Title: SGLT2 inhibitors & HFPEF

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Keywords: heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, chronic kidney disease, diabetes, SGLT2 inhibitors, hospitalizations, mortality

Word count 4999 words.

Key Points

Secondary analyses of the trials of SGLT2 inhibitors in patients with type 2 diabetes suggested a benefit of this class of drugs in HFPEF

The EMPEROR-Preserved trial randomized patients with HFPEF to empagliflozin or placebo.

Empagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure by 21%, mainly due to a reduction in hospitalization for heart failure with no effect on cardiovascular mortality

Empagliflozin is the first drug to reduce the primary outcome in a trial of patients with HFPEF and more trials with other SGLT2 inhibitors in patients with HFPEF are due to conclude.

It is likely that SGLT2 inhibitors will become the new standard of care in HFPEF

Synopsis

The trials of SLGT2 inhibitors in type 2 diabetes suggested a potential benefit of these drugs in patients with heart failure. When randomized trials confirmed their benefit in heart failure with reduced ejection fraction, attention turned to heart failure with preserved ejection fraction. In the EMPEROR-Preserved trial the SGLT2 inhibitor empagliflozin reduced the risk of cardiovascular death or hospitalization for heart failure (HR 0.79 95%CI 0.69-0.9, p<0.001). This was driven by a reduction in worsening HF events. SGLT2 inhibitors are likely to become the new standard of care in patients with heart failure with preserved ejection fraction.

Since the publication of the EMPAREG-Outcome trial there has been huge interest in the potential benefit of SGLT2 inhibitors in patients with heart failure[1]. The dramatic results of EMPAREG-Outcome trial demonstrated a reduction in heart failure hospitalizations with the SGLT2 inhibitor empagliflozin, and whether these drugs would be of benefit in patients with heart failure became a subject of much investigation. A number of other trials of SGLT2 inhibitors in patients with type 2 diabetes soon followed[2–5], replicating the results of the EMPAREG-Outcome trial. More recently, there have been two large placebo controlled randomized trials of SGLT2 inhibitors (dapagliflozin and then empagliflozin) which have reported a reduction in morbidity and mortality in patients with heart failure with reduced ejection fraction (HFREF)[6,7]. However, a large proportion of the population with heart failure have heart failure with preserved ejection fraction (HFPEF) and what was previously known as mid-range ejection fraction heart failure or what is now recognized as mildly reduced ejection fraction heart failure. In some epidemiological studies up to 50% of patients presenting with heart failure have an ejection fraction of over 40%[8]. This leaves a large proportion of patients who have currently not been eligible for treatment with SGLT2 inhibitor based on current guidelines[9]. This review will examine the efficacy of SGLT2 inhibitors in patients with HFPEF.

Diabetes, HFPEF and SGLT2 inhibitors

There have been a number of trials of SGLT2 inhibitors in patients with type 2 diabetes[1–5]. When these trials were initiated the benefit of SGLT2 inhibitors on heart failure hospitalizations, and the degree to which these drugs would reduce the risk of heart failure hospitalizations, was not anticipated. As such when patients were enrolled into these trials detailed information about left ejection fraction (LVEF) was

not always collected. However, several investigators did record LVEF and all recorded whether a patient had a history of heart failure and therefore were able to provide some insights into the potential benefit of SGLT2 inhibitors in patients with HFPEF. The EMPA-REG Outcome trial was the first to report the benefit of SGLT2 inhibitors in type 2 diabetes. Data on LVEF was not collected but the efficacy of empagliflozin was similar in those with and without heart failure[10]. The CANVAS program, with the SGLT2 inhibitor canagliflozin, in patients with type 2 diabetes and at high risk for developing cardiovascular disease included 10,142 patients and did not collect LVEF data. The investigators did report that the benefit of canagliflozin was greater in those with a history of heart failure[3]. In a trial of canagliflozin (this time enrolling those with kidney disease caused by type 2 diabetes) a reduction in kidney and cardiovascular events in those with a prior history of heart failure at baseline (15%) was observed in those randomized to canagliflozin[4]. However, it was not until an analysis of the DECLARE-TIMI 58 trial with the SGLT2 inhibitor dapagliflozin that some insight into the potential benefit of SGLT2 inhibitors in HFPEF in particular were reported[11] (Figure 1). In the trial there were 17,160 patients enrolled and of those 1987 (12%) had a history of heart failure. Of this group 671 (3.9%) had an ejection fraction of <45% and 1316(7.7%) had heart failure without reduced ejection fraction including 808 with ejection fraction of ≥45%. Although the treatment benefit with dapagliflozin appeared to be greater in those with HFREF (hazard ratio (HR) 0.62 95%CI 0.45-0.86) than those with HFPEF (HR 0.88 95%CI 0.66-1.17) there was no interaction between treatment and type of heart failure (P for interaction = 0.45). In keeping with a subsequent analysis of the DAPA-HF trial[12], the benefit of dapagliflozin in those with HFREF was observed very early during follow up (almost immediately) whereas in those with HFPEF, the divergence in the rates of CV death

