https://doi.org/10.37901/jcphp22-00003

Evidence-Based Appraisal of the EMPEROR-Preserved Trial

Jungyeon Moon, PharmD, BScPhm, MScPhm, PhD; Cynthia Jackevicius, BScPhm, PharmD, MSc, BCPS, BCCP, FCSHP, FAHA, FCCP, FCCS, FACC

Citation: S.D. Anker, J. Butler, G. Filippatos, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021; 385:1451-1461. doi: 10.1056/NEJMoa2107038.

Patient Population:

Patients ≥18 years old with New York Heart Association (NYHA) class II-IV heart failure (HF) and left ventricular ejection fraction (LVEF) ≥40%, elevated N-terminal (NT)-pro hormone BNP (NT-proBNP) ≥300pg/m without atrial fibrillation (≥900pg/mL with atrial fibrillation), and chronic HF diagnosed ≥3 months before visit 1 and at least one of: hospitalization for heart failure or structural heart disease characterized by left atrial enlargement and/or left ventricular hypertrophy and body mass index (BMI) <45 kg/m^2. Those with myocardial infarction, coronary artery bypass graft surgery (CABG) or other major cardiovascular surgery, stroke or transient ischemic attack (TIA) in prior 90 days, heart transplant recipient, any severe valvular heart disease, atrial fibrillation or atrial flutter with resting heart rate >110 at screening, systolic blood pressure (SBP) ≥180 or <100 mmHg or symptomatic hypotension, estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2, history of ketoacidosis or acute or chronic liver disease were excluded.

Intervention (n=2997): Empagliflozin 10mg PO daily

Comparison (n=2991): Matching placebo PO daily

Outcomes: The primary outcome was a composite of the time to first event of cardiovascular death or hospitalization for heart failure with preserved ejection fraction (HFpEF). The main secondary outcome included a composite of total adjusted hospitalization for heart failure or slope of eGFR. Selected safety outcomes included: hypotension, acute renal failure, diabetic ketoacidosis (DKA) and genital infections. The median follow-up for the primary outcome was 26.2 months.

Trial Validity	Risk of Bias
Start of Trial	
Randomization/Concealment	
• Patients were randomized to empagliflozin and placebo in a 1:1 ratio, stratified by geographical region, status of diabetes mellitus (DM) (DM, pre-DM, no DM), LVEF (<50%, ≥50%) and eGFR (Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI) (<60 mL/min/1.73 m^2, ≥ 60 mL/min/1.73 m^2) at the screening visit. Concealment was achieved through use of an interactive voice/web-based response system (see Study Appendix).	Low
Baseline Characteristics	
• There was no clinically meaningful difference in the baseline characteristics of the patients in control and treatment groups. The use of concurrent cardiovascular medications was evaluated in both groups and was also well balanced (see Study Appendix).	Low
During Trial	
Blinding	
• Patients, clinicians, outcome assessors, data collectors and data analysts were all blinded. Per protocol, investigators and everyone involved in trial conduct or analysis in this double-blind trial remained blinded with regard to the randomized treatment assignments until after database lock (see Study Appendix).	Low

Trial Validity	Risk of Bias
During Trial	
Equal Treatment	
• Clinicians were encouraged to treat patients to the best standard of care in compliance with the local guidelines and recommendations for HF and diabetes if patient has it. Per study protocol, standard medical care (prophylactic, diagnostic and therapeutic procedures) remained the responsibility of the treating physician. Cardiovascular medications at baseline were similar in both groups but there is no information on whether crossover occurred or whether patients started or stopped other cardiovascular medications completely. Subsequent treatments for each group after baseline were not reported. In terms of cointervention, patients in either group may have added/decreased/discontinued cardiovascular medications that could impact the trial outcomes, such as spironolactone. In terms of contamination, patients in the placebo group may have been prescribed empagliflozin outside of the study, which may introduce contamination and create a smaller difference between groups (see Study Appendix). • It is possible that there is cointervention or contamination given lack of reporting of related information, but the direction of the bias is unknown.	Possible/ Unclear
End of Trial	
Completeness of Outcome Data	
• Of the 2,997 patients in the empagliflozin group, 84 patients (2.8%) had incomplete follow-up for the primary end point. Of the 2,991 patients in the placebo group, 88 patients (2.9%) had incomplete follow-up for the primary end point. Incomplete follow-up refers to incomplete information on either vital status or hospitalization until the end of the trial (consent withdrawn, site closure, limited follow-up but agreed to collection of vital status data and lost to follow-up). In terms of handling of missing data, the authors state they used different imputation methods for each type of data; multiple imputation for continuous variable endpoints, and censoring for time-to-event analyses (See Study Appendix). • The absolute risk reduction of 3.3% for the primary outcome is close to the percentage of patients with incomplete follow-up from both groups (2.8% for empagliflozin and 2.9% for placebo), which makes it difficult to be certain that the difference in outcomes between groups is a true difference.	Possible/ Unclear
Method of Outcome Analysis	
• The authors state that both primary and secondary outcomes analysis followed the intention-to treat (ITT) basis assigning patients to the original treatment groups. • Of note, 2 patients in the placebo group and 1 patient in the empagliflozin group did not start treatment, and they were excluded from the safety analyses. Therefore, the denominators in the safety outcome analyses are different from those for the efficacy outcome.	Low

