Effects of empagliflozin on symptoms, physical limitations and quality of life in acute heart failure – results from the EMPULSE trial

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Disclosures

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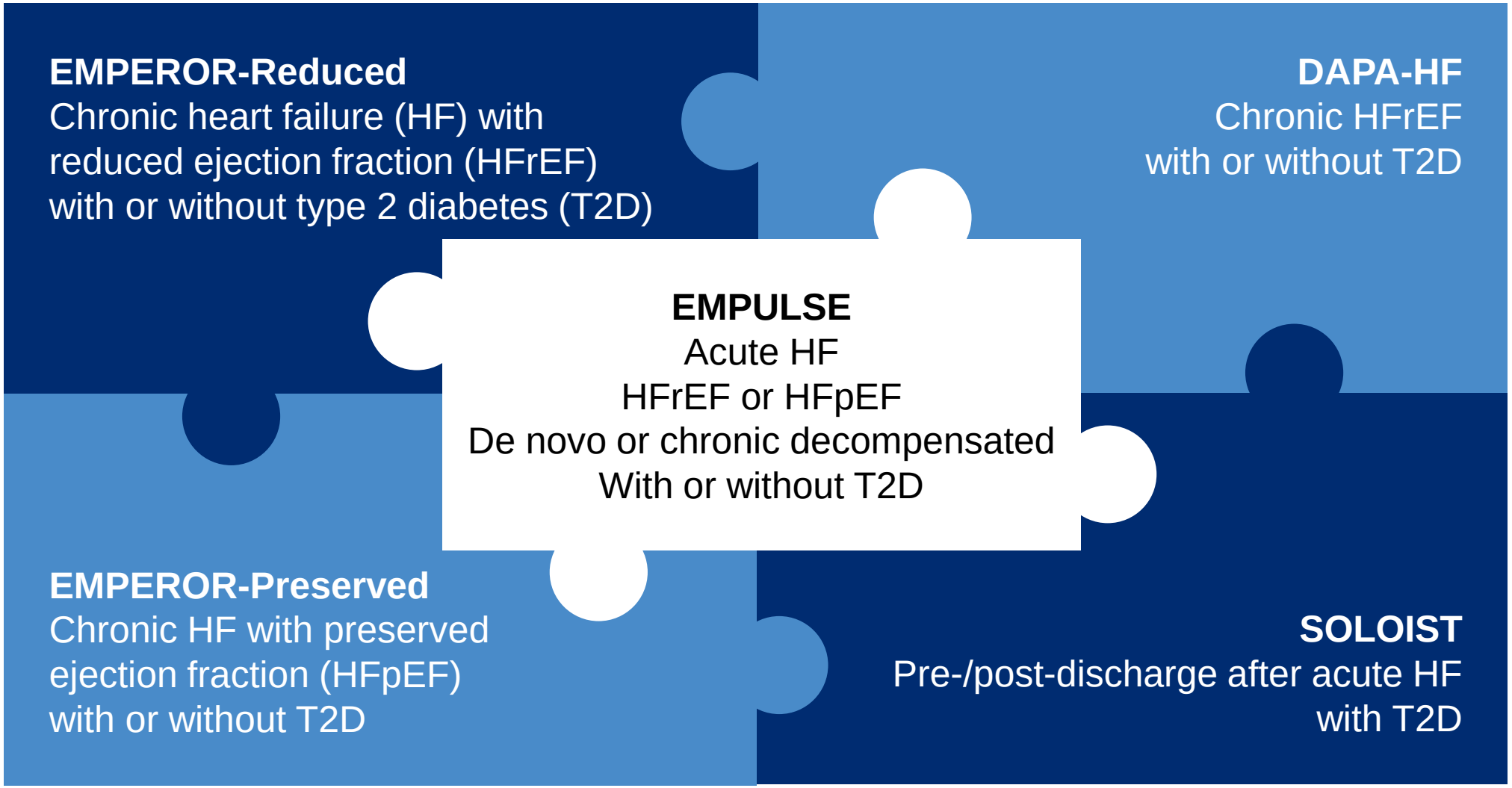
Background

