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RESEARCH ARTICLE

Effect of dapagliflozin on health status and quality of life across the spectrum of ejection fraction: Participant-level pooled analysis from the DAPA-HF and DELIVER trials

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Aims

Patients with heart failure experience a high burden of symptoms and physical limitations, and poor quality of life. Dapagliflozin reduces heart failure hospitalization and cardiovascular death in patients with reduced, mildly reduced, and preserved ejection fractions. We examined the effects of dapagliflozin on health status, measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), across the full spectrum of left ventricular ejection fraction (LVEF).

Methods and results

Participant-level data were pooled from the DAPA-HF and DELIVER trials. Both trials were randomized, global, double-blind, placebo-controlled trials of patients with symptomatic heart failure and elevated natriuretic peptides. DAPA-HF and DELIVER included patients with LVEF ≤40% and LVEF >40%, respectively. KCCQ was evaluated at randomization and at 4 and 8 months post-randomization; the effect of dapagliflozin versus placebo on KCCQ total symptom score (TSS) was a pre-specified secondary outcome in both trials. Interaction testing was performed to assess potential heterogeneity in the effects of dapagliflozin versus placebo on KCCQ-TSS, clinical summary score (CSS), overall summary score (OSS), and physical limitation score (PLS), by continuous LVEF using restricted cubic splines. Responder analyses examining the proportion of patients with meaningful deterioration (≥5 point decline) and meaningful improvements (≥5 point increase) in KCCQ-TSS was assessed across LVEF categories. Of 11 007 randomized participants, 10 238 (93%) had full data on KCCQ-TSS at randomization. Benefits of dapagliflozin versus placebo on KCCQ-TSS, -CSS, -OSS, -PLS, at 8 months were consistent across the full range of LVEF ($p_{interaction}$ = 0.19, 0.10, 0.12, 0.10, respectively). In responder analyses, fewer dapagliflozin- versus placebo-treated patients had clinically meaningful deteriorations in KCCQ-TSS (overall: 21% vs. 23%; LVEF ≤40%: 21% vs. 29%; LVEF 41–60%: 21% vs. 26%; LVEF >60%: 22% vs. 27%). A greater proportion of patients randomized to dapagliflozin experienced at least small improvements in KCCQ-TSS (overall: 50% vs. 45%; LVEF ≤40%: 48% vs. 41%; LVEF 41–60%: 51% vs. 49%; LVEF >60%: 53% vs. 45%). The effects of dapagliflozin versus placebo on clinically meaningful deteriorations and improvements in

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health status by KCCQ-TSS were consistent across the full spectrum of LVEF assessed continuously ($p_{interaction} = 0.20$ and 0.64, respectively). Across the LVEF spectrum, the number needed to treat to affect ≥5 point improvement in health status assessed by KCCQ-TSS was 20. Health status declines preceding a HF hospitalization by ~10 points were observed in both trials, evident up to 3 months prior to hospitalization.

Conclusions In participant-level pooled analyses of DAPA-HF and DELIVER, dapagliflozin improved all key domains of health status across the full range of LVEF. Clinically meaningful improvements in health status were also observed consistently across LVEF, including in those with LVEF >60%.
Clinical Trial Registration: NCT03036124 and NCT03619213.

Keywords Heart failure • Quality of life • Ejection fraction

Introduction

Patients with heart failure (HF) experience a high burden of symptoms, physical limitations, and poor quality of life regardless of left ventricular ejection fraction (LVEF). Improving health status and quality of life is a central goal in the treatment of HF. Importantly, many therapies have demonstrated most pronounced benefits on clinical and patient reported outcomes in patients with HF with reduced ejection fraction, with relative attenuation in clinical benefits at higher LVEF.[1] Contemporary descriptions of the relationship between health status and ejection fraction have been underexplored.

Dapagliflozin reduces HF hospitalization and cardiovascular death and improves quality of life in patients with reduced, mildly reduced, and preserved ejection fractions and is guideline-recommended for the treatment of HF across the spectrum of ejection fraction.[2–4] Whether favourable effects on health status and quality of life are present equally across the LVEF spectrum has not been as fully elucidated. Therefore, we examined the effects of dapagliflozin on health status, measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ), across the full spectrum of LVEF using pooled, participant-level data from the DAPA-HF and DELIVER randomized clinical trials.

Methods

We used a participant-level, pooled dataset of the DAPA-HF and DELIVER trials. DAPA-HF was a double-blind, placebo-controlled, global trial which randomized 4744 ambulatory patients with symptomatic HF, elevated natriuretic peptide and LVEF ≤40% to receive either dapagliflozin 10 mg daily or placebo. DELIVER similarly randomized 6263 participants to dapagliflozin 10 mg daily versus placebo, but enrolled patients with HF and mildly reduced or preserved ejection fraction (LVEF >40%). With the exception of included LVEF ranges, trial inclusion and exclusion criteria were similar. The primary efficacy endpoint in both trials was a composite of the time-to-first worsening HF event (defined as hospitalization for HF or an urgent HF visit requiring intravenous HF therapies) or cardiovascular death.

