Empagliflozin in Heart Failure With A Preserved Ejection Fraction ≥50%

Results From The Emperor-Preserved Clinical Trial

Stefan D. Anker on behalf of the EMPEROR-Preserved
Executive Committee, Trial Committees, Investigators & Coordinators

Dept of Cardiology & BCRT
Charité (CVK), Berlin, Germany

s.anker@cachexia.de

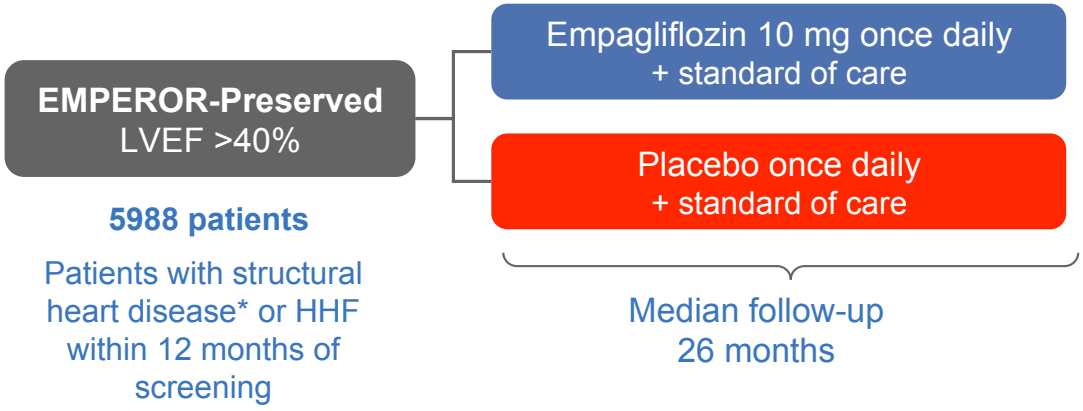
Disclosures for presenter: Fees from Abbott, Bayer, Boehringer Ingelheim, Brahms GmbH, Cardiac Dimension, Cordio, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma

EMPEROR-Preserved – Study Design

Phase III, randomized, double-blind, placebo-controlled trial

Aim: to evaluate efficacy and safety of empagliflozin versus placebo, on top of standard of care, in **patients with HFpEF** with or without diabetes

Population: T2DM & non-T2DM, aged ≥18 years, chronic HF (NYHA class II–IV), eGFR ≥20 and raised NT-BNP (>300 pg/mL in SR & >900 pg/mL in AF)



Left atrial enlargement or LV hypertrophy

COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated cardiovascular death or adjudicated HHF

SECONDARY ENDPOINTS

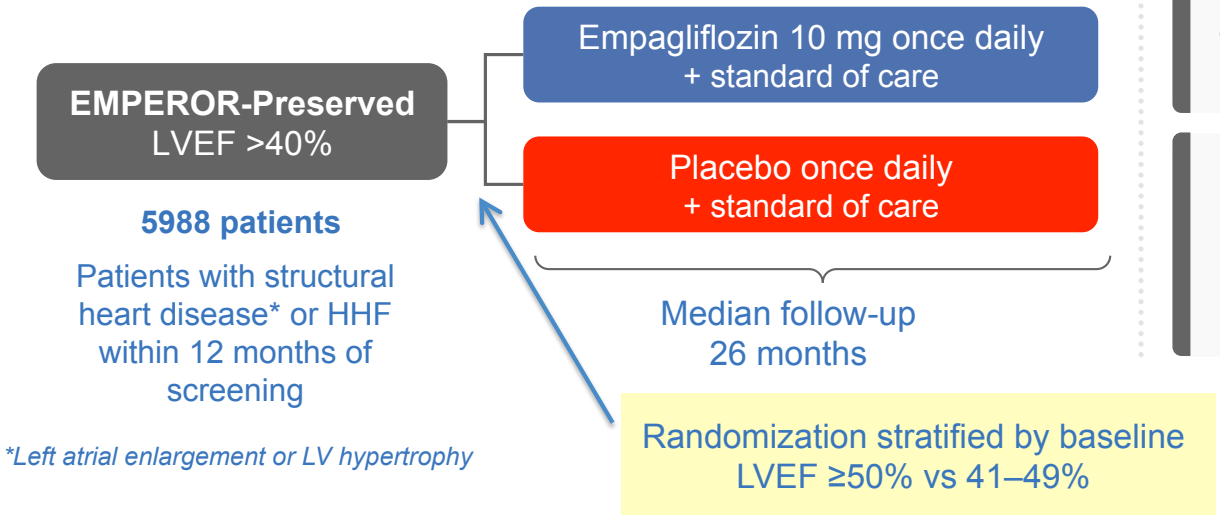
- **First and recurrent adjudicated HF hospitalization events**
- **Slope of change in eGFR (CKD-EPI)**

