EMPEROR-Preserved Trial
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<table>
<tr><th colspan="3">BACKGROUND AND OVERVIEW</th></tr>
<tr><td>Article Citation</td><td colspan="2">● Anker S, et al. "Empagliflozin in Heart Failure with a Preserved Ejection Fraction". New England Journal of Medicine. 2021. epub 2021-08-27:1-11.</td></tr>
<tr><td>Background</td><td colspan="2">● 3 types of congestive heart failure (CHF):
o 1. Reduced ejection fraction (EF < 40%)
o 2. Moderately reduced ejection fraction (EF 40-50%)
o 3. Preserved ejection fraction (EF > 50%)
● Previous studies have shown mortality benefits with sodium glucose co-transporter 2 inhibitors (SGLT2i) in HFrEF, but their effects on patients with HFpEF are unknown
● MOA of SGLT2i: inhibit sodium glucose co-transporter 2 channels in the proximal renal tubules; reduces reabsorption of filtered glucose and increases glucose excretion
● SGLT2 inhibitors also have proven benefits in HFrEF, chronic kidney disease and diabetes mellitus (type 2)
● Few therapies exist that have shown benefit in HFpEF. Treatment options are limited for patients with preserved ejection fraction
● Minimal benefits have been shown with sacubitril/valsartan and mineralocorticoid receptor antagonists, but were modest at best
● One 2019 study by Kato et al (DECLARE-TIMI 58) found that dapagliflozin reduced hospitalizations for heart failure in CHF patients with preserved ejection fraction, but did NOT reduce all-cause mortality in these patients

Relevant guidelines:
● 2022 ACC/AHA/HFSA heart failure guidelines:
○ SGLT2i can be useful for lowering HF mortality and HF hospitalizations in both patients with HFrEF <u>and</u> HFpEF (Class IIa recommendation)
○ In symptomatic HFrEF, SGLT2i are recommended to reduce HF hospitalizations and CVD mortality, regardless of diabetes status (Class I recommendation)</td></tr>
<tr><td>Funding</td><td colspan="2">● Study sponsors: Boehringer Ingelheim and Eli Lilly (producer of empagliflozin)
● Boehringer Ingelheim was responsible for data collection and storage</td></tr>
<tr><td>Study Objective</td><td colspan="2">● To determine whether empagliflozin reduces the risk of the composite of cardiovascular death or hospitalization for heart failure in patients with heart failure with mid-range or preserved ejection fraction</td></tr>
<tr><th colspan="3">METHODS</th></tr>
<tr><td>Study Design</td><td colspan="2">● Multicenter, double-blind, parallel-group, randomized, controlled trial
● Patients were randomly assigned in a 1:1 ratio to receive either placebo or empagliflozin 10 mg daily in addition to usual therapy
● 5,988 patients included
o Empagliflozin: 2,997 patients
o Placebo: 2,991 patients
● Recruitment time: 18 months
● Follow up time: 20 months
● Empgaliflozin dosing for this trial = dose currently used in clinical practice
● Intention-to-treat analysis</td></tr>
<tr><td rowspan="2">Patient Criteria</td><td>Inclusion:</td><td>Exclusion</td></tr>
<tr><td>● NYHA class II-IV with LVEF >40%
● NT-proBNP >300 pg/mL if no AF or >900 pg/mL if AF
● Aged ≥18 years</td><td>● MI, CABG or other major CV surgery, or stroke/TIA in prior 90 days
● Cardiomyopathy based on infiltrative diseases, muscular dystrophies,</td></tr>
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	● Evidence of hypertensive heart failure or structural heart disease characterized by left atrial enlargement or LVH ● Stable diuretic use ● BMI <45 kg/m2	hypertrophic obstructive cardiomyopathy, or pericardial constriction ● Severe valvular heart disease ● Acute decompensated heart failure requiring intravenous diuretics, vasodilators, inotropic agents, or mechanical support within 1 week of screening ● Atrial fibrillation or atrial flutter with resting HR >110 at screening ● SBP ≥180 or <100 mm Hg or symptomatic hypotension ● ICD in prior 3 mo ● Prior receipt of cardiac resynchronization therapy ● Significant comorbidities listed on page 17 of the supplemental appendix
Enrollment and Baseline Characteristics	● Study conducted in 622 centers in 23 countries ● Baseline characteristics were well matched o Average age: 71 o Females well represented (44%) o Race is not well represented- 75% of both groups were white o Majority of patients had NYHA Class II HF (81% in both groups) ▪ < 1% of patients had NYHA Class I and Class IV (both groups) o Average BMI: 29.9 o Average BNP: 994 o HTN present in ~90% of both groups o Mean GFR in both groups was ~60 mL/min o ~50% had GFR < 60 mL/min in each group	
Statistics	● 841 primary events were needed to give 90% power to detect a hazard ratio of 0.8 and an alpha of 0.05 ● Intention-to-treat analysis ● Cox proportional hazards model used for statistical analysis ● Safety: o Serious adverse events occurred in 47.9% of empagliflozin patients and 51.6% of placebo patients ▪ Uncomplicated genital and urinary tract infections were common in the empagliflozin group ▪ High number of adverse events in the placebo group could indicate that cause was from comorbidities rather than the drug of interest (empagliflozin) o AEs leading to discontinuation: ▪ 19.1% empagliflozin patients ▪ 18.4% in placebo group o Overall, no significant difference in rates of urinary tract infections, hypoglycemic events, ketoacidosis, acute renal failure, or lower limb amputation between trial arms.	
RESULTS		
Outcome Summary	Primary endpoint ● Composite of hospitalizations and death: o 415 (13.8%) in empagliflozin group o 511 (17.1%) in placebo group o HR 0.79, 95% CI 0.69- 0.9, P < 0.001 ● NNT of 31 patients in 26 months Secondary endpoints	