The KCCQ was completed by trial participants and evaluated at randomization, 4 and 8 months in both trials. The 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. Domains include the total symptom score (TSS), physical limitation score (PLS), clinical summary score (CSS), and overall summary score (OSS); KCCQ has been validated in patients across the spectrum of LVEF.[5] Scores are transformed to a range of 0–100, in which higher scores reflect better health status. Change in KCCQ-TSS from randomization to 8 months was a pre-specified secondary outcome in both trials.

We evaluated the relationship between baseline KCCQ-TSS, -CSS, -OSS, -PLS and ejection fraction modeled by categories of LVEF (≤40%, 41–60%, >60%). We also examined the treatment effect of dapagliflozin versus placebo on the mean 8-month change in all four domains of KCCQ across the spectrum of LVEF, with LVEF modeled continuously using restricted cubic spline models. Tests for statistical interaction were performed to assess for potential heterogeneity in the treatment effect on KCCQ by LVEF. A linear regression model was fit using the month 8 KCCQ value as the outcome, baseline KCCQ value as a covariate and the corresponding treatment-by-subgroup interaction terms. Interaction *p*-values are obtained from a global test of the treatment-subgroup interaction terms. KCCQ in follow-up could only be assessed among survivors, and no imputation was performed to account for missing data.

We also conducted a responder analysis, comparing the proportion of dapagliflozin- and placebo-treated participants with meaningful deteriorations (≥5 point decline) and small, moderate, and large improvements (≥5, ≥10, and ≥15-point increases, respectively) on KCCQ-TSS using logistic regression models. Models were generated across baseline LVEF categorized into three categories: (≤40%, 41–60%, >60%) and formal interaction testing for heterogeneity was undertaken. Models were repeated across KCCQ-CSS, -OSS, and -PLS summary scores. *P*-values of <0.05 were considered statistically significant. Statistical analyses were performed using STATA version 16.0 (StataCorp, College Station, TX, USA).

Applying previously established methods,[6] we examined KCCQ-TSS trajectory prior to HF hospitalization using restricted cubic splines; models were created for DAPA-HF and DELIVER separately. The time scale was the number of days preceding HF hospitalization. All available KCCQ reports were integrated to estimate health status trajectory as if it was assessed continuously; a mixed effect linear regression model with fixed piecewise linear effects for time and random patient-level intercepts was used.

Results

Of 11 007 patients randomized, 10 238 (93%) had full data on KCCQ-TSS at randomization. Patients had a mean age of