EMPEROR-Preserved – Study Design

Phase III, randomized, double-blind, placebo-controlled trial

Aim: to evaluate efficacy and safety of empagliflozin versus placebo, on top of standard of care, in **patients with HFpEF** with or without diabetes

Population: T2DM & non-T2DM, aged ≥18 years, chronic HF (NYHA class II–IV), eGFR ≥20 and raised NT-BNP (>300 pg/mL in SR & >900 pg/mL in AF)



COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated cardiovascular death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HF hospitalization events**
- **Slope of change in eGFR (CKD-EPI)**

Objectives of This Analysis

- **Summarize the effects of empagliflozin in HF patients with preserved LVEF of ≥50% (i.e. HFpEF) observed in the EMPEROR-Preserved trial**

→ This are the patients with “True” HFpEF (according to recent HF guidelines)

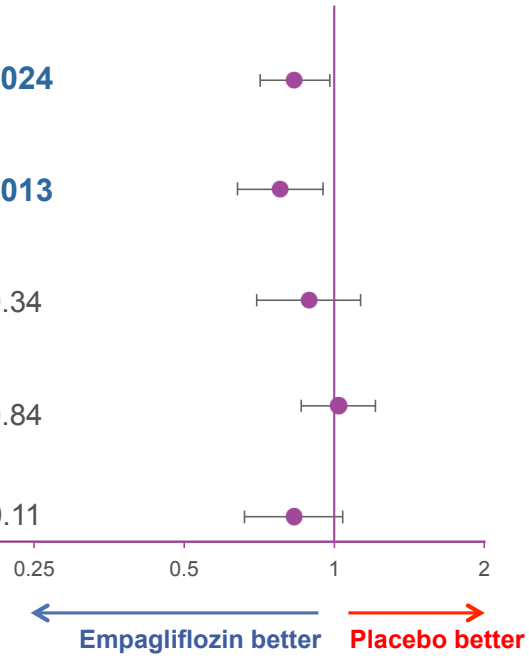
- Contrast the results observed in patients with HFpEF with the results in HF patients with mildly reduced LVEF of 41–49% (i.e. HFmrEF)
- Compare the results observed in patients with HFpEF (LVEF ≥50%) in EMPEROR-Preserved with the results of other relevant trials

Demographics and Baseline Characteristics

	HFpEF (≥50%) (n=4,005)	HFmrEF (41–49%) (n=1,983)	P-value
Age, years (±SD)	72.8 ± 9.2	70.1 ± 9.7	<0.001
Women, n (%)	2019 (50)	657 (33)	<0.001
Diabetes, n (%)	1913 (48)	1025 (52)	0.004
Ischaemic HF, n (%)	1134 (28)	983 (50)	<0.001
NYHA functional class II, n (%)	3255 (81)	1628 (82)	0.58
NT-proBNP (median, IQR), pg/mL	946 (482, 1677)	1025 (550, 1882)	<0.001
Atrial fibrillation or flutter, n (%)	2224 (56)	911 (46)	<0.001
Baseline eGFR (mL/min/1.73 m^2)	59.4 ± 19.5	63.0 ± 20.3	<0.001
Co-medications of interest, n (%)			
ACE inhibitors/ARBs/ARNi	3149 (79)	1690 (85)	0.001
Beta blocker	3375 (84)	1792 (90)	<0.001
MRA	1320 (33)	924 (47)	<0.001
Diuretics	3246 (81)	1563 (79)	0.041

