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Dapagliflozin and Days of Full Health Lost in the DAPA-HF Trial

Toru Kondo, MD, PhD,[a,b] Ulrik M. Mogensen, MD, PhD,[c] Atefeh Talebi, PhD,[a] Samvel B. Gasparyan, PhD,[d] Ross T. Campbell, MBChB, PhD,[a] Kieran F. Docherty, MBChB, PhD,[a] Rudolf A. de Boer, MD, PhD,[e] Silvio E. Inzucchi, MD,[f] Lars Køber, MD, DMSc,[g] Mikhail N. Kosiborod, MD,[h] Felipe A. Martinez, MD,[i] Marc S. Sabatine, MD, MPH,[j] Olof Bengtsson, PhLic,[d] Mikaela Sjöstrand, MD, PhD,[d] Muthiah Vaduganathan, MD, MPH,[k] Scott D. Solomon, MD,[k] Pardeep S. Jhund, MBChB, MSc, PhD,[a] John J.V. McMurray, MD[a]

ABSTRACT

BACKGROUND Conventional time-to-first-event analyses cannot incorporate recurrent hospitalizations and patient well-being in a single outcome.

OBJECTIVES To overcome this limitation, we tested an integrated measure that includes days lost from death and hospitalization, and additional days of full health lost through diminished well-being.

METHODS The effect of dapagliflozin on this integrated measure was assessed in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, which examined the efficacy of dapagliflozin, compared with placebo, in patients with NYHA functional class II to IV heart failure and a left ventricular ejection fraction ≤40%.

RESULTS Over 360 days, patients in the dapagliflozin group (n = 2,127) lost 10.6 ± 1.0 (2.9%) of potential follow-up days through cardiovascular death and heart failure hospitalization, compared with 14.4 ± 1.0 days (4.0%) in the placebo group (n = 2,108), and this component of all measures of days lost accounted for the greatest between-treatment difference (−3.8 days [95% CI: −6.6 to −1.0 days]). Patients receiving dapagliflozin also had fewer days lost to death and hospitalization from all causes vs placebo (15.5 ± 1.1 days [4.3%] vs 20.3 ± 1.1 days [5.6%]). When additional days of full health lost (ie, adjusted for Kansas City Cardiomyopathy Questionnaire-overall summary score) were added, total days lost were 110.6 ± 1.6 days (30.7%) with dapagliflozin vs 116.9 ± 1.6 days (32.5%) with placebo. The difference in all measures between the 2 groups increased over time (ie, days lost by death and hospitalization −0.9 days [−0.7%] at 120 days, −2.3 days [−1.0%] at 240 days, and −4.8 days [−1.3%] at 360 days).

CONCLUSIONS Dapagliflozin reduced the total days of potential full health lost due to death, hospitalizations, and impaired well-being, and this benefit increased over time during the first year. (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; NCT03036124) (J Am Coll Cardiol 2024;83:1973-1986) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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From the [a]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [b]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [c]Department of Cardiology, Zealand University Hospital, Roskilde, Denmark; [d]Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [e]Erasmus Medical Center, Rotterdam, the Netherlands; [f]Yale School of Medicine, New Haven, Connecticut, USA; [g]Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [h]Saint Luke's Mid America Heart Institute, University of Missouri-Kansas City, Kansas City, Missouri, USA; [i]University of Cordoba, Cordoba, Argentina; [j]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; and the [k]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

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ABBREVIATIONS AND ACRONYMS

DAOH = days alive and out of hospital

EQ-5D VAS = EuroQol-5D visual analogue scale

HF = heart failure

HRQL = health-related quality of life

KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score

The primary outcome in most trials testing new treatments for heart failure (HF) is a composite endpoint such as HF hospitalization or cardiovascular mortality, tested as time-to-first-event.[1-3] The use of such composite endpoints has the advantage, over all-cause mortality, of increasing the event rate and reducing sample size, but also has limitations including treating cardiovascular death and hospitalization as equally important, not accounting for recurring events, and not taking the duration of hospitalization into account.[2] These problems are exemplified by a short HF hospitalization occurring early during follow-up carrying greater importance in the analysis than a cardiovascular death occurring later in the trial. An additional limitation is that a conventional composite outcome of this type does not incorporate patient well-being or "health status," which is often greatly diminished in HF and the improvement of which is a key therapeutic goal in heart failure.[4] Indeed improvement in symptoms and quality of life are particularly important for patients and the incorporation of "health status" helps create a more patient-centered outcome.

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Potential days of follow-up lost by death and hospitalization, which is the counterpart of days alive and out of hospital (DAOH), is an alternative measure of efficacy that addresses several of these concerns in that it includes both mortality and hospitalization and takes into account the duration of hospitalization.[5,6] If improved, its interpretation is straightforward (fewer days lost through death and hospitalization) and it has a clear clinical value.

Patients, physicians, scientific organizations, and regulatory agencies have recently emphasized the importance of evaluating patient-reported outcomes when assessing the efficacy of therapeutic interventions in cardiovascular medicine.[7-10] A next step, therefore, may be to adjust the remaining potential days of healthy follow-up not lost through death and hospitalization for impaired well-being to give an overall measure of all days of potential full health lost.

DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) was a trial comparing dapagliflozin with placebo in patients with HF and reduced ejection fraction.[11-13] Dapagliflozin reduced the risk of the primary composite endpoint of cardiovascular death or a worsening HF event. In addition, several patient-reported outcomes and the standard physician-assessed assessment of functional limitation (NYHA functional class) were improved by dapagliflozin.[14] In this post hoc study, we developed several integrated measures that quantified days of full health lost through death, hospitalization, and due to impaired well-being, the latter based on both patient-reported outcomes and physician-assessed functional limitation, and representing more patient-centered outcomes.[5,6] We compared the effect of dapagliflozin with placebo on these integrated measures.

METHODS

STUDY PATIENTS. The design and primary results of DAPA-HF are published.[11-13] Briefly, this trial enrolled patients with a left ventricular ejection fraction ≤40% and NYHA functional class II to IV. Patients were required to have an N-terminal pro-B-type natriuretic peptide level ≥600 pg/mL (or ≥400 pg/mL if HF hospitalization was within 12 months). Patients with atrial fibrillation or atrial flutter on electrocardiography were required to have an N-terminal pro-B-type natriuretic peptide level ≥900 pg/mL, regardless of HF hospitalization history. Patients were randomized to receive dapagliflozin 10 mg once daily, or a matching placebo. Exclusion criteria included type 1 diabetes mellitus, symptoms of hypotension or systolic blood pressure of <95 mm Hg, and estimated glomerular filtration rate <30 mL/min/1.73 m^2. A composite of a worsening HF event or death from cardiovascular causes was evaluated as the primary outcome.

The trial was approved by each site's ethics committees and written informed consent was obtained from each patient.

