

BCS Editorial

The EMPEROR-Preserved Trial: The Emperor's New Clothes?

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Introduction

On the 6th July 2021, Boehringer-Ingelheim announced the preliminary positive results of the EMPEROR-Preserved trial of empagliflozin for patients with heart failure (HF) with a normal (or “preserved”) left ventricular ejection fraction (HeFNEF), declaring that EMPEROR-Preserved “...is the first and only successful trial for heart failure with preserved ejection fraction” (1).

The heart failure world waited for the full publication of the study in the *New England Journal of Medicine* in October 2021 with great excitement (2). In the event, treatment with empagliflozin was associated with a 21% reduction in the risk of first HF hospitalisation or cardiovascular (CV) death compared to placebo. Amid the hyperbole, there has been very little consideration of the detail of the EMPEROR-Preserved study and the subsequent post-hoc analyses, on which this editorial will focus.

Take Home Messages

- Heart failure with a normal (or “preserved”) ejection fraction (HeFNEF) is an enormously difficult diagnosis to make.
- There are many cardiovascular (CV) and non-CV diseases that may present with heart failure symptoms which have to be excluded before a diagnosis of HeFNEF can be made.
- EMPEROR-Preserved is the first trial to demonstrate outcome benefit with medical therapy for patients with HeFNEF. However, on closer look, the data is far from convincing.
- Empagliflozin was associated with a reduction in HF hospitalisations but these were an uncommon cause of morbidity during the trial. There was no effect on mortality.
- It is not clear how empagliflozin will fit into clinical guidelines – the biggest challenge in patients with HeFNEF remains establishing an accurate diagnosis.

Background

The condition

Approximately half of patients who appear superficially to have the clinical syndrome of heart failure (breathlessness, ankle swelling, fatigue) have a “preserved” or normal left ventricular ejection fraction (LVEF) on imaging (3). However, establishing that a patient’s symptoms are due to cardiac dysfunction is a major challenge. There are many potential causes for “true” HeFNEF (HF symptoms due to structural heart disease with normal LVEF on echocardiogram) such as amyloidosis, hypertensive and valvular heart disease which require treatment of the underlying pathology.

About the author

Joe Cuthbert graduated from the Hull York Medical School (HYMS) in 2012 and completed foundation and core medical training in and around the East Riding of Yorkshire. After completing his MD entitled “Venous Congestion in Humans” in 2018, he is now a Clinical Lecturer and Honorary Specialty Registrar in Cardiology at HYMS and the Hull University Teaching Hospitals Trust.



There are also many potential non-cardiac diseases which may cause HF symptoms in a patient with normal-range LVEF on echocardiography, such as obesity, deconditioning, atrial fibrillation (AF), lung disease and pulmonary hypertension, each of which has to be ruled out before a diagnosis of HeFNEF can be made (figure 1) (4).

The European Society of Cardiology (ESC) Heart Failure guidelines recommend broad diagnostic criteria for HeFNEF (figure 1) which rely

predominantly on the clinical judgement that there is a high pre-test probability of HF (and the absence of other conditions) based on the presence of symptoms and signs (5). The NTproBNP cut-off for excluding the diagnosis of HF in the ESC guideline is lower than the median NTproBNP of some groups of patients who have HF ruled out by thorough assessment (6). Applied liberally and without thorough evaluation, the diagnosis of HeFNEF may be given to patients with diagnoses other than HF.