Effect of Empagliflozin vs Placebo: Primary and Secondary Outcomes – LVEF ≥50%

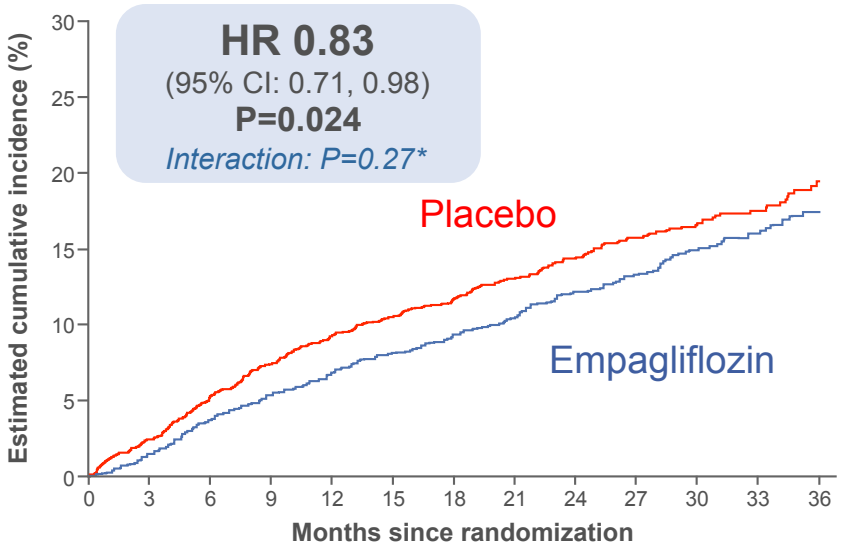
Endpoint	Events		Events/100 patient-years		HR (95% CI)	P-value	HR (95% CI)
	Placebo (n=2,003)	Empagliflozin (n=2,002)	Placebo	Empagliflozin			
Primary endpoint							
LVEF ≥50%	318	270	8.0	6.7	**0.83** (0.71, 0.98)	**0.024**	
First HHF							
LVEF ≥50%	226	182	5.7	4.5	**0.78** (0.64, 0.95)	**0.013**	
CV death							
LVEF ≥50%	144	126	3.4	3.0	0.89 (0.70, 1.13)	0.34	
All-cause mortality							
LVEF ≥50%	260	259	6.1	6.1	1.02 (0.86, 1.21)	0.84	
Total HHF*							
LVEF ≥50%	332	285	7.9	6.8	0.83 (0.66, 1.04)	0.11	



*Adjusted for baseline age, sex, eGFR, diabetes status and region.

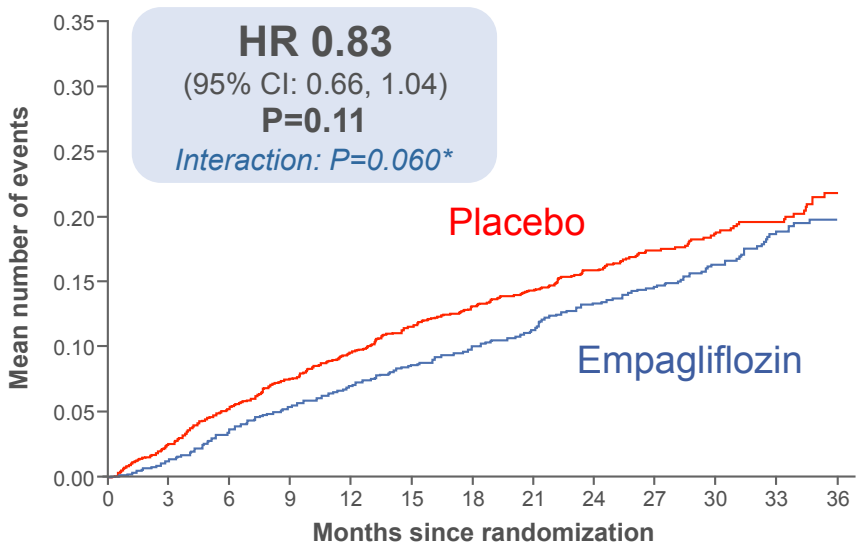
Effect of Empagliflozin vs Placebo: Outcomes in Patients with LVEF ≥50%

Primary outcome



Patients at risk							
Placebo	2003	1880	1779	1377	1021	639	264
Empagliflozin	2002	1898	1811	1408	1054	670	266

Total HHF**

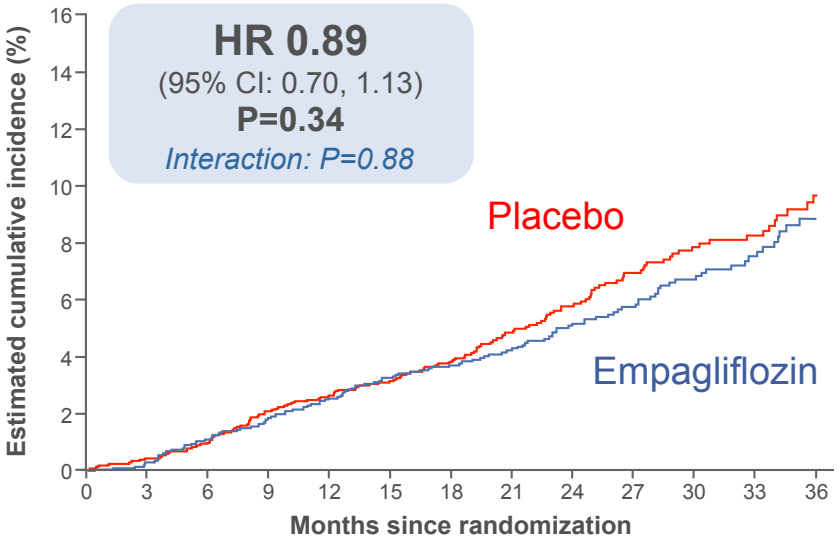


Patients at risk							
Placebo	2003	1956	1902	1502	1124	703	299
Empagliflozin	2002	1948	1887	1484	1129	724	298

*Interaction of treatment by LVEF category **Joint frailty model.

