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RESEARCH ARTICL

Efficacy and safety of sodium–glucose co-transporter 2 inhibition according to left ventricular ejection fraction in DAPA-HF

Pooja Dewan[1], Scott D. Solomon[2], Pardeep S. Jhund[1], Silvio E. Inzucchi[3], Lars Køber[4], Mikhail N. Kosiborod[5], Felipe A. Martinez[6], Piotr Ponikowski[7], David L. DeMets[8], Marc S. Sabatine[9], Olof Bengtsson[10], Mikaela Sjöstrand[10], Anna Maria Langkilde[10], Inder S. Anand[11], Jan Bělohlávek[12], Vijay K. Chopra[13], Andrej Dukát[14], Masafumi Kitakaze[15], Béla Merkely[16], Eileen O'Meara[17], Morten Schou[18], Pham Nguyen Vinh[19], and John J.V. McMurray[1]*, DAPA-HF Investigators and Committees

[1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [2]Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; [3]Section of Endocrinology, Yale University School of Medicine, New Haven, CT, USA; [4]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [5]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO, USA; [6]National University of Cordoba, Cordoba, Argentina; [7]Wroclaw Medical University, Wroclaw, Poland; [8]Department of Biostatistics & Medical Informatics, University of Wisconsin, Madison, WI, USA; [9]TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [10]AstraZeneca R&D, Gothenburg, Sweden; [11]VA Medical Center, University of Minnesota, MN, USA; [12]2nd Department of Internal Medicine, Cardiovascular Medicine, General University Hospital, Charles University in Prague, Czech Republic; [13]Department of Cardiology, Max Super Specialty Hospital, New Delhi, India; [14]Department of Internal Medicine, Comenius University in Bratislava, Bratislava, Slovakia; [15]Cardiovascular Division of Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan; [16]Heart and Vascular Center, Semmelweis University, Budapest, Hungary; [17]Montreal Heart Institute and Université de Montreal, Montreal, Canada; [18]Department of Clinical Medicine, Herlev-Gentofte Hospital, Herlev, Denmark; and [19]Department of Internal Medicine, Tan Tao University, Tan Duc city, Vietnam

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Aims

The aim of this study was to examine whether left ventricular ejection fraction (LVEF) modified efficacy and safety of dapagliflozin 10 mg compared with placebo in the 4744 patients with LVEF ≤40% randomized in the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF).

Methods and results

We examined whether LVEF, analysed categorically or continuously, modified the effect of dapagliflozin. The primary efficacy outcome was the composite of a worsening heart failure (HF) event (unplanned HF hospitalization/an urgent HF visit requiring intravenous therapy) or cardiovascular death. Mean LVEF was 31.1% and LVEF categories analysed were: <26% (n = 1143), 26–30% (n = 1018), 31–35% (n = 1187), and >35% (n = 1396). Each 5% decrease in LVEF was associated with a higher risk of the primary outcome [hazard ratio (HR) 1.18; 95% confidence interval (CI) 1.13–1.24]. The benefit of dapagliflozin was consistent across the spectrum of LVEF: the dapagliflozin vs. placebo HR was 0.75 (95% CI 0.59–0.95) for LVEF <26%, 0.75 (0.57–0.98) for LVEF 26–30%, 0.67 (0.51–0.89) for LVEF 31–35%, and 0.83 (0.63–1.09) for LVEF >35% (P for interaction = 0.762). Similarly, the effect of dapagliflozin on the components of the primary endpoint was not modified by baseline LVEF (P for interaction for cardiovascular death = 0.974, and for worsening HF = 0.161). Safety of dapagliflozin was also consistent across the range of LVEF and neither efficacy nor safety were modified by diabetes status.

*Corresponding author. British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow, G12 8TA, UK. Tel: +44 141 3303479, Fax: +44 141 3306955, Email: john.mcmurray@glasgow.ac.uk

Conclusion Left ventricular ejection fraction was a significant predictor of hospitalization and mortality in patients with HF with reduced ejection fraction but did not modify the beneficial effect of dapagliflozin, overall or separately, in patients with and without diabetes.
Clinical Trial Registration: ClinicalTrials.gov Identifier NCT03036124

Keywords Heart failure • Dapagliflozin • Left ventricular ejection fraction

Introduction

Left ventricular ejection fraction (LVEF) is the most commonly used measure of left ventricular systolic function. Not only does it help diagnose heart failure (HF) with reduced ejection fraction (HFrEF), and distinguish between patients with HFrEF and HF with preserved ejection fraction (HFpEF), but it is also an important predictor of morbidity and mortality.[1,2] Both the risk of HF hospitalization and cardiovascular mortality are higher in patients with lower LVEF.[1]

In the Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure trial (DAPA-HF), 4744 patients with HF and a LVEF ≤40% were randomized to receive either the sodium–glucose co-transporter 2 (SGLT2) inhibitor dapagliflozin or matching placebo.[3] Patients allocated to dapagliflozin had a 26% lower risk of the primary outcome of a worsening HF event (HF hospitalization or an urgent HF visit requiring intravenous therapy) or cardiovascular death, compared with placebo. In the present report, we evaluated whether LVEF at baseline modified the effects of dapagliflozin in the patients enrolled in DAPA-HF, overall and in participants with and without diabetes separately.

Methods

Patients and study design

The design and primary results of the DAPA-HF trial are published.[3,4] The trial was approved by ethics committees at 410 participating centres in 20 countries and all participants gave written informed consent.

Patients were eligible at screening if they were at least 18 years of age, were in New York Heart Association (NYHA) functional classes II to IV, had a LVEF ≤40%, and an elevated N-terminal pro brain natriuretic peptide (NT-proBNP, ≥600 pg/mL or ≥400 pg/mL if hospitalized for HF within the previous 12 months). In patients with atrial fibrillation or atrial flutter on their baseline electrocardiogram, NT-proBNP had to be ≥900 pg/mL, regardless of history of hospitalization for HF. Patients were required to receive standard HF drug and device therapy, including an angiotensin-converting enzyme inhibitor (ACEI), an angiotensin receptor blocker (ARB) or an angiotensin receptor–neprilysin inhibitor (ARNI), along with a beta-blocker and mineralocorticoid receptor antagonist (MRA), unless contraindicated or not tolerated. Glucose-lowering therapy (including insulin) was continued in patients with diabetes, with adjustments made, as required, during follow-up.

Left ventricular ejection fraction was required to have been measured within 12 months of enrolment, by echocardiography, radionuclide ventriculography, contrast angiography, or cardiac magnetic resonance imaging. Patients without a LVEF measurement within the previous 12 months were required to have LVEF measured at the time of enrolment.

Key exclusion criteria included symptoms of hypotension or systolic blood pressure (SBP) <95 mmHg, estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 and type 1 diabetes.

Patients were randomized to receive either dapagliflozin (10 mg once daily) or matching placebo in a 1:1 ratio. Randomization was stratified based on either history of diabetes or on a glycated haemoglobin level of ≥6.5% at enrolment (but for analyses, baseline diabetes was defined as a medical history of diabetes or a glycated haemoglobin level of ≥6.5% at both the enrolment and randomization visits).

