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Dapagliflozin and Physical and Social Activity Limitations in Heart Failure With Reduced Ejection Fraction

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ABSTRACT

BACKGROUND Heart failure (HF) is associated with impaired physical function and poor quality of life and affects health status more profoundly than many other chronic diseases.

OBJECTIVES The authors examined the effects of dapagliflozin on specific physical and social limitations as reported by patients in the DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) trial.

METHODS The effect of dapagliflozin on the change from baseline to 8 months in each of the individual physical and social activity limitation questions answered by patients completing the Kansas City Cardiomyopathy Questionnaire (KCCQ), and overall scores, were examined with mixed-effects models and responder analyses.

RESULTS In total, 4,269 (90.0%) and 3,955 (83.4%) patients had complete data for both the physical and social activity limitation scores at baseline and 8 months, respectively. Compared with placebo, dapagliflozin significantly increased (improved) the mean KCCQ physical and social activity limitation scores at 8 months (placebo-corrected mean difference 1.94 [95% CI: 0.73-3.16] and 1.84 [95% CI: 0.43-3.25], respectively). Dapagliflozin also increased each of the individual components that comprise the physical and social activity limitations domains at 8 months, with the largest improvement seen in "hobbies or recreational activities" (placebo-corrected mean difference: 2.76 [95% CI: 1.06-4.46]) and "doing yardwork, housework, or carrying groceries" (placebo-corrected mean difference: 2.59 [95% CI: 0.76-4.42]). The proportion of patients with a 5-point improvement from baseline to 8 months in the KCCQ physical and social activity limitation scores was greater with dapagliflozin than with placebo (ORs: 1.23 [95% CI: 1.09-1.40] and 1.19 [95% CI: 1.05-1.35], respectively).

CONCLUSIONS In patients with HFrEF, dapagliflozin, compared with placebo, improved physical and social activity limitations as measured by KCCQ. (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure [DAPA-HF]; NCT03036124). (J Am Coll Cardiol HF 2023;11:1411-1423) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ABBREVIATIONS AND ACRONYMS

CSS = Clinical Summary Score

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

KCCQ = Kansas City Cardiomyopathy Questionnaire

NT-proBNP = N-terminal pro-B-type natriuretic peptide

OSS = Overall Summary Score

TSS = Total Symptom Score

Heart failure (HF) is associated with impaired physical function and poor quality of life and affects health status more profoundly than many other chronic diseases.[1-5] For many patients with HF, improving symptoms, physical function, and quality of life is as important (if not more) as prolonging life.[6] Consequently, a fundamental goal of the management of patients with HF is to reduce symptoms and improve physical and social function and quality of life.[7,8]

In the DAPA-HF (Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure) trial, health status was assessed using the 23-item Kansas City Cardiomyopathy Questionnaire (KCCQ), which evaluates 7 domains (ie, symptom frequency, symptom burden, symptom stability, physical limitations, social limitations, quality of life, and self-efficacy). The symptom frequency and burden domains are used to create the Total Symptom Score (TSS), and this combined with the physical limitation domain creates the Clinical Summary Score (CSS); the CSS combined with the social limitations and quality-of-life domains is used to create the Overall Summary Score (OSS).

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Dapagliflozin, compared with placebo, reduced the risk of worsening HF events and death and improved the KCCQ-TSS when added to standard therapy in 4,744 patients with HF with reduced ejection fraction (HFrEF).[9,10] In post hoc analyses, the KCCQ-CSS and KCCQ-OSS were also improved.[10] However, these integrated scores lack granularity and do not describe the limitations in specific activities experienced by patients. Restrictions imposed by HF on ordinary activities through symptoms or other mechanisms represent some of the most significant negative effects of HF. However, there is likely to be heterogeneity in particular physical and social activities among patients and how important these different activities are to patients. Furthermore, various therapies may affect individual physical and social activities differently.[11] Therefore, a better understanding of the change in each activity may inform clinicians and patients about the expected benefits of a given therapy. Consequently, we examined the effects of dapagliflozin on the overall physical and social activity scores of the KCCQ, and each of their components, in the DAPA-HF trial.

METHODS

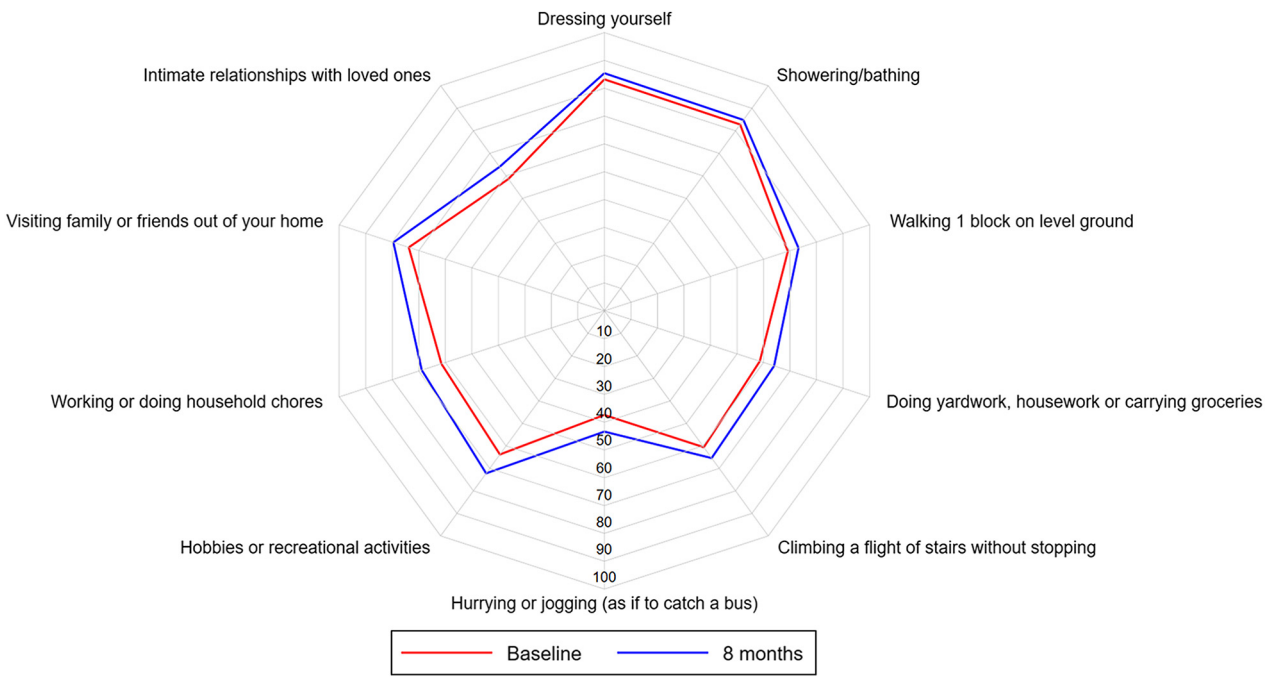
The DAPA-HF trial was a randomized, double-blind, placebo-controlled trial in patients with HFrEF, evaluating the efficacy and safety of dapagliflozin 10 mg once daily compared with a matching placebo, added to standard care. The design, baseline characteristics, and primary results of the DAPA-HF trial are published.[9,12,13] The trial protocol was approved by the Ethics Committee at all participating institutions, and all patients provided written informed consent.