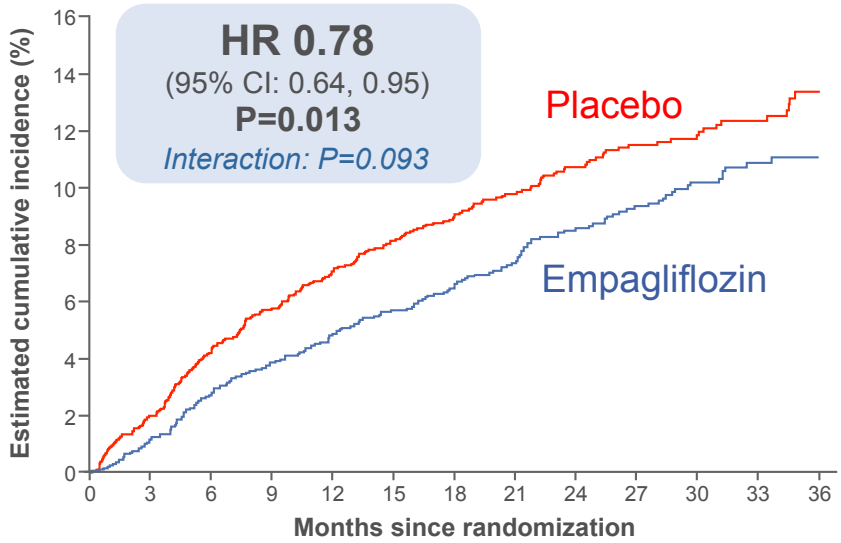
Effect of Empagliflozin vs Placebo: Outcomes in Patients with LVEF ≥50%

CV death



Patients at risk							
Placebo	2003	1967	1919	1529	1151	736	318
Empagliflozin	2002	1959	1909	1511	1156	750	309

First HHF

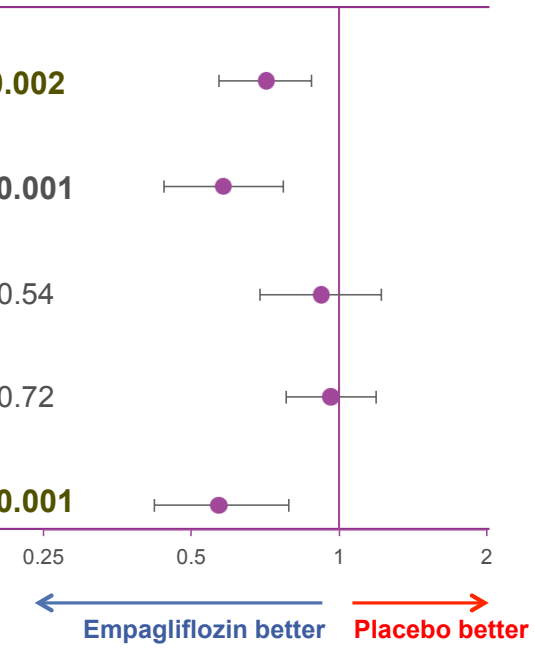


Patients at risk							
Placebo	2003	1880	1779	1377	1021	639	264
Empagliflozin	2002	1898	1811	1408	1054	670	266

