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Association of Dapagliflozin vs Placebo With Individual Kansas City Cardiomyopathy Questionnaire Components in Patients With Heart Failure With Mildly Reduced or Preserved Ejection Fraction
A Secondary Analysis of the DELIVER Trial

Alexander Peikert, MD; Alvin Chandra, MD; Mikhail N. Kosiborod, MD; Brian L. Claggett, PhD; Akshay S. Desai, MD, MPH; Pardeep S. Jhund, MBChB, MSc, PhD; Carolyn S. P. Lam, MD; Silvio E. Inzucchi, MD; Felipe A. Martinez, MD; Rudolf A. de Boer, MD; Adrian F. Hernandez, MD; Sanjiv J. Shah, MD; Stefan P. Janssens, MD; Jan Bělohlávek, MD; C. Jan Willem Borleffs, MD; Dan Dobreanu, MD; Anna Maria Langkilde, MD, PhD; Olof Bengtsson, PhLic; Magnus Petersson, MD, PhD; John J. V. McMurray, MD; Scott D. Solomon, MD; Muthiah Vaduganathan, MD, MPH

IMPORTANCE Dapagliflozin has been shown to improve overall health status based on aggregate summary scores of the Kansas City Cardiomyopathy Questionnaire (KCCQ) in patients with heart failure (HF) with mildly reduced or preserved ejection fraction enrolled in the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial. A comprehensive understanding of the responsiveness of individual KCCQ items would allow clinicians to better inform patients on expected changes in daily living with treatment.

OBJECTIVE To examine the association of dapagliflozin treatment with changes in individual components of the KCCQ.

DESIGN, SETTING, AND PARTICIPANTS This is a post hoc exploratory analysis of DELIVER, a randomized double-blind placebo-controlled trial conducted at 353 centers in 20 countries from August 2018 to March 2022. KCCQ was administered at randomization and 1, 4, and 8 months. Scores of individual KCCQ components were scaled from 0 to 100. Eligibility criteria included symptomatic HF with left ventricular ejection fraction greater than 40%, elevated natriuretic peptide levels, and evidence of structural heart disease. Data were analyzed from November 2022 to February 2023.

MAIN OUTCOMES AND MEASURES Changes in the 23 individual KCCQ components at 8 months.

INTERVENTIONS Dapagliflozin, 10 mg, once daily or placebo.

RESULTS Baseline KCCQ data were available for 5795 of 6263 randomized patients (92.5%) (mean [SD] age, 71.5 [9.5] years; 3344 male [57.7%] and 2451 female [42.3%]). Dapagliflozin was associated with larger improvements in almost all KCCQ components at 8 months compared with placebo. The most significant improvements with dapagliflozin were observed in frequency of lower limb edema (difference, 3.2; 95% CI, 1.6-4.8; $P < .001$), sleep limitation by shortness of breath (difference, 3.0; 95% CI, 1.6-4.4; $P < .001$), and limitation in desired activities by shortness of breath (difference, 2.8; 95% CI, 1.3-4.3; $P < .001$). Similar treatment patterns were observed in longitudinal analyses integrating data from months 1, 4, and 8. Higher proportions of patients treated with dapagliflozin experienced improvements, and fewer had deteriorations across most individual components.

CONCLUSIONS AND RELEVANCE In this study of patients with HF with mildly reduced or preserved ejection fraction, dapagliflozin was associated with improvement in a broad range of individual KCCQ components, with the greatest benefits in domains related to symptom frequency and physical limitations. Potential improvements in specific symptoms and activities of daily living might be more readily recognizable and easily communicated to patients.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Scott D. Solomon, MD, Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis St, Boston, MA 02115 (ssolomon@bwh.harvard.edu).

