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Effect of Dapagliflozin on Health Status in Patients With Preserved or Mildly Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Patients with heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) experience a high burden of symptoms, physical limitations, and poor quality of life; improving health status is a key goal of management.

OBJECTIVES In a prespecified analysis of the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial, we examine effects of dapagliflozin on health status using the Kansas City Cardiomyopathy Questionnaire (KCCQ).

METHODS The DELIVER trial randomized patients with symptomatic HFmrEF/HFpEF to dapagliflozin 10 mg or placebo. KCCQ was evaluated at randomization, 1, 4, and 8 months; KCCQ Total Symptom Score (TSS) was a key secondary endpoint. Patients were stratified by KCCQ-TSS tertiles; Cox models examined effects of dapagliflozin on clinical outcomes. We evaluated the effects of dapagliflozin on KCCQ-TSS, Physical Limitations (PLS), Clinical Summary (CSS), and Overall Summary (OSS) domains. Responder analyses compared proportions of dapagliflozin vs placebo-treated patients with clinically meaningful changes in KCCQ.

RESULTS A total of 5,795 patients had baseline KCCQ (median KCCQ-TSS 72.9). The effects of dapagliflozin on reducing cardiovascular death/worsening HF appeared more pronounced in patients with greater baseline symptom burden (lowest-to-highest KCCQ-TSS tertile: HR: 0.70 [95% CI: 0.58-0.84]; 0.81 [95% CI: 0.65-1.01]; 1.07 [95% CI: 0.83-1.37]; $P_{interaction} = 0.026$). Dapagliflozin improved KCCQ-TSS, -PLS, -CSS, and -OSS at 8 months (2.4, 1.9, 2.3, and 2.1 points higher vs placebo; $P < 0.001$ for all). Dapagliflozin-treated patients experienced improvements in KCCQ-TSS regardless of EF ($P_{interaction} = 0.85$). Fewer dapagliflozin-treated patients had deterioration, and more had improvements in all KCCQ domains at 8 months.

CONCLUSIONS The clinical benefits of dapagliflozin in HFmrEF/HFpEF appear especially pronounced in those with greater baseline symptom impairment. Dapagliflozin improved all KCCQ domains and the proportion of patients experiencing clinically meaningful changes in health status. (Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure [DELIVER]; NCT03619213) (J Am Coll Cardiol 2023;81:460-473)

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Heart failure (HF) with mildly reduced and preserved ejection fraction (EF) now represents the majority of all HF in the community, and its prevalence is continuing to increase.[1] In addition to the risk of death and hospitalizations, patients with HF and mildly reduced or preserved EF also experience an especially high burden of symptoms, physical limitations, and a poor quality of life.[2] Improving health status is, therefore, a key goal of management in this patient group, and its importance is increasingly recognized by the regulators, practice guidelines, and clinicians.[3-5]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to improve health status in patients with HF and mildly reduced or preserved EF in several randomized controlled trials.[6-9] However, most of these trials were relatively modest in size,[6-8] were limited geographically[6,7] or in terms of a clinical setting,[6-8] were not specifically focused on individuals with mildly reduced or preserved EF,[7,8] or had relatively short follow-up.[6-8] One large global clinical trial (EMPEROR-Preserved [Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction]),[9] which specifically evaluated patients with mildly reduced or preserved EF, demonstrated a modest improvement in KCCQ with empagliflozin vs placebo but suggested an attenuation of this effect in individuals with EF >60%[10]; however, such heterogeneity was not observed in other trials.[6] Therefore, there remains uncertainty about the magnitude and consistency of the effects of SGLT2 inhibitors on health status, especially in individuals with HF and truly normal EF.

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In the placebo-controlled DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial, dapagliflozin reduced the risk of cardiovascular (CV) death and worsening HF.[11] These data expand the evidence of clinical benefit of this therapy to a more comprehensive HF population.[12] In this prespecified analysis of DELIVER, we sought to address the following 2 objectives: 1) to evaluate whether the effects of dapagliflozin on clinical outcomes in the DELIVER trial varied according to the degree of symptomatic impairment at baseline; and 2) to examine the effects of dapagliflozin on the broad range of health status outcomes as measured by the various domains of the Kansas City Cardiomyopathy Questionnaire (KCCQ)—a validated, self-administered instrument that quantifies HF-related symptoms, function, and quality of life—and the consistency of these effects across patient subgroups, including EF categories.[13]

ABBREVIATIONS AND ACRONYMS

CSS = Clinical Summary Score

HF = heart failure

KCCQ = Kansas City Cardiomyopathy Questionnaire

OSS = Overall Summary Score

PLS = Physical Limitations Score

SGLT2 = sodium-glucose cotransporter 2

TSS = Total Symptom Score

METHODS

Data underlying the findings described in this paper may be obtained in accordance with AstraZeneca's data sharing policy.

TRIAL DESIGN AND PATIENTS. The design and primary results of the DELIVER trial have been described previously.[14] DELIVER was an international, prospective, randomized, double-blind, placebo-controlled trial testing the efficacy and safety of dapagliflozin compared with placebo in patients with HF and mildly reduced or preserved EF. The study enrolled patients age 40 years or older with symptomatic HF (New York Heart Association [NYHA] functional class II-IV), left ventricular ejection fraction (LVEF) >40% (within 12 months of enrollment), elevated natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] of at least 300 pg/mL among those without atrial fibrillation or flutter, or at least 600 pg/mL in those in atrial fibrillation or flutter), and evidence of structural heart disease (left atrial enlargement or left ventricular hypertrophy). Participants were randomized in a 1:1 fashion to dapagliflozin 10 mg or matched placebo daily, stratified by type 2 diabetes status. The protocol was approved by local ethics committees at each participating site.

OUTCOMES. The primary outcome was a composite of CV death or worsening HF event (defined as unplanned HF hospitalization or urgent HF visit

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics for Tertiles of KCCQ-Total Symptom Score