or HF hospitalization occurred around 1 year of follow up. Subsequent to these seminal trials of SGLT2 inhibitors in patients with type 2 diabetes, the VERTIS CV trial reported[5]. This was a placebo-controlled trial of ertugliflozin in patients with type 2 diabetes and established atherosclerotic cardiovascular disease. In this trial the benefit of ertugliflozin was similar in those with and without heart failure and in those with an ejection fraction of over 45% versus those with an ejection fraction ≤45%. Prior to the results of a trial of SGLT2 inhibitors in patients with HFPEF, two other trials in patients with type 2 diabetes provided further insight into whether these drugs may be beneficial in HFPEF. A trial of an SGLT1/2 inhibitor, sotagliflozin, the SOLOIST-WHF trial[13], randomized patients with type 2 diabetes and decompensated heart failure to sotagliflozin or placebo. Randomization was stratified according to LVEF allowing subsequent examination of the HFPEF group. Unfortunately, this trial was terminated early due to loss of funding, but overall, there was a benefit of sotagliflozin on the primary composite endpoint of cardiovascular death and total heart failure hospitalizations. However, despite the early termination of the trial there were substantial number of events after 1222 patients were enrolled of which 21% had HFPEF. The authors reported that there was no difference in the benefit of sotagliflozin according to HF type. At the same time the SCORED trial[14] was published, again using sotagliflozin, but in this trial in patients with type 2 diabetes high cardiovascular risk and chronic kidney disease and again a number of patients had heart failure. The benefit again was the same in those with HFREF and HFPEF. In a presentation of a combined analysis of SOLOIST and SCORED the benefit of sotagliflozin was clear in the combined HFPEF subgroups from both trials with no evidence of interaction by ejection fraction (p for interaction=0.33)[15] (Figure 1). However, given that both trials were terminated early and that these were not

primary analyses, these data had to be viewed with caution until adequately powered trials in patients with HFPEF could be completed.

Empagliflozin and HFPEF

Having observed that SGLT2 inhibitors improved outcomes in the HFREF population with and without type 2 diabetes in two large randomized trials[6,7], combined with the exploratory analyses of trials in patients with type 2 diabetes, the results of an adequately powered trial in HFPEF with and SGLT2 inhibitor were keenly awaited. Trials of pharmacotherapies in HFPEF had been neutral and the most recent drug to demonstrate a benefit in HFREF, sacubitril/valsartan, was tested in a population with HFPEF and again the result of the primary outcome was neutral[16]. The EMPEROR-Preserved trial was a multicenter randomized double blind placebo controlled trial designed to evaluate whether empagliflozin would improve morbidity and mortality in patients with HFPEF[17,18]. The trial enrolled patients who had had heart failure for at least 3 months (in New York Heart Association Class II, III or IV) and in whom LVEF was >40% at its most recent assessment with no prior measurement of ejection fraction being ≤40%. They were required to have elevated N-terminal pro brain natriuretic peptide (NT-proBNP) levels (i.e. >300 pg/mL in patients without atrial fibrillation and >900 pg/mL in patients with atrial fibrillation) and to show evidence of structural changes in the heart (as evidenced by increases in left atrial size or left ventricular mass) on echocardiography or a documented hospitalization for heart failure within 12 months of screening.

