Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR-Reduced)

BACKGROUND[1,2]

- In patients with type 2 diabetes, sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown that they reduce the risk of:
  - Heart failure hospitalizations by 30% to 35% (versus placebo)
  - Renal disease progression (death or need for dialysis) by 35% to 50% (versus placebo)
- The 2019 DAPA-HF trial showed that dapagliflozin reduced the risk of cardiovascular death and heart failure hospitalizations in patients with and without type 2 diabetes.
- It remains unclear whether empagliflozin, another SGLT2 inhibitor, extends its heart failure and renal benefits to patients without diabetes

METHODS[1]

Study Design	Randomized, double blind, parallel-group, placebo-controlled, event-driven, multinational trial	
Objectives	To evaluate empagliflozin in a population of patients with chronic heart failure and a reduced ejection fraction with or without diabetes.	
Interventions	• Group 1: empagliflozin 10mg daily • Group 2: placebo	
Endpoints	Primary	Composite event of cardiovascular death or first heart failure hospitalization
	Secondary	• Total number of heart failure exacerbations • Mean slope of change in eGFR • Composite renal outcome: includes chronic dialysis, renal transplantation, or sustained reductions in eGFR defined by study investigators • All-cause mortality
Follow-Up	Every 2 – 3 months, for a median of 16 months	

Patient Population	Inclusion	○ 18 years of age and older
		○ HFrEF NYHA Class II, III, or IV with a:
		  ○ History of heart failure hospitalization within the last 12 months <u>OR</u>
		  ○ Elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP), defined as:
		  ▪ ≥ 600 pg/mL in patients with an ejection fraction of 30% or less
		  ▪ ≥ 1000 pg /mL in patients with an ejection fraction of 31% - 35%
		  ▪ ≥ 2500 pg/mL in patients with an ejection fraction of 36% - 40%
		  ▪ Above thresholds for NT-proBNP were doubled for patients with atrial fibrillation
		○ On appropriate pharmacological treatment for heart failure

	Exclusion	○ Acute coronary syndrome, stroke, or transient ischemic attack (TIA) within 90 days ○ Acute decompensated HF ○ Severe valvular heart disease ○ Currently implanted LV assist device (LVAD) ○ eGFR <20 mL/min/1.73m^2 or on dialysis

RESULTS[1]

Study Flow: 3730 patients randomized: 1863 randomized to empagliflozin, 1867 randomized to placebo

Population Demographics

	Empagliflozin	Placebo
Age	67	67
Female Sex	23.5%	24.4%
Diabetes	49.8%	49.8%
NYHA Functional Class		
Class II	75.1%	75.0%
Class III	24.4%	24.4%
Class IV	0.5%	0.6%
Mean left ventricular ejection fraction (LVEF)	27.7%	27.2%
Hospitalization for heart failure (HF) in ≤12 months	31.0%	30.7%
Median NT-proBNP pg/mL	1887	1926
Mean eGFR (mL/min/1.73m^2)	61.8	62.2

Primary Endpoint

	Empagliflozin	Placebo	HR and 95% CI	P-value	NNT
Composite of first HF hospitalization or cardiovascular mortality	19.4%	24.7%	0.75; (0.65 to 0.86)	P < 0.001	19
Composite endpoint in patients with diabetes	21.5%	28.5%	0.72; (0.60 to 0.87)	Not calculated	
Composite endpoint in patients without diabetes	17.2%	21.0%	0.78; (0.66 to 0.93)	Not calculated	
First HF hospitalization	13.2%	18.3%	0.69; (0.59 to 0.81)	Not calculated	
Cardiovascular death	10.0%	10.8%	0.92, (0.75 to 1.12)	Not calculated	

Secondary Endpoints

	Empagliflozin vs Placebo	HR, 95% CI	P-value
Total number of HF hospitalizations	388 vs 553	0.70, (0.58 to 0.85)	P < 0.001
Mean slope of change in eGFR per year (mL/min/1.73m^2)	-0.55 vs -2.28	1.73, (1.10 to 2.37)	P < 0.001
Composite renal outcome	1.6% vs 3.1%	0.50, (0.32 to 0.77)	Not calculated
Death from any cause	13.4% vs 14.2%	0.92, (0.77 to 1.10)	Not significant

Safety

	Empagliflozin	Placebo
Hypotension	9.4%	8.7%
Volume depletion	10.6%	9.9%
Urinary tract infection	4.9%	4.5%
Genital infections	1.7%	0.6%

AUTHORS' CONCLUSIONS[1]

Compared to placebo, empagliflozin was associated with a lower combined risk of cardiovascular death or heart failure hospitalization, as well as slower progressive decline in renal function in patients with chronic heart failure with reduced ejection fraction, regardless of the presence or absence of diabetes.

DISCUSSION[1,2]

Strengths

- Large, multicenter, placebo-controlled, double blinded study
- Most patients in this trial were on guideline recommended treatment for HF and treatment arms were well balanced
- Approximately 50% of patients did not have diabetes

Limitations

- Patients in the EMPEROR-Reduced trial had more severe heart failure than did patients in the DAPA-HF trial based on their baseline natriuretic peptides, and ejection fractions. This limits the ability to compare empagliflozin's efficacy against that of dapagliflozin.
- Trial duration was relatively short to detect significant differences in mortality
- Renal outcomes were not powered for in this trial
- Statistical analysis not conducted for adverse events

Conclusions and Implications

- Patients in this trial, who had significantly reduced ejection fractions at baseline, were 31% less likely to experience a HF hospitalization if on empagliflozin compared to patients on placebo
- Empagliflozin significantly reduced the composite of heart failure exacerbations or cardiovascular mortality, regardless of the presence or absence of diabetes
- Empagliflozin did not significantly reduce cardiovascular mortality
- In subgroup analyses, patients with a BMI ≥ 30, baseline eGFR < 60 mL/min/1.73m^2, a history of a HF exacerbation in the last 12 months, baseline NYHA class III or IV heart failure, or LVEF > 30% did not show significant benefit with respect to the primary composite endpoint
- Empagliflozin significantly slowed progression of eGFR and improved renal outcomes compared to placebo
- With respect to comparative efficacy to dapagliflozin, empagliflozin showed similar benefits in heart failure outcomes with two notable exceptions: (1) dapagliflozin was associated with a significant cardiovascular mortality benefit in an ad hoc analysis, where as empagliflozin was not. (2) Empagliflozin was studied in patients with more severe heart failure than patients who were studied in DAPA-HF
- Empagliflozin may gain an additional indication to reduce the risk of heart failure hospitalizations in patients with significantly reduced ejection fractions and will likely be incorporated in updated HF guidelines. More trials may be needed to confirm empagliflozin's effect on cardiovascular mortality in patients with HF and without diabetes

CITATIONS

1. Packer M, Anker SD, Butler J, et al., on behalf of the EMPEROR-Reduced Trial Investigators. Cardiovascular and Renal Outcomes With Empagliflozin in Heart Failure. *N Engl J Med* 2020;Aug 29:[Epub ahead of print].
2. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303

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