JAMA Cardiology | Original Investigation

Safety and Efficacy of Empagliflozin and Diuretic Use in Patients with Heart Failure and Preserved Ejection Fraction

A Post Hoc Analysis of the EMPEROR-Preserved Trial

JAMA Cardiol. 2023;8(7):640-649. doi:10.1001/jamacardio.2023.1090
Published online May 24, 2023.

Introduction

- EMPEROR-Preserved trial evaluated the efficacy of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, for the treatment of HFpEF.
- significantly reduce the risk of first hospitalization for heart failure (HHF) or cardiovascular (CV) death, slow the decline in estimated glomerular filtration rate (eGFR), and improve health-related quality of life (HRQoL)

- SGLT2 inhibitors prevent the absorption of sodium and glucose in the proximal renal tubule, resulting in natriuresis, glucosuria, and increased urine output
- increased autophagy, reduced inflammation, improvement of energy metabolism, and prevention of adverse cardiac remodeling
- It has been suggested that SGLT2 inhibitors primarily act through a diuretic mechanism, Thus their benefit may be ***attenuated*** in patients already taking other diuretics
- risk of volume depletion events, acute kidney injury, and other adverse effects

Main Objective of the study

What are the safety and efficacy of empagliflozin in patients with heart failure and preserved ejection fraction (HFpEF) **with background diuretic use**?

Methods

- EMPEROR-Preserved was a double-blind, randomized, placebo-controlled, event-driven trial conducted from March 2017 to April 2021.
- chronic heart failure (HF), New York Heart Association (NYHA) class II to IV, with left ventricular ejection fraction greater than 40% an N-terminal prohormone B-type natriuretic peptide (NT-proBNP) level greater than 300 pg/mL (greater than 900 pg/mL for patients with atrial fibrillation) and HHF in the past 6 months or left atrial or left ventricular structural changes on echocardiography

- A total of 5988 patients were enrolled and randomized to receive either empagliflozin, 10 mg, or placebo.
- The median (IQR) follow-up time was 26.2 (18.1-33.1) months

Baseline Diuretic Use

- 5815 had data on baseline diuretic use and were included
- torsemide, 20 mg; bumetanide, 1 mg; azosemide, 60 mg; and ethacrynic acid, 100 mg, were considered equivalent to furosemide, 40 mg intravenously or 80 mg orally
- Baseline diuretics gropus:
- no diuretic use and furosemide-equivalent doses of less than 40mg, 40 mg, and greater than 40 mg
- nonloop diuretic agent: the group with less than 40 mg
- MRAs were not classified as diuretics for the current analysis

Outcomes

- the composite end point of first HHF or CV death
- total (first and recurrent) HHF
- first HHF
- CV death
- all-cause death
- rate of decline in eGFR
- composite kidney end point (chronic dialysis or kidney transplant or sustained reduction of 50% or greater in eGFR or sustained eGFR less than 15 mL/min/1.73 m2 or renal death).

outcomes

- Change in HRQoL was assessed using Kansas City Cardiomyopathy Questionnaire 23 (KCCQ-23): baseline, 12, 32, 52 weeks
- Changes in key physiologic outcomes, including glycated hemoglobin, hematocrit, NT-proBNP, weight, systolic blood pressure, and uric acid, were also studied

Adverse events

- adverse events leading to trial drug discontinuation (including fatal events), hyperkalemia, acute kidney failure, and volume depletion events
- Volume depletion: hypotension, orthostatic hypotension, hypovolemic shock, circulatory collapse, syncope, presyncope, dehydration, and hypovolemia

Statistical Analysis

- Categorical variables were summarized as frequencies and percentages and compared across categories with the $\chi 2$ test
- continuous variables were summarized as means and standard deviations and compared using the t-test
- To evaluate a trend across doses, an ordinal regression likelihood ratio test was used.
- Clinical outcomes and changes in diuretic therapy (initiation, increase in dose, de-escalation, and permanent discontinuation) were analyzed in a time-to-first–event fashion

- Time-to first-event outcomes were analyzed using a multivariable Cox regression model to obtain hazard ratios (HRs)
- Total HHF was analyzed using a joint frailty model together with cardiovascular death to obtain HRs and 95% CIs.
- models adjusted : left ventricular ejection fraction, age, and eGFR (as continuous covariates) as well as sex, diabetes status, and region
- Changes in KCCQ summary scores and physiologic outcomes were also analyzed using amixedmodel with repeatedmeasures. The analysismodel included age, eGFR, and left ventricular ejection fraction as linear covariates, and sex, region, diabetes, sex, interaction of visit by treatment by baseline dose of diuretics, and interaction of baseline value by visit as fixed effects

- Outcomes were studied in the placebo group alone to characterize the natural history of patients by baseline diuretic dose
- the treatment effect of empagliflozin (vs placebo) by baseline diuretic therapy was assessed for each outcome
- HRs and mean differences across subgroups were compared by adding subgroup-by-treatment interaction terms to the models

Results

- Of 5815 patients (mean [SD] age, 71.9 [9.4] years; 2594 [44.6%] female
- 1179 (20.3%) were not taking diuretics, 1725 (29.7%) were taking less than 40 mg, 1772 (30.5%) were taking 40 mg, and 1139 (19.6%) were taking greater than 40 mg furosemide-equivalent doses
- Patients taking diuretics were more likely to be older and female; a higher BMI, heart rate, higher NYHA class, and NT-proBNP level; had a lower KCCQ clinical summary score, had a greater frequency of recent HHF; and had a higher burden of comorbidities, including atrial fibrillation, hypertension, chronic kidney disease, and diabetes

