ORIGINAL RESEARCH ARTICLE

Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF

Editorial, see p 1055

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BACKGROUND: In the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure), the sodium-glucose cotransporter 2 inhibitor dapagliflozin reduced the risk of worsening heart failure and death in patients with heart failure and reduced ejection fraction. We examined the efficacy and tolerability of dapagliflozin in relation to background diuretic treatment and change in diuretic therapy after randomization to dapagliflozin or placebo.

METHODS: We examined the effects of study treatment in the following subgroups: no diuretic and diuretic dose equivalent to furosemide <40, 40, and >40 mg daily at baseline. We examined the primary composite end point of cardiovascular death or a worsening heart failure event and its components, all-cause death and symptoms.

RESULTS: Of 4616 analyzable patients, 736 (15.9%) were on no diuretic, 1311 (28.4%) were on <40 mg, 1365 (29.6%) were on 40 mg, and 1204 (26.1%) were taking >40 mg. Compared with placebo, dapagliflozin reduced the risk of the primary end point across each of these subgroups: hazard ratios were 0.57 (95% CI, 0.36–0.92), 0.83 (95% CI, 0.63–1.10), 0.77 (95% CI, 0.60–0.99), and 0.78 (95% CI, 0.63–0.97), respectively (P for interaction=0.61). The hazard ratio in patients taking any diuretic was 0.78 (95% CI, 0.68–0.90). Improvements in symptoms and treatment toleration were consistent across the diuretic subgroups. Diuretic dose did not change in most patients during follow-up, and mean diuretic dose did not differ between the dapagliflozin and placebo groups after randomization.

CONCLUSIONS: The efficacy and safety of dapagliflozin were consistent across the diuretic subgroups examined in DAPA-HF.

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Clinical Perspective

What Is New?

- Inhibition of the sodium-glucose cotransporter 2 in the proximal renal tubule results in natriuresis, increased urinary glucose, and water loss.
- In the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure), 84% of patients randomized were treated with a conventional diuretic such as a loop or thiazide diuretic.
- Little is known about the safety and efficacy of combining treatment with a sodium-glucose cotransporter 2 inhibitor and conventional diuretics in patients with heart failure and reduced ejection fraction.

What Are the Clinical Implications?

- Our findings show that treatment with dapagliflozin is safe and effective regardless of diuretic use or diuretic dose.
- The majority of patients in the DAPA-HF trial did not change their diuretic dose throughout follow-up, and although a decrease in diuretic dose was more frequent with dapagliflozin than with placebo, the between-group difference was small.
- There was an elevation in hematocrit that persisted regardless of baseline diuretic dose and despite a reduction in diuretic dose during follow-up, suggesting that mechanisms other than hemoconcentration might, in part, account for this observation.

Because sodium-glucose cotransporter 2 (SGLT2) reabsorbs sodium, in addition to glucose, in the proximal renal tubule, SGLT2 inhibition leads to natriuresis, as well as an increase in urinary glucose and accompanying water excretion.[1] Consequently, SGLT2 inhibitors have a diuretic action in healthy volunteers and in individuals with type 2 diabetes mellitus. Clearly, a diuretic action might be beneficial in patients with heart failure and reduced ejection fraction (HFrEF) but could also be a double-edged sword. Patients with HFrEF are usually treated with a conventional diuretic, most often a loop diuretic. However, little is known about the effects of adding an SGLT2 inhibitor in people treated with conventional diuretic therapy. It is possible that SGLT2 inhibitors might augment the effect of conventional diuretics, with attendant risk of volume depletion. Conversely, because the diuretic effect of SGLT2 inhibitors is modest, they may add little, if anything, to the potent effect of loop diuretics (and the combination of a loop diuretic and a mineralocorticoid receptor antagonist [MRA]). Alternatively, an intermediate possibility is that SGLT2 inhibitors might have a diuretic-sparing effect in patients with HFrEF.

Kidney function is clearly another key consideration in patients with HFrEF, many of whom have renal impairment. If there is significant augmentation of diuresis resulting from the addition of an SGLT2 inhibitor to conventional therapy, this might lead to worsening kidney function through volume depletion and decreased renal perfusion, especially in the setting of renin-angiotensin-aldosterone system blockade. Conversely, because the glycosuric effect of SGLT2 inhibitors diminishes as renal function declines, so might the diuretic action of these agents, rendering them less effective in patients with HFrEF with chronic kidney disease.[1]

Therefore, understanding the interaction between the effects of SGLT2 inhibitors and diuretic therapy is of fundamental importance to the use of SGLT2 inhibitors in HFrEF. The DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) demonstrated that SGLT2 inhibition reduced the risk of worsening HF or death resulting from cardiovascular causes compared with placebo in patients with HFrEF.[2] In DAPA-HF, 84% of patients were prescribed a diuretic at baseline in addition to other standard therapy, including a renin-angiotensin inhibitor in 94% and an MRA in 71%.[2] We examined the effect of dapagliflozin compared with placebo on efficacy and safety outcomes according to baseline diuretic therapy and on change in diuretic requirement and possible markers of volume status over time.

METHODS

Study Design and Criteria

The design and primary results of DAPA-HF have been published.[2,3] The Ethics Committee for each participating institution approved the protocol, and all patients gave written informed consent. Eligibility for the trial included New York Heart Association class II to IV symptoms, an ejection fraction of ≤40%, and an elevated NT-proBNP (N-terminal B-type natriuretic peptide) level. For patients who had been hospitalized within the preceding 12 months, the NT-proBNP threshold was ≥400 pg/mL; for any patient with atrial fibrillation or flutter, the threshold was ≥900 pg/mL; and for patients who met neither of these criteria, the threshold was ≥600 pg/mL. Investigators were asked to ensure that patients were optimally treated with pharmacological and device therapy for HFrEF, in keeping with local guidelines. The protocol advised that an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, or sacubitril/valsartan and a β-blocker, as well as an MRA, should be used at guideline-recommended doses unless contraindicated or not tolerated. The protocol also stated that in patients taking diuretics, the goal of treatment was achieving optimal fluid volume status in each individual. The main exclusion criteria included recent treatment with an SGLT2 inhibitor, symptomatic hypotension or a systolic blood pressure of <95 mmHg, an estimated glomerular filtration rate of <30 mL·min^{-1}·1.73 m^{-2}, rapidly declining renal function, or type 1 diabetes mellitus.

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data-sharing policy.

Trial Procedures

After a 14-day screening period, patients were randomized in a 1:1 fashion to receive dapagliflozin at a dose of 10 mg once daily or placebo. Randomization was stratified according to diabetes mellitus status (either a history of diabetes mellitus or a glycated hemoglobin level of ≥6.5% at screening). Patients were evaluated after randomization at 14 days, 2 and 4 months, and every 4 months thereafter.