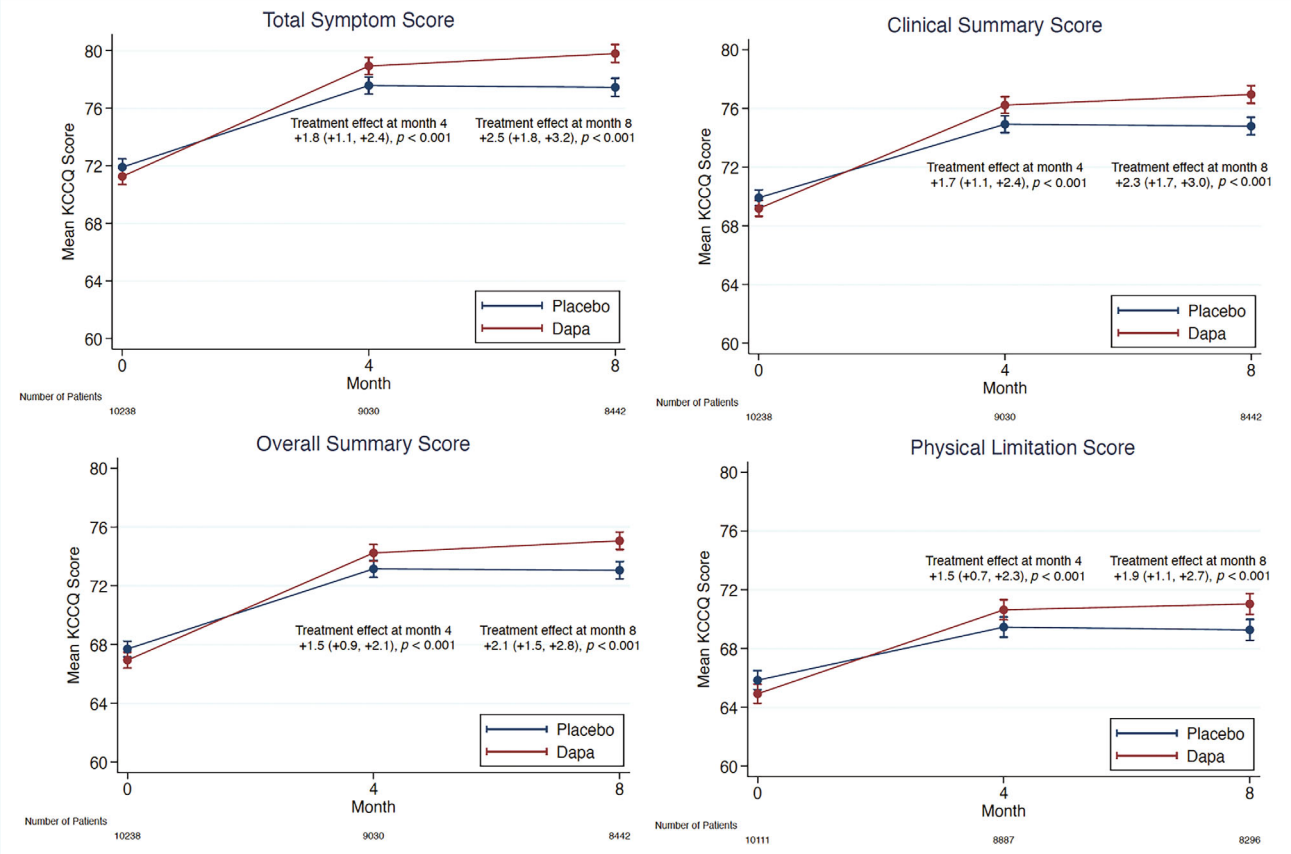

Figure 1 Mean changes in Kansas City Cardiomyopathy Questionnaire (KCCQ) domains over time by treatment allocation using pooled data from DAPA-HF and DELIVER. Individual graphs for KCCQ domains including total symptom score, clinical summary score, overall summary score, and physical limitation score. Values represent change in KCCQ (in points) from baseline to 4 and 8 months with dapagliflozin versus placebo, with 95% confidence intervals.

69 ± 10 years, 35% were female and 3.5% were Black. Median LVEF was 44% (interquartile range [IQR] 34–55%); 4747 (43%), 4865 (44%) and 1395 (13%) patients had LVEF ≤40%, 41–60%, and >60%, respectively. Median KCCQ-TSS at randomization was 75 (IQR 57–90). Patients with LVEF ≤40% were less symptomatic by KCCQ-TSS scores at randomization (77; IQR 58–92), compared with patients with LVEF 41–60%, (73; IQR 55–88) and LVEF >60% (73; IQR 54–88; $p < 0.001$). Similar trends were observed across additional KCCQ summary scores (online supplementary *Table S1*).

In a pooled analysis including participants in DAPA-HF and DELIVER, participants treated with dapagliflozin had a significant improvement in mean KCCQ-TSS at 4 months (mean difference: +1.8 (95% confidence interval [CI] +1.4, +2.4) and 8 months (mean difference: +2.5 [95% CI +1.8, +3.2] post-randomization [*Figure 1*]). Results were consistent across additional KCCQ domains (*Figure 1*) and most key subgroups of interest (*Figure 2*). Mean improvements in KCCQ-TSS at 8 months in those treated with dapagliflozin vs. placebo were greater in those with type 2 diabetes (+3.4; 95% CI +2.3, +4.6) compared to those without (+1.8; 95% CI +0.9, +2.7; $p_{interaction} = 0.026$). Dapagliflozin improved health status compared with placebo from randomization to 8 months across KCCQ-TSS, -CSS, -OSS, -PLS domains in a manner that was consistent across the full range of ejection fraction, including among those with LVEF >60% ($p_{interaction} = 0.19$, 0.10, 0.12, 0.10, respectively; *Figure 3*).

In responder analyses, fewer dapagliflozin- versus placebo-treated patients had clinically meaningful deteriorations (≥5 point decline) in KCCQ-TSS by 8 months post-randomization (21% vs. 29%, odds ratio [OR] 0.71; 95% CI 0.64–0.79; $p < 0.001$). Results were consistent across patients with LVEF ≤40% (21% vs. 29%, OR 0.66; 95% CI 0.57–0.77), LVEF 41–60% (21% vs. 29%, OR 0.76; 95% CI 0.65–0.89), and LVEF >60% (22% vs. 27%, OR 0.78; 95% CI 0.58–1.04; $p_{interaction} = 0.20$).

A greater proportion of patients randomized to dapagliflozin experienced large (≥15 point increase) improvements in KCCQ-TSS by 8 months post-randomization (28% vs. 25%, OR 1.15; 95% CI 1.04–1.27; $p = 0.005$). Large improvements in health status among dapagliflozin- versus placebo-treated patients were consistent across LVEF ($p_{interaction} = 0.94$), including patients with LVEF ≤40% (24% vs. 21%, OR 1.19; 95% CI 1.03–1.39), LVEF 41–60% (31% vs. 29%, OR 1.07; 95% CI 0.93–1.24), and LVEF