Patients with heart failure (HF) experience substantial limitations in symptoms, function, and quality of life.[1] In the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial, in addition to reducing HF events or cardiovascular mortality,[2] the sodium-glucose cotransporter-2 (SGLT-2) inhibitor dapagliflozin was shown to improve overall health status based on aggregate summary scores of the Kansas City Cardiomyopathy Questionnaire (KCCQ) in patients with HF with mildly reduced or preserved ejection fraction (EF) with a mean 2.1-point improvement in KCCQ-overall summary score (OSS).[3] Although individual limitations in symptoms, function, and quality of life are of particular importance to patients, aggregate summary scores are typically reported to quantify health status effects of an intervention. These might be challenging for patients to translate to specific activities of daily living.[4] Whether the treatment effect of dapagliflozin varies across components of health status and which components of the KCCQ may benefit most from this treatment remains unknown. A more comprehensive understanding of the responsiveness of each individual KCCQ item would allow clinicians to better inform patients on realistic expectations on changes in daily living with treatment. In this post hoc exploratory analysis of the DELIVER trial, we examine the association of dapagliflozin with changes in the 23 individual components of the KCCQ.

Key Points

Question What is the association between improvement in individual components of the Kansas City Cardiomyopathy Questionnaire (KCCQ) and treatment with dapagliflozin vs placebo in patients with heart failure with mildly reduced or preserved ejection fraction?

Findings In this post hoc exploratory analysis of the DELIVER trial, treatment with dapagliflozin was associated with improvements in almost all individual KCCQ components, with the greatest benefits in domains related to symptom frequency and physical limitations emerging as early as 1 month after treatment initiation.

Meaning The findings suggest that dapagliflozin is associated with rapid improvement in a broad range of symptoms, function, and quality of life in patients with heart failure with mildly reduced or preserved ejection fraction.

Methods

The DELIVER trial was a multicenter randomized double-blind event-driven trial conducted at 353 centers in 20 countries from August 2018 to March 2022 that compared dapagliflozin, 10 mg, or placebo once daily in patients with HF with mildly reduced or preserved ejection fraction.[5] Key eligibility criteria included left ventricular ejection fraction greater than 40%, New York Heart Association functional classes II to IV, evidence of structural heart disease, and elevated concentrations of natriuretic peptides. The study was approved by institutional review boards or ethics committees at each individual study site, and each patient provided written informed consent. The trial is registered at ClinicalTrials.gov (NCT03619213). The trial protocol can be found in Supplement 1.

The KCCQ is a validated, self-administered, HF-specific instrument quantifying symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy within a 2-week recall period based on 23 individual components.[6] KCCQ was administered at randomization and 1, 4, and 8 months. Scores of each of the 23 KCCQ components were scaled from 0 to 100, with scores of 100 representing no symptoms or limitations and lower scores indicating more severe symptoms and limitations.

For descriptive purposes, baseline characteristics were compared across quartiles of KCCQ-OSS (summarizing symptoms, physical limitations, social limitations, and quality of life) using the *t* test, Wilcoxon rank sum test, or χ^2 test.

The primary analyses of mean score changes between baseline and 8 months included all patients with complete data, with no imputation for missing data. Mean score changes between baseline and 8 months were examined for each individual KCCQ component by multivariable linear regression models, including the Δ between baseline and 8 months, randomized treatment, and the score of each component at baseline. Overall mean score changes were analyzed by longitudinal regression models with patient-level intercepts as a random effect, including data from baseline and 1-, 4-, and 8-month follow-up. Additional models determined mean score changes between baseline and 1 and 4 months. Sensitivity analyses additionally included patients who died before the 8-month follow-up in the primary models, assigning scores of 0 to each individual item at 8 months. Responder analyses compared the proportions of patients with any worsening, no change, and any improvement on the original question-level scale (with all changes corresponding to more than 5 points on a 100-point scale) between baseline and at 8 months for each component by treatment group using an ordered logistic regression model, adjusted for the baseline score of each component. Additional sensitivity analyses examined the proportions of patients according to all possible categories of worsening, improvement, and no change on the original question-level scale. Statistical analyses were conducted using Stata version 17.0 (StataCorp). *P* values <.05 were considered statistically significant. Data were analyzed from November 2022 to February 2023.