STUDY PATIENTS. Key inclusion criteria were a diagnosis of HF for at least 2 months, NYHA functional class II to IV, a left ventricular ejection fraction of ≤40%, optimal treatment with pharmacological and device therapy, and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 pg/mL (≥400 pg/mL if hospitalized for HF within the previous 12 months; ≥900 pg/mL if atrial fibrillation/flutter on the electrocardiogram at enrollment, irrespective of history of HF hospitalization). Key exclusion criteria were symptomatic hypotension or systolic blood pressure <95 mm Hg, estimated glomerular filtration rate <30 mL/min/1.73 m^2 or rapidly declining renal function, type 1 diabetes, and conditions likely to prevent patient participation in the trial or greatly limit life expectancy. A complete list of exclusion criteria is provided in the design manuscript.[12] After randomization, follow-up visits were scheduled at 14, 60, and 120 days and then every 4 months thereafter.

PHYSICAL AND SOCIAL LIMITATION DOMAINS OF THE KCCQ. The KCCQ is a validated 23-item, self-administered, disease-specific instrument that quantifies symptoms, physical function, social function, and quality of life over the previous 2 weeks (Supplemental Table 1).[14] In the DAPA-HF trial, the KCCQ was administered at randomization, 4 months, 8 months, and 12 months, and annually thereafter, and completed electronically by patients, without assistance by site study staff (as validated).[10] Responses at randomization, 4 months, and 8 months were considered in the present analysis.

For each of the activities in the physical limitation domain, patients were asked to respond to the

FIGURE 1 Mean Activity Scores at Baseline and 8 Months



Responses to each of the questions in the physical and social activity domain were scaled from 0 to 100, with 0 indicating extremely or severely limited and 100 indicating not at all limited.

following: "Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks: dressing yourself; showering/bathing; walking 1 block on level ground; doing yardwork, housework or carrying groceries; climbing a flight of stairs without stopping; hurrying or jogging (as if to catch a bus)." The response options were "extremely limited," "quite a bit limited," moderately limited," "slightly limited," "not at all limited," and "limited for other reasons or did not do the activity."

For each of the social activities in the social limitation domain, patients were asked the following question: "How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks: Hobbies or recreational activities; working or doing household chores; visiting family or friends out of your home; intimate relationships with loved ones." The response options were "severely limited," "limited quite a bit," moderately limited," "slightly limited," "did not limit at all," "does not apply or did not do for other reasons."

Responses to each of the questions in the physical and social activity domain were scaled from 0 to 100, with 0 indicating extremely or severely limited and 100 indicating not at all limited. Responses of "limited for other reasons or did not do the activity" or "does not apply or did not do for other reasons" were considered to be nonresponses.

A 1-step change in the response to any of the individual social limitation domain questions corresponds to a change of 6.25 in the overall social limitation activity score. A 1-step change in the response to any of the individual physical limitation domain questions corresponds to a change of 4.2 in the overall social limitation activity score.

OUTCOMES. In the present analysis, we examined the change from baseline to 8 months in the physical and social limitation domain scores of the KCCQ as well as the combined mean score of all physical and social activities (ie, the sum of the physical and social limitation domain scores divided by 2). We also examined the change from baseline to 8 months in

TABLE 1 Baseline Characteristics of the Study Population According to Tertiles of the Combined Mean Score of All Physical and Social Activities