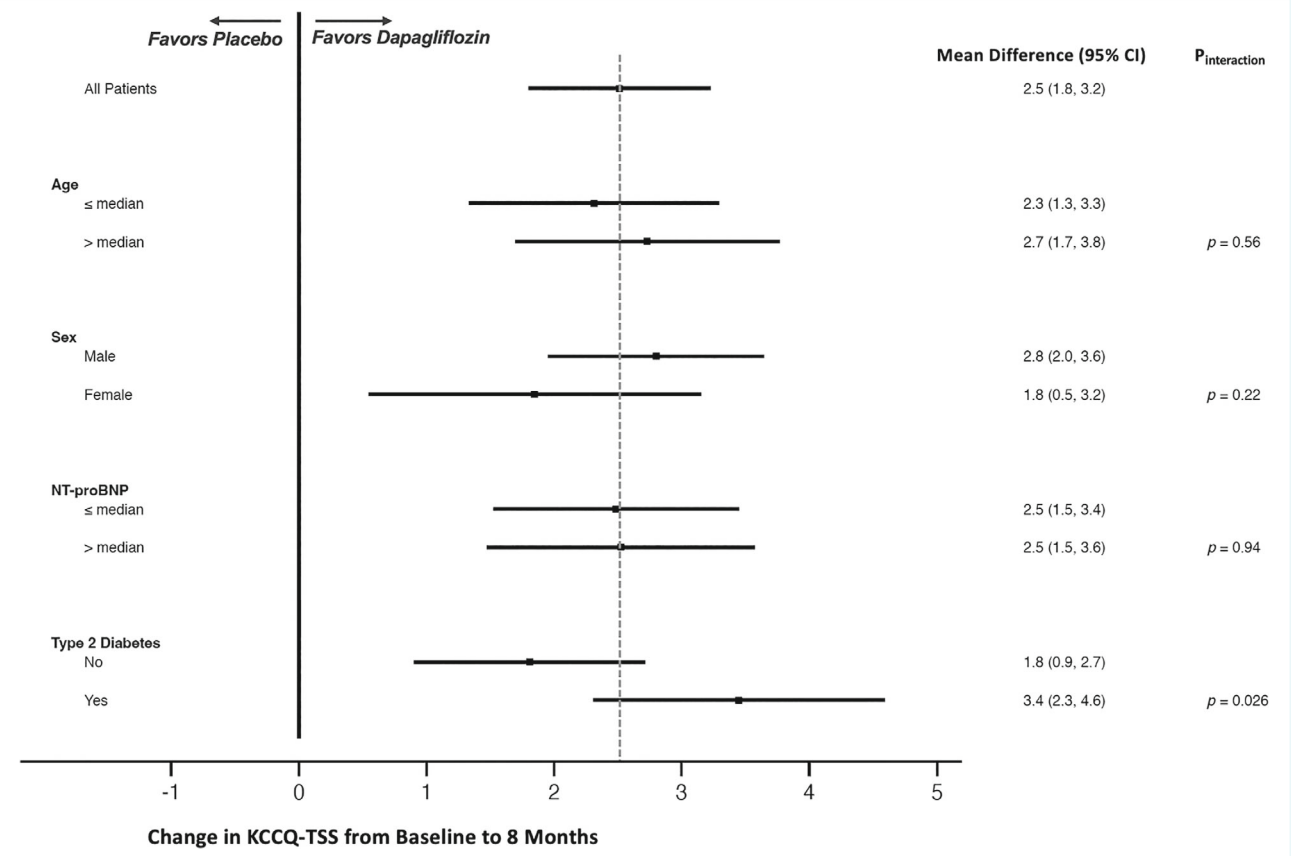

Figure 2 Effects of dapagliflozin versus placebo on Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) across key patient subgroups. Forest plot of effects of dapagliflozin versus placebo on KCCQ-TSS at 8 months across various demographic and clinical subgroups. Treatment effect refers to placebo-adjusted change in KCCQ-TSS from baseline to 8 months. *p*-values for interaction are presented. Median values represent pooled median from the pooled DAPA-HF and DELIVER cohorts. CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

>60% (32% vs. 26%, OR 1.31; 95% CI 0.99–1.73). The effects of dapagliflozin versus placebo on small (≥5 point increase) and moderate (≥10 point increase) in health status by KCCQ-TSS were also consistent across the full spectrum of LVEF ($p_{interaction} = 0.64$ and 0.97, respectively; *Figure 4*). Results were largely similar when considering KCCQ-CSS, -OSS, and -PLS (*Table 1*). Across the LVEF spectrum, the number needed to treat to affect an at least 5 point improvement at 8 months in health status assessed by KCCQ-TSS, -CSS, -OSS, and -PLS was 20, 17, 24, and 22, respectively.

Among those who experienced HF hospitalization during the timeframe in which KCCQ measurements were available, health status, as measured by KCCQ-TSS, declined on average ~10 points prior to HF hospitalization, particularly evident in the 3 months preceding the event. Results were qualitatively similar in those with LVEF ≤40% (DAPA-HF) and LVEF >40% (DELIVER) (*Figure 5*).

Discussion

In participant-level pooled analyses of DAPA-HF and DELIVER, dapagliflozin improved multiple domains of health status as measured by KCCQ, regardless of LVEF. Significant improvements in health status were observed consistently across the full range of LVEF, including in those with LVEF >60%. Patients randomized to dapagliflozin were less likely to experience meaningful deteriorations in health status and more likely to experience small, moderate, and large improvements in health status than those randomized to placebo; these beneficial effects were also observed consistently across the full range of LVEF.