The primary endpoint of EMPEROR-Preserved was a composite end point of cardiovascular death or first hospitalization for heart failure. The patients who were randomized into EMPEROR-Preserved were as expected based on the inclusion criteria and the population with HFPEF. Around half of the patients had type 2 diabetes and chronic kidney disease and around 1/4 had experienced a hospitalization for heart failure within the past year. The mean ejection fraction was 54%. The authors reported that there was a significant reduction of 21% in the primary comes outcome of cardiovascular death or heart hospitalizations for heart failure (HR 0.79 95%CI 0.69-0.9, p<0.001) (Figure 1) with a 29% relative risk reduction in heart failure hospitalizations (HR 0.71 95%CI 0.60-0.83) but no significant reduction in cardiovascular death (HR 0.91 95%CI 0.76-1.09) (Figure 2). Of the secondary endpoints specified in the hierarchical testing procedure, there was a significant reduction in the total number of heart failure hospitalizations (407 in the empagliflozin group versus 541 in the placebo group, a 17% relative risk reduction HR 0.73 95%CI 0.61-0.88)) and kidney function slope measured by mean change in estimated glomerular filtration rate (eGFR). In other prespecified analyses there was an improvement in the Kansas City cardiomyopathy questionnaire clinical summary score at 52 weeks in favor of improving symptoms with empagliflozin. There was a reduction in the composite renal outcome as a prespecified analysis, but this did not reach statistical significance neither did the reduction in the onset of new diabetes in patients with prediabetes and there was no effect on death from any cause (HR 1.00 95% CI 0.87-1.15) (Figure 2). Of the key prespecified subgroups there was no evidence of interaction of treatment effects by diabetes at baseline or age, kidney function, body mass index, NT-proBNP or by prior use of inhibitors of the renin angiotensin aldosterone system. Much of the prior literature of the benefit of drugs in

HFREF, when examined across the ejection fraction spectrum, had demonstrated a gradient in benefit by ejection fraction with those at the higher end of the ejection fraction spectrum appearing to derive less benefit[19–21]. In EMPEROR-Preserved the point estimate for the treatment effect for the group with an ejection fraction of ≥60% just failed to reach statistical significance. While ordinarily this would be viewed as a subgroup analysis and not of importance given the primary outcome was met, the prior literature and similar gradients having been reported for other therapies for heart failure meant that further dissection of the relationship with ejection fraction was of interest in determining if the results were applicable to all patients with HFPEF.

Ejection fraction and empagliflozin in HFPEF

In a secondary analysis of the EMPEROR-Preserved trial, the effect of empagliflozin on outcomes by ejection fraction was explored[22]. There has been much debate in the literature about the point at which we define HFREF and HFPEF at the lower end of the ejection fraction spectrum. Based on secondary analyses of prior trials there has been a move towards viewing HFREF and heart failure with mildly reduced ejection fraction as the same group in recent guidelines[9], recognizing that patients with an ejection fraction of <50% tend to derive benefit from the traditionally used drugs for heart failure (ACE inhibitors, angiotensin receptor blockers, betablockers and mineralocorticoid receptor antagonists). In the PARAGON-HF trial with sacubitril/valsartan an ejection fraction of around 55% seemed to similarly define those who benefited from the angiotensin receptor neprilysin inhibitor[19]. Following from this the EMPEROR-Preserved investigators reported that when LVEF was

examined as a categorical variable or as a continuous variable a very clear gradient in benefit of impact of empagliflozin with an ejection fraction below what would be called normal (<55%). As the investigators were able to combine the EMPEROR-Preserved and EMPEROR-Reduced trials there enough events to examine each of the categories of ejection fraction to define where a cut off in benefit may lie. They found that above and ejection fraction of 65% there was attenuation of the benefit of empagliflozin although overall there was no evidence of heterogeneity in the treatment effect by ejection fraction (P value for interaction equal to 0.3). They also examined the interaction with sex as an analysis of the PARAGON-HF trial suggested that there was an interaction with sex which may have been in part explained by different ejection fraction thresholds for normal in men and women[23]. The EMPEROR-Preserved investigators did not find a treatment by sex by LVEF interaction. While these are interesting data and confirm the findings of other recent analyses in HFPEF with other drugs they are exploratory in nature and the results of the primary analysis of EMPEROR-Preserved stand, empagliflozin reduced the risk of cardiovascular death or heart failure hospitalization in patients with heart failure and an ejection fraction of >40%.