	Highest Tertile (Score ≥79.3) (n = 1,416)	Middle Tertile (Score 55.3-79.2) (n = 1,430)	Lowest Tertile (Score ≤55.2) (n = 1,423)	*P* Value
Age, y	66.4 ± 10.6	66.2 ± 10.8	65.9 ± 10.6	0.24
Male	1,188 (83.9)	1,113 (77.8)	1,019 (71.6)	<0.001
Race				<0.001
White	978 (69.1)	1,038 (72.6)	1,070 (75.2)	
Black	52 (3.7)	52 (3.6)	99 (7.0)	
Asian	368 (26.0)	325 (22.7)	223 (15.7)	
Other	18 (1.3)	15 (1.0)	31 (2.2)	
Geographic region				<0.001
Asia/Pacific	356 (25.1)	325 (22.7)	217 (15.2)	
Europe	597 (42.2)	703 (49.2)	710 (49.9)	
North America	213 (15.0)	193 (13.5)	215 (15.1)	
South America	250 (17.7)	209 (14.6)	281 (19.7)	
Physiological measures				
Systolic blood pressure, mm Hg	122.7 ± 15.9	121.3 ± 15.9	121.4 ± 16.8	0.03
Heart rate, beats/min	69.9 ± 11.1	71.6 ± 11.7	72.5 ± 12.0	<0.001
BMI, kg/m^2	27.6 ± 5.3	28.1 ± 5.7	29.3 ± 6.6	<0.001
Creatinine, μmol/L	102.6 ± 27.7	103.7 ± 29.6	107.7 ± 32.3	<0.001
eGFR, mL/min/1.73 m^2	67.5 ± 18.9	66.2 ± 18.9	63.6 ± 19.5	<0.001
eGFR				<0.001
<60 mL/min/1.73 m^2	503 (35.5)	560 (39.2)	663 (46.6)	
≥60 mL/min/1.73 m^2	912 (64.5)	869 (60.8)	760 (53.4)	
NT-proBNP, pg/mL	1,251 (793-2,091)	1,456 (864-2,590)	1,627 (921-3,233)	<0.001
Hemoglobin A1c, %	6.0 (5.6-6.7)	6.1 (5.7-6.8)	6.2 (5.7-7.1)	<0.001
Main cause of HF				0.05
Ischemic	775 (54.7)	816 (57.1)	820 (57.6)	
Nonischemic	543 (38.3)	493 (34.5)	480 (33.7)	
Unknown	98 (6.9)	121 (8.5)	123 (8.6)	
Duration of HF				0.53
0-3 mo	52 (3.7)	38 (2.7)	42 (3.0)	
3-6 mo	107 (7.6)	120 (8.4)	117 (8.2)	
6-12 mo	182 (12.9)	152 (10.6)	158 (11.1)	
1-2 y	206 (14.5)	211 (14.8)	197 (13.8)	
2-5 y	335 (23.7)	329 (23.0)	333 (23.4)	
>5 y	534 (37.7)	580 (40.6)	576 (40.5)	
LVEF, %	30.9 ± 6.9	31.4 ± 6.6	31.0 ± 6.9	0.49
NYHA functional class				<0.001
II	1,149 (81.1)	985 (68.9)	742 (52.1)	
III-IV	267 (18.9)	445 (31.1)	681 (47.9)	
KCCQ-TSS	90.4 ± 11.5	75.0 ± 15.7	54.6 ± 20.2	<0.001
KCCQ-CSS	89.9 ± 9.1	72.6 ± 12.1	50.0 ± 16.6	<0.001
KCCQ-OSS	88.5 ± 7.9	69.7 ± 9.8	45.5 ± 14.2	<0.001

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each of the individual physical and social activity items. Finally, we examined the association between tertiles of the combined mean score of all physical and social activities.

STATISTICAL ANALYSES. Baseline characteristics were summarized as frequency and percentage, mean ± SD, or median (IQR). Differences in baseline characteristics according to tertiles of the combined mean score of all physical and social activities were tested using the Cochran-Armitage trend test for binary variables, the Cochran-Mantel-Haenszel test for categorical variables, and the Jonckheere-Terpstra test and linear regression for non-normal and normally distributed continuous variables, respectively.

Time-to-event data were evaluated using Cox proportional hazards models, stratified according to diabetes mellitus status, and adjusted for a history of HF hospitalization and treatment group assignment, and HRs with 95% CIs were reported. In addition, HRs from models stratified according to diabetes mellitus

TABLE 1 Continued

	Highest Tertile (Score ≥79.3) (n = 1,416)	Middle Tertile (Score 55.3-79.2) (n = 1,430)	Lowest Tertile (Score ≤55.2) (n = 1,423)	*P* Value
Medical history				
Hospitalization for HF	701 (49.5)	671 (46.9)	663 (46.6)	0.12
Previous MI	621 (43.9)	649 (45.4)	636 (44.7)	0.65
History of atrial fibrillation/flutter	519 (36.7)	584 (40.8)	613 (43.1)	<0.001
Atrial fibrillation/flutter on ECG at enrolment	293 (20.7)	348 (24.3)	370 (26.0)	<0.001
Type 2 diabetes	587 (41.5)	632 (44.2)	708 (49.8)	<0.001
Hypertension	1,030 (72.7)	1,040 (72.7)	1,120 (78.7)	<0.001
COPD	133 (9.4)	167 (11.7)	228 (16.0)	<0.001
Treatment				
ACE inhibitor/ARB	1,169 (82.6)	1,183 (82.7)	1,190 (83.6)	0.45
ARNI	168 (11.9)	154 (10.8)	152 (10.7)	0.32
ACE inhibitor/ARB/ARNI	1,329 (93.9)	1,333 (93.2)	1,338 (94.0)	0.85
Beta-blocker	1,369 (96.7)	1,379 (96.4)	1,362 (95.7)	0.17
MRA	940 (66.4)	1,037 (72.5)	1,053 (74.0)	<0.001
Loop diuretic	1,065 (75.2)	1,158 (81.0)	1,223 (85.9)	<0.001
Digoxin	222 (15.7)	276 (19.3)	279 (19.6)	0.007
Oral anticoagulant	590 (41.7)	612 (42.8)	614 (43.1)	0.42
Antiplatelet	778 (54.9)	749 (52.4)	784 (55.1)	0.93
CRT-P/CRT-D	104 (7.3)	114 (8.0)	113 (7.9)	0.55
ICD/CRT-D	396 (28.0)	380 (26.6)	391 (27.5)	0.77

Values are mean ± SD, n (%), or median (IQR). A lower score represents greater limitation.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; CSS = clinical summary score; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; OSS = overall summary score; TSS = total symptom score.

status and adjusted for a history of HF hospitalization, treatment group assignment, age, sex, geographical region, heart rate, systolic blood pressure, body mass index, HF etiology, left ventricular ejection fraction, NYHA functional class, log of NT-proBNP, estimated glomerular filtration rate, hypertension, and a history of atrial fibrillation/flutter and chronic obstructive pulmonary disease were reported. The models for all-cause death did not include an adjustment for a history of HF hospitalization.