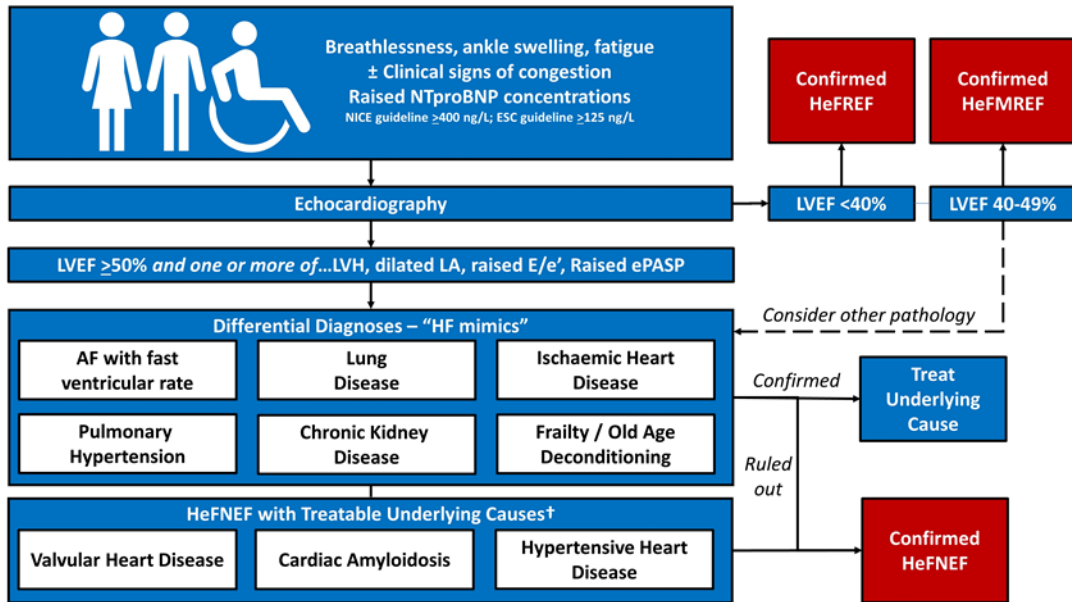


Figure 1. Establishing a diagnosis of HeFNEF. Adapted from Gevaert et al (2022) (4). NTproBNP - N-terminal pro-b-type natriuretic peptide, NICE – National Institute of Health and Clinical Excellence, ESC – European Society of Cardiology, LVEF – left ventricular ejection fraction, LVH – left ventricular hypertrophy, LA – left atrium, ePASP – estimated pulmonary artery systolic pressure, AF – atrial fibrillation, HeFNEF – heart failure with a normal ejection fraction.

The treatment

Sodium glucose co-transporter 2 inhibitors (SGLT2I) were developed as anti-hyperglycaemic medications. They induce glycosuria by inhibition of the sodium glucose co-transporter in the proximal tubule (figure 2) (7).

Initially investigated in patients with diabetes, phase III studies found a reduction in HF hospitalisation regardless of the presence of HF at baseline (8,9). Trials in patients with heart failure with a reduced ejection fraction (HeFREF) soon followed.

The DAPA-HF trial (N=4744, mean age 66 years,

23% female, 67% New York Heart Association (NYHA) class II, mean LVEF 31%, median N-terminal pro-B-type natriuretic peptide (NTproBNP) 1428 ng/L in the treatment arm) found that treatment with dapagliflozin was associated with a 26% reduction in HF hospitalisation or cardiovascular mortality after a median 18 months follow up. The EMPEROR-Reduced trial (N=3730, mean age 67 years, 24% female, 75% NYHA class II, mean LVEF 27%, median NTproBNP 1887 ng/L in the treatment arm) found that treatment with empagliflozin was associated with a 25% reduction in the risk of HF hospitalisation or CV mortality after a median 16 months follow up.

