Dapagliflozin Effects on Symptoms, Function and Quality of Life in Patients with Heart Failure and Mildly Reduced or Preserved Ejection Fraction: *Results from the DELIVER Trial*

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on behalf of the DELIVER Committees, Investigators, Sponsor & Participants

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Disclosures

- Research Grants:
  - AstraZeneca, Boehringer Ingelheim

- Clinical Trial Leadership/Consultant:
  - Alnylam, AstraZeneca, Amgen, Bayer, Boehringer Ingelheim, Cytokinetics, Janssen, Esperion, Eli Lilly, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pfizer, Pharmacosmos, Sanofi, Vifor

- DELIVER Trial was sponsored by AstraZeneca

Background

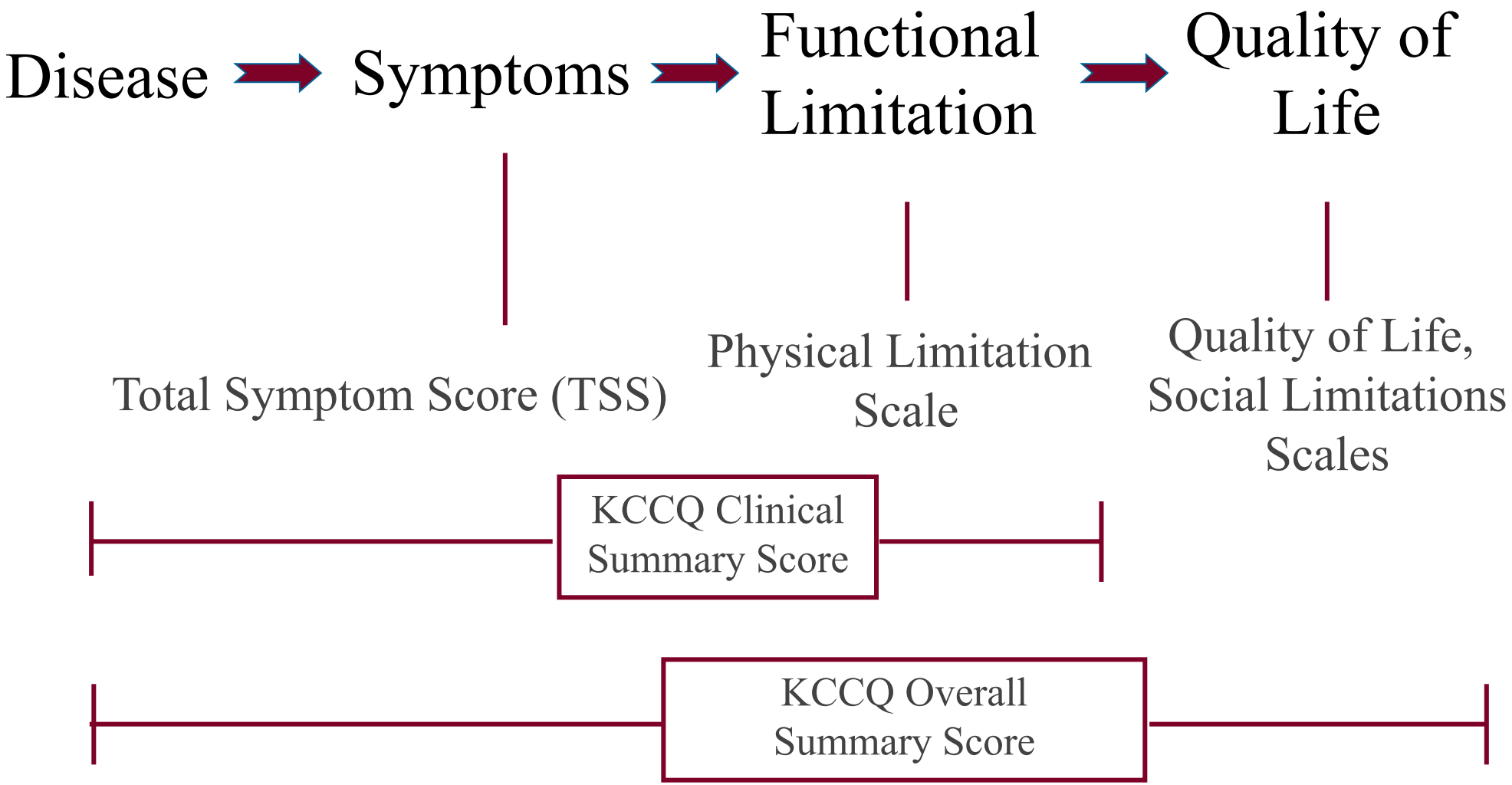
- Patients with HF and mildly reduced or preserved EF experience an especially high burden of symptoms, physical limitations, and a poor quality of life
- Improving health status (symptoms, function and quality of life) is a key goal of management, increasingly recognized by regulators, practice guidelines, and clinicians
- SGLT2 inhibitors have been shown to improve health status in patients with heart failure and mildly reduced or preserved EF in several randomized controlled trials
  - Most were modest in size, limited geographically or in terms of a clinical setting, not specifically focused on individuals with mildly reduced and preserved EF, or had a short follow up
- The EMPEROR-Preserved trial showed a modest improvement in health status with empagliflozin in this patient population, but suggested an attenuation of this benefit in individuals with EF ≥ 65%
- Uncertainty remains regarding the magnitude and consistency of SGLT2 inhibitor effects on symptoms, function and quality of life, especially in individuals with HF in the highest part of the ejection fraction range

Objectives of this Analysis

- Evaluate whether the effects of dapagliflozin on clinical outcomes in the DELIVER trial varied according to the degree of symptomatic impairment at baseline measured by KCCQ Total Symptom Score – a pre-specified secondary endpoint

- Examine the effects of dapagliflozin on the broad range of health status outcomes, measured by the various domains of the KCCQ; and the consistency of these effects across subgroups, including EF categories

Mapping the KCCQ Scales



Statistical Analysis

- Patients stratified based on baseline KCCQ-TSS tertiles
- Effects of dapagliflozin on clinical outcomes across the KCCQ tertiles evaluated using Cox proportional-hazards models
  - Additional analyses evaluated effects of dapagliflozin on clinical events across the range of KCCQ as a continuous variable using restricted cubic splines
- Differences between treatment groups in KCCQ domains at 1, 4 and 8 months assessed with mixed models for repeated measures, adjusted for baseline KCCQ
- Effects of dapagliflozin on KCCQ-TSS assessed across subgroups, including LVEF
  - LVEF also modeled as continuous variable
- Responder analyses examined proportions of patients with a deterioration (≥ 5 point worsening), and clinically meaningful improvements in KCCQ at 8 months (≥5 point [at least small], ≥10 point [at least moderate], and ≥15 point [large] change)