We observed a steep decline in KCCQ preceding a HF hospitalization, with health status worsening starting as early as 3 months prior to HF hospitalization; trends were similar in DAPA-HF and DELIVER. These data are similar to those from other published trials in HF and suggest that clinical deteriorations may be preceding by large changes in symptomatic burden and health status.[6] These data suggest that prospective, frequent assessments of patient-reported health status might aid in early identification, management, and triage of patients at risk for clinical decompensation, a hypothesis which requires further study.

Importantly, we observed no attenuation in benefit of dapagliflozin versus placebo on health status as measured by

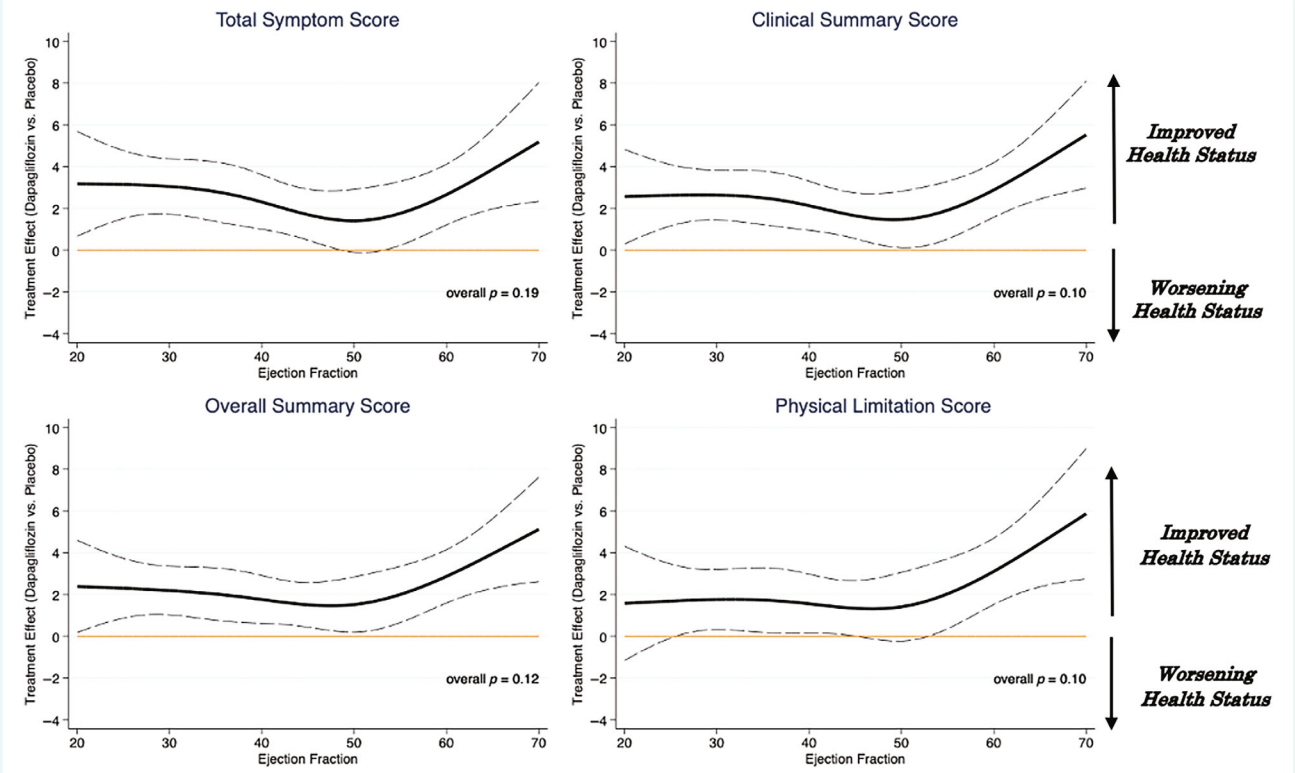

Figure 3 Treatment effects of dapagliflozin versus placebo on mean 8-month change in health status. Treatment effects shown as the placebo-controlled change in health status from randomization to month 8 in Kansas City Cardiomyopathy Questionnaire domains including total symptom score, clinical summary score, overall summary score, and physical limitation score across the spectrum of ejection fraction modelled as a continuous variable.

various KCCQ domains among patients at the highest end of LVEF; numerically, mean improvements in health status were greater at the higher end of the LVEF spectrum. These patients experienced an especially high burden of health status impairment at baseline, on average greater than that of patients with reduced LVEF.[7] These impairments in patients with the highest LVEF may be the result of higher burden of cardiovascular and non-cardiovascular comorbidities among this population, and it has been postulated that therefore health status in this group may be less modifiable by traditional HF therapies.[8] However, this was not apparent for the sodium–glucose cotransporter 2 inhibitor dapagliflozin in this pooled analysis of DAPA-HF and DELIVER. Of note, our results differ from those previously reported utilizing participant-level pooled data from EMPEROR-Reduced and EMPEROR-Preserved in which improvements in KCCQ appeared to be attenuated in patients at the highest ranges of LVEF.[9,10] Similar attenuation in benefit was seen with respect to total HF hospitalizations in these trials; subsequent detailed analyses dispute these discordant findings in the EMPORER programme as possibly a chance finding.[11] Importantly, presented data from a participant-level pooled analysis from the two more modestly sized DEFINE-HF (LVEF ≤40%)[12] and PRESERVED-HF (LVEF ≥45%)[13] trials demonstrated consistent benefits of dapagliflozin on shorter term (3 months) health status across the spectrum of LVEF, with no suggestion of attenuated benefit at higher LVEF.[14] These benefits, numerically larger than those seen in the present analysis, were observed in a highly symptomatic contemporary US population with greater health status burden at baseline than in patients enrolled in DAPA-HF and DELIVER.