Heart failure outcomes

As may be expected from the primary results of EMPEROR-Preserved, there are a number of analyses that support using the SGLT2 inhibitor empagliflozin to reduce the risk of worsening heart failure outcomes. A broad range of outcomes related to heart failure were recorded in EMPEROR-Preserved (Figure 2). These included

heart failure hospitalizations, total HF hospitalizations, requirement for intravenous vasopressor or inotropic support, admission to intensive care unit, requirement for urgent care/ emergency department visits and outpatient intravenous diuretic therapy[24]. For all of these outcomes, and for multiple composite outcomes composed of these different heart failure related outcomes, there was a clear reduction in the risk of each with empagliflozin in patients with HFPEF. Only the reduction in total hospitalizations for any reason was not statistically significantly reduced in the empagliflozin group.

Heart Failure related quality of life and functional capacity

Patients with HFPEF are characterized by marked limitation in physical functioning and a high burden of heart failure related symptoms. Therefore, improving heart failure related health status (symptoms, functional status and quality of life) is a key aim of the treatment of HFPEF. One of the key pre-specified secondary endpoints in EMPEROR-Preserved was improvement in a self-reported measure of heart failure related symptoms, function and quality of life, measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ)[18]. The domain used in the prespecified secondary analysis was the total symptom score. This was improved by empagliflozin and in further analyses, both the clinical summary score and overall summary score were also improved[25]. There was also a clear increase in the proportion of patients reporting an improvement of 5 points, 10 points, and 15 points in the patients randomized to empagliflozin and conversely a reduction in the number of patients reporting a deterioration by 5 points or more. Importantly there is no evidence that the benefit of empagliflozin differed by baseline KCCQ score. These

results were in contrast to the EMPERIAL trial [26,27] which examined if empagliflozin improved 6 minute walk distance in 315 patients with an LVEF >40%. They did not find any effect of empagliflozin on 6 minute walk distance (median difference between placebo and empagliflozin of 4.0 m (−5.0, 13.0; P = 0.37)). Another trial, PRESERVED-HF [28] did however report an improvement in 6 minute walk test distance with dapagliflozin in 324 patients with and LVEF ≥ 45% as well as replicating the benefits on KCCQ scores seen with empagliflozin in EMPEROR-Preserved (Figure 2).

Kidney outcomes

There is ample evidence from prior trials of SGLT2 inhibitors that they preserve kidney function and reduce the risk of kidney outcomes[4,29]. As chronic kidney disease is a common comorbidity in HFPEF, any effect of SGLT2i on kidney outcomes would be beneficial. In a pre-specified secondary outcome in the hierarchical testing of the EMPEROR-Preserved trial the reduction in the slope of eGFR was statistically significant in favor of empagliflozin[18]. This was similar to the findings in HFREF with dapagliflozin and empagliflozin[30,31]. However, slowing of decline in eGFR may not always mirror the effect on kidney outcomes and is not a perfect surrogate measure. There was no reduction in endpoint of the combined kidney outcomes in EMPEROR-Preserved in contrast to EMPEROR-Reduced and a meta-analysis of EMPEROR-Reduced and DAPA-HF[32]. In a pre-specified pooled analysis of EMPEROR-Preserved and EMPEROR-Reduced there was a statistically significant interaction between trial and randomized therapy on kidney outcomes (profound and sustained decreases in eGFR or renal-replacement therapy)[33]. The

hazard ratios were 0.51 (95% CI 0.33 -0.79) in the EMPEROR-Reduced trial and 0.95 (95% CI 0.73-1.24) in the EMPEROR-Preserved trial (P=0.016 for interaction). Therefore, whether SLGT2 inhibitors improve kidney outcomes in HFPEF is still unknown.