The difference between treatment groups in the change in the KCCQ physical and social activity limitation domain scores, the combined mean score of all physical and social activities, and the individual components that comprise the physical and social activity scores, from baseline to 8 months, were analyzed using mixed-effects models for repeated measurements and adjusted for baseline value, visit (months 4 and 8), randomized treatment, and interaction of treatment and visit. Least-squares mean differences with 95% CIs between treatment groups were reported.

Responder analyses examining proportions of patients with an improvement (5-point or greater increase) or deterioration (5-point or greater decrease) in the physical and social activity limitation scores and the combined physical and social activity score at 8 months were performed using logistic regression models adjusted for baseline value and randomized treatment. Reported were ORs with 95% CI. The 5-point improvement analyses accounted for the "ceiling effect" (ie, because these scores cannot exceed 100, patients with a baseline value of ≥95 were considered to have a 5-point improvement if their values remained ≥95 at 8 months). Similarly, the 5-point deterioration analyses accounted for the "floor effect" (ie, patients with a baseline value of ≥5 were considered to have a 5-point deterioration if their values remained ≤5 at 8 months). Patients who died before the 8-month assessment were considered as not improved and deteriorated in the 5-point improvement and 5-point deterioration analyses, respectively. Patients who were alive, but did not complete the 8-month KCCQ, were excluded from the analysis. These analyses were repeated with a 10-point threshold. In a sensitivity analysis, patients who died before the 8-month assessment were excluded. In another sensitivity analysis, in addition to patients who died before the 8-month assessment,

those who did not complete the 8-month KCCQ were considered as not improved and deteriorated in the 5-point improvement and 5-point deterioration analyses, respectively.

In addition, ordinal logistic regression, adjusted for baseline value and randomized treatment, was performed to calculate ORs for patients moving up the scale (ie, an increase of 25, 50, 75, and 100) for the individual physical and social activity component. Patients who died before the 8-month assessment were considered as not improved, and those who were alive, but did not complete the 8-month KCCQ, or answered "limited for other reasons or did not do the activity" or "does not apply or did not do for other reasons" were excluded. In a sensitivity analysis, patients who died before the 8-month assessment were excluded. In another sensitivity analysis, in addition to patients who died before the 8-month assessment, those who did not complete the 8-month KCCQ were considered as not improved.

All analyses were conducted using SAS version 9.4 (SAS Institute) and STATA version 17.0 (StataCorp). A value of $P = 0.05$ was considered statistically significant.

RESULTS

Of the 4,744 patients randomized in the DAPA-HF trial, 4,443 (93.7%) patients had available KCCQ data, and 4,269 patients (90.0% of all patients; 96.1% of patients with baseline KCCQ data) had complete data for both the physical and social activity limitation scores at baseline. These proportions were similar in patients assigned to dapagliflozin and placebo. The number and proportion of patients with available individual physical and social activity scores at baseline, 4 months, and 8 months are presented in Supplemental Table 2. Among patients with available KCCQ data at baseline, the proportion of patients with data for the overall physical and social activity limitation scores was >95% and for the individual scores 90%, except for "hurrying or jogging" (88.8%) and "intimate relationships with loved ones" (64.4%) (Supplemental Table 2).

BASELINE PHYSICAL AND SOCIAL LIMITATIONS. The mean physical and social activity scores at baseline were 66.0 ± 24.0 and 65.5 ± 27.4, respectively, and the combined mean score of all physical and social activities was 65.7 ± 23.5. The mean scores at baseline were similar in patients randomized to dapagliflozin and placebo. The mean scores of each individual physical and social activities at baseline, 4 months, and 8 months are shown in **Figure 1** and Supplemental Table 3. At baseline, "hurrying or jogging (as if to catch a bus)" and "intimate relationships with loved ones" had the lowest scores (ie, the greatest limitation), whereas "dressing yourself" and "showering/bathing" had the highest scores (ie, the fewest limitations).

BASELINE CHARACTERISTICS ACCORDING TO PHYSICAL AND SOCIAL LIMITATIONS. Baseline characteristics according to tertiles of the combined mean score of all physical and social activities are presented in **Table 1**. Compared with those with higher (better) scores, those with lower (worse) scores were more often female and White (and less often Asian) and were more likely to have atrial fibrillation/flutter (both as a history and on electrocardiogram), diabetes, hypertension, and chronic obstructive pulmonary disease. Patients with low scores also had higher heart rate, body mass index, glycosylated hemoglobin, and NT-proBNP but lower estimated glomerular filtration rate. They also had worse NYHA functional class and lower (ie, worse) KCCQ scores. Regarding background HF therapy, there were no meaningful differences except for mineralocorticoid receptor antagonist, which was more frequently used in those with lower scores.

CLINICAL OUTCOMES ACCORDING TO PHYSICAL AND SOCIAL LIMITATION SCORES AT BASELINE. Compared with patients in the highest (best) tertile of the combined mean physical and social activity scores at baseline, those in lower tertiles had a greater risk of worsening HF or cardiovascular death, HF hospitalization or cardiovascular death (and each of the components), and all-cause death. The unadjusted risk of all outcomes was doubled, and the risk remained elevated after adjustment for prognostic variables (**Table 2**).

Each of the questions contributing to these scores were associated with risk of the primary outcome, with a similar risk increment per 25-point decrease (Supplemental Table 4).

CHANGE IN PHYSICAL AND SOCIAL LIMITATIONS FROM BASELINE TO 8 MONTHS. At 8 months, 3,955 (83.4% of all patients; 88.1% of surviving patients) patients had available KCCQ data (257 missing KCCQ data due to death, 532 missing KCCQ data for reasons other than death) and 3,772 (79.5% of all patients; 84.1% of surviving patients) had complete data for both the physical and social activity limitation scores. The proportion of surviving patients with available KCCQ data and complete data for both the physical and social activity limitation scores at 8 months were similar in the dapagliflozin and placebo groups. Among patients with available KCCQ data at

8 months, the proportion of patients with data for the overall physical and social activity limitation scores was >95% and for the individual scores 90%, except for "hurrying or jogging" (86.6%) and "intimate relationships with loved ones" (60.2%) (Supplemental Table 2).