Trial Results

Efficacy Outcome	Empagliflozin 10mg N=2,997	Placebo N=2,991	Hazard Ratio(HR) and 95% confidence interval (CI)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT)	p-value
Primary endpoint: Hospitalization for HF or cardiovascular death	415 (13.8%)	511 (17.1%)	HR 0.79 (95% CI 0.69 – 0.90)	19.3%	3.3%	31	< 0.001
• Primary endpoint: hospitalization for HF	259 (8.6%)	352 (11.8%)	HR 0.71 (95% CI 0.60-0.83)	27.1%	3.2%	32	Not reported
• Primary endpoint: cardiovascular death	219 (7.3%)	244 (8.2%)	HR 0.91 (95% CI 0.76-1.09)	11.0%	0.9%	N/A	Not reported
Secondary endpoint: Total number of hospitalizations for HF	407	541	HR 0.73 (95% CI 0.61-0.88)	N/A	134	N/A	Not reported
eGFR mean slope change per year	-1.25±0.11	-2.62±0.11	Difference 1.36 (95% CI 1.06 – 1.66)	N/A	-1.37	N/A	Not reported

Trial Results

Safety outcome	Empagliflozin 10mg N=2,996	Placebo N=2,989	RR* and 95% confidence interval (CI)	Relative Risk Increase (RRI)/ Relative Risk Reduction (RRR)	Absolute Risk Increase (ARI)/ Absolute Risk Reduction (ARR)	Number Needed to Harm (NNH)	p-value
Hypotension	311 (10.4%)	257 (8.6%)	RR 1.21 (95% CI 1.03-1.41)	RRI 21%	ARI 1.8%	NNH 55	Not reported
Genital infections	67 (2.2%)	22 (0.7%)	RR 3.04 (95% CI 1.88-4.91)	RRI 204%	ARI 1.5%	NNH 66	Not reported
Acute renal failure	363 (12.1%)	384 (12.8%)	RR 0.94 (95% CI 0.82-1.08)	RRR 5.7%	ARR 0.7%	N/A	Not reported
Hypoglycemic events	73 (2.4%)	78 (2.6%)	RR 0.93 (95% CI 0.68-1.28)	RRR 6.6%	ARR 0.2%	N/A	Not reported

* Not in an article, calculated; N/A: not applicable

The primary composite outcome included hospitalization for HF and cardiovascular death. The individual components of the composite were reported separately. Empagliflozin significantly reduced HF hospitalization or cardiovascular death by 21% among patients with symptomatic stable heart failure with preserved EF (HR 0.79, p-value <0.001). For every 31 patients with HFpEF treated with empagliflozin 10mg daily instead of standard of care treatment alone, one patient will avoid HF hospitalization or cardiovascular death with 26.2 months of follow-up. However, this effect was primarily driven by a 27.1% relative risk reduction for HF hospitalization (HR 0.71, CI 0.60-0.83). There was no significant reduction in cardiovascular mortality (HR 0.91, CI 0.76-1.09). Hypotension and genital infection events were significantly higher in the empagliflozin group than placebo.

