The EMPEROR-Preserved Trial: *SGLT2-Inhibitor Success in HFPEF!*

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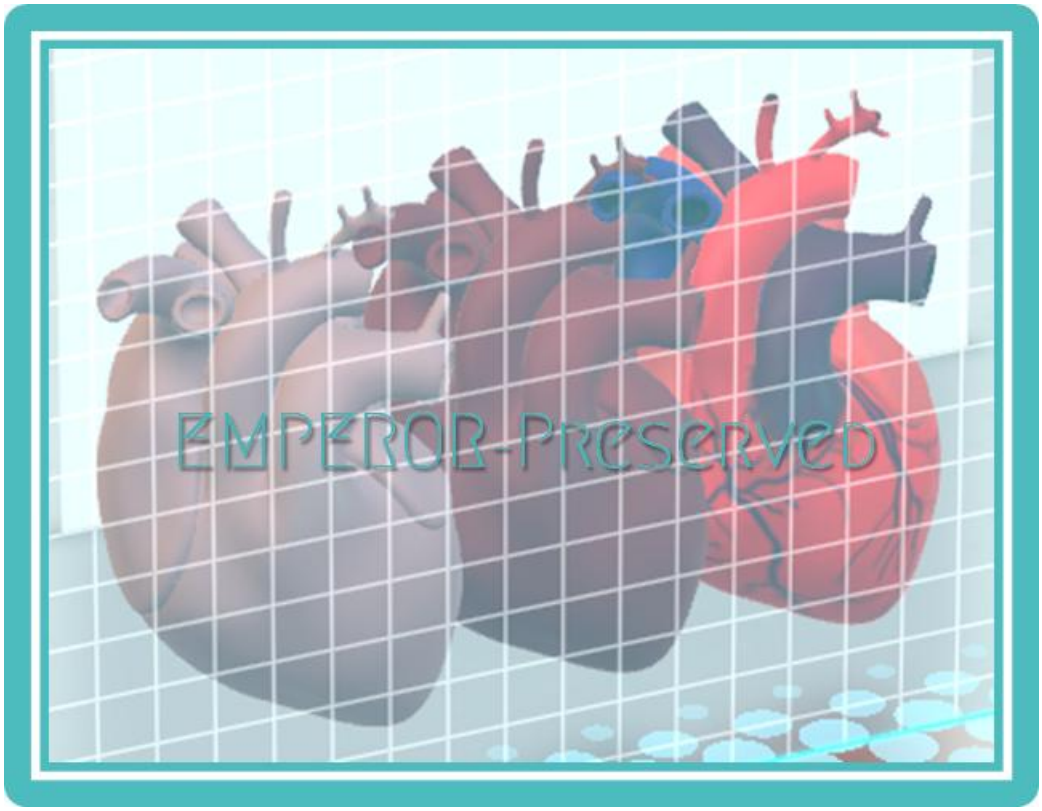

Abstract

Therapeutic options for patients with congestive heart failure (CHF) and preserved left ventricular ejection fraction (LVEF) remain limited [1]. Although equivocal benefits have been reported with mineralocorticoid-receptor antagonists [2] and neprilysin inhibitors [3], the benefits are modest and only subgroups of patients have shown benefits. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce the development and progression of heart failure in those patients with reduced LVEF (HFREF) and diabetes [4]. However, the effects in patients with heart failure and preserved LVEF (HFPEF) have not been well documented.

The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) was carried out to evaluate the effects of SGLT2 inhibition with empagliflozin on major heart failure outcomes in patients with symptomatic heart failure and a preserved ejection fraction [5].

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Study Details

Rationale & Design as previously published [6]:

- Screening period: 4 – 28 days.
- Structure: Phase III,randomized, double blind.
- Treatment Model: Parallel 1:1 assignment.
- Intervention: Empagliflozin 10 mg/d vs placebo.
- Subjects: 11,583 screened; 5,988 randomized.
- Location: 622 centers; 23 countries.
- Started 03/02/2017; completed 04/26/2021

Inclusion criteria:

1. Males or Females ≥ 18yrs at screening.
2. Chronic CHF, NYHA II – IV; LVEF >40% & NT-proBNP >300 pg/ml (>900 pg/ml in patients with atrial fibrillation).
3. Structural heart disease within 6 months or documented hospitalization for CHF within 12 months of visit 1.
4. Stable dose of oral diuretic.