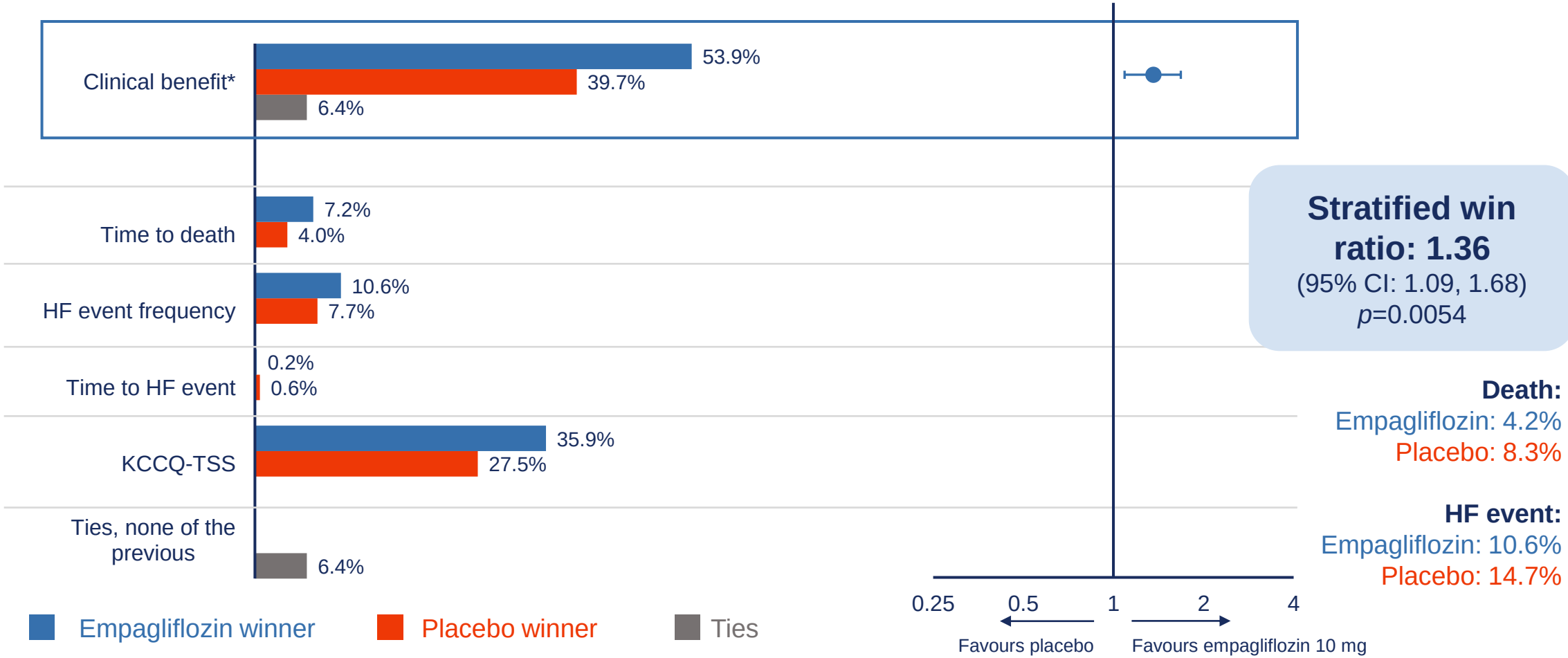
- Patients hospitalized for acute heart failure (AHF) experience poor health status, including high burden of symptoms and physical limitations, and poor quality of life
- Improving health status is a key goal of management
- To date, there has been a lack of therapies with compelling benefit on these outcomes in AHF, highlighting a critical unmet need
- Sodium-glucose-cotransporter-2 (SGLT2) inhibitors improve health status in chronic heart failure, but their effects in AHF have not been well characterized

EMPULSE: the missing link



HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; T2D, type 2 diabetes.

EMPULSE main results



Stratified win ratio: 1.36
(95% CI: 1.09, 1.68)
p=0.0054

Death:
Empagliflozin: 4.2%
Placebo: 8.3%

HF event:
Empagliflozin: 10.6%
Placebo: 14.7%

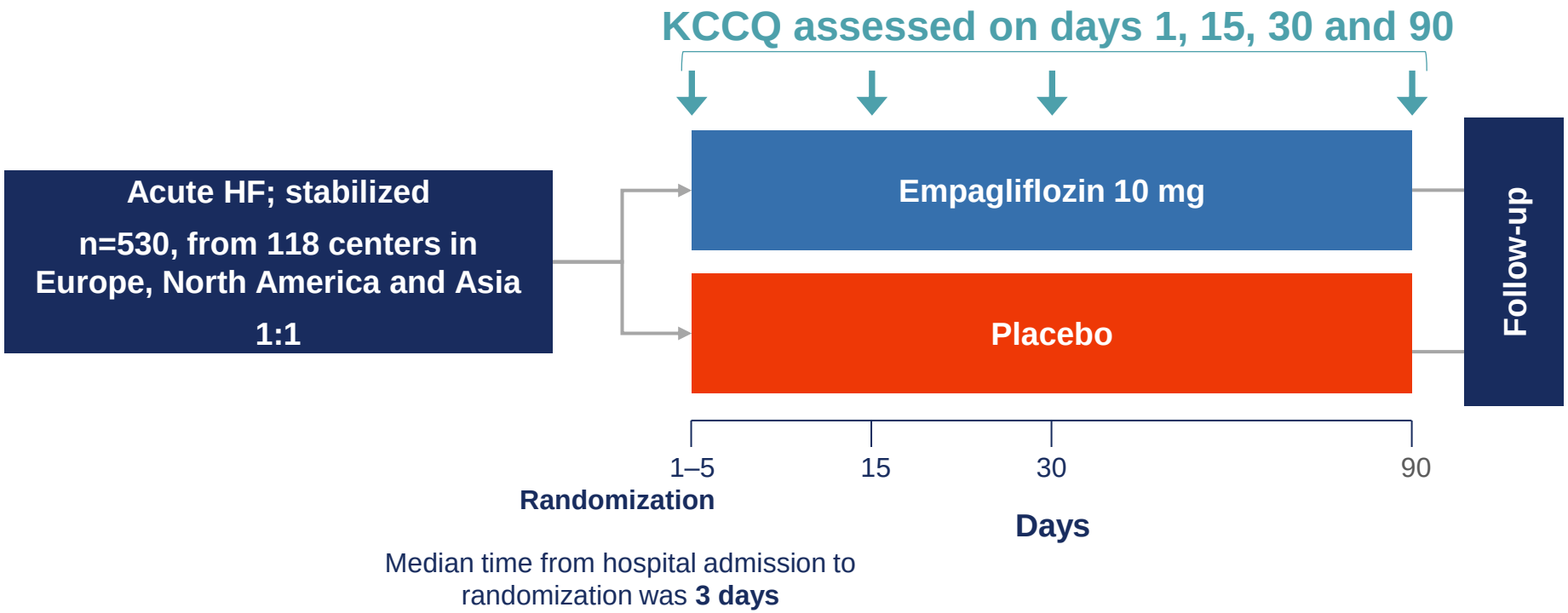
Numbers reflect percentage of comparisons. For the components of the win ratio these numbers do not reflect randomized comparisons. *Composite of death, number of HFEs (including HHFs, urgent HF visits and unplanned outpatient visits), time to first HFE and ≥5 point difference in the KCCQ-TSS change from baseline after 90 days of treatment. CI, confidence interval; HFE, heart failure event; HHF, hospitalization for heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score. Voors AA *et al. Nat Med.* 2022;doi:10.1038/s41591-021-01659-1.