Baseline Characteristics by Tertiles of KCCQ-Total Symptom Score

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	Tertile 1: <63 n=2040	Tertile 2: 63-84 n=1955	Tertile 3: >84 n=1800	P-value
Age	71.5 ± 9.5	71.9 ± 9.5	71.0 ± 9.6	p=0.024
Sex: Men	1022 (50.1%)	1109 (56.7%)	1213 (67.4%)	p<0.001
Race				p<0.001
White	1631 (80.0%)	1456 (74.5%)	1101 (61.2%)	
Asian	192 (9.4 %)	330 (16.9%)	604 (33.6%)	
Black or African American	66 (3.2 %)	46 (2.4 %)	28 (1.6 %)	
American Indian or Alaska Native	72 (3.5 %)	70 (3.6 %)	28 (1.6 %)	
Other	79 (3.9 %)	53 (2.7 %)	39 (2.2 %)	
Geographic Region				p<0.001
Europe and Saudi Arabia	1072 (52.5%)	993 (50.8%)	753 (41.8%)	
Asia	178 (8.7 %)	316 (16.2%)	595 (33.1%)	
Latin America	443 (21.7%)	357 (18.3%)	281 (15.6%)	
North America	347 (17.0%)	289 (14.8%)	171 (9.5 %)	
Comorbidities				
Atrial Fib/Flutter (AFF)	1183 (58.0%)	1108 (56.7%)	1007 (55.9%)	p=0.43
Type 2 Diabetes Mellitus	992 (48.6%)	815 (41.7%)	754 (41.9%)	p<0.001
COPD	289 (14.2%)	219 (11.2%)	145 (8.1 %)	p<0.001
Sleep Apnea	228 (11.2%)	152 (7.8 %)	84 (4.7 %)	p<0.001
Prior HF Hospitalization	884 (43.3%)	767 (39.2%)	743 (41.3%)	p=0.031
Baseline Body Mass Index	31.4 ± 6.5	29.9 ± 5.8	28.2 ± 5.4	p<0.001

Baseline Characteristics for Tertiles of KCCQ-Total Symptom Score

	Tertile 1: <63 n=2040	Tertile 2: 63-84 n=1955	Tertile 3: >84 n=1800	p-value
NYHA Class				p<0.001
I	0 (0.0 %)	1 (0.1 %)	0 (0.0 %)	
II	1241 (60.8%)	1542 (78.9%)	1594 (88.6%)	
III	790 (38.7%)	407 (20.8%)	204 (11.3%)	
IV	9 (0.4 %)	5 (0.3 %)	2 (0.1 %)	
LVEF (%)	54.3 ± 8.5	53.9 ± 8.7	53.9 ± 9.1	p=0.27
NT-proBNP (ng/L)	1104 [652, 2027]	977 [615, 1687]	965 [607, 1606]	p<0.001
Systolic BP (mmHg)	128.8 ± 14.8	127.8 ± 15.1	128.0 ± 15.6	p=0.07
HbA1c (%)	6.7 ± 1.5	6.5 ± 1.3	6.5 ± 1.3	p<0.001
Pulse Rate (beats/min)	72.1 ± 12.0	71.1 ± 11.3	71.0 ± 11.6	p=0.008
eGFR (mL/min/1.73m^2)	60.0 ± 19.0	61.3 ± 19.0	62.5 ± 19.3	p<0.001
Medication Use				
Loop diuretics	1672 (82.0%)	1484 (75.9%)	1301 (72.3%)	p<0.001
ACEi	776 (38.0%)	726 (37.2%)	658 (36.6%)	p=0.63
ARB	748 (36.7%)	715 (36.6%)	612 (34.0%)	p=0.15
ARNI	59 (2.9 %)	98 (5.0 %)	126 (7.0 %)	p<0.001
Beta Blocker	1701 (83.4%)	1639 (83.9%)	1473 (81.8%)	p=0.22
Mineralocorticoid RA	884 (43.3%)	810 (41.5%)	796 (44.2%)	p=0.21

Treatment Effect Estimates (Dapagliflozin vs. Placebo): Primary and Secondary Outcomes, by Tertiles of KCCQ-TSS at Baseline

