Annals of Internal Medicine ORIGINAL RESEARCH

Efficacy and Safety of Dapagliflozin According to Frailty in Heart Failure With Reduced Ejection Fraction

A Post Hoc Analysis of the DAPA-HF Trial

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Background: Frailty may modify the risk–benefit profile of certain treatments, and frail patients may have reduced tolerance to treatments.

Objective: To investigate the efficacy of dapagliflozin according to frailty status, using the Rockwood cumulative deficit approach, in DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure).

Design: Post hoc analysis of a phase 3 randomized clinical trial. (ClinicalTrials.gov: NCT03036124)

Setting: 410 sites in 20 countries.

Patients: Patients with symptomatic heart failure (HF) with a left ventricular ejection fraction of 40% or less and elevated natriuretic peptide.

Intervention: Addition of once-daily 10 mg of dapagliflozin or placebo to guideline-recommended therapy.

Measurements: The primary outcome was worsening HF or cardiovascular death.

Results: Of the 4744 patients randomly assigned in DAPA-HF, a frailty index (FI) was calculable in 4742. In total, 2392 patients (50.4%) were in FI class 1 (FI ≤0.210; not frail), 1606 (33.9%) in FI class 2 (FI 0.211 to 0.310; more frail), and 744 (15.7%) in FI class 3 (FI ≥0.311; most frail). The median follow-up time was 18.2 months. Dapagliflozin reduced the risk for worsening HF or cardiovascular death, regardless of FI class. The differences in event rate per 100 person-years for dapagliflozin versus placebo from lowest to highest FI class were −3.5 (95% CI, −5.7 to −1.2), −3.6 (CI, −6.6 to −0.5), and −7.9 (CI, −13.9 to −1.9). Consistent benefits were observed for other clinical events and health status, but the absolute reductions were generally larger in the most frail patients. Study drug discontinuation and serious adverse events were not more frequent with dapagliflozin than placebo, regardless of FI class.

Limitation: Enrollment criteria precluded the inclusion of very high-risk patients.

Conclusion: Dapagliflozin improved all outcomes examined, regardless of frailty status. However, the absolute reductions were larger in more frail patients.

Primary Funding Source: AstraZeneca.

Ann Intern Med. doi:10.7326/M21-4776 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 26 April 2022.

Frailty is a syndrome of increased vulnerability to endogenous and exogenous stressors due to loss of homeostatic reserves ("intrinsic capacity") across several physiologic systems, leading to poor health outcomes (1, 2). Frailty is related to, but distinct from, both aging and comorbidity. Physiologic reserves ("resilience") decline with age but do so at a different rate in people of the same age. Diseases may cumulatively reduce resilience and act also as stressors on these reserves. Young people can be frail and the consequences of frailty are not specific to a particular disease and may include effects on appetite and cognition, and frailty may lead to falls, disability, dependency, and premature death (1, 3, 4). Health care use in frail patients is several-fold greater than in nonfrail patients (1, 3, 4).

The relationship between frailty and heart failure (HF) is of particular interest because these conditions often coexist, and each increases the likelihood of the other. Thus, patients with HF are up to 6 times more likely to be frail than the general population, and, due to shared pathophysiologic mechanisms, including inflammation, HF may accelerate the development of frailty, and frail persons may be at higher risk for developing HF (4–7). Therefore, frailty can be regarded as both a cause and consequence of HF. Frail patients with HF also have a substantially higher risk for death, hospitalizations, and functional decline than nonfrail patients with HF, and reducing the risk for developing frailty, slowing its progression, and even reversing frailty are now recognized goals in the holistic management of HF (8–14).

The effects of new HF therapies in frail patients are also of interest for several reasons. First, frailty may modify the risk–benefit profile of certain treatments, for example, that of cardiac resynchronization therapy, where the benefit may be less in frail persons (15, 16). Second, due to greater associated comorbidity, polypharmacy, and

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other factors, frail patients may have reduced tolerance to treatments, experience more adverse drug reactions, have poorer adherence, and be more likely to discontinue treatment than nonfrail patients (2, 8). Third, clinicians may be more reluctant to initiate new therapies in such persons due to doubts about the benefit of treatments in frail patients and apprehensions about predisposing them to potential new adverse effects (2, 17–19). In light of these concerns, it is important to evaluate the efficacy and safety of new HF with reduced ejection fraction (HFrEF) treatments according to frailty status.

Therefore, we examined the efficacy and safety of dapagliflozin according to frailty status, using the Rockwood cumulative deficit approach (20, 21), in a post hoc analysis of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, which demonstrated that dapagliflozin, compared with placebo, reduced the risk for worsening HF events and death, and improved symptoms, when added to standard therapy in 4744 patients with HFrEF (22).

METHODS

The DAPA-HF trial was randomized, double blind, and placebo controlled in patients with HFrEF and evaluated the efficacy and safety of 10 mg of dapagliflozin once daily compared with matching placebo, added to standard care. The design, baseline characteristics, and primary results of DAPA-HF are published (22–24). 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 included a diagnosis of HF for at least 2 months, New York Heart Association (NYHA) functional class II to IV, a left ventricular ejection fraction (LVEF) of 40% or less, optimal treatment with pharmacologic and device therapy, and an *N*-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration of 600 pg/mL or more (≥400 pg/mL if hospitalized for HF within the previous 12 months; ≥900 pg/mL if there was atrial fibrillation on the electrocardiogram at enrollment, regardless of history of HF hospitalization). Exclusion criteria included symptomatic hypotension or systolic blood pressure lower than 95 mm Hg; current acute decompensated HF or hospitalization due to decompensated HF fewer than 4 weeks before enrollment; recent (<12 weeks before enrollment) myocardial infarction, angina, stroke, or transient ischemic attack; recent or planned coronary revascularization, valvular repair/replacement, or implantation of a cardiac resynchronization therapy device; previous or expected cardiac transplantation or implantation of a ventricular assistance device; estimated glomerular filtration rate less than 30 mL/min/1.73 m^2 or unstable or rapidly declining renal function; type 1 diabetes; hepatic impairment; any condition outside of the cardiovascular and renal disease area with a life expectancy of fewer than 2 years; active malignancy; and inability to understand and/or comply with study medications, procedures, or follow-up, or any condition that may prevent completion of the study. A complete list of exclusion criteria is provided in the design paper (23). After random assignment, follow-up visits were scheduled at 14, 60, and 120 days and then every 4 months thereafter.