Trial Outcomes

The primary outcome was the composite of an episode of worsening HF or cardiovascular death, whichever occurred first. An episode of worsening HF was either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for HF. Secondary outcomes included change in Kansas City Cardiomyopathy Questionnaire total symptom score from baseline to 8 months (a lower score equates to worse symptoms) and a composite of worsening renal function and death resulting from any cause. Safety outcomes included all serious adverse events and specific adverse events, including those associated with discontinuation of the study drug and other events of interest such as volume depletion and renal events. Changes in laboratory and clinical findings from baseline to 8 months were also examined.

Statistical Analysis

We included patients treated and not treated with a diuretic at baseline. Patients treated with a diuretic were included if they had information on dose. MRAs were not classed as a diuretic for the purposes of this analysis. Bumetanide 1 mg, torsemide 20 mg, azosemide 60 mg, and etacrynic acid 100 mg were considered equivalent to furosemide 40 mg intravenously and furosemide 80 mg orally. If at any time the loop diuretic dose was indeterminate, the patient was excluded from the analyses at that time point only and included again as soon as the dose could be determined. If a patient was not taking a loop diuretic, the patient was classified as being on 0 mg until he or she either was started on a loop diuretic or died (at which point the dose was recorded as missing). The following furosemide-equivalent oral daily dose categories were generated: <40 mg, 40 mg exactly, and >40 mg, in addition to a "no diuretic" category. Patients on a nonloop diuretic only (eg, a thiazide diuretic alone) were included in the group of <40 mg of furosemide-equivalent loop diuretic. Only a small number of patients were taking a combination (mostly a loop and thiazide or thiazide-like diuretic; see Results).

Baseline characteristics were compared across diuretic therapy categories with the use of ANOVA, Kruskal-Wallis tests, and χ^2 tests. Proportional changes in diuretic dose from baseline to 14 days and to 2, 6, 12, and 18 months were modeled with logistic regression. As a sensitivity analysis, a partial proportional odds model was also used to examine change in diuretic dose at different time points.

Changes in hematocrit, creatinine, NT-proBNP, systolic blood pressure, and weight were analyzed with a mixed model for repeated measures (adjusted for baseline values, randomized treatment, and interaction of treatment and visit, with a random intercept and slope per patient), and the between-treatment-group differences at 8 months after randomization were presented by diuretic subgroup as least-square-means

difference and 95% CI. Because improvement in clinical status with any treatment for HFrEF may reduce diuretic requirement, for comparison, we also examined change in diuretic dose over time in the CHARM trials (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) of low left ventricular ejection fraction.[4]

Time-to-first-event outcomes (the primary composite outcome and its components, hospitalization for heart failure/urgent heart failure visit or cardiovascular death, worsening renal function, and death resulting from any cause) were analyzed with Cox regression. Cumulative first events were displayed with Kaplan-Meier curves. The interaction between diuretic therapy and the effect of treatment was assessed with the respective statistical model for that measure or outcome and with a logistic regression model for the safety outcomes. All models were stratified by or adjusted for diabetes mellitus status and, except in the cases of death resulting from any cause and the composite worsening renal function end point (the latter included baseline estimated glomerular filtration rate), previous hospitalization for heart failure. Additional variables included in adjusted models were age, sex, race, New York Heart Association class, left ventricular ejection fraction, cause of heart failure, NT-proBNP (log), heart rate, systolic blood pressure, estimated glomerular filtration rate, atrial fibrillation/flutter, and previous hospitalization for heart failure if not already included in the model (except for death resulting from any cause). All analyses were conducted with STATA version 16 (StataCorp LLC, College Station, TX). A value of $P<0.05$ was considered statistically significant.

RESULTS

Of the 4744 patients randomized, 736 (15.5%) were not taking a diuretic, and of the remaining 4008 participants, 3880 had a determinable diuretic dose (expressed as the furosemide-equivalent dose). Of those receiving a diuretic (n=3880), the largest number (1365 patients; 29.6% of all analyzed patients and 35.2% of patients receiving a diuretic) were taking a furosemide-equivalent dose of 40 mg (Table 1). The number taking >40 mg was 1204 (26.1% and 31.0%, respectively), and the number taking <40 mg or a nonloop diuretic only was 1311 (28.4% and 33.8%, respectively). The most commonly used loop diuretic among those prescribed a loop diuretic was furosemide. Bumetanide was used more frequently in patients on a dose of >40 mg furosemide equivalent than in patients on lower doses of loop diuretic. Overall, 320 (6.9% and 8.2%, respectively) were taking a combination of diuretics; in most cases (272, 85.0%), this was the combination of a loop and thiazide or thiazide-like diuretic alone. A similar proportion of patients in each diuretic group were randomized to dapagliflozin or placebo.

Patient Characteristics

There were several differences between patients in the different diuretic groups (Table 1). Compared with

