New Trial Evidence on Heart Failure: Highlights from the European Society of Cardiology Congress 2021

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Long-awaited results from several heart failure (HF) trials were presented at the European Society of Cardiology (ESC) Congress 2021.

EMPEROR-Preserved Trial and EMPEROR-Pooled Analysis

For the first time, the EMPEROR-Preserved trial proved the efficacy of a pharmacological product in patients with HF with preserved ejection fraction (HFpEF).[1] In this study, 5,988 patients with symptomatic HF, ejection fraction (EF) >40% and high levels of natriuretic peptides were randomised to the sodium–glucose cotransporter-2 inhibitor (SGLT2i) empagliflozin (10 mg once daily) or a placebo.

Compared with placebo, empagliflozin was able to significantly reduce the primary outcome – a composite of hospitalisation for HF (HHF) and cardiovascular death – by 21% over a median follow-up of 26.2 months.[1] It was the reduction in HHF that drove this result, with the risk of cardiovascular death alone not significantly lower.

The effect of empagliflozin on the primary outcome was consistent across several pre-specified subgroups and regardless of the presence of diabetes. The rate of decline in estimated glomerular filtration rate (eGFR) was slower in patients who received empagliflozin than in those given the placebo.

Since the benefit of empagliflozin in patients with HF with reduced EF (HFrEF) had previously been showed in the EMPEROR-Reduced trial, a pooled analysis of the two EMPEROR trials was performed to investigate the whole EF spectrum.[2] A total of 9,718 patients (of whom 4,860 received empagliflozin and 4,858 received a placebo) were divided into six groups according to EF: <25%, 25–34%, 35–44%, 45–54%, 55–64% and ≥65%.[3] The magnitude of the effect of empagliflozin on HHF and cardiovascular death was similar in the groups with EF <25% up to EF <55–64%, with a relative risk reduction in a range of 25–35% compared with placebo; however, it was attenuated in patients with an EF ≥65% (HR 1.05; 95% CI [0.70–1.58]).[3]

This pattern of effects was consistent in both sexes and was also observed for other HF outcomes, including time to first HHF, total (first and recurrent) HHF and change in Kansas City Cardiomyopathy Questionnaire clinical summary score at 52 weeks.[3]

Major renal events, including a sustained decrease in eGFR by ≥40% or to <10–15 ml/min/1.73 m^2, dialysis initiation or renal transplantation were investigated in EMPEROR-Pooled.[4] Significant heterogeneity was found between the two trials, with a HR for renal events of 0.51 (95% CI [0.33–0.79]) in EMPEROR-Reduced and 0.95 (95% CI [0.73–1.24]) in EMPEROR-Preserved (p=0.016).

Therefore, the effect of empagliflozin on major renal outcomes might be affected by EF in patients with HF, with virtually no benefit in HFpEF. This finding also challenges whether eGFR slope analysis, used in EMPEROR-Preserved to show the effect of empagliflozin, is an appropriate surrogate marker for renal outcomes in HF.

Effect of Dapagliflozin on Ventricular Arrhythmias, Resuscitated Cardiac Arrest or Sudden Death

This post-hoc analysis of the DAPA-HF trial investigated the hypothesis that dapagliflozin is able to reduce the risk of ventricular arrhythmias, resuscitated cardiac arrest and sudden death, which are major causes of death in HFrEF.[5]

In particular, in DAPA-HF, there were 115 ventricular arrhythmias, eight resuscitated cardiac arrests and 206 sudden deaths, the last accounting for 41% of all cardiovascular deaths in DAPA-HF. The risk of the primary outcome was lower in the dapagliflozin group than in the control group (HR 0.79; 95% CI [0.63-0.99]); independent predictors included natriuretic peptides concentration, previous ventricular arrhythmias, EF, previous MI, BMI, systolic blood pressure, male sex and serum sodium levels.

The Kaplan-Meier curves for the primary outcome diverged after approximately 9 months, suggesting a benefit of dapagliflozin through

cardiac remodelling. This finding was consistent across the subgroups, except for the subgroup characterised by levels of natriuretic peptides above the median value, who showed no benefit from dapagliflozin.

The results were consistent regardless of the presence of an ICD although, plausibly, dapagliflozin is less likely to reduce the risk of events in patients who already have a device.[5]

GUIDE-HF Trial

GUIDE-HF tested the hypothesis that haemodynamic-guided treatment in HF could reduce HF hospitalisations.[6] One thousand patients with symptomatic HF and either a recent HF hospitalisation or elevated natriuretic peptides were implanted with a pulmonary artery pressure monitoring system, and randomly assigned to either haemodynamic-guided HF management or standard care.[6]

There was no difference between the two groups in the primary outcome, which was a composite of all-cause death, HF hospitalisations and urgent HF hospital visits. However, a prespecified COVID-19 sensitivity analysis suggested the COVID-19 pandemic had a significant impact, warranting a separate analysis of pre-pandemic data only. In this subset, patients who were treated according to haemodynamic data had a significantly lower risk of the primary endpoint than those receiving standard care (HR 0.81; 95% [CI 0.66–1.00]; p=0.0049). ❑

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