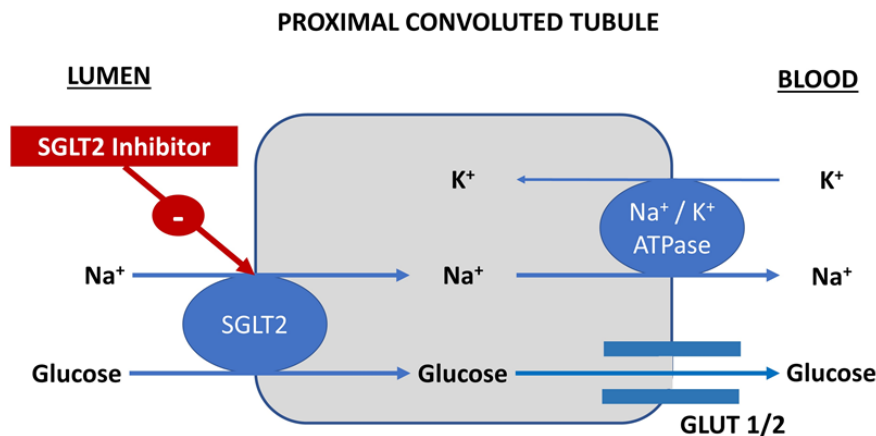


Figure 2. Mechanism of action of sodium-glucose co-transporter 2 inhibitors. SGLT2 – sodium glucose co-transporter 2.

A meta-analysis of the two trials concluded that treatment with SGLT2I in patients with HeFREF was associated with a 13% reduction in the risk of all-cause mortality, 14% reduction in the risk of CV mortality, and a 26% reduction in the risk of HF hospitalisation or CV mortality compared to placebo (10).

EMPEROR-Preserved

The EMPEROR-Preserved study investigated whether the beneficial effects of SGLT2Is seen in patients with HeFREF would translate to patients with HeFNEF.

Patient population

Over 11,000 patients were screened. Of the 5595 that failed screening, the majority (78%) had an NTproBNP that was too low (box 1). Only a minority of patients failed screening for low LVEF (5%), poor renal function (2%), cardiomyopathy (1%), anaemia (1%), liver disease (1%), or AF with a heart rate >110 / min (0.3%). No patients were reported to have severe lung disease or pulmonary hypertension at screening (2).

Amongst those participating in the trial (N=5988), mean age was 72 years, 45% were female, mean BMI was 30 kg/m², approximately half of patients had AF, half had diabetes, and half had chronic kidney disease (CKD) (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m²). Mean LVEF was 54% with approximately a third of patients having an LVEF of 40-49%, a third having an LVEF of 50-59%, and a third having an LVEF of >60%. Median NTproBNP was 994 ng/L in the treatment arm (2).

Findings

The primary outcome was a composite of first hospitalisation for HF or CV mortality. Secondary outcomes are shown in box 2.

Effect on clinical outcomes

During a median follow up of 26 months, the primary outcome occurred in 13.8% of patients in the empagliflozin group and 17.1% in the placebo group: a relative risk reduction of 21% (95% confidence interval 10 – 31%) with an absolute risk reduction of 3.3%, equating to 1.8 events per 100 patient-years. The number needed to treat to prevent one CV death or hospitalisation with HF was 31 (table 1) (2).

The result was driven *entirely* by a reduction in HF hospitalisations: empagliflozin had no effect on mortality. Alongside a reduction in HF hospitalisation, post-hoc analyses showed a lower chance of emergency or urgent care visits for HF, or intensification of oral diuretic treatment (11). The effect on HF hospitalisation reached statistical significance on day 18 after randomisation and was maintained throughout the trial (10). In pre-specified sub-group analysis and post-hoc analysis of patients stratified by LVEF, the benefit of empagliflozin was seen in patients with an LVEF 40-49% and 50-59% but not in those with an LVEF >60% (2,12).

Alongside a reduction in first hospitalisations for HF, there was an 8% reduction in the risk of first hospitalisations for any cause (P=0.03) (11). However, there was no effect on the total number of hospitalisations for any cause (a prespecified endpoint).

Box 1 – Inclusion and Exclusion Criteria for EMPEROR-Preserved**Inclusion**

- Aged ≥ 18 years
- Chronic heart failure for ≥ 3 months – NYHA II or worse
- LVEF $\geq 40\%$ within 6 months of screening and >90 days after an MI with no previous measurement $<40\%$
- NTproBNP >300 ng/L for patients in sinus rhythm
- NTproBNP >900 ng/L for patients in atrial fibrillation
- LA enlargement and/or LVH on echocardiography **or** admission with HF in last 12 months
- Stable dose of oral diuretic
- BMI <45 kg/m²