Objectives of this EMPULSE analysis

- Evaluate the effects of empagliflozin on the primary endpoint of total clinical benefit in the EMPULSE trial according to the degree of symptomatic impairment at baseline

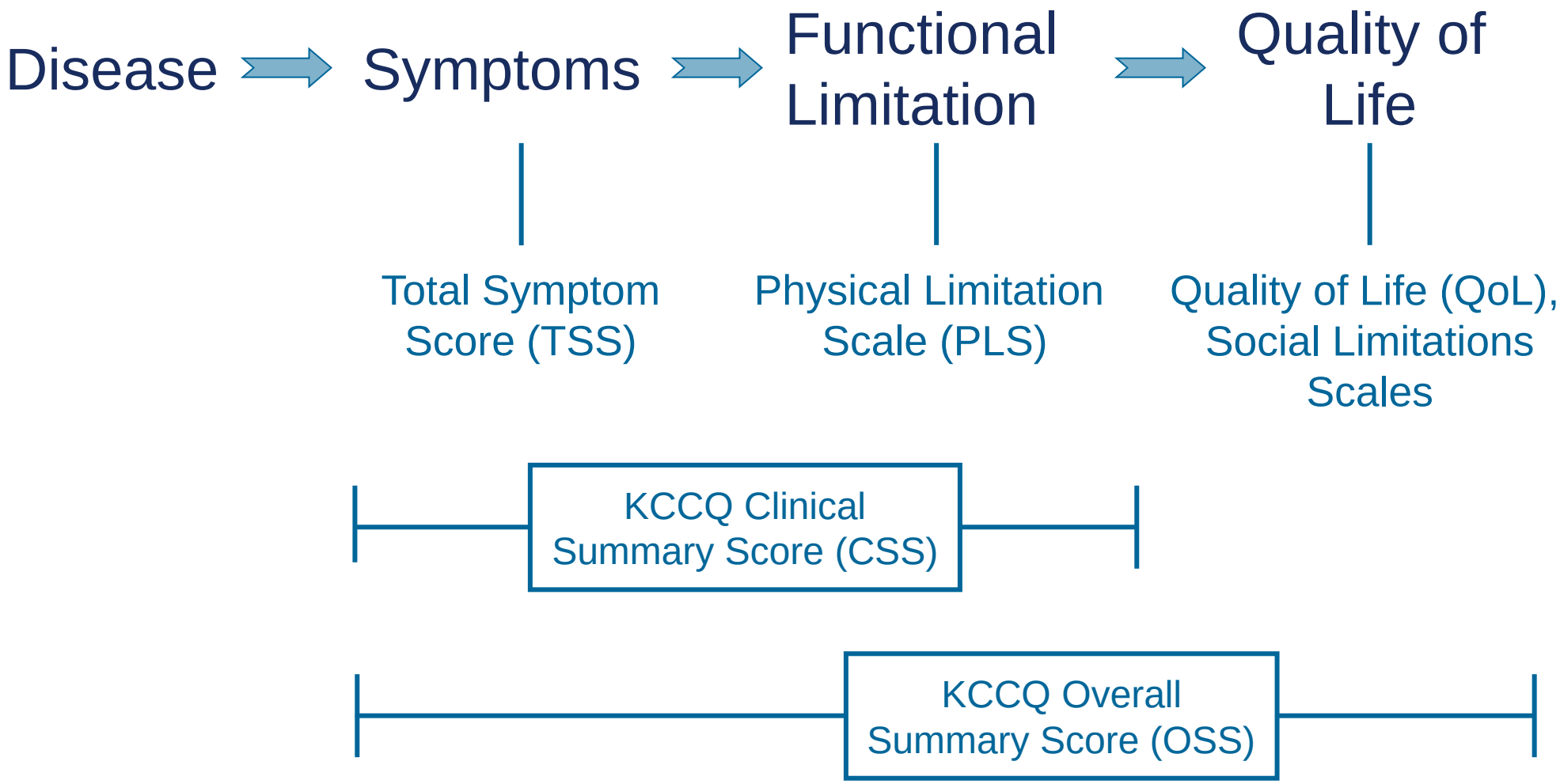
- Examine the impact of empagliflozin on the broad range of health status outcomes, as measured by various domains of the Kansas City Cardiomyopathy Questionnaire (KCCQ), and time course of these effects