Results

Of 6263 randomized patients, KCCQ data were available for 5795 (92.5% of the overall population) at randomization, 4411 of whom (70.4% of the overall population) completed KCCQ assessments at 8 months. Among those with available KCCQ evaluations at baseline, the mean (SD) age was 71.5 (9.5) years, 3344 were male (57.7%), and 2451 were female (42.3%). eTable 1 in Supplement 2 displays baseline characteristics by quartiles of KCCQ-OSS. Considerably fewer

Table 1. Change in Individual Kansas City Cardiomyopathy Questionnaire (KCCQ) Components at 8 Months

KCCQ component	8-mo Mean score change (SE)[a]		8-mo Mean score change difference (95% CI)[b]	*P* value for 8-mo follow-up[c]
	Dapagliflozin	Placebo		
Swelling in feet/ankles/legs	9.5 (0.6)	6.3 (0.6)	3.2 (1.6 to 4.8)	<.001
Sleep limitation by shortness of breath	6.6 (0.5)	3.6 (0.5)	3.0 (1.6 to 4.4)	<.001
Intimate relationships with loved ones	5.9 (1.1)	3.0 (1.1)	2.9 (−0.2 to 6.0)	.07
Ability limitation by shortness of breath	8.8 (0.5)	6.0 (0.5)	2.8 (1.3 to 4.3)	<.001
Climbing a flight of stairs without stopping	6.4 (0.6)	3.7 (0.6)	2.7 (1.1 to 4.4)	.001
Visiting family/friends out of home	5.1 (0.5)	2.5 (0.5)	2.7 (1.1 to 4.2)	.001
Bothered by shortness of breath	8.3 (0.5)	6.0 (0.5)	2.3 (0.9 to 3.6)	.001
Yardwork/housework, carrying groceries	6.3 (0.6)	4.0 (0.6)	2.3 (0.7 to 3.9)	.004
Bothered by swelling in feet/ankles/legs	6.8 (0.4)	4.6 (0.4)	2.2 (0.9 to 3.4)	.001
Bothered by fatigue	7.9 (0.5)	5.8 (0.5)	2.1 (0.7 to 3.5)	.002
Walking 1 block on level ground	4.7 (0.5)	2.8 (0.5)	1.9 (0.4 to 3.4)	.01
Hobbies, recreational activities	8.3 (0.5)	6.5 (0.6)	1.9 (0.3 to 3.4)	.02
Hurrying or jogging	5.0 (0.7)	3.1 (0.7)	1.9 (0.1 to 3.8)	.04
HF-related limitations in enjoyment of life	6.8 (0.5)	5.0 (0.5)	1.8 (0.5 to 3.1)	.005
Dressing yourself	2.9 (0.4)	1.2 (0.4)	1.7 (0.6 to 2.9)	.004
Showering/bathing	2.2 (0.4)	0.6 (0.4)	1.7 (0.5 to 2.9)	.007
Ability limitation by fatigue	8.1 (0.5)	6.4 (0.5)	1.7 (0.2 to 3.2)	.03
Feeling about life with HF	10.3 (0.5)	8.7 (0.5)	1.6 (0.2 to 3.1)	.03
Working or doing household chores	7.4 (0.5)	5.9 (0.5)	1.5 (0.0 to 3.0)	.046
Feeling discouraged/down with HF	6.1 (0.5)	4.7 (0.5)	1.3 (0.0 to 2.7)	.04
Change in HF symptoms	3.4 (0.4)	2.4 (0.4)	1.0 (−0.2 to 2.2)	.09
Knowing what to do if HF gets worse	7.3 (0.4)	6.7 (0.4)	0.6 (−0.6 to 1.9)	.30
Understanding HF symptoms getting worse	6.8 (0.4)	6.6 (0.4)	0.2 (−1.0 to 1.3)	.74

Abbreviation: HF, heart failure.

[a] Mean score changes are based on multivariable linear regression models. All models were adjusted for the score of each component at baseline.

[b] Positive numbers in mean score change difference favor dapagliflozin.

[c] *P* values are reported for differences in mean score change between patients treated with dapagliflozin and those treated with placebo.

patients provided information about limitations in their intimate relationships at randomization and 8 months (n = 1332 [21.3% of the overall population]).