	Tertile 1: <63 (n = 2,040)	Tertile 2: 63-84 (n = 1,955)	Tertile 3: >84 (n = 1,800)	*P* Value
Age, y	71.5 ± 9.5	71.9 ± 9.5	71.0 ± 9.6	0.024
Age group				0.16
≤65 y	510 (25.0)	456 (23.3)	455 (25.3)	
>65-75 y	783 (38.4)	742 (38.0)	718 (39.9)	
>75 y	747 (36.6)	757 (38.7)	627 (34.8)	
Men	1,022 (50.1)	1,109 (56.7)	1,213 (67.4)	<0.001
Race				<0.001
White	1,631 (80.0)	1,456 (74.5)	1,101 (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				<0.001
Europe and Saudi Arabia	1,072 (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 fibrillation/flutter	1,183 (58.0)	1,108 (56.7)	1,007 (55.9)	0.43
Stroke	202 (9.9)	179 (9.2)	163 (9.1)	0.61
Dyslipidemia	1,337 (65.5)	1,240 (63.4)	1,111 (61.7)	0.048
Type 2 diabetes mellitus	992 (48.6)	815 (41.7)	754 (41.9)	<0.001
Chronic obstructive pulmonary disease	289 (14.2)	219 (11.2)	145 (8.1)	<0.001
Peripheral vascular intervention	46 (2.3)	57 (2.9)	33 (1.8)	0.09
Sleep apnea	228 (11.2)	152 (7.8)	84 (4.7)	<0.001
Myocardial infarction	535 (26.2)	526 (26.9)	471 (26.2)	0.85
Prior HF hospitalization	884 (43.3)	767 (39.2)	743 (41.3)	0.031
History of atherosclerotic cardiovascular disease	1,186 (58.1)	1,097 (56.1)	1,010 (56.1)	0.33
Smoking status				0.009
Current	153 (7.5)	151 (7.7)	167 (9.3)	
Former	716 (35.1)	747 (38.2)	696 (38.7)	
Never	1,171 (57.4)	1,057 (54.1)	937 (52.1)	
Baseline body mass index, kg/m^2	31.4 ± 6.5	29.9 ± 5.8	28.2 ± 5.4	<0.001
Duration of HF				0.003
0-3 mo	158 (7.8)	181 (9.3)	176 (9.8)	
>3-6 mo	195 (9.6)	165 (8.4)	200 (11.1)	
>6-12 mo	244 (12.0)	290 (14.8)	260 (14.5)	
>1-2 y	336 (16.5)	305 (15.6)	282 (15.7)	
>2-5 y	514 (25.2)	500 (25.6)	414 (23.0)	
>5 y	590 (29.0)	513 (26.3)	467 (26.0)	
NYHA functional class at baseline				<0.001
I	0 (0.0)	1 (0.1)	0 (0.0)	
II	1,241 (60.8)	1,542 (78.9)	1,594 (88.6)	
III	790 (38.7)	407 (20.8)	204 (11.3)	
IV	9 (0.4)	5 (0.3)	2 (0.1)	
Baseline LVEF, %	54.3 ± 8.5	53.9 ± 8.7	53.9 ± 9.1	0.27
LVEF grouping, %				0.10
≤40	2 (0.1)	0 (0.0)	2 (0.1)	
≥41-49	660 (32.4)	665 (34.0)	658 (36.6)	
50-59	769 (37.7)	703 (36.0)	613 (34.1)	
≥60	609 (29.9)	587 (30.0)	527 (29.3)	
Baseline NT-proBNP, ng/L	1,104 (652-2,027)	977 (615-1,687)	965 (607-1,606)	<0.001
NT-proBNP in AFF	1,484 (996-2,484)	1,400 (955-2,118)	1,309 (934-1,992)	<0.001
NT-proBNP when not in AFF	768 (477-1,452)	699 (471-1,210)	696 (460-1,227)	0.002
Atrial fibrillation/flutter on screening ECG	906 (44.4)	818 (41.8)	734 (40.8)	0.06

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TABLE 1 Continued

	Tertile 1: <63 (n = 2,040)	Tertile 2: 63-84 (n = 1,955)	Tertile 3: >84 (n = 1,800)	*P* Value
Baseline systolic blood pressure, mm Hg	128.8 ± 14.8	127.8 ± 15.1	128.0 ± 15.6	0.07
Baseline diastolic blood pressure, mm Hg	74.5 ± 10.2	74.1 ± 10.1	73.9 ± 10.3	0.18
Baseline HbA1c, %	6.7 ± 1.5	6.5 ± 1.3	6.5 ± 1.3	<0.001
Baseline pulse rate, beats/min	72.1 ± 12.0	71.1 ± 11.3	71.0 ± 11.6	0.008
Baseline creatinine, μmol/L	102.8 ± 31.2	101.7 ± 30.3	103.1 ± 31.0	0.38
Baseline eGFR, mL/min/1.73 m^2	60.0 ± 19.0	61.3 ± 19.0	62.5 ± 19.3	<0.001
Baseline medication use				
Loop diuretics	1,672 (82.0)	1,484 (75.9)	1,301 (72.3)	<0.001
ACE inhibitor	776 (38.0)	726 (37.2)	658 (36.6)	0.63
Angiotensin receptor blocker	748 (36.7)	715 (36.6)	612 (34.0)	0.15
Angiotensin receptor neprilysin inhibitor	59 (2.9)	98 (5.0)	126 (7.0)	<0.001
Beta-blocker	1,701 (83.4)	1,639 (83.9)	1,473 (81.8)	0.22
Mineralocorticoid receptor antagonist	884 (43.3)	810 (41.5)	796 (44.2)	0.21
Pacemaker	231 (11.3)	227 (11.6)	171 (9.5)	0.08
ICD	39 (1.9)	33 (1.7)	36 (2.0)	0.76

Values are mean ± SD, n (%), or median (IQR).
ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator.

requiring intravenous therapy). Change in KCCQ-Total Symptom Score (TSS) from baseline to month 8 was a prespecified secondary endpoint of DELIVER. Additional analyses based on multiple KCCQ domains at 1, 4, and 8 months were prespecified in the Academic SAP that was finalized before database lock and unblinding. In addition, the Academic SAP prespecified responder analyses based on clinically meaningful deterioration and small, moderate, or large improvements in these domains over time.

STUDY PROCEDURES. After randomization, follow-up study visits took place at or around 1, 4, 8, 12, and 16 months, and then every 4 months thereafter. KCCQ was completed by patients, without assistance from site study staff (as validated), and evaluated at randomization, 1, 4, and 8 months. KCCQ is a 23-item, self-administered HF-specific instrument that quantifies symptoms (frequency, severity, and recent change), physical function, quality of life, and social function over the prior 2 weeks. In the KCCQ, the TSS quantifies the symptom frequency and severity, Physical Limitation Score (PLS) evaluates the physical function, Clinical Summary Score (CSS) includes the symptoms and physical function domains, and Overall Summary Score (OSS) summarizes all key domains (TSS, physical function, quality of life, and social function). For each domain, the validity, reproducibility, responsiveness, and interpretability have been independently established. Scores are transformed to a range of 0 to 100, in which higher scores reflect better health status.[13]

STATISTICAL ANALYSIS. Patients were divided into 3 subgroups based on the tertiles of baseline KCCQ-TSS (which was the KCCQ domain prespecified as the secondary endpoint): 1) <63 points; 2) 63 to 84 points; and 3) >84 points. Baseline characteristics were summarized as mean ± SD, median (IQR), or percentages. Analysis of variance, Kruskal-Wallis, and chi-square tests were used to test for differences in baseline characteristics across KCCQ-TSS tertiles. The relative risks of time-to-first event outcomes (CV death and worsening HF, worsening HF events, CV death) were obtained from Cox proportional hazards models and recurrent-event outcomes (total HF events or CV death) were analyzed using the semiparametric proportional rates method of Lin et al.[15,16] Cox models were adjusted for age, sex, race, geographic region, history of type 2 diabetes, chronic obstructive pulmonary disease, sleep apnea, prior HF hospitalization, smoking, body mass index (BMI), HF duration, pro-B-type natriuretic peptide, history of atrial fibrillation/flutter, hemoglobin A1c, estimated glomerular filtration rate, and baseline use of loop diuretic agents and angiotensin receptor neprilysin inhibitor. Schoenfeld residuals were used to assess the proportional hazards assumptions in Cox models used to estimate the covariate-adjusted associations between KCCQ-TSS tertiles and clinical outcomes. The event rates of clinical outcomes as a function of KCCQ as a continuous variable were estimated using Poisson and negative binomial regression models, adjusted for the same variables as previously mentioned, with KCCQ values expressed using

TABLE 2 Treatment Effect Estimates (Dapagliflozin vs Placebo): Primary and Secondary Outcomes, by Tertiles of the Kansas City Cardiomyopathy Questionnaire-Total Symptom Score at Baseline