Exclusion

- MI, CABG, or other major cardiovascular surgery in previous 90 days
- Received or listed for a heart transplant or LVAD
- Other possible causes of HF – amyloidosis, haemochromatosis, Fabry's disease, muscular dystrophy, hypertrophic cardiomyopathy, pericardial constriction, severe (obstructive or regurgitant) valvular disease expected to lead to surgery within trial period, AF or flutter with ventricular rate >110 bpm, primary pulmonary hypertension
- Admission with HF 1 week prior to screening
- ICD or CRT implant
- SBP ≥ 180 mmHg (if SBP 151-179 mmHg patient should be on ≥ 3 antihypertensives to be eligible) and SBP <100 mmHg or symptomatic hypotension
- COPD requiring LTOT, oral steroid, or a hospitalisation within 12 months or other "significant" pulmonary disease
- Acute or chronic liver disease
- eGFR <20 ml/min/1.73m²
- Anaemia – haemoglobin <9 g/dL
- Major surgery planned or performed within 90 days of screening
- Active or suspected malignancy except for treated BCC, uterine cancer, or low risk prostate cancer

Derived from Anker et al (2021). Abbreviations used: NYHA - New York Heart Association, LVEF – left ventricular ejection fraction, MI – myocardial infarction, NTproBNP – N-terminal pro-B-type natriuretic peptide, LA – left atrial, LVH – left ventricular hypertrophy, HF – heart failure, BMI – body mass index, CABG – coronary artery bypass graft, LVAD – left ventricular assist device, AF – atrial fibrillation, bpm – beats per minute, ICD – implantable cardioverter defibrillator, CRT – cardiac resynchronisation device, SBP – systolic blood pressure, COPD – chronic obstructive pulmonary disease, LTOT – long term oxygen therapy, eGFR – estimated glomerular filtration rate, BCC – basal cell carcinoma.

Box 2 Pre-specified Primary & Secondary Outcomes

- Total number of hospitalisations for heart failure
- Rate of decline of eGFR
- Composite renal endpoint: first occurrence of dialysis; renal transplantation; sustained $\geq 40\%$ reduction in eGFR from baseline, sustained eGFR <15 ml/min/1.73m² in patients with eGFR ≥ 30 ml/min/1.73m² at baseline, or sustained eGFR <10 ml/min/1.73m² for patients with an eGFR <30 ml/min/1.73m² at baseline.
- Change in the clinical summary score on the KCCQ between baseline and 1 year
- Total hospitalisations for any cause
- All-cause mortality
- Incident diabetes

Derived from Anker et al (2021). Abbreviations used: eGFR – estimated glomerular filtration rate; KCCQ – Kansas City Cardiomyopathy Questionnaire.

Table 1 – Notable results from EMPEROR-Preserved & post-hoc analyses				
Outcome	Empagliflozin N = 2997	Placebo N = 2991	Hazard Ratio (95% CI)	P
Primary composite endpoint	13.8%	17.1%	0.79 (0.69 – 0.90)	<0.001
First HF hospitalisation	8.6%	11.8%	0.71 (0.60 – 0.83)	<0.001
Total HF hospitalisations	407	541	0.73 (0.61 – 0.88)	<0.001
First increase in oral diuretic dose	16.1%	20.4%	0.76 (0.67 - 0.86)	<0.001
Total increases in oral diuretic dose	838	626	0.73 (0.65 - 0.82)	<0.001
First all-cause hospitalisation	42.4%	44.8%	0.92 (0.85 – 0.99)	0.03
Total all-cause hospitalisations	2566	2769	0.93 (.85 – 1.01)	NS
Composite renal outcome	3.6%	3.7%	0.95 (0.73 – 1.24)	NS
Incident diabetes	12.0%	14.0%	0.84 (0.65 – 1.07)	NS
CV mortality	7.3%	8.2%	0.91 (0.76 – 1.09)	NS
All-cause mortality	14.1%	14.3%	1.00 (0.87 – 1.15)	NS
Data derived from references 2 and 10. N – number, CI – confidence interval, HF – heart failure; CV - cardiovascular				

Empagliflozin had no effect on the composite renal outcome or incidence of diabetes. Although the rate of decline of eGFR was slower with empagliflozin compared to placebo, this was offset by an early initial drop in eGFR in the empagliflozin arm soon after randomisation: ultimately, at the end of the trial, the adjusted mean change in eGFR from baseline was -8 ml/min/1.73m² in both groups (2).

