Efficacy of Empagliflozin in Heart Failure With Preserved Ejection Fraction Is Related to the Presence of Echocardiographic Features of Diastolic Dysfunction in the EMPEROR-Preserved Trial

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BACKGROUND

- The EMPEROR-Preserved trial evaluated the efficacy and safety of the SGLT2 inhibitor empagliflozin, vs placebo, added to standard of care in patients with HFpEF with or without diabetes.[1]
- In this trial, empagliflozin significantly reduced the risk of the composite primary outcome of CV death or HHF (HR 0.79; 95% CI 0.69, 0.90; p<0.001).
- The impact of baseline diastolic function on the effects of empagliflozin therapy in patients with HFpEF is currently unknown.

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OBJECTIVE

- To analyze the effects of empagliflozin in patients with HFpEF in the EMPEROR-Preserved Trial, according to the presence or absence of baseline echocardiographic features of DD.

METHODS

- DD was defined as the presence of LAVI ≥34 mL/m², E/e' ≥13 or LVMi >115 (males) or >95 (females) g/m².
  - 3 categories of increasing DD were defined as 0, 1, or ≥2 DD criteria present at baseline.
- Differences in treatment effects across 3 DD categories were assessed by a Cox proportional hazards model for time-to-first-event analyses and joint frailty model for total events.
- To assess the consistency of effects across subgroups, subgroup-by-treatment interaction terms with trend tests were added in the model.
- The primary endpoint was a composite of first HHF or CV death. Additional endpoints included total HHF, quality of life using the KCCQ, and AEs.

RESULTS

- Of 5988 participants from the EMPEROR-Preserved trial, 63% had no baseline DD, 27% had 1, and 10% had ≥2 measures (**Table 1**).
- The percentage of males decreased with DD category (57.2% for no baseline DD, 54.2% for 1, and 46.6% for ≥2 measures, p<0.0001).
- Race, ethnicity, age, HR, diastolic blood pressure, LVEF, ischemia etiology, body weight, and eGFR were also associated with DD categories.
- The frequency of measures of DD was associated significantly with an ischemic etiology of HF and higher LVEF but was not associated with baseline NT-proBNP or a history of T2D or COPD.
- The presence of DD (with minor variations between individual markers) was marginally associated with certain baseline medication usage, although this varied between the individual markers of DD.
- DD was not consistently associated with any particular therapy or HF medication (p>0.0001).

Table 1. Demographics and baseline characteristics

	DD=0 (n=3766; 63%)	DD=1 (n=1619; 27%)	DD≥2 (n=603; 10%)	Total (N=5988; 100%)	p-value
Age, years	71.7±9.4	71.8±9.6	73.1±9.1	71.9±9.4	0.0035
Women, n (%)	1612 (42.8)	742 (45.8)	322 (53.4)	2676 (44.7)	<0.0001
Heart rate, bpm	71.0±11.6	69.7±12.3	68.6±12.2	70.4±11.9	<0.0001
Weight, kg	83.33±19.41	80.24±19.13	76.63±18.98	81.82±19.41	<0.0001
Ischemic HF, n (%)	1433 (38.1)	523 (32.3)	161 (26.7)	2117 (35.4)	<0.0001
LV ejection fraction, %	53.8±8.7	55.1±8.7	55.8±9.3	54.3±8.8	<0.0001
NT-proBNP (median, IQR), pg/mL	971.5 (491–1697.5)*	945 (491–1748)	1057 (557–1890)	974 (499–1731)*	NS†
Glomerular filtration rate, mL/min/1.73 m²	61.5±19.7*	59.5±19.8	58.3±20.1	60.6±19.8*	<0.0001
NYHA functional class, n (%)					NS
I	2 (0.1)	2 (0.1)	0	4 (0.1)	
II	3050 (81.0)	1328 (82.0)	505 (83.7)	4883 (81.5)	
III	704 (18.7)	283 (17.5)	96 (15.9)	1083 (18.1)	
IV	10 (0.3)	6 (0.4)	2 (0.3)	18 (0.3)	

Data given as mean ± standard deviation unless otherwise stated
*Data available for 3764 patients (DD=0), 5986 patients (total)
†Based on log-transformed results

- In the placebo group alone:
  - DD categories did not significantly predict the primary outcome (p=0.2362 for trend test of the 3 DD categories).
  - DD categories showed a weak trend for an increased HR for the secondary outcome of total HHF for DD ≥2 (HR 1.56 [95% CI, 1.06, 2.30]; p=0.0254).
- A progressive treatment effect across DD categories was seen for time to HHF or CV death (HR: 0.91 for none, 0.64 for 1, and 0.49 for ≥2 measures; interaction p-value 0.0014) (**Figure 1**), and total number of HHF (HR: 0.95 for none, 0.52 for 1, and 0.29 for ≥2 measures) (**Figure 2**).