WELL-BEING: PATIENT-REPORTED WELL-BEING AND PHYSICIAN-ASSESSED FUNCTIONAL LIMITATION. Patient-reported well-being was evaluated at baseline, 120 days, 240 days, and 360 days, and yearly thereafter using the Kansas City Cardiomyopathy Questionnaire (KCCQ), a 23-item self-administered questionnaire developed to independently measure the patient's perception of their health status.[15] For this study, we used the Kansas City Cardiomyopathy Questionnaire-Overall Summary Score (KCCQ-OSS), which is the mean of the symptom, physical limitations, social limitations, and quality of life domains, ranging from 0 to 100 (the higher the score, the better the patient's self-perceived health). As an additional measure of more general health-related quality of life (HRQL), we used the EuroQol-5D visual analogue scale (EQ-5D VAS) where patients' self-rated health state was reported on a vertical scale ranging from

0 (worst imaginable) to 100 (best imaginable), which was completed by the patient, along with the KCCQ assessment.[16] NYHA functional class was assessed by a physician at baseline, 120 days, and 240 days.

MEASURES OF POTENTIAL FOLLOW-UP DAYS OF FULL HEALTH LOST. The potential follow-up days of full health lost (and proportion of days of full health lost) were calculated for each patient and evaluated using 6 different integrated measures: 1) days lost by cardiovascular death and HF hospitalization; 2) days lost by death (due to cardiovascular causes and non-cardiovascular causes) and hospitalization (due to HF and non-HF); and 3 to 6) days lost by death and hospitalization and impaired well-being, with days of potential full health adjusted for KCCQ-OSS, EQ-5D VAS score, or NYHA functional class (the latter using 2 different weighting methods).

The number of potential follow-up days was defined as the number of days from randomization until 360 days. A fixed follow-up period of up to 360 days was used for analysis because NYHA functional class was available until 240 days (see later in this paper). For patients with incomplete follow-up, the censoring date was used as the final date to determine the potential follow-up days. For patients who died, the days after the date of death until the end of potential follow-up were defined as days dead. Patients were counted as hospitalized for each day of any admission that occurred. Additional days of full health lost as a result of impaired well-being were calculated by adjusting the remaining days (ie, DAOH), of the potential total of 360, using a "well-being adjustment factor" (see later in this paper). DAOH was calculated by subtracting days lost by death and hospitalization from the potential follow-up days (ie, 360 days lost by death and hospitalization).[5,6]

Days lost due to hospital admission for HF were obtained from events adjudicated as a component of the primary outcome of the trial. Data on other hospitalizations not due to HF were obtained from information entered on the case report form by investigators and were not adjudicated.

ADJUSTMENT FOR WELL-BEING. Patients without either KCCQ-OSS, EQ-5D VAS score, or NYHA functional class at baseline were excluded from the analysis in this study. For each of these measures, a comprehensive score using 120-day windows was derived as a linear combination of days lost due to death and hospitalization in each interval, weighted using well-being during that interval.

For each day during follow-up, patients were assigned the last known KCCQ-OSS, EQ-5D VAS score, or NYHA functional class (eg, the measurement of well-being attributed to the period 240 days to 360 days after randomization was based on the value reported at 240 days, and, when the value at 120 days or 240 days was missing, the most recent available previously collected visit data were applied). Accordingly, the window for analysis was 120 days (ie, days lost by impaired well-being were calculated separately for the first 120 days, the next 120 days up to 240 days, and the last 120 days up to 360 days).

When using KCCQ-OSS or EQ-5D VAS score to obtain days lost through impaired well-being, DAOH were adjusted for the last known value of KCCQ-OSS or EQ-5D VAS. For example, if during the first 120 days, a patient had 1 hospitalization lasting 20 days and the KCCQ-OSS at baseline was 90, the days lost by impaired well-being would be 10 days: 120 − 20 days = 100 DAOH at potential full health; but KCCQ-OSS of 90 of a possible 100 points results in only 90 days of full health (ie, a loss of 10 days) (Supplemental Methods).

To use NYHA functional class to adjust for DAOH, we weighted NYHA functional class using 2 methods. First, we calculated the median of KCCQ-total symptom scores, collected at the same time as NYHA functional class, by each NYHA functional class across all visits (ie, this integrated measure represents patients' contemporaneous weighting of physicians' assessments). In this study, the weights were 0.97 for NYHA functional class I, 0.85 for NYHA functional class II, 0.67 for NYHA functional class III, and 0.67 for NYHA functional class IV (Supplemental Table 1). Second, we also applied other weights for NYHA functional class, used in prior studies (ie, 1.0, 0.86, 0.76, and 0.60 for classes I to IV, respectively), to be able to compare the present findings with previous ones.[17] The same approach as for KCCQ-OSS was used to adjust DAOH, using the weight of the last known NYHA functional class. For example, in the first NYHA adjustment method, if a patient had one hospitalization lasting 20 days and spent the remaining 100 days of the first 120 days in NYHA functional class II, the days lost by death, hospitalization, and well-being would total 35 days (29.2%) (Supplemental Methods).

STATISTICAL ANALYSES. Patients whose duration of hospitalization was missing (n = 4), whose potential follow-up time was <360 days (n = 156), or whose baseline KCCQ-OSS (n = 296) or EQ-5D VAS score (n = 53) was missing were excluded from the analysis (Supplemental Figure 1).

Baseline characteristics according to randomized treatment are presented as means with SDs or median (Q1-Q3) for continuous variables and frequencies with