Frailty Index

We constructed a 32-item Frailty Index (FI) using the Rockwood cumulative deficit approach, as described previously (8, 9, 20, 21, 25) and in the **Supplement** (available at Annals.org). Briefly, to create an FI using this approach, at least 30 items are required, and these items should cover a range of body systems and be associated with health and not be a part of normal aging (although deficits should generally increase with age). The items included in the present FI were derived from medical history, vital signs, laboratory data, and the EuroQoL-5 Domain (EQ-5D) questionnaire (quality-of-life measures, including functional status) (**Supplement Table 1**, available at Annals.org). Each patient was assigned a score for each nonmissing item, and the FI score was calculated as the sum of these scores divided with the total number of nonmissing items, with higher scores indicating greater frailty. For example, if a patient had data on 31 of the 32 components, the sum of the score for these 31 components was divided with 31 (rather than 32). Binary variables were scored 0/1 (absent/present), ordinal variables were scored from 0 to 1 (1 indicating the greatest severity), and continuous variables were categorized and scored as 0/1 (normal/abnormal). Patients with 20% or more missing items were excluded. This cutoff is commonly applied in studies using the Rockwood cumulative deficits approach and allows for maximum use of available data without excessive reliance on substitution procedures (8, 9, 26–28). In the present analysis, patients were divided into 3 subgroups: FI ≤0.210 (FI class 1; classified as nonfrail patients, as defined previously) (8, 28), FI 0.211 to 0.310 (FI class 2; that is, more frail), and FI ≥0.311 (FI class 3; that is, most frail).

Trial Outcomes

The primary outcome in DAPA-HF was the composite of worsening HF (HF hospitalization or an urgent visit for worsening HF and administration of intravenous therapy) or cardiovascular death. The secondary outcomes in the trial were HF hospitalization or cardiovascular death (we also examined the components of this composite); total HF hospitalizations (first and repeat) or cardiovascular death; change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score (KCCQ-TSS) (we also examined the change in the overall and clinical summary score [KCCQ-OSS and KCCQ-CSS, respectively]); a composite worsening renal function end point (this end point was not examined in the present analysis due to the small number of these events overall); and death from any cause.

In the present analysis, we also examined the change from baseline to 8 months in the individual physical and social activity items of the KCCQ. Responses to each of the questions (6 in the physical activity domain and 4 in the 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" were considered to be nonresponses.

Finally, we also examined the risk for new-onset type 2 diabetes, defined as a glycated hemoglobin A_{1c} level of 6.5% or more, measured in the central laboratory, on 2 consecutive follow-up visits or a clinical diagnosis of diabetes outside of the trial leading to the initiation of a glucose-lowering agent; patients who had a prior diagnosis of type 2 diabetes or a hemoglobin A_{1c} level of 6.5% or more at both the enrollment and randomization visit were excluded from this analysis (29).

Prespecified safety analyses included serious adverse events, adverse events leading to discontinuation of trial treatment, and adverse events of interest, including volume depletion, renal adverse events, bone fracture, amputation, major hypoglycemia, and diabetic ketoacidosis. Safety analyses were only performed in patients who had enrolled and received at least 1 dose of either dapagliflozin or placebo; a total of 8 randomly assigned patients were excluded from the safety analysis.

Statistical Analysis

Baseline characteristics were summarized as frequencies with percentages, means with SDs, or medians with interquartile ranges. Time-to-event data, regardless of treatment allocation, were evaluated using the Kaplan–Meier estimator (all-cause death), the Aalen–Johansen estimator (all outcomes except all-cause death), and Cox proportional hazards models, stratified according to diabetes mellitus status, with a history of HF hospitalization and treatment-group assignment as fixed-effect factors to calculate hazard ratios (HRs) with 95% CIs. In addition, HRs, stratified according to diabetes mellitus status, and adjusted for a history of HF hospitalization, treatment-group assignment, age, sex, geographic region, log of NT-proBNP, HF cause, HF duration, LVEF, and NYHA functional class were reported (variables that were part of the FI were not adjusted for because the categorization of FI into the 3 classes was conditioned on these variables). The models for noncardiovascular and all-cause death did not include adjustment for a history of HF hospitalization.

To compare the effects of dapagliflozin versus placebo, time-to-event data were evaluated with Cox proportional hazards models, stratified according to diabetes mellitus status, with a history of HF hospitalization and treatment-group assignment as fixed-effect factors (the model for all-cause and noncardiovascular death and new-onset type 2 diabetes was not adjusted for a history of HF hospitalization). The effect of dapagliflozin was also examined according to continuous FI as a fractional polynomial. Total, including recurrent, events were evaluated with semiparametric proportional-rates models (30). The difference between treatment groups in the change in KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS, as well as the individual physical and social activity items of the KCCQ, from baseline to 8 months was analyzed using mixed-effect models for repeated measurements, adjusted for baseline value, visit (months 4 and 8), randomized treatment, and interaction of treatment and visit. The least-squares mean differences with 95% CI between treatment groups were reported. Responder analyses examining proportions of patients with a deterioration (decrease of ≥5 points) and a clinically important improvement (increase of ≥5 points) in KCCQ-TSS, KCCQ-CSS, and KCCQ-OSS at 8 months were performed (31). The 5-point threshold was prespecified and chosen because this change is clinically meaningful and is associated with adverse outcomes, including HF hospitalization and death (32).

All analyses were conducted using SAS version 9.4 (SAS Institute) and STATA version 17.0.

Role of the Funding Source

Representatives of AstraZeneca were involved with the executive committee in the design and conduct of the study. Site monitoring and data management were carried out by AstraZeneca. Data analysis was carried out at Glasgow University. Interpretation of the data and preparation of the manuscript were carried out by the executive committee, including representatives of AstraZeneca. Review and approval of the of the manuscript, as well as the decision to submit the manuscript for publication, were taken by all authors, including representatives of AstraZeneca. AstraZeneca had no veto of the right to publish or control over which journal to submit.