*Interaction of treatment by LVEF category

Effect of Empagliflozin vs Placebo: Primary and Secondary Outcomes – LVEF 41–49%

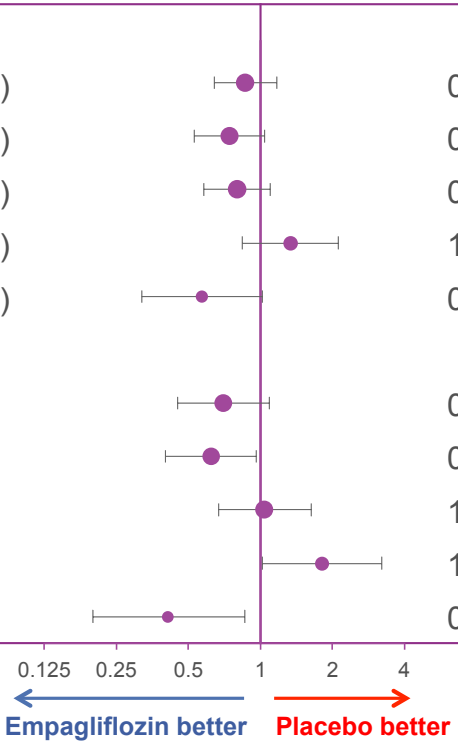
Endpoint	Events		Events/100 patient-years		HR (95% CI)	P-value	HR (95% CI)
	Placebo (n=988)	Empagliflozin (n=995)	Placebo	Empagliflozin			
Primary endpoint							
LVEF 41–49%	193	145	10.0	7.2	**0.71** (0.57, 0.88)	**0.002**	
First HHF							
LVEF 41–49%	126	77	6.5	3.8	**0.58** (0.44, 0.77)	**<0.001**	
CV death							
LVEF 41–49%	100	93	4.7	4.4	0.92 (0.69, 1.22)	0.54	
All-cause mortality							
LVEF 41–49%	167	163	8.0	7.7	0.96 (0.78, 1.19)	0.72	
Total HHF*							
LVEF 41–49%	209	122	10.1	5.8	**0.57** (0.42, 0.79)	**<0.001**	



*Adjusted for baseline age, sex, eGFR, diabetes status and region.

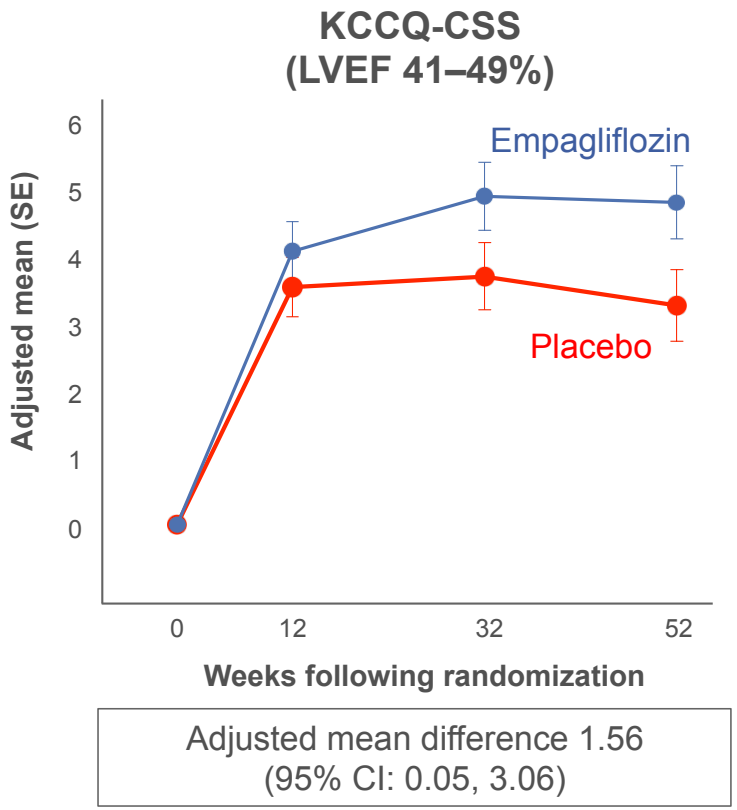
Effect of Empagliflozin vs Placebo: Primary Outcome and Total HHF by LVEF at Baseline

LVEF	Empagliflozin Events/total*	Placebo Events/total*	HR (95% CI)
Primary outcome			
≥50 to <55%	76/504 (7.5)	97/545 (9.0)	0.86 (0.64, 1.17)
≥55 to <60%	62/524 (5.9)	76/485 (7.9)	0.74 (0.53, 1.04)
≥60 to <65%	72/546 (6.5)	85/536 (8.0)	0.80 (0.58, 1.10)
≥65 to <70%	41/263 (8.1)	32/283 (5.8)	1.34 (0.84, 2.12)
≥70%	19/165 (5.6)	28/154 (9.4)	0.57 (0.32, 1.02)
Total HHF			
≥50 to <55%	58/504	91/545	0.70 (0.45, 1.09)
≥55 to <60%	71/524	91/485	0.62 (0.40, 0.96)
≥60 to <65%	69/546	70/536	1.04 (0.67, 1.63)
≥65 to <70%	64/263	37/283	1.81 (1.02, 3.21)
≥70%	23/165	43/154	0.41 (0.20, 0.86)