TABLE 1 Baseline Characteristics

	Dapagliflozin (n = 2,127)	Placebo (n = 2,108)	*P* Value
Age, y	66.1 ± 10.7	66.5 ± 10.5	0.16
Female	479 (22.5)	469 (22.2)	0.83
Region			0.70
Asia/Pacific	462 (21.7)	485 (23.0)	
Europe	1,040 (48.9)	997 (47.3)	
North America	243 (11.4)	246 (11.7)	
South America	382 (18.0)	380 (18.0)	
Race			0.20
White	1,523 (71.6)	1,511 (71.7)	
Black or African American	101 (4.7)	80 (3.8)	
Asian	467 (22.0)	491 (23.3)	
Other	36 (1.7)	26 (1.2)	
Body mass index, kg/m^2	28.3 ± 5.9	28.2 ± 5.9	0.56
Vital signs			
Heart rate, beats/min	71.5 ± 11.6	71.5 ± 11.7	0.85
Systolic blood pressure, mm Hg	122.3 ± 16.2	121.7 ± 16.2	0.20
Diastolic blood pressure, mm Hg	73.9 ± 10.4	73.3 ± 10.4	0.076
Laboratory values and ECG findings			
HbA1c, %	6.5 ± 1.3	6.5 ± 1.3	0.89
Creatinine, μmol/L	104.0 ± 29.0	105.1 ± 31.2	0.21
eGFR, mL/min/1.73 m^2	66.1 ± 19.3	65.4 ± 19.0	0.27
eGFR <60 mL/min/1.73 m^2	856 (40.3)	854 (40.5)	0.87
NT-proBNP, ng/L	1,407 (850-2,616)	1,441 (853-2,607)	0.54
NT-proBNP if baseline ECG in AF/AFL, ng/L	1,994 (1,286-3,183)	1,985 (1,258-3,317)	0.87
NT-proBNP if baseline ECG not in AF/AFL, ng/L	1,247 (758-2,343)	1,280 (768-2,348)	0.34
AF/AFL on ECG	524 (24.6)	509 (24.1)	0.71
HF characteristics			
Prior HF hospitalization	1,022 (48.0)	1,033 (49.0)	0.53
Time from diagnosis of HF			0.025
≤6 mo	224 (10.5)	256 (12.1)	
>6-12 mo	238 (11.2)	248 (11.8)	
>1-2 y	282 (13.3)	327 (15.5)	
>2-5 y	528 (24.8)	460 (21.8)	
>5 y	855 (40.2)	817 (38.8)	
NYHA functional class			0.94
II	1,423 (66.9)	1,400 (66.4)	
III	684 (32.2)	687 (32.6)	
IV	20 (0.9)	21 (1.0)	
Baseline KCCQ-OSS	67.8 ± 21.0	68.5 ± 20.3	0.25
Baseline KCCQ-TSS	73.1 ± 22.2	74.0 ± 21.4	0.16
Baseline KCCQ-CSS	70.7 ± 21.1	71.5 ± 20.5	0.20
Baseline EQ-5D VAS score	67.7 ± 17.5	68.0 ± 17.2	0.63
LVEF, %	31.3 ± 6.6	31.0 ± 6.9	0.19
Principal cause of HF			0.34
Ischemic	1,194 (56.1)	1,216 (57.7)	
Nonischemic	752 (35.4)	736 (34.9)	
Unknown	181 (8.5)	156 (7.4)	

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percentages for categorical variables. Differences in baseline characteristics between patients included and excluded, and between randomized treatment groups, were compared using the chi-square test for categorical variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables, as appropriate.

The changes in potential follow-up days of full health lost, and DAOH (and these proportions) were analyzed using mixed-effect models for repeated measurements, with adjustment for time, treatment-group assignment, and interaction between treatment and time for the mixed-effect models, and the least-squares mean differences with 95% CI were reported. The assumptions of the mixed model were examined by plotting the residuals, which were normally distributed. Days lost at 120 and 240 days as well as at 360 days were obtained and illustrated to evaluate these over time. Considering differences in the duration of hospitalization and well-being by region, we analyzed days of full health lost by 360 days according to region. We also illustrated the proportion of potential follow-up days that a patient spent in KCCQ-OSS categories (0-24, very poor to poor; 25-49, poor to fair; 50-74, fair to good; and 75-100, good to excellent, as previously described), as well as days lost through hospitalization or lost by death at 120 days, 240 days, and 360 days. In addition, the distributions of the percentage of days lost at 360 days were illustrated as histograms.

We added 3 sensitivity analyses: 1) days lost by death, hospitalization, and impaired well-being adjusted for KCCQ-OSS with a KCCQ-OSS of 75-100 as "adequate" health[18]; 2) days lost by death, hospitalization, and impaired well-being adjusted for KCCQ-OSS for the population without KCCQ-OSS missing at any visit (and similar analyses excluding subjects with missing data were performed for the EQ-5D VAS score and NYHA functional class adjusted models, respectively); and 3) days lost by death, hospitalization, and impaired well-being adjusted for KCCQ-OSS with missing values imputed by multiple imputation. Potential follow-up days lost in the sensitivity analyses were shown at 360 days.

STATA version 17.0 (StataCorp, LLC) was used for statistical analyses. A *P* value <0.05 was considered statistically significant.

RESULTS

Of 4,744 patients included in the original intention-to-treat analysis, a total of 4,235 patients (89.3%) with data on the duration of hospitalization, at least 360 days of the potential follow-up period, and information on well-being ("health status") were analyzed.

Treatment groups were well-balanced at baseline (Table 1). Excluded patients were more often female, more often from North America, had better NYHA

functional class and EQ-5D VAS scores, and generally had less comorbidity (Supplemental Table 2).

The number of patients with assessments of KCCQ-OSS, EQ-5D VAS score, and NYHA functional class at study visits at 120, and 240 days, relative to the number of patients alive, is shown in Supplemental Table 3. Of patients alive at each visit (4,124 patients at 120 days and 4,011 patients at 240 days), KCCQ-OSS was assessed in 94.2% of patients (n = 3,884) at 120 days and 92.5% (n = 3,712) at 240 days; EQ-5D VAS score was assessed in 93.6% (n = 3,859) at 120 days and 92.1% (n = 3,694) at 240 days; and NYHA functional class was assessed in 99.0% (n = 4,081) at 120 days and 98.1% (n = 3,933) at 240 days.

TABLE 1 Continued

	Dapagliflozin (n = 2,127)	Placebo (n = 2,108)	*P* Value
Clinical history			
Type 2 diabetes	883 (41.5)	888 (42.1)	0.69
AF	830 (39.0)	818 (38.8)	0.88
Hypertension	1,595 (75.0)	1,577 (74.8)	0.89
Myocardial infarction	939 (44.1)	954 (45.3)	0.47
Stroke	208 (9.8)	210 (10.0)	0.84
Medical therapy			
ACEI	1,213 (57.0)	1,195 (56.7)	0.82
ARB	604 (28.4)	568 (26.9)	0.29
ARNI	209 (9.8)	208 (9.9)	0.96
ACEI, ARB, or ARNI	2,006 (94.3)	1,960 (93.0)	0.076
Beta-blocker	2,044 (96.1)	2,029 (96.3)	0.79
Mineralocorticoid receptor antagonist	1,537 (72.3)	1,497 (71.0)	0.37
Loop diuretic	1,718 (80.8)	1,705 (80.9)	0.93
Digitalis	395 (18.6)	391 (18.5)	0.99
CRT-D or CRT-P	168 (7.9)	152 (7.2)	0.40
CRT-D or ICD	554 (26.0)	550 (26.1)	0.97

Values are mean ± SD, n (%), or median (Q1-Q3). Body mass index is missing in 2 patients; HbA1c in 7 patients; creatinine, eGFR, NT-proBNP in 1 patient.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; CRT = cardiac resynchronization therapy; ECG = electrocardiography; eGFR = estimated glomerular filtration rate; EQ-5D VAS = EuroQol-5D visual analogue scale; HbA1c = glycated hemoglobin; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