EMPULSE study design[1,2]



1. Tromp J *et al. Eur J Heart Fail.* 2021;23:826; 2. Voors AA *et al. Nat Med.* 2022;doi:10.1038/s41591-021-01659-1.

Mapping the KCCQ scales



Statistical analysis

- Patients stratified based on baseline KCCQ-TSS tertiles
- Effects of empagliflozin on the primary endpoint across the KCCQ tertiles evaluated using win ratio with Cochran's Q statistic (*post hoc*)
- Between-group differences in KCCQ domains at 15, 30 and 90 days assessed using mixed models for repeated measures, adjusted for heart failure status and baseline KCCQ (pre-specified)
- Responder analyses compared proportions of patients with a deterioration, and clinically meaningful improvements in KCCQ-TSS at 90 days using logistic regression models (pre-specified and *post hoc*)

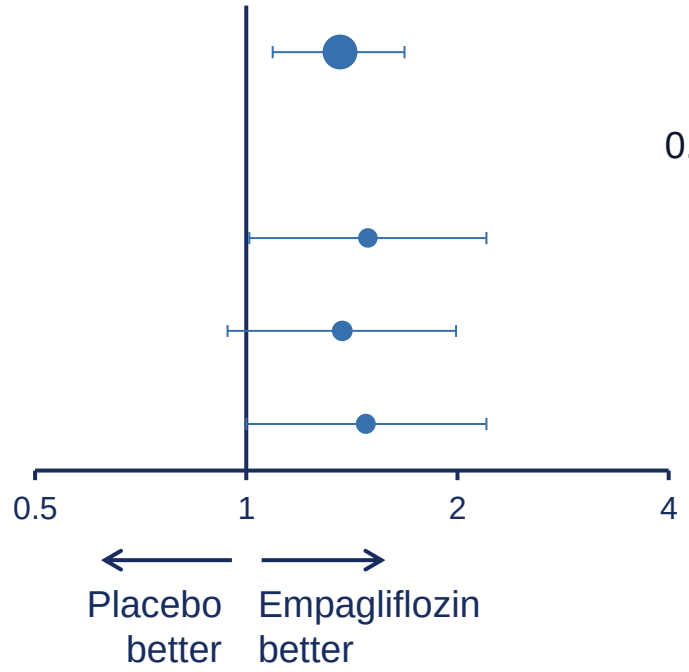
Baseline characteristics of the EMPULSE study population by tertiles of KCCQ

			KCCQ-TSS at baseline				*p*-value for trend
			Tertile 1 (n=166)	Tertile 2 (n=184)	Tertile 3 (n=176)	Total (n=526)	
Demographic characteristics	Age, years, mean (SD)		66.5 (13.4)	69.5 (12.9)	69.4 (13.3)	68.5 (13.3)	0.04
	Sex, female n (%)		68 (41)	59 (32)	50 (28)	177 (34)	0.01
	Race, n (%)	White	130 (78)	150 (82)	129 (73)	409 (78)	<0.001
		Black/African-American	22 (13)	19 (10)	13 (7)	54 (10)	
		Asian	11 (7)	12 (7)	34 (19)	57 (11)	
		Other	2 (1)	3 (2)	0	5 (1)	
Medical history	T2D, n (%)		93 (56)	78 (42)	66 (38)	237 (45)	<0.001
	Atrial fibrillation, n (%)		84 (51)	92 (50)	84 (48)	260 (49)	0.59
HF characteristics	HF status, n (%)	De novo	43 (26)	65 (35)	66 (38)	174 (33)	0.02
		Decompensated chronic	123 (74)	119 (65)	110 (62)	352 (67)	
	LVEF, n (%)	≤40%	108 (65)	119 (65)	125 (71)	352 (67)	0.30
		>40%	55 (33)	62 (34)	50 (28)	167 (32)	
	NYHA class, n (%)	II	26 (16)	76 (41)	84 (48)	186 (35)	<0.001
		III–IV	138 (83)	106 (58)	82 (47)	326 (62)	
	KCCQ-TSS (points), mean (SD)		14.4 (7.8)	37.9 (7.3)	68.8 (12.6)	40.8 (24.0)	<0.001
Laboratory values	eGFR, mL/min per 1.73 m^2, mean (SD)		52.8 (20.9)	55.1 (20.6)	54.2 (19.5)	54.1 (20.3)	0.57
	NT-proBNP, pg/mL, median (IQR)		3687.3 (2143.9–6446.8)	3188.7 (1725.2–5936.8)	2520.2 (1463.1–6012.9)	3245.8 (1735.4–6104.3)	<0.01
Heart failure treatments	ACEi/ARB/ARNI, n (%)		107 (64)	136 (74)	125 (71)	368 (70)	0.19
	Beta-blocker, n (%)		136 (82)	137 (74)	145 (82)	418 (79)	0.88
	MRA, n (%)		83 (50)	89 (48)	102 (58)	274 (52)	0.13
	Diuretics other than MRA, n (%)		144 (87)	154 (84)	143 (81)	441 (84)	0.17

