JACC: HEART FAILURE VOL. 10, NO. 5, 2022

CLINICAL RESEARCH

Relationship of Dapagliflozin With Serum Sodium

Findings From the DAPA-HF Trial

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ABSTRACT

OBJECTIVES This study aimed to assess the prognostic importance of hyponatremia and the effects of dapagliflozin on serum sodium in the DAPA-HF (Dapagliflozin And Prevention of Adverse outcomes in Heart Failure) trial.

BACKGROUND Hyponatremia is common and prognostically important in hospitalized patients with heart failure with reduced ejection fraction, but its prevalence and importance in ambulatory patients are uncertain.

METHODS We calculated the incidence of the primary outcome (cardiovascular death or worsening heart failure) and secondary outcomes according to sodium category (≤135 and >135 mmol/L). Additionally, we assessed: 1) whether baseline serum sodium modified the treatment effect of dapagliflozin; and 2) the effect of dapagliflozin on serum sodium.

RESULTS Of 4,740 participants with a baseline measurement, 398 (8.4%) had sodium ≤135 mmol/L. Participants with hyponatremia were more likely to have diabetes, be treated with diuretics, and have lower systolic blood pressure, left ventricular ejection fraction, and estimated glomerular filtration rate. Hyponatremia was associated with worse outcomes even after adjustment for predictive variables (adjusted HRs for the primary outcome 1.50 [95% CI: 1.23-1.84] and all-cause death 1.59 [95% CI: 1.26-2.01]). The benefits of dapagliflozin were similar in patients with and without hyponatremia (HR for primary endpoint: 0.83 [95% CI: 0.57-1.19] and 0.73 [95% CI: 0.63-0.84], respectively, *P* for interaction = 0.54; HR for all-cause death: 0.85 [95% CI: 0.56-1.29] and 0.83 [95% CI: 0.70-0.98], respectively, *P* for interaction = 0.96). Between baseline and day 14, more patients on dapagliflozin developed hyponatremia (11.3% vs 9.4%; *P* = 0.04); thereafter, this pattern reversed and at 12 months fewer patients on dapagliflozin had hyponatremia (4.6% vs 6.7%; *P* = 0.003).

CONCLUSIONS Baseline serum sodium concentration was prognostically important, but did not modify the benefits of dapagliflozin on morbidity and mortality in heart failure with reduced ejection fraction. (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure [DAPA-HF]: NCT03036124) (J Am Coll Cardiol HF 2022;10:306-318) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ISSN 2213-1779 https://doi.org/10.1016/j.jchf.2022.01.019

Hyponatremia is common in patients hospitalized with decompensated heart failure (HF), occurring in 20% to 30% of such individuals.[1-4] In these patients, hyponatremia is an established predictor of adverse outcomes, associated with both inpatient and longer-term mortality.[1-4] The causes of hyponatremia in HF are complex, but they can be simplified into those causing impaired water excretion and those increasing sodium loss (both reduced water excretion and increased sodium loss can contribute to hyponatremia).[4-7] Renin-angiotensin-aldosterone system and sympathetic nervous system activation lead to a nonosmotically mediated release of arginine vasopressin which inhibits free-water excretion and stimulates thirst, leading to increased water intake.[4-7] Reduced glomerular filtration (and as a result, renal tubular flow) leads to an impaired ability of the kidney to excrete free water.[4-7] Large doses of diuretic agents may lead to excessive sodium loss, especially if coupled with restriction of sodium intake; thiazide diuretic agents may also inhibit urinary dilution.[4-7] Whether hyponatremia is causally related to mortality or is simply a marker of the severity of HF remains unknown, although low serum sodium concentration remains an independent predictor of mortality in adjusted models incorporating other prognostic variables.[4-6,8]

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Much less is known about the prevalence or the prognostic significance of hyponatremia in ambulatory patients with heart failure and reduced ejection fraction (HFrEF), especially in such individuals receiving contemporary treatments.[9-11] Sodium glucose cotransporter 2 (SGLT2) inhibitors have been recently introduced as a treatment for HFrEF.[12-14] SGLT2 inhibitors inhibit proximal renal tubular reabsorption of glucose, coupled with sodium, leading to an initial osmotic diuresis and natriuresis. The effects of these agents (added to conventional diuretic agents and mineralocorticoid receptor antagonists) on serum sodium concentration in HFrEF are unknown and probably complex. Therefore, we investigated the effect of dapagliflozin on serum sodium in the DAPA-HF (Dapagliflozin And Prevention of Adverse Outcomes in Heart Failure; "Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure") trial.[12] We also examined whether sodium concentration at baseline modified the effects of dapagliflozin on clinical outcomes in the DAPA-HF trial.

ABBREVIATIONS AND ACRONYMS

eGFR = estimated glomerular filtration rate

HF = heart failure

HFrEF = heart failure and reduced ejection fraction

KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-total symptom score

LVEF = left ventricular ejection fraction

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

SBP = systolic blood pressure

SGLT2 = sodium-glucose cotransporter 2

HYPOTHESIS

This study was designed to investigate the prognostic significance of hyponatremia in ambulatory patients with HFrEF, the efficacy of dapagliflozin according to baseline serum sodium concentration, and the effect of dapagliflozin on serum sodium in the DAPA-HF trial.

METHODS

DAPA-HF was a prospective, randomized, double-blind, controlled trial in patients with HFrEF, which evaluated the efficacy and safety of dapagliflozin 10 mg once daily, compared with matching placebo, added to standard care.[12] The ethics committees at each of the 410 participating institutions (in 20 countries) approved the protocol, and all patients gave written informed consent.

STUDY PATIENTS. Patients ≥18 years of age in New York Heart Association (NYHA) functional class II-IV with a left ventricular ejection fraction (LVEF) ≤40% and an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) level were eligible if receiving optimal pharmacological and device therapy.[12] The main exclusion criteria included type 1 diabetes mellitus, symptomatic hypotension/systolic blood pressure (SBP) <95 mm Hg, and estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. There was no serum sodium concentration inclusion or exclusion criterion.

MEASUREMENT OF SERUM SODIUM (CREATININE AND OTHER ELECTROLYTES). Blood samples were

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 12, 2021; revised manuscript received January 20, 2022, accepted January 24, 2022.