Overall physical and social limitation scores. Compared with placebo, dapagliflozin significantly increased (improved) the mean physical and social activity limitation scores, and the combined mean score of all physical and social activities, at 8 months (placebo-corrected mean difference: 1.94 [95% CI: 0.73-3.16], 1.84 [95% CI: 0.43-3.25], and 2.01 [95% CI: 0.84-3.18], respectively).

In responder analyses, dapagliflozin, compared with placebo, increased the odds of a 5-point increase (improvement) from baseline to 8 months in the physical and social activity limitation scores, and the combined score of all physical and social activities (OR: 1.23 [95% CI: 1.09-1.40], OR: 1.19 [95% CI: 1.05-1.35], and OR: 1.28 [95% CI: 1.13-1.46], respectively). The corresponding ORs for a 10-point increase were OR: 1.22 (95% CI: 1.07-1.38), OR: 1.21 (95% CI: 1.07-1.37), and OR: 1.19 (95% CI: 1.05-1.35), respectively.

Conversely, dapagliflozin, compared with placebo, reduced the odds of a 5-point decrease (deterioration) from baseline to 8 months in these scores (OR: 0.77 [95% CI: 0.67-0.88], OR: 0.83 [95% CI: 0.73-0.95], and OR: 0.77 [95% CI: 0.67-0.88], respectively). The corresponding ORs for a 10-point decrease were OR: 0.76 (95% CI: 0.66-0.88), OR: 0.89 (95% CI: 0.77-1.03), and OR: 0.84 (95% CI: 0.72-0.97), respectively.

In sensitivity analyses, patients who died before the 8-month assessment were excluded from the responder analyses. These analyses yielded results consistent with those produced using the primary approach (Supplemental Table 5). In other sensitivity analyses, in which patients who did not complete the 8-month KCCQ were considered as not improved and deteriorated in the 5-point improvement and 5-point deterioration analyses, respectively, similar results were obtained (Supplemental Table 6).

Individual components of physical and social limitations domains. Compared with placebo, dapagliflozin significantly increased (improved) each of the physical and social activity limitation scores at 8 months, except for "intimate relationships with loved ones" (**Table 3**, **Figure 2**). The largest adjusted change score differences were seen in "hobbies or recreational activities" (placebo-corrected mean difference: 2.76 [95% CI: 1.06-4.46]) and "doing yard work, housework, or carrying groceries" (placebo-corrected mean difference: 2.59 [95% CI: 0.76-4.42]).

TABLE 2 Outcomes According to Tertiles of the Combined Mean Score of All Physical and Social Activities

	Highest Tertile (Score ≥79.3) (n = 1,416)	Middle Tertile (Score 55.3-79.2) (n = 1,430)	Lowest Tertile (Score ≤55.2) (n = 1,423)
Worsening HF event or cardiovascular death			
n (%)	186 (13.1)	252 (17.6)	354 (24.9)
Event rate per 100 person-y (95% CI)	9.3 (8.0-10.7)	12.7 (11.2-14.4)	18.9 (17.0-20.9)
HR (95% CI)[a]	Ref.	1.36 (1.13-1.65)	2.01 (1.68-2.40)
HR (95% CI)[b]	Ref.	1.20 (0.99-1.46)	1.53 (1.26-1.84)
HF hospitalization or cardiovascular death			
n (%)	185 (13.1)	250 (17.5)	348 (24.5)
Event rate per 100 person-y (95% CI)	9.2 (8.0-10.7)	12.6 (11.1-14.2)	18.5 (16.6-20.5)
HR (95% CI)[a]	Ref.	1.36 (1.12-1.64)	1.98 (1.65-2.36)
HR (95% CI)[b]	Ref.	1.19 (0.98-1.45)	1.50 (1.24-1.81)
HF hospitalization			
n (%)	111 (7.8)	164 (11.5)	219 (15.4)
Event rate per 100 person-y (95% CI)	5.5 (4.6-6.7)	8.3 (7.1-9.6)	11.6 (10.2-13.3)
HR (95% CI)[a]	Ref.	1.48 (1.17-1.89)	2.07 (1.65-2.60)
HR (95% CI)[b]	Ref.	1.27 (1.00-1.62)	1.51 (1.18-1.92)
Cardiovascular death			
n (%)	101 (7.1)	133 (9.3)	211 (14.8)
Event rate per 100 person-y (95% CI)	4.9 (4.0-5.9)	6.3 (5.4-7.5)	10.4 (9.1-11.9)
HR (95% CI)[a]	Ref.	1.30 (1.00-1.68)	2.10 (1.66-2.67)
HR (95% CI)[b]	Ref.	1.11 (0.86-1.45)	1.51 (1.18-1.94)
All-cause death			
n (%)	122 (8.6)	163 (11.4)	250 (17.6)
Event rate per 100 person-y (95% CI)	5.9 (4.9-7.0)	7.8 (6.7-9.1)	12.3 (10.9-14.0)
HR (95% CI)[a]	Ref.	1.31 (1.04-1.66)	2.07 (1.66-2.57)
HR (95% CI)[b]	Ref.	1.15 (0.91-1.46)	1.52 (1.21-1.92)

[a]Cox proportional hazards models stratified according to diabetes mellitus status and adjusted for a history of HF hospitalization (apart from all-cause death), randomized treatment and stratified by diabetes status. [b]Cox proportional hazards models stratified according to diabetes mellitus status and adjusted for a history of HF hospitalization (apart from all-cause death), randomized treatment allocation, age, sex, geographical region, heart rate, systolic blood pressure, BMI, HF etiology, LVEF, NYHA functional class, log of NT-proBNP, eGFR, hypertension, and a history of atrial fibrillation/flutter, and COPD.

Ref. = Reference; other abbreviations as in **Table 1**.

Dapagliflozin, compared with placebo, increased the odds of an improvement from baseline to 8 months in each of the physical and social activity limitation scores, but this was not statistically significant for "climbing a flight of stairs without stopping" and "intimate relationships with loved ones" (**Figure 3**).