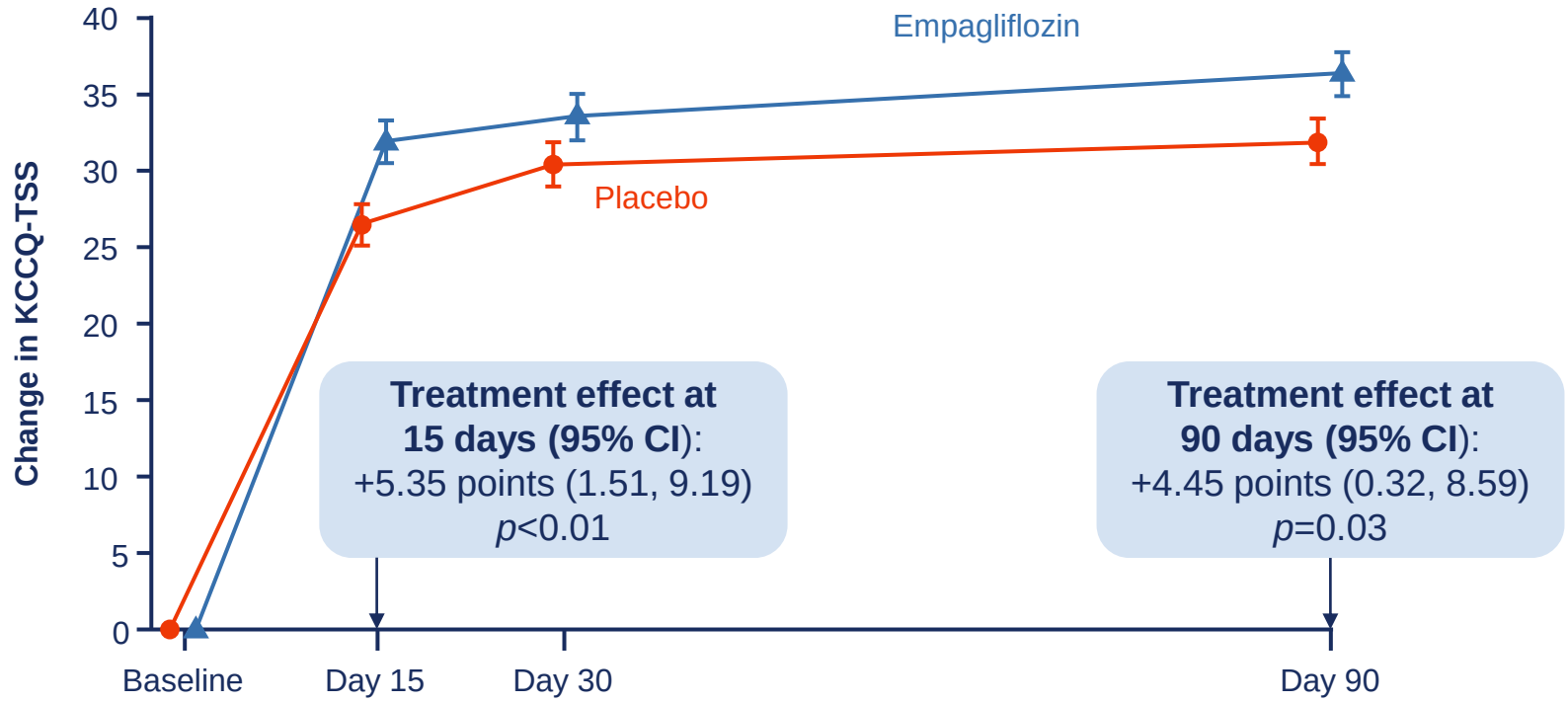
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NHYA, New York Heart Association.

Effects of empagliflozin versus placebo on the primary hierarchical composite endpoint of clinical benefit across tertiles of KCCQ-TSS

Subgroup	N analysed		Win ratio (95% CI)	Interaction *p*-value
Category	Empagliflozin 10 mg	Placebo		
All patients	265	265	1.36 (1.09,1.68)	
Baseline KCCQ-TSS				0.94
<27.1	84	82	1.49 (1.01, 2.20)	
≥27.1 and <52.1	93	91	1.37 (0.94, 1.99)	
≥52.1	85	91	1.48 (1.00, 2.20)	

