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/).
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.1-5 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 nonsmotically 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.1-7 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

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 m². There was no serum sodium concentration inclusion or exclusion criterion.

MEASUREMENT OF SERUM SODIUM (CREATININE AND OTHER ELECTROLYTES). Blood samples were...
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, 96.1%) | P Value |
|-----------------|-------------------------------|-------------------------------|---------|
| Age, y          |                               |                               | 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/m²      | 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 ± 21 | 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 m² | 61.2 ± 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. 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. 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. 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, randomised 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 $\leq 135$ 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 $\leq 135$ 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 m² vs 66.0 ± 19.4 mL/min/1.73 m²). 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 border-line 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.

### 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 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/ECG (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 m²) | 138 (46.0)         | 1,741 (40.1)                    | 0.022     |
| Anemia*         | 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      |
| ICD/CRT-D       | 139 (34.9)                     | 1,263 (29.1)                    | 0.015     |
| CRT-P/CRT-D     | 108 (27.1)                     | 1,132 (26.8)                    | 0.64      |

Values are mean ± SD, n (%), or median (IQR). *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; HbA1c = 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 = selective serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
### TABLE 2 Event Rate (Per 100 Person-Years) and Hazard Ratios for Trial Outcomes According to Baseline Sodium Category

| Event Rate per 100 person-y (95% CI) | Unadjusted HR (95% CI) | Adjusted HR (95% CI) | P Value |
|-------------------------------------|------------------------|----------------------|---------|
| Primary endpoint (worsening HF or cardiovascular death) | 13.1 (10.4-16.7) | 1.59 (1.26-2.01) | 0.001 |
| Cardiovascular death | 12.9 (10.3-16.3) | 1.81 (1.41-2.33) | 0.001 |
| All-cause mortality, number of events | 15.6 (12.6-19.2) | 1.81 (1.45-2.28) | 0.001 |
| Event rate per 100 person-y (95% CI) | 12.9 (10.3-16.3) | 1.49 (1.16-1.93) | 0.001 |
| Adjusted HR (95% CI) | 1.36 (1.05-1.77) | 1.00 (ref) | 0.001 |
| Hospitalization or urgent visit for HF | 13.1 (10.4-16.7) | 1.49 (1.16-1.93) | 0.001 |
| Event rate per 100 person-y (95% CI) | 12.9 (10.3-16.3) | 1.49 (1.16-1.93) | 0.001 |
| Adjusted HR (95% CI) | 1.31 (1.05-1.77) | 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 pre-specified 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,
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....
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
the prevalence of hyponatremia in ambulatory patients with HFpEF 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

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

| Study Endpoints | Sodium >135 mmol/L | Sodium ≤135 mmol/L | *P* for Interaction |
|-----------------|---------------------|---------------------|---------------------|
| Primary endpoint (worsening HF or cardiovascular death) | | |
| n (%)           | 61 (31.6)           | 54 (26.3)           | 640 (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)    |                     |                     |

### FIGURE 2  Dapaglirozin Treatment Effect

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

### Table 4

| Visit | Resolution of Hyponatremia | New Hyponatremia |
|-------|---------------------------|-----------------|
|       | 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

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.

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

| Category                              | Na⁺ ≤ 135 mmol/L | Na⁺ > 135 mmol/L | P for Interaction |
|---------------------------------------|------------------|------------------|------------------|
|                                       | Placebo (n = 193) | Dapa (n = 205)   | Placebo (n = 2,174) | Dapa (n = 2,161) |
| 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.

*Interaction between sodium category and effect of randomized treatment.

AE = adverse event; Dapa = dapagliatin.

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, dapagliatin improved mortality and worsening HF events and symptoms, regardless of serum sodium concentration. Dapagliatin led to a small early and transient increase in the risk of hyponatremia but a long-term sustained decrease in this risk.

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**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.

**REFERENCES**

1. Chiong JR, Kim S, Lin J, Christian R, Dasta JF. Evaluation of costs associated with tolvaptan-mediated length-of-stay reduction among heart failure patients with hyponatremia in the US, based on the EVEREST trial. J Med Econ. 2012;15(2):276-284. https://doi.org/10.3111/13696998.2011.643329

2. Sato N, Gheorghide M, Kajimoto K, et al. Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). Am J Cardiol. 2013;111(7):1019-1025. https://doi.org/10.1016/j.amjcard.2012.12.019

3. Dunlap ME, Hauptman PJ, Amin AN, et al. Current management of hyponatremia in acute heart failure: a report from the Hyponatremia Registry for Patients With Euvolemic and Hypervolemic Hyponatremia (HN Registry). J Am Heart Assoc. 2017;6(8):e005261. https://doi.org/10.1161/JAHA.116.005261

4. Rodríguez M, Hernandez M, Cheungpasitporn W, et al. Hyponatremia in heart failure: pathogenesis and management. Curr Cardiovasc Risk Rep. 2019;15(4):252-261. https://doi.org/10.1007/s11886-019-00498-4