Between baseline and 8 months, treatment with dapagliflozin was associated with larger improvements in nearly all individual KCCQ components compared with placebo (**Table 1** and **Figure**). The greatest significant improvements with dapagliflozin were observed in frequency of lower limb edema (difference, 3.2; 95% CI, 1.6 to 4.8; *P* < .001), sleep limitation by shortness of breath (difference, 3.0; 95% CI, 1.6 to 4.4; *P* < .001), and limitation in desired activities by shortness of breath (difference, 2.8; 95% CI, 1.3 to 4.3; *P* < .001) (Table 1 and Figure). Moreover, the third largest difference between treatment groups in favor of dapagliflozin was seen in sexual relationships (difference, 2.9; 95% CI, −0.2 to 6.0; *P* = .07). Longitudinal analyses integrating data from months 1, 4, and 8 observed similar improvements in almost all components (eTable 2 in Supplement 2). Changes in individual KCCQ components at 1, 4, and 8 months are shown in eTable 2 in Supplement 2. Sensitivity analyses that additionally included patients who died before 8-month follow-up with assigned values of 0 to each component at 8 months revealed comparable treatment patterns on the individual KCCQ components as observed in the primary analysis (eTable 3 in Supplement 2).

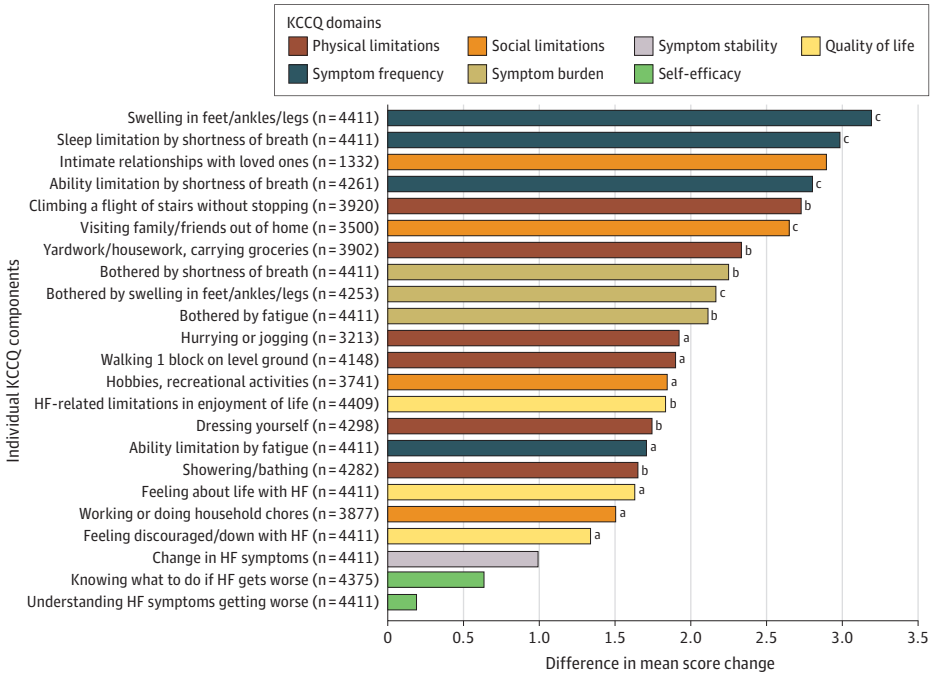
In responder analyses, a higher proportion of patients treated with dapagliflozin experienced clinically meaningful net improvements (of more than 5 points), and fewer patients treated with dapagliflozin experienced deteriorations across all individual components. The greatest odds of significant improvements were seen in sleep limitations by shortness of breath (OR, 1.33; 95% CI, 1.15 to 1.53; *P* < .001), feeling bothered by lower limb edema (OR, 1.24; 95% CI, 1.09 to 1.42; *P* = .001), feeling bothered by shortness of breath (OR, 1.22; 95% CI, 1.08 to 1.37; *P* = .001), and difficult dressing oneself (OR, 1.20; 95% CI, 1.06 to 1.37; *P* = .005) at 8 months (**Table 2**). Consistent treatment effects were observed when assessing improvements across all possible categories of worsening and improvement (eTable 4 in Supplement 2).