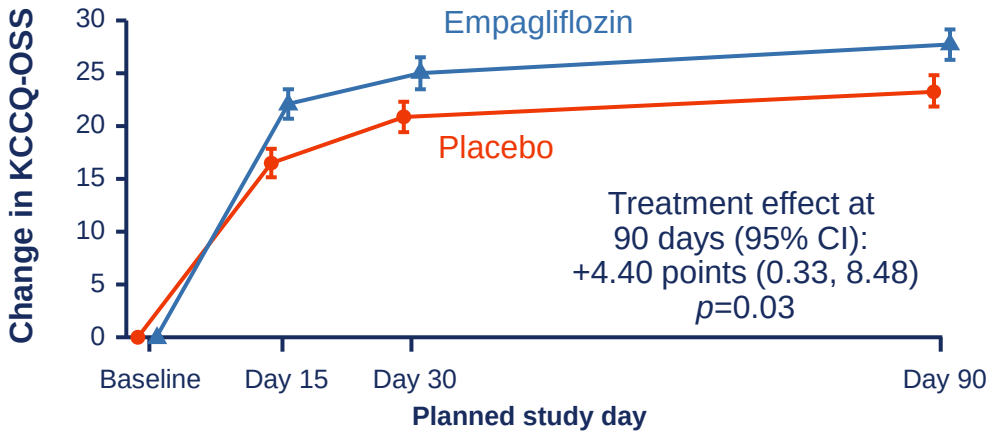


Effects of empagliflozin versus placebo on change in KCCQ-TSS



N with data at visit				
Placebo	250	240	234	221
Empagliflozin	245	233	237	230

Effects of empagliflozin versus placebo on change in KCCQ-OSS, -CSS, -PLS and -QoL



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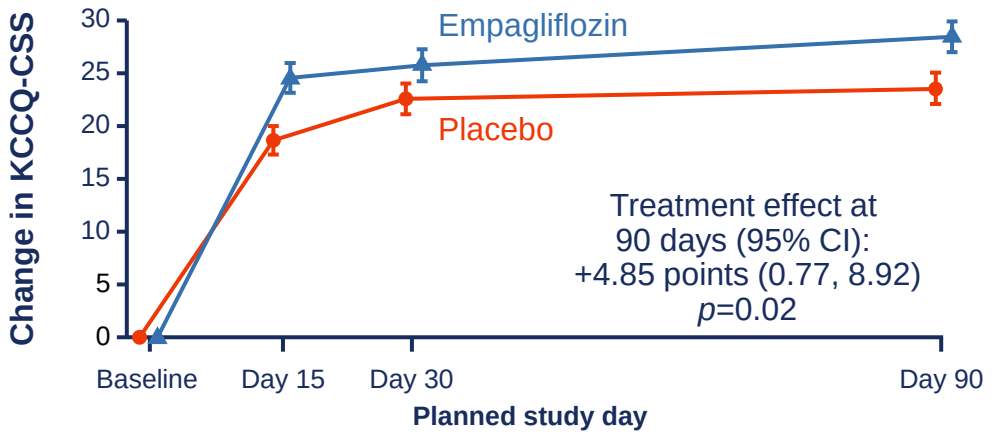

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Placebo	250	240	234	221
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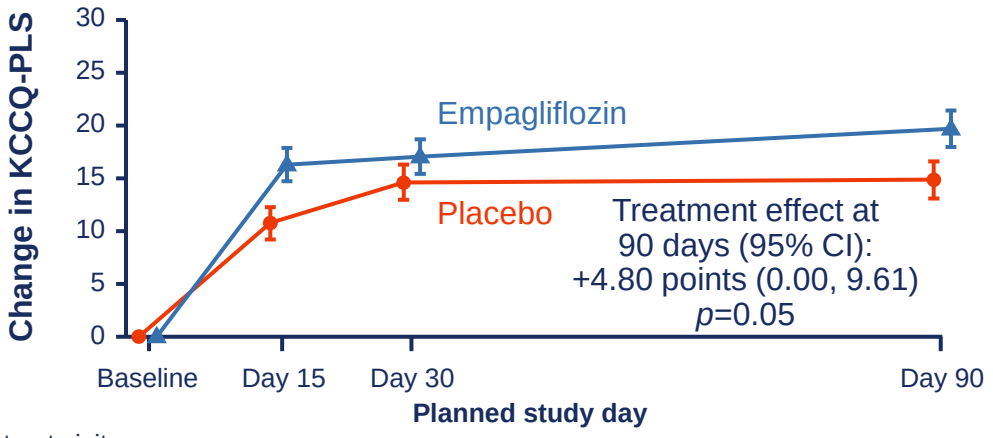
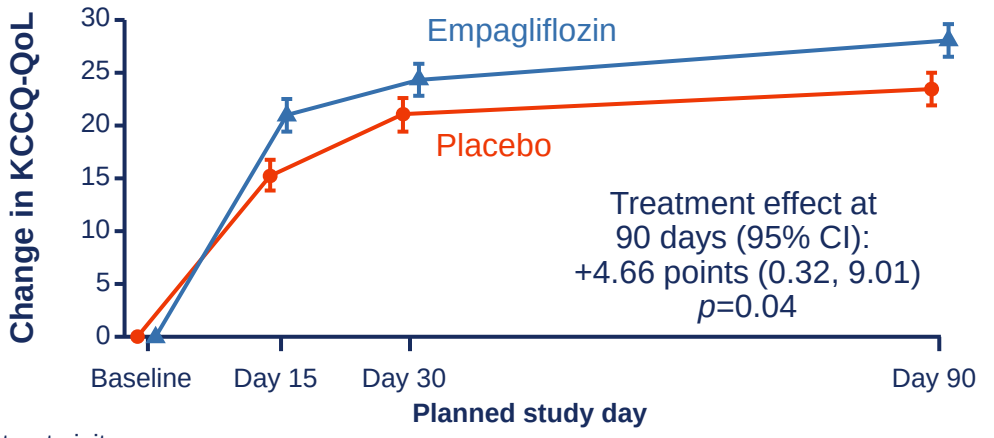


