Empagliflozin and HRQoL Outcomes in Patients with HFrEF

The EMPEROR-Reduced Trial

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on behalf of the EMPEROR-Reduced Executive Committee
Trial Committees, Investigators and Coordinators

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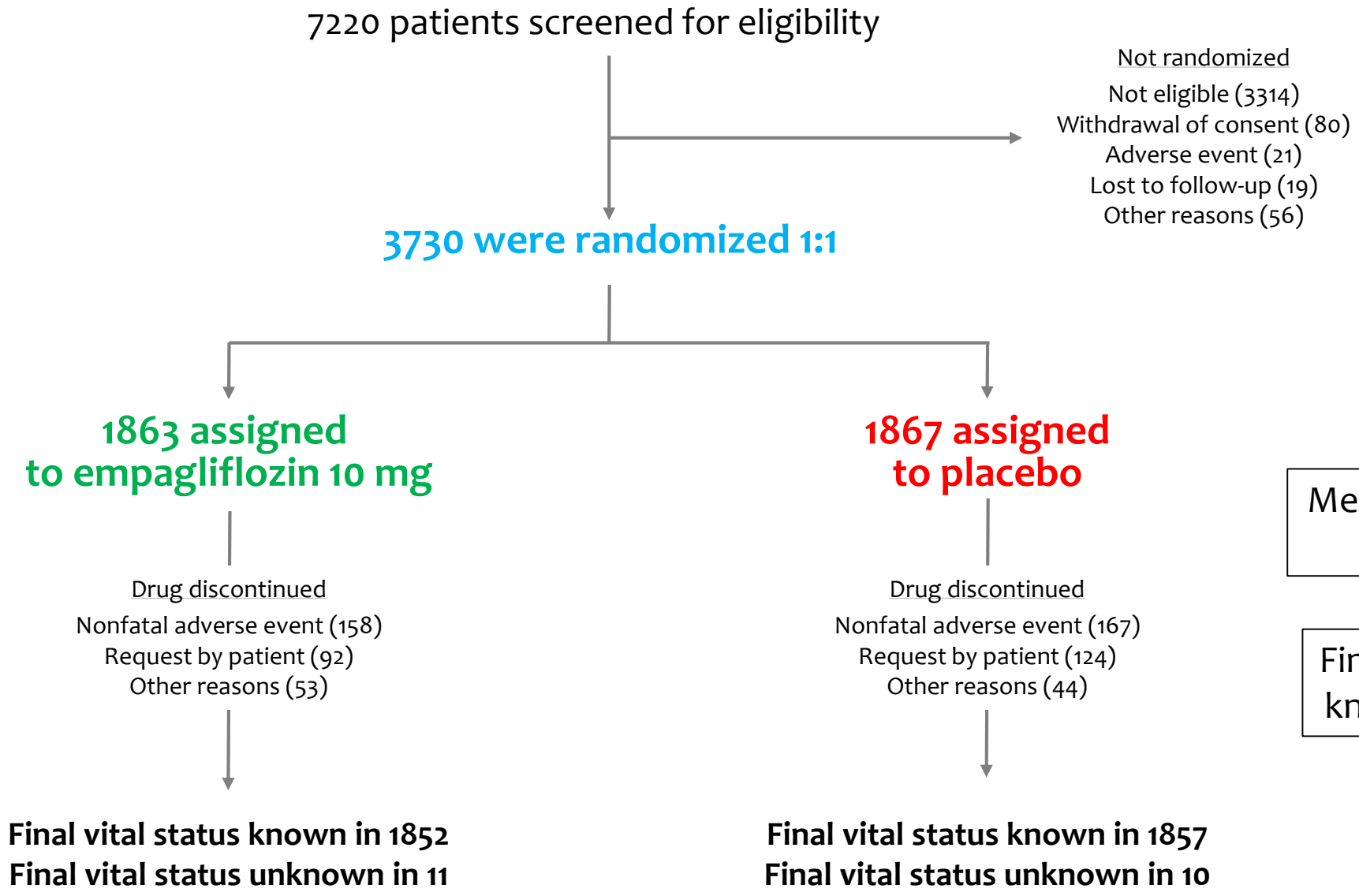
Disclosures for presenter: Astra Zeneca, Array, Amgen, Boehringer Ingelheim, CVRx, G3 Pharma, Impulse Dynamics, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sequana, V-Wave Ltd., and Vifor.