In sensitivity analyses, patients who died before the 8-month assessment were excluded. These analyses yielded results consistent with those produced using the primary approach (Supplemental Table 7). In other sensitivity analyses, in which patients who did not complete the 8-month KCCQ were considered not improved, similar results were obtained (Supplemental Table 8).

TABLE 3 Mean Change in Activity Scores From Baseline to 8 Months

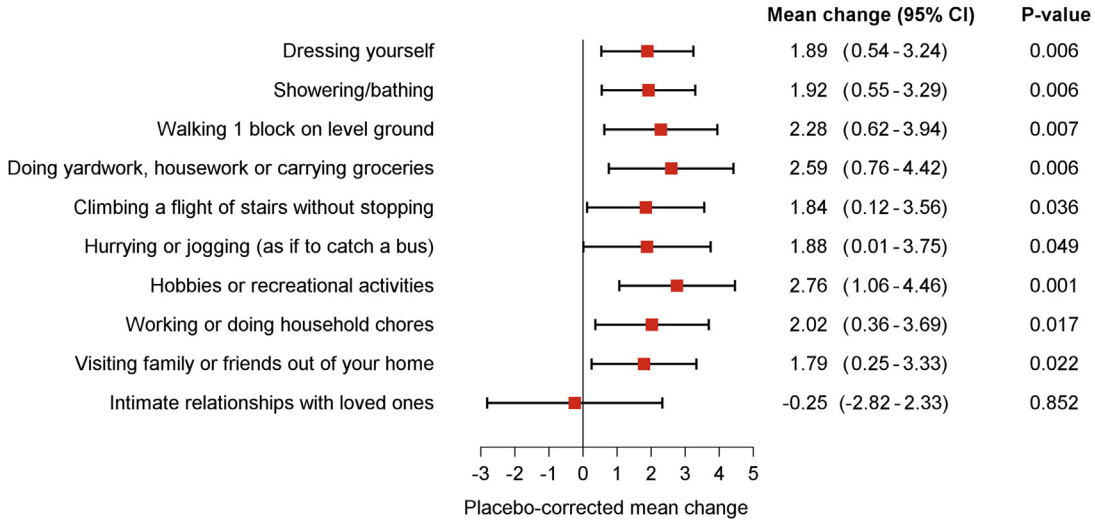
	Mean Change From Baseline to 8 mo (SE)		Placebo-Corrected Mean Change From Baseline to 8 mo (95% CI)	*P* Value
	Placebo	Dapagliflozin		
Overall scores				
Physical limitation score	2.23 (0.44)	4.18 (0.44)	1.94 (0.73–3.16)	0.002
Social limitation score	4.59 (0.51)	6.43 (0.50)	1.84 (0.43–3.25)	0.010
Combined physical and social limitation score	3.33 (0.43)	5.34 (0.42)	2.01 (0.84–3.18)	<0.001
Individual scores				
Dressing yourself	0.82 (0.49)	2.71 (0.48)	1.89 (0.54–3.24)	0.006
Showering/bathing	0.58 (0.49)	2.50 (0.49)	1.92 (0.55–3.29)	0.006
Walking 1 block on level ground	1.67 (0.60)	3.95 (0.59)	2.28 (0.62–3.94)	0.007
Doing yardwork, housework or carrying groceries	2.94 (0.67)	5.53 (0.66)	2.59 (0.76–4.42)	0.006
Climbing a flight of stairs without stopping	2.35 (0.62)	4.19 (0.62)	1.84 (0.12–3.56)	0.036
Hurrying or jogging (as if-catch a bus)	3.59 (0.68)	5.47 (0.67)	1.88 (0.01–3.75)	0.049
Hobbies or recreational activities	5.80 (0.62)	8.57 (0.61)	2.76 (1.06–4.46)	0.001
Working or doing household chores	5.17 (0.60)	7.20 (0.59)	2.02 (0.36–3.69)	0.017
Visiting family or friends out of your home	3.54 (0.56)	5.33 (0.55)	1.79 (0.25–3.33)	0.022
Intimate relationships with loved ones	3.39 (0.93)	3.14 (0.93)	−0.25 (−2.82 to 2.33)	0.852

Mixed-effects models for repeated measurements, adjusted for baseline value, visit (months 4 and 8), randomized treatment, and interaction of treatment and visit. A positive placebo-corrected mean difference favors dapagliflozin.

DISCUSSION

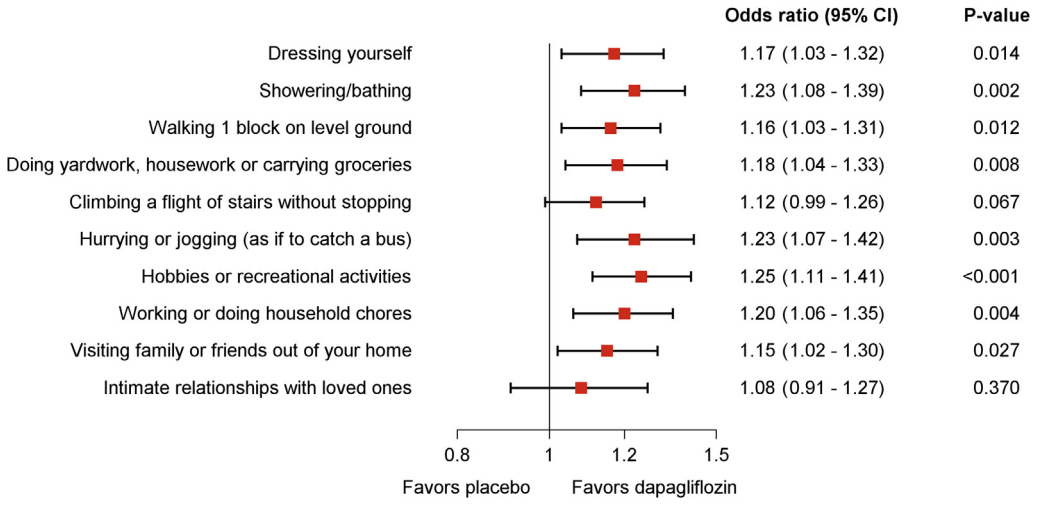
In this post hoc analysis of over 4,440 patients in the DAPA-HF trial, we found that HFrEF was associated with multiple physical and social limitations as measured by the KCCQ, although the extent to which specific physical and social activities were reduced varied considerably. Greater limitation of physical and social activities was associated with markedly higher risks of death and hospital admission.