While mean changes in KCCQ were relatively modest, we observed that the proportion of patients experiencing at least moderate (≥10 point increases) and large (≥15 point increases) in health status was significantly greater in those randomized to dapagliflozin versus placebo; results were consistent across the full range of LVEF. The use of patient-reported health status is increasingly recognized as a clinically important endpoint[15]; in HF, regulatory guidance includes patient-reported health status endpoints as potentially providing evidence of effectiveness of a therapy (in the absence of important safety considerations).[16] However, challenges remain in defining the minimum magnitude of benefit considered to be clinically meaningful[17]; while some studies suggest even small changes (5+ points) may be clinically important,[18] moderate and large changes as defined in this analysis are generally considered meaningful. Therefore, the greater proportion of moderate to large health gains in those treated with dapagliflozin, across the spectrum of ejection fraction, including those with LVEF>60%, further adds to the evidence supporting the efficacy of this therapy in HF.

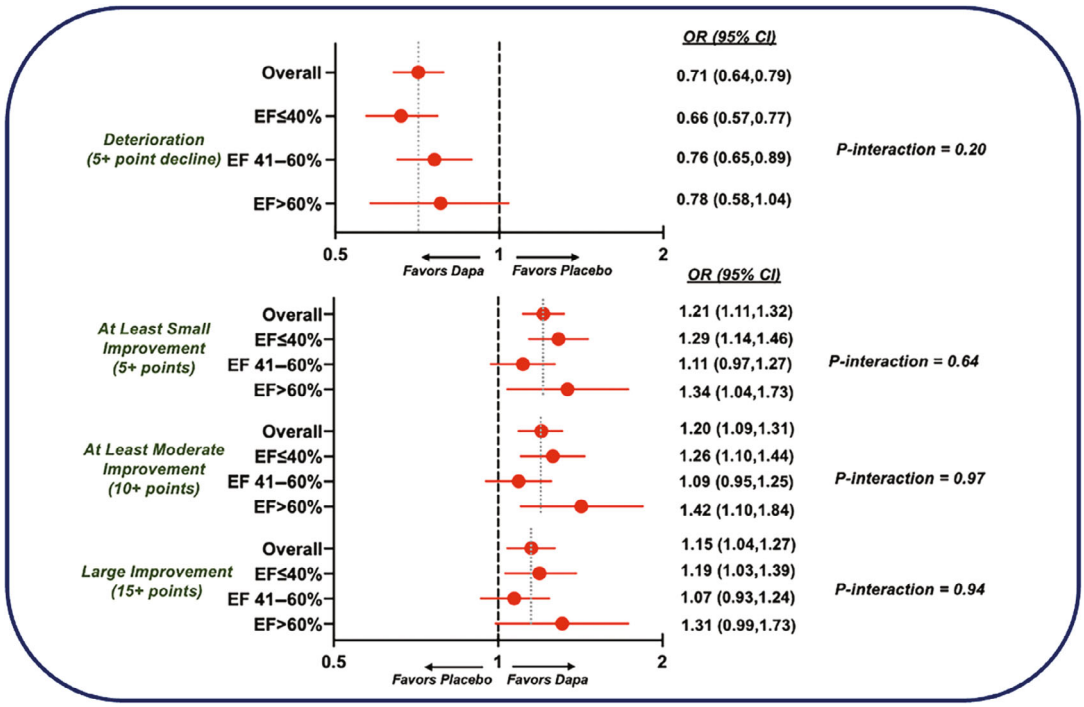

Figure 4 Responder analyses of clinically meaningful change in Kansas City Cardiomyopathy Questionnaire TSS domains at 8 months with dapagliflozin versus placebo. Responder analyses of clinically meaningful deteriorations and small, moderate, and large improvements in health status across Kansas City Cardiomyopathy Questionnaire total symptom score by ejection fraction (EF) modelled as a categorical variable. CI, confidence interval; OR, odds ratio.