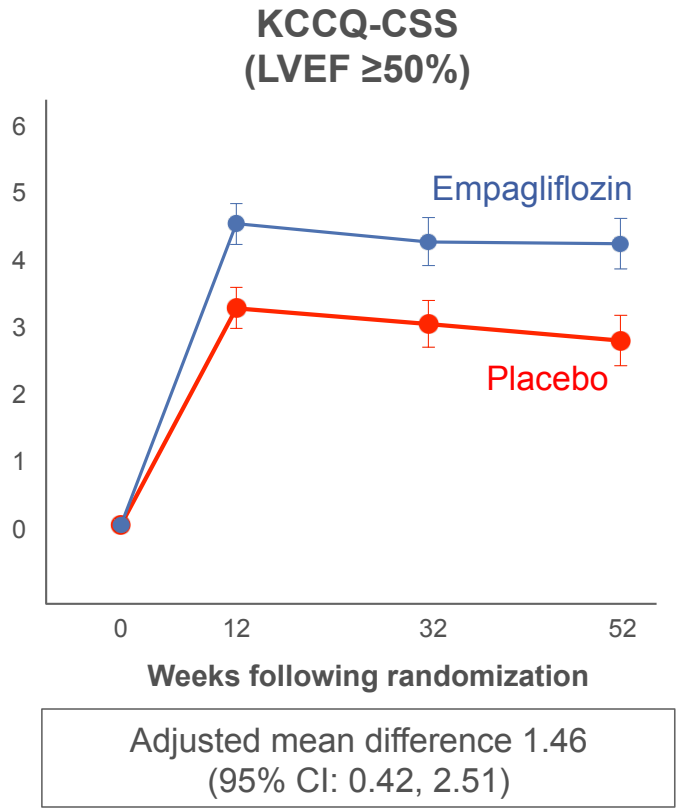


*For the primary outcome, the events/100 patient-years are reported in parentheses. These data are not reportable for total HHF.

Treatment Effect on KCCQ-CSS by LVEF Category



Adjusted mean difference 1.56
(95% CI: 0.05, 3.06)



Adjusted mean difference 1.46
(95% CI: 0.42, 2.51)