Effect on Symptoms and Quality of Life

Although more than 4 in 5 patients had only NYHA class II symptoms (2), those taking empagliflozin had greater likelihood of reducing NYHA class (11). Approximately half of patients in both arms experienced a >5 point improvement in the KCCQ score; a slightly greater proportion in the empagliflozin arm compared to placebo (51.6% vs. 46.5%; P<0.05) (13). This is, perhaps, to view the results through rose-tinted spectacles: there was no effect on the overall mean KCCQ summary score or KCCQ score in the physical domain (2,13). Consistent with this finding are the results of the EMPERIAL-Preserved trial of empagliflozin vs. placebo in patients with HeFNEF which found no difference in 6-minute walk test distance or KCCQ score after 12 weeks of treatment with empagliflozin compared to placebo (14).

Interpretation

The goal of a heart failure treatment is to reduce HF-related events such as cardiovascular death,

hospitalisation with HF and worsening symptoms. EMPEROR-Preserved was only partially successful in this respect. The online supplementary data show the Kaplan-Meier curves for all cause and cardiovascular mortality: both showing no effect of empagliflozin (2). Heart failure as a cause of death affected less than 2% of all patients, and accounted for only around 11% of all deaths. Death from cancer was equally likely, even though patients with active malignancy were excluded. The number of non-HF hospitalisations was over 4 times greater than the number of HF hospitalisations and there was no effect on overall hospitalisations.

One of the most important findings of EMPEROR-preserved is thus that the greatest risk patients with HeFNEF face may not be HF-related events. Only half of readmissions in the 5 years after discharge for patients admitted with HeFNEF are due to heart failure (15), and non-cardiovascular death is more common than cardiovascular death, and far more common than death due to heart failure (16). In the last year of life of patients with HeFNEF, admissions for non-cardiovascular causes far outweigh those for cardiovascular causes (17,18).

EMPEROR-preserved showed that treatment with empagliflozin reduced the risk of an uncommon event (HF hospitalisation) in patients with HeFNEF, but had no overall effect on all-cause morbidity or mortality: empagliflozin changed the reason for hospitalisation rather than reducing the overall hospitalisation rate.

The possible quality of life and symptom benefits of empagliflozin in the EMPEROR-Preserved trial are difficult to interpret: empagliflozin was associated with an increased likelihood of improving NYHA class (2). Over 4 in 5 patients in the empagliflozin group had NYHA class II symptoms (2), thus, in the majority, empagliflozin was associated with patients transitioning from being mildly symptomatic to being asymptomatic. However, empagliflozin had no effect on the physical limitation domain of the KCCQ (13), and no overall effect on KCCQ score (2). These two findings appear conflicting; any effect on quality of life is very modest.

The applicability of EMPEROR-Preserved to clinical practice in the UK is limited. Establishing an unequivocal diagnosis of HeFNEF is difficult in practice as there is a huge overlap with other conditions. There are two proposed diagnostic algorithms for HeNEF HFA-PEFF and H2FPEF (19,20), but neither has consistent diagnostic accuracy when applied to populations of patients with HeFNEF (21,22,23,24). Patients with HeFNEF represent a heterogeneous group of patients with multiple co-morbidities such as AF, hypertension, chronic kidney disease, COPD, obesity, deconditioning, frailty and diabetes. Such complexity cannot be captured in a simple diagnostic calculator. That there is debate over the name of the condition – HF with a normal vs. persevered ejection fraction – is indicative of how poorly these complexities are understood.