Discussion

In this post hoc analysis of the DELIVER trial, we found significant improvements in a broad range of individual KCCQ components at 8 months in patients with HF and mildly reduced or preserved EF randomized to dapagliflozin, with the greatest benefits seen in the domains of symptom frequency and physical limitations. Similar treatment patterns were seen in longitudinal analyses that integrated data from months 1, 4, and 8.

Our findings on the association of dapagliflozin with improvements across all individual KCCQ components contribute to a more detailed understanding of previously reported benefits with SGLT-2 inhibitors on aggregated summary scores of the KCCQ.[3,7] The mean 2.1-point improvement in KCCQ-OSS with dapagliflozin originally reported in DELIVER[3]

Figure. Differences in Mean Score Change of Individual Kansas City Cardiomyopathy Questionnaire (KCCQ) Components Between Dapagliflozin and Placebo at 8 Months



Differences in mean score are based on multivariable linear regression models. All models were adjusted for the mean score of each component at baseline. Positive values indicate greater improvement with dapagliflozin compared to placebo. *P* values for differences in mean score change are shown in **Table 1**.

[a] $P < .05$.

[b] $P < .01$.

[c] $P < .001$.

appears to have been driven by small improvements in nearly every one of the 23 individual components, ranging across the domains of symptom frequency, symptom burden, physical limitations, and social limitations. Correlates of congestion have been previously shown to be the strongest surrogates for poor health-related quality of life in patients with HF.[8] We found the greatest benefits with dapagliflozin in the frequency of lower extremity edema, limitations in desired activities, and sleep limitation due to dyspnea. Similarly, HF-related impairments in physical function are among the most common health-related quality of life limitations, with the largest treatment benefit with dapagliflozin on physical limitations observed for climbing stairs.[9]

While sexual relationships ranked as the component with the third largest magnitude of improvement overall, this measure appeared to have limited precision, as only one-fifth of patients provided information on sexual limitations. Although sexual health has a major impact on health-related quality of life and more than two-thirds of individuals with HF report sexual problems,[10] patients may perceive barriers to communicating about sexual function.[11] A quantitively similar benefit (2.7 points) for sexual relationships was seen with sacubitril/valsartan in patients with HF with reduced EF in PARADIGM-HF.[12] Adding to previously demonstrated clinically meaningful improvements in aggregated KCCQ summary scores with SGLT-2 inhibitors,[3,7] higher proportions of patients treated with dapagliflozin tended to achieve net improvements for almost all KCCQ components, with the highest odds for individual symptom frequencies, symptom burdens, and physical limitations.

We believe these data are clinically informative in communicating the broad and most apparent benefits observed with SGLT-2 inhibitors with respect to individual KCCQ items to patients, caregivers, and clinicians. While we recognize that the KCCQ was validated and intended to be used as domains and summary scores, expected improvements in specific symptoms and activities of daily living might be more readily recognizable and easily communicated to patients. Benefits on multiple dimensions of health status emerged even at the 1-month KCCQ assessment, reinforcing the potential rapid benefits with these therapies, whereas other improvements occurred over time.

Limitations

The KCCQ was designed as a composite measure summarizing patient-reported outcomes; analyses of individual KCCQ components were performed post hoc and should be considered exploratory. As with other similar trials, the analyses were affected by missing KCCQ data and the possibility of a nonresponder bias, although missing KCCQ scores were equally distributed between treatment groups and sensitivity analyses assigning worst case health status scores to patients who had died yielded similar findings. The considerably smaller sample size for intimate relationships relative to the other KCCQ components limited statistical power in assessing this item. While the median follow-up time was 2.3 years, KCCQ was administered at randomization, 1, 4, and 8 months, precluding conclusions about treatment effects on these health status components beyond this period.