TABLE 1 Patient Characteristics According to Baseline Sodium Category

	Baseline Sodium		
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	Na^+ >135 mmol/L (n = 4,342, 91.6%)	*P* Value
Age, y	66.1 ± 10.6	66.4 ± 10.9	0.61
Age >75 y	73 (18.3)	928 (21.4)	0.31
Female	82 (20.6)	1,027 (23.7)	0.17
Race or ethnic group			0.009
White	266 (66.8)	3,063 (70.5)	
Black	17 (4.3)	209 (4.8)	
Asian	102 (25.6)	1,014 (23.4)	
Other	13 (3.3)	56 (1.3)	
Region			<0.001
North America	74 (18.6)	601 (13.8)	
Latin America	90 (22.6)	727 (16.7)	
Europe	135 (33.9)	2,017 (46.5)	
Asia Pacific	99 (24.9)	997 (23.0)	
SBP, mm Hg	118 ± 16	122 ± 16	<0.001
Heart rate, beats/min	72 ± 12	71 ± 12	0.31
BMI, kg/m^2	27.1 ± 5.4	28.3 ± 6.0	<0.001
Classification			0.027
Obesity (≥30)	116 (29.1)	1,554 (35.8)	
Overweight (25-29.9)	147 (36.9)	1,573 (36.2)	
Normal weight (18.5-24.9)	126 (31.7)	1,135 (26.2)	
Underweight (<18.5)	9 (2.3)	78 (1.8)	
Hemoglobin, g/L	132.6 ± 16.3	135.8 ± 16.2	<0.001
Hematocrit, %	40.7 ± 5.2	41.5 ± 5.0	0.002
HbA1c, %	7.3 ± 2.2	6.4 ± 1.2	<0.001
Serum creatinine, μmol/L	111.0 ± 35.5	103.8 ± 29.8	<0.001
Serum sodium, mmol/L	133.4 ± 2.1	140.2 ± 2.5	<0.001
Serum urea, mg/dL	26.2 ± 13.4	23.0 ± 9.7	<0.001
eGFR, mL/min/1.73 m^2	63.2 ± 19.0	66.0 ± 19.4	0.005
Clinical HF features			
Ischemic cardiomyopathy	233 (58.5)	2,438 (56.1)	0.36
LVEF, %	29.8 ± 7.2	31.2 ± 6.7	<0.001
NT-proBNP, pg/mL	1,531 (891-3,019)	1,431 (853-2,626)	0.055
NYHA functional class			0.85
II	265 (66.6)	2,934 (67.6)	
III	130 (32.7)	1,368 (31.5)	
IV	3 (0.8)	40 (0.9)	
KCCQ-TSS (baseline)	73.2 ± 22.5	73.7 ± 21.7	0.67

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obtained at randomization 14 days, 2, 4, 8, and 12 months, and every 4 months thereafter.

PRESPECIFIED TRIAL OUTCOMES. The primary outcome of DAPA-HF was the composite of worsening HF (HF hospitalization or urgent visit for HF requiring intravenous therapy) or cardiovascular death, whichever occurred first. Prespecified secondary endpoints included HF hospitalization or cardiovascular death, HF hospitalizations (first and recurrent), and cardiovascular deaths. The change from baseline to 8 months in Kansas City Cardiomyopathy Questionnaire-total symptom score (KCCQ-TSS) was an additional secondary endpoint, with the proportion having a 5-point or more increase or decrease in their score at 8 months determined as previously described. There was also a prespecified secondary renal composite outcome, but this was not evaluated further in this study because of the small number of events.

SERUM SODIUM, DEFINITION OF HYPONATREMIA, AND CLINICAL OUTCOMES. Hyponatremia was defined as serum sodium concentration ≤135 mmol/L.[7] Sodium concentration and sodium category (normal or reduced, ie, >135 mmol/L vs ≤135 mmol/L) were defined at baseline and each follow-up visit to 1 year. The association between baseline sodium category and subsequent clinical outcomes was also analyzed, along with the effects of dapagliflozin on clinical outcomes according to baseline sodium concentration, as described in the statistical analysis section below.

STATISTICAL ANALYSIS. Baseline characteristics were summarized as mean ± SD, median (IQR), or percentages. We used the Kaplan-Meier estimate and Cox proportional hazards models, stratified by diabetes status, and adjusted for history of HF hospitalization (except for all-cause death) and treatment-group assignment to examine the primary and secondary outcomes, with further models adjusted for known predictors of risk in patients with HF, including: age, sex, race, geographic region, HF duration, heart rate, SBP, body mass index, NYHA functional class, LVEF, eGFR, serum hemoglobin, NT-proBNP, etiology of HF, history of atrial fibrillation, history of chronic obstructive pulmonary disease, use of loop diuretic therapy, use of other diuretics, and use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker or angiotensin receptor-neprilysin inhibitors. Effect modification of treatment effect by baseline hyponatremia status was assessed by a likelihood ratio test. The differences between treatment groups in the proportion of patients with a clinically significant (≥5 points) improvement or deterioration in KCCQ-TSS at 8 months was analyzed using the methods described previously and presented as an odds ratio for each baseline sodium category.[12] Safety analyses were performed in randomized patients who had received at least 1 dose of dapagliflozin or placebo. The interaction between baseline sodium category and randomized treatment on the occurrence of the prespecified safety outcomes was tested in a logistic regression model.

The relationship between baseline sodium as a continuous variable (adjusted for randomized treatment and history of HF hospitalization [apart from all-cause death] with stratification by diabetes status) and the risk of the primary outcome, its composite, and all-cause death was examined as a restricted

cubic spline.[15] This was repeated with additional adjustment for the known HF risk predictors listed above. The effect of dapagliflozin compared with placebo on each of the major clinical endpoints over baseline sodium as a continuous variable was modelled as a fractional polynomial. Changes in serum sodium, SBP, eGFR and hematocrit were analyzed using a mixed model for repeated measurements (adjusted for baseline values, visit, randomized treatment, and interaction of treatment and visit with a random intercept and slope per patient).

All analyses were conducted using Stata version 16.0 (StataCorp) and SAS version 9.4 (SAS Institute). A value of $P < 0.05$ was considered statistically significant.

RESULTS

A baseline serum sodium measurement was available in 4,740 patients and showed a normal distribution (Supplemental Figure 1); 398 (8.4%) participants had a value ≤135 mmol/L (**Table 1**), of which 379 participants (8.0%) had a baseline serum sodium of 130 to 135 mmol/L, 16 (0.34%) with baseline sodium of 125 to 129 mmol/L, and 3 (0.06%) with baseline sodium <125 mmol/L. There were many statistically significant differences between the 2 groups. Participants with hyponatremia were more likely to have diabetes (58.3% vs 43.9%), compared to those with serum sodium >135 mmol/L. Patients with a serum sodium ≤135 mmol/L had a lower SBP (118 ± 16 mm Hg vs 122 ± 16 mm Hg), lower LVEF (29.8 ± 7.2% vs 31.2 ± 6.7%), and lower eGFR (63.2 ± 19.0 mL/min/1.73 m^2 vs 66.0 ± 19.4 mL/min/1.73 m^2). Other differences between patients with and without hyponatremia included a lower body mass index and lower hemoglobin in the former group; patients with hyponatremia had a borderline higher NT-proBNP than those with sodium >135 mmol/L (**Table 1**). Patients with hyponatremia were more often treated with a diuretic, mineralocorticoid receptor antagonist (MRA), and digoxin compared to those with sodium >135 mmol/L.

The baseline characteristics independently associated with hyponatremia are shown in Supplemental Table 1. Geographic region (North America and South America), lower SBP, body mass index, and hemoglobin level were each associated with hyponatremia, as was treatment with an MRA and a non-loop diuretic. The baseline characteristics of patients treated with loop diuretic, other (mainly thiazide) diuretics, both types of diuretic, or no diuretic (including concomitant MRA use) are shown in Supplemental Table 2.