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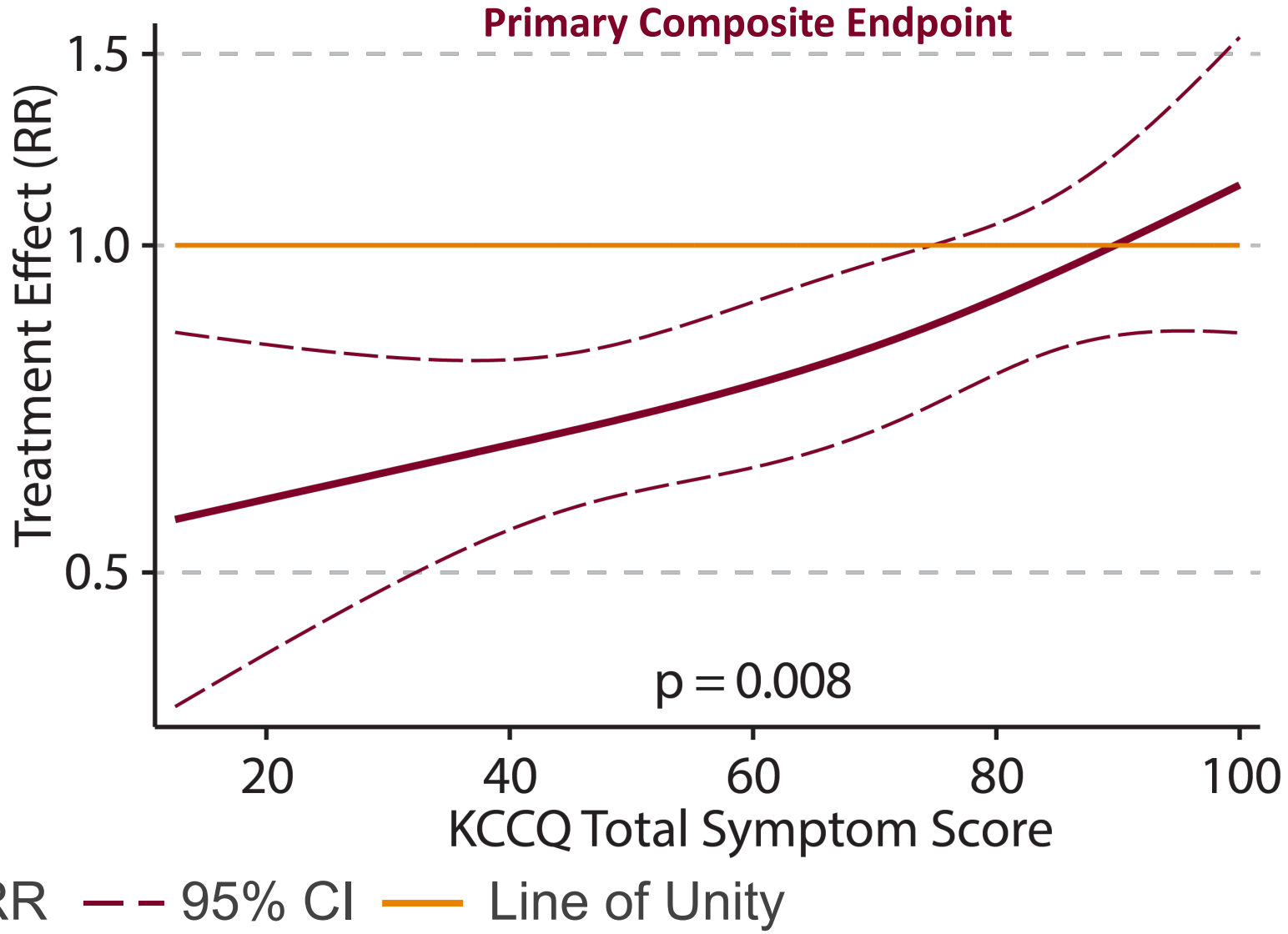
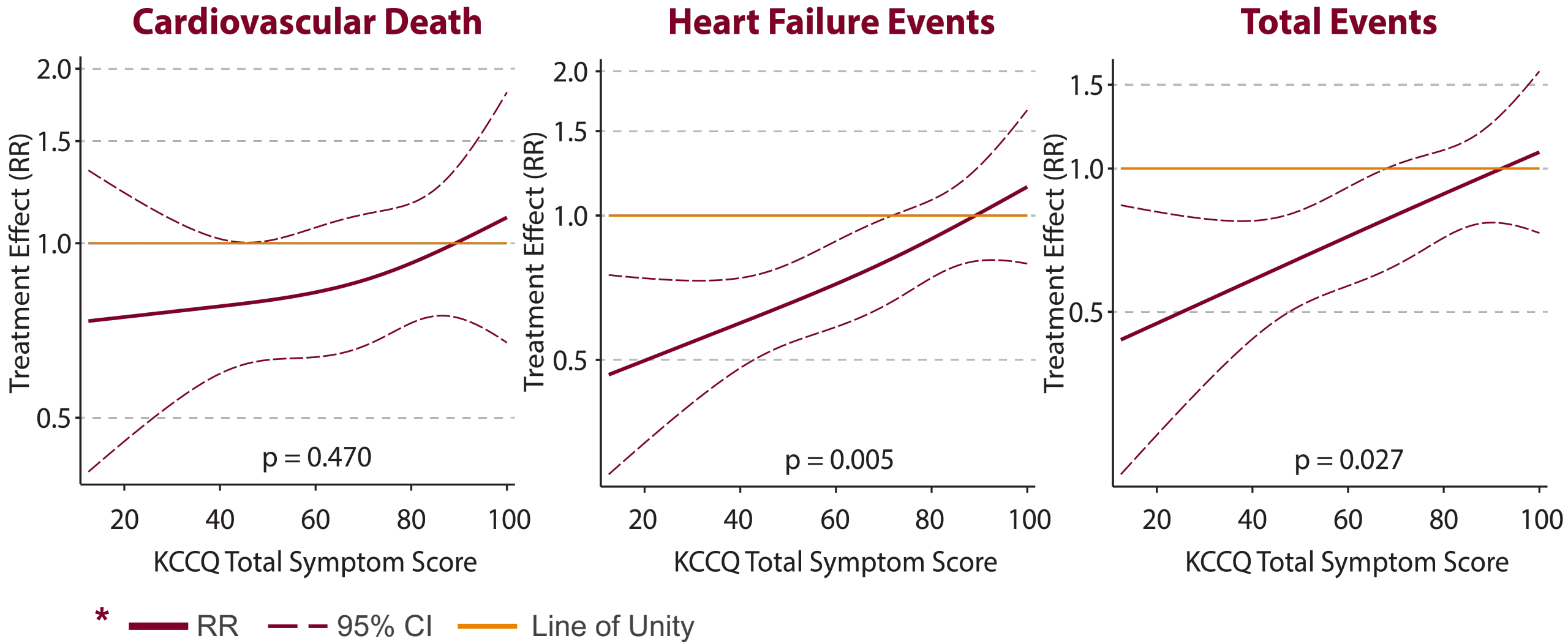
*Primary endpoint = Time to first CV death or HF event. #HF Event = HF Hospitalization or Urgent HF visit requiring IV diuretic therapy.

Treatment Effect of Dapagliflozin on CV Death or Worsening HF by Baseline KCCQ-TSS*