	Tertile 1: TSS <63 (n = 2,040)		Tertile 2: TSS 63-84 (n = 1,955)		Tertile 3: TSS >84 (n = 1,800)		Interaction *P* Value
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	
Primary composite[a]	9.0 per 100 py	13.1 per 100 py	6.9 per 100 py	8.5 per 100 py	6.7 per 100 py	6.3 per 100 py	0.026
	HR: 0.70 (95% CI: 0.58-0.84)		HR: 0.81 (95% CI: 0.65-1.01)		HR: 1.07 (95% CI: 0.83-1.37)		
	P < 0.001		*P* = 0.06		*P* = 0.62		
CV death	4.2 per 100 py	5.0 per 100 py	3.2 per 100 py	3.6 per 100 py	2.4 per 100 py	2.5 per 100 py	0.81
	HR: 0.83 (95% CI: 0.63-1.09)		HR: 0.87 (95% CI: 0.63-1.20)		HR: 0.97 (95% CI: 0.65-1.45)		
	P = 0.17		*P* = 0.41		*P* = 0.89		
Worsening HF Events[b]	6.1 per 100 py	9.6 per 100 py	4.8 per 100 py	6.4 per 100 py	5.1 per 100 py	4.5 per 100 py	0.032
	HR: 0.59 (95% CI: 0.45-0.78)		HR: 0.76 (95% CI: 0.56-1.04)		HR: 1.07 (95% CI: 0.75-1.53)		
	P < 0.001		*P* = 0.08		*P* = 0.70		
Composite of CV death and Total HF events	13.1 per 100 py	20.3 per 100 py	10.6 per 100 py	13.4 per 100 py	10.0 per 100 py	9.6 per 100 py	0.046
	RR: 0.65 (95% CI: 0.52-0.81)		RR: 0.79 (95% CI: 0.61-1.03)		RR: 1.04 (95% CI: 0.77-1.41)		
	P < 0.001		*P* = 0.08		*P* = 0.78		

[a]Primary endpoint = Time to first cardiovascular (CV) death or heart failure (HF) event. [b]HF event = HF hospitalization or urgent HF visit requiring intravenous diuretic therapy. py = person-years; TSS = Total Symptom Score.

restricted cubic splines with 3 knots, placed at the 10th, 50th, and 90th percentiles of the data.[17]

To compare the effects of dapagliflozin vs placebo on clinical outcomes across the KCCQ-TSS tertiles, we evaluated time-to-event data using Cox proportional-hazards models and the semiparametric proportional rates method of Lin et al,[16] as appropriate, stratified according to diabetes status to calculate HRs, 95% CIs, and 2-sided *P* values. The effects of dapagliflozin on clinical events were then assessed across the entire range of KCCQ, modeling it as a continuous variable using restricted cubic splines.

As prespecified in the regulatory statistical analysis plan and previously described,[12] the KCCQ-TSS was first assessed using the rank analysis of covariance method and win ratio, stratified for type 2 diabetes status at randomization, adjusted for baseline KCCQ-TSS, and using multiple imputation for missing data. We also estimated the differences between treatment groups in mean KCCQ-TSS, -PLS, -CSS, and -OSS at 1, 4, and 8 months in surviving patients, using a repeated measures mixed-effects model, with baseline KCCQ values as a fixed effect and random patient-level intercept terms. Responder analyses were conducted, comparing the proportions of patients with a deterioration (worsening of 5 points or more), as well as clinically important improvements in KCCQ-TSS, -PLS, -CSS, and -OSS at 8 months (≥5-point [at least small], ≥10-point [moderate], and ≥15-point [large] change) using logistic regression models. We also estimated the numbers needed to treat for these thresholds of KCCQ-TSS as the inverse of the difference in proportions.

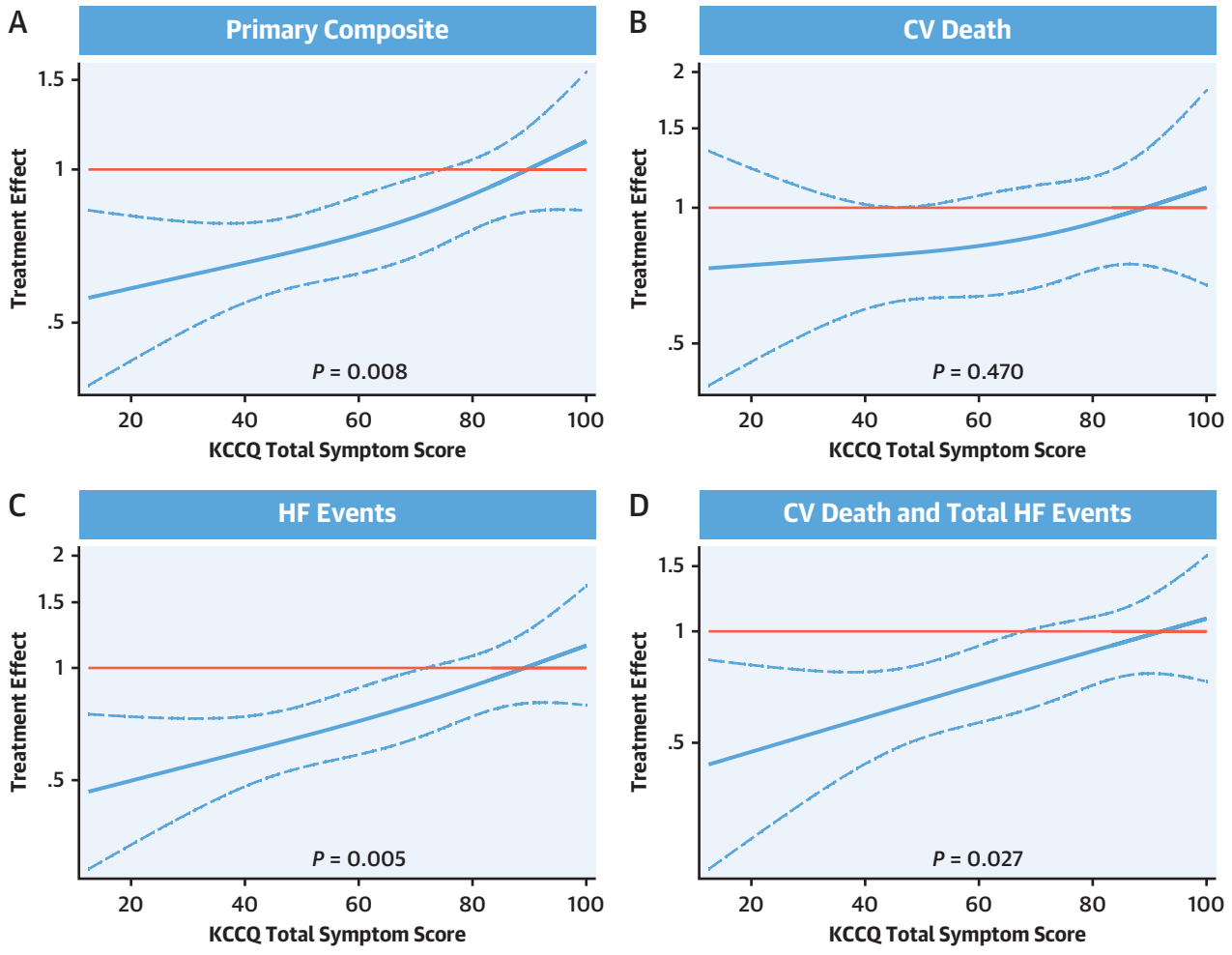
We examined the effects of dapagliflozin vs placebo on KCCQ-TSS at 8 months across relevant subgroups, which stratified participants according to several demographic and clinical characteristics, including LVEF; these models included the interaction terms for the appropriate variables. For each subgroup, a linear regression model was fit using the month 8 TSS value as the outcome, baseline TSS value as a covariate, as well as the treatment indicator, the categorical subgroup variable, and the corresponding treatment-by-subgroup interaction terms. Interaction *P* values are obtained from a global test of the treatment-subgroup interaction terms.