TABLE 1 Continued

	Baseline Sodium		
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	Na^+ >135 mmol/L (n = 4,342, 91.6%)	*P* Value
Medical history			
Hypertension	287 (72.1)	3,233 (74.5)	0.31
Diabetes	232 (58.3)	1,907 (43.9)	<0.001
Atrial fibrillation (history)	145 (36.4)	1,673 (38.5)	0.41
Atrial fibrillation/flutter (ECG)	100 (25.1)	1,028 (23.7)	0.52
Prior HF hospitalization	185 (46.5)	2,062 (47.5)	0.70
MI	180 (45.2)	1,910 (44.0)	0.63
Stroke	47 (11.8)	419 (9.6)	0.17
COPD	47 (11.8)	537 (12.4)	0.75
CKD (eGFR<60 mL/min/1.73 m^2)	183 (46.0)	1,741 (40.1)	0.022
Anemia[a]	144 (36.5)	1,157 (26.8)	<0.001
Treatments at randomization			
ACEi	221 (55.5)	2,438 (56.1)	0.81
ARB	105 (26.4)	1,200 (27.6)	0.59
ACEi/ARB/ARNI	366 (92.0)	4,072 (93.8)	0.15
Beta blocker	376 (94.5)	4,178 (96.2)	0.085
Any diuretic	354 (88.9)	3,651 (84.1)	0.01
Loop diuretic	332 (83.4)	3,490 (80.4)	0.14
Other diuretic	65 (16.3)	447 (10.3)	<0.001
Digitalis	97 (24.4)	790 (18.2)	0.002
MRA	313 (78.6)	3,056 (70.4)	<0.001
Anticoagulant	169 (42.5)	1,800 (41.5)	0.70
Antiplatelet	228 (57.3)	2,361 (54.4)	0.26
Statin	271 (68.1)	2,903 (66.9)	0.62
SSRI/SNRI	26 (6.5)	187 (4.3)	0.04
PPI	139 (34.9)	1,263 (29.1)	0.015
ICD/CRT-D	108 (27.1)	1,132 (26.1)	0.64
CRT-P/CRT-D	34 (8.5)	320 (7.4)	0.39

Values are mean ± SD, n (%), or median (IQR). [a]Anemia: Hemoglobin <130 g/L in males and hemoglobin <120 g/L in females.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy with pacemaker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; Hb1Ac = hemoglobin A1c; HF = heart failure; ICD = implantable cardioverter-defibrillator; KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire-total symptom score; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PPI = proton pump inhibitor; SBP = systolic blood pressure; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

CARDIOVASCULAR OUTCOMES ACCORDING TO BASELINE SERUM SODIUM. Primary and secondary trial outcomes related to hyponatremia. Incidence rates of the primary and secondary outcomes of the trial were substantially higher in patients with hyponatremia at baseline, compared to those without (**Table 2, Central Illustration,** Supplemental Figure 2). The elevated risk associated with hyponatremia persisted after comprehensive adjustment for other predictors of worse outcomes, including NT-proBNP, with an adjusted HR for the primary outcome of 1.50 (95% CI: 1.23-1.84). The adjusted HR for all-cause death (compared to patients with normal serum sodium) was 1.59 (95% CI: 1.26-2.01).

TABLE 2 Event Rate (Per 100 Person-Years) and Hazard Ratios for Trial Outcomes According to Baseline Sodium Category

	Baseline Sodium		
	Na^+ ≤135 mmol/L (n = 398, 8.4%)	Na^+ >135 mmol/L (n = 4,342, 91.6%)	*P* Value
Primary endpoint (worsening HF or cardiovascular death)	115 (28.9)	772 (17.8)	
Event rate per 100 person-y (95% CI)	22.2 (18.5-26.7)	13.0 (12.1-13.9)	<0.001
Unadjusted HR (95% CI)	1.63 (1.34-1.99)	1.00 (ref)	<0.001
Adjusted HR (95% CI)	1.50 (1.23-1.84)	1.00 (ref)	<0.001
Hospitalization or urgent visit for HF	68 (17.1)	494 (11.4)	
Event rate per 100 person-y (95% CI)	13.1 (10.4-16.7)	8.3 (7.6-9.1)	<0.001
Unadjusted HR (95% CI)	1.49 (1.16-1.93)	1.00 (ref)	0.002
Adjusted HR (95% CI)	1.36 (1.05-1.77)	1.00 (ref)	0.022
Cardiovascular death	73 (18.3)	427 (9.8)	
Event rate per 100 person-y (95% CI)	12.9 (10.3-16.3)	6.8 (6.2-7.5)	<0.001
Unadjusted HR (95% CI)	1.81 (1.41-2.33)	1.00 (ref)	<0.001
Adjusted HR (95% CI)	1.52 (1.18-1.97)	1.00 (ref)	0.001
All-cause mortality, number of events	88 (22.1)	517 (11.9)	
Event rate per 100 person-y (95% CI)	15.6 (12.6-19.2)	8.2 (7.6-9.0)	<0.001
Unadjusted HR (95% CI)	1.81 (1.45-2.28)	1.00 (ref)	<0.001
Adjusted HR (95% CI)	1.59 (1.26-2.01)	1.00 (ref)	<0.001

Values are n (%) or HR (95% CI). Models for death/hospitalization outcomes adjusted for age; sex; treatment arm; race; region; duration of HF; previous HF hospitalization; heart rate; SBP; BMI; NYHA functional classification; LVEF; eGFR; etiology of HF; history of atrial fibrillation, diabetes, and chronic obstructive pulmonary disease; serum hemoglobin; NT-proBNP; and use of loop diuretic therapy, other diuretic therapy, beta-blocker therapy, and ACEi or ARB or ARNI.

ref = reference value; other abbreviations as in Table 1.

Analyses using baseline sodium as a continuous variable showed that the nadir in event rates for all the outcomes of interest was around a sodium concentration of approximately 141 mmol/L to 142 mmol/L (**Figure 1,** Supplemental Figure 3). There was a linear increase in event rates as sodium concentration decreased below this level. The increase in risk per 1 mmol/L decrease in sodium below 142 mmol/L was 5% for the primary endpoint and 6% for each of cardiovascular and all-cause mortality. Inspection of the restricted cubic spline Figures also suggested the possibility of a J-shaped relationship, where high sodium concentration was also associated with worse outcomes, but this was not statistically significant for any of the prespecified endpoints.

Effect of dapagliflozin on primary and secondary trial outcomes according to baseline sodium concentration. The efficacy of dapagliflozin in preventing the primary outcome of cardiovascular death or worsening HF did not differ between those with hyponatremia and those without (*P* for interaction = 0.54). The efficacy of dapagliflozin in preventing cardiovascular death, HF hospitalizations, or urgent HF visits and all-cause death also did not differ by sodium group (**Table 3, Figure 2**). The results were similar when serum sodium was treated as a continuous variable (*P* for interaction = 0.96 for the primary outcome) (Supplemental Figure 4).