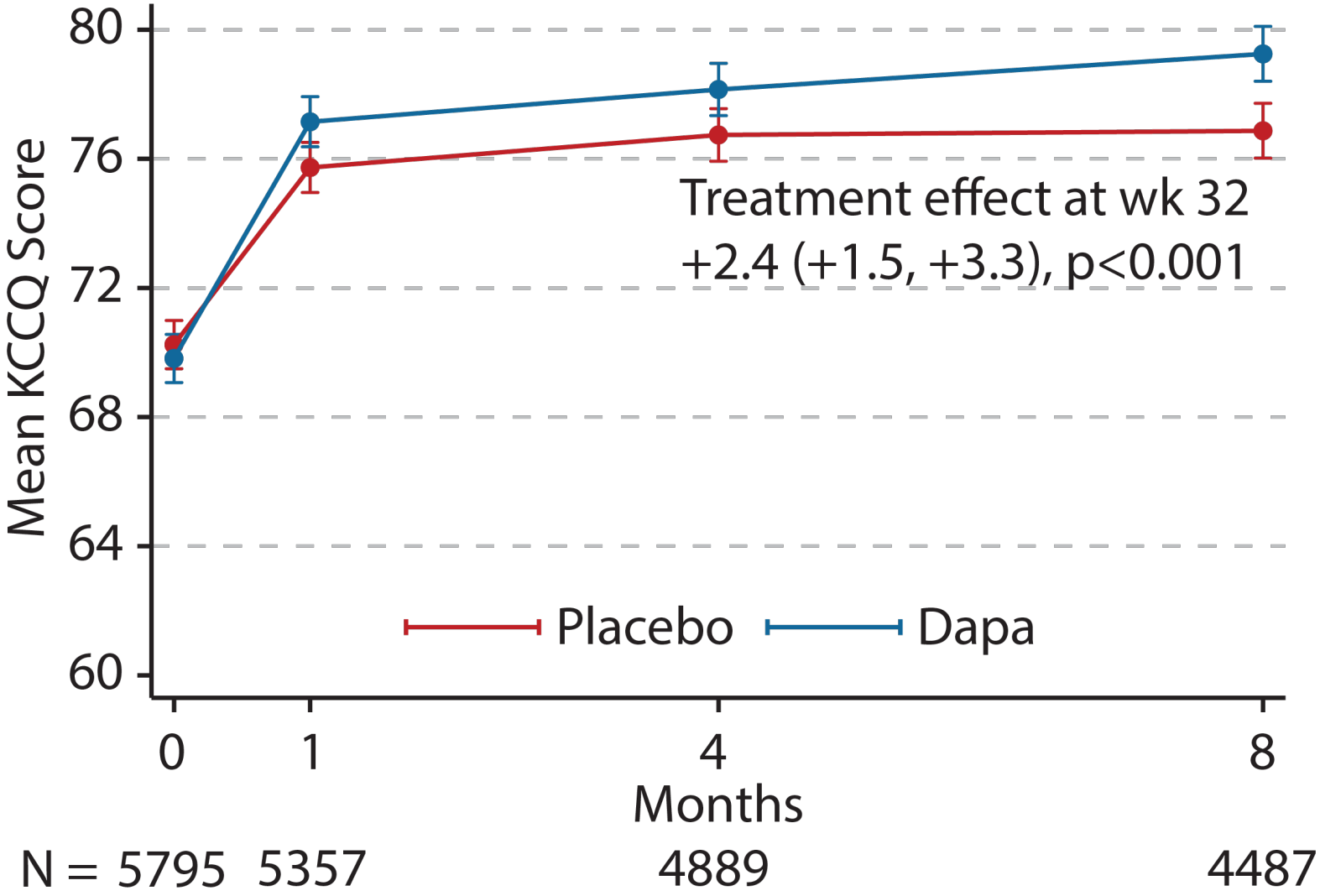


Treatment Effect of Dapagliflozin on Clinical Outcomes by Baseline KCCQ-TSS*

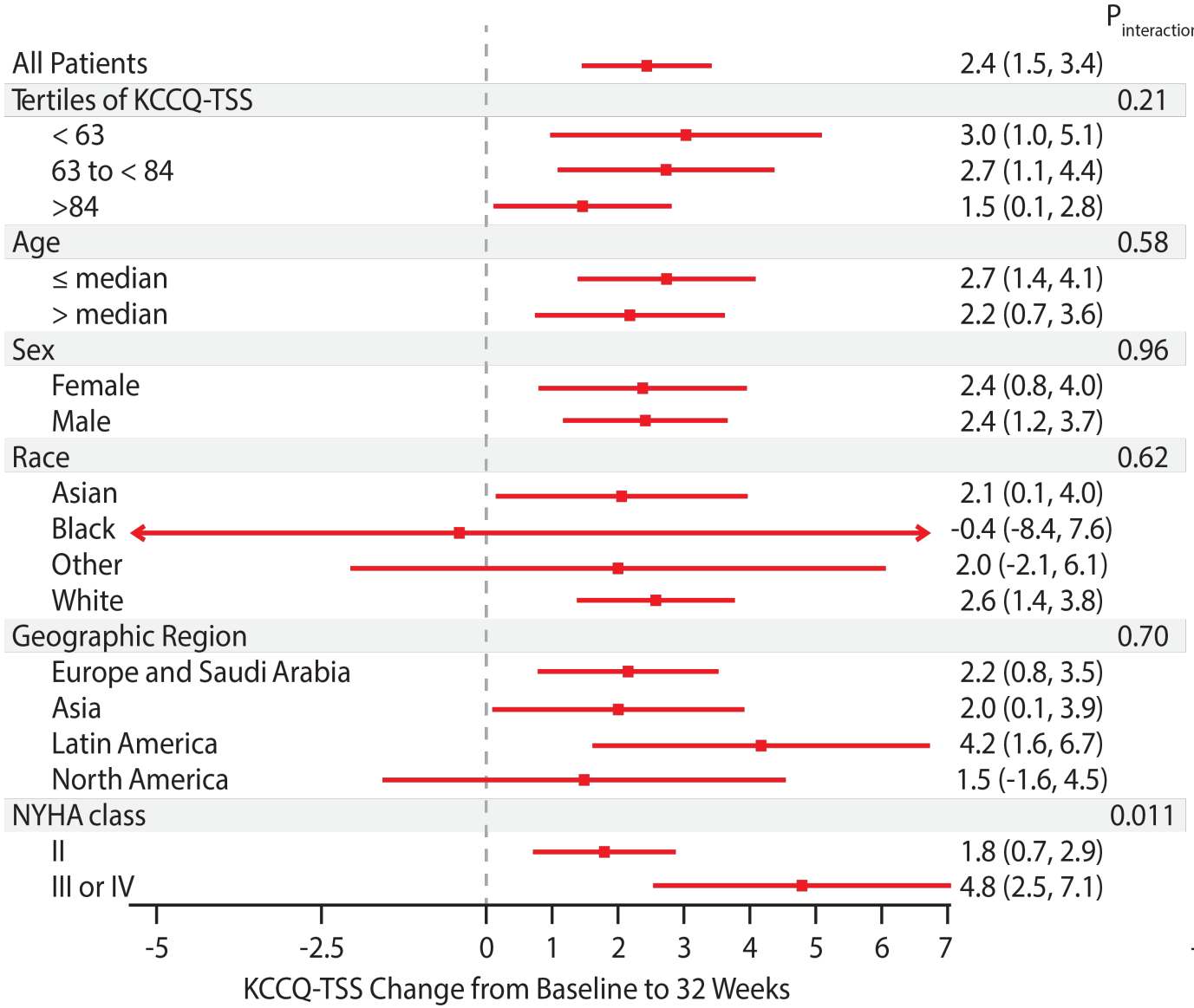