Outcomes and Adverse Events in the Placebo Arm

- the diuretic group had a higher risk of HHF or CV death (HR, 1.81; 95% CI, 1.38-2.39; P < .001), total HHF (HR, 3.21; 2.15-4.80; P < .001), first HHF (HR, 2.75; 95% CI, 1.85- 4.07;P < .001), and all-cause mortality (HR, 1.40; 95% CI, 1.06- 1.85; P = .02).
- neither baseline diuretic use status nor dose was associated with the risk of the composite kidney end point, or eGRF slope
- Patients taking higher doses of diuretics in the placebo arm experienced greater **increases** in NT-proBNP and greater **reductions** in body weight at 52 weeks

- diuretic use was associated with a lesser improvement in KCCQ clinical summary score at all time points (12, 32, and 52 weeks). When analyzed by dose, a stepwise **decrease** in the **magnitude of KCCQ clinical summary score improvement** was seen with increasing diuretic dose
- Patients in the placebo arm who were receiving a diuretic had a numerically higher risk of adverse events leading to placebo discontinuation (10.5 vs 7.9 events per 100 patientyears), volume depletion events (5.6 vs 4.1 events per 100 patient-years), and acute kidney failure (7.9 vs 4.9 events per 100 patient-years).

Empagliflozin

- Baseline diuretic status was not associated with changes in the benefit of empagliflozin for the primary end point,), total HHF, or first HHF
- No treatment by diuretic status interaction was noted for CV death or all-cause death end points
- Compared with placebo, empagliflozin was associated with a slower rate of decline in the eGFR, regardless of baseline diuretic use or dose
- Empagliflozin was also associated with improved KCCQ clinical summary scores similarly in both the diuretic and nondiuretic groups

- Compared with placebo, empagliflozin was associated with decreased NT-proBNP levels similarly in the diuretic and nondiuretic groups
- Empagliflozin was associated with reduced weight and hemoglobin A1c
- patients taking **higher doses of diuretics** were significantly **less likely** to experience weight loss or a decrease in hemoglobin A1c at week 52.
- Empagliflozin was associated with increased hematocrit and decreased systolic blood pressure and uric acid, with no effect modification by diuretic status or dose.

- a higher incidence of volume depletion events in the diuretic group, but not the nondiuretic group
- Volume depletion: the most commonly reported was hypotension, followed by syncope and dehydration
- the treatment arms did not differ in the frequency of acute kidney failure, hyperkalemia, or adverse events leading to trial drug discontinuation (including fatal events).

Changes in diuretic therapy

- empagliflozin was associated with a lesser likelihood of diuretic initiation (HR, 0.73; 95% CI, 0.59-0.90; P = .004) compared to placebo
- empagliflozin use was associated with a significantly greater probability of diuretic discontinuation (HR, 1.43; 95% CI, 1.15-1.78; P = .002), and de-escalation (HR, 1.15; 95% CI, 1.02-1.30; P = .02) and a decreased likelihood of diuretic dose escalation (HR, 0.74; 95% CI, 0.65-0.84; P < .001)
- Likelihood of diuretic discontinuation, de-escalation, and escalation did not vary by baseline diuretic dose

Discussion

- Patients who were not treated with diuretics at baseline had themost favorable clinical profile and better outcomes. Higher baseline doses of diuretics were associated with more severe HF, poorer HRQoL, greater burden of comorbidities, and a higher risk of adverse outcomes
- r, the benefit of empagliflozin on the primary outcome (first HHF or CV death), first HHF, total HHF, eGFR slope, and HRQoL was consistent regardless of baseline diuretic status or dose
- This is in line with findings from HFrEF patients in the DAPA-HF trial,where baseline diuretic therapy did not modify the benefit of dapagliflozin on these outcomes

- activate a transcriptional paradigm that mimics oxygen and nutrient deprivation, which in turn upregulates autophagy of damaged organelles
- decreased inflammasome activation, which lessens cardiomyocyte dysfunction and coronary microvascular injury
- o improve cardiac energy metabolism, specifically by enhancing oxidation of long-chain fatty acids
- SGLT2 inhibitors also reduce the mass and proinflammatory state of epicardial adipose tissue

- inhibit sodium and glucose reabsorption in the proximal renal tubule and thus promote both natriuretic and osmotic diuresis
- the diuretic effects are short lived and, even if durable, it is not clear whether these effects contribute in any way to the heart failure benefits seen with these drugs
- The finding that statistical significance was achieved in the EMPEROR-Preserved trial as early as 18 days following randomization
- between-group differences in the use of diuretics in EMPEROR-Preserved began to emerge 60 to 90 days following randomization, a time course that is inconsistent with an immediate natriuretic effect of SGLT2 inhibitors

- a reduced requirement for diuretics has been noted with other disease-modifying HF drugs, including drugs that have no diuretic effects (sacubitril/valsartan)
- At the time an SGLT2 inhibitor is initiated, most patients with HFpEF would not require a change in diuretic dose
- In the longer term, as HF status improves in patients taking empagliflozin, the need for diuretics may be reduced.

- Limitation: Markers of diuresis and natriuresis, such as urine volumes and urinary sodium excretion, were not assessed.

Conclusions

- In this analysis, empagliflozin use was associated with improvement in HHF or CV death, first HHF, total HHF, eGFR slope, and KCCQ scores in patients with HFpEF, regardless of background diuretics use or dose. Empagliflozin was associated with a slightly increased risk of volume depletion in patients taking diuretics. Empagliflozin also reduced the likelihood of diuretic initiation and dose escalation and increased the likelihood of diuretic de-escalation and permanent discontinuation.