Table 1. Baseline Characteristics According to Diuretic Therapy at Baseline

	Furosemide-Equivalent Dose					
	No Diuretic (n=736)	<40 mg* (n=1311)	40 mg (n=1365)	>40 mg (n=1204)	Any Dose (n=3880)	P Value†
Dose (furosemide equivalent), mg						
Mean in all patients	…	16.4±8.7	40	120.6±150.0	57.0±94.4	<0.001
Mean in patients on loop diuretic	…	19.1±6.1	…	…	59.9±95.9	
Median in all patients	…	20 (10–20)	40	80 (80–120)	40 (20–80)	<0.001
Median in patients on loop diuretic	…	20 (20–20)	…	…	40 (20–80)	
Loop diuretic‡, n (%)						<0.001
Azosemide	…	47 (4.2)	0 (0.0)	24 (2.0)	71 (1.9)	
Bumetanide	…	0 (0.0)	1 (0.1)	74 (6.1)	75 (2.0)	
Furosemide	…	780 (69.1)	1078 (79.0)	782 (65.0)	2640 (71.4)	
Torsemide	…	296 (26.2)	282 (20.7)	250 (20.8)	828 (22.4)	
Combination	…	5 (0.4)	4 (0.3)	74 (6.1)	83 (2.2)	
Nonloop diuretic, n (%)	…	268 (20.4)	114 (8.4)	121 (10.0)	503 (13.0)	<0.001
Randomized to dapagliflozin, n (%)	372 (50.5)	668 (51.0)	688 (50.4)	582 (48.3)	1938 (49.9)	0.58
Age, y	67.3±10.6	66.8±10.7	66.7±10.6	64.8±11.4	66.1±10.9	<0.001
Female, n (%)	166 (22.6)	326 (24.9)	345 (25.3)	246 (20.4)	917 (23.6)	0.015
Race, n (%)						<0.001
Asian	225 (30.6)	461 (35.2)	187 (13.7)	213 (17.7)	861 (22.2)	
Black or African American	11 (1.5)	29 (2.2)	86 (6.3)	95 (7.9)	210 (5.4)	
Other	10 (1.4)	14 (1.1)	22 (1.6)	23 (1.9)	59 (1.5)	
White	490 (66.6)	807 (61.6)	1070 (78.4)	873 (72.5)	2750 (70.9)	
Region, n (%)						<0.001
Asia/Pacific	218 (29.6)	456 (34.8)	183 (13.4)	212 (17.6)	851 (21.9)	
Europe	218 (29.6)	588 (44.9)	707 (51.8)	580 (48.2)	1875 (48.3)	
North America	150 (20.4)	146 (11.1)	152 (11.1)	191 (15.9)	489 (12.6)	
South America	150 (20.4)	121 (9.2)	323 (23.7)	221 (18.4)	665 (17.1)	
NYHA functional classification, n (%)						<0.001
II	588 (79.9)	916 (69.9)	876 (64.2)	731 (60.7)	2523 (65.0)	
III	142 (19.3)	384 (29.3)	473 (34.7)	464 (38.5)	1321 (34.0)	
IV	6 (0.8)	11 (0.8)	16 (1.2)	9 (0.7)	36 (0.9)	
NT-proBNP, pg/mL	1168 (731–1823)	1296 (802–2320)	1573 (898–2971)	1827 (1023–3205)	1529 (890–2820)	<0.001
KCCQ total symptom score	85.4 (68.8–95.8)	80.2 (62.5–93.8)	76.0 (57.3–90.6)	70.8 (51.0–87.5)	76.0 (57.3–91.7)	<0.001
Left ventricular ejection fraction, %	32.1±6.3	32.1±6.4	31.0±6.7	29.4±7.1	30.9±6.8	<0.001
Estimated GFR, mL·min⁻¹·1.73 m⁻²	70.4±18.6	67.4±19.4	65.0±18.9	62.5±19.7	65.0±19.4	<0.001
Estimated GFR <60 mL·min⁻¹·1.73 m⁻², n (%)	216 (29.4)	497 (37.9)	572 (41.9)	575 (47.8)	1644 (42.4)	<0.001
Creatinine, µmol/L	95.8±26.3	100.9±29.1	104.6±28.7	112.8±33.6	105.9±30.8	<0.001
Hematocrit, %	41.5±4.8	41.4±4.8	41.7±5.0	41.2±5.2	41.5±5.0	0.053
Heart rate, bpm	69.9±11.8	71.3±11.6	71.7±11.0	72.8±12.4	71.9±11.7	<0.001
Systolic blood pressure, mm Hg	123.5±17.2	123.1±16.1	122.1±16.0	119.4±16.2	121.6±16.1	<0.001
Weight, kg	76.2±17.4	75.7±18.1	82.7±19.5	86.4±23.1	81.5±20.7	<0.001
Body mass index, kg/m²	26.7±5.0	26.9±5.3	28.8±5.9	29.8±6.7	28.4±6.1	<0.001
Principal cause of heart failure, n (%)						0.007
Ischemic	424 (57.6)	781 (59.6)	780 (57.1)	625 (51.9)	2186 (56.3)	
Nonischemic	247 (33.6)	436 (33.3)	477 (34.9)	479 (39.8)	1392 (35.9)	
Unknown	65 (8.8)	94 (7.2)	108 (7.9)	100 (8.3)	302 (7.8)	

(Continued)

Table 1. Continued

	Furosemide-Equivalent Dose					
	No Diuretic (n=736)	<40 mg* (n=1311)	40 mg (n=1365)	>40 mg (n=1204)	Any Dose (n=3880)	P Value†
Medical history, n (%)						
Hospitalization for heart failure	271 (36.8)	606 (46.2)	654 (47.9)	666 (55.3)	1926 (49.6)	<0.001
Atrial fibrillation	217 (29.5)	477 (36.4)	536 (39.3)	526 (43.7)	1539 (39.7)	<0.001
Diabetes mellitus	243 (33.0)	494 (37.7)	585 (42.9)	606 (50.3)	1685 (43.4)	<0.001
Device therapy, n (%)						
Implantable cardioverter-defibrillator§	167 (22.7)	274 (20.9)	326 (23.9)	422 (35.0)	1022 (26.3)	<0.001
Cardiac resynchronization	46 (6.2)	78 (5.9)	89 (6.5)	116 (9.6)	283 (7.3)	0.001
Other medical therapy, n (%)						
ACE inhibitor or ARB	603 (81.9)	1140 (87.0)	1172 (85.9)	947 (78.7)	3259 (84.0)	<0.001
Sacubitril-valsartan	91 (12.4)	97 (7.4)	134 (9.8)	148 (12.3)	379 (9.8)	<0.001
β-Blocker	695 (94.4)	1259 (96.0)	1316 (96.4)	1166 (96.8)	3741 (96.4)	0.054
MRA	425 (57.7)	939 (71.6)	1004 (73.6)	923 (76.7)	2866 (73.9)	<0.001
Digoxin	80 (10.9)	230 (17.5)	249 (18.2)	304 (25.2)	783 (20.2)	<0.001
Glucose-lowering medication, n (%)‖						
Biguanide	131 (53.9)	232 (47.0)	317 (54.2)	305 (50.3)	854 (50.7)	0.089
Sulfonylurea	42 (17.3)	104 (21.1)	135 (23.1)	149 (24.6)	388 (23.0)	0.11
DPP-4 inhibitor	46 (18.9)	98 (19.8)	76 (13.0)	84 (13.9)	258 (15.3)	0.005
GLP-1 receptor agonist	1 (0.4)	6 (1.2)	5 (0.9)	8 (1.3)	19 (1.1)	0.63
Insulin	40 (16.5)	117 (23.7)	157 (26.8)	206 (34.0)	480 (28.5)	<0.001

Data are presented as mean±SD or median (interquartile range) for continuous measures and number (percent) for categorical variables. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRA, mineralocorticoid receptor antagonist; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Patients on a nonloop diuretic only are included in this group (n=183).

†P value for the comparison of no diuretic, <40 mg, 40 mg, and >40 mg.

‡In patients on a loop diuretic (ie, excluding those on a nonloop diuretic only).

§Implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator.

‖In patients with a history of diabetes mellitus at baseline; no diuretic, n=243; <40 mg, n=494; 40 mg, n=585; and >40 mg, n=606.

those not receiving a diuretic, patients in the highest diuretic dose category (>40 mg) were younger; had worse symptoms, functional class, and renal function; had higher NT-proBNP levels and body mass index and lower left ventricular ejection fraction and systolic blood pressure; and were more likely to have a history of heart failure hospitalization, atrial fibrillation, and diabetes mellitus. Hematocrit was similar between groups at baseline. Patients in the highest diuretic dose category at baseline were more often treated with an MRA and digoxin. The small group (n=320) of patients taking the combination of a loop and another diuretic had a more severe profile overall (Table I in the Data Supplement).

Change in Diuretic Dose After Randomization

The mean (SD) furosemide-equivalent dose in patients taking any diuretic was 57.0 (94.4) mg; in patients taking a loop diuretic, it was 59.9 (95.9) mg, with no statistically significant difference between treatment groups (Table 2). There was no change in the loop diuretic dose in most patients at 2 weeks and at 2, 6, 12, and 18 months (97.1%, 91.4%, 83.3%, 77.2%, and 73.6%, respectively); this was the case in patients randomized to placebo or dapagliflozin. Throughout follow-up, the mean dose of loop diuretic rose at a similar rate in both treatment arms (Figure 1), and this was the case regardless of baseline dose (Figure I in the Data Supplement). The findings were very similar in CHARM (Figure II in the Data Supplement).