Background and Study Design

- In addition to the risk for mortality and hospitalizations, patients with heart failure with reduced ejection fraction (HFrEF) also suffer from impaired health status.
- Improvements in health-related quality of life constitute a major treatment goal in these patients.
- The Kansas City Cardiomyopathy Questionnaire (KCCQ) reflects key health status domains, including HF symptom burden, physical limitation and quality of life.
- In the EMPEROR-Reduced trial, empagliflozin reduced the risk of hospitalization for HF (HHF) or CV death; total HHF; and reduced progression of renal function decline
- In the present analysis we evaluated:
  - Whether the observed benefits of empagliflozin varied by baseline health status
  - The impact of empagliflozin on health status outcomes as measured by the KCCQ

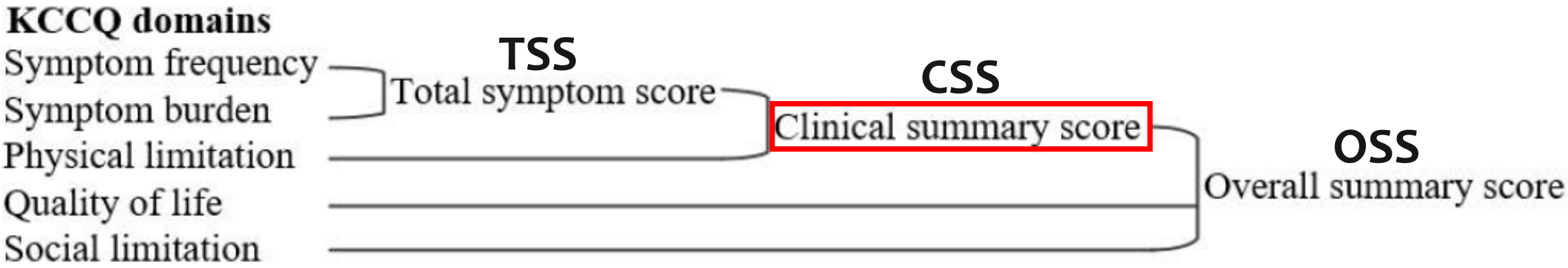
EMPEROR-Reduced: Patient Disposition



Median follow-up
16 months

Final vital status
known in 99.4%

KCCQ summary scores and domains



KCCQ-CSS broadly reflects the impact of HF symptoms in daily life

Impact of empagliflozin on KCCQ-CSS was a pre-specified secondary endpoint.

Key Characteristics by KCCQ tertile

	KCCQ-CSS at baseline		
	Tertile <62.5 (N=1220)	Tertile 62.6–85.4 (N=1253)	Tertile ≥85.4 (N=1232)
Age (years)	66.6 (11.4)	67.3 (10.5)	66.7 (11.1)
Women	393 (32.2%)	292 (23.3%)	200 (16.2%)
Body Mass Index ≥30 (kg/m²)	461 (37.8%)	411 (32.8%)	288 (23.4%)
eGFR <60 (ml/min/1.73m²)	605 (49.6%)	623 (49.7%)	559 (45.4%)
NTproBNP (pg/ml) – median (Q1-Q3)	2227 (1280-4274)	1846 (1115-3347)	1679 (993-2912)
NYHA II	670 (54.9%)	990 (79.0%)	1121 (91.0%)
NYHA III	532 (43.6%)	263 (21.0%)	109 (8.8%)
Diabetes	656 (53.8%)	595 (47.5%)	593 (48.1%)
Atrial Fibrillation	490 (40.2%)	457 (36.5%)	414 (33.6%)

Background treatment by baseline KCCQ tertile

	KCCQ-CSS at baseline		
	Tertile <62.5 (N=1220)	Tertile 62.6–85.4 (N=1253)	Tertile ≥85.4 (N=1232)
ACE Inhibitor	545 (44.7%)	572 (45.7%)	570 (46.3%)
Angiotensin Receptor Blocker	306 (25.1%)	303 (24.2%)	293 (23.8%)
ARNI	226 (18.5%)	241 (19.2%)	258 (20.9%)
Diuretic	1107 (90.7%)	1099 (87.7%)	1020 (82.8%)
Beta Blocker	1156 (94.8%)	1186 (94.7%)	1168 (94.8%)
Mineralocorticoid Receptor Antagonist	896 (73.4%)	889 (70.9%)	855 (69.4%)
Implantable Cardiac Defibrillator	379 (31.1%)	431 (34.4%)	357 (29.0%)
Cardiac Resynchronization Therapy	139 (11.4%)	169 (13.5%)	131 (10.6%)

EMPEROR-Reduced

The Effect on all three Endpoints Specified for Hierarchical Testing were Significant