Figure 1. Effect of empagliflozin vs placebo: CV death or HHF by baseline DD category

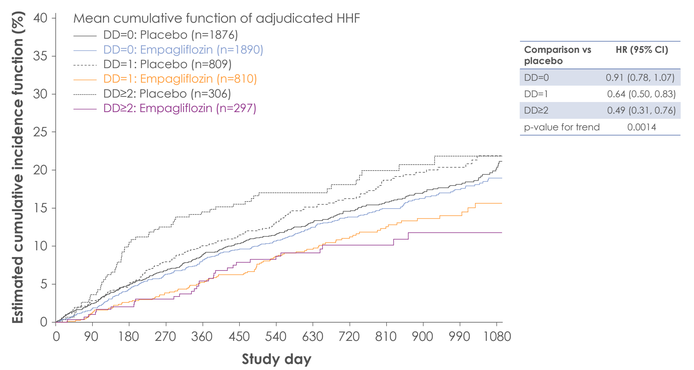
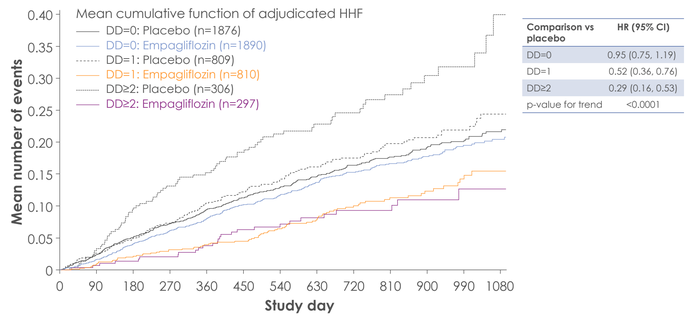


Figure 2. Effect of empagliflozin vs placebo: total HHF by baseline DD category



- Improvement in KCCQ score by ≥10-points at Week 52 showed consistent treatment-induced change across DD categories (interaction p-value 0.92).
- The safety profile of empagliflozin was consistent across DD categories (**Table 2**).

Table 2. Selected AEs for empagliflozin and placebo by DD category

	DD=0		DD=1		DD≥2	
	Empagliflozin (n=1889)	Placebo (n=1875)	Empagliflozin (n=810)	Placebo (n=808)	Empagliflozin (n=297)	Placebo (n=306)
Any AE	1588 (84.1)	1605 (85.6)	726 (89.6)	713 (88.2)	260 (87.5)	267 (87.3)
Serious AEs	489 (25.9)	514 (27.4)	215 (26.5)	239 (29.6)	82 (27.6)	98 (32.0)
Renal failure	61 (3.2)	52 (2.8)	20 (2.5)	26 (3.2)	5 (1.7)	13 (4.2)
Urinary tract infections	133 (7.0)	101 (5.4)	77 (9.5)	58 (7.2)	26 (8.8)	22 (7.2)
Genital infection (fungal)	2 (0.1)	0	3 (0.4)	0	1 (0.3)	0
Limb traumatic amputation	1 (0.1)	0	-	-	-	-
Multiple fractures	1 (0.1)	0	-	-	0	1 (0.3)
Hypoglycemia	47 (2.5)	49 (2.6)	25 (3.1)	31 (3.8)	11 (3.7)	13 (4.2)
Symptomatic hypotension	112 (5.9)	88 (4.7)	61 (7.5)	47 (5.8)	24 (8.1)	21 (6.9)
Hypotension	138 (7.3)	111 (5.9)	66 (8.1)	55 (6.8)	28 (9.4)	22 (7.2)

CONCLUSIONS

- The baseline detection of 3 echocardiographic measures of DD predicted an improved clinical response to empagliflozin in a graded fashion.
- A ≥10-point improvement in KCCQ Clinical Summary Score at Week 52 was consistent across DD categories.
- The safety profile of empagliflozin was consistent across DD categories.
- These results raise the prospect that the mode of action of empagliflozin may target specific changes in diastolic performance.

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References
1. Anker S, et al. *N Engl J Med*. 2021;385(16):1451–61.

Abbreviations
AE, adverse event; bpm, beats per minute; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DD, diastolic dysfunction; E/e', E-wave e-prime ratio; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; HR, hazard ratio; IQR, interquartile range; LV, left ventricular; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVMi, left ventricular mass index; NS, not significant; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes.

Disclosures
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