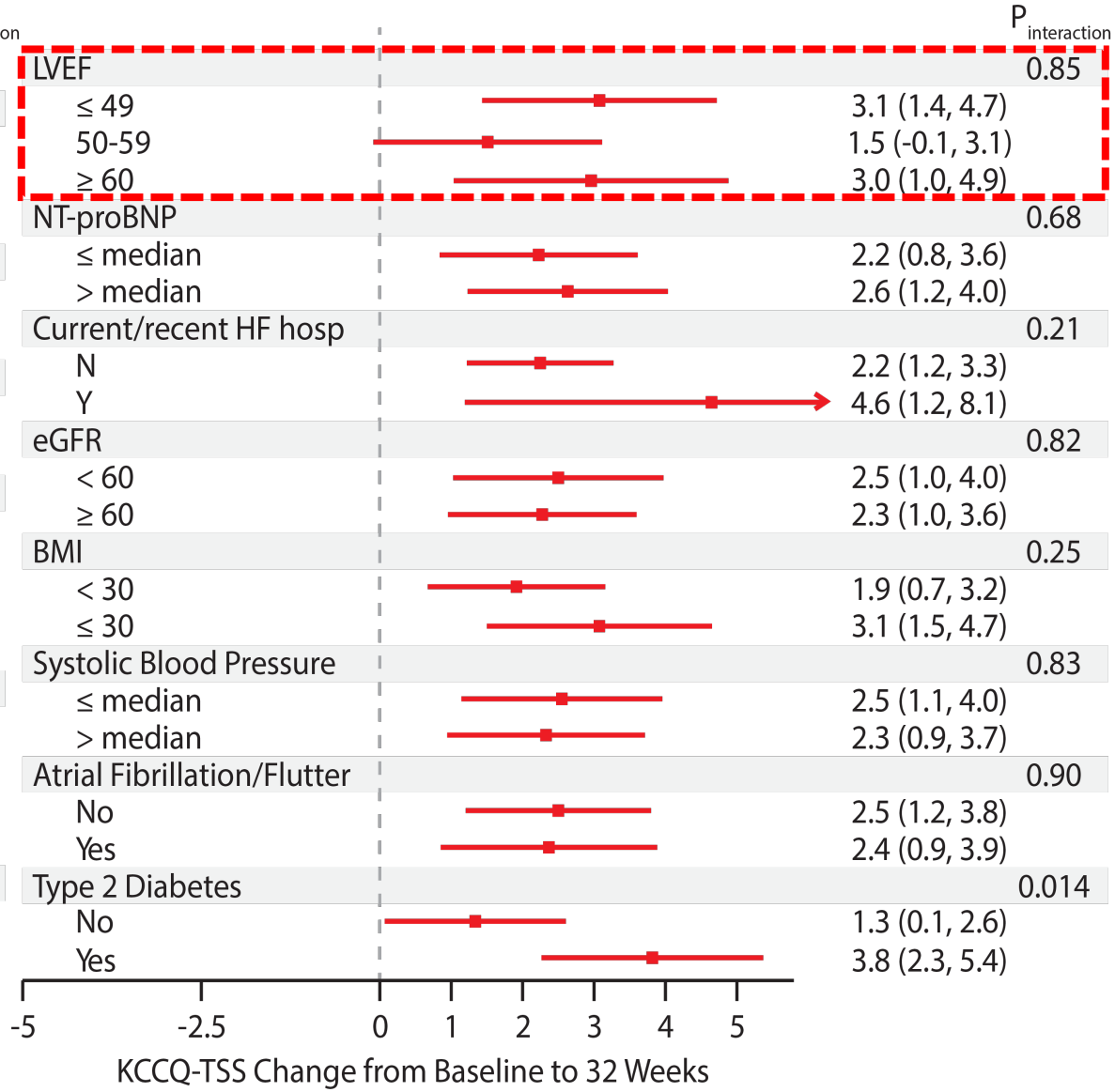
HF Events include a HF Hospitalization or Urgent HF visit requiring IV therapy.