All analyses were performed in Stata version 16 (StataCorp, LLC).

RESULTS

PATIENT CHARACTERISTICS. Overall, 5,795 patients (92.5% of the overall trial population) had available KCCQ data at baseline. Baseline characteristics of patients with recorded vs missing KCCQ-TSS at randomization are presented in Supplemental Table 1. Randomization to dapagliflozin vs placebo was equally distributed among those with recorded and missing KCCQ-TSS at baseline. Of these, 5,278 patients (91% of surviving patients remaining in the study) had KCCQ evaluated at 1 month, 4,808 (84% of surviving patients remaining in the study) had KCCQ evaluated at 4 months, and 4,411 (79% of surviving patients remaining in the study) had KCCQ evaluated at 8 months. The median KCCQ-TSS was 72.9 (IQR: 55.2-87.5).

FIGURE 1 Effects of Dapagliflozin vs Placebo on Clinical Events According to the Baseline Kansas City Cardiomyopathy Questionnaire-Total Symptom Score

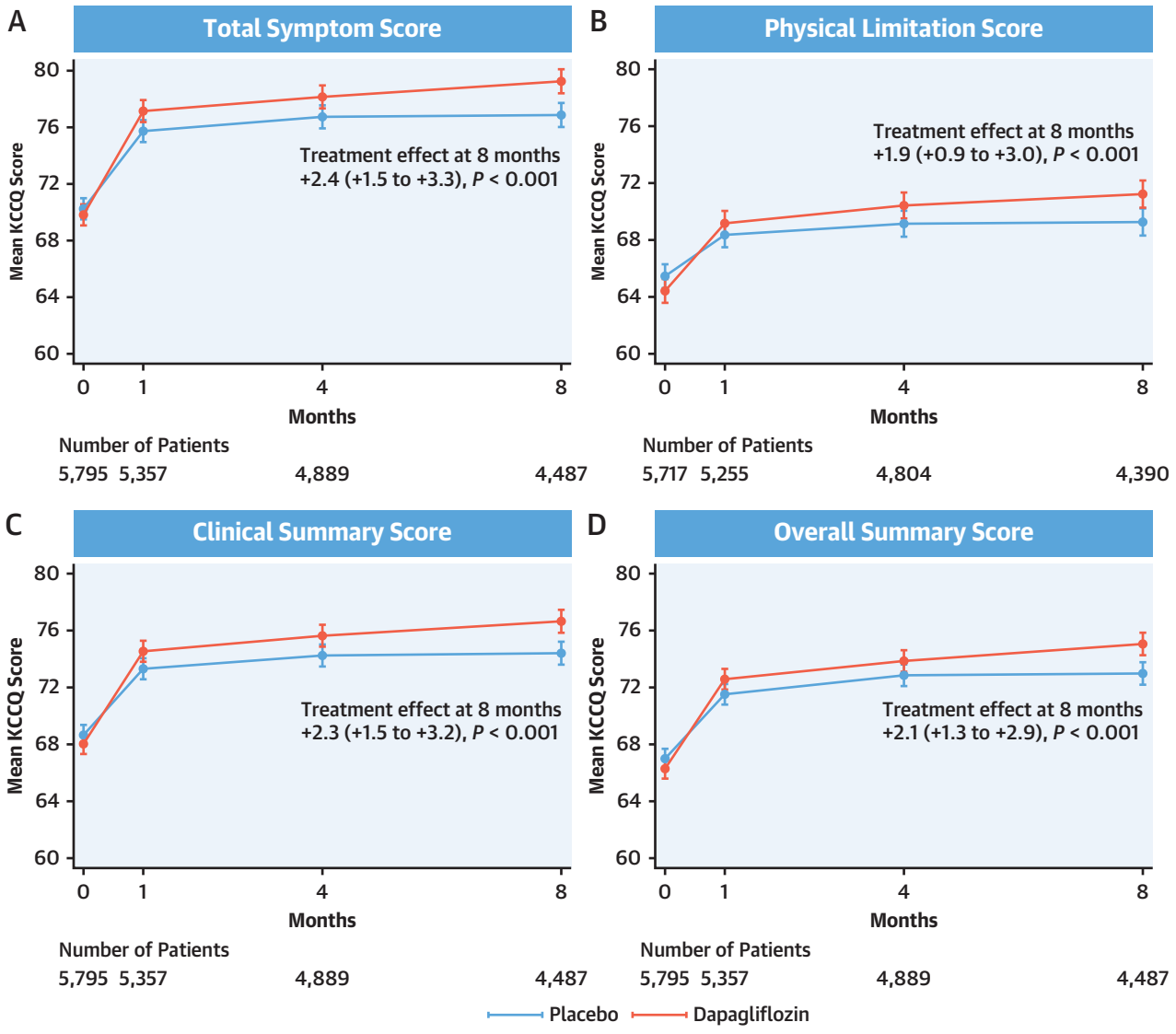


Separate curves indicated for the primary composite endpoint **(A)**, cardiovascular (CV) death **(B)**, heart failure (HF) events **(C)**, and CV death and total HF events **(D)**. HF events include HF hospitalization or urgent HF visit requiring intravenous therapy. Treatment Effect represents rate ratio with corresponding 95% CI for dapagliflozin vs placebo.

The baseline characteristics of patients according to the KCCQ-TSS tertiles are shown in Table 1. Compared with participants with higher KCCQ-TSS scores at baseline, those with lower scores were more often women, White, and enrolled in Europe and the Americas (and less likely to be enrolled in Asia). Participants with lower baseline KCCQ-TSS also had a higher proportion of comorbidities, such as type 2 diabetes, chronic obstructive pulmonary disease, and sleep apnea; had a longer duration of HF and higher likelihood of being previously hospitalized for HF; had higher body mass index and natriuretic peptide levels; had a lower estimated glomerular filtration rate (Table 1); and were more likely to be in NYHA functional class III/IV than in class II. With respect to background HF medications, patients with lower baseline KCCQ-TSS were more frequently treated with diuretic agents and less frequently with angiotensin receptor neprilysin inhibitors. The use of beta-blockers, ACE inhibitors and angiotensin receptor blockers, and mineralocorticoid receptor antagonists was similar across KCCQ tertiles.