N with data at visit				
Placebo	245	232	225	217
Empagliflozin	240	225	228	225



N with data at visit				
Placebo	250	240	234	221
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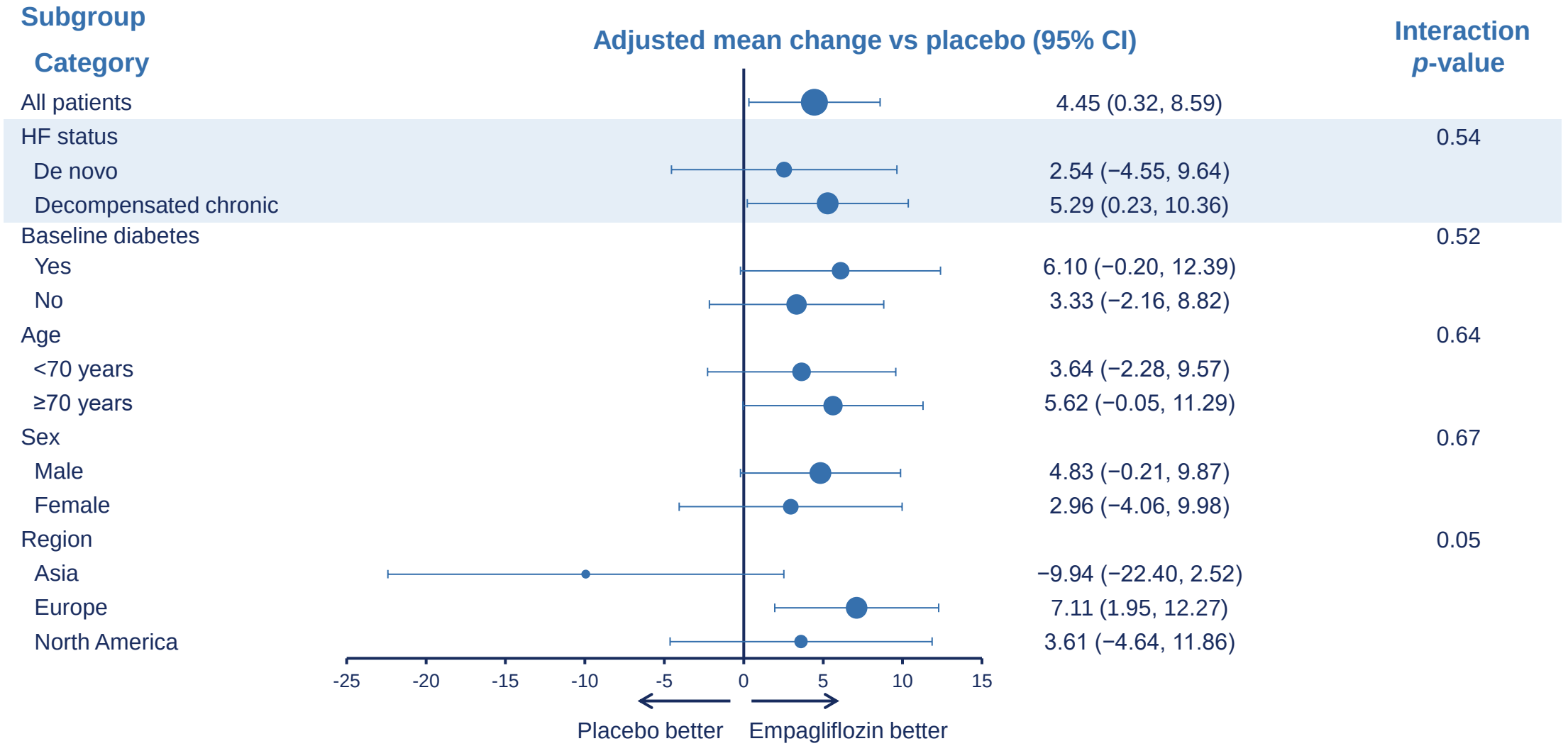
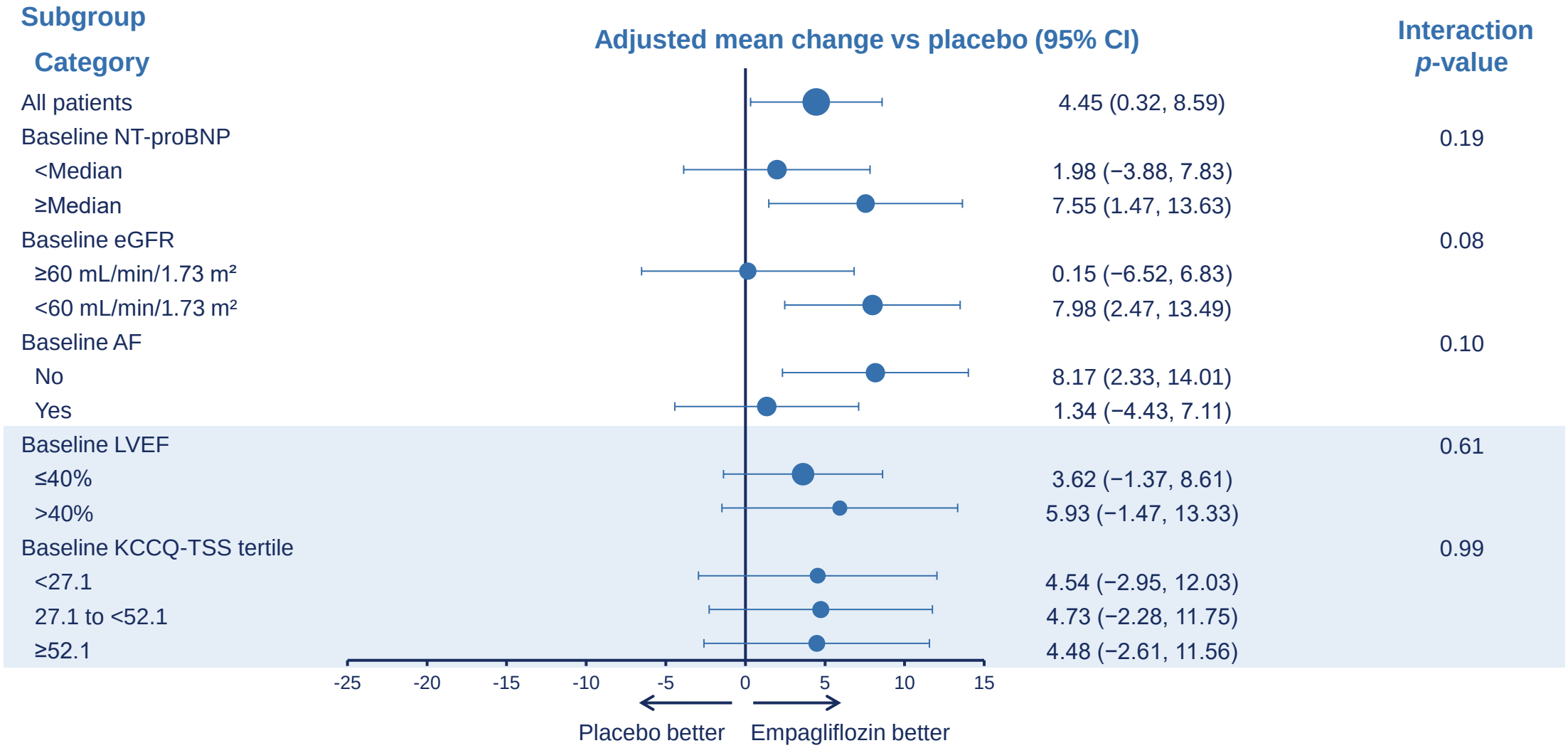
Effects of empagliflozin versus placebo on KCCQ-TSS at Day 90 across pre-specified subgroups (1/2)