	● Total number of hospitalizations for heart failure:
	  o 259 (8.6%) in empagliflozin group
	  o 352 (11.8%) in placebo group
	  o HR 0.73, CI 0.61- 0.88, P < 0.001
	  o NNT of 22 patients in 26 months
	● Rate of decline in GFR:
	  o eGFR mean slope change per year:
	  ▪ -1.25 mL/min/1.73m2 in empagliflozin group
	  ▪ -2.62 mL/min/1.73m2 in placebo group
	  o HR 1.36, CI 1.06–1.66, P < 0.001
	
	Safety:
	● Serious adverse events occurred in 47.9% of empagliflozin patients and 51.6% of placebo patients
	  o Uncomplicated genital and urinary tract infections were common in the empagliflozin group
	  o High number of adverse events in the placebo group could indicate that cause was from comorbidities rather than the drug of interest (empagliflozin)
	  o AEs leading to discontinuation:
	  ▪ 19.1% empagliflozin patients
	  ▪ 18.4% in placebo group
	  o Overall, no significant difference in rates of urinary tract infections, hypoglycemic events, ketoacidosis, acute renal failure, or lower limb amputation between trial arms.

DISCUSSION	
Authors' Main Points in the Discussion	● In patients with HFpEF, the results of the primary outcome primarily came from the 29% lower risk of hospitalization for heart failure (rather than death from cardiovascular causes) ● Empagliflozin led to a lower total number of hospitalizations for heart failure and a longer time to first hospitalization for heart failure. The benefits seen are similar to the results seen in the EMPEROR-Reduced trial o Suggests that the effects of SGLT2 inhibition on heart failure events do not vary meaningfully with the heart failure phenotype ● Previous studies have failed to demonstrate unequivocal benefits of drug interventions in patients with HFpEF ● "Treatment with empagliflozin led to a lower incidence of hospitalization for heart failure, but it did not appear to affect the number of deaths from cardiovascular or other causes in the current trial"
Strengths	● Many sites with a large sample size ● Placebo controlled, double blind, randomized ● Appropriate dosing of empagliflozin ● Appropriate inclusion/exclusion criteria
Limitations	● Composite primary outcome ● Boehringer Ingelheim designed the protocol and statistical analysis plan o Also supervised the data analysis
Personal Conclusions	● In my opinion, this study was well-conducted. The patients included in this trial are similar to the patients seen in clinical practice and the comparable safety outcomes between each group showed that empagliflozin is safe to use ● While I would recommend the use of empagliflozin to heart failure patients in NYHA Class II-III, I would not recommend its use for patients in NYHA Classes I and IV as they were not well represented in this study