Potential mechanisms of benefit of SGLT2i in HFPEF

As described above, SGLT2 inhibitors improve morbidity and mortality in HFPEF, improve heart failure related symptoms and improve functional capacity and slow the deterioration in kidney function. There is much speculation about the proposed mechanism of action of SGLT2 inhibitors [34]and a number of studies are being conducted to try and illuminate a particular pathway[35]. In HFREF, one mechanism that has been demonstrated is improvement in LV size[36]. This is not likely to be the same in HFPEF where cardiac structure and function is different. However, in most trials of pharmacotherapy in HFPEF, there is a requirement of some structural heart disease to be present (either left atrial enlargement or left ventricular hypertrophy), as these are thought to be hallmarks of the disease. It is possible that these two parameters may be improved by SGLT2i, with experimental evidence suggesting that SGLT2i improves cardiac hypertrophy and diastolic function[37,38] and evidence that alterations in myocardial energy utilization may be the other important factor[39,40]. Another potential mechanism is the general improvement in kidney function. This has already been shown in patients with HFREF and the benefits of SGLT2i are also evident in those with chronic kidney disease and therefore a kidney benefit may

translate into improved HF status, particularly in HFPEF where renal dysfunction is common.

Future trials of SGLT2 inhibitors in HFPEF

While the EMPEROR-Preserved results were a landmark for the treatment of HFPEF, being only one trial, which did not show any benefit on mortality, the results of other trials of SGLT2 inhibitors in HFPEF are keenly awaited. The DELIVER trial randomized 6263 patients with a left ventricular ejection fraction of >40% with elevated natriuretic peptides (≥300 pg/mL if in sinus rhythm or ≥600 pg/mL if in atrial fibrillation/flutter) and evidence of structural heart disease (LA enlargement or LV hypertrophy) to dapagliflozin 10mg/day or placebo on top of usual medication according to regional standard of care[41]. The primary composite of worsening heart failure episodes (either unplanned hospitalization or urgent heart failure visit requiring intravenous therapy but not requiring a hospital admission) or cardiovascular death, will be analysed as time-to-first event. However, given the information gained from PARAGON-HF, and now EMPEROR-Preserved, the endpoint will be assessed in a dual primary analysis in the full study population and those with and ejection fraction of <60%.

The results of the DELIVER trial are keenly anticipated to see if they confirm the results of EMPEROR-Preserved. Furthermore, there is interest in whether DELIVER will demonstrate a benefit of a SGLT2i in reducing mortality in HFPEF which was not seen in EMPEROR-Preserved. There is hope that this might be plausible given that dapagliflozin reduced mortality in DAPA-HF but empagliflozin did not in EMPEROR-

Reduced and meta-analysis of the two trials confirmed the mortality reduction with SGLT2 inhibitors in HFREF[32], we can hope for the same in HFPEF. However, on the basis of the analyses of EMPEROR-Preserved described, the European Medicines Agency Committee for Medicinal Products for Human Use adopted a positive opinion recommending a change to the terms of the marketing authorization for empagliflozin[42]. The indication will be changed from "…adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction" to "…adults for the treatment of symptomatic chronic heart failure" thereby removing the ejection fraction requirement and opening up the therapy to patients with HFPEF. How this new indication is incorporated into guidelines remains to be resolved. Given the lack of any disease modifying drugs for HFPEF in the guidelines it is likely that empagliflozin will be the initial therapy of choice for HFPEF and may also be joined by dapagliflozin dependent on the results of DELIVER should a class effect be observed.

Summary

Patients with HFPEF now join patients with type 2 diabetes, HFREF and patients with CKD as a group who can derive benefit from the SGLT2 inhibitors. After many failures, in empagliflozin we finally have a therapy for HFPEF that can alter the prognosis of patients as well as improve heart failure related symptoms. This is a major step forward in the treatment of HFPEF and will undoubtedly shape future guidelines on the management of heart failure.

Disclosure

PSJs employer has been remunerated by AstraZeneca, Bayer, Novartis and NovoNordisk for work on clinical trials. PSJ has received speakers fees and advisory board fees from AstraZeneca, Boehringer Ingelheim and Novartis and research funding from Boehringer Ingelheim and Analog Devices Inc.