POTENTIAL FOLLOW-UP DAYS OF FULL HEALTH LOST. In the dapagliflozin group (n = 2,127), 149 (7.0%) patients died by 360 days compared with 188 (8.9%) in the placebo group (n = 2,108); 122 (5.7%) patients died due to a cardiovascular cause in the dapagliflozin group, and 158 (7.5%) in the placebo group. The numbers of potential follow-up days of full health lost, and the proportion of potential days, according to the treatment group are shown in **Figure 1**, **Table 2**, and Supplemental Table 4. By 360 days, dapagliflozin-treated patients lost 10.6 ± 1.0 days (2.9%) of potential follow-up days due to cardiovascular death and HF hospitalization, compared with 14.4 ± 1.0 days (4.0%) of potential follow-up days in the placebo group (difference −3.8 days [95% CI: −6.6 to −1.0 days]; $P = 0.009$), resulting in 26.4% relative reduction (**Central Illustration**). Similarly, the number of days lost due to death and hospitalization for any cause at 360 days was smaller in the dapagliflozin group than in the placebo group (15.5 ± 1.1 days [4.3%] vs 20.3 ± 1.1 days [5.6%], difference: −4.8 days [95% CI: −7.9 to −1.7 days]; $P = 0.003$), resulting in 23.6% relative reduction. DAOH at 360 days, the counterpart of days lost due to death and hospitalization, were 344.5 ± 1.1 days (95.7%) in the dapagliflozin group and 339.7 ± 1.1 days (94.4%) in the placebo group.

KCCQ-OSS, EQ-5D VAS score, and NYHA functional class in each visit are summarized in Supplemental Table 5. When KCCQ-OSS was used to calculate additional days lost due to impaired well-being, patients in the dapagliflozin group had significantly fewer days lost compared with those in the placebo group at 360 days (110.6 ± 1.6 days [30.7%] vs 116.9 ± 1.6 days [32.5%], difference: −6.3 days [95% CI −10.8 to −1.7 days]; $P = 0.007$), resulting in 5.4% relative reduction. Whether impaired well-being was adjusted for EQ-5D VAS score or NYHA functional class, fewer days were lost in the dapagliflozin group than in the placebo group at 360 days, although the numbers of days lost through incorporating patient-reported well-being were greater than the number lost calculated using physician-assessed functional limitation.

When looking at the trend over time, the number of days lost increased proportionally using all measures from 120 days to 360 days, as did the differences between the dapagliflozin and placebo (**Figure 1**, **Table 2**, Supplemental Table 4). When evaluated according to region, the effect of dapagliflozin on potential days of full health lost was consistent across regions (Supplemental Figure 2). **Figure 2** shows the proportion of potential follow-up days that a patient spent in KCCQ-OSS categories, in hospital, or lost through death by randomized treatment.

BREAKDOWN OF DAYS LOST TO DEATH, HOSPITALIZATION, AND IMPAIRED WELL-BEING. The breakdown of days lost at 360 days is shown in **Table 3**. Days lost by any death at 360 days were fewer in the dapagliflozin group compared with the placebo group (11.5 ± 1.0 days vs 14.9 ± 1.0 days), and this component of all the types

FIGURE 1 Potential Days of Full Health Lost During 360 Days of Follow-Up

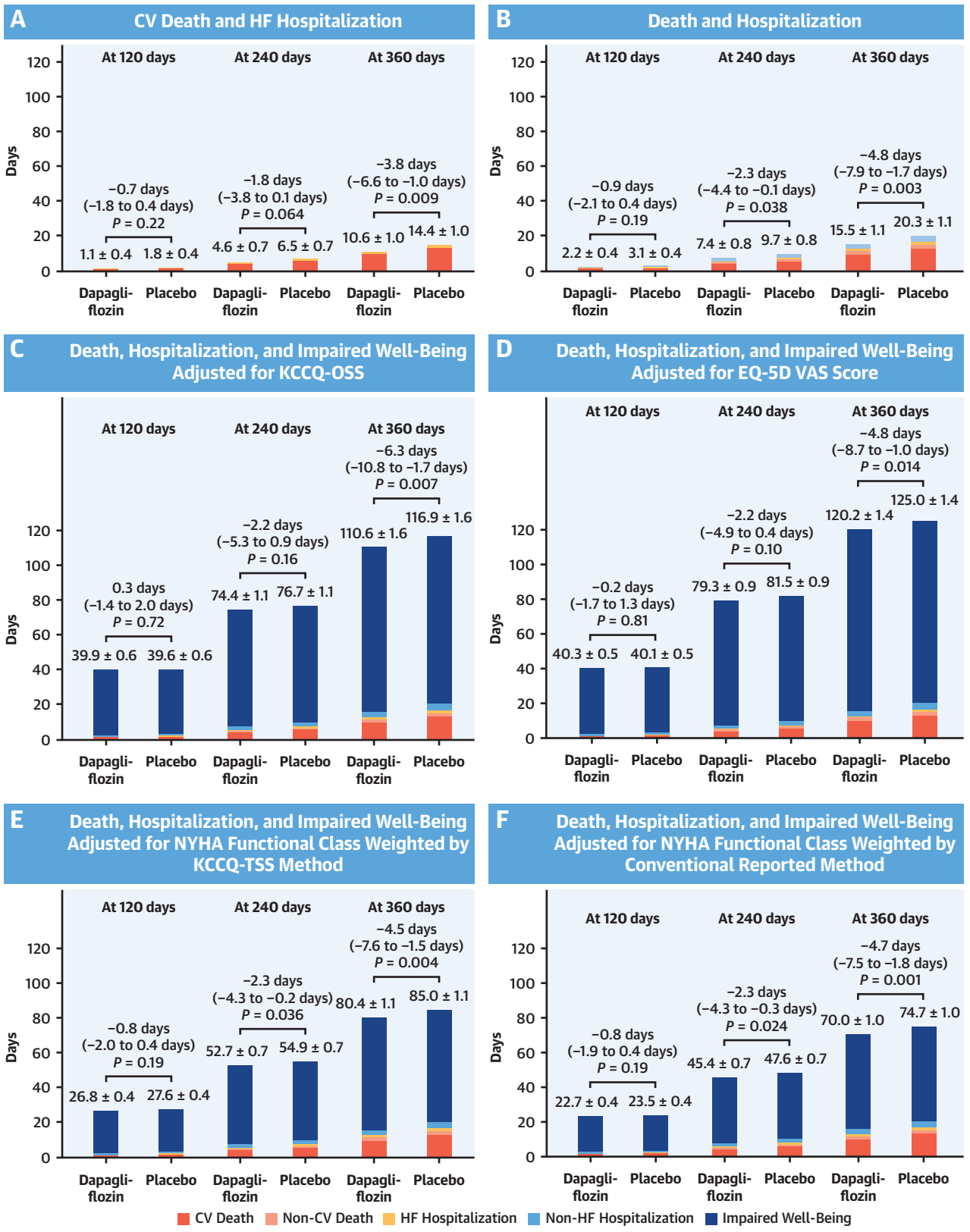

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TABLE 2 Proportion of Potential Days of Full Health Lost During Follow-Up