Table 2. Ordinal Responder Analysis of the Association of Dapagliflozin With Net Improvement in Individual Kansas City Cardiomyopathy Questionnaire (KCCQ) Components at 8 Months

KCCQ component	Participants with any worsening at 8 mo, No./total No. (%)		Participants with any improvement at 8 mo, No./total No. (%)		Odds ratio (95% CI) for net improvement[a]	*P* value for net improvement
	Dapagliflozin	Placebo	Dapagliflozin	Placebo		
Sleep limitation by shortness of breath	207/2207 (9.4)	292/2204 (13.2)	499/2207 (22.6)	438/2204 (19.9)	1.33 (1.15-1.53)	<.001
Bothered by swelling in feet/ankles/or legs	272/2131 (12.8)	343/2122 (16.2)	627/2131 (29.4)	570/2122 (26.9)	1.24 (1.09-1.42)	.001
Bothered by shortness of breath	367/2207 (16.6)	453/2204 (20.6)	801/2207 (36.3)	761/2204 (34.5)	1.22 (1.08-1.37)	.001
Dressing yourself	354/2144 (16.5)	393/2154 (18.2)	541/2144 (25.2)	458/2154 (21.3)	1.20 (1.06-1.37)	.005
Swelling in feet/ankles/legs	323/2207 (14.6)	394/2204 (17.9)	699/2207 (31.7)	664/2204 (30.1)	1.20 (1.06-1.36)	.004
Ability limitation by shortness of breath	454/2134 (21.3)	542/2127 (25.5)	905/2134 (42.4)	853/2127 (40.1)	1.19 (1.06-1.34)	.004
Showering/bathing	369/2129 (17.3)	416/2153 (19.3)	510/2129 (24.0)	451/2153 (20.9)	1.19 (1.05-1.35)	.008
Bothered by fatigue	399/2207 (18.1)	465/2204 (21.1)	826/2207 (37.4)	786/2204 (35.7)	1.18 (1.05-1.32)	.007
Climbing a flight of stairs without stopping	429/1960 (21.9)	469/1960 (23.9)	726/1960 (37.0)	673/1960 (34.3)	1.17 (1.04-1.32)	.01
Visiting family/friends out of home	330/1748 (18.9)	369/1752 (21.1)	532/1748 (30.4)	496/1752 (28.3)	1.17 (1.02-1.33)	.02
Change in HF symptoms	427/2207 (19.3)	493/2204 (22.4)	667/2207 (30.2)	617/2204 (28.0)	1.15 (1.02-1.30)	.03
Feeling about life with HF	412/2207 (18.7)	453/2204 (20.6)	986/2207 (44.7)	905/2204 (41.1)	1.14 (1.02-1.29)	.03
Yardwork/housework, carrying groceries	430/1935 (22.2)	462/1967 (23.5)	742/1935 (38.3)	683/1967 (34.7)	1.14 (1.01-1.29)	.03
Hurrying or jogging	348/1583 (22.0)	388/1630 (23.8)	539/1583 (34.0)	518/1630 (31.8)	1.14 (1.00-1.30)	.06
Intimate relationships with loved ones	142/659 (21.5)	156/673 (23.2)	217/659 (32.9)	200/673 (29.7)	1.14 (0.92-1.40)	.23
Knowing what to do if HF gets worse	382/2190 (17.4)	407/2185 (18.6)	792/2190 (36.2)	749/2185 (34.3)	1.11 (0.98-1.26)	.09
Working or doing household chores	385/1929 (20.0)	402/1948 (20.6)	722/1929 (37.4)	690/1948 (35.4)	1.10 (0.97-1.25)	.13
HF-related limitations in enjoyment of life	460/2206 (20.9)	473/2203 (21.5)	837/2206 (37.9)	780/2203 (35.4)	1.09 (0.97-1.23)	.13
Ability limitation by fatigue	552/2207 (25.0)	559/2204 (25.4)	947/2207 (42.9)	942/2204 (42.7)	1.08 (0.96-1.21)	.22
Hobbies, recreational activities	379/1879 (20.2)	359/1862 (19.3)	715/1879 (38.1)	679/1862 (36.5)	1.08 (0.95-1.23)	.22
Walking 1 block on level ground	452/2083 (21.7)	472/2065 (22.9)	700/2083 (33.6)	663/2065 (32.1)	1.07 (0.95-1.21)	.26
Feeling discouraged/down with HF	428/2207 (19.4)	469/2204 (21.3)	764/2207 (34.6)	748/2204 (33.9)	1.07 (0.95-1.20)	.29
Understanding HF symptoms getting worse	390/2207 (17.7)	392/2204 (17.8)	801/2207 (36.3)	803/2204 (36.4)	1.02 (0.90-1.15)	.76