The median duration of follow-up was 18.2 months (minimum of 5 days and maximum of 27.8 months).

Outcomes

The primary outcome was a composite of a worsening HF event (an unplanned hospitalization for HF or an urgent HF visit requiring intravenous therapy) or cardiovascular death.

The first secondary outcome was the composite of hospitalization for HF or cardiovascular death. Other secondary outcomes included a composite of the total number of hospitalizations for HF (first and repeat) and cardiovascular death, and change from baseline to 8 months in the total symptom score (TSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ).[5] The KCCQ is scored from 0 to 100 with higher scores indicating better status and a change of ≥5 points is regarded as a clinically meaningful change. A further secondary endpoint was a composite of worsening renal function, including: (i) a sustained decline in eGFR of ≥50%; (ii) end-stage renal disease – defined as a sustained (≥28 day) eGFR of <15 mL/min/1.73 m^2, sustained dialysis or renal transplantation; or (iii) renal death. Lastly, death from any cause was also analysed. Safety outcomes included serious adverse events, adverse events leading to treatment discontinuation and other adverse events of special interest (adverse events related to volume depletion, renal adverse events, major hypoglycaemic episodes, bone fractures, diabetic ketoacidosis, amputations). Fournier's gangrene and laboratory findings of note.

Statistical analysis

In this analysis, patients were divided into four LVEF categories, similar to those used in prior analyses and reflective of clinical practice, namely: (i) <26%; (ii) 26–30%; (iii) 31–35%; and (iv) >35%.[1,6,7] Baseline characteristics are reported for each LVEF category as means ± standard deviation, median with interquartile range and proportions, as appropriate. A non-parametric Wilcoxon-type rank sum test and chi-square tests were used for continuous and categorical variables, respectively.

The effect of dapagliflozin, compared to placebo, on each outcome across the different LVEF categories was examined using Cox regression. Event rates per 100 person-years and hazard ratios (HRs) adjusted for previous HF hospitalization (except for all-cause death and

replaced by baseline eGFR for the renal outcomes) and stratified by diabetes status are reported for each LVEF category. The proportional hazards assumption was fulfilled for all major outcomes. The relationship between LVEF as a continuous variable, and the risk of each major clinical outcome, was also examined in restricted cubic spline analyses. LVEF was modelled as a fractional polynomial to assess its interaction as a continuous variable with treatment and displayed as a graph using the mfpi function in Stata.[8] The interaction between LVEF and treatment on change in KCCQ-TSS at 8 months was tested in a linear regression model with interaction between LVEF and treatment tested for using the Wald method. The proportion of patients experiencing a 5-point increase, and a 5-point decrease, in KCCQ-TSS at 8 months was examined in a logistic regression model, with the interaction term between LVEF and treatment described using the Wald test. The HR per 5-point decrease in baseline LVEF was calculated for the primary outcome and its components, the composite outcome of cardiovascular death or hospitalization for HF, hospitalization for HF and all-cause death, and was adjusted for treatment and previous HF hospitalization (except for all-cause death). All models were stratified by diabetes status as specified.

All analyses were conducted using Stata version 16 (Stata Corp., College Station, TX, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Left ventricular ejection fraction ranged from 2% to 40% (although one patient had a LVEF of 45%). The mean and median LVEF were $31.1 \pm 6.8\%$ and 32% (IQR 26–37%), respectively. There were 1143 patients with a LVEF <26%, 1018 patients with a LVEF between 26% and 30%, 1187 with a LVEF between 31% and 35%, and 1396 patients had a LVEF >35%.

Patient characteristics

As shown in *Table 1*, patients with a lower LVEF were younger (mean 64 years in the lowest vs. 68 years in the highest LVEF category), more likely to be male, less likely to be from Europe or of white race, compared to patients with a higher LVEF. Fewer patients with a lower LVEF had hypertension, diabetes, a previous myocardial infarction, or atrial fibrillation. A higher proportion of patients in the lowest LVEF category had a non-ischaemic aetiology and more had a previous hospitalization for HF. Conversely, there was no significant difference in median KCCQ-TSS score, or in the proportion of patients in NYHA class II vs. III/IV, across the LVEF categories. Patients with a lower LVEF had a higher NT-proBNP level (median 1827 pg/mL in the lowest vs. 1275 pg/mL in the highest LVEF category) and higher creatinine concentration. When patients with and without diabetes were examined separately, those with diabetes more often had a history of hypertension and myocardial infarction (and an ischaemic aetiology), as well as worse NYHA class, higher NT-proBNP and lower eGFR, compared to participants without diabetes, across the range of LVEF (online supplementary *Table S1*).

A greater proportion of patients with low LVEF were prescribed diuretics. Use of sacubitril/valsartan, a MRA, digoxin, cardiac resynchronization therapy and an implantable cardioverter-defibrillator increased with decreasing LVEF, whereas the opposite trend was observed with an ACEI or ARB. These patterns were similar in patients with and without diabetes and according to randomization arm (online supplementary *Table S1* and *Table S4*).

Among patients with diabetes at baseline, there was no significant difference in the use of specific glucose-lowering medications and insulin across the LVEF categories (*Table 1* and online supplementary *Table S1*).

Relationship between baseline left ventricular ejection fraction and hospitalization and mortality outcomes

The rate of the primary outcome in placebo-treated patients in the lowest LVEF category was 20.7 [95% confidence interval (CI) 17.7–24.1] per 100 patient-years, compared with 11.9 (9.9–14.3) per 100 patient-years in patients in the highest LVEF category (*Table 2*). The corresponding rates of the primary outcome in patients with diabetes in the lowest and highest LVEF categories were 26.8 (95% CI 21.8–33.0) and 14.6 (95% CI 11.5–18.6) per 100 patient-years, respectively. In participants without diabetes these rates were 16.1 (95% CI 12.8–20.3) and 9.5 (95% CI 7.1–12.6) per 100 patient-years, respectively (online supplementary *Table S2* and *Figure S4*).

As illustrated in *Figure 1* and online supplementary *Figure S3*, the risk of the clinical outcomes of interest increased as LVEF decreased. *Table 3* shows that each 5-point decrease in LVEF was associated with an 18% higher risk of the primary outcome (HR 1.18, 95% CI 1.13–1.24) in the overall cohort. Corresponding HR for a 5-point decrease in LVEF in participants with diabetes was 1.20 (95% CI 1.12–1.27) compared to 1.17 (95% CI 1.10–1.26) in patients without diabetes.

In the overall population, the increment in risk of cardiovascular death was 20% per 5-point decrease in LVEF (HR 1.20, 95% CI 1.13–1.28) with a similar increment in risk for an episode of worsening HF (HR 1.20, 95% CI 1.14–1.27). The HR for all-cause death was 1.13 (95% CI 1.07–1.20). The increase in HR per 5-point decrease in LVEF for each of the latter three outcomes was similar in participants with and without diabetes (*Table 3*).