5. Sica DA. Hyponatremia and heart failure—pathophysiology and implications. Congest Heart Fail. 2005;11(5):274-277. https://doi.org/10.1111/j.1525-2299.2005.01480.x

6. Tee SL, Sindone A, Roger S, et al. Hyponatremia in heart failure. Intern Med J. 2020;50(6):659-666. https://doi.org/10.1111/imj.14624

7. Adrogue HJ, Madias NE. Diagnosis and treatment of hyponatremia. Am J Kidney Dis. 2014;64(5):681-684. https://doi.org/10.1053/j.ajkd.2014.06.001

8. Rahimi K, Bennett D, Conrad N, et al. Risk prediction in patients with heart failure: a systematic review and analysis. J Am Coll Cardiol HF. 2014;2(5):440-446. https://doi.org/10.1016/j.jchf.2014.04.008

9. Bettari L, Fiuzat M, Shaw LK, et al. Hyponatremia and long-term outcomes in chronic heart failure—an observational study from the Duke Databank for Cardiovascular Diseases. J Card Fail. 2012;18(1):74-81. https://doi.org/10.1016/j.cardfail.2011.09.005

10. Bavišč C, Ather S, Bambhriya A, et al. Prognostic significance of hyponatremia among ambulatory patients with heart failure and preserved and reduced ejection fractions. Am J Cardiol. 2014;113(11):1834-1838. https://doi.org/10.1016/j.amjcard.2014.03.017

11. Balling L, Schou M, Videbaek L, et al. Prevalence and prognostic significance of hyponatremia in outpatients with chronic heart failure. Eur J Heart Fail. 2011;13(9):968-973. https://doi.org/10.1093/eurheartj/hfr086

12. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008. https://doi.org/10.1056/NEJMoa1911303

13. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413-1424. https://doi.org/10.1056/NEJMoa202190

14. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117-128. https://doi.org/10.1056/NEJMoa2030183

15. Gheorghide M, Abraham WT, Albert NM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J. 2007;28(8):980-988. https://doi.org/10.1093/eurheartj/ehi542

16. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. JAMA. 2003;290(19):2581-2587. https://doi.org/10.1001/jama.290.19.2581

17. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure model: prediction of survival in heart failure. Circulation. 2006;113(11):1424-1433. https://doi.org/10.1161/CIRCULATIONAHA.105.584102

18. Chung S, Kim S, Son M, et al. Empagliflozin contributes to polyuria via regulation of sodium transporters and water channels in diabetic rat kidneys. Front Physiol. 2019;10:271. https://doi.org/10.3389/fphys.2019.00271

19. Eichhoff MK, Dekkers CJJ, Kramers BJ, et al. Effects of dapagliflozin on volume status when added to renin-angiotensin system inhibitors. J Clin Med. 2019;8(6):779. https://doi.org/10.3390/jcm8060779

20. Masuda T, Muto S, Fukuda K, et al. Osmotic diuresis by SGLT2 inhibition stimulates vasopressin-induced water reabsorption to maintain body fluid volume. Physiol Rep. 2020;8(2):e14360. https://doi.org/10.14814/phy2.14360

21. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the RECEDE-CHF trial. (published correction Circulation. 2020 Nov 3;142(18):e316). Circulation. 2020;142(18):1713-1724. https://doi.org/10.1161/CIRCULATIONAHA.120.048739

22. Sen T, Heerspink HJL. A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. Cell Metab. 2021;33(4):732-739. https://doi.org/10.1016/j.cmet.2021.02.016

23. van Bommel EJM, Lytvyn Y, Perkins BA, et al. Renal hemodynamic effects of sodium-glucose co-transporter 2 inhibitors in hyperfiltering people with type 1 diabetes and people with type 2 diabetes and normal kidney function. Kidney Int. 2020;97(4):631-635. https://doi.org/10.1016/j.kint.2019.12.021

24. Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in heart failure: diuretic and cardio renal effects. Circulation. 2020;142(11):1028-
Boorsma EM, Beusekamp JC, Ter Maaten JM, et al. Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. *Eur J Heart Fail*. 2021;23(1):68-78. https://doi.org/10.1002/ejhf.2066

Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes Metab*. 2018;20(3):479-487. https://doi.org/10.1111/dom.13127

Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446. https://doi.org/10.1056/NEJMoa2024816

Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *Lancet Diabetes Endocrinol*. 2020;8(1):27-35. https://doi.org/10.1016/S2213-8587(19)30384-5

Li J, Woodward M, Perkovic V, et al. Mediators of the effects of canagliflozin on heart failure in patients with type 2 diabetes. *J Am Coll Cardiol HF*. 2020;8(1):57-66. https://doi.org/10.1016/j.jchf.2019.08.004

**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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