References

1 Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine* 2015; **373**: 2117–28.

2 Wiviott SD, Raz I, Bonaca MP, *et al.* Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *New England Journal of Medicine* 2019; **380**: 347–57.

3 Neal B, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England journal of medicine* 2017; **377**: 644–57.

4 Perkovic V, Jardine MJ, Neal B, *et al.* Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *The New England journal of medicine* 2019; **380**: 2295–306.

5 Cannon CP, Pratley R, Dagogo-Jack S, *et al.* Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes. *The New England journal of medicine* 2020; **383**: 1425–35.

6 McMurray JJV, Solomon SD, Inzucchi SE, *et al.* Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine* 2019; **381**: 1995–2008.

7 Packer M, Anker SD, Butler J, *et al.* Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *New England Journal of Medicine* 2020; : NEJMoa2022190.

8 Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017; **14**: 591–602.

9 Authors/Task Force Members:, McDonagh TA, Metra M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022; **24**: 4–131.

10 Fitchett D, Zinman B, Wanner C, *et al.* Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. *European heart journal* 2016; **37**: 1526–34.

11 Kato ET, Silverman MG, Mosenzon O, *et al.* Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation* 2019; **139**: 2528–36.

12 Berg DD, Jhund PS, Docherty KF, *et al.* Time to Clinical Benefit of Dapagliflozin and Significance of Prior Heart Failure Hospitalization in Patients With Heart Failure With Reduced Ejection Fraction. *JAMA cardiology* 2021. DOI:10.1001/jamacardio.2020.7585.

13 Bhatt DL, Szarek M, Steg PG, *et al.* Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2020; **384**: 117–28.

14 Bhatt DL, Szarek M, Pitt B, *et al.* Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med* 2021; **384**: 129–39.

15 Bhatt DL et al. American College of Cardiology Virtual Annual Scientific Session (ACC 2021), May 17, 2021 https://www.acc.org/latest-in-cardiology/clinical-trials/2020/11/11/22/00/soloist-whf. Accessed 10th February 2022.

16 Solomon SD, McMurray JJV, Anand IS, *et al.* Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019; **381**: 1609–20.

17 Anker SD, Butler J, Filippatos GS, *et al.* Evaluation of the effects of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. *European Journal of Heart Failure* 2019; **21**: 1279–87.

18 Anker SD, Butler J, Filippatos G, *et al.* Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 2021; **385**: 1451–61.

19 Solomon SD, Vaduganathan M, L Claggett B, *et al.* Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. *Circulation* 2020; **141**: 352–61.

20 Lund LH, Claggett B, Liu J, *et al.* Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *European Journal of Heart Failure* 2018; **20**: 1230–9.

21 Abdul-Rahim AH, Shen L, Rush CJ, Jhund PS, Lees KR, McMurray JJV. Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. *European Journal of Heart Failure* 2018; **20**: 1139–45.

22 Butler J, Packer M, Filippatos G, *et al.* Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *European Heart Journal* 2022; **43**: 416–26.

23 McMurray JJV, Jackson AM, Lam CSP, *et al.* Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared with Men with Heart Failure and Preserved Ejection Fraction: Insights from PARAGON-HF. *Circulation* 2020. DOI:10.1161/CIRCULATIONAHA.119.044491.

24 Packer M, Butler J, Zannad F, *et al.* Effect of Empagliflozin on Worsening Heart Failure Events in Patients With Heart Failure and Preserved Ejection Fraction: EMPEROR-Preserved Trial. *Circulation* 2021; **144**: 1284–94.

25 Butler J, Filippatos G, Jamal Siddiqi T, *et al.* Empagliflozin, Health Status, and Quality of Life in Patients With Heart Failure and Preserved Ejection Fraction: The EMPEROR-Preserved Trial. *Circulation* 2022; **145**: 184–93.

26 Abraham WT, Ponikowski P, Brueckmann M, *et al.* Rationale and design of the EMPERIAL-Preserved and EMPERIAL-Reduced trials of empagliflozin in patients with chronic heart failure. *Eur J Heart Fail* 2019; **21**: 932–42.