RESULTS

Patient Characteristics

Of the 4744 patients randomly assigned in DAPA-HF, FI was calculable for 4742 patients, and 4339 patients did not have missing data for any of the components of the FI. The number of patients with missing data for the components of the FI, and the components of the FI with missing data, are shown in **Supplement Tables 2** and **3** (available at Annals.org). The distribution of FI is shown in **Supplement Figure 1** (available at Annals.org). Based on the histogram, quantile–quantile plot, and Anderson–Darling test for normality, FI was not normally distributed. Mean FI was 0.216 (SD, 0.091) and median FI was 0.210 (interquartile range, 0.153 to 0.281; total range, 0 to 0.531), with a higher FI indicating greater frailty. In total, 2392 patients (50.4%) had class 1 frailty (FI ≤0.210; that is, not frail), 1606 (33.9%) were in class 2 (FI 0.211 to 0.310; that is, more frail), and 744 (15.7%) had class 3 frailty (FI ≥0.311; that is, most frail).

Baseline characteristics according to FI class are presented in **Table 1**. Compared with patients with lower FI, those with higher FI (worse frailty) were older, more often White (and less often Asian), and more likely to have cardiovascular and noncardiovascular comorbidities. They also had higher blood pressure (both systolic and diastolic), heart rate, body mass index, and NT-proBNP, but lower estimated glomerular filtration rate. Patients with higher FI were more likely to have an ischemic cause, longer duration of HF, and higher LVEF, but worse NYHA functional class, KCCQ scores, and EuroQoL visual analog score than those with lower FI. Regarding background HF therapy, patients with higher FI were less often treated with a renin-angiotensin system blocker/angiotensin receptor-neprilysin inhibitor and mineralocorticoid-receptor antagonist and were more likely to have a defibrillating device.

Baseline characteristics according to treatment assignment for each FI class are shown in **Supplement Tables 4** to

Table 1. Baseline Characteristics of the Study Population According to FI

Characteristic	FI ≤0.210 (Not Frail) (*n* = 2392)	FI 0.211–0.310 (More Frail) (*n* = 1606)	FI ≥0.311 (Most Frail) (*n* = 744)
Mean age (SD), *y*	63.6 (11.6)	68.8 (9.4)	69.8 (9.0)
Sex, *n (%)*			
Female	548 (22.9)	381 (23.7)	180 (24.2)
Male	1844 (77.1)	1225 (76.3)	564 (75.8)
Race, *n (%)*			
Asian	769 (32.1)	265 (16.5)	82 (11.0)
Black	100 (4.2)	82 (5.1)	44 (5.9)
Other	39 (1.6)	22 (1.4)	8 (1.1)
White	1484 (62.0)	1237 (77.0)	610 (82.0)
Geographic region, *n (%)*			
Asia/Pacific	758 (31.7)	260 (16.2)	78 (10.5)
Europe	930 (38.9)	827 (51.5)	397 (53.4)
North America	255 (10.7)	239 (14.9)	181 (24.3)
South America	449 (18.8)	280 (17.4)	88 (11.8)
Physiologic measures			
Mean systolic blood pressure (SD), *mm Hg*	117.8 (14.1)	124.5 (16.7)	128.9 (18.7)
Mean diastolic blood pressure (SD), *mm Hg*	72.9 (9.7)	74.1 (11.0)	74.2 (11.4)
Mean heart rate (SD), *beats/min*	72.0 (11.7)	71.1 (12.0)	70.8 (11.1)
Mean BMI (SD), *kg/m^2*	26.9 (5.7)	28.9 (5.8)	30.6 (6.1)
Mean creatinine level (SD)			
µmol/L	94.7 (23.4)	109.8 (30.8)	124.2 (36.4)
mg/dL	1.1 (0.3)	1.2 (0.3)	1.4 (0.4)
Median glycated hemoglobin level (IQR), %	5.9 (5.6–6.4)	6.2 (5.8–7.0)	6.7 (6.0–7.7)
Mean eGFR (SD), *mL/min/1.73 m^2*	73.0 (18.4)	60.9 (17.4)	53.0 (16.6)
eGFR, *n (%)*			
<60 mL/min/1.73 m^2	568 (23.7)	831 (51.7)	527 (70.8)
≥60 mL/min/1.73 m^2	1824 (76.3)	775 (48.3)	217 (29.2)
Median NT-proBNP level (IQR), *pg/mL*			
Atrial fibrillation/flutter on enrollment ECG	1796 (1217–2911)	2085 (1293–3265)	2267 (1376–3685)
No atrial fibrillation/flutter on enrollment ECG	1212 (735–2197)	1316 (789–2561)	1578 (921–3037)
Mean sodium level (SD), *mmol/L*	139.7 (2.9)	139.6 (3.2)	139.2 (3.7)
Mean potassium level (SD), *mmol/L*	4.5 (0.5)	4.5 (0.5)	4.5 (0.6)
Mean hemoglobin level (SD), *g/L*	138.0 (14.9)	134.2 (16.6)	130.5 (17.6)
Mean alanine aminotransferase level (SD), *U/L*	18 (14–25)	17 (13–24)	17 (12–24)
Mean bilirubin level (SD)			
µmol/L	10.0 (7.0–14.0)	10.0 (7.0–14.-0)	10 (6.8–14.0)
mg/dL	0.58 (0.41–0.82)	0.58 (0.41–0.82)	0.58 (0.40–0.82)
Ischemic cause of HF, *n (%)*	959 (40.1)	1120 (69.7)	593 (79.7)
Duration of HF, *n (%)*			
0–3 mo	87 (3.6)	50 (3.1)	13 (1.7)
3–6 mo	227 (9.5)	125 (7.8)	41 (5.5)
6–12 mo	314 (13.1)	178 (11.1)	63 (8.5)
1–2 y	375 (15.7)	221 (13.8)	90 (12.1)
2–5 y	553 (23.1)	389 (24.2)	162 (21.8)
>5 y	836 (34.9)	643 (40.0)	375 (50.4)
Mean LVEF (SD), %	30.2 (7.0)	31.9 (6.5)	32.2 (6.3)
NYHA class, *n (%)*			
II	1761 (73.6)	1037 (64.6)	403 (54.2)
III/IV	631 (26.4)	569 (35.4)	341 (45.8)
Mean KCCQ score (SD)			
KCCQ-TSS	78.9 (19.3)	70.7 (21.9)	63.3 (23.9)
KCCQ-CSS	76.6 (18.3)	68.1 (20.8)	60.2 (22.5)
KCCQ-OSS	73.4 (18.6)	65.4 (20.5)	57.7 (22.2)
Mean EQ-VAS score (SD)	71.5 (16.1)	66.3 (17.3)	61.1 (18.7)
Mean MAGGIC risk score (SD)	20.2 (5.7)	22.4 (5.7)	24.1 (5.5)