Change in KCCQ-Total Symptom Score Over Time by Treatment Allocation

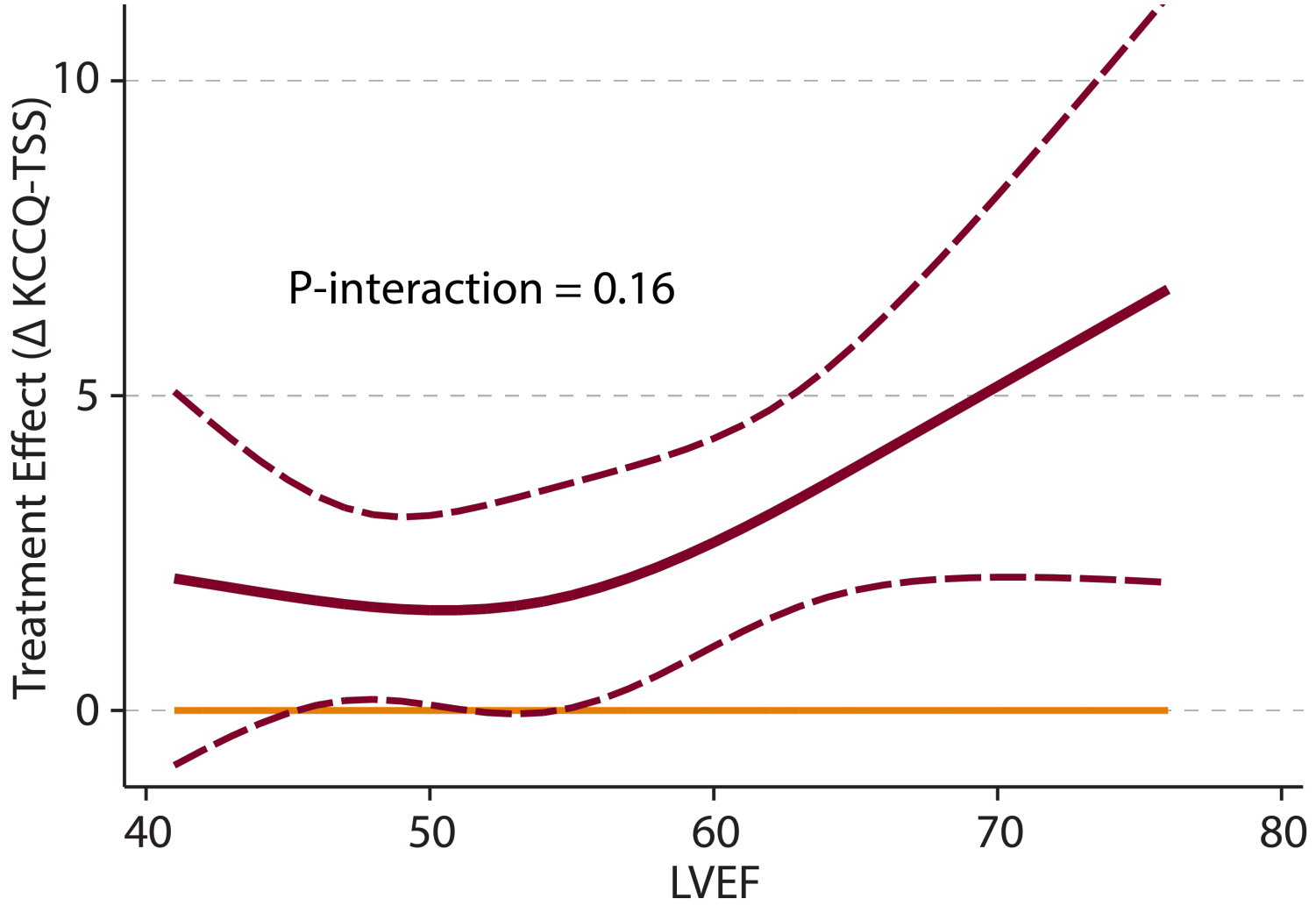


Effects of Dapagliflozin on KCCQ-TSS across Subgroups



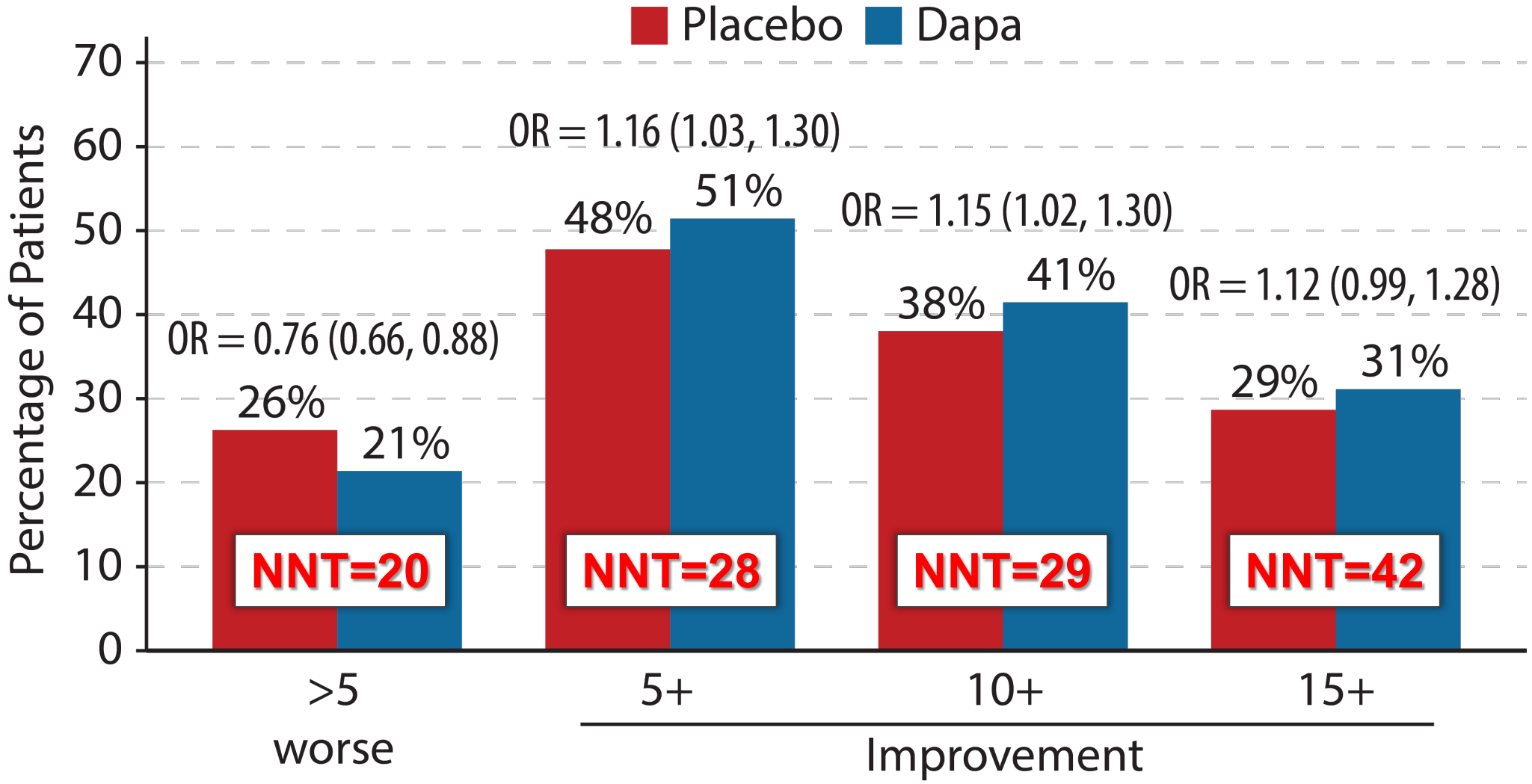


Effects of Dapagliflozin on KCCQ-TSS across the Spectrum of Ejection Fraction*