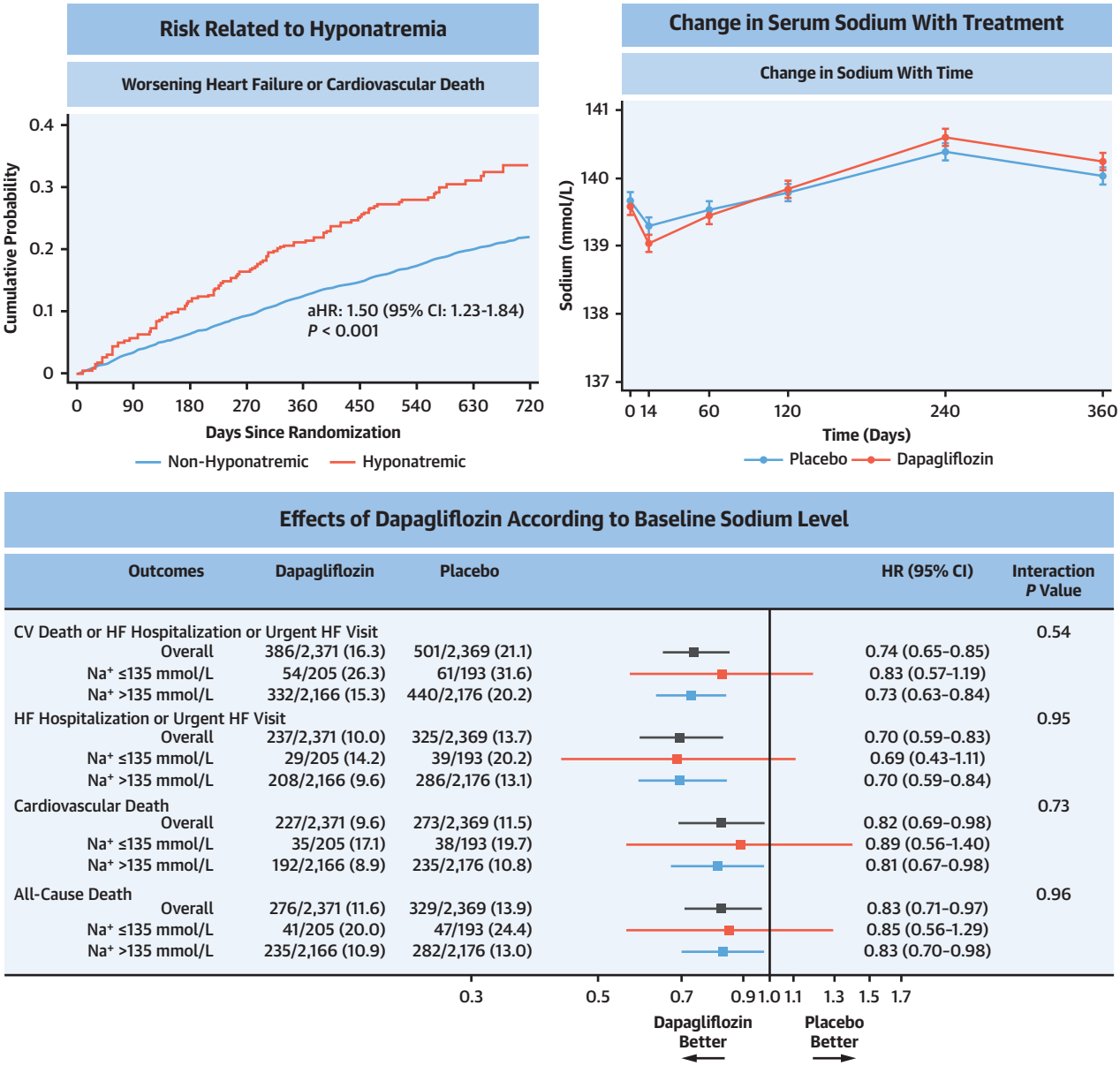
EFFECT OF DAPAGLIFLOZIN ON SERUM SODIUM. Mean serum sodium concentration. There was a small and transient decline in mean sodium concentration between baseline and 14 days in both treatment groups which was slightly greater in the dapagliflozin, compared with the placebo group (-0.55 mmol/L vs -0.38 mmol/L; *P* = 0.042). Thereafter, sodium tended to be slightly higher in the dapagliflozin group, but again the differences were small and although statistically significant were clinically negligible (**Figure 3**). For example, the change in sodium concentration from baseline to 8 months was +1.01 mmol/L in the dapagliflozin group vs +0.71 mmol/L in the placebo group (*P* = 0.001). Looking specifically at participants with hyponatremia at baseline, the effects of dapagliflozin on improvement in sodium levels were more marked, with consistently higher sodium concentration at all follow-up timepoints from baseline.

Development of hyponatremia (in participants with normal baseline sodium). Between baseline and day 14, 159 of 2,104 participants (7.6%) in the dapagliflozin group with sodium measurements had developed transient hyponatremia compared with 120 of 2,118 participants (5.7%) in the placebo group (*P* = 0.013) (**Table 4**). After day 14, the opposite pattern was observed and by 12 months, 48 of 1,870 surviving participants (2.6%) in the dapagliflozin group with sodium measurements had new hyponatremia compared with 89 of 1,848 participants (4.8%) in the placebo group (*P* < 0.001) (**Table 4**).

Resolution of hyponatremia (in participants with baseline hyponatremia). Nearly half of patients showed rapid resolution of baseline hyponatremia by 14 days with 99 of 200 (49.5%) surviving patients with sodium measurements in the dapagliflozin group and 92 of 190 (48.4%) in the placebo group (*P* = 0.83); the proportions were much larger among survivors at 1 year with 126 of 171 (73.7%) in the dapagliflozin group and 102 of 147 (69.4%) in the placebo group (*P* = 0.40) (**Table 4**).

The net result of these changes was that more patients in the dapagliflozin group had hyponatremia (n = 260, 11.3%) than in the placebo group (n = 218,

CENTRAL ILLUSTRATION **Hyponatremia in the DAPA-HF Trial**



Effects of Dapagliflozin According to Baseline Sodium Level

Outcomes	Dapagliflozin	Placebo	HR (95% CI)	Interaction *P* Value
CV Death or HF Hospitalization or Urgent HF Visit				0.54
Overall	386/2,371 (16.3)	501/2,369 (21.1)	0.74 (0.65-0.85)	
Na^+ ≤135 mmol/L	54/205 (26.3)	61/193 (31.6)	0.83 (0.57-1.19)	
Na^+ >135 mmol/L	332/2,166 (15.3)	440/2,176 (20.2)	0.73 (0.63-0.84)	
HF Hospitalization or Urgent HF Visit				0.95
Overall	237/2,371 (10.0)	325/2,369 (13.7)	0.70 (0.59-0.83)	
Na^+ ≤135 mmol/L	29/205 (14.2)	39/193 (20.2)	0.69 (0.43-1.11)	
Na^+ >135 mmol/L	208/2,166 (9.6)	286/2,176 (13.1)	0.70 (0.59-0.84)	
Cardiovascular Death				0.73
Overall	227/2,371 (9.6)	273/2,369 (11.5)	0.82 (0.69-0.98)	
Na^+ ≤135 mmol/L	35/205 (17.1)	38/193 (19.7)	0.89 (0.56-1.40)	
Na^+ >135 mmol/L	192/2,166 (8.9)	235/2,176 (10.8)	0.81 (0.67-0.98)	
All-Cause Death				0.96
Overall	276/2,371 (11.6)	329/2,369 (13.9)	0.83 (0.71-0.97)	
Na^+ ≤135 mmol/L	41/205 (20.0)	47/193 (24.4)	0.85 (0.56-1.29)	
Na^+ >135 mmol/L	235/2,166 (10.9)	282/2,176 (13.0)	0.83 (0.70-0.98)	