CLINICAL OUTCOMES. Patients with lower baseline KCCQ-TSS experienced higher rates of CV death or worsening HF (7.8, 5.6, and 4.8 per 100 patient-years in patients across KCCQ-TSS tertiles of <63, 63-84, >84, respectively; $P < 0.001$). In the adjusted Cox proportional hazards models, patients with lower baseline KCCQ-TSS had a higher risk of CV death or

CENTRAL ILLUSTRATION **Mean Changes in KCCQ Domains Over Time by Treatment Allocation**



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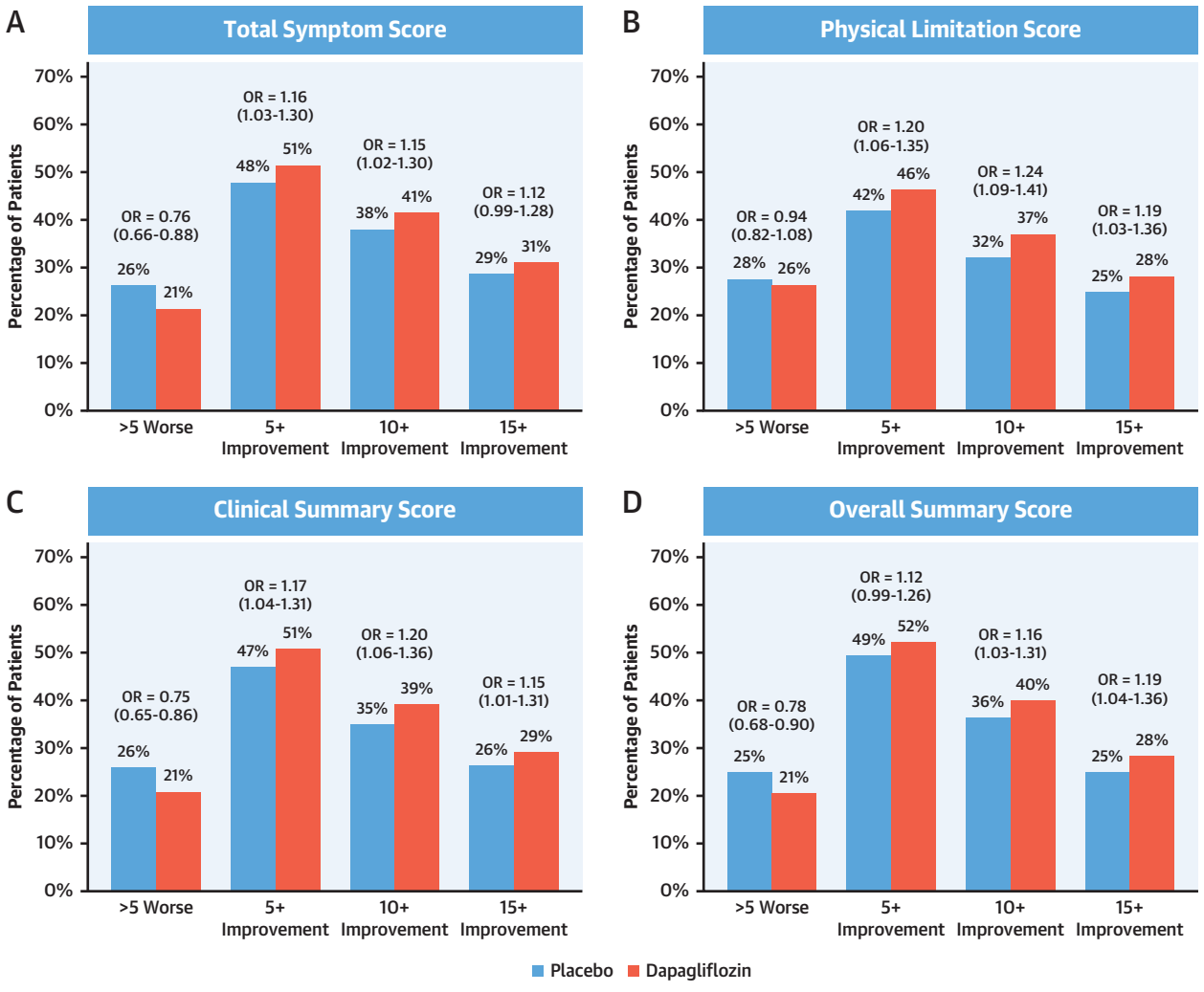
Individual graphs for Kansas City Cardiomyopathy Questionnaire (KCCQ) domains including Total Symptom Score (TSS) **(A)**, Physical Limitations Score (PLS) **(B)**, Clinical Summary Score (CSS) **(C)**, and Overall Summary Score (OSS) **(D)**. Change in KCCQ parameters (dapagliflozin vs placebo): Month 1: TSS: +1.8 (0.9-2.7); PLS: +1.5 (0.6-2.5); CSS: +1.8 (1.0-2.5); OSS: +1.6 (0.9-2.4). Month 4: TSS: +1.9 (1.0-2.8); PLS: +1.7 (0.7-2.7); CSS: +1.9 (1.1-2.7); OSS: +1.5 (0.8-2.3). Month 8: TSS: +2.4 (1.5-3.3); PLS: +1.9 (0.9-3.3); CSS: +2.3 (1.5-3.2); OSS: +2.1 (1.3-2.9). TSS quantifies the symptom frequency/severity, physical limitation score (PLS) evaluates physical function, clinical summary score (CSS) includes the symptoms and physical function, and overall summary score (OSS) summarizes all key domains (total symptom score, physical function, quality of life and social function). Scores are transformed to a range of 0-100; higher scores reflect better health status. Values represent change in KCCQ (in points) from baseline to 8 months with dapagliflozin vs placebo, with 95% CIs.

worsening HF (tertile >84: referent; tertile <63: HR: 1.42 [95% CI: 1.20-1.69]; tertile 63-84: HR: 1.16 [95% CI: 0.98-1.38]; overall $P < 0.001$). Similar results were observed with other clinical outcomes, including CV death, worsening HF events, and the total (first and recurrent) events of HF hospitalizations and CV death (Supplemental Table 2). Covariate-adjusted models were not found to significantly violate the assumption of proportional hazards (global $P > 0.30$). When examined as a

FIGURE 2 **Responder Analyses Across KCCQ Domains at 8 Months**



Responder analyses of clinically meaningful changes (dapagliflozin vs placebo) in Kansas City Cardiomyopathy Questionnaire (KCCQ)-total symptom score **(A)**, KCCQ-physical limitation score **(B)**, KCCQ-clinical summary score **(C)**, and KCCQ-overall summary score **(D)**.

continuous variable, there were significant relationships between lower KCCQ-TSS and higher risk of all clinical outcomes examined (Supplemental Figures 1A to 1D).

The effects of dapagliflozin on the range of clinical outcomes across KCCQ-TSS tertiles are summarized in **Table 2**. The effects of dapagliflozin vs placebo on reducing CV death or worsening HF appeared more pronounced in patients who had a greater burden of symptoms at baseline (lowest to highest KCCQ-TSS tertile: HR: 0.70 [95% CI: 0.58-0.84]; 0.81 [95% CI: 0.65-1.01]; 1.07 [95% CI: 0.83-1.37]; P for interaction = 0.026). Similar results were observed for worsening HF events and total (first and recurrent) hospitalizations for HF or CV death but not CV death, which was not reduced with dapagliflozin vs placebo regardless of KCCQ-TSS at baseline. When examined as a continuous variable, there was a graded relationship between lower KCCQ-TSS at baseline and greater reduction in the primary endpoint of CV death or worsening HF, worsening HF events and total (first and recurrent) hospitalizations, and CV death, with dapagliflozin vs placebo (**Figures 1A, 1C, and 1D**). Although the directionality was similar for the effects of dapagliflozin vs placebo on CV death, these were not statistically significant across the range of KCCQ-TSS (**Figure 1B**).