Median time from measurement of LVEF to randomization was 48 days (Q1–Q3 14–130). A total of 3962 (84%) patients had their LVEF measured within 6 months prior to randomization. The incremental increase in risk of clinical outcomes with decreasing LVEF was also consistent in both those who had LVEF measured ≤6 months prior to randomization and in those who had LVEF measured >6 months prior to randomization (*Table 3*).

Effect of dapagliflozin, compared with placebo, on hospitalization and mortality outcomes, according to baseline left ventricular ejection fraction

For each of the hospitalization and mortality outcomes examined, the event rate was lower in patients receiving dapagliflozin, than in

Table 1 Baseline characteristics according to left ventricular ejection fraction

	<26% (*n* = 1143)	26–30% (*n* = 1018)	31–35% (*n* = 1187)	>35% (*n* = 1396)	*P*-value for trend
LVEF (%)	22.4 ± 3.7	28.8 ± 1.4	33.7 ± 1.4	38.4 ± 1.4	<0.001
Age (years)	64.2 ± 11.3	66.0 ± 10.8	66.8 ± 10.6	68.1 ± 10.5	<0.001
Women	230 (20.1)	215 (21.1)	277 (23.3)	387 (27.7)	<0.001
Region					<0.001
Europe	406 (35.5)	398 (39.1)	556 (46.8)	794 (56.9)	
Asia/Pacific	283 (24.8)	262 (25.7)	258 (21.7)	293 (21.0)	
North America	241 (21.1)	140 (13.8)	171 (14.4)	125 (9.0)	
Latin America	213 (18.6)	218 (21.4)	202 (17.0)	184 (13.2)	
Race					<0.001
White	728 (63.7)	695 (68.3)	857 (72.2)	1053 (75.4)	
Black	104 (9.1)	43 (4.2)	48 (4.0)	31 (2.2)	
Asian	288 (25.2)	266 (26.1)	263 (22.2)	299 (21.4)	
Other	23 (2.0)	14 (1.4)	19 (1.6)	13 (0.9)	
Heart rate (bpm)	72.6 ± 12.4	71.5 ± 11.6	70.9 ± 11.5	71.0 ± 11.3	0.001
SBP (mmHg)	116.5 ± 15.1	120.0 ± 15.3	123.4 ± 16.7	126.1 ± 16.2	<0.001
DBP (mmHg)	71.9 ± 10.1	72.9 ± 10.7	74.0 ± 10.7	74.8 ± 10.2	<0.001
BMI (kg/m^2)	27.7 ± 6.4	27.8 ± 5.8	28.4 ± 5.9	28.6 ± 5.8	<0.001
Medical history					
Hypertension	720 (63.0)	743 (73.0)	907 (76.4)	1153 (82.6)	<0.001
Diabetes	453 (39.6)	432 (42.4)	485 (40.9)	613 (43.9)	0.062
Myocardial infarction	455 (39.8)	485 (47.6)	538 (45.3)	614 (44.0)	0.123
Atrial fibrillation	384 (33.6)	352 (34.6)	462 (38.9)	620 (44.4)	<0.001
Stroke	103 (9.0)	104 (10.2)	107 (9.0)	152 (10.9)	0.210
COPD	137 (12.0)	111 (10.9)	143 (12.1)	194 (13.9)	0.088
Features of HF					
HF aetiology					<0.001
Ischaemic	548 (47.9)	575 (56.5)	703 (59.2)	848 (60.7)	
Non-Ischaemic	493 (43.1)	373 (36.6)	393 (33.1)	428 (30.7)	
Unknown	102 (8.9)	70 (6.9)	91 (7.7)	120 (8.6)	
Prior HF hospitalization	577 (50.5)	486 (47.7)	548 (46.2)	640 (45.8)	0.016
KCCQ-TSS	77 [59–92]	79 [58–94]	79 [58–92]	76 [57–92]	0.265
NYHA class					0.995
II	754 (66.0)	712 (69.9)	805 (67.8)	932 (66.8)	
III/IV	389 (34.0)	306 (30.1)	382 (32.2)	464 (33.2)	
NT-proBNP (pg/mL)	1827 [1055–3385]	1551 [886–2806]	1317 [798–2353]	1275 [790–2232]	<0.001
eGFR (mL/min/1.73 m^2)	67.3 ± 19.9	64.8 ± 19.2	65.9 ± 19.7	65.2 ± 18.9	0.062
Creatinine (μmol/L)	105.1 ± 30.5	106.6 ± 31.8	104.3 ± 30.4	102.5 ± 29.2	0.006
Haemoglobin (g/L)	136.6 ± 15.9	135.7 ± 16.0	135.0 ± 16.2	135.0 ± 16.6	0.005
Treatment					
Diuretic	1100 (96.2)	960 (94.3)	1098 (92.5)	1275 (91.3)	<0.001
ACEI	590 (51.6)	582 (57.2)	655 (55.2)	834 (59.7)	<0.001
ARB	283 (24.8)	269 (26.4)	329 (27.7)	426 (30.5)	0.001
ARNI	188 (16.4)	118 (11.6)	130 (11.0)	72 (5.2)	<0.001
Any RAS blocker[a]	1051 (92.0)	958 (94.1)	1109 (93.4)	1324 (94.8)	0.009
Beta-blocker	1100 (96.2)	979 (96.2)	1146 (96.5)	1333 (95.5)	0.403
MRA	855 (74.8)	755 (74.2)	841 (70.9)	919 (65.8)	<0.001
Digoxin	265 (23.2)	207 (20.3)	193 (16.3)	222 (15.9)	<0.001
Ivabradine	66 (5.8)	51 (5.0)	61 (5.1)	50 (3.6)	0.014
PCI	346 (30.3)	374 (36.7)	404 (34.0)	500 (35.8)	0.020
CABG	178 (15.6)	177 (17.4)	197 (16.6)	247 (17.7)	0.231
CRT	116 (10.1)	86 (8.4)	90 (7.6)	62 (4.4)	<0.001
ICD	358 (31.3)	250 (24.6)	216 (18.2)	129 (9.2)	<0.001
Diabetes medications[b]					
Biguanide	230 (50.8)	221 (51.2)	261 (53.8)	304 (50.0)	0.828
DPP-4 inhibitor	68 (15.0)	67 (15.5)	76 (15.7)	99 (16.2)	0.614
GLP-1 analogues	7 (1.6)	5 (1.2)	4 (0.8)	5 (0.8)	0.225
Sulfonylurea	93 (20.5)	105 (24.3)	107 (22.1)	133 (21.7)	0.919
Insulin	112 (24.7)	122 (28.2)	144 (29.7)	162 (26.4)	0.554

Values are shown as mean ± standard deviation, *n* (%), or median [interquartile range].

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; DPP, dipeptidyl peptidase; eGFR, estimated glomerular filtration rate; GLP, glucagon-like peptide; HF, heart failure; ICD, implantable cardioverter-defibrillator; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RAS, renin–angiotensin system; SBP, systolic blood pressure.