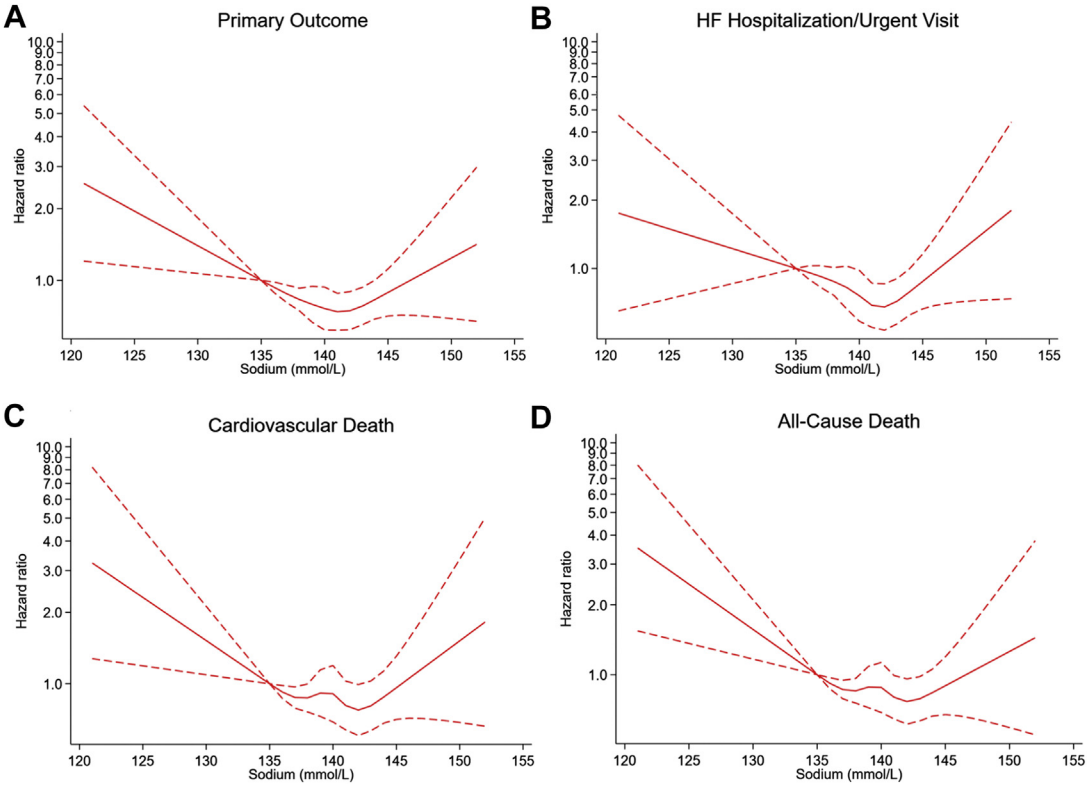
Yeoh SE, et al. J Am Coll Cardiol HF. 2022;10(5):306-318.

Relationship of dapagliflozin with serum sodium based on findings from the DAPA-HF trial. aHR = adjusted hazard ratio; CV = cardiovascular; HF = heart failure.

9.4%) at 14 days ($P = 0.04$), whereas by 12 months the opposite was true, with 93 cases (4.6%) in the dapagliflozin group and 134 cases (6.7%) in the placebo group ($P = 0.003$).

CHANGE IN SBP, eGFR, AND HEMATOCRIT ACCORDING TO BASELINE HYPONATREMIA STATUS. The pattern and extent of change in SBP, eGFR, and hematocrit with dapagliflozin were similar in patients with and without hyponatremia at baseline (Figure 4, Supplemental Figure 5). Participants in the dapagliflozin group showed a sustained and statistically significant increase in hematocrit levels from baseline to all follow-up timepoints regardless of baseline

FIGURE 1 Key Trial Outcomes According to Baseline Serum Sodium Concentration



(A to D) These restricted cubic splines show the risk of each outcome modeling serum sodium concentration as a continuous variable, adjusted for prognostic variables. The **dashed lines** represent corresponding 95% CIs (reference sodium level = 135 mmol/L). HF = heart failure.

hyponatremia status, whereas there was no significant change in hematocrit for participants in the placebo group. For example, the change in hematocrit from baseline to 14 days was +0.7% in the dapagliflozin group vs -0.15% in the placebo group ($P < 0.001$), with the difference increasing to +2.4% in the dapagliflozin group vs -0.15% in the placebo group from baseline to 4 months ($P < 0.001$), and levels in both groups remaining relatively stable thereafter.

SAFETY AND ADVERSE EVENTS. Each of the adverse events of interest was uncommon. There was a higher rate of adverse events related to volume depletion and renal dysfunction in the low-sodium group compared with the normal-sodium group (Table 5). The other adverse events of interest were very infrequent in each sodium subgroup. Baseline serum sodium did not notably modify the rate of adverse events in patients assigned to either placebo or dapagliflozin (Table 5).

DISCUSSION

In a contemporary, well-treated ambulatory cohort of patients with HFrEF, most of whom had mild symptoms, the prevalence of hyponatremia was low (8.4%) and there were few cases of severe hyponatremia (0.06%). However, hyponatremia remained an independent predictor of outcomes despite adjustment for other prognostic variables, including NT-proBNP. The benefit of dapagliflozin was consistent across the range of sodium concentrations measured at baseline. Dapagliflozin had a small biphasic effect on serum sodium concentration. Initially, compared with placebo, dapagliflozin led to a small, although statistically significant, decrease in sodium. However, after 2 weeks, the opposite pattern was observed.