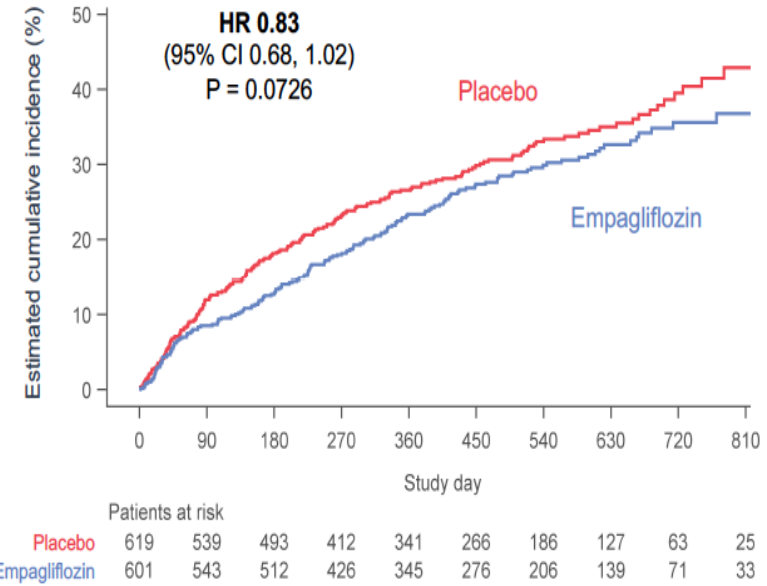
Primary endpoint: Adjudicated CV death or Heart failure hospitalization	Confirmatory*	**HR 0.75 (95% CI: 0.65, 0.86) *p*<0.001**	✓
Key secondary endpoint: Adjudicated first and recurrent heart failure hospitalizations	Confirmatory†	**HR 0.70 (95% CI: 0.58, 0.85) *p*<0.001**	✓
Key secondary endpoint: eGFR slope	Confirmatory‡	**Slope difference 1.73 ml/min/1.73 m² per year, (95% CI: 1.1, 2.4) *p*<0.001**	✓

*Cox regression with a=0.0496, †Joint frailty model of adjudicated HHF and CV death with a=0.0496, ‡Random intercept random slope model with a=0.001
All models include covariates age, baseline eGFR, region, baseline diabetes status, sex and LVEF
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure, LVEF, left ventricular ejection fraction; Data on file

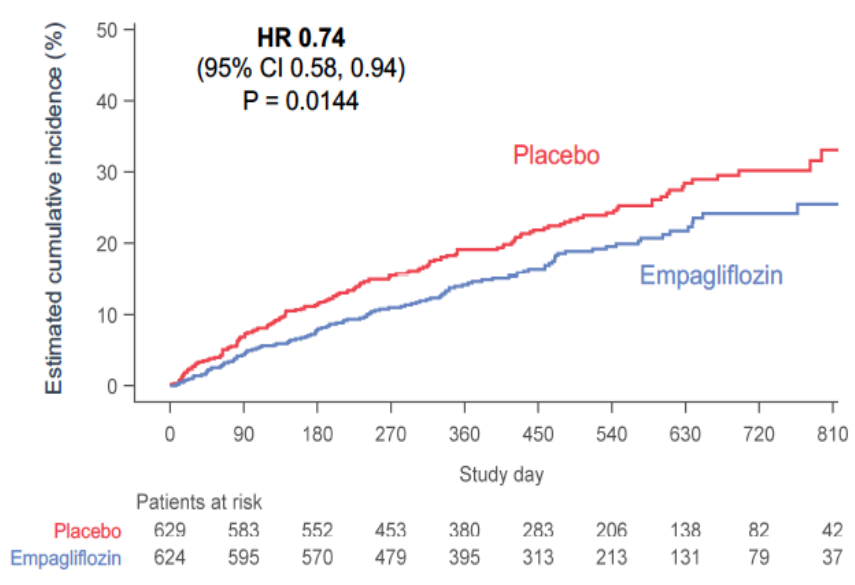
Empagliflozin vs placebo by KCCQ-CSS tertile
Primary Endpoint: HHF or CV death

Baseline health status did not influence empagliflozin benefit

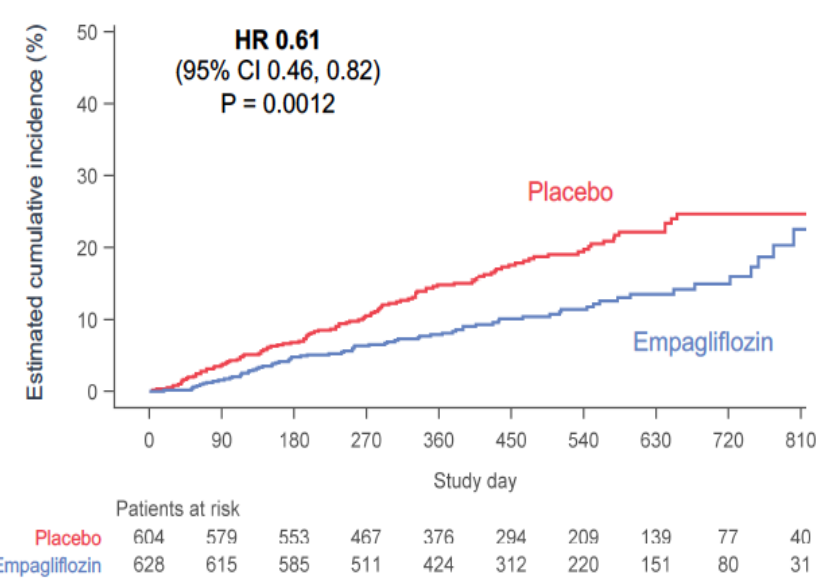
Lowest tertile (placebo event rate)