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Table 1–Continued

Characteristic	FI ≤0.210 (Not Frail) (*n* = 2392)	FI 0.211–0.310 (More Frail) (*n* = 1606)	FI ≥0.311 (Most Frail) (*n* = 744)
Medical history, *n* (%)			
Hospitalization for HF	1100 (46.0)	788 (49.1)	361 (48.5)
Previous MI	677 (28.3)	895 (55.7)	519 (69.8)
PCI/CABG	610 (25.5)	893 (55.6)	536 (72.0)
Angina	255 (10.7)	491 (30.6)	366 (49.2)
Peripheral artery disease	61 (2.6)	105 (6.5)	158 (21.2)
Atrial fibrillation/flutter	736 (30.8)	744 (46.3)	405 (54.4)
Type 2 diabetes	694 (29.0)	882 (54.9)	563 (75.7)
Hypertension	1394 (58.3)	1416 (88.2)	712 (95.7)
Chronic obstructive pulmonary disease	157 (6.6)	237 (14.8)	190 (25.5)
Gout	131 (5.5)	206 (12.8)	151 (20.3)
Stroke	113 (4.7)	194 (12.1)	159 (21.4)
Cancer	66 (2.8)	76 (4.7)	66 (8.9)
Syncope	72 (3.0)	82 (5.1)	77 (10.3)
Sleep apnea	57 (2.4)	88 (5.5)	125 (16.8)
Neuropathy	23 (1.0)	82 (5.1)	132 (17.7)
Osteoporosis	35 (1.5)	58 (3.6)	47 (6.3)
Dyslipidemia	1024 (42.8)	1185 (73.8)	660 (88.7)
Treatment, *n* (%)			
ACEI/ARB	2008 (83.9)	1339 (83.4)	603 (81.0)
ARNI	265 (11.1)	162 (10.1)	81 (10.9)
ACEI/ARB/ARNI	2266 (94.7)	1495 (93.1)	679 (91.3)
β-Blocker	2301 (96.2)	1547 (96.3)	708 (95.2)
Mineralocorticoid-receptor antagonist	1800 (75.3)	1100 (68.5)	470 (63.2)
Digoxin	472 (19.7)	303 (18.9)	112 (15.1)
Amiodarone	259 (10.8)	206 (12.8)	104 (14.0)
Oral anticoagulant*	861 (36.0)	731 (45.5)	377 (50.7)
Antiplatelet†	1157 (48.4)	961 (59.8)	472 (63.4)
CRT-P/CRT-D	153 (6.4)	130 (8.1)	71 (9.5)
ICD/CRT-D	564 (23.6)	426 (26.5)	251 (33.7)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; BMI = body mass index; CABG = coronary artery bypass graft surgery; CRT-D = cardiac resynchronization therapy–defibrillator; CRT-P = cardiac resynchronization therapy–pacemaker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EQ-VAS = EuroQoL visual analogue scale; FI = frailty index; HF = heart failure; ICD = implantable cardioverter-defibrillator; IQR = interquartile range; 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; MAGGIC = The Meta-analysis Global Group in Chronic Heart Failure; MI = myocardial infarction; NT-proBNP = *N*-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

* Vitamin K antagonists (warfarin) and "direct" oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban).

† Aspirin, adenosine diphosphate receptor inhibitors (clopidogrel, ticagrelor, prasugrel), and adenosine reuptake inhibitors (dipyridamole).

6 (available at Annals.org). Overall, characteristics were balanced between the dapagliflozin and placebo group in each FI class.

Outcomes According to Frailty Index

The median follow-up time was 18.2 months (25th to 75th percentile, 14.2 to 21.5 months). The cumulative incidence and HRs for time-to-event outcomes according to FI class are shown in Supplement Figure 2 and Supplement Table 7 (both available at Annals.org), respectively.

Compared with patients in FI class 1, those in FI class 3 had a higher risk for worsening HF or cardiovascular death; HF hospitalization or cardiovascular death (and each of the components); noncardiovascular death; and all-cause death, even after adjustment for prognostic variables (Supplement Table 7). Compared with people in FI class 1, patients in FI class 2 also had a higher risk for these outcomes (except for HF hospitalization). After adjustment for known prognostic variables, there was no statistically significant difference between these 2 FI classes, although there was a trend toward a higher risk for adverse outcomes in patients with FI class 2 compared with those in FI class 1.

When examining FI as a continuous variable, a 0.1-unit increase in FI was associated with a higher risk for adverse outcomes (Supplement Table 7).

Effects of Dapagliflozin on Clinical Outcomes According to Frailty Index

Primary Composite Outcome

Dapagliflozin, compared with placebo, reduced the risk for worsening HF or cardiovascular death across FI classes: the HRs from lowest to highest class were 0.72 (95% CI, 0.59 to 0.89), 0.77 (CI, 0.62 to 0.97), and 0.71 (CI, 0.54 to 0.93), respectively (Table 2). The number of patients needed to treat to prevent 1 event per 100 person-years were 31, 25, and 15 in the lowest to highest class, respectively. The effect of dapagliflozin was also consistent across the spectrum of continuous FI (Figure 1).