Although hyponatremia is recognized as the most common electrolyte disorder among hospitalized patients with HF, there are few reports of

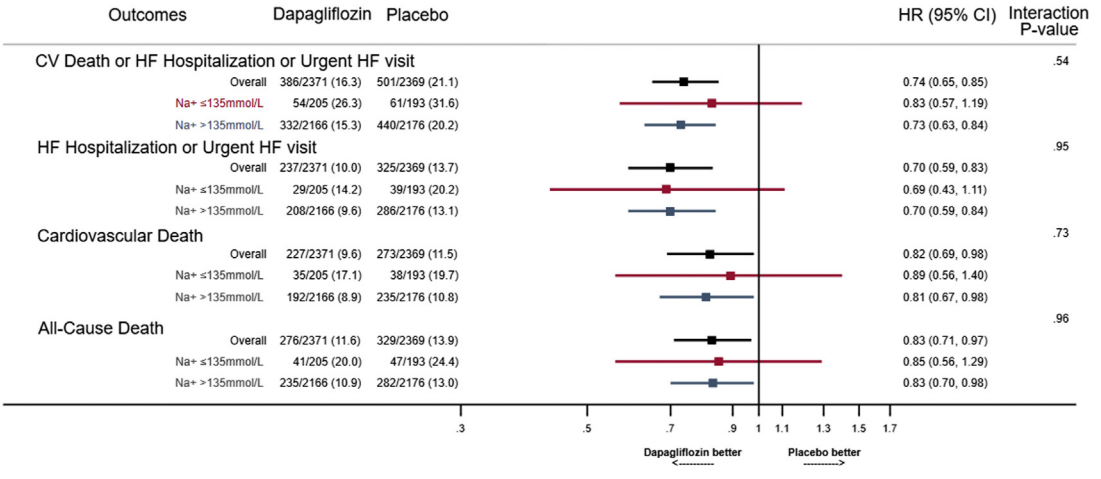
TABLE 3 Effect of Dapagliflozin on the Primary and Secondary Outcomes According to Baseline Sodium Category

	Na^+ ≤135 mmol/L		Na^+ >135 mmol/L		
	Placebo (n = 193)	Dapagliflozin (n = 205)	Placebo (n = 2,176)	Dapagliflozin (n = 2,166)	*P* for Interaction
Primary endpoint (worsening HF or cardiovascular death)					
n (%)	61 (31.6)	54 (26.3)	440 (20.2)	332 (15.3)	0.54
Rate per 100 person-y (95% CI)	24.6 (19.1-31.6)	20.1 (15.4-26.2)	15.0 (13.7-16.5)	11.0 (9.9-12.3)	
HR (95% CI)	0.83 (0.57-1.19)		0.73 (0.63-0.84)		
Hospitalization or urgent visit for HF					
n (%)	39 (20.2)	29 (14.2)	286 (13.1)	208 (9.6)	0.95
Rate per 100 person-y (95% CI)	15.7 (11.5-21.5)	10.8 (7.5-15.5)	9.8 (8.7-11.0)	6.9 (6.0-7.9)	
HR (95% CI)	0.69 (0.43-1.11)		0.70 (0.59-0.84)		
Cardiovascular death					
n (%)	38 (19.7)	35 (17.1)	235 (10.8)	192 (8.9)	0.73
Rate per 100 person-y (95% CI)	13.8 (10.1-19.0)	12.1 (8.7-16.8)	7.5 (6.6-8.5)	6.1 (5.3-7.0)	
HR (95% CI)	0.89 (0.56-1.40)		0.81 (0.67-0.98)		
All-cause death					
n (%)	47 (24.4)	41 (20.0)	282 (13.0)	235 (10.9)	0.96
Rate per 100 person-y (95% CI)	17.1 (12.9-22.8)	14.1 (10.4-19.2)	9.0 (8.0-10.1)	7.5 (6.6-8.5)	
HR (95% CI)	0.85 (0.56-1.29)		0.83 (0.70-0.98)		
Significant worsening in KCCQ-TSS (≥5) at 8 months					
Proportion ± SE	0.39 ± 0.04	0.27 ± 0.03	0.32 ± 0.01	0.25 ± 0.01	0.55
OR (95% CI)	0.78 (0.63-0.98)		0.84 (0.78-0.90)		
Significant improvement in KCCQ-TSS (≥5) at 8 months					
Proportion ± SE	0.46 ± 0.04	0.57 ± 0.04	0.51 ± 0.01	0.58 ± 0.01	0.52
OR (95% CI)	1.23 (0.99-1.51)		1.15 (1.07-1.22)		

OR = odds ratio; other abbreviations as in Tables 1 and 2.

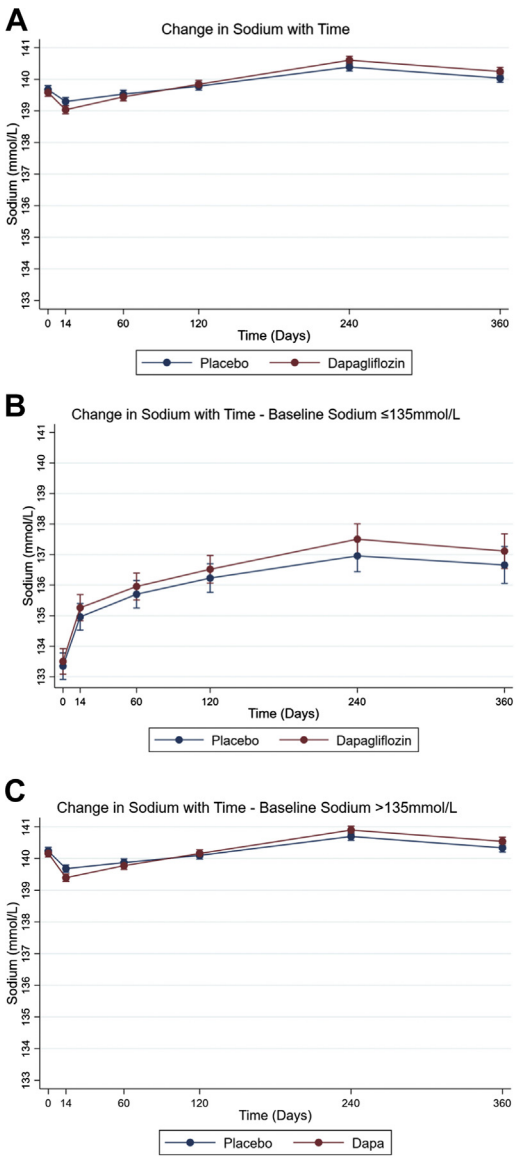
the prevalence of hyponatremia in ambulatory patients with HFrEF and none in patients comprehensively managed with contemporary guideline-recommended medical therapy.[9-11] Even accounting for different definitions, the prevalence of hyponatremia in our outpatient cohort (8.4%) was less than half that reported in hospitalized patients (generally 20% to 25%).[1-4]

FIGURE 2 Dapagliflozin Treatment Effect



Effect of dapagliflozin on key outcomes in patients with and without hyponatremia at baseline. CV = cardiovascular; other abbreviation as in Figure 1.

FIGURE 3 Effect of Dapagliflozin on Serum Sodium Concentration Between Baseline and 12 Months



(A) Overall. **(B)** Patients with baseline sodium ≤135 mmol/L. **(C)** Patients with baseline sodium >135 mmol/L.