FIGURE 2 Mean Change in Individual Physical and Social Activity Scores from Baseline to 8 Months



Responses to each of the questions in the physical and social activity domain were scaled from 0 to 100, with 0 indicating extremely or severely limited and 100 indicating not at all limited. Reported are placebo-corrected mean differences derived from mixed-effects models for repeated measurements, adjusted for baseline value, visit (months 4 and 8), randomized treatment, and interaction of treatment and visit. The change in the placebo-corrected mean difference is on a scale from −100 to +100, and a positive change favors dapagliflozin.

FIGURE 3 **Improvements in Individual Physical and Social Activity Scores From Baseline to 8 Months**



Reported are ORs derived from ordinal logistic regression models adjusted for baseline value and randomized treatment. An OR >1 favors dapagliflozin.

Dapagliflozin, compared with placebo, improved KCCQ physical and social activity limitation domains, as well as most of their individual components, from baseline to 8 months (**Central Illustration**).

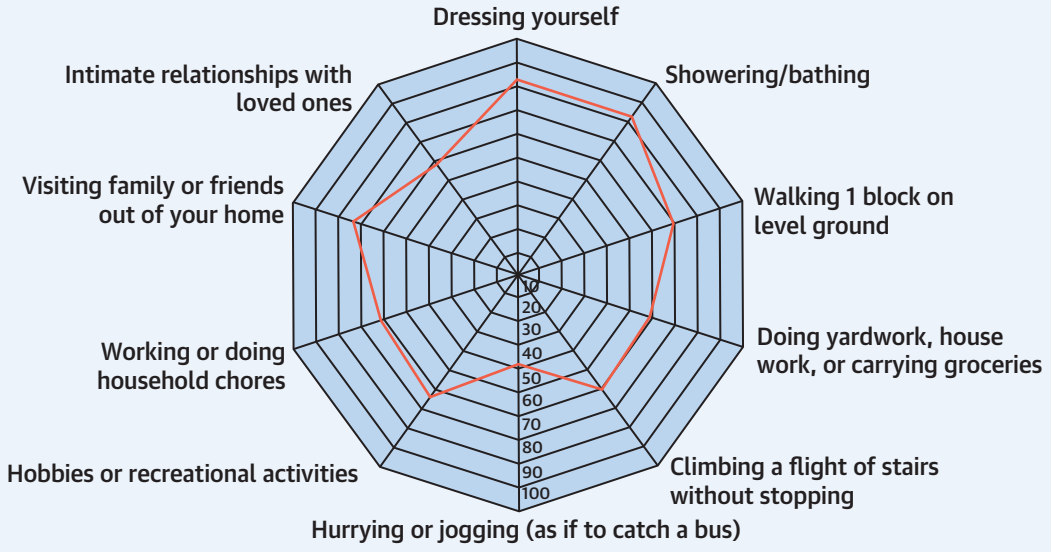
The degree of impairment in physical and social activities in patients with HF has been reported to be comparable to that of patients undergoing hemodialysis and those with depression, respectively.[1,15] Consistent with this, patients enrolled in the DAPA-HF trial reported significant limitations in all physical and social activities at baseline. The greatest impairment was related to hurrying or jogging (mean score: 37.4), as might be expected, but doing housework/carrying groceries (mean score: 58.6) and even climbing a flight of stairs (mean score: 60.6) were also substantially impaired. Less physically demanding activities, such as dressing (mean score: 83.2) or showering/bathing (mean score: 82.8) were less limited. Interestingly, among social activities, the ability to visit family and friends was only moderately limited (mean score: 73.8), whereas "intimate relationships with loved ones" was the second-most-limited activity evaluated (mean score: 58.6). An almost identical pattern and magnitude of physical and social limitations were observed in the PARADIGM-HF (Prospective comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, including for "intimate relationships with loved ones".[11] The latter impact is particularly striking, although this question was only answered by 64% of participants compared with >90% for the other questions. Qualitative and other research studies have suggested that erectile dysfunction in men and fearfulness on the part of a partner/spouse are barriers to intimate relationships, although this problem is rarely discussed with patients, in part reflecting several sensitivities.[11,16] Our findings suggest that education to improve this deficiency is important as counselling and pharmacological and other support may be helpful.[17-19]

Consistent with what had been observed regarding physician-assessed functional limitations using the NYHA functional classification and patient-reported symptoms measured by KCCQ,[10] we found that patient-reported physical and social limitations had a strong association not only with the risk of hospital admission for worsening HF, but also with mortality. Indeed, patients in the lowest tertile of score had double the risk of all outcomes of interest and this risk remained approximately 50% higher after adjustment for other prognostic variables. Interestingly, each question contributing to these scores was also associated with a similar risk.