Serious adverse events occurred infrequently but were more common in patients with lower baseline KCCQ-TSS (tertile 1) (Supplemental Table 3). Within

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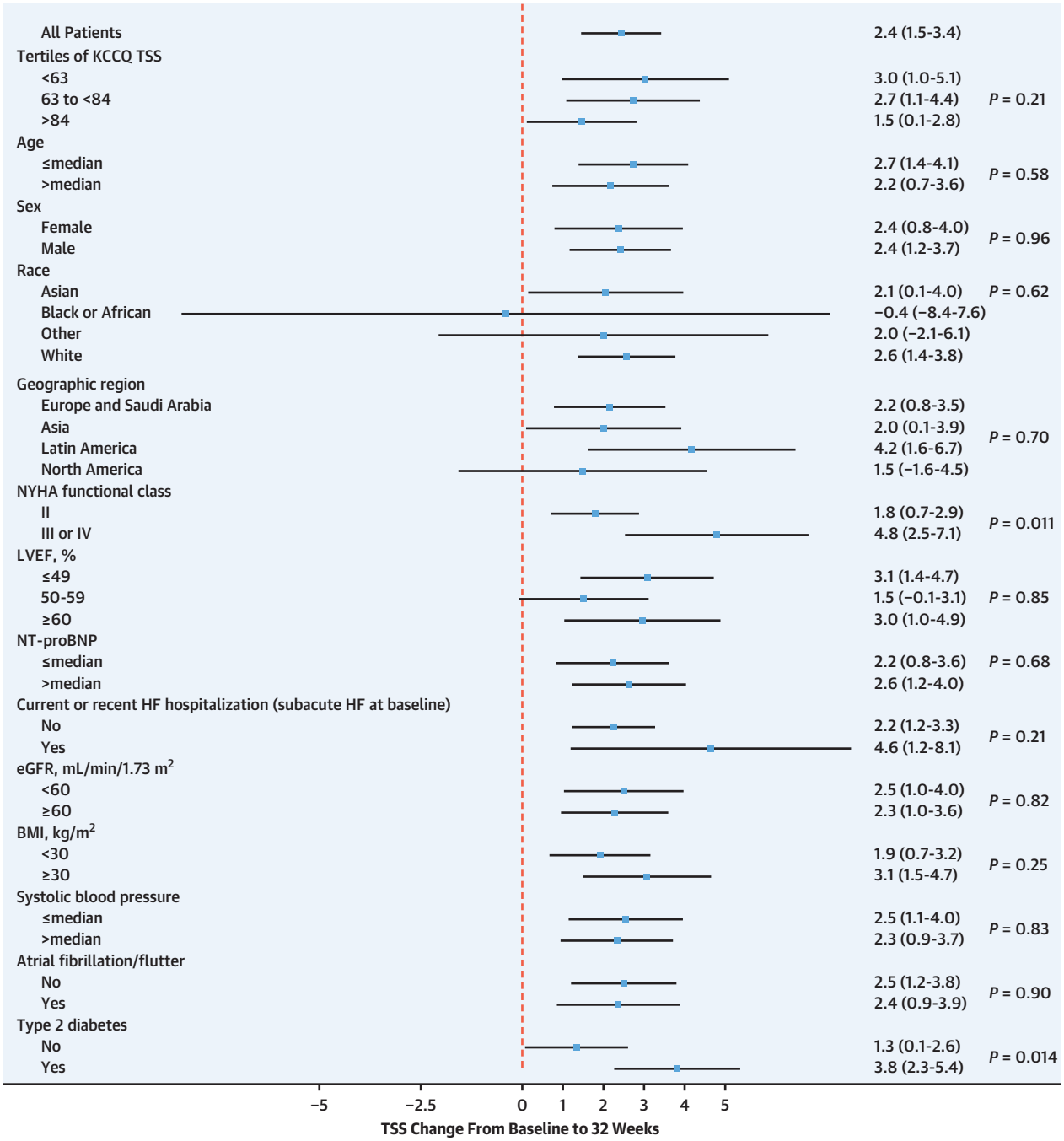
FIGURE 3 **Effects of Dapagliflozin vs Placebo on KCCQ-TSS Across Key Patient Subgroups**

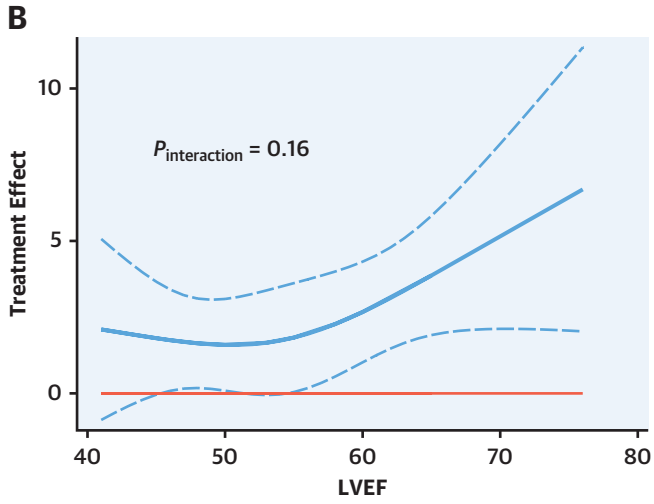
A



Forest plot of effects of dapagliflozin vs placebo on Kansas City Cardiomyopathy Questionnaire (KCCQ)-Total Symptom Score (TSS) at 8 months across various demographic and clinical subgroups **(A)** and across the spectrum of EF **(B).** Treatment effect refers to placebo-adjusted change in KCCQ-TSS from baseline to 8 months. *P* values for interaction are presented.

Continued on the next page

FIGURE 3 Continued



each tertile, adverse events were similarly distributed in those randomized to placebo vs dapagliflozin (Supplemental Tables 4A to 4C).

HEALTH STATUS OUTCOMES. As previously reported, the change in the KCCQ-TSS indicated symptom benefit in the dapagliflozin group compared with the placebo group (win ratio 1.11; 95% CI: 1.03-1.21; $P = 0.009$). The mean changes in KCCQ-TSS, -PLS, -CSS, and -OSS over time using the repeated measurements models are presented in the **Central Illustration** (panels A, B, C, and D, respectively). Patients treated with dapagliflozin had a significant improvement in mean KCCQ-TSS, -PLS, -CSS and -OSS at 8 months (2.4, 1.9, 2.3, and 2.1 points higher vs placebo; $P < 0.001$, for all). These improvements were observed at 1 month and became more amplified over time.

The results of the responder analysis are shown in **Figures 2A to 2D**. Fewer patients treated with dapagliflozin had a clinically significant deterioration (≥5-point decline), and more patients treated with dapagliflozin had at least small, moderate, and large improvements in KCCQ-TSS, PLS, CSS, and OSS (all comparisons statistically significant, except 5-point or greater improvement in KCCQ-OSS and 15-point or greater improvement in KCCQ-TSS) (**Figures 2A to 2D**). The numbers needed to treat to prevent a 5-point deterioration, as well as produce at least small, moderate, and large improvements in KCCQ-TSS at 8 months with dapagliflozin vs placebo, were 20, 28, 29, and 42, respectively.