Table 1 Responder analyses in Kansas City Cardiomyopathy Questionnaire (KCCQ) domains at 8 months across additional KCCQ domains

	Deterioration (5+ point decline)		At least small improvement (5+ points)		At least moderate improvement (10+ points)		Large improvement (15+ points)	
KCCQ domain	**OR (95% CI)**	$p_{interaction}$	**OR (95% CI)**	$p_{interaction}$	**OR (95% CI)**	$p_{interaction}$	**OR (95% CI)**	$p_{interaction}$
KCCQ-CSS								
Overall	0.75 (0.67, 0.83)	0.41	1.26 (1.16, 1.38)	0.77	1.29 (1.18, 1.41)	0.46	1.17 (1.06, 1.29)	0.72
LVEF ≤40%	0.74 (0.64, 0.86)		1.39 (1.23, 1.58)		1.41 (1.23, 1.62)		1.20 (1.03, 1.40)	
LVEF 41–60%	0.73 (0.62, 0.86)		1.09 (0.95, 1.25)		1.10 (0.96, 1.26)		1.06 (0.91, 1.23)	
LVEF >60%	0.81 (0.60, 1.09)		1.48 (1.15, 1.91)		1.65(1.26, 2.15)		1.56 (1.17, 2.09)	
KCCQ-OSS								
Overall	0.76 (0.68, 0.84)	0.82	1.18 (1.08, 1.28)	0.89	1.21 (1.11, 1.33)	0.58	1.21 (1.09, 1.33)	0.52
LVEF ≤40%	0.73 (0.63, 0.84)		1.25 (1.10, 1.41)		1.28 (1.12, 1.46)		1.23 (1.06, 1.43)	
LVEF 41–60%	0.78 (0.67, 0.92)		1.05 (0.92, 1.20)		1.10 (0.96, 1.26)		1.11 (0.96, 1.29)	
LVEF >60%	0.79 (0.58, 1.06)		1.39 (1.08, 1.79)		1.42 (1.09, 1.85)		1.52 (1.13, 2.04)	
KCCQ-PLS								
Overall	0.85 (0.77, 0.94)	0.36	1.21 (1.10, 1.32)	0.16	1.22 (1.11, 1.33)	0.53	1.21 (1.10, 1.34)	0.20
LVEF ≤40%	0.75 (0.65, 0.87)		1.22 (1.07, 1.38)		1.19 (1.04, 1.36)		1.24 (1.07, 1.44)	
LVEF 41–60%	1.00 (0.86, 1.17)		1.11 (0.97, 1.27)		1.15 (1.00, 1.33)		1.10 (0.94, 1.28)	
LVEF >60%	0.76 (0.57, 1.02)		1.59 (1.22, 2.06)		1.64 (1.25, 2.16)		1.59 (1.18, 2.13)	

CI, confidence interval; CSS, clinical summary score; LVEF, left ventricular ejection fraction; OR, odds ratio; OSS, overall summary score; PLS, physical limitation score.

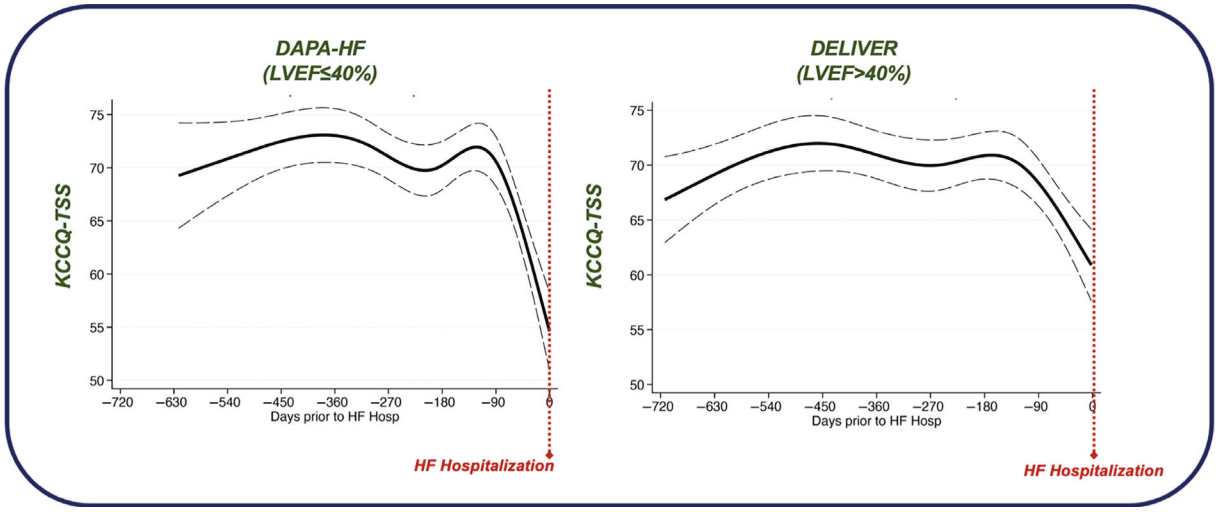

Figure 5 Change in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) prior to first heart failure (HF) hospitalization across the spectrum of ejection fraction. Modelled KCCQ-TSS over time prior to a HF hospitalization in DAPA-HF and DELIVER, respectively. Time 0 = date of HF hospitalization. In DAPA-HF, a total of 1273 KCCQ assessments were made from 526 unique individuals who experienced a first HF hospitalization during the trial. In DELIVER, a total of 1768 KCCQ assessments were made from 655 unique individuals who experienced a first HF hospitalization during the trial. LVEF, left ventricular ejection fraction.