Secondary Outcomes

The effect of dapagliflozin was consistent across FI classes for HF hospitalization or cardiovascular death, HF hospitalization, cardiovascular death, all-cause death, and recurrent HF hospitalization or cardiovascular death,

Table 2. Effects of Dapagliflozin Compared With Placebo on Clinical Events According to FI

Outcome	FI ≤0.210 (Not Frail) (*n* = 2392)		FI 0.211-0.310 (More Frail) (*n* = 1606)		FI ≥0.311 (Most Frail) (*n* = 744)	
	Placebo (*n* = 1206)	Dapagliflozin (*n* = 1186)	Placebo (*n* = 806)	Dapagliflozin (*n* = 800)	Placebo (*n* = 358)	Dapagliflozin (*n* = 386)
Worsening HF event or cardiovascular death						
Patients, *n (%)*	207 (17.2)	152 (12.8)	176 (21.8)	138 (17.3)	119 (33.2)	96 (24.9)
Event rate per 100 person-years (95% CI)	12.6 (11.0 to 14.4)	9.1 (7.8 to 10.7)	15.7 (13.5 to 18.2)	12.1 (10.2 to 14.3)	26.3 (22.0 to 31.5)	18.4 (15.0 to 22.4)
Difference in event rate per 100 person-years (95% CI)	−3.5 (−5.7 to −1.2)		−3.6 (−6.6 to −0.5)		−7.9 (−13.9 to −1.9)	
Hazard ratio (95% CI)*	0.72 (0.59 to 0.89)		0.77 (0.62 to 0.97)		0.71 (0.54 to 0.93)	
HF hospitalization or cardiovascular death						
Patients, *n (%)*	206 (17.1)	149 (12.6)	172 (21.3)	137 (17.1)	117 (32.7)	96 (24.9)
Event rate per 100 person-years (95% CI)	12.5 (10.9 to 14.3)	8.9 (7.6 to 10.4)	15.2 (13.1 to 17.7)	12.0 (10.1 to 14.2)	25.8 (21.5 to 30.9)	18.4 (15.0 to 22.4)
Difference in event rate per 100 person-years (95% CI)	−3.6 (−5.8 to −1.4)		−3.2 (−6.3 to −0.2)		−7.4 (−13.4 to −1.5)	
Hazard ratio (95% CI)*	0.71 (0.58 to 0.88)		0.79 (0.63 to 0.99)		0.72 (0.55 to 0.94)	
HF hospitalization						
Patients, *n (%)*	135 (11.2)	87 (7.3)	99 (12.3)	79 (9.9)	84 (23.5)	65 (16.8)
Event rate per 100 person-years (95% CI)	8.2 (6.9 to 9.7)	5.2 (4.2 to 6.4)	8.8 (7.2 to 10.7)	6.9 (5.5 to 8.6)	18.5 (15.0 to 22.9)	12.4 (9.7 to 15.9)
Difference in event rate per 100 person-years (95% CI)	−3.0 (−4.7 to −1.2)		−1.8 (−4.1 to 0.5)		−6.1 (−11.1 to −1.1)	
Hazard ratio (95% CI)*	0.63 (0.48 to 0.83)		0.79 (0.59 to 1.07)		0.68 (0.49 to 0.94)	
Cardiovascular death						
Patients, *n (%)*	115 (9.5)	85 (7.2)	102 (12.7)	84 (10.5)	56 (15.6)	58 (15.0)
Event rate per 100 person-years (95% CI)	6.6 (5.5 to 8.0)	4.9 (4.0 to 6.1)	8.5 (7.0 to 10.3)	7.0 (5.7 to 8.7)	10.9 (8.4 to 14.1)	10.4 (8.1 to 13.5)
Difference in event rate per 100 person-years (95% CI)	−1.7 (−3.3 to −0.1)		−1.5 (−3.7 to 0.7)		−0.5 (−4.4 to 3.5)	
Hazard ratio (95% CI)*	0.74 (0.56 to 0.98)		0.83 (0.62 to 1.10)		0.97 (0.67 to 1.40)	
Noncardiovascular death						
Patients, *n (%)*	20 (1.7)	14 (1.2)	17 (2.1)	20 (2.5)	19 (5.3)	15 (3.9)
Event rate per 100 person-years (95% CI)	1.2 (0.7 to 1.8)	0.8 (0.5 to 1.4)	1.4 (0.9 to 2.3)	1.7 (1.1 to 2.6)	3.7 (1.4 to 5.8)	2.7 (1.6 to 4.5)
Difference in event rate per 100 person-years (95% CI)	−0.3 (−1.0 to 0.3)		0.3 (−0.7 to 1.2)		−1.0 (−3.1 to 1.2)	
Hazard ratio (95% CI)*	0.70 (0.35 to 1.38)		1.18 (0.62 to 2.24)		0.72 (0.37 to 1.43)	
All-cause death						
Patients, *n (%)*	135 (11.2)	99 (8.3)	119 (14.8)	104 (13.0)	75 (20.9)	73 (18.9)
Event rate per 100 person-years (95% CI)	7.8 (6.6 to 9.2)	5.7 (4.7 to 7.0)	9.9 (8.3 to 11.8)	8.7 (7.1 to 10.5)	14.6 (11.6 to 18.3)	13.1 (10.4 to 16.5)
Difference in event rate per 100 person-years (95% CI)	−2.1 (−3.8 to −0.3)		−1.2 (−3.7 to 1.2)		−1.4 (−5.9 to 3.0)	
Hazard ratio (95% CI)*	0.73 (0.57 to 0.95)		0.88 (0.67 to 1.14)		0.91 (0.66 to 1.26)	
Recurrent HF hospitalization or cardiovascular death						
Events, *n*	317	212	238	196	187	159
Rate ratio (95% CI)†	0.67 (0.53 to 0.85)		0.83 (0.65 to 1.06)		0.79 (0.59 to 1.06)	
New-onset type 2 diabetes						
Patients, *n/N (%)*	47/854 (5.5)	30/844 (3.6)	36/367 (9.8)	24/357 (6.7)	10/85 (11.8)	10/96 (10.4)
Event rate per 100 person-years (95% CI)	3.8 (2.9 to 5.1)	2.5 (1.7 to 3.5)	6.9 (5.0 to 9.6)	4.6 (3.1 to 6.8)	8.6 (4.6 to 15.9)	7.4 (4.0 to 13.7)
Difference in event rate per 100 person-years (95% CI)	−1.4 (−2.8 to 0.0)		−2.3 (−5.2 to 0.6)		−1.2 (−8.2 to 5.8)	
Hazard ratio (95% CI)*	0.64 (0.41 to 1.02)		0.67 (0.40 to 1.12)		0.87 (0.36 to 2.10)	

FI = Frailty Index; HF = heart failure.