[a]Any patient on ACEI/ARB/ARNI.

[b]Only in patients with a medical history of diabetes (*n* = 1983).

Table 2 Clinical outcomes according to left ventricular ejection fraction

	Overall ($n = 4744$)		<26% ($n = 1143$)		26–30% ($n = 1018$)		31–35% ($n = 1187$)		>35% ($n = 1396$)		*P*-value for interaction
	Placebo ($n = 2371$)	Dapagliflozin ($n = 2373$)	Placebo ($n = 601$)	Dapagliflozin ($n = 542$)	Placebo ($n = 498$)	Dapagliflozin ($n = 520$)	Placebo ($n = 581$)	Dapagliflozin ($n = 606$)	Placebo ($n = 691$)	Dapagliflozin ($n = 705$)	
Primary composite outcome											
Events, *n* (%)	502 (21.2)	386 (16.3)	161 (26.8)	110 (20.3)	114 (22.9)	94 (18.1)	113 (19.5)	84 (13.9)	114 (16.5)	98 (13.9)	
Event rate per 100 pt-years	15.8 (14.5–17.2)	11.7 (10.6–13.0)	20.7 (17.7–24.1)	15.2 (12.7–18.4)	17.4 (14.5–20.9)	13.2 (10.8–16.2)	14.4 (12.0–17.3)	9.9 (8.0–12.3)	11.9 (9.9–14.3)	9.7 (8.0–11.8)	
Unadjusted hazard ratio	0.74 (0.65–0.85) <0.001		0.75 (0.59–0.95)		0.75 (0.57–0.98)		0.67 (0.51–0.89)		0.83 (0.63–1.09)		0.762
Cardiovascular death											
Events (%)	273 (11.5)	227 (9.6)	93 (15.5)	69 (12.7)	61 (12.3)	57 (11.0)	59 (10.2)	49 (8.1)	60 (8.7)	52 (7.4)	
Event rate per 100 pt-years	8.0 (7.1–9.0)	6.6 (5.8–7.5)	11.0 (9.0–13.5)	9.0 (7.1–11.4)	8.7 (6.7–11.1)	7.7 (5.9–10.0)	7.0 (5.4–9.1)	5.6 (4.2–7.4)	5.9 (4.6–7.6)	4.9 (3.8–6.5)	
Unadjusted hazard ratio	0.82 (0.69–0.98) 0.030		0.84 (0.61–1.14)		0.88 (0.62–1.27)		0.77 (0.53–1.13)		0.85 (0.59–1.24)		0.974
HF hospitalization/urgent visit[a]											
Events (%)	326 (13.7)	237 (10.0)	104 (17.3)	70 (12.9)	80 (16.1)	51 (9.8)	76 (13.1)	51 (8.4)	66 (9.6)	65 (9.2)	
Event rate per 100 pt-years	10.3 (9.2–11.4)	7.2 (6.3–8.2)	13.3 (11.0–16.2)	9.7 (7.7–12.3)	12.2 (9.8–15.2)	7.2 (5.4–9.4)	9.7 (7.7–12.1)	6.0 (4.6–7.9)	6.9 (5.4–8.8)	6.4 (5.0–8.2)	
Unadjusted hazard ratio	0.70 (0.59–0.83) <0.001		0.74 (0.54–1.00)		0.57 (0.40–0.81)		0.61 (0.43–0.87)		0.95 (0.67–1.34)		0. 161
Total HF hospitalization/ CV death											
Events	742	567	250	175	178	130	160	125	154	137	
Event rate per 100 pt-years	21.9 (20.4–23.5)	16.5 (15.2–18.0)	29.8 (26.4–33.8)	23.0 (19.8–26.6)	25.3 (21.8–29.3)	17.5 (14.8–20.8)	19.1 (16.4–22.3)	14.3 (12.0–17.0)	15.3 (13.0–17.9)	13.0 (11.0–15.4)	
Unadjusted hazard ratio	0.75 (0.65–0.88) <0.001		0.78 (0.59–1.03)		0.68 (0.51–0.92)		0.72 (0.53–1.00)		0.87 (0.64–1.18)		0.702
Mean ± SD change in KCCQ-TSS at 8 months											
Mean ± SD change at 8 months	3.3 ± 19.2	6.1 ± 18.6	3.2 ± 19.6	6.1 ± 19.8	2.0 ± 18.8	5.9 ± 19.0	3.3 ± 19.7	6.4 ± 17.4	4.3 ± 18.8	6.0 ± 18.6	0.607
Between treatment difference[b]	2.8 (1.6–4.0)		2.9 (0.4–5.5)		3.9 (1.3–6.5)		3.1 (0.8–5.5)		1.7 (−0.5–3.8)		
Proportion with increase in score ≥5 at 8 months	50.9	58.3	48.1	57.6	51.7	58.8	51.3	60.1	52.5	56.8	0.754
Proportion with decrease in score ≥5 at 8 months	32.9	25.3	35.3	29.1	34.5	24.9	32.9	22.2	29.6	25.5	0.734
All-cause death											
Events (%)	329 (13.9)	276 (11.6)	100 (16.6)	77 (14.2)	72 (14.5)	68 (13.1)	75 (12.9)	59 (9.7)	82 (11.9)	72 (10.2)	
Event rate per 100 pt-years	9.7 (8.7–10.8)	8.0 (7.1–9.0)	11.8 (9.7–14.4)	10.1 (8.1–12.6)	10.2 (8.1–12.9)	9.1 (7.2–11.6)	8.9 (7.1–11.2)	6.7 (5.2–8.7)	8.1 (6.5–10.0)	6.8 (5.4–8.6)	
Unadjusted hazard ratio	0.83 (0.71–0.97) 0.022		0.87 (0.64–1.17)		0.89 (0.64–1.24)		0.73 (0.52–1.03)		0.86 (0.62–1.17)		0.866

CV, cardiovascular; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; pt, patient; SD, standard deviation.

Hazard ratio represents comparison of dapagliflozin against placebo with 95% confidence interval.

Hazard ratios adjusted for previous HF hospitalization at baseline (except all-cause death) and stratified by diabetes status.

[a]Requiring intravenous therapy for HF.

[b]Expressed as difference with 95% confidence interval in () in dapagliflozin compared to placebo.

