcome: death from CV causes, nonfatal MI, or nonfatal stroke	HR: 0.86 (0.74- 0.99)	Zinman	2015
						HHF	HR: 0.65 (0.50 - 0.85)		
CANVAS	Type 2 diabetes and high CV risk	3.6 y	10,142	1461	Effects of treatment with canagliflozin on CV, renal, and safety outcomes.	The primary composite outcome: death from CV causes, nonfatal MI, or nonfatal stroke	HR: 0.86 (0.75 -0.97).	Neal	2017
						HHF	HR: 0.67(0.52- 0.87)		
DECLARE-TIMI	Type 2 diabetes	4.2	17160	1724	Evaluated the effects of dapagliflozin on CV and renal outcomes in patients who had or were at risk for atherosclerotic CV disease.	The primary efficacy outcomes were MACE and a composite of CV death or HHF	HR: 0.93 (0.84 - 1.03)	Wiviott	2018
						HHF	HR: 0.73 (0.61-0.88)		
VERTIS-CV	Patients with type 2 diabetes and atherosclerotic CV disease	3.5 years	8246	1958	The long-term effects of ertugliflozin on CV and renal outcomes	The primary composite outcome: of death from CV causes, nonfatal MI, or nonfatal stroke	HR: 0.97 (0.85- 1.11)	Cannon	2020
						HHF	HR: 0.70 (0.54-0.90)		
SCORED	Patients with diabetes with CKD with or without albuminuria	16 months	10,584	3283	The efficacy and safety of sotagliflozin in preventing CV events in patients with diabetes with CKD with or without albuminuria	Composite of the total number of deaths from CV causes, HHF, and urgent visits for HF	HR:0.74 (0.63 - 0.88)	Bhatt	2021
						Total nb or hospitalisations for HF and urgent visits for HF	HR: 0.67 (0.55-0.82)		
CREDESCENCE	Type 2 diabetes and albuminuric CKD	2.62 years	4401		To assess the effects of canagliflozin on renal outcomes in patients with type 2 diabetes and albuminuric CKD	A composite of ESKD (dialysis, transplantation, or a sustained eGFR of <15 ml/min/1.73 m2), a doubling of serum creatinine level, or death from renal or CV causes	The HR 0.70 (0.59 - 0.82).	Perkovic	2019

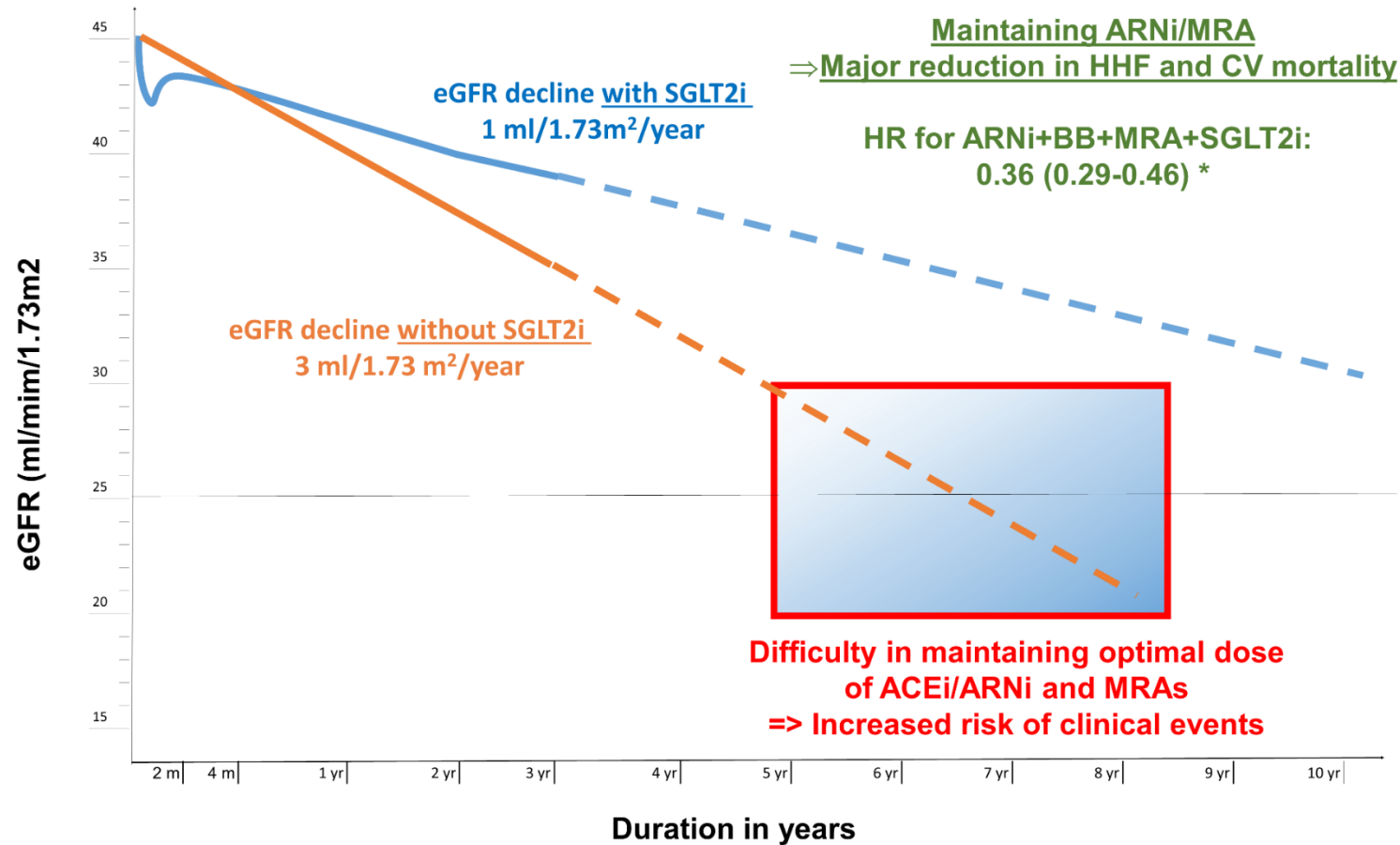
HHF

HR 0.61 (0.47 - 0.80).