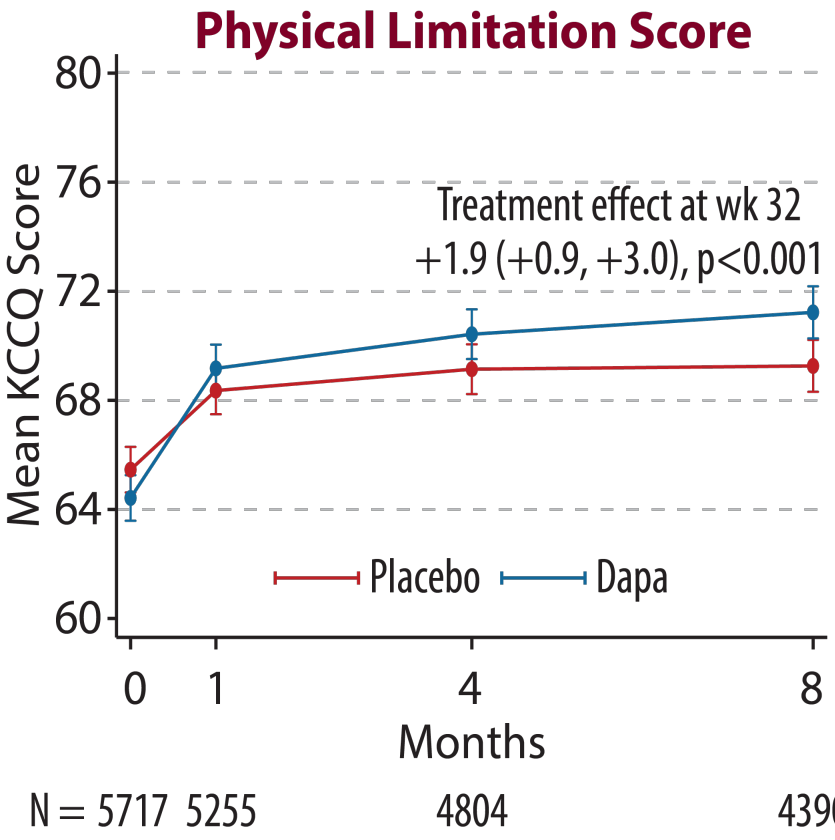


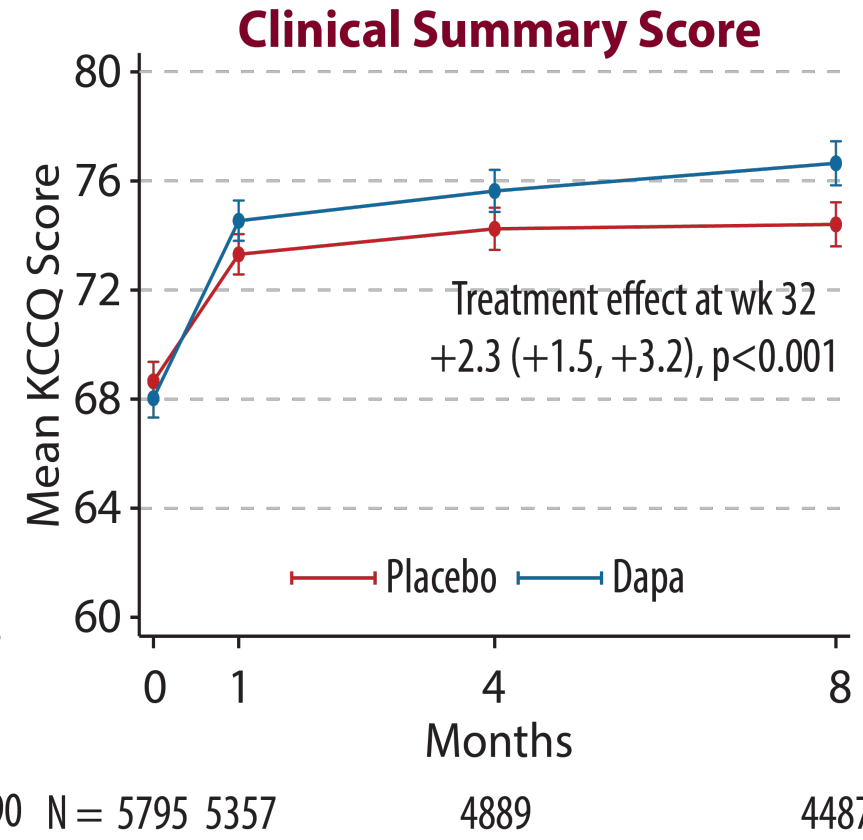
Treatment Effect refers to placebo-adjusted change in KCCQ-TSS from baseline to 8 months.

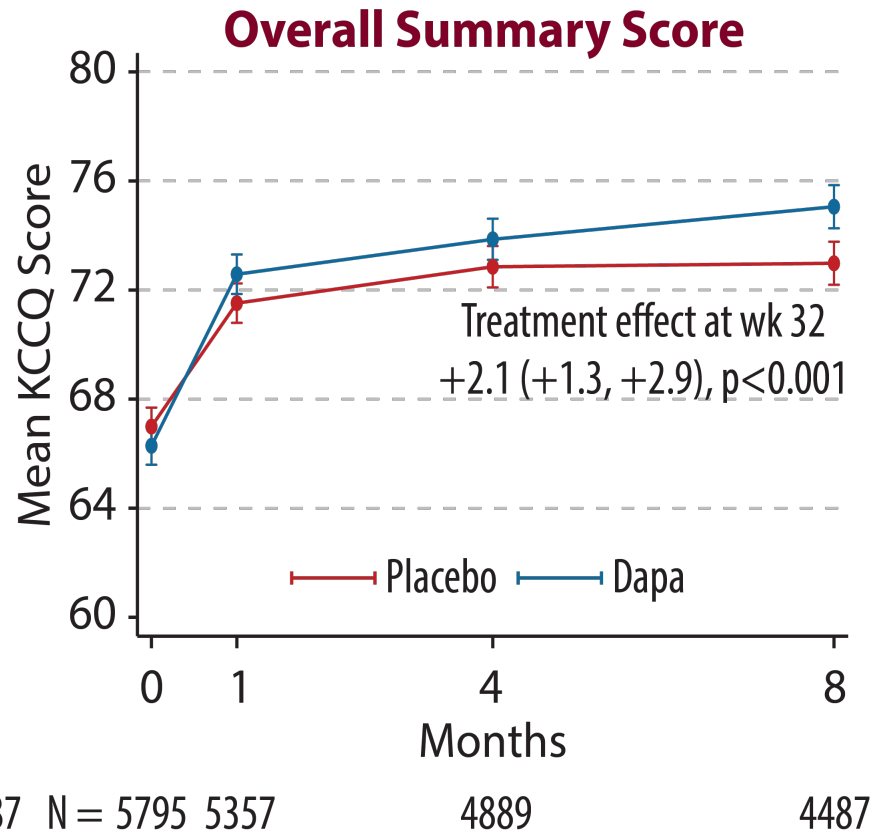
Responder Analyses of Clinically Meaningful Change in KCCQ-TSS at 8 Months with Dapagliflozin vs. Placebo