Although most cases of hyponatremia in the DAPA-HF trial were mild, low sodium still predicted worse outcomes. This excess risk persisted despite adjustment for other recognized prognostic variables, many of which showed an imbalance between patients with and without hyponatremia. Indeed, we know of no prior study where such extensive adjustment was made, including for natriuretic peptide level, in ambulatory patients. [9-11] Moreover, most studies to date have only reported the association between hyponatremia and all-cause mortality, whereas we have also shown that low sodium was independently predictive of worsening HF events (principally HF hospitalization) and symptoms.[16,17]

The prognostic importance of a single sodium measurement was remarkable given the rapid and frequent resolution of hyponatremia on rechecking blood chemistry. In the placebo group, almost half of cases of hyponatremia had resolved at the 2-week measurement after randomization and about two-thirds of cases had resolved by 8 months. This substantial recategorization occurred because the initial measurement was only slightly below normal in many patients. However, almost as many people in the placebo group developed new hyponatremia at each timepoint during follow-up as showed resolution of hyponatremia. Dapagliflozin had a surprising, previously unrecognized, biphasic effect on new hyponatremia. The incidence of hyponatremia was increased during the first 14 days after randomization but was decreased thereafter in patients treated with dapagliflozin compared to placebo. The explanation for this pattern is uncertain. The initial osmotic and natriuretic diuresis induced by SGLT2 inhibitors causes an increase in vasopressin secretion and a reduction in free-water clearance, experimentally and clinically, which might account for the early transient reduction in serum sodium concentration.[18-21] The subsequent effects on serum sodium concentration are harder to predict given the direct effects of SGLT2 inhibitors and the compensatory responses to these. The diuresis induced by SGLT2 inhibitors is believed to lead to a reduction in intravascular volume and blood pressure, and the increased delivery of sodium to the distal nephron results in a decline in eGFR by inducing tubuloglomerular feedback.[22-25] However, it has been hypothesized that SGLT2 inhibitors reduce blood volume less than conventional diuretics.[26] Although the initial decrease in sodium mirrors the early decline in eGFR after starting dapagliflozin, subsequently, serum sodium concentration increased more in the dapagliflozin group than the placebo group, to the extent that the mean concentration was eventually

significantly higher in the dapagliflozin group. Although the initial decrease in eGFR also partially recovers, eGFR does not recover back to the same level as in the placebo group (as is also observed in other trials and real-world data over the same period) and eGFR does not crossover as for sodium.[27,28] So, it seems unlikely that the effect of SGLT2 inhibitors of eGFR alone explain the early effect on sodium, although it might explain the longer-term effect if there is a relative increase in free-water clearance with these agents (as seems likely) and sodium excretion is maintained (and sodium retention does not occur), which may be the case if eGFR is maintained. The complexity of these effects is reflected in the seeming paradox of the early decline in serum sodium concentration occurring contemporaneously with an increase in hematocrit, questioning whether the latter can be wholly explained by volume contraction. Although detailed analyses of change in hemoglobin have been reported in other trials, the effect of other SGLT2 inhibitors on serum sodium has not been reported.[29] Irrespective of the possible mechanisms, the important overarching finding was that after 14 days, patients treated with dapagliflozin were less likely to develop new hyponatremia and more likely to show resolution of existing hyponatremia than individuals treated with placebo, which may be a favorable effect of SGLT2 inhibition in HF. The benefits of dapagliflozin on the primary and secondary cardiovascular outcomes were consistent in patients with and without hyponatremia (and across the range of serum sodium concentration at baseline), despite the initial transient small decline in serum sodium concentration. Indeed, the absolute risk reduction with dapagliflozin was 1.5- to 2.0-fold greater in patients with hyponatremia than in those without. Similarly, dapagliflozin was also well-tolerated in patients with hyponatremia, and the safety of dapagliflozin was similar in patients with and without hyponatremia.

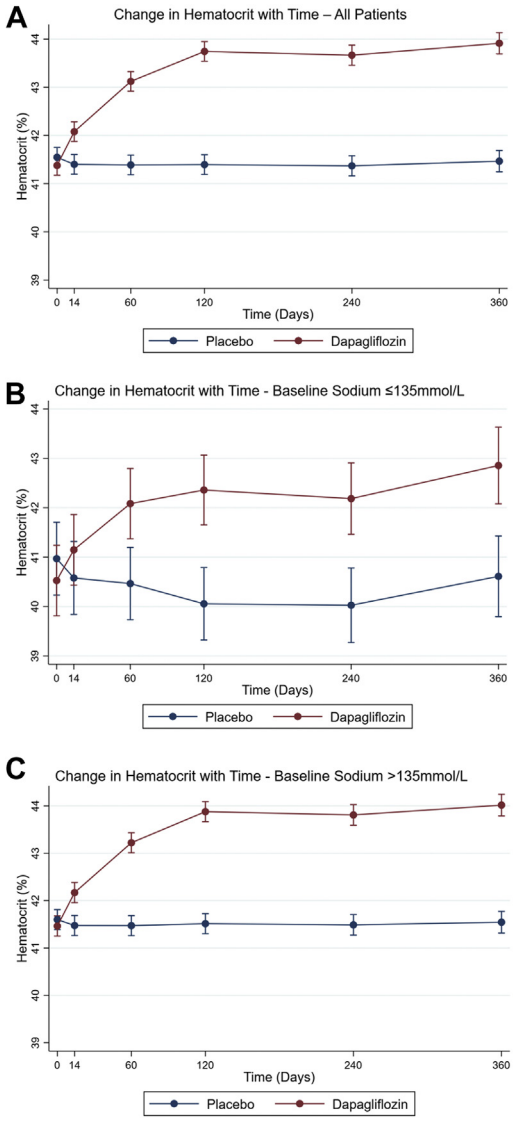
STUDY LIMITATIONS. Analysis of the effect of dapagliflozin on outcomes according to baseline sodium concentration was not a prespecified outcome, although assessment of the effect of dapagliflozin on sodium level was a prespecified safety outcome. Measurement of urinary sodium and water excretion, along with osmolality, might have suggested possible mechanisms underlying the biphasic effect of dapagliflozin on serum sodium concentration. The low prevalence of hyponatremia in DAPA-HF may have reflected the enrollment of relatively low-risk patients as a result of the specific inclusion and exclusion criteria used in the trial. Our patients were

TABLE 4 Proportion of Patients Showing Resolution of Baseline Hyponatremia (Na^+ ≤135 mmol/L) After Randomization or Developing New Hyponatremia After Baseline

	Resolution of Hyponatremia			New Hyponatremia		
Visit	Dapagliflozin	Placebo	*P* Value	Dapagliflozin	Placebo	*P* Value
14 d	99/200 (49.5)	92/190 (48.4)	0.83	159/2104 (7.6)	120/2118 (5.7)	0.013
2 mo	117/190 (61.6)	108/184 (58.7)	0.57	118/2048 (5.8)	108/2076 (5.2)	0.43
4 mo	113/186 (60.8)	105/174 (60.3)	0.94	78/2033 (3.8)	103/2021 (5.1)	0.052
8 mo	134/177 (75.7)	111/165 (67.3)	0.084	50/1954 (2.6)	74/1938 (3.8)	0.025
12 mo	126/171 (73.7)	102/147 (69.4)	0.40	48/1870 (2.6)	89/1848 (4.8)	<0.001
16 mo	109/138 (79.0	86/124 (69.4)	0.074	51/1563 (3.3)	48/1554 (3.1)	0.78

Values are n/N (%). The analysis was truncated at 16 months because there were fewer than 100 people in one or both treatment groups among those who had hyponatremia at baseline.