Change from baseline (SE) at Week 52

LVEF 41–49%

Empagliflozin: 4.86 ± 0.54
Placebo: 3.30 ± 0.55
P-value = 0.043

LVEF ≥50%

Empagliflozin: 4.24 ± 0.38
Placebo: 2.78 ± 0.38
P-value = 0.006

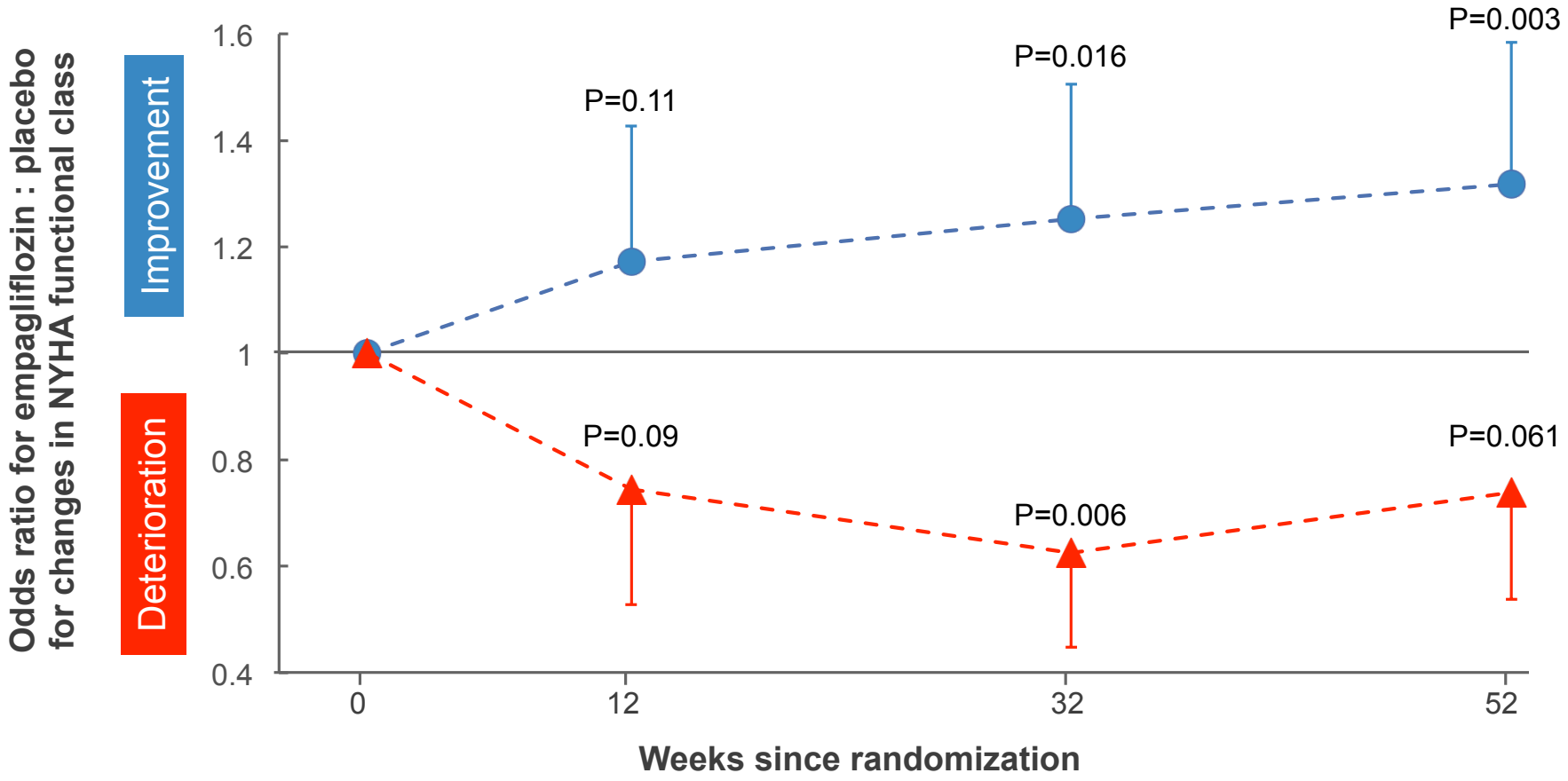
P-interaction value = 0.92

Treatment Effect on KCCQ Summary Score by LVEF Category

	Difference of empagliflozin vs placebo for LVEF ≥50% (n=4,005)	**P-value**	**Difference of empagliflozin vs placebo** for LVEF 41–49% (n=1,983)	**P-value**	**P-value for interaction***
KCCQ-CSS, mean change from baseline (95% CI)					
Week 52	1.46 (0.42, 2.51)	0.006	1.56 (0.05, 3.06)	0.043	0.92
KCCQ-TSS, mean change from baseline (95% CI)					
Week 52	2.14 (1.02, 3.26)	<0.001	1.91 (0.29, 3.53)	0.021	0.82
KCCQ-OSS, mean change from baseline (95% CI)					
Week 52	1.63 (0.60, 2.65)	0.002	1.55 (0.08, 3.03)	0.039	0.93

*Interaction of treatment by LVEF category.

Effect of Empagliflozin vs Placebo on NYHA Functional Class: Patients with HFpEF (LVEF ≥50%)



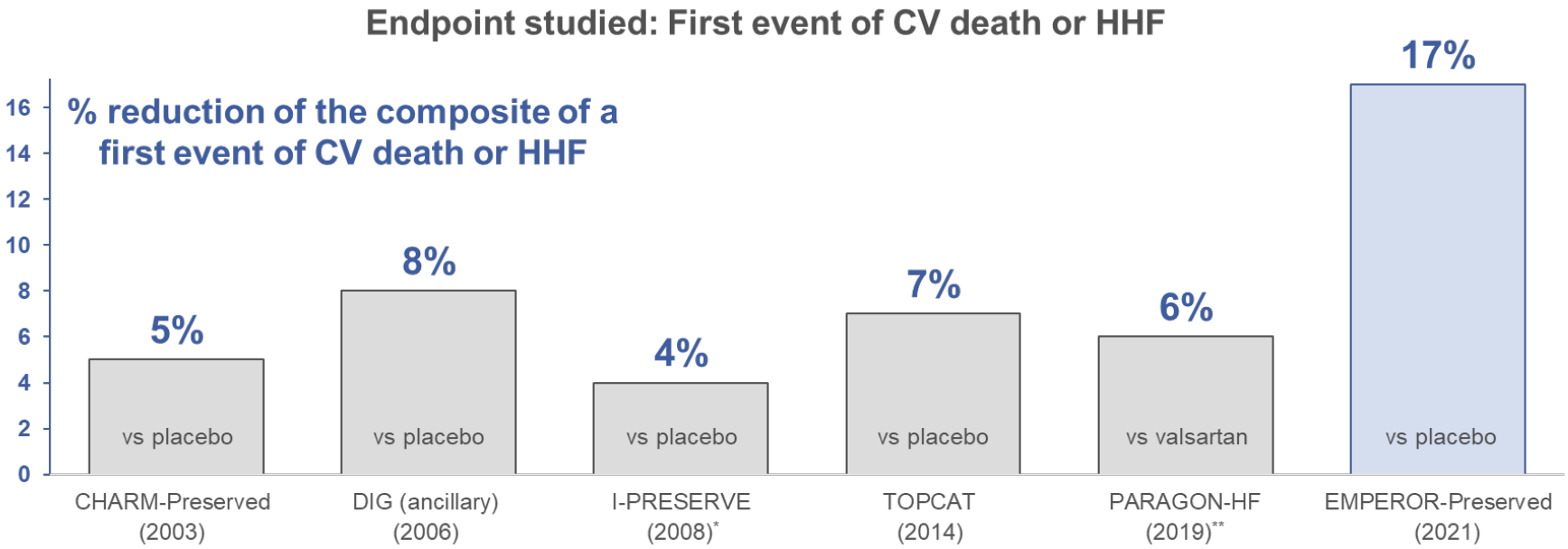
Vital Signs and Biomarkers in HFpEF patients (≥50%)