The effects of dapagliflozin vs placebo on KCCQ-TSS at 8 months across various demographic and clinical subgroups are shown in **Figure 3A**. The treatment effects of dapagliflozin were generally consistent across most subgroups, including LVEF ≤49%, 50% to 59%, and ≥60% (P for interaction = 0.85). There was also no significant interaction between the effects of dapagliflozin vs placebo on KCCQ-TSS at 8 months across the range of LVEF when it was analyzed as a continuous variable (P for interaction = 0.16) (**Figure 3B**). Patients with higher NYHA functional class III-IV appeared to derive a greater symptomatic benefit than those with NYHA functional class II (4.8 points vs 1.8 points; P for interaction = 0.01). A similar directionality was observed for tertiles of baseline KCCQ-TSS, although this was not significant (P for interaction = 0.21). In addition, patients with vs without diabetes appeared to have a greater KCCQ-TSS improvement with dapagliflozin (3.8 points vs 1.3 points; P for interaction = 0.014).

DISCUSSION

In this study, which included prespecified assessments of health status using KCCQ in the DELIVER trial, we observed that dapagliflozin reduced the primary endpoint of CV death and worsening HF to a greater extent in patients with mildly reduced and preserved EF who had a higher burden of symptomatic impairment at baseline. Dapagliflozin improved KCCQ-TSS, -PLS, -CSS, and -OSS as

early as 1 month, with benefits sustained at 8 months. Significantly fewer patients treated with dapagliflozin experienced clinically meaningful deterioration, and more experienced clinically meaningful improvements in symptoms. Finally, the benefits of dapagliflozin on symptomatic improvement at 8 months were generally consistent across key demographic and clinical subgroups, including baseline LVEF, with no evidence of effect attenuation in those with LVEF ≥60%.

Our results have several important implications. First, we found that dapagliflozin significantly improved symptoms, physical limitations, and quality of life, as measured by KCCQ across all key domains. Of note, KCCQ was not a prespecified secondary endpoint nor was it included in the hierarchical testing sequence in EMPEROR-PRESERVED[14] or in PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor-neprilysin inhibitor] with ARB [angiotensin-receptor blockers] Global Outcomes in HF with Preserved Ejection Fraction)[15] with sacubitril-valsartan. In DELIVER, KCCQ-TSS was a prespecified secondary endpoint and was included in the hierarchical testing sequence, demonstrating benefits at 8 months and additional time points, and with consistent findings when analyzed using a win ratio approach, assessing mean changes over time, and in a responder analysis. Thus, to our knowledge, this is the first report of a convincing benefit for any agent (including SGLT2 inhibitors) on symptom burden from a large, global outcomes trial in patients with mildly reduced or preserved EF.

Second, our analyses of the clinical outcomes across the subgroups of baseline KCCQ-TSS suggest that the benefits of dapagliflozin on important clinical events appear to be more pronounced in patients with mildly reduced or preserved LVEF who have a greater burden of symptoms at baseline. To our knowledge, this is a novel observation. Although patients with greater symptom burden are at a higher *absolute* risk of clinical events, and therefore would be expected to derive the greatest *absolute* benefit with dapagliflozin (or other SGLT2 inhibitors), the relationship between the greater *relative* risk reduction in clinical events with greater symptom burden at baseline has not been observed in previous SGLT2 inhibitor trials in HF, regardless of EF criteria. Given the fact that individuals with mildly reduced and preserved EF experience especially poor health status,[3,18] these findings should prompt clinicians to prioritize the use of this therapy even more among those individuals with HF and mildly reduced and preserved EF with substantial symptom burden.

Third, our findings expand on the previously reported effects of dapagliflozin on health status, as measured by KCCQ, in patients with mildly reduced or preserved EF. In PRESERVED-HF, a multicenter, randomized, placebo-controlled trial performed in the United States, dapagliflozin was also shown to have favorable effects on multiple domains of KCCQ with quantitatively higher mean differences with dapagliflozin vs placebo (ie, 5.8 points for KCCQ-TSS) than those observed in DELIVER after 12 weeks of treatment—and with no heterogeneity of treatment benefit in individuals with LVEF either below or above 60%.[6] Our findings confirm these beneficial effects of dapagliflozin on symptoms, function, and quality of life in a larger, global trial, with a longer duration of follow-up and the ability to assess the effects of dapagliflozin on clinical outcomes across the range of baseline KCCQ. Collectively, these complementary findings from both the PRESERVED-HF and DELIVER trials indicate that dapagliflozin significantly improves HF-related health status, as measured by KCCQ, in individuals with mildly reduced or preserved EF, with the benefits emerging early and being sustained long term. Given the dearth of efficacious therapies that have been demonstrated to improve symptoms, function, and quality of life in this group,[15,18] and that many patients value their symptoms and physical function at least equally with avoidance of death,[19] these results are of clinical relevance.

Fourth, we observed no difference in the benefits of dapagliflozin on KCCQ-TSS regardless of baseline LVEF. These results are highly consistent with those of PRESERVED-HF but differ from a previously reported pooled patient-level analysis of the EMPEROR program (EMPEROR-Reduced and EMPEROR-Preserved), which showed modest but statistically significant KCCQ improvements with empagliflozin vs placebo across the range of EF except for individuals with EF ≥65%, in whom there was an attenuation of this effect, and no significant placebo-adjusted KCCQ increase was noted.[10] Given the fact that the benefits of dapagliflozin on clinical events were also consistent regardless of LVEF, we believe that the suggested attenuation of health status benefits of LVEF >65% observed in the EMPEROR Program may represent a chance finding. However, we cannot conclude this definitively, and our findings may not necessarily be generalized to other SGLT2 inhibitors.

The magnitude of KCCQ benefit observed with dapagliflozin in DELIVER was modestly higher than that seen with empagliflozin in the EMPEROR-PRESERVED trial,[20] but less pronounced than in the

PRESERVED-HF.[6] One explanation for these variations between DELIVER, EMPEROR-PRESERVED, and PRESERVED-HF are differences in patient populations. Patients in PRESERVED-HF were exclusively recruited in the United States and had a greater proportion of under-represented minorities and substantially higher BMI (with BMI being the strongest correlate of patient-reported health status in HF with preserved EF). More importantly, patients in PRESERVED-HF were more symptomatic at baseline, with lower baseline KCCQ values, and the proportion of those with NYHA functional class III-IV being nearly twice as high when compared with DELIVER and EMPEROR-PRESERVED. Although patients in DELIVER (and EMPEROR-PRESERVED) were required to have symptoms of HF as reflected by NYHA functional class, the baseline KCCQ scores were only modestly reduced; these discrepancies between the KCCQ scores and NYHA functional class have been well documented previously[21] and reflect the fact that KCCQ is reported by the patients, whereas NYHA functional class is documented by clinicians. Of importance, we found that patients in DELIVER who had NYHA functional class III-IV functional class derived a significantly greater KCCQ benefit (which was quantitatively similar to that seen in PRESERVED-HF) than those with NYHA functional class II.

STUDY LIMITATIONS. Similar to other outcome trials, some patients had missing KCCQ values, although these were equally distributed between dapagliflozin and placebo. KCCQ was collected at randomization and at 1, 4, and 8 months; the impact of treatment with dapagliflozin on longer-term health status was not assessed in the context of this study. Although DELIVER is one of the largest trials of individuals with HF and mildly reduced or preserved EF, some of the subgroups were modest in size, and subgroup analyses were not adjusted for multiple comparisons. As in other trials, the prespecified inclusion and exclusion criteria may have limited the enrollment of some very high-risk patients, which could affect the generalizability of our results.

CONCLUSIONS

The benefits of dapagliflozin on CV death and worsening HF in patients with mildly reduced or preserved EF appeared especially pronounced in those with greater degree of symptomatic impairment at baseline. Dapagliflozin improved symptom burden, physical limitations, and quality of life as measured by KCCQ, which was consistent across the range of LVEF, and increased the proportion of patients experiencing at least small, moderate, and large improvements in health status.