Middle tertile (placebo event rate)



Highest tertile (placebo event rate)



Total heart failure hospitalizations

Benefit of empagliflozin similar across tertiles

Outcome	Empagliflozin	Placebo	HR (95% CI)	P-Trend
KCCQ CSS Tertile 1 (<62.5)	195/601	235/619	0.80 (0.59-1.09)	0.161
KCCQ CSS Tertile 2 (62.6–85.4)	118/624	188/629	0.65 (0.47-0.91)	
KCCQ CSS Tertile 3 (≥85.4)	75/628	129/604	0.59(0.40-0.85)	

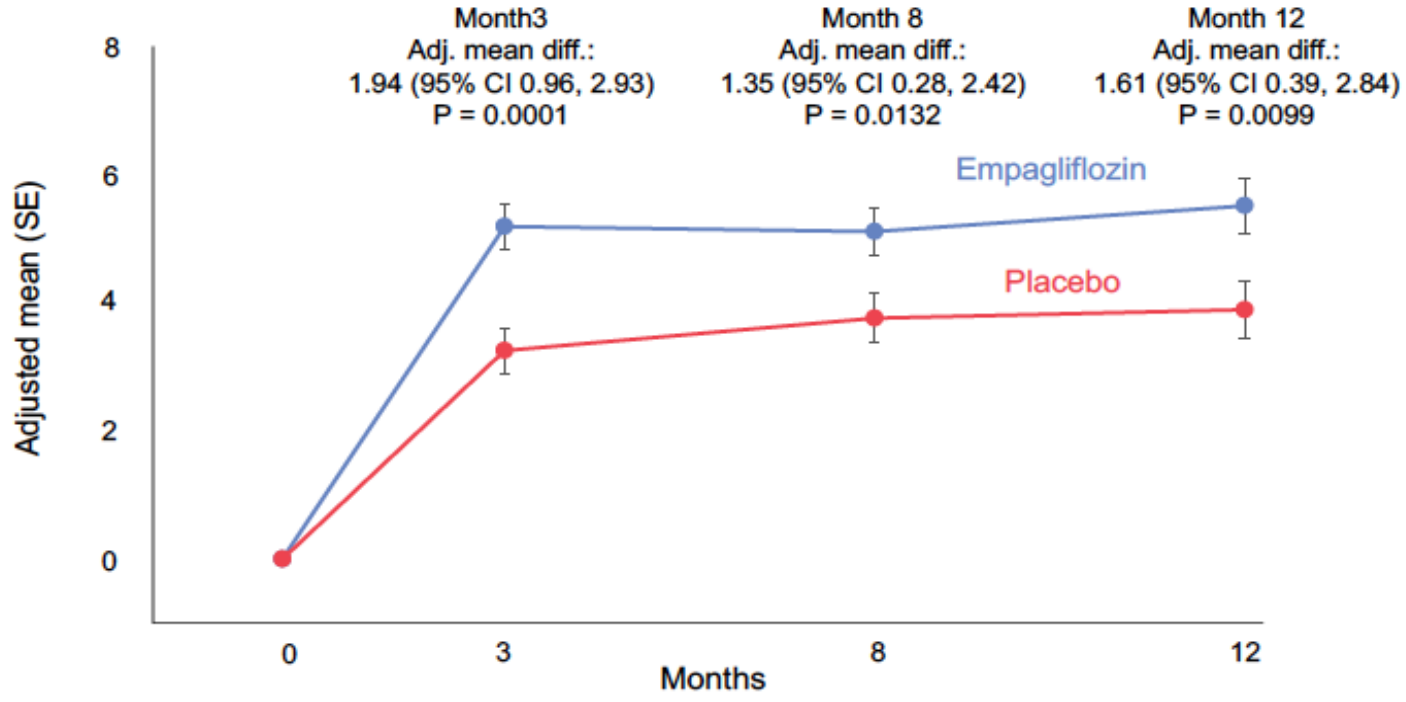
eGFR slope

Benefit of empagliflozin similar across tertiles

Outcome	Empagliflozin	Placebo	Difference in slope (SE)	P-Trend
Slope of Change in eGFR (ml/min/ 1.73 m^2/year)				
KCCQ CSS Tertile 1 (<62.5)	-1.0 (0.41)	-2.2 (0.42)	1.25 (0.59)	0.74
KCCQ CSS Tertile 2 (62.6–85.4)	-0.33 (0.40)	-2.6 (0.39)	2.27 (0.56)	
KCCQ CSS Tertile 3 (≥85.4)	-0.37 (0.38)	-1.9 (0.39)	1.56 (0.54)	