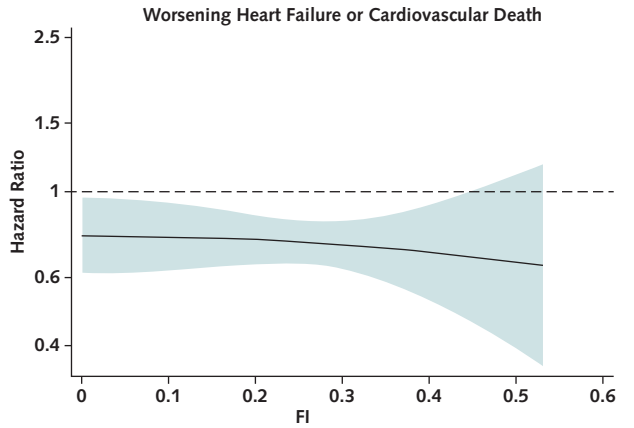
* Cox proportional hazards models stratified according to diabetes mellitus status and adjusted for a history of HF hospitalization. The model for all-cause and noncardiovascular death and new-onset type 2 diabetes was not adjusted for a history of HF hospitalization.

† Semiparametric proportional-rates models stratified according to diabetes mellitus status and adjusted for a history of HF hospitalization.

although the absolute reductions were generally larger in the most frail patients (Table 2).

At baseline, 4441 patients (93.7%) had available KCCQ data. At 8 months, 3953 patients (83.4% of the study population; 88.1% of the study population alive) had available KCCQ data and 789 did not (257 due to death, 532 due to other reasons than death). The effect of dapagliflozin on the mean change in KCCQ scores seemed to be modified by FI class; larger increases (improvements) were seen with dapagliflozin, compared with placebo, among patients with a higher FI, that is, greater frailty (Table 3). Missing data on individual physical and social activity items of the KCCQ at baseline and 8 months are shown in Supplement Table 8 (available at

Figure 1. Effect of dapagliflozin according to continuous FI.



Fractional polynomial analysis showing the effect of dapagliflozin on the risk for worsening heart failure or cardiovascular death across the range of FI. Higher FI indicates greater frailty. Dashed line represents a hazard ratio of 1. FI = Frailty Index.

Annals.org). Dapagliflozin, compared with placebo, increased (improved) the score of each of the physical and social activity limitation items of the KCCQ from baseline to 8 months. For most items, there was a trend toward a greater benefit with dapagliflozin in patients with higher FI class, that is, worse frailty (**Figure 2**; **Supplement Table 9** [available at Annals.org]).

The proportion of patients with an increase in KCCQ scores of 5 or more points was greater with dapagliflozin, compared with placebo across FI classes. Similarly, the proportion of patients with a decrease in KCCQ scores of 5 or more points was smaller in those treated with dapagliflozin, compared with placebo regardless of FI class (**Table 3**).

The effect of dapagliflozin on diabetes prevention was consistent across FI classes (**Table 2**).

We also examined the effects of dapagliflozin compared with placebo on clinical events according to FI among patients with no missing data for any of the components of the FI. The point estimates for the treatment effect were similar to those of the main analysis (**Supplement Table 10**, available at Annals.org).

Safety Analyses

The proportions of patients who discontinued trial treatment or had adverse events increased with increasing frailty (**Supplement Table 11**, available at Annals.org). However, the between-treatment (dapagliflozin vs. placebo) differences were similar across FI classes (**Supplement Table 12**, available at Annals.org).

DISCUSSION

In DAPA-HF, we found that approximately 50% of patients were frail, and greater frailty was associated with more impairment in health status and worse clinical outcomes, including HF hospitalization and death. Dapagliflozin, compared with placebo, substantially reduced the risk for worsening HF events, cardiovascular death, and all-cause death, and improved symptoms, physical function, and quality of life, regardless of frailty class. The absolute reductions in clinical events and improvements in health status were generally larger in the most frail patients.

The prevalence of frailty in DAPA-HF, assessed using the Rockwood cumulative deficits approach, was broadly consistent with that in the PARADIGM-HF (Prospective comparison of ARNI with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure) and the ATMOSPHERE (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure) trials, taking into account differences between the trials (8). However, because the exclusion criteria in DAPA-HF and other clinical HFrEF trials precluded the enrollment of very high-risk and frail patients (for example, those with unstable or severe HF and renal function, hepatic impairment, active malignancy, impaired cognitive function, and conditions likely to limit life expectancy), the FI and the prevalence of frailty are likely to be higher in "real-world" HFrEF populations. Nevertheless, patients with HF have a consistently higher FI compared with persons without HF, despite a similar age, suggesting that frailty is substantially more common in patients with HF and that frailty is not confined to the very elderly (**Supplement**).

In keeping with previous studies (8–12), we found a graded relationship between FI, regardless of how it was measured, and adverse outcomes, with a substantially higher risk with increasing FI (indicating greater frailty). This finding highlights why prevention, treatment, and, if possible, reversal of frailty have become important goals in medicine generally and HF specifically (2, 13, 14). Although targeted interdisciplinary and multifaceted treatment programs, including nutritional, exercise, and other lifestyle interventions, have been investigated in HF, conventional therapy may also play an important role in the management of frailty (2, 33). Frail patients lack the resilience to recover after exposure to internal and external stressors. One of the most important external stressors is hospitalization and worsening of HF, and consequent hospital admission likely creates a repetitive pattern of clinical setback leading to progressive frailty in patients with HFrEF. Symptom control and maintenance of physical activity are believed to be key in preventing such a vicious cycle.