Trial Applicability

Patient Applicability

- This study applies to patients ≥18 years of age with chronic HF with NYHA class II-IV and a preserved ejection fraction (LVEF ≥40%) receiving standard of care treatment for HF, with or without diabetes.
- Patients had a mean age of 72 years, and 45% were women. The majority of patients in this study were Caucasian (76%). At baseline, mean LVEF was 54%, median NT-proBNP was 994, and mean eGFR was 61 mL/min/1.73 m^2. LVEF >40% to <50% comprised 33.2% and 33.0% of the empagliflozin and placebo group, respectively. Out of all patients, 81% had NYHA class II, with 91% having hypertension and 64% with nonischemic HF. Furthermore, the majority of patients were taking angiotensin-converting enzyme (ACE) inhibitors /angiotensin receptor blockers (81%) and beta-blockers (87%) at baseline.
- Patients were excluded if they had myocardial infarction, CABG or other major cardiovascular surgery or stroke/TIA in the prior 90 days, decompensated HF, uncontrolled atrial fibrillation or atrial flutter, hypertension, eGFR <20 mL/min/1.73 m^2, history of ketoacidosis or liver disease.

Intervention Applicability

- Empagliflozin is available as an oral once daily medication. It is FDA-approved to improve glycemic control in patients with type 2 DM and reduce cardiovascular death in patients with type 2 DM and cardiovascular disease and reduce HF hospitalization or cardiovascular death in patients with HF. Many commercial plans use step therapy requirements, and Medicaid plans have formulary restrictions using prior authorization or quantity limits. Average monthly costs for patients having commercial insurance is $0-$203, for Medicare Part D, $0 to $163, for Medicaid, $1 to $10. If patients do not have insurance, they would pay the full retail price, which is greater than $600 for a one-month supply. Although empagliflozin treatment is accessible and feasible in a typical patient's setting, there are substantial formulary restrictions and high co-payments that may impact some patients.
- The control arm was a reasonable comparison, as physicians were encouraged to treat patients based on guideline-directed standard therapy for HFpEF. There are few treatments available to improve morbidity and mortality of HFpEF. The two main trials both failed to meet their primary endpoints, but benefit was found in secondary endpoints. These include the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Preserved trial, which showed that candesartan reduced HF-related hospitalization compared with placebo (15.9% vs. 18.3%; adjusted HR 0.84; 95% CI 0.70-1.00; P=0.047), and the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial which demonstrated that spironolactone was associated with a reduction in HF hospitalizations compared with placebo (12.0% vs. 14.2%; HR 0.83; 95% CI 0.69-0.99; P=0.04). These agents were used in both groups in a similar proportion of patients.

Patient-Important Outcomes Measured

- The outcomes in the study included both clinical and surrogate endpoints. The primary endpoint was a clinical composite of cardiovascular death or HF hospitalization. In addition, the secondary clinical endpoints, such as total hospitalizations, composite renal outcome, all-cause mortality and new-onset diabetes among patients with prediabetes, were also evaluated. Secondary outcome of change in mean eGFR slope/year was a surrogate endpoint.
- The study measured any adverse and any serious adverse event. Selected adverse events of interest included hypotension, genital infections, hypoglycemic events and acute renal failure. Most outcomes, in terms of the primary, secondary and safety were clinically meaningful.

Balance of Benefits vs. Harms

- The EMPEROR-Preserved study showed that in patients with HF with mid-range or preserved EF (LVEF>40%), empagliflozin 10mg daily decreased the risk of the cardiovascular death or HF hospitalization significantly compared with standard of care treatment alone, but the benefit is driven by hospitalization for HF rather than cardiovascular death. If 1,000 patients with HFpEF and on standard care were treated with empagliflozin instead of standard care of treatment alone for 26.2 months, there would be 33 fewer hospitalizations for HF. However, there would be additional 18 cases of hypotension and 15 more genital infections.
- During a mean follow-up period of 26.2 months, in patients with HFpEF, the risk of cardiovascular death or HF hospitalization was lower among those who received empagliflozin than those who received standard care of treatment alone irrespective of diabetes status with an NNT of 31 and an absolute risk reduction of 3.3% ($p<0.001$). For every 31 patients with HF treated with empagliflozin 10mg daily instead of standard care of treatment alone, one patient will avoid hospitalization or cardiovascular death. In contrast, empagliflozin led to a higher genital infection risk compared with placebo with an NNH 66. This means that for every 66 patients with HFpEF receiving empagliflozin, one patient will experience genital infection, when compared with placebo.
- Overall, empagliflozin is superior to placebo in reduction of HF hospitalization or cardiovascular mortality among patient with HFpEF on optimal standard care of treatment for HF, and the benefits outweigh the risks. However, the risk of some adverse effects, such as, hypotension and genital infection may outweigh the benefits in certain vulnerable patients, like the elderly and some women.