Empagliflozin effect on KCCQ during trial
Mean difference between empagliflozin and placebo

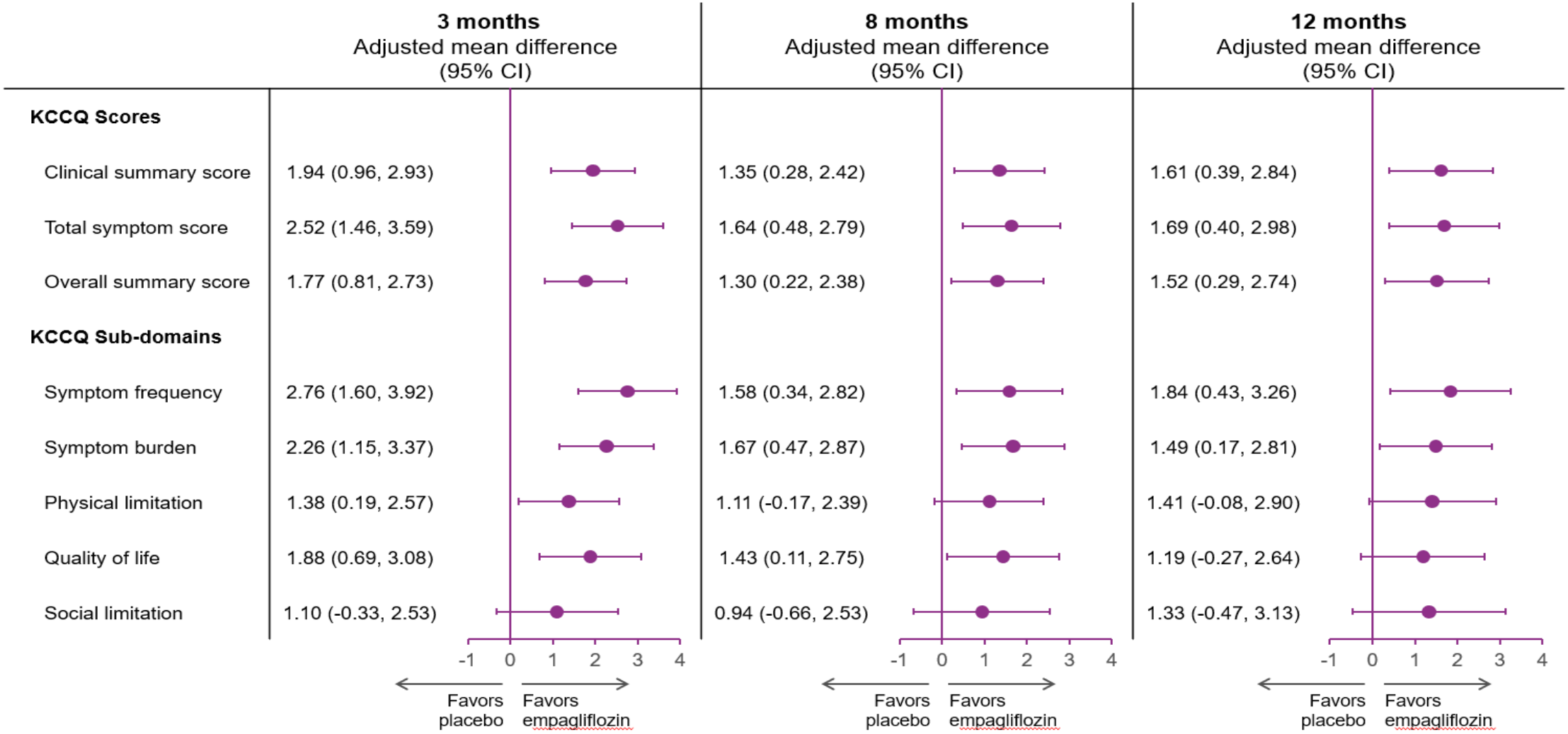
Early and sustained empagliflozin benefit on KCCQ-CSS



Analyzed patients (n)				
Placebo	1753	1732	1568	1218
Empagliflozin	1776	1755	1618	1239

Empagliflozin effect on KCCQ during trial
Mean difference between empagliflozin and placebo

