# Research in brief: Empagliflozin for patients with heart failure and preserved ejection fraction

**Authors:** Rajan S Pooni[A] and Tevfik F Ismail[B]

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## Background

Summary of 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.[1]

Heart failure with preserved ejection fraction (HFpEF) is a term used to describe patients with clinical 'symptoms and signs of heart failure with [a left ventricular ejection fraction (LVEF)] ≥50%' and is thought to encompass about 50% of all heart failure patients.[2] In common with heart failure with reduced ejection fraction (HFrEF), it is associated with significant morbidity and mortality, but in contrast, no treatment has been shown to improve prognosis for HFpEF.[2,3]

Recent randomised controlled trials have provided an evidence base for sodium-dependent glucose cotransporter-2 (SLGT2) inhibitors as prognostic medications for patients in HFrEF. Previously thought to reduce heart failure-related hospitalisation and adverse renal events in patients solely with type 2 diabetes, further trials have shown SGLT2 inhibitors to improve outcomes in heart failure regardless of diabetes status.[4–6] The mechanism by which SGLT2 inhibitors provide cardiorenal benefit remains unclear. The anti-hyperglycaemic actions of SGLT2 inhibitors cannot fully explain their mechanism given that other anti-diabetic medications have greater hypoglycaemic effects without an impact on heart failure prognosis. Proposed mechanisms of actions include reduction in sodium and water retention in the proximal renal tubule leading to improving renal function, which in turn may reduce afferent sympathetic supply to the heart and reduce cardiac inflammation.[7]

While the benefits of SGLT2 inhibitors in HFrEF are now established and in nascent treatment guidelines, their role in managing patients with HFpEF is unclear.[2] In this summary, we review a recent multicentre randomised controlled trial (EMPEROR-Preserved) that evaluated the benefits of the SGLT2 inhibitor empagliflozin in patients with apparent HFpEF.

**Authors:** [A]internal medicine trainee, St Bartholomew's Hospital, London, UK; [B]clinical senior lecturer, King's College London, London, UK and consultant cardiologist, Guy's and St Thomas' NHS Foundation Trust, London, UK

## Study review

After screening 11,500 patients across 622 centres, a total of 5,988 patients underwent randomisation, with 2,997 patients assigned to the intervention group (empagliflozin 10 mg daily) and 2,991 to the placebo group. Key inclusion criteria included patients with a New York Heart Association (NYHA) class of II–IV, a preserved (or mildly reduced) ejection fraction (ie, EF >40%) and an N-terminal – pro hormone B-type natriuretic peptide (NT-proBNP) level of >300 pg/mL (without atrial fibrillation (AF)) or >900 pg/mL (with AF). Patients with acutely decompensated heart failure, recent myocardial infarction or significant renal impairment were excluded. Baseline characteristics, including the number of patients with diabetes (~49% of patients enrolled), were similar across both groups.

The primary endpoint was a composite of cardiovascular death or heart failure-related hospitalisation. The median duration of follow-up across both groups was 26.2 months. The primary endpoint was observed in 13.8% in the intervention group compared with 17.1% in the placebo group (intention-to-treat analysis).

A secondary outcome evaluating the decline in estimated glomerular filtration rate (eGFR) was also noted to be slower in the intervention group compared with the placebo group (-1.25 mL/min/1.73m$^2$ per year versus -2.62 mL/min/1.73m$^2$ per year). Such results are similar to findings in previous studies involving patients with HFrEF (LVEF <40%), albeit the observed renal benefits were significantly lower in this study. With uncertainty existing for the relationship between change in the eGFR slope and major adverse renal outcomes, the authors performed a prospective pooled analysis of patients with LVEF <40% and LVEF ≥40%, concluding that ejection fraction influences the effects of empagliflozin on major renal outcomes.[8,9] Specifically, while the decline in eGFR was noted to be slower in both groups, this only correlated with lower serious renal outcomes (ie, profound and sustained decreases in eGFR or renal replacement therapy) in the LVEF <40% population. As such, using eGFR slope analysis may have limitations as a surrogate for drug-induced renal outcomes. With a recent meta-analysis suggesting that eGFR slope is a strong predictor of long-term renal outcome in early chronic kidney disease (CKD), further study is needed in this area.[10]

While touted as an HFpEF trial, it is interesting that this trial enrolled patients with both mildly reduced ejection fraction (EF 40%–50%) and preserved ejection fraction (>50%). This is relevant as it is likely that patients with mildly reduced ejection fraction behave more like patients with HFrEF than true HFpEF.[11] The use of a LVEF of 40% as a dividing line is artificial and reflects the ability of LVEF values below this value to identify patients in historical observational studies at increased risk of mortality with heart failure post-myocardial infarction.[12] This, in turn, was used to identify cohorts of patients with asymptomatic left ventricular dysfunction with high event rates most likely to accrue benefit from an angiotensin-converting enzyme inhibitor in the original clinical trials for these agents, motivated by the need to keep sample sizes and trial costs feasible.[13] Subsequent heart failure trials have used this cut-off or similar values for the past 30 years, creating the 'condition' HFrEF.

Pre-specified exploratory subgroup analysis showed that patients with EF ≥60% at baseline derived no statistically significant benefit (hazard ratio (HR) 0.87; but with 95% confidence interval (CI) 0.69–1.10) with respect to the primary outcome. Similarly, the benefit was of borderline significance in the 50%–60% range (HR 0.80; 95% CI 0.64–0.99). This is of relevance given likely differences in EF reference ranges for men and women and the imprecision with which LVEF is measured when evaluated by echocardiography.

Despite a statistically significant primary outcome, on further evaluation, cardiovascular mortality was not significantly lower in the empagliflozin group. Furthermore, a similar finding was observed in the trial involving empagliflozin in patients with HFrEF (EMPEROR-Reduced). Statistically significant benefit appeared to be driven by reduced heart failure-related hospitalisation rather than mortality.

## Key points

- As for patients with HFrEF, SGLT2 inhibitors appear to improve some cardiorenal outcomes in heart failure patients with LVEF ≥40%.
- However, there was no difference in cardiovascular mortality between the treatment and placebo arms. Differences in outcomes appeared to be driven by reductions in hospitalisation for heart failure. The number of patients needed to treat (NNT) with empagliflozin to prevent one adverse cardiovascular outcome was ~31 (absolute risk reduction 3.3%).
- Whether benefits accrue equally to patients with true HFpEF (defined as LVEF ≥50%) or those with mildly reduced EF (40%–50%) remains unclear. Specific further prospective evaluation of patients with higher ejection fractions (ie, true HFpEF), as opposed to mildly reduced ejection fractions, is needed.
- The decline in eGFR was slower in the treatment arm, however, it is unclear whether this is a relevant surrogate renal outcome. ■

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