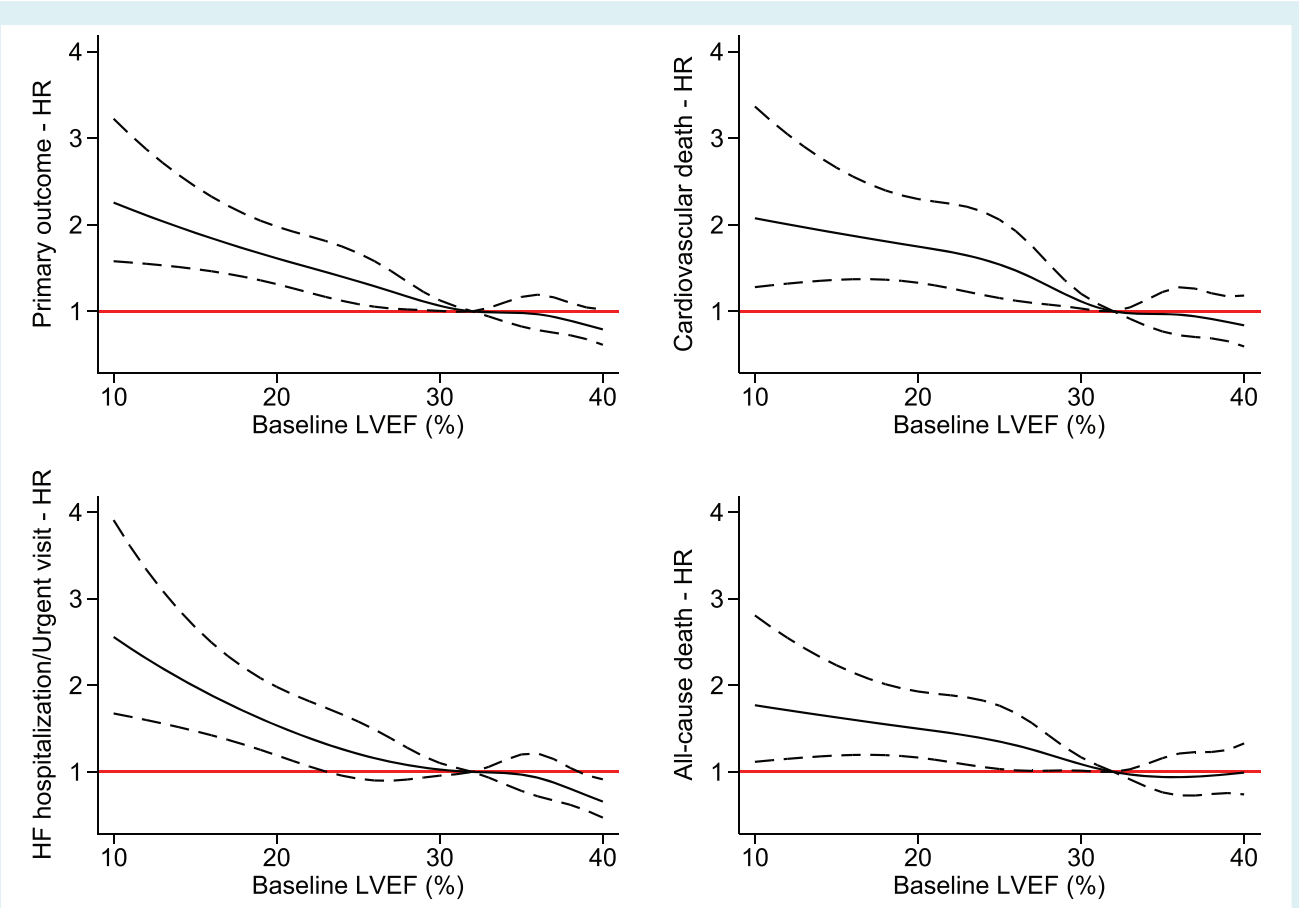

Figure 1 Clinical outcomes according to baseline left ventricular ejection fraction (LVEF). Restricted cubic spine analyses of clinical outcomes according to baseline LVEF: primary composite outcome, cardiovascular death, heart failure (HF) hospitalization/urgent visit for HF, and all-cause death. Figures have been restricted to 10–40% LVEF but the results are derived from models based on the entire spectrum of LVEF in DAPA-HF. HR, hazard ratio.

those assigned to placebo, across all the LVEF categories (*Table 2* and online supplementary *Figure S2*).

The effect of dapagliflozin was consistent across the range of LVEF for the primary composite outcome [*P*-value for interaction: 0.762 (categorical) and 0.205 (continuous)], cardiovascular death [*P*-value for interaction: 0.974 (categorical) and 0.997 (continuous)] and HF hospitalization or urgent visit for HF [*P*-value for interaction: 0.161 (categorical) and 0.150 (continuous)] and all-cause death [*P*-value for interaction: 0.866 (categorical) and 0.962 (continuous)] (*Table 2* and *Figure 2*).

The benefit of dapagliflozin over placebo for these outcomes was also consistent in patients with and without diabetes analysed separately, across the range of LVEF studied (online supplementary *Table S2* and *Figure S5*). Similarly, beneficial effects of dapagliflozin also remained constant across the range of LVEF regardless of the time of measurement of LVEF (online supplementary *Figure S6*).

The favourable effect of dapagliflozin on the composite of HF hospitalization (first and repeat) and cardiovascular death was also consistent across the spectrum of LVEF studied (in the overall cohort, and in participants with and without diabetes analysed separately).

Because the absolute risk of events was highest in patients in the lowest LVEF category, the absolute benefit of dapagliflozin was larger in patients with a lower LVEF. For example, applying the overall relative risk reduction of 26% to patients with a LVEF of <26% yielded an absolute risk reduction of 54 fewer patients with an event per 1000 person-years of follow-up, compared with 31 per 1000 person-years of follow-up in the LVEF >35% category.

Relationship between baseline left ventricular ejection fraction and change in Kansas City Cardiomyopathy Questionnaire total symptom score

The mean change in KCCQ-TSS in the placebo group was similar in each of the LVEF categories analysed (*Table 2*). The proportion of patients in the placebo group exhibiting a ≥5 point increase (improvement) in KCCQ-TSS was similar across LVEF categories. The same was true for the proportion of patients reporting a

Table 3 Change in risk of clinical outcomes per 5-point decrease in baseline left ventricular ejection fraction – overall, by diabetes status and by time of left ventricular ejection fraction measurement

	Overall ($n = 4744$)	No diabetes ($n = 2605$)	Diabetes ($n = 2139$)	LVEF measured ≤6 months before randomization ($n = 3962$)[a]	LVEF measured >6 months before randomization ($n = 779$)[a]
Primary outcome	1.18 (1.13–1.24) <0.001	1.17 (1.10–1.26) <0.001	1.20 (1.12–1.27) <0.001	1.19 (1.13–1.25) <0.001	1.14 (1.02–1.27) 0.018
CV death or HF hospitalization	1.18 (1.13–1.24) <0.001	1.19 (1.11–1.27) <0.001	1.18 (1.11–1.26) <0.001	1.18 (1.13–1.25) <0.001	1.15 (1.03–1.28) 0.015
CV death	1.20 (1.13–1.28) <0.001	1.20 (1.10– 1.32) <0.001	1.20 (1.11–1.31) <0.001	1.22 (1.14–1.30) <0.001	1.09 (0.94–1.27) 0.234
HF hospitalization/urgent visit[b]	1.20 (1.14–1.27) <.0.001	1.16 (1.06–1.26) 0.001	1.24 (1.15–1.34) <0.001	1.20 (1.12–1.27) <0.001	1.20 (1.05–1.37) 0.008
HF hospitalization	1.20 (1.13–1.27) <0.001	1.17 (1.07–1.28) <0.001	1.22 (1.13–1.32) <0.001	1.19 (1.12–1.27) <0.001	1.21 (1.06–1.39) 0.006
Total HF hospitalization/CV death	1.22 (1.16–1.28) <0.001	1.19 (1.10–1.28) <0.001	1.24 (1.15–1.33) <0.001	1.22 (1.15–1.29) <0.001	1.19 (1.05–1.35) 0.005
All-cause death	1.13 (1.07–1.20) <0.001	1.15 (1.06–1.24) 0.001	1.12 (1.04–1.21) 0.004	1.15 (1.08–1.22) <0.001	1.03 (0.90–1.18) 0.663