Similar early and sustained benefits observed for all three scores



Empagliflozin effect on KCCQ during trial: *Responder analysis*

Less deterioration and more improvement in KCCQ-CSS for empagliflozin over time

Figure 4a: KCCQ-CSS, Month 3

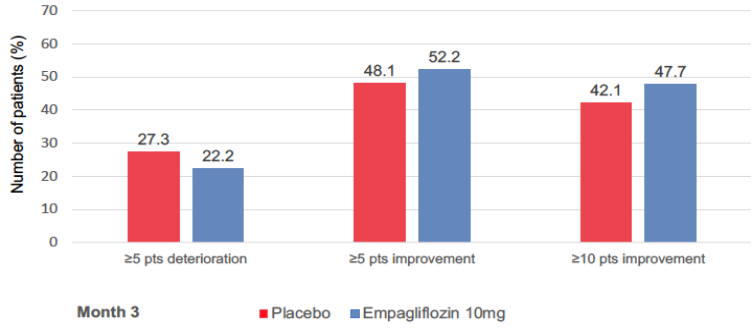


Figure 4a: KCCQ-CSS, Month 8

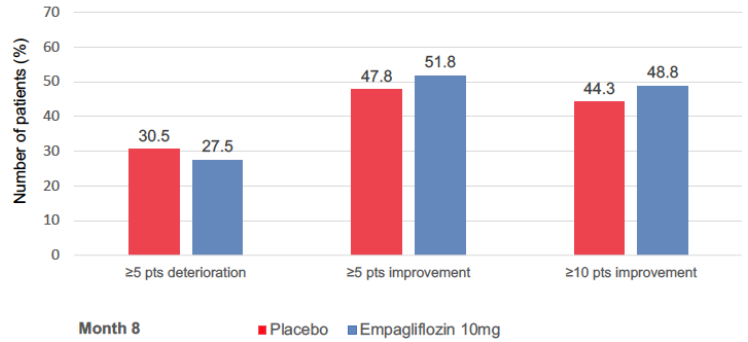


Figure 4a: KCCQ-CSS, Month 12

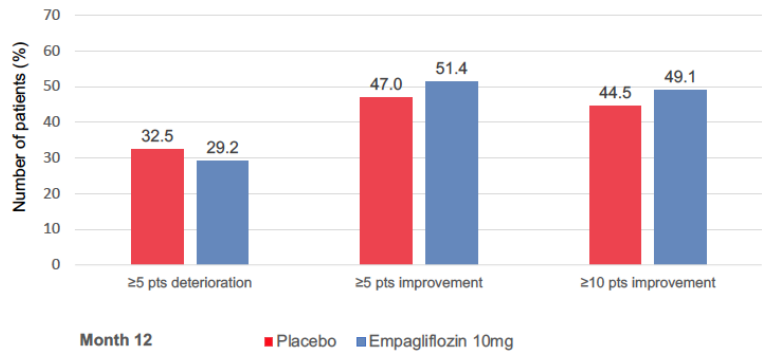