27 Abraham WT, Lindenfeld JA, Ponikowski P, *et al.* Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *European Heart Journal* 2021; **42**: 700–10.

28 Nassif ME, Windsor SL, Borlaug BA, *et al.* The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nature Medicine 2021 27:11* 2021; **27**: 1954–60.

29 Heerspink HJL, Stefánsson BV, Correa-Rotter R, *et al.* Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med* 2020; **383**: 1436–46.

30 Jhund PS, Solomon SD, Docherty KF, *et al.* Efficacy of Dapagliflozin on Renal Function and Outcomes in Patients With Heart Failure With Reduced Ejection Fraction: Results of DAPA-HF. *Circulation* 2021; **143**: 298–309.

31 Zannad F, Ferreira JP, Pocock SJ, *et al.* Cardiac and Kidney Benefits of Empagliflozin in Heart Failure Across the Spectrum of Kidney Function: Insights From EMPEROR-Reduced. *Circulation* 2021; **143**: 310–21.

32 Zannad F, Ferreira JP, Pocock SJ, *et al.* SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *The Lancet* 2020; **396**: 819–29.

33 Packer M, Butler J, Zannad F, *et al.* Empagliflozin and Major Renal Outcomes in Heart Failure. *N Engl J Med* 2021; **385**: 1531–3.

34 Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. *JACC Basic Transl Sci* 2020; **5**: 632–44.

35 Lee MMY, Petrie MC, McMurray JJV, Sattar N. How Do SGLT2 (Sodium-Glucose Cotransporter 2) Inhibitors and GLP-1 (Glucagon-Like Peptide-1) Receptor Agonists Reduce Cardiovascular Outcomes?: Completed and Ongoing Mechanistic Trials. *Arteriosclerosis, thrombosis, and vascular biology* 2020; **40**: 506–22.

36 Lee MMY, Brooksbank KJM, Wetherall K, *et al.* Effect of Empagliflozin on Left Ventricular Volumes in Patients with Type 2 Diabetes, or Prediabetes, and Heart Failure with Reduced Ejection Fraction (SUGAR-DM-HF). *Circulation* 2021; **143**: 516–25.

37 Verma S, Mazer CD, Yan AT, *et al.* Effect of Empagliflozin on Left Ventricular Mass in Patients with Type 2 Diabetes and Coronary Artery Disease: The EMPA-HEART CardioLink-6 Randomized Clinical Trial. *Circulation* 2019; : 8–11.

38 Connelly KA, Zhang Y, Visram A, *et al.* Empagliflozin Improves Diastolic Function in a Nondiabetic Rodent Model of Heart Failure With Preserved Ejection Fraction. *JACC: Basic to Translational Science* 2019; **4**: 27–37.

39 Ferrannini E, Muscelli E, Frascerra S, *et al.* Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *The Journal of clinical investigation* 2014; **124**: 499–508.

40 Ferrannini E, Baldi S, Frascerra S, *et al.* Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes. *Diabetes* 2016; **65**: 1190–5.

41 Solomon SD, Boer RA, DeMets D, *et al.* Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. *Eur J Heart Fail* 2021; **23**: 1217–25.

42 https://www.ema.europa.eu/en/medicines/human/summaries-opinion/jardiance-0. Accessed 10th February 2022.

Figure 1

Effect of SGLT2 inhibitors on cardiovascular (CV) death or heart failure (HF) hospitalization in trials of SGLT2 inhibitors in patients with type 2 diabetes where information on HFPEF was available versus the treatment estimate of empagliflozin reported from EMPEROR-Preserved