CV, cardiovascular; HF, heart failure; LVEF, left ventricular ejection fraction.
Numbers represent hazard ratio with 95% confidence interval for each 5-point decrease in LVEF. Rate ratio for total HF hospitalization/CV death.
Hazard ratios (and relative risk) adjusted for randomized treatment, previous HF hospitalization at baseline (except all-cause death) and stratified by diabetes status.
[a]Date of LVEF measurement was set to missing for three patients.
[b]Requiring intravenous therapy for HF.

≥5 point decrease (deterioration) in KCCQ-TSS. These findings were similar in patients with and without diabetes (online supplementary *Table S2*).

Effect of dapagliflozin, compared with placebo, on change in Kansas City Cardiomyopathy Questionnaire total symptom score, according to baseline left ventricular ejection fraction

The mean increase (improvement) in KCCQ-TSS with dapagliflozin, compared with placebo, was similar in each of the LVEF categories (*P*-value for interaction: 0.607) (*Table 2*; online supplementary *Figure S1*). Compared with placebo, more patients treated with dapagliflozin showed a ≥5 point improvement, and fewer a ≥5 point deterioration, in each of the LVEF categories analysed. These findings were similar in patients with and without diabetes.

Relationship between baseline left ventricular ejection fraction and pre-specified safety outcomes

There was no significant difference in the proportion of those on placebo who discontinued the study due to any reason across the LVEF categories (*Table 4* and online supplementary *Table S3*). Similarly, no difference was seen in the proportion of patients on placebo with adverse events due to renal causes, fractures, amputation, or major hypoglycaemic events. However, the proportion of patients with volume depletion was higher in the lower LVEF categories. A fall in SBP among those on placebo during follow-up was slightly higher in those with LVEF >35% but no such observation was made with respect to change in creatinine (*Table 4*).

Effect of dapagliflozin, compared with placebo, on pre-specified safety outcomes, according to baseline left ventricular ejection fraction

There was no significant difference in the proportion of patients who discontinued for any reason or those who discontinued due to an adverse event between the treatment groups in any of the LVEF categories, including due to volume depletion (*P*-value for interaction: 0.548 and 0.544, respectively) (*Table 4*). Similarly, no difference in the magnitude of change in SBP or creatinine during follow-up was seen between the treatment groups in each LVEF category (*P*-value for interaction: 0.529 and 0.258, respectively) (*Table 4*).

Discussion

In this analysis of 4744 patients with HFrEF in DAPA-HF, the baseline characteristics of patients varied across the spectrum of LVEF, as expected. Patients with and without diabetes also

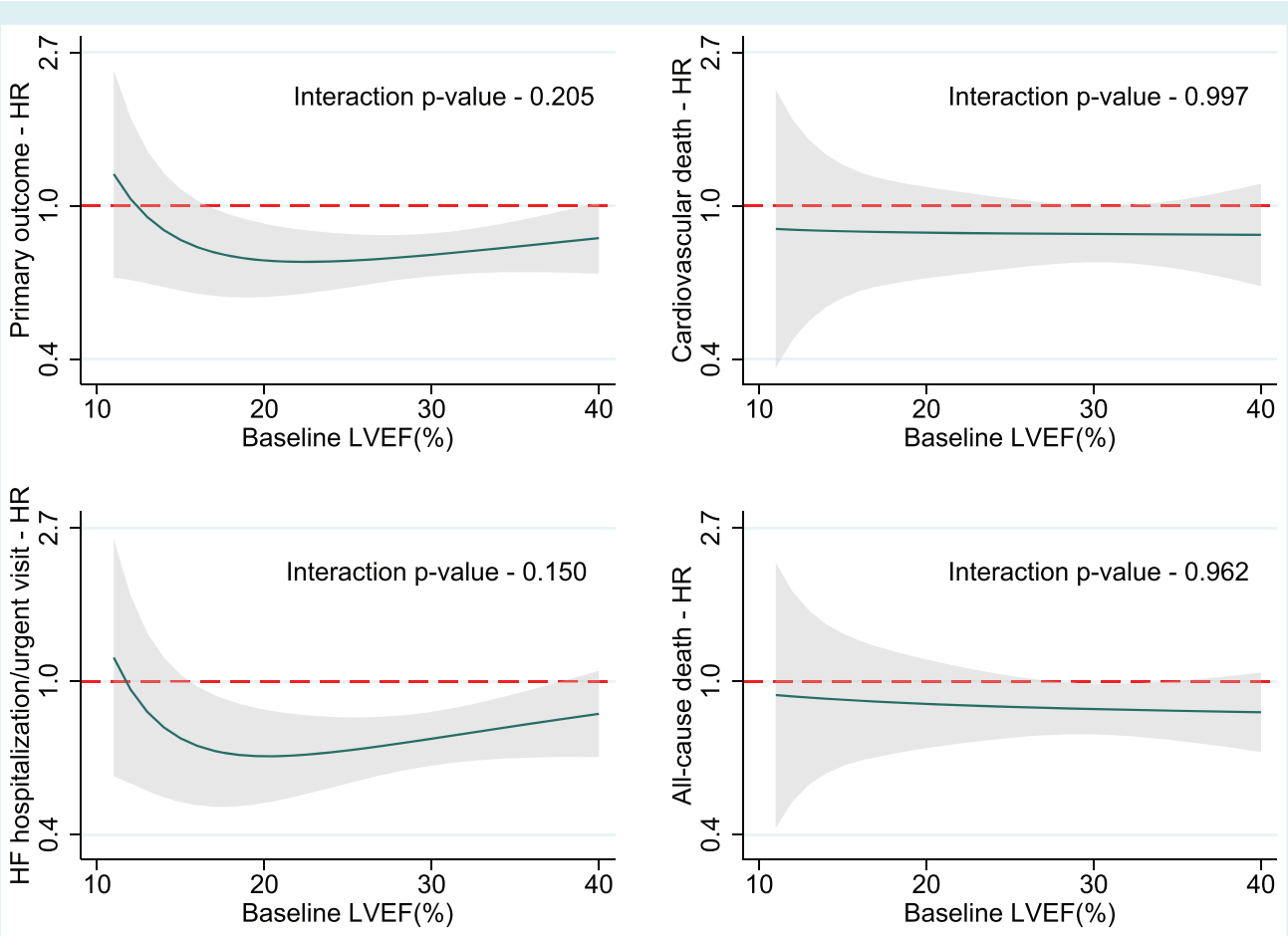

Figure 2 Effect of dapagliflozin on clinical outcomes according to baseline left ventricular ejection fraction (LVEF). Fractional polynomial analyses showing the effect of dapagliflozin treatment on clinical outcomes across the range of LVEF: primary composite outcome, cardiovascular death, heart failure (HF) hospitalization/urgent visit for HF, and all-cause death. Figures have been restricted to 10-40% LVEF but the results are derived from models based on the entire spectrum of LVEF in DAPA-HF. HR, hazard ratio.