Figure 4b: KCCQ-TSS, Month 3

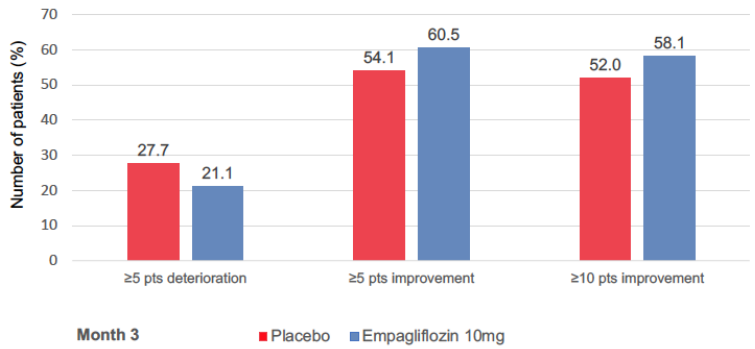


Figure 4b: KCCQ-TSS, Month 8

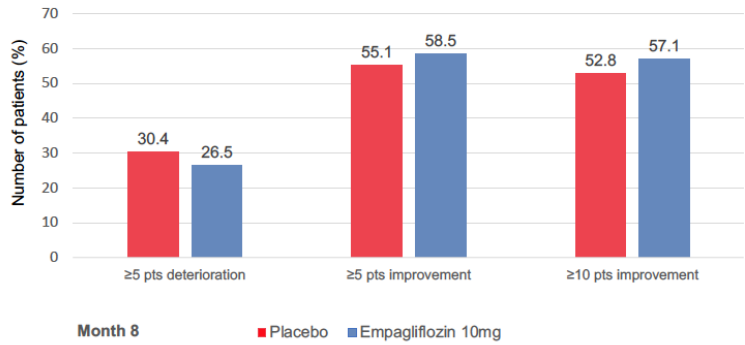


Figure 4b: KCCQ-TSS, Month 12

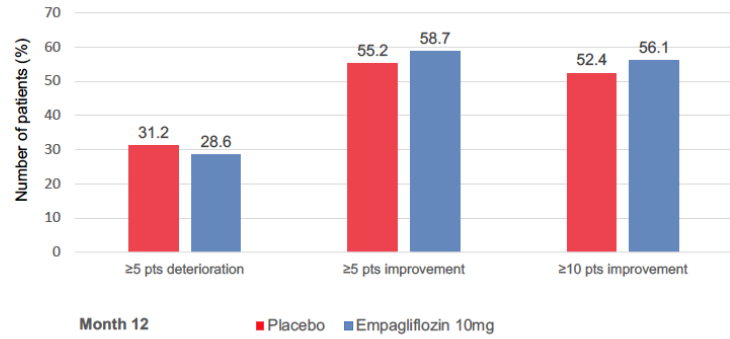


Figure 4c: KCCQ-OSS, Month 3

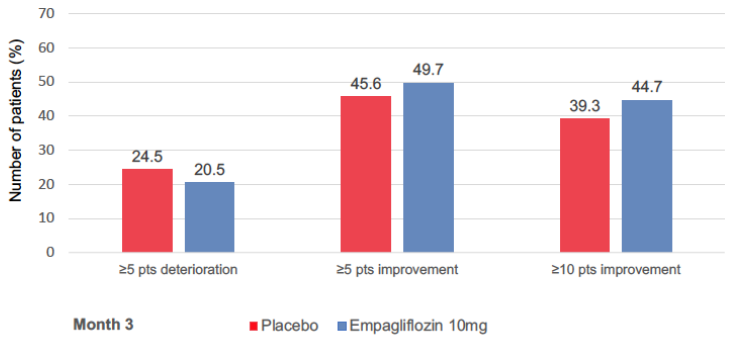


Figure 4c: KCCQ-OSS, Month 8

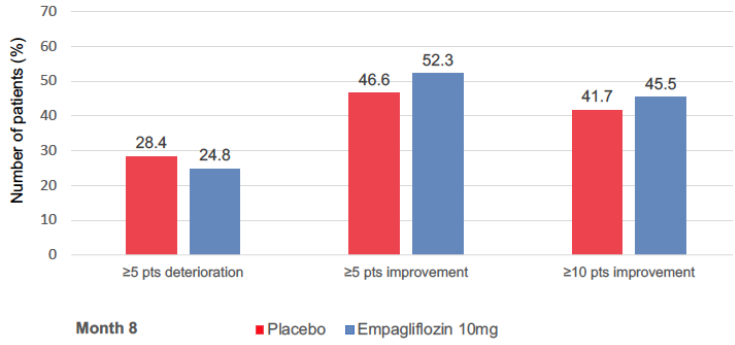
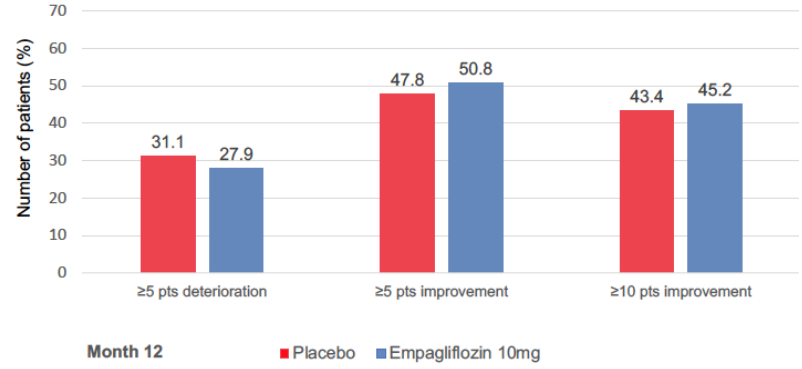
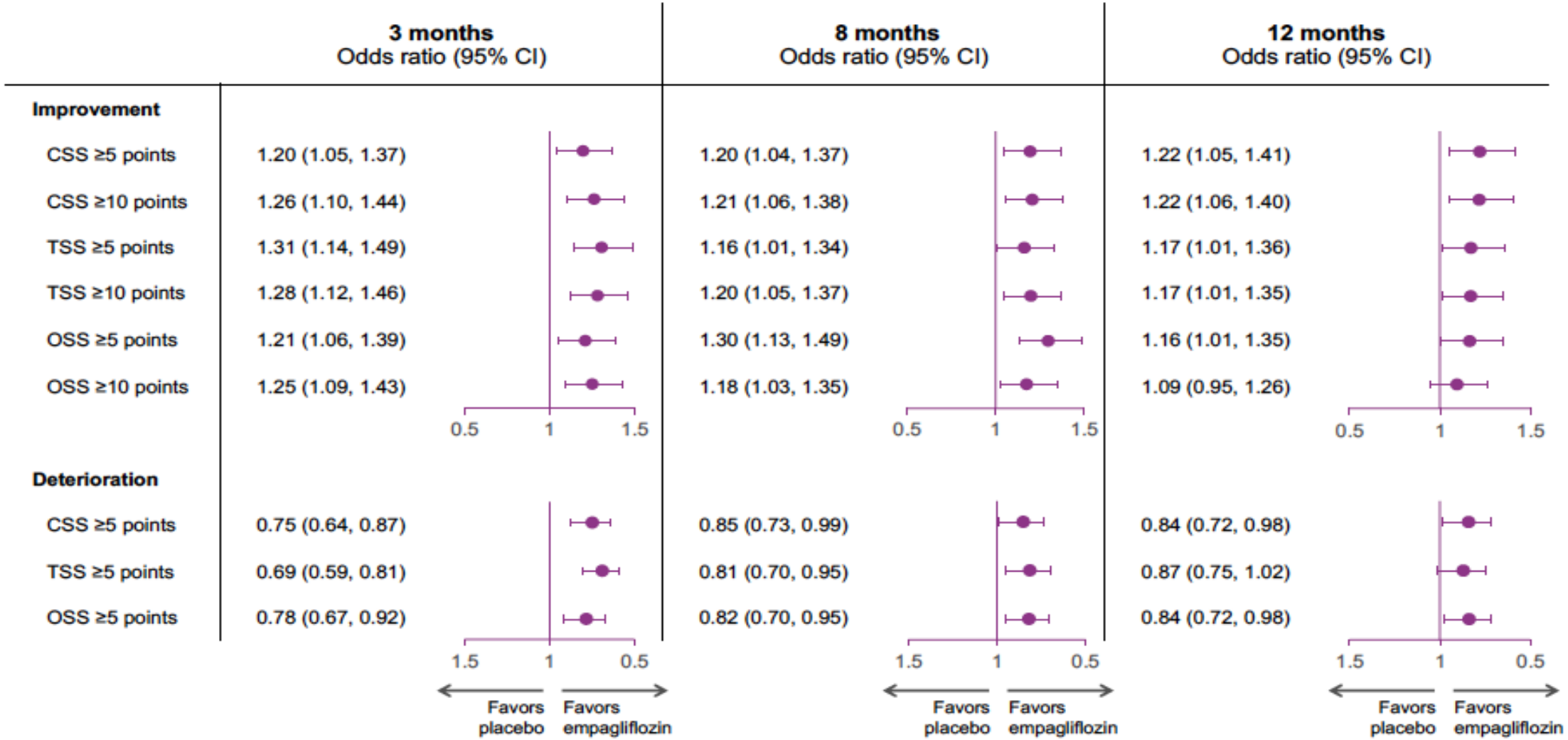