Lost By	Time	Dapagliflozin (n = 2,127)	Placebo (n = 2,108)	Difference, % (95% CI)	*P* Value
CV death and HF hospitalization	At 120 d	0.9 ± 0.1%	1.5 ± 0.1%	−0.6 (−1.0 to −0.2)	0.005
	At 240 d	1.9 ± 0.2%	2.7 ± 0.2%	−0.8 (−1.4 to −0.1)	0.025
	At 360 d	2.9 ± 0.3%	4.0 ± 0.3%	−1.0 (−2.0 to −0.1)	0.030
Death and hospitalization	At 120 d	1.9 ± 0.2%	2.6 ± 0.2%	−0.7 (−1.2 to −0.2)	0.004
	At 240 d	3.1 ± 0.3%	4.0 ± 0.3%	−1.0 (−1.7 to −0.2)	0.014
	At 360 d	4.3 ± 0.4%	5.6 ± 0.4%	−1.3 (−2.4 to −0.3)	0.014
Death, hospitalization, and impaired well-being adjusted for KCCQ-TSS	At 120 d	33.3 ± 0.3%	33.0 ± 0.3%	0.3 (−0.6 to 1.1)	0.56
	At 240 d	31.0 ± 0.4%	31.9 ± 0.4%	−0.9 (−2.1 to 0.2)	0.12
	At 360 d	30.7 ± 0.5%	32.5 ± 0.5%	−1.7 (−3.3 to −0.2)	0.026
Death, hospitalization, and impaired well-being adjusted for EQ-5D VAS score	At 120 d	33.4 ± 0.2%	33.6 ± 0.2%	−0.2 (−0.9 to 0.6)	0.69
	At 240 d	33.0 ± 0.3%	34.0 ± 0.3%	−0.9 (−1.9 to 0.1)	0.073
	At 360 d	33.4 ± 0.5%	34.7 ± 0.5%	−1.3 (−2.7 to 0.0)	0.047
Death, hospitalization, and impaired well-being adjusted for NYHA functional class weighted by KCCQ-TSS method	At 120 d	22.4 ± 0.2%	23.0 ± 0.2%	−0.7 (−1.2 to −0.1)	0.012
	At 240 d	22.0 ± 0.3%	22.9 ± 0.3%	−0.9 (−1.7 to −0.2)	0.016
	At 360 d	22.3 ± 0.4%	23.6 ± 0.4%	−1.3 (−2.3 to −0.2)	0.018
Death, hospitalization, and impaired well-being adjusted for NYHA functional class weighted by conventional reported method	At 120 d	19.0 ± 0.1%	19.6 ± 0.1%	−0.6 (−1.1 to −0.2)	0.006
	At 240 d	18.9 ± 0.2%	19.9 ± 0.2%	−0.9 (−1.7 to −0.2)	0.008
	At 360 d	19.5 ± 0.3%	20.7 ± 0.3%	−1.3 (−2.3 to −0.3)	0.010

Proportions of days lost are presented as means ± SE. The difference in the mean proportions of days lost between the dapagliflozin and placebo groups are shown as mean (95% CI). The medians (Q1-Q3) are shown in Supplemental Table 4.

CV = cardiovascular; other abbreviations as in Table 1.

of days lost accounted for the greatest between-treatment difference (−3.4 days [95% CI: −6.3 to −0.5 days]; $P = 0.021$). Patients in the dapagliflozin group lost fewer days due to cardiovascular death than patients in the placebo group, whereas days lost due to noncardiovascular death were similar between the 2 groups. The number of days lost due to hospitalization was also smaller in the dapagliflozin group than in the placebo group (4.0 ± 0.3 days vs 5.4 ± 0.3 days; difference: −1.4 days [95% CI: −2.2 to −0.5 days]; $P = 0.001$); a similar observation was made for HF hospitalization days (1.0 ± 0.1 days vs 1.6 ± 0.1 days; difference: −0.5 days [95% CI: −0.9 to −0.1 days]; $P = 0.010$) and non-HF hospitalization days (3.0 ± 0.2 days vs 3.8 ± 0.2 days; difference: −0.8 days [95% CI: −1.5 to −0.2 days]; $P = 0.015$). The number of days lost due to impaired well-being at 360 days was similar between the 2 groups.

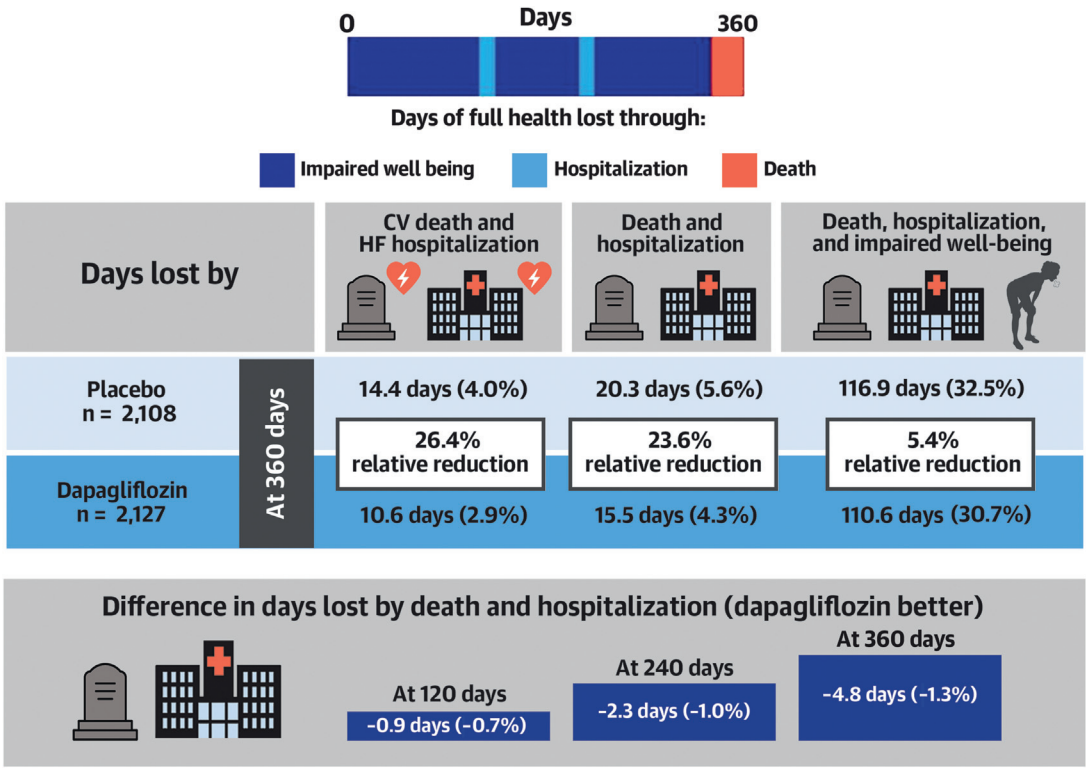
PERCENT OF DAYS LOST AT 360 DAYS ACCORDING TO RANDOMIZED TREATMENT. Figure 3 illustrates the distributions of the percentage of days lost by 360 days for the 6 measures examined. The distributions showed a leftward shift in the dapagliflozin group compared with the placebo group for all measures.