This study has some limitations. While the pooling of DAPA-HF and DELIVER was pre-specified in the regulatory statistical analysis plan, changes in health status were not pre-specified in the hierarchy of outcomes. We relied on LVEF that was site-reported, and core laboratory standardization was not undertaken in either trial. KCCQ was assessed through 8 months in both trials and not at later time points.

Conclusion

In participant-level pooled analyses of DAPA-HF and DELIVER, dapagliflozin improved multiple domains of health status regardless of LVEF. Clinically meaningful improvements in health status were observed consistently across the full range of LVEF, including in those with LVEF >60%. These data support treatment with dapagliflozin to improve symptoms, physical limitations and quality of life in patients with HF regardless of baseline LVEF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References

1. Kondo T, McMurray JJV. Re-emergence of heart failure with a normal ejection fraction? *Eur Heart J*. 2022;**43**:427–429. https://doi.org/10.1093/eurheartj/ehab828
2. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;**381**:1995–2008. https://doi.org/10.1056/NEJMoa1911303
3. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al.; DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;**387**:1089–1098. https://doi.org/10.1056/NEJMoa2206286
4. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;**145**:e895–e1032. https://doi.org/10.1161/CIR.0000000000001063
5. Joseph SM, Novak E, Arnold SV, Jones PG, Khattak H, Platts AE, et al. Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. *Circ Heart Fail*. 2013;**6**:1139–1146. https://doi.org/10.1161/CIRCHEARTFAILURE.113.000359
6. Vaduganathan M, Claggett BL, McMurray JJV, Solomon SD. Health status trajectories before and after hospitalization for heart failure. *Circulation*. 2022;**145**:1872–1874. https://doi.org/10.1161/CIRCULATIONAHA.122.059282
7. Kosiborod MN, Bhatt AS, Claggett BL, Vaduganathan M, Kulac IJ, Lam CSP, et al. Effect of dapagliflozin on health status in patients with preserved or mildly reduced ejection fraction. *J Am Coll Cardiol*. 2023;**81**:460–473. https://doi.org/10.1016/j.jacc.2022.11.006
8. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, Dunlay S, et al. Quality of life in heart failure with preserved ejection fraction: Importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail*. 2020;**22**:1009–1018. https://doi.org/10.1002/ejhf.1788
9. Butler J, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, 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. https://doi.org/10.1093/eurheartj/ehab798
10. Butler J, Filippatos G, Jamal Siddiqi T, Brueckmann M, Böhm M, Chopra VK, 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. https://doi.org/10.1161/CIRCULATIONAHA.121.057812
11. Anker SD, Butler J, Usman MS, Filippatos G, Ferreira JP, Bocchi E, et al. Efficacy of empagliflozin in heart failure with preserved versus mid-range ejection fraction: A pre-specified analysis of EMPEROR-Preserved. *Nat Med*. 2022;**28**:2512–2520. https://doi.org/10.1038/s41591-022-02041-5
12. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: The DEFINE-HF trial. *Circulation*. 2019;**140**:1463–1476. https://doi.org/10.1161/CIRCULATIONAHA.119.042929
13. Nassif ME, Windsor SL, Borlaug BA, Kitzman DW, Shah SJ, Tang F, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. *Nat Med*. 2021;**27**:1954–1960. https://doi.org/10.1038/s41591-021-01536-x
14. Nassif ME, Windsor SL, Gosch K, Borlaug BA, Husain M, Inzucchi SE, et al. Dapagliflozin improves heart failure symptoms and physical limitations across the full range of ejection fraction: Pooled patient-level analysis from DEFINE-HF and PRESERVED-HF Trials. *Circ Heart Fail*. 2023;**19**:e009837. https://doi.org/10.1161/CIRCHEARTFAILURE.122.009837
15. Psotka MA, Abraham WT, Fiuzat M, Filippatos G, Lindenfeld J, Ahmad T, et al. Functional and symptomatic clinical trial endpoints: The HFC-ARC scientific expert panel. *JACC Heart Fail*. 2022;**10**:889–901. https://doi.org/10.1016/j.jchf.2022.09.012
16. U.S. Food and Drug Administration. Treatment for Heart Failure: Endpoints for Drug Development Guidance for Industry. June 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/treatment-heart-failure-endpoints-drug-development-guidance-industry. Accessed 15 May 2023.
17. Stogios N, Fezza G, Wong JV, Ross HJ, Farkouh ME, Nolan RP. Current challenges for using the Kansas City Cardiomyopathy Questionnaire to obtain a standardized patient-reported health status outcome. *Eur J Heart Fail*. 2021;**23**:205–207. https://doi.org/10.1002/ejhf.2139
18. Butler J, Khan MS, Mori C, Filippatos GS, Ponikowski P, Comin-Colet J, et al. Minimal clinically important difference in quality of life scores for patients with heart failure and reduced ejection fraction. *Eur J Heart Fail*. 2020;**22**:999–1005. https://doi.org/10.1002/ejhf.1810