Figure 4c: KCCQ-OSS, Month 12



Empagliflozin effect on KCCQ during trial: *Responder analysis*

Consistently higher likelihood of improvement and lower likelihood of deterioration



KCCQ changes with heart failure interventions

Intervention	Study	KCCQ Improvement	Citation
Empagliflozin	EMPEROR-Reduced	+1.64 (TSS), +1.35 (CSS), +1.30 (OSS) at 8 months +1.69 (TSS), +1.61 (CSS), +1.52 (OSS) at 12 months ↑≥5 points (CSS) in 52% (vs 48% placebo) at 8 months ↑≥5 points (CSS) in 51% (vs 47% placebo) at 12 months	
Dapagliflozin	DAPA-HF	+2.8 (TSS), +2.5 (CSS), +2.3 (OSS) at 8 months ↑≥5 points (TSS) in 58% (vs 51% placebo)	Kosiborod 2019
Exercise	HF-Action	+1.9 (OSS) at 3 months	Flynn 2019
Ivabradine	SHIFT	+2.4 (OSS), +1.8 (CSS) at 12 months ↑≥5 points in 51% (OSS), 48% (CSS) (vs 48%, 44% placebo)	Ekman 2011
Sacubitril/Valsartan	PARADIGM-HF	+1.6 (CSS) at 8 months ↑≥5 points (OSS) in 35% (vs 33% enalapril)	McMurray 2014 Lewis 2017

Conclusions

- The observed benefits of empagliflozin on the primary (HHF or CV death) and key secondary endpoints (total HHF and eGFR slope) were not influenced by baseline health status.
- Empagliflozin resulted in early benefits on KCCQ which were sustained over time.
- In a responder analysis, significantly more patients on empagliflozin improved and fewer deteriorated, compared to placebo, at all three measured time points.
- The observed benefits on health status were comparable to those of other HF treatments, including those observed in DAPA HF, and further underscores the role of empagliflozin as a foundational HFrEF therapy.

EMPEROR-Reduced Trial Committees

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