SENSITIVITY ANALYSES. Sensitivity analyses for days lost by death, hospitalization, and impaired well-being adjusted for KCCQ-OSS using KCCQ-OSS >75 points (ie, 75-100 points) as "adequate" health

FIGURE 1 Continued

Potential follow-up days of full health lost by 120 days, 240 days, and 360 days, shown according to randomized treatment group, as mean ± SE; days lost due to (A) CV death and HF hospitalization, (B) death and hospitalization for any reason, (C) death, hospitalization, and days lost due to impaired well-being adjusted for KCCQ-OSS, (D) death, hospitalization, and days lost due to impaired well-being adjusted for EQ-5D VAS score, (E) death, hospitalization, and days lost due to impaired well-being adjusted for NYHA functional class weighted according to KCCQ-TSS, and (F) death, hospitalization, and days lost due to impaired well-being adjusted for NYHA functional class weighted according to previously published values. The difference in mean days lost between the dapagliflozin and placebo groups is shown as mean (95% CI). CV = cardiovascular; EQ-5D VAS = EuroQol-5D visual analogue scale; HF = heart failure; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-Total Symptom Score.

CENTRAL ILLUSTRATION **Effect of Dapagliflozin on Days of Full-Health Lost in HFrEF**



Kondo T, et al. J Am Coll Cardiol. 2024;83(20):1973–1986.

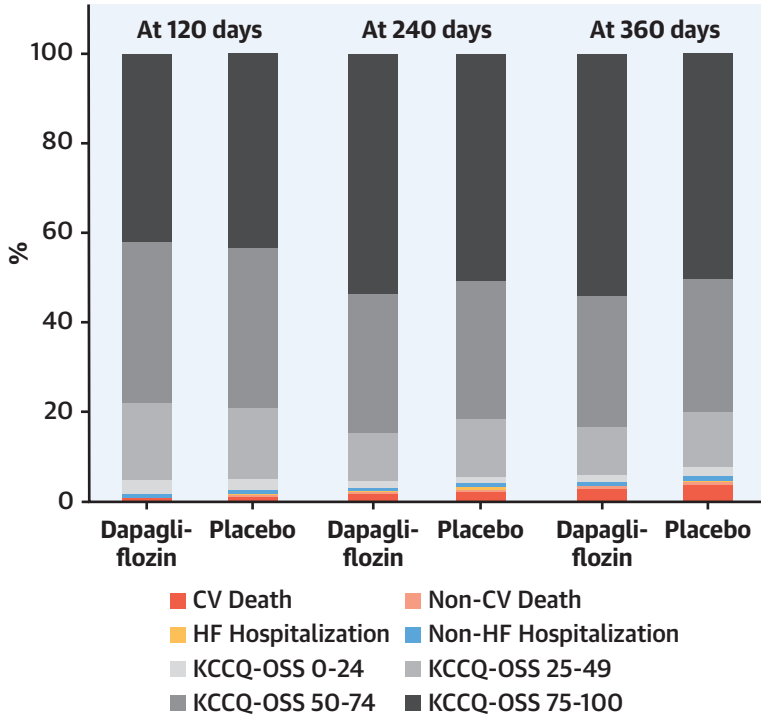
Days lost were compared between patients who received dapagliflozin (n = 2,127) and placebo (n = 2,108). At 360 days, dapagliflozin reduced the days lost due to CV death and HF hospitalization by 3.8 (26.4% relative reduction compared with placebo), due to death and hospitalization for any reason by 4.8 days (23.6% relative reduction), and due to death, hospitalization, and impaired well-being by 6.3 days (5.4% relative reduction). Days lost due to death and hospitalization were lower in the dapagliflozin than in the placebo group by 0.9 days (0.7%) at 120 days, 2.3 days (1.0%) at 240 days, and 4.8 days (1.3%) at 360 days. Days lost due to death, hospitalization, and impaired well-being were adjusted for KCCQ-OSS. CV = cardiovascular; HF = heart failure; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; LVEF = left ventricular ejection fraction.

(Supplemental Figure 3), days lost by death, hospitalization, and impaired well-being for the population without missing information on impaired-well at any visit (Supplemental Figure 4) and days lost by death, hospitalization, and impaired well-being adjusted for KCCQ-OSS with missing values imputed by multiple imputation (Supplemental Figure 5) yielded similar results as the primary analyses.

DISCUSSION. During the first 360 days after randomization in DAPA-HF, dapagliflozin reduced all measures assessed of days of full health lost, compared with placebo; 26.4% relative reduction in days lost due to cardiovascular death and HF hospitalization, 23.6% in days lost due to death and hospitalization, and 3.8% to 6.3% in days lost due to death, hospitalization, and impaired well-being. For all measures, the reductions in the number of days lost (and the proportions of days lost) by dapagliflozin increased over time. In terms of the types of days lost, dapagliflozin reduced the days lost due to cardiovascular death and the days lost due to hospitalization (both HF and non-HF hospitalizations), with death accounting for the biggest difference between treatments (3.4 days).

Several of the measures analyzed are robust, even stringent because they take account of days lost due to death from any cause and days lost due to hospitalization for any cause (ie, these resemble the composite of all-cause deaths and total [first and recurrent] all-cause hospitalization), accepting that treatments are likely to have less impact on noncardiovascular hospitalization and noncardiovascular deaths. Moreover, our measures take into account not

FIGURE 2 Days Lost Through Death, Hospitalization, and Reductions in KCCQ-OSS



Proportions of potential follow-up days that a patient spent in KCCQ-OSS categories (0-24, 25-49, 50-74, or 75-100), in hospital, or lost through death, according to randomized treatment, at 120 days, 240 days, and 360 days. Abbreviations as in Figure 1.