Abbreviation: HF, heart failure.

[a] Odds ratios for net improvement (any improvement vs no change vs any worsening) on the original question-level scale in each KCCQ component between baseline and 8 months were obtained from ordered logistic regression models, adjusted for the score of each component at baseline. All changes on the original question-level scale correspond to more than 5 points on a 100-point scale.

Conclusions

In this study of patients with HF with mildly reduced or preserved EF, dapagliflozin was associated with improvement in almost all individual KCCQ components, with the greatest improvement observed in domains of symptom frequency and physical limitations. These results complement previous findings from the DELIVER trial and highlight the broad range of improvements in symptoms, function, and quality of life seen with dapagliflozin that are apparent within months of treatment initiation.

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Author Affiliations: Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Peikert, Claggett, Desai, Solomon, Vaduganathan); Division of Cardiology, University of Texas Southwestern Medical Center, Dallas (Chandra); Saint Luke's Mid America Heart Institute and University of Missouri - Kansas City (Kosiborod); British Heart Foundation Glasgow Cardiovascular Research Center, School of Cardiovascular and Metabolic Health, University of Glasgow, Glasgow, Scotland, United Kingdom (Jhund, McMurray); National Heart Centre Singapore & Duke-National University of Singapore, Singapore (Lam); Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Lam); Yale School of Medicine, New Haven, Connecticut (Inzucchi); Universidad Nacional de Córdoba, Córdoba, Argentina (Martinez); Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (de Boer); Duke University Medical Center, Durham, North Carolina (Hernandez); Northwestern University Feinberg School of Medicine, Chicago, Illinois (Shah); Cardiac Intensive Care, Department of Cardiovascular Diseases, University Hospitals Leuven, Leuven, Belgium (Janssens); Department of Internal Medicine II, Cardiology and Angiology, General University Hospital, 1st Medical School, Charles University, Prague, Czech Republic (Bělohlávek); Haga Teaching Hospital, The Hague, the Netherlands (Borleffs); University of Medicine, Pharmacy, Science and Technology, George Emile Palade, Târgu Mureș, Romania (Dobreanu); Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals Research and Development, AstraZeneca, Gothenburg, Sweden (Langkilde, Bengtsson, Petersson).

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Concept and design: Peikert, Chandra, Kosiborod, Lam, Shah, Langkilde, Solomon, Vaduganathan.

Acquisition, analysis, or interpretation of data: Peikert, Chandra, Kosiborod, Claggett, Desai, Jhund, Inzucchi, Martinez, de Boer, Hernandez, Shah, Janssens, Bělohlávek, Borleffs, Dobreanu, Langkilde, Bengtsson, Petersson, McMurray, Solomon, Vaduganathan.
Drafting of the manuscript: Peikert, Chandra, Lam, Vaduganathan.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Peikert, Chandra, Claggett, Jhund, Bengtsson.
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Dr Inzucchi has served on clinical trial committees or as a consultant for AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Lexicon, Merck, Pfizer, vTv Therapeutics, Abbott, and Esperion; has given lectures sponsored by AstraZeneca and Boehringer Ingelheim; and has received personal fees from Bayer outside the submitted work. Dr Martinez has received personal fees from AstraZeneca. Dr de Boer has received research grant support, served on advisory boards, or had speaker engagements with AstraZeneca, Abbott, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardior Pharmaceuticals, Ionis Pharmaceuticals, Novartis, Novo Nordisk, and Roche. 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