A small proportion of patients had their dose of diuretic reduced, and this happened more frequently with dapagliflozin than with placebo (at 6 months, 10.4% versus 7.3%, respectively, P<0.001; at 12 months, 12.4% versus 8.7%, P<0.001). Conversely, fewer patients in the dapagliflozin arm compared with the placebo arm had an increase in diuretic dose during follow-up, although again the proportion of patients in either treatment arm with an increase in diuretic dose was small (at 6 months, 5.8% versus 9.9%, P<0.001; at 12 months, 10.2% versus 14.2%,

Table 2. Loop Diuretic Doses and Changes in Loop Diuretic Dose From Baseline

	Placebo	Dapagliflozin	P Value	Odds Ratio (95% CI)
Baseline				
Daily dose (n=3697)*				
Median, mg	40 (20–80)	40 (20–80)	0.35	
Mean, mg	60.8±96.8	59.0±94.9	0.57	
14 d (n=4595)†				
Daily dose (n=3688)*				
Median, mg	40 (20–80)	40 (20–80)	0.41	
Mean, mg	60.9±97.5	59.3±97.0	0.62	
Decrease	32 (1.4)	35 (1.5)	0.72	1.10 (0.67–1.78)
Increase	40 (1.7)	27 (1.2)	0.11	0.67 (0.41–1.10)
No change	2222 (96.9)	2239 (97.3)	0.37	1.17 (0.83–1.65)
2 mo (n=4547)†				
Daily dose (n=3630)*				
Median, mg	40 (20–80)	40 (20–80)	0.24	
Mean, mg	62.2±102.3	59.1±99.1	0.36	
Decrease	81 (3.6)	117 (5.1)	0.009	1.47 (1.10–1.97)
Increase	116 (5.1)	76 (3.3)	0.003	0.64 (0.48–0.86)
No change	2074 (91.3)	2083 (91.5)	0.81	1.02 (0.83–1.26)
6 mo (n=4404)†				
Daily dose (n=3472)*				
Median, mg	40 (20–80)	40 (20–80)	0.019	
Mean, mg	62.8±104.6	58.9±101.4	0.26	
Decrease	161 (7.3)	230 (10.4)	<0.001	1.49 (1.20–1.84)
Increase	217 (9.9)	128 (5.8)	<0.001	0.56 (0.45–0.70)
No change	1817 (82.8)	1851 (83.8)	0.37	1.07 (0.91–1.26)
12 mo (n=4044)†				
Daily dose (n=3203)*				
Median, mg	40 (20–80)	40 (20–80)	0.027	
Mean, mg	65.6±109.4	59.8±104.2	0.13	
Decrease	176 (8.7)	252 (12.4)	<0.001	1.50 (1.22–1.84)
Increase	285 (14.2)	208 (10.2)	<0.001	0.69 (0.57–0.83)
No change	1551 (77.1)	1572 (77.4)	0.84	1.01 (0.87–1.17)
18 mo (n=2371)†				
Daily dose (n=1880)*				
Median, mg	40 (22.9–80)	40 (20–80)	0.086	
Mean, mg	71.0±140.1	60.6±119.0	0.084	
Decrease	122 (10.4)	154 (12.9)	0.055	1.29 (1.00–1.67)
Increase	184 (15.6)	166 (13.9)	0.24	0.87 (0.69–1.09)
No change	871 (74.0)	874 (73.2)	0.66	0.95 (0.79–1.15)

Data are presented as mean±SD or median (interquartile range) for continuous measures and number (percent) for categorical variables.

*Number of patients on a loop diuretic at given time point.

†Number of patients with determinate loop diuretic dose at both time points (including patients on no loop diuretic as 0 mg).

P<0.001). The likelihood of a change in diuretic dose was similar whether a logistic regression or a proportional odds model was used. In comparison, the findings were very similar in CHARM (Table II in the Data Supplement).

After an initial change in dose of diuretic, further changes tended to reverse the original change; for example, when the initial change was an increase in dose, the subsequent change was more likely to be a decrease (Figure III in the Data Supplement).

Table 3. Treatment Effect on Outcomes, Safety, and Events of Interest According to Diuretic Therapy at Baseline

| | No Diuretic (n=736) | | Furosemide-Equivalent Dose | | | |
| | | | <40 mg* (n=1311) | | 40 mg (n=1365) | |
	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin
Efficacy						
Primary composite outcome						
No.	45	28	108	96	134	109
Rate	9.0 (6.7–12.0)	5.2 (3.6–7.5)	12.1 (10.0–14.6)	10.1 (8.2–12.3)	14.0 (11.8–16.6)	10.9 (9.0–13.1)
Unadjusted HR	0.57 (0.36–0.92)		0.83 (0.63–1.10)		0.77 (0.60–0.99)	
Adjusted HR	0.53 (0.32–0.86)		0.83 (0.63–1.10)		0.76 (0.59–0.98)	
Hospitalization or urgent HF visit						
No.	28	15	65	54	87	63
Rate	5.6 (3.9–8.1)	2.8 (1.7–4.6)	7.3 (5.7–9.3)	5.7 (4.3–7.4)	9.1 (7.4–11.2)	6.3 (4.9–8.1)
Unadjusted HR	0.49 (0.26–0.91)		0.78 (0.55–1.12)		0.68 (0.49–0.94)	
Adjusted HR	0.43 (0.22–0.84)		0.77 (0.53–1.11)		0.67 (0.49–0.93)	
Urgent HF visit						
No.	3	1	7	2	6	2
Rate	0.6 (0.2–1.8)	0.2 (0.0–1.3)	0.8 (0.4–1.6)	0.2 (0.1–0.8)	0.6 (0.3–1.3)	0.2 (0.0–0.8)
Unadjusted HR	0.28 (0.03–2.70)		0.27 (0.06–1.32)		0.33 (0.07–1.63)	
Adjusted HR	…		0.22 (0.04–1.27)		0.29 (0.05–1.56)	
Cardiovascular death						
No.	25	16	62	54	76	68
Rate	4.8 (3.2–7.1)	2.9 (1.8–4.7)	6.6 (5.1–8.4)	5.5 (4.2–7.1)	7.5 (6.0–9.4)	6.5 (5.2–8.3)
Unadjusted HR	0.61 (0.32–1.14)		0.82 (0.57–1.18)		0.87 (0.63–1.21)	
Adjusted HR	0.60 (0.31–1.14)		0.85 (0.58–1.23)		0.87 (0.63–1.21)	
Hospitalization for HF or cardiovascular death						
No.	44	27	106	95	132	109
Rate	8.7 (6.5–11.7)	5.0 (3.4–7.3)	11.8 (9.8–14.3)	9.9 (8.1–12.2)	13.8 (11.6–16.3)	10.9 (9.0–13.1)
Unadjusted HR	0.57 (0.35–0.92)		0.84 (0.64–1.11)		0.78 (0.61–1.01)	
Adjusted HR	0.52 (0.32–0.87)		0.84 (0.64–1.12)		0.77 (0.60–1.00)	
Worsening renal function						
Number	4	2	3	5	8	5
Rate	0.8 (0.3–2.2)	0.4 (0.1–1.5)	0.3 (0.1–1.0)	0.5 (0.2–1.3)	0.8 (0.4–1.7)	0.5 (0.2–1.2)
Unadjusted HR	0.49 (0.09–2.69)		1.63 (0.39–6.81)		0.59 (0.19–1.82)	
Adjusted HR	0.11 (0.00–2.49)		2.10 (0.45–9.72)		0.57 (0.18–1.80)	
Death resulting from any cause						
No.	31	23	71	64	95	78
Rate	5.9 (4.2–8.4)	4.1 (2.8–6.2)	7.5 (6.0–9.5)	6.5 (5.1–8.3)	9.4 (7.7–11.5)	7.5 (6.0–9.3)
Unadjusted HR	0.71 (0.41–1.21)		0.86 (0.61–1.20)		0.80 (0.59–1.08)	
Adjusted HR	0.72 (0.42–1.26)		0.86 (0.61–1.21)		0.79 (0.59–1.07)	
Change in KCCQ TSS at 8 mo	3.1±1.1	5.8±1.1	2.8±0.8	4.6±0.8	2.7±0.8	7.6±0.8
Difference	2.6 (0.0 to 5.2)		1.9 (−0.1 to 3.9)		4.9 (2.6 to 7.1)	
Safety						
Discontinuation because of adverse event, n (%)	19 (5.2)	12 (3.3)	25 (3.9)	26 (3.9)	20 (3.0)	29 (4.2)
Volume depletion, n (%)	31 (8.5)	16 (4.3)	34 (5.3)	37 (5.5)	33 (4.9)	55 (8.0)
Renal adverse event, n (%)	21 (5.8)	8 (2.2)	31 (4.8)	27 (4.0)	46 (6.8)	44 (6.4)

