Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

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INTRODUCTION

- Sodium-glucose co-transporter-2 (SGLT2) inhibitors reduce the risk of hospitalisation for heart failure (HHF) in patients with or without diabetes.
- In the Phase 3, placebo-controlled Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial,[1] the SGLT2 inhibitor dapagliflozin improved outcomes in patients with heart failure (HF) and a reduced ejection fraction (EF) (with or without diabetes). This benefit was seen largely in those with mild-to-moderate left ventricular (LV) systolic dysfunction and increases in natriuretic peptides.
- In EMPEROR-Reduced, we evaluated the effects of the SGLT2 inhibitor empagliflozin in a broad population of patients with chronic HF and reduced EF (with and without diabetes) that was enriched for patients with more severe LV systolic dysfunction and marked increases in natriuretic peptides.

OBJECTIVE

- To evaluate the effects of empagliflozin versus placebo on cardiovascular (CV) and renal outcomes in patients with chronic HF and reduced EF ≤40%, with or without diabetes.

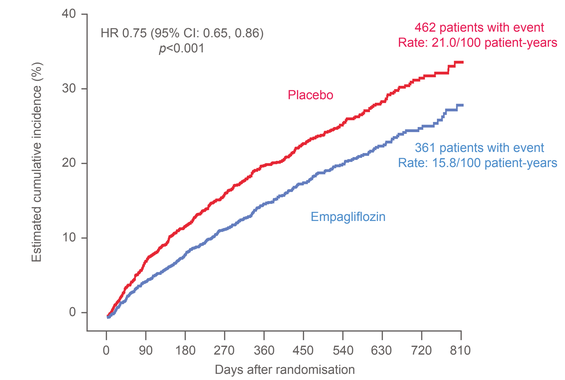
METHODS

- In this double-blind, placebo-controlled trial, we randomly assigned 3730 patients with functional class II, III, or IV HF and an EF of ≤40% to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. If EF was in the range 31–40%, eligible patients were required to show very high levels of N-terminal pro B-type natriuretic peptide (NTproBNP) or an HHF within 12 months.
- EMPEROR-Reduced specified 3 endpoints to be tested in a hierarchical manner:
  - Primary endpoint: composite of CV death or HHF
  - First secondary endpoint: total (first and recurrent) HHF
  - Second secondary endpoint: slope of decline in estimated glomerular filtration rate (eGFR) over time.
- An additional prespecified efficacy outcome that was not part of the testing hierarchy was a composite renal outcome (chronic dialysis or renal transplantation or a profound, sustained reduction in eGFR).

RESULTS

- Over a median of 16 months, the primary outcome occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio [HR] 0.75; 95% confidence interval [CI]: 0.65, 0.86; $p<0.001$)[2] (**Figure 1**).

Figure 1. Time to CV death or HHF (primary endpoint)



Patients at risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio.

- The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes.
- The effect of empagliflozin and placebo on the individual components of the primary endpoint are reported in **Table 1**.

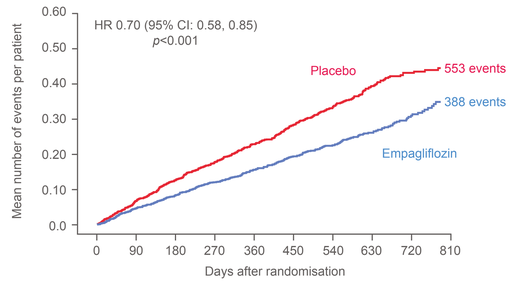
Table 1. Effect of empagliflozin and placebo on individual components of the primary endpoint

	Empagliflozin (n=1863)		Placebo (n=1867)			
	Events, n (%)	Events/100 patient-years	Events, n (%)	Events/100 patient-years	HR (95% CI)	p-value
Primary composite outcome	361 (19.4)	15.8	462 (24.7)	21.0	0.75 (0.65, 0.86)	<0.001
First HHF	246 (13.2)	10.7	342 (18.3)	15.5	0.69 (0.59, 0.81)	
CV death	187 (10.0)	7.6	202 (10.8)	8.1	0.92 (0.75, 1.12)	

CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio.

- The total HHF events was lower in the empagliflozin group than in the placebo group (HR 0.70; 95% CI: 0.58, 0.85; $p<0.001$)[2] (**Figure 2**).

Figure 2. Total (first and recurrent) HHF (first secondary endpoint)



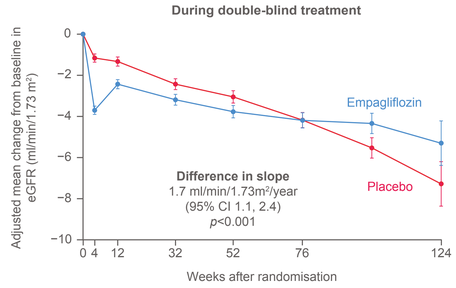
Patients at risk

Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

CI, confidence interval; HHF, hospitalisation for heart failure; HR, hazard ratio.

- The rate of decline in eGFR (Chronic Kidney Disease Epidemiology Collaboration) was slower in the empagliflozin group than in the placebo group (–0.55 vs –2.28 ml/min/1.73 m^2/year, $p<0.001$)[2] (**Figure 3**).

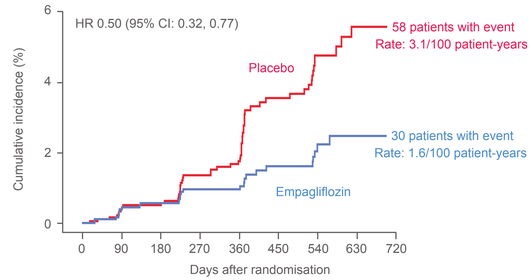
Figure 3. Changes in eGFR* (second secondary endpoint)



*CKD-EPI.
Error bars show standard error.
CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate.

- The composite renal outcome occurred in 30 patients (1.6%) in the empagliflozin group and in 58 patients (3.1%) in the placebo group (HR, 0.50; 95% CI, 0.32 to 0.77) (**Figure 4**).

Figure 4. Composite renal endpoint



Patients at risk

Placebo	1867	1592	1501	1136	1058	681	357	259	76	
Empagliflozin	1863	1599	1532	1155	1062	687	391	276	78	

CI; confidence interval; HR, hazard ratio.

- Uncomplicated genital tract infections (N/%) were reported more frequently with empagliflozin (31/1.7) than with placebo (12/0.6).

CONCLUSIONS

- In patients with chronic HF and a reduced EF, EMPEROR-Reduced achieved all 3 endpoints prespecified as key outcomes by hierarchical testing, each with a $p<0.001$.
- The 25% decrease in the risk of the composite of CV death and HHF in EMPEROR-Reduced was identical to that seen in DAPA-HF.[1]
- Empagliflozin reduced the total number of HHF events and slowed the rate of progression of renal disease.
- Taken together, the concordant results of DAPA-HF and EMPEROR-Reduced should be sufficient to establish SGLT2 inhibitors as a new standard of care for patients with HF and reduced EF.

Disclosures

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Presenter: Professor Iain Squire, University of Leicester, Department of Cardiovascular Sciences, and NIHR Biomedical Research Centre, Leicester, UK; email: is11@le.ac.uk.

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