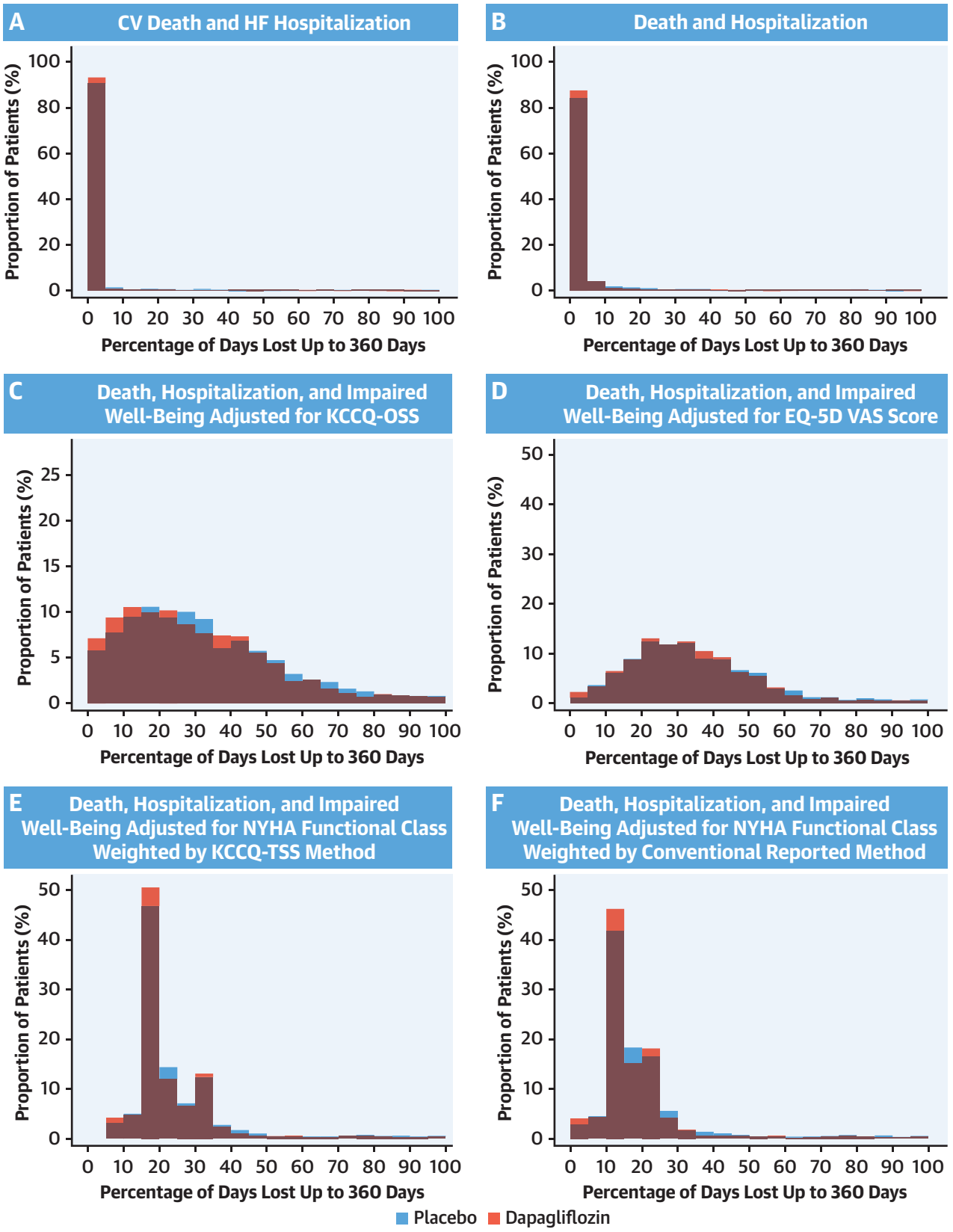
just first and recurrent admissions, but the duration of these, which contribute substantially to the burden of chronic diseases such as HF. The outcome of days lost due to death from any cause and days lost due to hospitalization for any cause also accounts for the competing risk that arises when a life-saving therapy is used (ie, the additional patients who survive do so to be at future risk of cardiovascular and

TABLE 3 Breakdown of Days Lost at 360 Days

Days Lost By	Dapagliflozin (n = 2,127)	Placebo (n = 2,108)	Difference (95% CI)	*P* Value
Any death	11.5 ± 1.0	14.9 ± 1.0	−3.4 (−6.3 to −0.5)	0.021
CV death	9.6 ± 1.0	12.8 ± 1.0	−3.2 (−6.0 to −0.5)	0.020
Non-CV death	1.9 ± 0.4	2.1 ± 0.4	−0.2 (−1.3 to 0.9)	0.72
Any hospitalization	4.0 ± 0.3	5.4 ± 0.3	−1.4 (−2.2 to −0.5)	0.001
HF hospitalization	1.0 ± 0.1	1.6 ± 0.1	−0.5 (−0.9 to −0.1)	0.010
Non-HF hospitalization	3.0 ± 0.2	3.8 ± 0.2	−0.8 (−1.5 to −0.2)	0.015
Impaired well-being				
Adjusted for KCCQ-OSS	95.1 ± 1.4	96.6 ± 1.4	−1.5 (−5.3 to 2.4)	0.45
Adjusted for EQ-5D VAS score	104.7 ± 1.1	104.7 ± 1.1	0.0 (−3.2 to 3.1)	0.99
Adjusted for NYHA functional class weighted by KCCQ-TSS method	65.0 ± 0.6	64.7 ± 0.6	0.3 (−1.4 to 1.9)	0.75
Adjusted for NYHA functional class weighted by conventional reported method	54.5 ± 0.4	54.4 ± 0.4	0.1 (−1.0 to 1.2)	0.82

Days lost at 360 days are presented as mean ± SE. The differences in mean days lost between the dapagliflozin and placebo groups are shown as mean (95% CI). Abbreviations as in Tables 1 and 2.

FIGURE 3 Percentage of Days Lost at 360 Days According to Randomized Treatment



Continued on the next page

noncardiovascular illnesses and events [and the decrement in HRQL that may accompany these]). Therefore, the integrated endpoints used in this study give a much more holistic patient-centered assessment of any new treatment, reflecting also the health economic and societal perspective more than traditional trial endpoints. Although more patient-focused, our integrated measures may be less attractive to sponsors and trialists because it is now well-recognized that cardiovascular therapies have a larger magnitude of effect on disease-specific endpoints and our measures are likely to show a smaller treatment effect size because they include noncardiovascular morbidity and mortality (as described earlier in this article). Moreover, by showing absolute rather than relative differences, the treatment effect size for the reduction in days lost due to death and hospitalization may appear modest (although more favorable when using a relative scale). Additionally, conventional patient-reported outcomes such as the KCCQ usually show modest effects of treatments when means across patient populations are analyzed. Consequently, there might also be concerns about study power if such an integrated endpoint were to be used. Despite these aforementioned concerns, dapagliflozin improved all our integrated measures compared with placebo. It is noteworthy that the difference in days lost or those proportions between the 2 groups exhibited a gradual but consistent increase over 1 year, indicating that the benefits of dapagliflozin increase cumulatively over time.