(Continued)

Table 3. Continued

| Furosemide-Equivalent Dose | | Any Dose (n=3880) | | Int. P Value | |
| >40 mg (n=1204) | | | | | |
Placebo	Dapagliflozin	Placebo	Dapagliflozin	Any Dose	Dose Levels
196	146	438	351		
24.8 (21.5–28.5)	19.5 (16.6–23.0)	16.6 (15.1–18.2)	13.0 (11.7–14.4)		
0.78 (0.63–0.97)		0.78 (0.68–0.90)		0.23	0.61
0.76 (0.61–0.94)		0.78 (0.68–0.90)			
131	101	283	218		
16.6 (14.0–19.6)	13.5 (11.1–16.4)	10.7 (9.5–12.0)	8.1 (7.1–9.2)		
0.81 (0.62–1.05)		0.75 (0.63–0.90)		0.21	0.51
0.78 (0.60–1.01)		0.74 (0.62–0.88)			
6	5	19	9		
0.7 (0.3–1.5)	0.6 (0.3–1.5)	0.7 (0.4–1.1)	0.3 (0.2–0.6)		
0.84 (0.26–2.76)		0.47 (0.21–1.04)		0.75	0.60
0.69 (0.19–2.48)		0.48 (0.21–1.06)			
102	84	240	206		
11.5 (9.5–14.0)	10.4 (8.4–12.8)	8.4 (7.4–9.6)	7.2 (6.3–8.3)		
0.90 (0.67–1.20)		0.86 (0.71–1.03)		0.31	0.74
0.90 (0.67–1.21)		0.88 (0.73–1.06)			
195	144	433	348		
24.6 (21.3–28.2)	19.2 (16.3–22.6)	16.3 (14.9–17.9)	12.9 (11.6–14.3)		
0.78 (0.63–0.97)		0.78 (0.68–0.90)		0.21	0.58
0.75 (0.60–0.93)		0.78 (0.68–0.90)			
22	14	33	24		
2.6 (1.7–4.0)	1.8 (1.1–3.1)	1.2 (0.9–1.7)	0.9 (0.6–1.3)		
0.69 (0.35–1.35)		0.73 (0.43–1.23)		0.66	0.65
0.72 (0.37–1.42)		0.74 (0.44–1.25)			
123	103	289	245		
13.9 (11.6–16.6)	12.7 (10.5–15.4)	10.2 (9.1–11.4)	8.6 (7.6–9.8)		
0.91 (0.70–1.18)		0.85 (0.71–1.00)		0.53	0.82
0.91 (0.70–1.19)		0.87 (0.73–1.03)			
5.3±0.8	7.8±0.9	3.6±0.5	6.6±0.5		
2.4 (−0.2 to 5.1)		3.0 (1.7 to 4.4)		0.75	0.98
47 (7.6)	39 (6.7)	92 (4.7)	94 (4.9)	0.20	0.31
55 (8.9)	61 (10.5)	122 (6.3)	153 (7.9)	0.004	0.012
68 (11.0)	67 (11.5)	145 (7.5)	138 (7.1)	0.024	0.12

(Continued)

Table 3. Continued

	No Diuretic (n=736)		Furosemide-Equivalent Dose			
			<40 mg* (n=1311)		40 mg (n=1365)	
	Placebo	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Dapagliflozin
Other changes at 8 mo						
Hematocrit, %	−0.3±0.2	2.6±0.2	−0.3±0.1	2.4±0.1	−0.1±0.1	2.1±0.1
Difference	2.9 (2.5 to 3.4)		2.7 (2.3 to 3.1)		2.2 (1.8 to 2.5)	
SBP, mm Hg	−2.2±0.8	−3.3±0.8	−1.0±0.6	−2.6±0.6	0.4±0.6	−1.6±0.6
Difference	−1.1 (−3.3 to 1.0)		−1.6 (−3.2 to −0.1)		−2.0 (−3.5 to −0.4)	
Weight, kg	−0.01±0.19	−0.98±0.19	0.22±0.14	−1.06±0.14	−0.08±0.14	−0.89±0.14
Difference	−0.97 (−1.40 to −0.54)		−1.28 (−1.62 to −0.94)		−0.81 (−1.22 to −0.39)	
Creatinine, mg/dL	0.05±0.01	0.07±0.01	0.04±0.01	0.05±0.01	0.03±0.01	0.07±0.01
Difference	0.02 (−0.01 to 0.05)		0.01 (−0.02 to 0.03)		0.04 (0.01 to 0.06)	
NT-proBNP, pg/mL	−65±149	−194±146	265±112	−173±110	−10±110	−365±108
Difference	−126 (−395 to 143)		−437 (−740 to −134)		−360 (−713 to −6)	

(Continued)

Clinical Outcomes According to Baseline Diuretic Treatment

The cumulative incidences of the primary composite outcome, hospitalization or urgent visit for heart failure, death resulting from cardiovascular causes, and death resulting from any cause were all lowest in patients not taking any diuretic and highest in those receiving a furosemide-equivalent dose of >40 mg (Figure IV in the Data Supplement).