CKD: chronic kidney disease; CV: cardiovascular; HF: Heart Failure; HHF: hospitalisation for heart failure; MI: myocardial infarction; HR: Hazard ratio; MACE: major cardiovascular event

Figure legends:

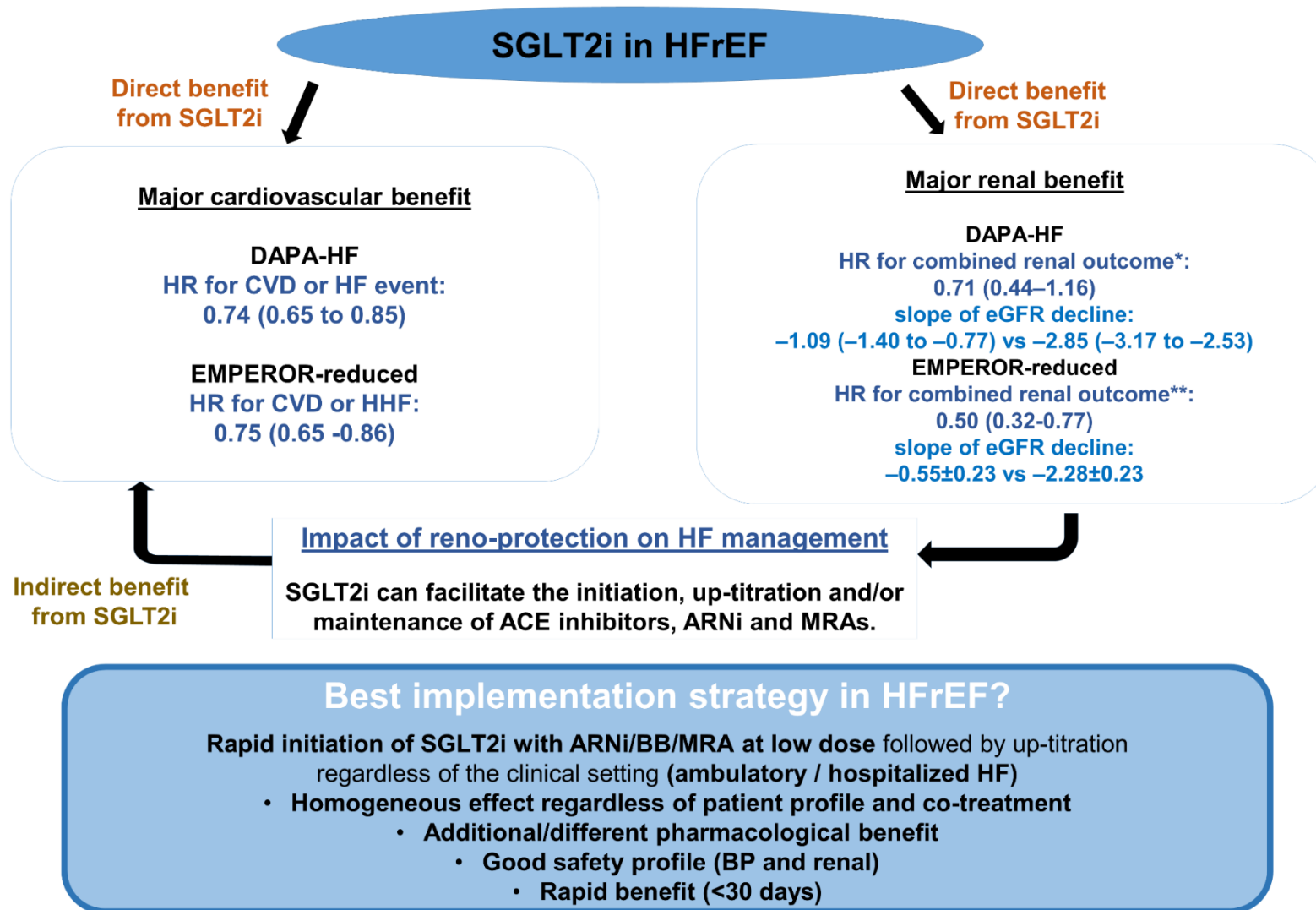
Figure 1: Schematic representation of reno-protective effects of SGLT2i on cardiovascular outcomes



*Tromp et al., A Systematic A Systematic Review and Network-Meta-Analysis of Pharmacological Treatment of HFrEF; 2021; JACC: HF
Dotted line represents extrapolated eGFR to longer follow-up than available evidence in DAPA-HF and COMMANDER-HF

ACEi: ACE inhibitors; ARNi: angiotensin receptor blocker/neprilysin inhibitor; BB: beta-blocker; CV: cardiovascular; HFrEF: hospitalisation for heart failure; MRA: mineralocorticoid receptor antagonists

Graphical abstract



* McMurray JJV, Solomon SD, Inzucchi SE, et al. 2019 doi:10.1056/NEJMoa1911303 and Jhund PS, Solomon SD, Docherty KF, et al. 2021 doi:10.1161/circulationaha.120.050391

** Packer M, Anker SD, Butler J, et al. 2020 doi:10.1056/NEJMoa2022190