NT-proBNP rises with age and comorbidities posing further problems in establishing a diagnosis of HeFNEF: NT-proBNP greater than 300 ng/L (entry criteria for patients in sinus rhythm) is

extremely common in the over-80s, assuming that the age of the participants in EMPEROR-Preserved was normally distributed at least one in six would be aged over 80. For patients in AF, the NT-proBNP entry threshold was 900 ng/L however values of >900 ng/L are almost universal in patients with AF (25,26).

SGLT2Is have an undoubted diuretic effect (27), and trial data show that treatment of the comorbidities associated with HeFNEF with diuretic agents reduces the risk of HF hospitalisation (figure 3) (28,29,30,31). The EMPEROR-Preserved investigators do not report the use of loop or thiazide diuretics in the treatment arms – this is an important confounding factor that needs to be clarified.

Conclusion

In many ways the results of the EMPEROR-Preserved trial are unsurprising - a diuretic agent reduces the risk of worsening fluid retention. However, hospitalisation for fluid retention is an uncommon event even in patients meeting the trial definition of HeFNEF. SGLT2Is are commonly used for patients with diabetes, and may soon be recommended for other co-morbidities common in patients with HeFNEF, such as CKD. Thus many patients with a label of HeFNEF may end up receiving SGLT2Is for a reason other than HF in the years to come. Regarding the use of empagliflozin specifically for the treatment of HeFNEF, amongst the clamour, the data are far from conclusive.

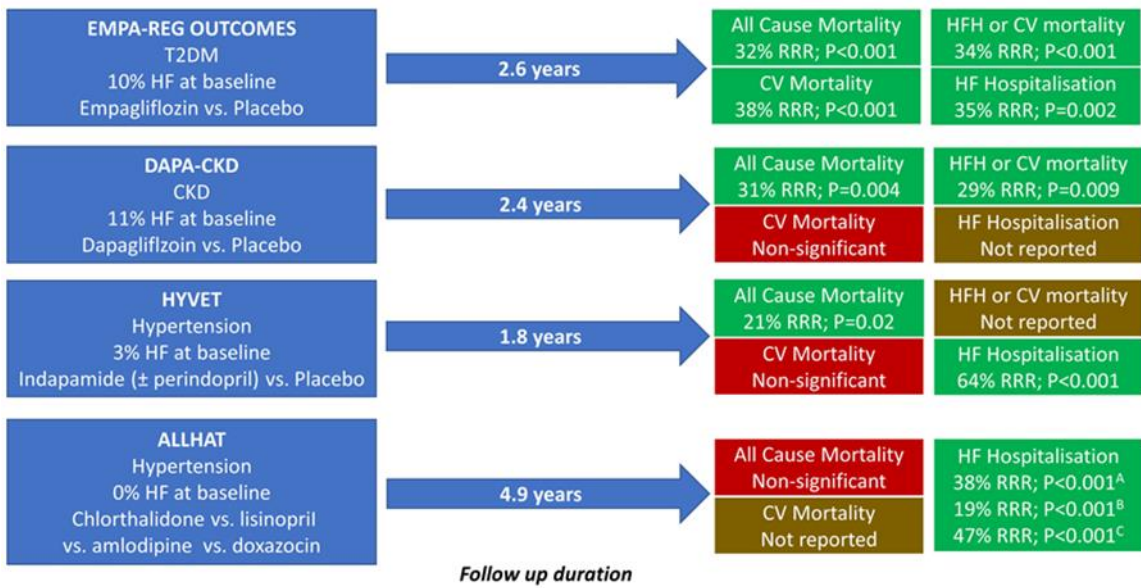


Figure 3. Clinical outcomes in trials of diuretic agents in patients with T2DM, CKD, or hypertension derived from references 28-31. A – chlorthalidone vs. amlodipine; B – chlorthalidone vs. lisinopril; C – chlorthalidone vs. doxazocin. T2DM – type 2 diabetes mellitus; HF – heart failure; RRR – relative risk reduction; CV – cardiovascular mortality; HFH – heart failure hospitalisation; CKD – chronic kidney disease; ACEI – angiotensin converting enzyme inhibitor

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