The risks of the primary composite outcome and its components (hospitalization or urgent visit for heart failure and death resulting from cardiovascular causes) were reduced by dapagliflozin compared with placebo in all patients, whether treated or not treated with a diuretic, and regardless of dose in patients receiving a diuretic (Table 3 and Figure 2). The single possible exception to this was in the group of patients taking a combination of a loop and another diuretic at baseline, although the number of events in this group was small, the 95% CI around the hazard ratio was wide, and the interaction P value was nonsignificant (Table I in the Data Supplement). Findings for the components of the primary end point and the other mortality/morbidity outcomes were consistent.

When the effect of randomized treatment was examined as a function of change in diuretic dose from baseline to 6 months (decrease, increase, or no change), the incidence of the primary composite outcome was lower with dapagliflozin compared with placebo in each diuretic dose change group (P for interaction=0.27; Figure V in the Data Supplement).
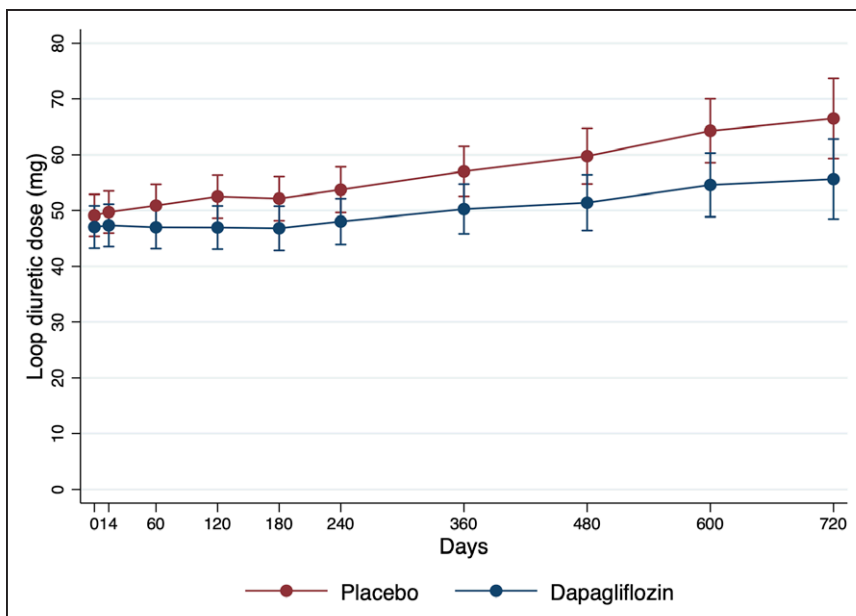

Figure 1. Change in loop diuretic dose over time in all patients.

Table 3. Continued

| Furosemide-Equivalent Dose | | | | Int. *P* Value | |
| >40 mg (n=1204) | | Any Dose (n=3880) | | | |
Placebo	Dapagliflozin	Placebo	Dapagliflozin	Any Dose	Dose Levels
−0.2±0.1	2.1±0.2	−0.2±0.1	2.2±0.1		
2.3 (1.8 to 2.7)		2.4 (2.1 to 2.6)		0.75	0.31
0.1±0.6	−0.5±0.6	−0.1±0.3	−1.6±0.3		
−0.7 (−2.4 to 1.1)		−1.5 (−2.4 to −0.6)		0.79	0.72
0.07±0.15	−0.51±0.15	0.07±0.08	−0.84±0.08		
−0.58 (−1.06 to -0.10)		−0.91 (−1.14 to −0.67)		0.97	0.83
0.06±0.01	0.08±0.01	0.04±0.01	0.07±0.01		
0.02 (−0.01 to 0.06)		0.02 (0.01 to 0.04)		0.27	0.10
−22±117	−148±120	78±65	−237±65		
−132 (−449 to 186)		−314 (−504 to −124)		0.47	0.59

Rates are per 100-patient years. Changes from baseline to 8 months are shown as estimate±standard error. All unadjusted models include prior heart failure hospitalization (except for death resulting from any cause and worsening renal function) and trial stratification. Unadjusted model for worsening renal function includes estimated glomerular filtration rate. All adjusted models include age, sex, race, New York Heart Association functional class, left ventricular ejection fraction, heart failure cause, NT-proBNP (log), heart rate, systolic blood pressure, estimated glomerular filtration rate, atrial fibrillation, and (except for death resulting from any cause) prior heart failure hospitalization. HR indicates hazard ratio; KCCQ TSS, Kansas City Cardiomyopathy Questionnaire total symptom score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and SBP, systolic blood pressure.

*Patients on a nonloop diuretic only are included in this group (n=183).

The placebo-corrected improvement in Kansas City Cardiomyopathy Questionnaire total symptom score

Figure 2. Forest plot of efficacy outcomes according to diuretic therapy at baseline.

was consistent in patients treated with dapagliflozin, regardless of diuretic treatment or no diuretic treatment or diuretic dose (Table 3).

Because the number of patients experiencing the prespecified renal composite outcome was small overall, meaningful interpretation of the subgroups was difficult. However, the rate of this outcome was highest in the patients on the highest diuretic dose and did not differ between dapagliflozin and placebo in that diuretic dose group.
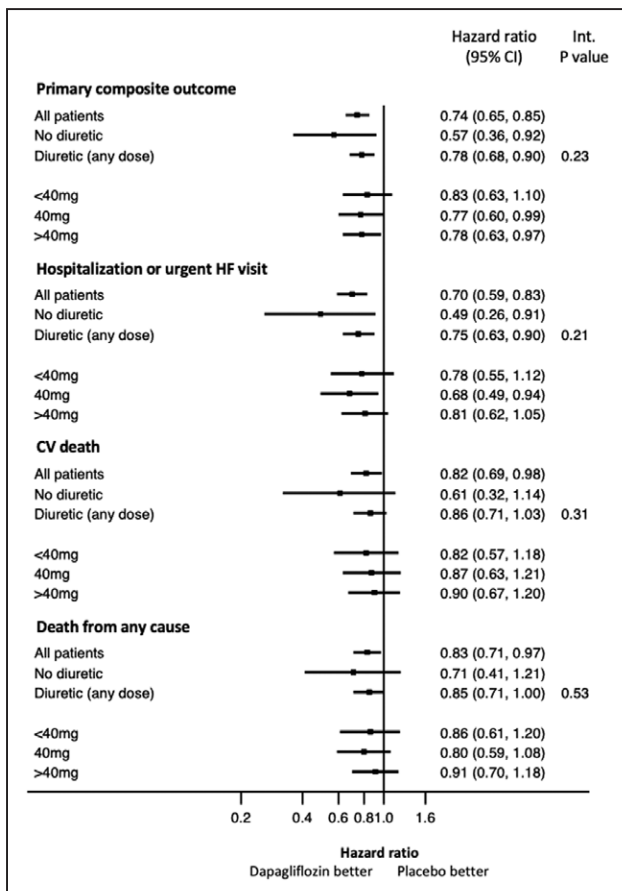
Safety

The frequency of volume depletion, renal adverse events, and study drug discontinuation as a result of an adverse event varied according to background diuretic therapy in the placebo arm. The rates of all adverse outcomes of interest were lower in patients not treated with a diuretic at baseline compared with patients treated with a diuretic. Among patients treated with a diuretic at baseline, the placebo rate of each adverse outcome was highest in patients on a dose of >40 mg furosemide equivalent (Table 3).