Health Care Professional Summary

The EMPEROR-Preserved study was a randomized, concealed, double-blind trial with ITT analysis. Potential co-intervention and contamination and proportion of patients without final outcome data at the end of the trial (2.9%) being close to the absolute risk reduction (3.3%) introduces possible risk of bias. The primary outcome of HF hospitalization and cardiovascular death had an absolute risk reduction of 3.3% and a relative risk reduction of 19.3% for empagliflozin, with an NNT of 31. However, this benefit was mainly driven by a reduction in time to first HF hospitalization and subgroup analysis showed there was no significant difference on cardiovascular mortality, all-cause death or total HF hospitalization. Patients taking empagliflozin had more adverse events, including hypotension (absolute risk increase 1.8%, NNH 55) and genital infection (ARI 1.5%, NNH 66). The ideal patient population for empagliflozin use is adults with symptomatic, stable HFpEF already optimized on HF GDMT, without an acute cardiovascular event in the prior 90 days and with an eGFR at least 20mL/min/1.73m^2.

Patient Summary

Empagliflozin is a prescription medication that is taken once daily by mouth. This medication was originally introduced as a drug to lower blood sugar for diabetes by helping your body eliminate sugar through the kidneys. The result of the EMPEROR-Preserved study showed a benefit in heart failure management. It found that patients with heart failure who received empagliflozin had a lower chance of being admitted to hospital for heart failure or death from heart disease compared with patients who received standard care of treatment for heart failure alone. This medication may cause low blood pressure and infections in the genital area, although these side effects can often be managed or prevented. Empagliflozin may be an additional treatment to improve heart failure management on top of standard care of treatment in those who have heart failure whether or not you have diabetes.

About the Authors

Jungyeon Moon, PharmD, BScPhm, MScPhm, PhD, received her PhD degree in clinical pharmacy in 2015 from Ewha Womans University in South Korea and her Doctor of Pharmacy degree in 2020 from Western University of Health Sciences. She is a cardiovascular outcomes research fellow at Western University of Health Sciences under Dr. Jackevicius. Dr. Moon has no conflicts of interest to report.

Cynthia Jackevicius, BScPhm, PharmD, MSc, BCPS, BCCP, FCSHP, FAHA, FCCP, FCCS, FACC, is a professor of pharmacy practice at Western University of Health Sciences and is the evidence-based practice section editor. Dr. Jackevicius teaches evidence-based practice skills to health care professionals. She advocates for the adoption of an evidence-based practice, incorporating the best available evidence, patients' values and preferences, and clinicians' expertise into clinical decision-making. Dr. Jackevicius has no conflicts of interest to report. She is the corresponding author and can be reached at cjackevicius@westernu.edu.

References

1. Tummalapalli SL, Montealegre JL, Warnock N, Green M, Ibrahim SA, Estrella MM. Coverage, Formulary Restrictions and Affordability of Sodium-Glucose Cotransporter 2 Inhibitors by U.S. Insurance Plan Types. *JAMA Health Forum* 2021;2(12):e214205. doi: 10.1001/jamahealthforum.2021.4205. PMCID: PMC8796944.

2. Jardiance.com [Internet]. Los Angeles: Pricing; c2022 [cited 2022Mar19]. Available from: www.jardiance.com/type-2-diabetes/jardiance-cost.

DID YOU KNOW?

Home-generated sharps disposal regulations have changed in California effective January 7th, 2022.

California Senate Bill 212 requires providing or initiating distribution of a sharps waste container and mail-back materials at the point of sale or prior at no cost to the ultimate user.

(CalRecycle Adopted Regulations. Pharmaceutical and Sharps Waste Stewardship Program. 18972.1 Definitions, Section 10)

The UltiGuard Safe Pack Sharps Container & Mail-Back Disposal Kit is the only fully compliant all-in-one solution.

COMPLETE 3-IN-1 SOLUTION

1

100 pen needles or syringes

2

FDA-cleared sharps container

3

Prepaid return shipping box and mail-back materials

GIVE YOUR PATIENTS MORE

- **FOR THE SAME COPAY AS PEN NEEDLES OR SYRINGES ALONE**
- **WITH NO CHANGE IN PHARMACY WORKFLOW**
- **IN ONE COMPLETE, PREPAID MAIL-BACK KIT**

UltiGuard® SafePack
Sharps Container & Mail-Back Disposal Kit

See how we make it easy to stay compliant:
www.disposemyneedles.com/CA