Paradoxically, however, concern has been raised about whether the benefit-to-risk balance of pharmacologic treatments remains favorable in frail patients and therapies may be underused (and even discontinued) in such persons (34). These concerns were highlighted in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) trial, in which the effects of an intensive glucose- and blood pressure-lowering regimen on major macrovascular and microvascular events in patients with type 2 diabetes were modified by frailty status, with an attenuation of benefit in frail patients (35). However, other studies have shown that frailty does not alter the effect of therapy. For example, in HYVET (Hypertension in the Very Elderly Trial), there was no evidence of an interaction between the effect of treatment of hypertension and frailty in older hypertensive adults aged 80 years and older (36). Given these conflicting

Table 3. Effects of Dapagliflozin Compared With Placebo on KCCQ Scores According to FI

Outcome	FI ≤0.210 (Not Frail) (*n* = 2392)		FI 0.211–0.310 (More Frail) (*n* = 1606)		FI ≥0.311 (Most Frail) (*n* = 744)	
	Placebo (*n* = 1206)	Dapagliflozin (*n* = 1186)	Placebo (*n* = 806)	Dapagliflozin (*n* = 800)	Placebo (*n* = 358)	Dapagliflozin (*n* = 386)
KCCQ-TSS						
Change in KCCQ-TSS score at 8 mo (95% CI)*	3.0 (2.0 to 3.9)	4.1 (3.2 to 5.1)	3.2 (1.9 to 4.5)	8.1 (6.8 to 9.4)	4.7 (2.5 to 6.9)	8.0 (5.9 to 10.0)
Placebo-corrected change in KCCQ-TSS at 8 mo (95% CI)*	1.2 (−0.1 to 2.5)		4.9 (3.1 to 6.7)		3.2 (0.2 to 6.3)	
≥5-point improvement in KCCQ-TSS at 8 mo						
Proportion of patients	52.3	58.6	50.2	59.9	48.3	53.7
Absolute difference in proportion (95% CI)	6.3 (2.3 to 10.3)		9.6 (4.8 to 14.4)		5.3 (−1.9 to 12.5)	
≥5-point decrease in KCCQ-TSS at 8 mo						
Proportion of patients	31.0	25.6	33.5	23.0	37.5	29.3
Absolute difference in proportion (95% CI)	−5.4 (−9.0 to −1.8)		−10.5 (−14.9 to −6.1)		−8.2 (−14.9 to −1.4)	
KCCQ-CSS						
Change in KCCQ-CSS score at 8 mo (95% CI)*	2.6 (1.8 to 3.5)	3.7 (2.9 to 4.6)	2.9 (1.7 to 4.0)	6.9 (5.7 to 8.1)	3.7 (1.7 to 5.8)	7.9 (6.0 to 9.9)
Placebo-corrected change in KCCQ-CSS at 8 mo (95% CI)*	1.1 (−0.2 to 2.3)		4.0 (2.3 to 5.7)		4.2 (1.4 to 7.1)	
≥5-point improvement in KCCQ-CSS at 8 mo						
Proportion of patients	45.8	52.4	44.1	55.4	43.1	51.9
Absolute difference in proportion (95% CI)	6.6 (2.6 to 10.6)		11.3 (6.5 to 16.2)		8.8 (1.6 to 15.9)	
≥5-point decrease in KCCQ-CSS at 8 mo						
Proportion of patients	29.6	25.4	32.0	22.9	35.7	29.2
Absolute difference in proportion (95% CI)	−4.2 (−7.8 to −0.6)		−9.1 (−13.5 to −4.8)		−6.5 (−13.2 to 0.2)	
KCCQ-OSS						
Change in KCCQ-OSS score at 8 mo (95% CI)*	3.5 (2.6 to 4.4)	4.7 (3.9 to 5.6)	3.5 (2.4 to 4.7)	7.1 (5.9 to 8.3)	5.2 (3.1 to 7.2)	8.5 (6.5 to 10.4)
Placebo-corrected change in KCCQ-OSS at 8 mo (95% CI)*	1.2 (−0.02 to 2.5)		3.6 (1.9 to 5.2)		3.3 (0.5 to 6.1)	
≥5-point improvement in KCCQ-OSS at 8 mo						
Proportion of patients	47.2	53.4	45.9	54.1	46.2	52.0
Absolute difference in proportion (95% CI)	6.2 (2.2 to 10.2)		8.2 (3.3 to 13.1)		6.0 (−1.2 to 13.2)	
≥5-point decrease in KCCQ-OSS at 8 mo						
Proportion of patients	29.6	23.3	31.7	24.1	33.3	29.1
Absolute difference in proportion (95% CI)	−6.3 (−10.0 to −2.8)		−7.6 (−12.0 to −3.3)		−4.2 (−10.9 to 2.4)	

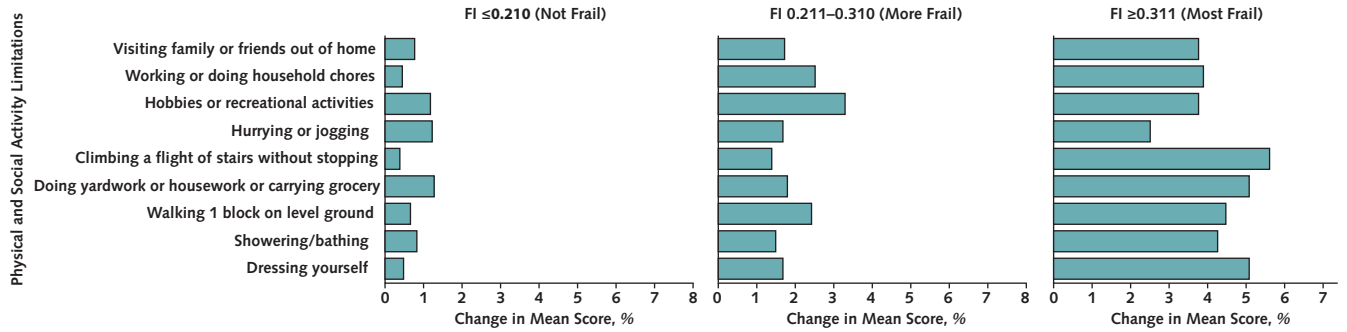
FI = Frailty Index; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire overall summary score; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire total symptom score.
* Mixed-effect models for repeated measurements adjusted for baseline value, visit (months 4 and 8), randomized treatment, and interaction of treatment and visit.