As recognized by recent guidelines, a key goal of HF management is to improve patients' health status

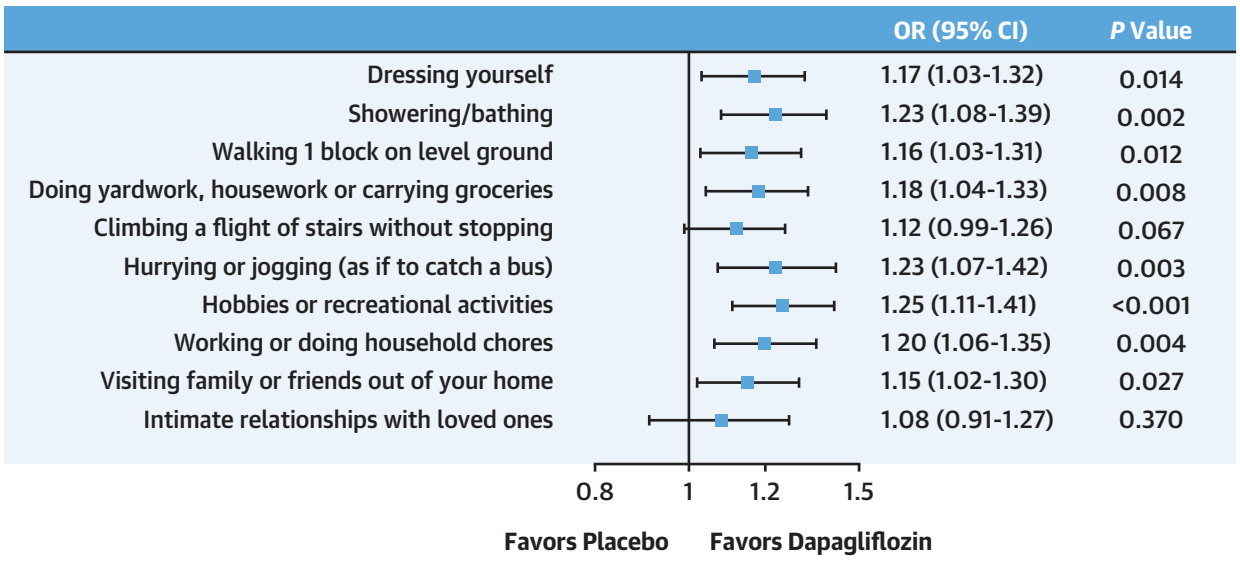
CENTRAL ILLUSTRATION **Mean Physical and Social Activity Scores at Baseline and Change in Activity Scores From Baseline to 8 Months**

HFrEF Was Associated With Multiple Physical and Social Limitations as Measured by the Kansas City Cardiomyopathy Questionnaire



Responses to each of the questions in the physical and social activity domain were scaled from 0 to 100, with 0 indicating extremely or severely limited and 100 indicating not at all limited.

Dapagliflozin, Compared With Placebo, Improved a Range of Physical and Social Activity Limitations From Baseline to 8 Months



Reported are ORs derived from ordinal logistic regression models adjusted for baseline value and randomized treatment. An OR above 1 favors dapagliflozin.

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HFrEF = heart failure with reduced ejection fraction.

by reducing the symptom burden and improving physical function and quality of life.[7,8] In addition, improvement in health-related quality of life is acknowledged as an important outcome by regulators.[20] More importantly, many patients with HF value an improvement in health status just as much (if not more) as prolonging life.[6] We have previously reported that dapagliflozin, compared with placebo, improved the KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS in patients with HFrEF and that these improvements were clinically meaningful, with some patients having large improvements.[10,21] The present analysis of the DAPA-HF trial complements and extends previous findings by demonstrating that dapagliflozin improved physical and social activity limitations after 8 months of treatment, and this was the case whether we examined the change in these scores as a mean change or as a 5-point or greater improvement in responder analyses. Recently, a study using qualitative interviews found that reductions in social/family interactions were the greatest concern of patients with HF and these were improved with dapagliflozin.[22] Similarly, physical limitations ranked highly among patient concerns and some of the greatest of these included hobbies and recreational activities, for which we found the largest absolute improvements, along with improvement in housework/carrying groceries, with each of the other limitation scores improving by a similar magnitude.[22] The exception was intimate relationships, which showed no improvement. Although the interpretation of this finding is hampered by the relatively low response rate, this domain did show improvement with sacubitril/valsartan in PARADIGM-HF trial, despite a similarly low response rate to the question.[11,16] The reason for this difference is uncertain.

Taken together, the improvements in physical and social limitations with dapagliflozin are clinically important, and the information about individual activities may enable clinicians to explain the expected benefits of dapagliflozin on activities of daily living to patients with HF.

STUDY LIMITATIONS. Like any other clinical trial, the DAPA-HF trial had prespecified eligibility criteria for enrollment in the trial, which may affect the generalizability of our results. Although KCCQ was a prespecified secondary endpoint, the examination of a change in physical and social limitation scores from baseline to 8 months was done post hoc. The KCCQ is a validated tool to quantify symptoms, physical function, social function, and quality of life, but the individual items (ie, the physical and social limitation scores) have not been validated independently. Our approach of handling the ceiling and floor effects in responder analyses was prespecified in the statistical analysis plan, and although there are different approaches to address these effects, other trialists have taken a similar approach in HF trials.[23] The relatively low response rate to the question about intimate relationships may hamper the interpretation of the effect of dapagliflozin on this limitation, and the mean score at baseline may not be representative of that of patients with HFrEF. However, the low response rate was consistent with that in PARADIGM-HF trial and other clinical trials and may reflect a variety of factors such as reluctance to discuss personal matters and perhaps death of partners in this relatively elderly population. In addition, we did not have information about marital or partner status or relevant medical history such as erectile dysfunction.

CONCLUSIONS

In the DAPA-HF trial, HFrEF was associated with multiple physical and social limitations as measured by the KCCQ, although the extent to which specific physical and social activities were reduced varied considerably. Greater limitation of physical and social activities was associated with markedly higher risks of death and hospital admission. Dapagliflozin, compared with placebo, improved a range of physical and social activity limitations in patients with HFrEF, with the largest absolute improvements in hobbies and housework/carrying groceries.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this post hoc analysis of a phase 3 randomized clinical trial, including 4,744 patients, dapagliflozin, as compared with placebo, significantly increased (improved) the mean KCCQ physical and social activity limitation scores at 8 months and each of the individual components that comprise the physical and social activity limitation domains. The proportion of patients with a 5-point improvement from baseline to 8 months in the KCCQ physical and social activity limitation scores was greater with dapagliflozin than with placebo.

TRANSLATIONAL OUTLOOK: These findings are important given that better physical function and health-related quality of life are as important as prolonging life for many patients with heart failure.

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KEY WORDS dapagliflozin, heart failure, quality of life, randomized trial

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