	Empagliflozin	Placebo	Treatment Difference	P-value
Glycated hemoglobin (%) in patients with diabetes– mean (SE)	– 0.13 ± 0.04	0.05 ± 0.04	– 0.18 (–0.28 to –0.09)	0.0002
Hematocrit (%) – mean (SE)	1.91 ± 0.08	– 0.26 ± 0.08	2.17 (1.95 to 2.40)	<0.0001
NT-proBNP (pg/mL) – median (IQR)	– 21 (-312, 261)	– 8 (-267, 296)	0.94* (0.90 to 0.99)	0.018
Body weight (kg) – mean (SE)	– 1.33 ± 0.11	– 0.35 ± 0.11	-0.99 (–1.30 to –0.67)	<0.0001
Systolic blood pressure (mm Hg) – mean (SE)	– 1.7 ± 0.4	– 0.8 ± 0.4	– 1.0 (–2.0 to 0.1)	0.074

*value given is geometric mean ratio

Change from baseline to 52 weeks

Effect of Different HF Therapies in Specific Trials Aiming to Recruit HFpEF Patients (LVEF ≥50%)



Event rate active vs control	8.6 vs 9.1	NA	5.48 vs 5.74	NA*** (5.9 vs 6.6)	NA** (12.8 vs 14.1)	6.7 vs 8.0
HR (95% CI)	0.95 (0.79, 1.14)	0.92 (0.71, 1.20)	0.96 (0.84, 1.09)	0.93 (0.79, 1.10)	0.94 (0.82, 1.08)	0.83 (0.71, 0.98)

*I-PRESERVE: patients with LVEF ≥45%. **PARAGON-HF: patients with LVEF >50%; event rate is for total HHF or CV death. *** event rate is for patients with LVEF ≥45%.

Clinical Outcomes in EMPEROR-Preserved and PARAGON-HF in Patients with LVEF >50%

	Results for sacubitril/valsartan vs valsartan in PARAGON-HF (N=4067)			Results for empagliflozin vs placebo in EMPEROR-Preserved (N=3501)		
	Events	HR (95% CI)	P-value	Events	HR (95% CI)	P-value
First HF hospitalization or CV death	869	0.94 (0.82, 1.08)	0.38	507	0.82 (0.69, 0.98)	**0.0263**
First heart failure hospitalization	692	0.93 (0.80, 1.08)	0.35	357	0.79 (0.64, 0.97)	**0.0242**
CV death	316	0.96 (0.77, 1.20)	0.71	226	0.90 (0.69, 1.17)	0.43
Total HF hospitalizations (recurrent events)	1233	0.88* (0.73, 1.06)	0.18	553	0.82** (0.64, 1.04)	0.11
Total HF hospitalizations and CV death	1549	0.90* (0.76, 1.06)	0.19	778	0.87* (0.71, 1.07)	0.18

*Analysed using the method of Lin, Wei, Yang and Ying **Analysed using a joint frailty model.

Results for key endpoints in the subgroup of patients with HFpEF (i.e. LVEF ≥50%)

	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**17% ↓ in risk** **P = 0.024**
	**Hospitalisation for HF** First heart failure hospitalization	**22% ↓ in risk** **P = 0.013**
	**QoL** KCCQ-CSS	**P = 0.006** Difference vs Placebo: 1.46 points improvement
	**Kidney Function** Slope of decline in glomerular filtration rate over time	**P < 0.0001** Difference vs Placebo: 1.24 mL/min/1.73 m^2 per year

Conclusions

- In the EMPEROR-Preserved trial, empagliflozin significantly improved the composite endpoint of a first event of CV death or hospitalization for HF in patients with LVEF ≥50% by 17%.
- Improvements were also observed in health-related QoL, measures of kidney function and symptom status.
- This is the first large-scale study to document meaningful and significant improvements associated with drug therapy in patients with True HFpEF.