We found that participants lost a mean of 20.3 days (5.6%) due to death and hospitalization and 14.4 days (4.0%) due to cardiovascular death and HF hospitalization; they also lost more days due to death (14.9 days; 4.1%) or cardiovascular death (12.8 days; 3.6%) than days due to all-cause hospitalization (5.4 days; 1.5%) or HF hospitalization (1.6 days; 0.4%). The very small proportion of time that patients with HF (and mild to moderate symptoms) spent in the hospital during the approximately 1 year of follow-up is striking, although this is often the focus of physicians in secondary care. Even more striking is the contribution of impaired well-being to days of full health lost - a much larger number than due to either death or hospital admission. This may help explain why some patients value their quality of life as much or more than quantity of life.

Of all the types of days lost, death (or cardiovascular death) accounted for the biggest difference between treatments (3.4 days or 3.2 days) because more days were lost due to death (or cardiovascular death) than due to hospitalization (or HF hospitalization) in the placebo group.

We were also able to look at whether who assessed patient well-being (patient or physician), and which instrument was used to make these assessments influenced our integrated outcome measures. Importantly, patient assessment resulted in a greater loss of days due to impaired well-being than physician assessment, although perhaps it is not surprising that investigators might underestimate the impact of HF on well-being compared with patients.[18,19] Next, when comparing 2 different patient-reported instruments, the use of the EQ5D-VAS score, a general HRQL instrument, seemed to result in more days lost than the use of the KCCQ-OSS, a HF-specific instrument. It is uncertain, however, whether this apparent difference reflects the specificity of 1 instrument over the other or their relative complexity/ease of use because the 2 instruments are quite different.[10] There is an important caveat concerning the interpretation of the effect of a treatment on days lost due to impaired well-being using the approach described here. When a treatment has a favorable effect on DAOH, its effect on patient well-being may be underestimated because the patients will spend more days alive, not in hospital but potentially with suboptimal health status.

Days lost to death and hospitalization have been reported in the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure) trial, with 8.2% in the sotagliflozin group vs 11.1% in the placebo group (per 100 days).[20] It is difficult to compare these findings with ours as the difference between treatments varies with the period evaluated. However, the difference looks larger in the SOLOIST-WHF trial (5.6% vs 4.3% at 360 days in the DAPA-HF). If correct, this might be explained by the higher all-cause death

FIGURE 3 Continued

Distributions of the percentage of days lost by 360 days are depicted according to randomized treatment; days lost due to (A) CV death and HF hospitalization, (B) death and hospitalization for any reason, (C) death, hospitalization, and days lost due to impaired well-being adjusted for KCCQ-OSS, (D) death, hospitalization, and days lost due to impaired well-being adjusted for EQ-5D VAS score, (E) death, hospitalization, and days lost due to impaired well-being adjusted for NYHA functional class weighted according to KCCQ-TSS, and (F) death, hospitalization, and days lost due to impaired well-being adjusted for NYHA functional class weighted according to previously published values. Abbreviations as in Figure 1.

rate in the SOLOIST-WHF trial (placebo group 16.3 per 100 person-years vs 9.5 per 100 person-years in the DAPA-HF) due to the inclusion of patients with HF and type 2 diabetes recently hospitalized for worsening HF, despite the similar hazard ratio for all-cause death in the 2 trials.[11,21] In the PARADIGM-HF (Prospective comparison of angiotensin receptor neprilysin inhibitor [ARNI] with angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and morbidity in Heart Failure) trial, the difference in days lost due to death and hospitalization was 1.4% between the sacubitril/valsartan and enalapril groups when evaluated to the end of the trial.[22] There are few studies with which to compare days lost incorporating impaired well-being. In an analysis using NYHA adjustment in COMET (Carvedilol Or Metoprolol European Trial), the proportion of days lost at 1 year in patients treated with carvedilol was 36.1% vs 37.2% in those treated with metoprolol, a 1% difference reflecting approximately 4 days (compared with 4.5-4.7 days in the present study).[6] In the CHARM (Candesartan in Heart Failure-Assessment of Reduction in Mortality and morbidity) trial, the difference in days lost due to death, hospitalization, and impaired well-being, estimated using NYHA functional class, was 1.7% when evaluated up to the end of the trial date (compared with 1.3% in the present study).

Due to the post hoc nature of this analysis, some patients had to be excluded mainly due to potential follow-up of <360 days (n = 156) or because of missing KCCQ-OSS data at baseline (n = 296). Although the baseline characteristics of the analyzed patients were generally well-balanced according to the randomized treatment groups, there were differences in the characteristics of included and excluded patients that may have led to an overestimation or underestimation of the days of full health lost. The randomized treatment itself was not associated with exclusion from the analysis ($P = 0.42$), which does not completely preclude causal inference, but the background factors (eg, sex, region) that contributed to exclusion may have affected the degree of the difference in days of full health lost between the 2 groups.

STUDY LIMITATIONS. First, data on hospitalizations not due to HF were based on investigator entries in the case report form and were not adjudicated. Days lost may have been underestimated because admissions to long-term care facilities (eg, nursing homes) after discharge from the hospital were not specifically collected. Second, we included only patients with baseline information on KCCQ-OSS, EQ-5D VAS score, and NYHA functional class measures who could be followed up for 360 days (89.3% of the patients in the main study). This was done to include the highest number of patients with complete information on well-being. However, this made the length of follow-up short compared with other studies, and treatment effects might have been underestimated because differences in days lost may increase with longer-term follow-up.[23] Third, the weights used to adjust for HRQL or symptoms remain debatable. For example, in the model adjusted for KCCQ-OSS, days lost were calculated based on the assumption that the KCCQ loses days in a linear relationship in the range 0 to 100, which is debatable. We presented the results using various weights, using both a HF-specific and a generic measure of HRQL and we included different cutoffs for these instruments in our sensitivity analyses. Last, for the weighting of each day of follow-up, it would have been ideal if patient well-being had been evaluated daily. Instead, the last known measurement of well-being was used in our calculations, which is a conservative approach.

CONCLUSIONS

In the DAPA-HF trial, compared with a placebo, dapagliflozin reduced the total days of potential full health lost due to death, hospitalizations, and impaired well-being. The benefit of dapagliflozin on these measures increased over time during the first year.

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ADDRESS FOR CORRESPONDENCE: Prof John J.V. McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Dapagliflozin reduced an integrated measure of days of full health lost due to death, hospitalization, and reduced well-being/health status, and this benefit increased over time.

TRANSLATIONAL OUTLOOK: Further research is needed to compare the effect of dapagliflozin on days lost due to death, hospitalization, and impaired well-being with that of other pillars of heart failure management.

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KEY WORDS dapagliflozin, health-related quality of life, heart failure, prognosis, trial

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