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The DELIVER study was funded by AstraZeneca. Dr Kosiborod has received research grant support from AstraZeneca and Boehringer Ingelheim; has served as a consultant or on an advisory board for Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Sanofi, Pharmacosmos, and Vifor Pharma; has received other research support from AstraZeneca; and has received honoraria from AstraZeneca, Boehringer Ingelheim, and Novo Nordisk. Dr Bhatt has previously received consulting fees from Sanofi Pasteur; and has been supported by the National Heart, Lung, and Blood Institute T32 postdoctoral training grant T32HL007604. Dr Claggett has received consulting fees from Amgen, Cardurion, Corvia, and Novartis. Dr Vaduganathan has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Novartis, Pharmacosmos, Relypsa, Roche Diagnostics, Sanofi, and Tricog Health; has had speaker engagements with AstraZeneca, Novartis, and Roche Diagnostics; and participates on clinical trial committees for studies sponsored by Galmed, Novartis, Bayer AG, Occlutech, and Impulse Dynamics. Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Bayer and Roche Diagnostics; has served as a consultant or on the advisory board/steering committee/executive committee for Actelion, Alleviant Medical, Allysta Pharma, Amgen, AnaCardio AB, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc, EchoNous Inc, Eli Lilly, Impulse Dynamics, Ionis Pharmaceutical, Janssen Research and Development LLC, Medscape/WebMD Global LLC, Merck, Novartis, Novo Nordisk, Prosciento Inc, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, Siemens Healthcare Diagnostics and Us2.ai; and serves as cofounder and nonexecutive director of Us2.ai. Dr Hernandez has received research grants from American Regent, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Merck, Novartis, Somologic, and Verily; and has served as a consultant or on the Advisory Board for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cytokinetics, Eidos, Intercept, Merck, and Novartis. Dr Martinez has received consultation fees and research grants from AstraZeneca, Baliarda, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Gador, Milestone, Novartis, Pfizer, and St Lukes University. Dr Inzucchi has served on clinical trial committees or as a consultant to AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion; and has given lectures sponsored by AstraZeneca and Boehringer Ingelheim. Dr Shah has received research grants from the National Institutes of Health (U54 HL160273, R01 HL107577, R01 HL127028, R01 HL140731, R01 HL149423), Actelion, AstraZeneca, Corvia, Novartis, and Pfizer; and has received consulting fees from Abbott, Actelion, AstraZeneca, Amgen, Aria CV, Axon Therapies, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiora, Coridea, CVRx, Cyclerion, Cytokinetics, Edwards Lifesciences, Eidos, Eisai, Imara, Impulse Dynamics, GlaxoSmithKline, Intellia, Ionis, Ironwood, Lilly, Merck, MyoKardia, Novartis, Novo Nordisk, Pfizer, Prothena, Regeneron, Rivus, Sanofi, Sardocor, Shifamed, Tenax, Tenaya, and United Therapeutics. Dr de Boer has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc, Novo Nordisk, and Roche; and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche. Dr Jhund's employer has been

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with HF and mildly reduced or preserved EF, dapagliflozin improves symptoms, functional status, and quality-of-life consistently across categories of LVEF.

TRANSLATIONAL OUTLOOK: Further efforts are needed to encourage early initiation of dapagliflozin in symptomatic patients with HF regardless of LVEF.

REFERENCES

1. Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. *Circ Res*. 2019;124:1598–1617.

2. Warraich HJ, Kitzman DW, Whellan DJ, et al. Physical function, frailty, cognition, depression, and quality of life in hospitalized adults ≥60 years with acute decompensated heart failure with preserved versus reduced ejection fraction. *Circ Heart Fail*. 2018;11:e005254.

3. Tsevat J, Weeks JC, Guadagnoli E, et al. Using health-related quality-of-life information: clinical encounters, clinical trials, and health policy. *J Gen Intern Med*. 1994;9:576–582.

4. Lewis EF, Johnson PA, Johnson W, Collins C, Griffin L, Stevenson LW. Preferences for quality of life or survival expressed by patients with heart failure. *J Heart Lung Transplant*. 2001;20:1016–1024.

5. Treatment for heart failure: endpoints for drug development guidance for industry. U.S. Food and Drug Administration. Accessed July 12, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/treatment-heart-failure-endpoints-drug-development-guidance-industry

6. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med*. 2021;27:1954–1960.

7. Spertus JA, Birmingham MC, Nassif M, et al. The SGLT2 inhibitor canagliflozin in heart failure: the CHIEF-HF remote, patient-centered randomized trial. *Nat Med*. 2022;28:809–813.

8. Kosiborod MN, Angermann CE, Collins SP, et al. Effects of empagliflozin on symptoms, physical limitations, and quality of life in patients hospitalized for acute heart failure: results from the EMPULSE trial. *Circulation*. 2022;146:279–288.

9. Butler J, Filippatos G, Jamal Siddiqi T, et al. Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: the EMPEROR-Preserved trial. *Circulation*. 2022;145:184–193.

10. Butler J, Packer M, Filippatos G, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J*. 2022;43:416–426.

11. Solomon SD, McMurray JJV, Claggett B, et al. DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;10(3):184–197.

12. Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med*. 2022;28(9):1956–1964. https://doi.org/10.1038/s41591-022-01971-4

13. Spertus JA, Jones PG, Sandhu AT, Arnold SV. Interpreting the Kansas City Cardiomyopathy Questionnaire in clinical trials and clinical care: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76:2379–2390.

14. Anker SD, Butler J, Filippatos G, et al, for the EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461.

15. Solomon SD, McMurray JJV, Anand IS, et al, for the PARAGON-HF Investigators and Committees. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–1620.

16. Lin DW, Wei LJ, Yang I, Ying Z. Semiparametric regression for the mean and rate functions of recurrent events. *J R Stat Soc B*. 2000;62:711–730.

17. Lewis EF, Kim H-Y, Claggett B, et al, for the TOPCAT Investigators. Impact of spironolactone on longitudinal changes in health-related quality of life in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. *Circ Heart Fail*. 2016;9:e001937.

18. Pieske B, Wachter R, Shah SJ, et al, for the PARALLAX Investigators and Committee Members. Effect of sacubitril/valsartan vs standard medical therapies on plasma NT-proBNP concentration and submaximal exercise capacity in patients with heart failure and preserved ejection fraction: the PARALLAX randomized clinical trial. *JAMA*. 2021;326:1919–1929.

19. Forman DE, Arena R, Boxer R, et al, for the American Heart Association Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Quality of Care and Outcomes Research; and Stroke Council. Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2017;135:e894–e918.

20. Butler J, Anker SD, Filippatos G, et al, for the EMPEROR-Reduced Trial Committees and Investigators. Empagliflozin and health-related quality of life outcomes in patients with heart failure with reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J*. 2021;42:1203–1212.

21. Greene SJ, Butler J, Spertus JA, et al. Comparison of New York Heart Association class and patient-reported outcomes for heart failure with reduced ejection fraction. *JAMA Cardiol*. 2021;6:522–531.

KEY WORDS dapagliflozin, health status, heart failure with mildly reduced ejection fraction, heart failure with preserved ejection fraction, KCCQ, SGLT2 inhibitors

APPENDIX For a supplemental figure and tables, please see the online version of this paper.