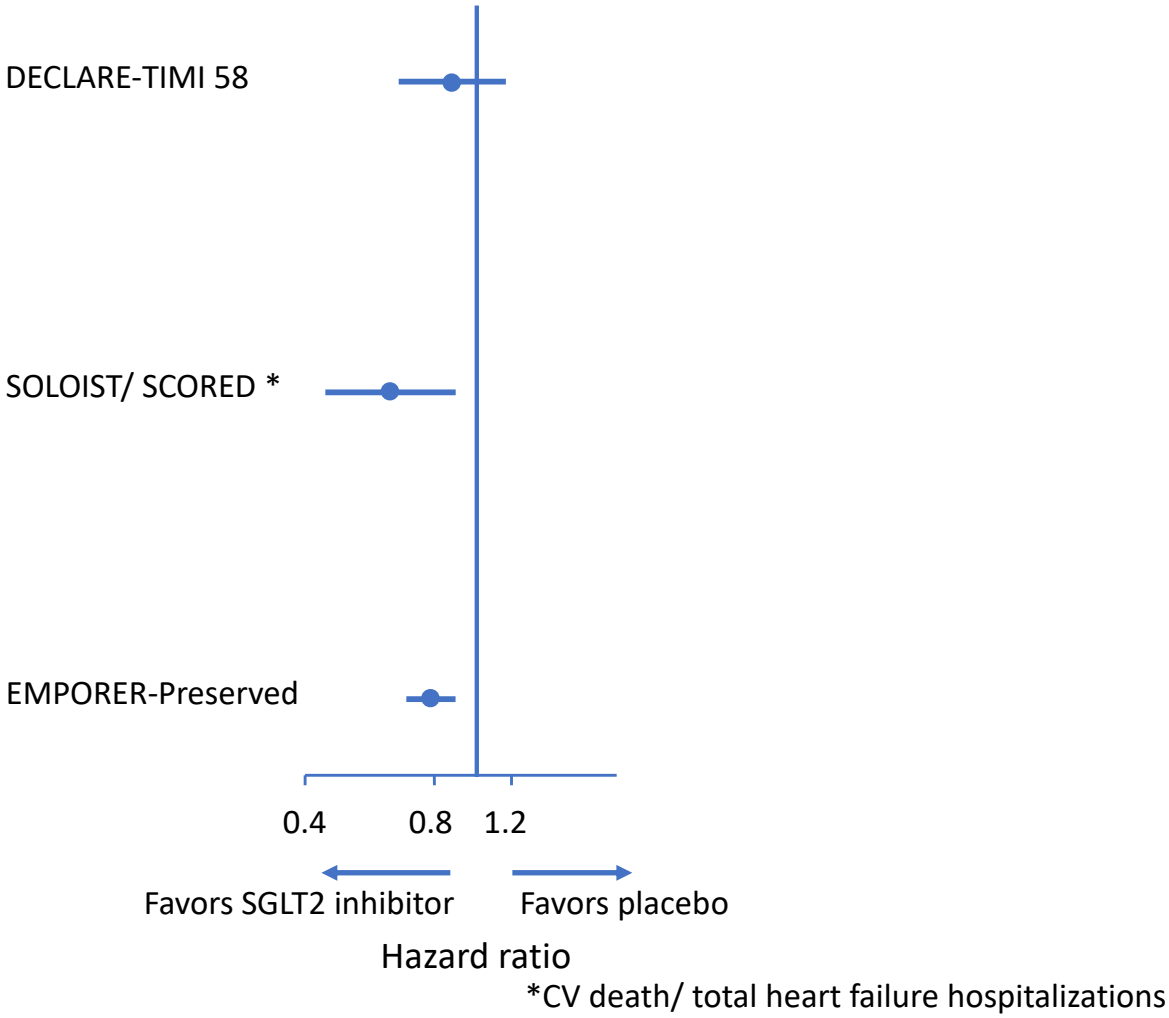

Figure 2

Benefits in patients with heart failure with preserved ejection fraction of SGLT2 inhibitors that are currently used for the treatment of heart failure with reduced ejection fraction

CV death/ HF hospitalization ✓ empagliflozin

HF hospitalization ✓ empagliflozin

Total HF hospitalizations ✓ empagliflozin

Worsening HF events * ✓ empagliflozin

Heart failure related symptoms and functional capacity ✓ empagliflozin and dapagliflozin

eGFR slope ✓

Renal outcomes ✗

All cause mortality ✗ empagliflozin

Cardiovascular mortality ✗ empagliflozin

Positive evidence from the primary outcome of a randomized trial

Positive evidence from a secondary outcome of a randomized trial

No evidence from a secondary outcome of a randomized trial