differed as expected, but these differences were consistent across the range of LVEF studied. LVEF was a powerful predictor of the risk of hospitalization and death overall and in patients with and without diabetes separately. The benefit of dapagliflozin on mortality/morbidity outcomes was not modified by baseline LVEF, irrespective of diabetes status. By contrast, symptom severity at baseline did not vary according to LVEF. Symptoms improved to a similar extent with dapagliflozin across the range of LVEF studied. The benefit of dapagliflozin on symptoms, in relation to LVEF, was consistent in patients with and without diabetes.

As in previous studies, patients with lower LVEF were younger, more likely to be male, had fewer comorbidities and less likely to have an ischaemic aetiology. Although there was no difference in NYHA class across the LVEF categories, NT-proBNP was substantially higher in patients in the lowest, compared with the highest, LVEF category (despite a much higher prevalence of atrial fibrillation in the latter).

We found that each 5-point decrement in baseline LVEF was associated with a 20% higher risk of cardiovascular death, a 20% higher risk of HF hospitalization and a 13% higher risk of all-cause death. These findings are very similar to what was reported in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF), where the corresponding increments in risk for each 5-point reduction in LVEF were 17%, 17% and 14%, respectively.[9] These findings are also consistent with earlier studies assessing the relationship between LVEF and outcomes in HFrEF.[1] The relative increase in risk of death and hospitalization for a 5-point decrement in baseline LVEF was similar in participants with and without diabetes, although the absolute risk for a given LVEF was higher in individuals with diabetes.

While the benefit of effective therapies for HFrEF has generally been found to be similar across the LVEF spectrum, the range of LVEF in such analyses has been limited as few landmark trials included patients with a LVEF >35%.[10–24] Furthermore, several earlier studies suggested greater benefit of therapy at the lower end of the LVEF spectrum.[6] However, we found that, compared with placebo, the benefit of dapagliflozin on the primary and secondary mortality/morbidity outcomes was consistent across the range of LVEF studied. This benefit according to LVEF was also

Table 4 Discontinuation, safety outcomes and laboratory measures according to left ventricular ejection fraction

	Overall (n = 4744)		<26% (n = 1143)		26–30% (n = 1018)		31–35% (n = 1187)		>35% (n = 1396)		P-value for interaction
	Placebo (n = 2371)	Dapagliflozin (n = 2373)	Placebo (n = 601)	Dapagliflozin (n = 542)	Placebo (n = 498)	Dapagliflozin (n = 520)	Placebo (n = 581)	Dapagliflozin (n = 606)	Placebo (n = 691)	Dapagliflozin (n = 705)	
Any discontinuation											
Events, n (%)	258 (10.9)	249 (10.5)	65 (10.8)	66 (12.2)	57 (11.5)	62 (11.9)	71 (12.2)	60 (9.9)	65 (9.4)	61 (8.7)	
Odds ratio	0.96 (0.80–1.15) 0.665		1.15 (0.80–1.65)		1.05 (0.71–1.53)		0.79 (0.55–1.13)		0.90 (0.63–1.30)		0.548
Discontinuation due to AE[a]											
Events, n (%)	116/2368 (4.9)	111/2368 (4.7)	30/600 (5.0)	31/540 (5.7)	19/498 (3.8)	26/518 (5.0)	33/579 (5.7)	27/606 (4.5)	34/691 (4.9)	27/704 (3.8)	
Odds ratio	0.95 (0.73–1.25) 0.734		1.16 (0.69–1.95)		1.32 (0.72–2.43)		0.76 (0.45–1.28)		0.76 (0.45–1.28)		0.544
Volume depletion[a]											
Events, n (%)	162/2368 (6.8)	178/2368 (7.5)	49/600 (8.2)	54/540 (10.0)	42/498 (8.4)	37/518 (7.1)	29/579 (5.0)	39/606 (6.4)	42/691 (6.1)	48/704 (6.8)	
Odds ratio	1.11 (0.89–1.38) 0.368		1.26 (0.84–1.89)		0.83 (0.53–1.32)		1.29 (0.79–2.12)		1.14 (0.74–1.75)		0.400
Renal[a]											
Events, n (%)	170/2368 (7.2)	153/2368 (6.5)	47/600 (7.8)	39/540 (7.2)	37/498 (7.4)	33/518 (6.4)	45/579 (7.8)	37/606 (6.1)	41/691 (5.9)	44/704 (6.3)	
Odds ratio	0.89 (0.71–1.12) 0.326		0.94 (0.60–1.46)		0.84 (0.52–1.37)		0.75 (0.48–1.18)		1.07 (0.69–1.67)		0.899
Fracture[a]											
Events, n (%)	50/2368 (2.1)	49/2368 (2.1)	13/600 (2.2)	9/540 (1.7)	12/498 (2.4)	14/518 (2.7)	11/579 (1.9)	11/606 (1.8)	14/691 (2.0)	15/704 (2.1)	
Odds ratio	0.98 (0.66–1.46) 0.919		0.78 (0.33–1.85)		1.13 (0.52–2.47)		0.95 (0.41–2.21)		1.07 (0.51–2.23)		0.857
Amputation[a]											
Events, n (%)	12/2368 (0.5)	13/2368 (0.5)	3/600 (0.5)	1/540 (0.2)	1/498 (0.2)	4/518 (0.8)	3/579 (0.5)	6/606 (1.0)	5/691 (0.7)	2/704 (0.3)	
Odds ratio	1.08 (0.49–2.38) 0.842		0.41 (0.04–3.97)		3.82 (0.43–34.35)		1.72 (0.43–6.95)		0.41 (0.08–2.12)		0.336
Major hypoglycaemic episode[a]											
Events, n (%)	4/2368 (0.2)	4/2368 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1/518 (0.2)	0 (0.0)	0 (0.0)	4/691 (0.6)	3/704 (0.4)	
Systolic BP, mmHg											
Change from baseline at 8 months	−0.38 ± 15.3	−1.92 ± 14.9	0.52 ± 15.6	−0.88 ± 15.2	−0.11 ± 14.8	−2.37 ± 13.8	−0.57 ± 15.9	−1.20 ± 14.9	−1.18 ± 14.7	−2.97 ± 15.4	0.529
Difference[b]	−1.40 (−2.27 to −0.52) 0.002		−1.13 (−2.87 to 0.61) 0.202		−2.09 (−3.96 to −0.22) 0.028		−0.63 (−2.40 to 1.14) 0.486		−1.69 (−3.32 to −0.05) 0.044		
Creatinine, mg/dl											
Change from baseline at 8 months	0.04 ± 0.25	0.07 ± 0.24	0.04 ± 0.2	0.08 ± 0.2	0.06 ± 0.3	0.07 ± 0.2	0.05 ± 0.2	0.05 ± 0.2	0.03 ± 0.2	0.06 ± 70.3	0.258
Difference[b]	0.02 (0.01 to 0.04) 0.009		0.04 (0.004 to 0.07) 0.029		0.01 (−0.02 to 0.05) 0.543		0.01 (−0.03 to 0.04) 0.675		−0.03 (0.001 to 0.06) 0.044		