When the randomized treatment arms were compared, volume depletion and renal adverse events were significantly less common in patients allocated to dapagliflozin compared with those randomized to placebo in patients not taking diuretics at baseline. In patients taking diuretics, volume depletion was slightly more common with dapagliflozin than with placebo in patients in the higher-dose diuretic groups. Other adverse effects were not different, and there was no difference

between treatment groups in study drug discontinuation for adverse events.

Other Measures of Interest

From baseline to 8 months, the placebo-corrected increases in hematocrit and creatinine and decreases in systolic blood pressure and weight with dapagliflozin were similar in patients receiving and those not receiving diuretics at baseline (Table 3 and Figure 3). Although the decrease in NT-proBNP was numerically greater in patients receiving diuretics, the variance in this measure was large, and the difference was not statistically significant.

In a comparison across the diuretic dose groups, none of the placebo-corrected changes with dapagliflozin differed significantly, although the changes tended to be smallest in the highest diuretic dose group.

The elevation in hematocrit with dapagliflozin was sustained, regardless of dose of loop diuretic (Table 3 and Figure 3). This persisted regardless of whether the dose of conventional diuretic was decreased, was increased, or remained the same at 6 and 12 months (Figure VI in the Data Supplement).

DISCUSSION

The key finding of the present analyses is that the benefits of dapagliflozin in DAPA-HF were obtained regardless of the use of background diuretic therapy or dose of diuretic therapy. Likewise, the tolerability and safety profile of dapagliflozin compared with placebo was similar regardless of concomitant treatment with a conventional diuretic or dose of conventional diuretic. Last, most patients did not have a change in dose of diuretic during follow-up, and the mean daily dose of diuretic did not differ between the dapagliflozin and placebo groups.

The use of diuretic therapy at baseline in DAPA-HF was in keeping with other reports in large cohorts of patients with HFrEF, predominantly in New York Heart Association class II and III. In DAPA-HF, 16% of patients were not treated with a diuretic at baseline (not counting an MRA as a diuretic), a proportion consistent with that reported in other recent trials and registries.[5–10]

Among all patients randomized in DAPA-HF, 81% were treated with a loop diuretic, also in keeping with other studies.[11–15] In DAPA-HF, the mean and median furosemide-equivalent doses were 60 and 40 mg, respectively, with the largest proportion receiving a daily dose of 40 mg (35.2% of patients taking any diuretic). In PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor Neprilysin Inhibitor] With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), the mean daily dose was 49 mg, and

60.6% of patients were treated with between 20 and 40 mg at baseline, although the dose conversion calculation was different in this study.[11] Additional information on loop diuretic dosing is hard to obtain; however, in the CHARM HFrEF trials, in the recent HFrEF registry from the Netherlands, and in the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), the median dose was also 40 mg.[4,12,15]

Despite notable differences in patient characteristics according to use of diuretic at baseline (and according to dose of diuretic among those taking diuretics), the benefit of dapagliflozin was consistent in all the diuretic groups studied. As expected, patients not receiving diuretics had a more favorable clinical profile and were at lowest risk of the clinical outcomes evaluated. The converse was true of patients in the highest diuretic dose category. Although the magnitude of the benefit from dapagliflozin appeared to be larger in patients not treated with a diuretic, there were relatively few patients in this group, and the CIs around the point estimate for the effect of treatment were wide. A statistical test for interaction between background diuretic therapy and the effect of randomized treatment was not significant. In addition, there was no suggestion of any dose response in relation to baseline diuretic therapy, and diuretic dose group did not modify the effect of randomized treatment in an interaction test. Consistent with this, the effect of dapagliflozin on other measures such as systolic blood pressure, weight, creatinine, and hematocrit did not vary substantially between patients treated and those not treated with a diuretic and across the diuretic dose groups.

The tolerability and safety of dapagliflozin were also consistent in patients treated and those not treated with diuretics and across the diuretic dose groups studied. In this analysis, our focus was on the prespecified adverse events related to volume depletion and renal dysfunction. Adverse events related to volume depletion were relatively infrequent overall but, as expected, were more common in patients receiving higher doses of diuretic (ranging from 5.3% to 8.9% in the placebo arm, from the lowest to highest diuretic dose group). These events were numerically slightly more common in patients randomly assigned to dapagliflozin compared with those assigned to placebo, although the excess was small (0.2% in the lowest diuretic dose group, 3.1% in the middle dose group, and 1.6% in the highest dose group). More surprisingly, the rate of adverse events related to volume depletion was as high in the patients not receiving diuretic at baseline as in patients in the highest diuretic dose group (8.5% and 8.9% in the placebo arms, respectively). In patients not receiving diuretic at baseline, the rate of adverse events related to volume depletion after randomization was lower in patients assigned to dapagliflozin than in those assigned to placebo. Similar patterns were seen for renal adverse
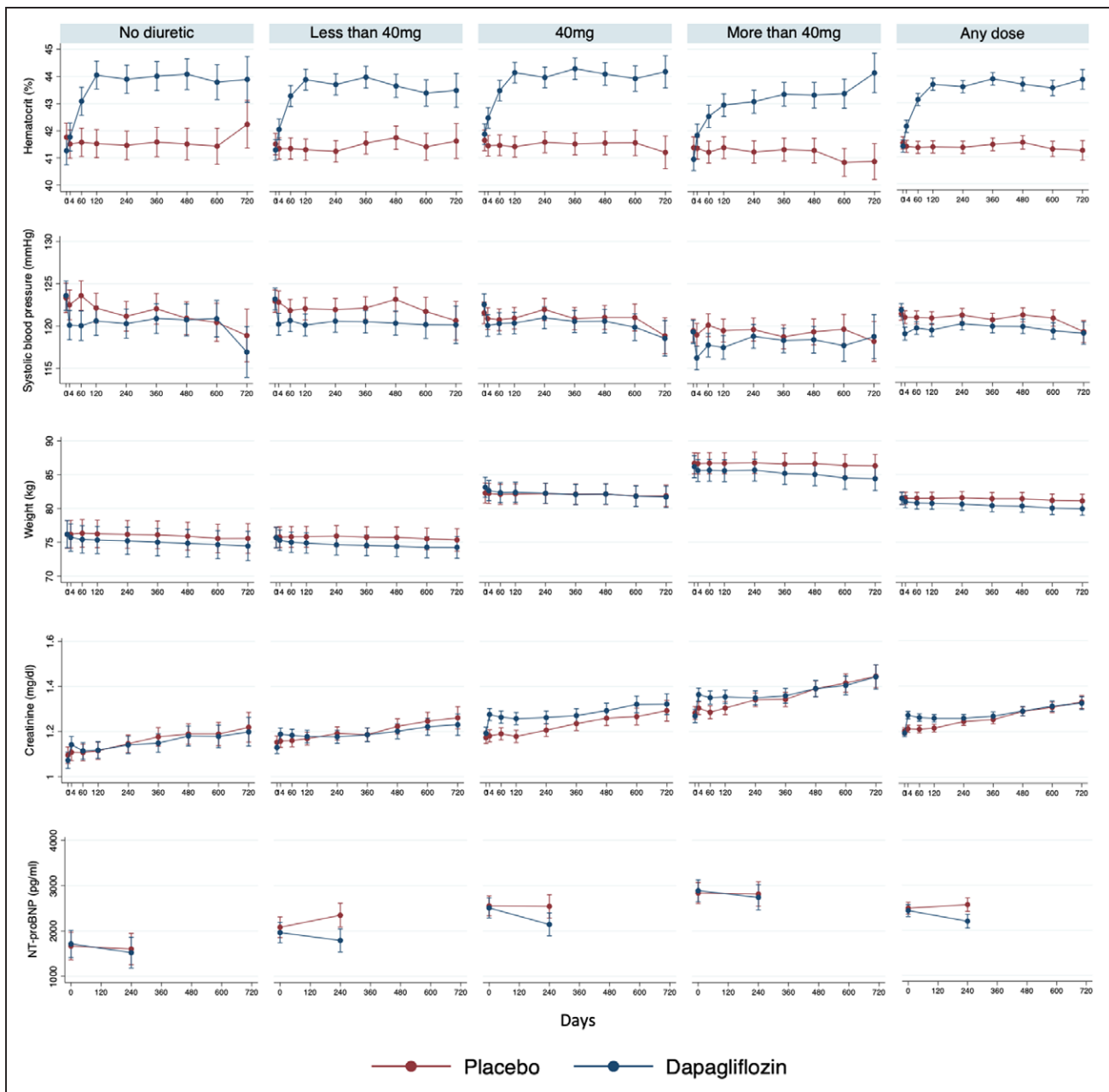
Figure 3. Changes in laboratory and clinical measures according to diuretic therapy at baseline.