findings and the common reluctance of clinicians to introduce medications to patients perceived to be frail (2, 17–19), it is important to investigate the efficacy and safety of new treatments in patients with HFrEF according to frailty status, although this has only been done once before in patients with HFrEF. The effect of sacubitril–valsartan was consistent, regardless of frailty class, in PARADIGM-HF (8). In line with this, we found that the beneficial effects of dapagliflozin on clinical outcomes in DAPA-HF were independent of baseline frailty class. Specifically, dapagliflozin, compared with placebo, significantly reduced the risk for worsening HF or cardiovascular death to a similar extent across frailty classes, and the benefits of dapagliflozin on HF hospitalization (both first and recurrent), cardiovascular death, and all-cause death were also consistent, regardless of frailty class.

A fundamental goal of the management of patients with HFrEF is to reduce symptoms and improve physical function and quality of life (13). Improving HF-related health status may be as important as extending life, particularly in the most frail patients who have a greater symptom burden, more physical limitations, and worse quality of life than nonfrail patients (8, 9, 12). Moreover, controlling symptoms and maintaining function may help prevent frailty and progression of existing frailty. In the present study, the effect of dapagliflozin on the mean change in KCCQ scores from baseline to 8 months seemed to be modified by FI class. In patients with FI class 1, there was a modest increase in KCCQ scores with dapagliflozin, compared with placebo, whereas the increase in patients with higher FI classes was substantially larger with dapagliflozin relative to placebo. Similarly, the improvement in individual physical and social activity items of the KCCQ with dapagliflozin also seemed more pronounced in patients with higher FI classes, suggesting that more frail patients may derive greater benefit in relation to symptom burden, physical function, and quality of life.

The substantial and clinically meaningful effects of dapagliflozin on "hard" clinical outcomes as well as symptoms, physical function, and quality of life, regardless of frailty status, are important to highlight and deserve emphasis considering the common reluctance of clinicians to introduce medications to patients perceived to be frail and the potential role of hospital admission in precipitating and accelerating frailty. Importantly, the benefit–risk balance is even more favorable with dapagliflozin in more frail

Figure 2. Mean change in individual physical and social activity items from baseline to 8 months with dapagliflozin versus placebo according to FI.



Responses to the questions were scaled to 0 to 100, with higher score indicating a lesser degree of limitation. Responses of "limited for other reasons" or "did not do the activity" were not allocated a score. The question about "Intimate relationships with loved ones" was excluded as only 64% of patients with baseline data from the Kansas City Cardiomyopathy Questionnaire responded to this question. Higher FI indicates greater frailty. FI = Frailty Index.

persons, given a greater absolute risk reduction in clinical events, and larger improvements in health status in this group.

Despite concerns that frail patients (due to a greater comorbidity burden, polypharmacy, and reduced tolerance to treatments) are more likely to discontinue treatment and have more adverse drug reactions than nonfrail patients (2, 8), data on safety and tolerability in DAPA-HF were reassuring. Not surprisingly, we found that frail patients overall were more likely to discontinue study treatment (including placebo) and more frequently had serious adverse events, although neither was common. Importantly, study drug discontinuation and serious adverse events were not more frequently reported in the dapagliflozin group than in the placebo group in any of the frailty classes. These data underline the safety and tolerability of dapagliflozin in patients with HFrEF, regardless of the degree of frailty.

Like any other clinical HFrEF trial investigating the efficacy and safety of a novel therapy, DAPA-HF had prespecified eligibility criteria for enrollment in the trial. This is important when interpreting the findings from the present study. First, patients enrolled in clinical HFrEF trials are not fully representative of the general HFrEF population (for example, the use of evidence-based, disease-modifying therapy is greater in clinical trials), which may affect the generalizability of our results to a "real-world" HFrEF population. Second, the most frail patients with HF are excluded from clinical HFrEF trials or only comprise a small proportion of the trial population, and this may affect the generalizability of our results to the very frail patients. Although the effect of dapagliflozin on the risk for the primary outcome was consistent across the range of FI (0 to 0.531) and a larger absolute risk reduction was observed in the most frail patients, it is possible that the beneficial effects of this therapy may be attenuated in very frail patients. Interestingly, in a population-based observational study of 6360 patients diagnosed with HF in the primary care sector in England, only 1.4% of the participants had an FI higher than 0.360 (11).

This study has some limitations. As discussed, the prespecified inclusion and exclusion criteria precluded the enrollment of very low-risk patients (for example, NYHA class I and NT-proBNP <400 pg/mL) and high-risk patients, which may affect the generalizability of our results. Although one of the main advantages of the Rockwood cumulative deficit approach, compared with many other frailty scores, is the incorporation of health deficits across several domains, including cognition, activities of daily living, social relations or support, comorbid diseases, and abnormal laboratory results, this approach may also be limited by, perhaps, simplifying a very complex syndrome by summarizing frailty into a single number. In this regard, it would have been interesting to directly compare this approach with other types of frailty scores in DAPA-HF. However, due to the lack of tests of muscle strength and functional capacity in DAPA-HF, we could not test other types of frailty scores. Although baseline characteristics were balanced between the dapagliflozin and placebo group in each FI class, it is conceivable that unmeasured confounders were not balanced between treatment groups. Finally, data on echocardiographic measures were not available in the present study.

In DAPA-HF, dapagliflozin, compared with placebo, reduced the risk for worsening HF events, cardiovascular death, and all-cause death, and improved symptoms, physical function, and quality of life, regardless of the level of frailty. However, the absolute reductions in clinical events and improvements in health status were larger in more frail patients. These findings are important considering the common reluctance of clinicians to introduce medications to patients that are perceived to be frail.

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Grant Support: The DAPA-HF trial was funded by AstraZeneca. Dr. McMurray was supported by British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-4776.

Data Sharing Statement: Trial data will be made available by the sponsor, AstraZeneca, in accordance with their data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Author contributions are available at Annals.org.

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