FIGURE 4 Effect of Dapagliflozin on Hematocrit



The graphs indicate the effect of dapagliflozin on **(A)** all patients, **(B)** patients with baseline sodium ≤135 mmol/L, and **(C)** patients with baseline sodium >135 mmol/L.

TABLE 5 Adverse Events Related to Randomized Therapy According to Baseline Sodium Category

	Na^+ ≤135 mmol/L		Na^+ >135 mmol/L		
	Placebo (n = 193)	Dapa (n = 205)	Placebo (n = 2,174)	Dapa (n = 2,161)	*P* for Interaction[a]
Any discontinuation	27 (14.0)	31 (15.1)	231 (10.6)	217 (10.0)	0.61
Discontinuation due to AE	11 (5.7)	11 (5.4)	105 (4.8)	100 (4.6)	0.97
Adverse events					
Volume depletion	19 (9.8)	20 (9.8)	143 (6.6)	158 (7.3)	0.74
Renal	20 (10.4)	20 (9.8)	150 (6.9)	133 (6.2)	0.85
Fracture	6 (3.1)	4 (2.0)	44 (2.0)	45 (2.1)	0.46
Amputation	1 (0.5)	1 (0.5)	11 (0.5)	12 (0.6)	0.94
Major hypoglycemia	1 (0.5)	0 (0)	3 (0.1)	4 (0.2)	—

Values are n (%). The safety analysis included only patients who took at least one dose of randomized treatment.
[a]Interaction between sodium category and effect of randomized treatment.
AE = adverse event; Dapa = dapagliflozin.

ambulatory, and understanding of the effects of SGLT2 inhibitors on sodium status in patients hospitalized with worsening HF would be of interest.

CONCLUSIONS

Hyponatremia predicts worse clinical outcomes in patients with HFrEF. Compared with placebo, dapagliflozin improved mortality and worsening HF events and symptoms, regardless of serum sodium concentration. Dapagliflozin led to a small early and transient increase in the risk of hyponatremia but a long-term sustained decrease in this risk.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The DAPA-HF trial was funded by AstraZeneca. Dr McMurray is supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217. Dr Docherty has received fees from AstraZeneca (sponsor of DAPA-HF) for his involvement in the DAPA-HF trial to his employer, The University of Glasgow; and has received personal fees from Eli Lilly outside the submitted work. Dr Jhund has been an employee of AstraZeneca and Novartis; has received grants and personal fees from Boehringer Ingelheim; has received personal fees from Cytokinetics and Vifor Pharma outside the submitted work; and is the director of Global Clinical Trials Partners Ltd. Dr Petrie has received fees from AstraZeneca and Eli Lilly during the conduct of the study; and has received personal fees from Novo Nordisk, AstraZeneca, NAPP Pharmaceuticals, Takeda Pharmaceutical, Alnylam, Bayer, Resverlogix, and Cardiorentis; and has received grants and personal fees from Boehringer Ingelheim and Novartis outside the submitted work. Dr Inzucchi has received personal fees from AstraZeneca during the conduct of the study; and has received personal fees from AstraZeneca, Boehringer Ingelheim, Merck, VTV Therapeutics, Sanofi/Lexicon, and Novo Nordisk outside the submitted work. Dr Kober has received grants from AstraZeneca to the institution for participation in the DAPA-HF trial steering committee during the conduct of the study; and has received personal fees from AstraZeneca and Novartis outside the submitted work. Dr Kosiborod has received grants and personal fees from AstraZeneca and Boehringer Ingelheim; and has received personal fees from Sanofi, Amgen, Novo Nordisk, Merck, Eisai, Janssen, Bayer, GlaxoSmithKline, Glytec, Intarcia, Novartis, Applied Therapeutics, Amarin, and Eli Lilly outside the submitted work. Dr Martinez has received personal fees from AstraZeneca during the conduct of the study. Dr Ponikowski has received personal fees and fees to his institution from participation as an investigator in clinical trials from AstraZeneca during the conduct of the study; and has received personal fees from Boehringer Ingelheim, Servier, Novartis, Berlin-Chemie, Bayer, Renal Guard Solutions, Pfizer, Respicardia, Cardiorentis, and Cibiem; and has received grants, personal fees, and fees to his institution from Impulse Dynamics; and has received fees to his institution from Vifor, Corvia, and Revamp Medical outside the submitted work. Dr Sabatine has received grants and personal fees from AstraZeneca during the conduct of the study; and has received grants and personal fees from Amgen, Intarcia, Janssen Research and Development, Medicines Company, MedImmune, Merck, and Novartis; and has received personal fees from Anthos Therapeutics, Bristol-Myers Squibb, CVS Caremark, DalCor, Dyrnamix, Esperion, IFM Therapeutics, Ionis; and has received grants from Daiichi-Sankyo, Bayer, Pfizer, Poxel, Eisai, GlaxoSmithKline, Quark Pharmaceuticals, and Takeda outside the submitted work; and is a member of the TIMI Study Group, which has also received institutional research grant support through Brigham and Women's Hospital from Abbott, Aralez, Roche, and Zora Biosciences. Dr Bengtsson has received personal fees from AstraZeneca outside the submitted work. Drs Boulton, Greasley, Langkilde, and Sjöstrand are employees and/or shareholders of AstraZeneca. Dr Boulton is a stockholder of Bristol-Myers Squibb Company. Dr Solomon has received grants from AstraZeneca during the conduct of the study; and has received grants from Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, Bristol-Myers Squibb, Celladon, Cytokinetics, Eidos, Gilead, GlaxoSmithKline, Ionis, Lone Star Heart, Mesoblast, MyoKardia, National Institutes of Health/National Heart, Lung, and Blood Institute, Novartis, Sanofi Pasteur, and Theracos; and has received personal fees from Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Bristol-Myers Squibb, Cardior, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GlaxoSmithKline, Ironwood, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, and Tenaya outside the submitted work. Dr McMurray has received grants from and his employer has been paid by AstraZeneca, Theracos, and GlaxoSmithKline during the conduct of the study; and he has received grants and his employer has been paid by Novartis, Amgen, Bristol-Myers Squibb, Bayer, Abbvie, Dal-Cor, Kidney Research UK, and Cardurion; and he has received grants from the British Heart Foundation outside the submitted work.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Dapagliflozin confers consistent benefits on mortality, worsening HF and symptoms regardless of baseline sodium levels in ambulatory patients with HFrEF, as well as a reduced long-term risk of hyponatremia. This is relevant to the management of HFrEF patients given the high prevalence and clinical implications of hyponatremia.

TRANSLATIONAL OUTLOOK: Further studies including measurements of plasma and urine osmolality, along with arginine vasopressin (antidiuretic hormone) levels, may help elucidate the mechanisms underlying the effect of SGLT2 inhibition on serum sodium concentration in patients with HFrEF.

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KEY WORDS dapagliflozin, heart failure, hyponatremia, sodium, sodium glucose cotransporter 2 inhibitor

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

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