BP, blood pressure.
[a]Only in safety analysis set.
[b]Dapagliflozin−placebo.

consistent in patients with and without diabetes. Consequently, patients with a low LVEF obtained a particularly large *absolute* benefit from dapagliflozin because individuals with a low LVEF, especially if diabetic, were at much greater absolute risk than patients with a higher LVEF. Whether the benefit of SGLT2 inhibition will extend to patients with HF and mid-range/mildly reduced and frankly preserved ejection fraction remains to be determined, especially in patients without type 2 diabetes. Retrospective subgroup analyses of prior trials with SGLT2 inhibitors in individuals with type 2 diabetes and predominantly atherosclerotic cardiovascular disease (or cardiovascular risk factors) have suggested that these drugs may be beneficial in patients with HFpEF, but these findings are far from conclusive.[25,26] This question will be answered, definitively, by the ongoing EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved; NCT03057951) and Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER; NCT03619213) trials, both of which have enrolled patients with LVEF >40%.[27]

Two novel aspects of this study were the analysis of symptoms and the analysis of recurrent events, in relation to baseline LVEF, and according to diabetes status, and the effect of treatment on these outcomes. The two large pharmacological therapy trials that have reported the effect of treatment on KCCQ in HFrEF have not described the relationship between KCCQ score and LVEF or the effect of therapy according to LVEF.[28,29] However, in the CHARM program, there was no clear association between LVEF and a different patient-reported outcome, a finding that is consistent with the current observations in DAPA-HF.[30] In addition, KCCQ scores are similar in patients with HFrEF and HFpEF, which also suggests little correlation between this patient-reported outcome and LVEF.[31] Interestingly, change in KCCQ-TSS from baseline was also independent of LVEF, and similar in patients with and without diabetes. The reason why symptoms and health-related quality of life correlate poorly with LVEF is uncertain but, importantly, dapagliflozin improved symptoms as well as other outcomes. This beneficial effect of dapagliflozin, whether assessed as mean change in KCCQ-TSS, or the proportion of patients with a clinically meaningful change (≥5 points), was similar across LVEF categories, both overall, and in patients with and without diabetes.

Analysis of recurrent non-fatal, along with fatal, events may provide a better quantification of the full burden of HF, compared with conventional time-to-first event analysis.[32–34] Repeat admissions are distressing for patients, a marker of disease progression, represent an adverse prognostic change, and are expensive. Likewise, analysis of recurrent events is a rigorous test of the effect of treatment, as it measures persistence of pharmacological effect and adherence (e.g. treatment discontinuation after a first event will reduce any effect of therapy on subsequent events).[35] That this type of analysis reflects disease burden is clearly shown by the very high event rates compared with time-to-first event analysis in the present analysis, e.g. reaching almost 40 per 1000 person-years of follow-up for HF hospitalization and cardiovascular death in patients with diabetes in the lowest LVEF category. However, the benefit of dapagliflozin was almost identical in the recurrent events and time-to-first analyses, and the relative risk reduction with dapagliflozin was consistent across the range of LVEF examined overall, and in patients with and without diabetes.

As has been shown previously, patients in DAPA-HF with lower LVEF were more likely to have adverse events related to volume depletion but no difference was seen between the treatment groups even in those with the lowest LVEF, allaying concerns of a potentially greater risk of volume depletion in HF patients in whom diuretic use is almost universal.[36,37] The only other significant observation among the safety outcomes was the larger fall in SBP in the highest LVEF category but this was most likely a function of their higher baseline SBP.

Study limitations

Our study had several limitations. This was a *post hoc* analysis in which patients were divided into arbitrary, clinically relevant LVEF categories.[1,6,7] Additionally, LVEF was measured using different methods at different sites and there was no core laboratory. Time of measurement of LVEF before randomization also varied, but this variation did not affect outcomes. We did not have information on the method used to measure LVEF. There was also digit preference in the reporting of LVEF measurements, as often found.[1,9] SBP below 95 mmHg and eGFR below 30 mL/min/1.73 m^2 were exclusion criteria in DAPA-HF and this may have skewed the characteristics of our patients in the lowest LVEF category, more of which might have been expected to have lower SBP and worse renal function.

Conclusion

Left ventricular ejection fraction at baseline was a significant predictor of hospitalization and mortality (but not symptoms) in patients with HFrEF enrolled in DAPA-HF. LVEF did not modify the beneficial effect of dapagliflozin on mortality/morbidity outcomes, or symptoms, in patients with HFrEF overall, and in those with and without diabetes separately.

Supplementary Information

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

Figure S1. Placebo corrected mean change in Kansas City Cardiomyopathy Questionnaire total summary score at 8 months according to left ventricular ejection fraction – overall and according to diabetic status.

Figure S2. Effect of randomized treatment on clinical outcomes, according to left ventricular ejection fraction: primary composite outcome, cardiovascular death, heart failure hospitalization/urgent visit, and all-cause death.

Figure S3. Restricted cubic spine analyses of clinical outcomes according to baseline left ventricular ejection fraction and diabetes status: primary composite outcome, cardiovascular death, heart failure hospitalization/urgent visit, and all-cause death.

Figure S4. Effect of randomized treatment on clinical outcomes, according to left ventricular ejection fraction and diabetes status:

primary composite outcome, cardiovascular death, heart failure hospitalization/urgent visit, and all-cause death.

Figure S5. Fractional polynomial analyses showing the effect of dapagliflozin treatment on clinical outcomes across the range of left ventricular ejection fraction, according to diabetes status: primary composite outcome, cardiovascular death, heart failure hospitalization/urgent visit, and all-cause death.

Figure S6. Forest plot showing the hazard ratios (95% confidence interval) for the major clinical outcomes in DAPA-HF according to left ventricular ejection fraction (LVEF) and the time of measurement of LVEF (≤6 months vs. >6 months)

Table S1. Baseline characteristics according to left ventricular ejection fraction and diabetes status at baseline.

Table S2. Clinical outcomes according to left ventricular ejection fraction and diabetes status at baseline.

Table S3. Safety outcomes according to left ventricular ejection fraction and diabetes status at baseline.

Table S4. Baseline characteristics according to left ventricular ejection fraction and randomization arm.

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