Mean changes in KCCQ Domains Over Time by Treatment Allocation*

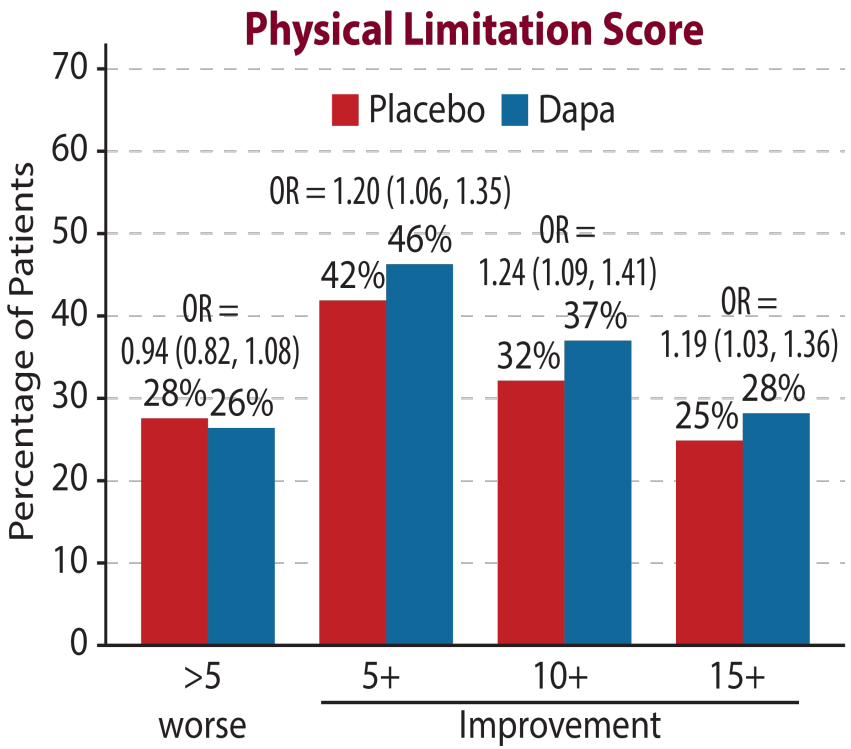


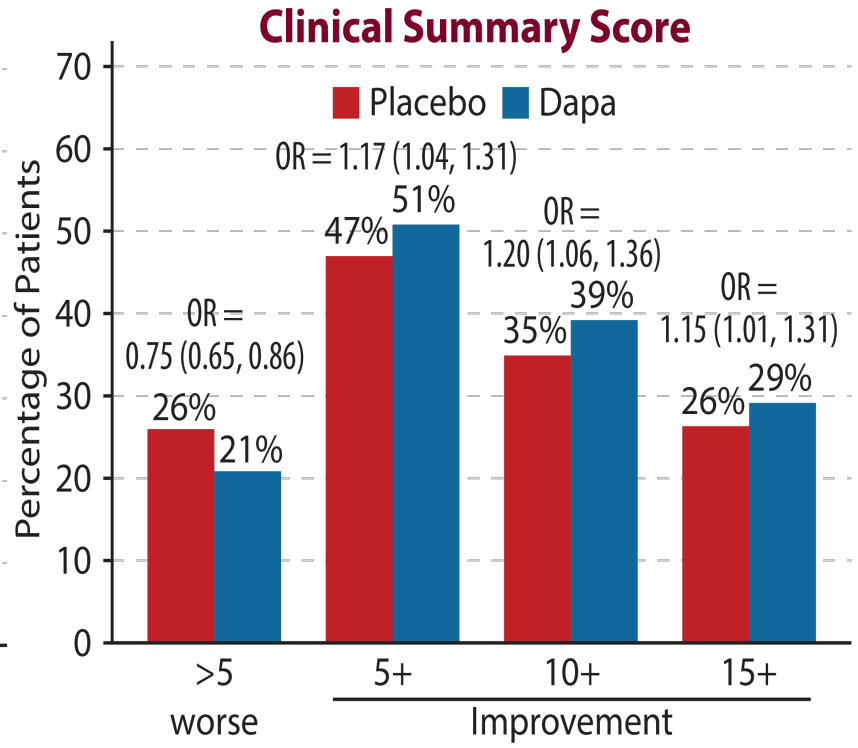


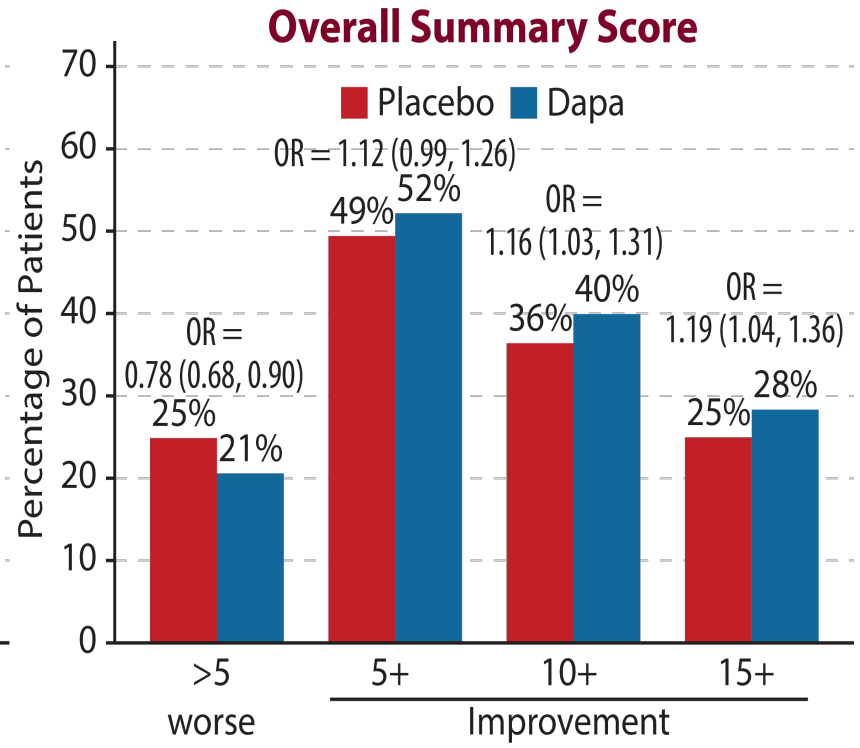


*Treatment Effect refers to placebo-adjusted change in KCCQ-TSS from baseline to 8 months.

Responder analyses of clinically meaningful change in KCCQ Domains at 8 months with dapagliflozin versus placebo







Conclusions

- Dapagliflozin (compared with placebo) reduced cardiovascular death and worsening HF to a greater extent in patients with mildly reduced and preserved ejection fraction who had a higher burden of symptomatic impairment at baseline
- Dapagliflozin (compared with placebo) improved all major components of KCCQ (which collectively encompass symptoms, physical limitations, and health-related quality of life) as early as 1 month, with benefits sustained at 8 months
- Fewer dapagliflozin-treated patients had significant deterioration, and more experienced small, moderate and large improvements across domains of KCCQ
- Benefits of dapagliflozin on symptomatic improvement were generally consistent across subgroups, with no effect attenuation in those with LVEF ≥ 65%
- Combined with prior trials, these findings establish dapagliflozin as an efficacious treatment option to improve symptoms, function and health-related quality of life in patients with heart failure regardless of ejection fraction or clinical setting

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