events in the placebo group in relation to baseline diuretic therapy (more common with increasing diuretic dose, more common in patients not taking diuretics than in those in the lowest diuretic dose group in the placebo arm). However, renal adverse events were generally less common in patients assigned to dapagliflozin compared with those assigned to placebo, a pattern opposite that observed for volume depletion. Few patients stopped study drug for an adverse event, generally <5% in any subgroup except patients taking >40 mg/d furosemide or equivalent, and in that subgroup, the proportion was 7.6% in the placebo group and 6.7% in the dapagliflozin group.

Although our findings go some way to assuaging the hypothetical safety concerns about combining SGLT2 inhibitors with conventional diuretics (and MRAs) in HFrEF, they do not directly address the reported diuretic action of SGLT2 inhibitors. However, our analyses provide evidence that the combination of dapagliflozin with conventional diuretics in DAPA-HF did not have a major impact on the use of loop diuretics in the majority of patients. The mean dose of furosemide did not differ between the dapagliflozin and placebo group during follow-up, and most patients did not change their diuretic dose. A small proportion did have an increase or decrease in dose, and an increase was less likely and a decrease was more

likely in the dapagliflozin arm compared with the placebo arm (between-treatment difference in proportion was <5% at all time points examined). Moreover, this small difference was similar to that seen with other treatments that improve symptoms and reduce worsening of heart failure status over time but do not have diuretic properties, as illustrated in the comparison with CHARM and in a report from the PARADIGM-HF trial.[11] These findings do not preclude a diuretic effect of dapagliflozin (and clinical benefit related to such an action), and previous studies have shown a short-lived initial natriuresis with SGLT2 inhibitors with restoration of a new sodium volume steady state within days to weeks of treatment starting.[16–19] In addition, the increased electrolyte-free water excretion induced by SGLT2 inhibitors and possible enhanced peripheral sodium storage are other factors that may contribute to the impact of these agents on whole-body sodium volume status.[20,21] However, the similar effects of dapagliflozin in patients with chronic kidney disease and in those without diabetes mellitus, 2 groups who should have had less diuretic effect from SGLT2 inhibition, argue for additional mechanisms of benefit.[2] Although the increase in hematocrit seen with SGLT2 inhibitors is also often said to reflect a diuretic-induced reduction in blood volume, this assumption may be overly simplistic. The increase in hematocrit in DAPA-HF was similar, regardless of use of diuretic at baseline or baseline loop diuretic dose, and was seen despite rates of volume depletion similar to those observed in the placebo group. The elevation in hematocrit also persisted in individuals with a reduction in loop diuretic dose at both 6 and 12 months. Collectively, these findings support the notion that factors other than hemoconcentration such as augmentation of erythropoiesis may account for the sustained increase in hematocrit seen with dapagliflozin. A reduction in circulating levels of hepcidin, an increase in levels of the hepcidin inhibitor erythroferrone, and an increase in erythropoietin have been shown to occur with the use of SGLT2 inhibitors.[22–24]

The study has some limitations. This was not a prespecified analysis. Furosemide-equivalent loop diuretic doses were not available for all patients. Dose changes were examined at specified time points, and fluctuations in doses in between these time points were not accounted for in this analysis. We did not have data on other markers of natriuresis and diuresis such as urine volumes and urinary sodium excretion. Our results apply only to ambulatory patients with HFrEF predominantly in New York Heart Association classes II and III who fulfilled the trial inclusion and exclusion criteria and received modest doses of conventional diuretic therapy. We do not know what the efficacy and safety of dapagliflozin might be in different patients receiving a different treatment in a different setting.

Conclusions

We found that the benefits of dapagliflozin were obtained regardless of background diuretic therapy and across the range of background doses of diuretic used in DAPA-HF. The tolerability and safety of dapagliflozin were similar regardless of whether patients were treated or not treated with a standard diuretic and dose of conventional diuretic. Treatment with dapagliflozin did not lead to a change in mean dose of background diuretic therapy in most trial participants.

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Dr Anand reports receiving fees for serving as US national leader of a trial from AstraZeneca; fees for serving on a steering committee from ARCA Biopharma, Amgen, LivaNova, and Novartis; fees for serving on an end-point committee from Boehringer Ingelheim; fees for serving as chair of a data and safety monitoring board from Boston Scientific; and advisory board fees from Zensun. Dr Bělohlávek reports receiving advisory board fees from Novartis and Pfizer and lecture fees from Getginge. Drs Bengtsson, Greasley, Lindholm, and Sjöstrand report being employed by AstraZeneca. Dr de Boer has received grant support (paid to University Medical Center Groningen [UMCG]), consulting fees, and lecture fees from AstraZeneca, grant support (paid to UMCG) from Bristol-Myers Squibb, grant support (paid to UMCG) and consulting fees from Abbott, grant support (paid to UMCG) and lecture fees from Roche, and consulting fees from MandalMed and is a minority shareholder in scPharmaceuticals. 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Supplemental Materials

Data Supplement Tables I and II
Data Supplement Figures I–VI

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