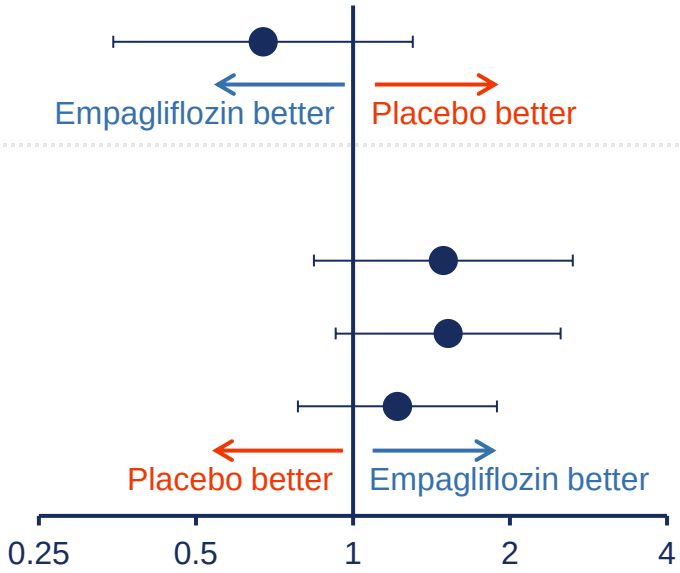


Effects of empagliflozin versus placebo on KCCQ-TSS at Day 90 across pre-specified subgroups (2/2)



Responder analysis for KCCQ-TSS deterioration and improvements at Day 90

	Odds ratio (95% CI)	Odds ratio (95% CI)	*p*-value
Deterioration at 90 days			
≥5 points		0.67 (0.35, 1.30)	0.24
Improvement at 90 days			
≥5 points		1.49 (0.84, 2.64)	0.17
≥10 points		1.52 (0.93, 2.50)	0.10
≥20 points		1.22 (0.78, 1.89)	0.38



Limitations

- Although KCCQ-TSS was a pre-defined secondary endpoint, and prospective assessments of KCCQ domains were pre-specified, several of the analyses were done *post hoc*

- The relatively modest sample size of this study did not provide sufficient power for the responder analyses

Conclusions

- Treatment with empagliflozin produced total clinical benefit among patients hospitalized with AHF across the entire range of KCCQ
  - Indicates that the benefits of empagliflozin in this patient group are independent of symptomatic impairment at baseline
- Empagliflozin significantly improved all key KCCQ domains (which collectively encompass symptoms, physical function, quality of life, and social function)
- Benefits generally consistent across demographic and clinical characteristics, seen as early as 15 days, and maintained through 90 days

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