Exclusion criteria:

1. MI, CABG or other major CV surgery, stroke/TIA in past 90 days prior to visit 1.
2. Heart transplant or transplant listing.
3. Acute decompensated CHF.
4. Systolic BP ≥ 180 mmHg at visit 2.
5. Symptomatic hypotension/SBP < 100 mmHg.
6. Liver disease.
7. GFR < 20 ml/min/1.73 m2.
8. Ketoacidosis history.
9. Current/prior SGLT-2/SGLT-1/2 inhibitor use.
10. Current enrollment in another clinical trial.
11. Allergy/hypersensitivity to SGLT-2 inhibitors
12. Pregnancy/nursing or planned during trial.

Results

Primary outcomes:

A composite of adjudicated cardiovascular death or CHF hospitalization, analyzed as time to first event:

- 415 (13.8%) in empagliflozin vs 511 (17.1%) in placebo (P < 0.001). Number needed to treat: 31.
- CHF hospitalization: 259 (8.6%) in empagliflozin vs 352 (11.8%) in placebo.
- Death from CV causes: 219 (7.3%) in empagliflozin vs 244 (8.2%) in placebo.

Secondary outcomes:

- First secondary outcome: Occurrence of all adjudicated CHF hospitalizations, including first and recurrent events.
  - CHF hospitalizations # was lower with empagliflozin than placebo (hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P < 0.001).
- Second secondary outcome was eGFR decline during double-blind treatment.
  - eGFR decline was slower in empagliflozin than in placebo group (- 1.25 vs. - 2.62 ml/min/ 1.73 m2 per year; P < 0.001).

Safety

- Serious adverse events: 1436 patients (47.9%) in the empagliflozin group and 1543 patients (51.6%) in the placebo group.
- Adverse events leading to discontinuation of treatment: 571 patients (19.1%) in the empagliflozin group and 551 patients (18.4%) in the placebo group.
- Uncomplicated genital and urinary tract infections and hypotension were more common in patients treated with empagliflozin compared to patients treated with placebo.

Discussion

The EMPEROR-Preserved trial demonstrated a significant benefit of empagliflozin on cardiovascular death or hospitalization in symptomatic CHF patients with HFPEF. The reported benefit remained consistent across subgroups of ejection fractions, regardless of the presence or absence of diabetes. The benefit seems to be largely driven by a 29% reduction in hospitalization for CHF, as the effect on cardiovascular or all cause mortality was not statistically significant. The authors acknowledge a high rate of discontinuation rate (23%) likely causing the neutral effect on death from any cause. Cardiovascular deaths were not significantly reduced by empagliflozin even in the EMPEROR-Reduced trial [7], in the setting of HFREF. However, the DAPA-HF trial [8] demonstrated lower cardiovascular deaths using dapagliflozin in patients with HFREF. Whether there is heterogeneity in the cardiovascular effects of SGLT2 inhibitors with regards to mortality remains to be seen, pending the results of the DELIVER trial [9] which will examine the effect of dapagliflozin in the setting of HFPEF.

Clinical Implications

Evidence for a favorable cardiovascular effect of the SGLT2 inhibitors has been mounting for many years, and their role in the treatment of HFREF has been well established and incorporated in the 2021 Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment [10]. Excitement about their role in CHF treatment is visible from their description as “A Momentous Victory in the War against Heart Failure” [11] and “the statins of the 21st century” [12] by Braunwald and colleagues.

Excitement about their role in HFPEF, where there remains little convincingly effective therapy, is early given the results of the EMPEROR-Preserved trial, and further trials in the pipeline. Such enthusiasm, however, may be hampered by their current cost [13], limiting their widespread use in eligible patients. Given their demonstrated cost-effectiveness in CHF treatment [14], public campaigns for cost containment may be worthwhile [15].

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KEYWORDS: Heart Failure; Preserved Ejection Fraction; SGLT2 Inhibitors

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