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CORRECTIONS

Marton A, Saffari SE, Rauh M, Sun R-N, Nagel AM, Linz P, Lim TT, Takase-Minegishi K, Pajarillaga A, Saw S, Morisawa N, Yam WK, Minegishi S, Totman JJ, Teo S, Teo LLY, Ta Ng C, Kitada K, Wild J, Kovalik J-P, Luft FC, Greasley PJ, Chin CWL, Sim DKL, Titze J

Water Conservation Overrides Osmotic Diuresis During SGLT2 Inhibition in Patients With Heart Failure

J Am Coll Cardiol. 2024;83:1386-1398.

On page 1386, in the Conclusions section of the abstract, the first sentence read:

Physiological-adaptive water conservation eliminated the expected osmotic diuretic potential of dapagliflozin and thereby prevented a glucose-driven increase in urine volume of approximately 10 mL/kg/d · 75 kg = 750 mL/kg/d.

But should have read:

Physiological-adaptive water conservation eliminated the expected osmotic diuretic potential of dapagliflozin and thereby prevented a glucose-driven increase in urine volume of approximately 10 mL/kg/d · 75 kg = 750 mL/d.

The authors apologize for this error.

The online version of the article has been corrected to reflect this change.

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Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, Deswal A, Eckhardt L, Goldberger ZD, Gopinathannair R, Gorenek B, Hess PL, Hlatky M, Hogan G, Ibeh C, Indik JH, Kido K, Kusumoto F, Link MS, Linta KT, Marcus GM, McCarthy PM, Patel N, Patton KK, Perez MV, Piccini JP, Russo AM, Sanders P, Streur MM, Thomas KL, Times S, Tisdale JE, Valente AM, Van Wagoner DR

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

J Am Coll Cardiol. 2024;83:109-279.

In the article by Joglar et al, "2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines," which published ahead of print on November 30, 2023, and appeared in the January 2, 2024, issue of the journal (*J Am Coll Cardiol*. 2024;83:109-279), a correction was needed.

1. On page 143, in Table 8, in the row for the "Risk Factor," "Hypertension," the entry for the "ATRIA" column was inadvertently omitted. It has been updated to read, "1."
2. On page 177, in Figure 17, the last row, in the third box from the left, the asterisk has been moved from the top portion of the box after "IV Amiodarone" to the bottom portion of the box after "Verapamil, diltiazem."

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Water Conservation Overrides Osmotic Diuresis During SGLT2 Inhibition in Patients With Heart Failure

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ABSTRACT

BACKGROUND Sodium-glucose cotransporter 2 inhibitors are believed to improve cardiac outcomes due to their osmotic diuretic potential.

OBJECTIVES The goal of this study was to test the hypothesis that vasopressin-driven urine concentration overrides the osmotic diuretic effect of glucosuria induced by dapagliflozin treatment.

METHODS DAPA-Shuttle1 (Hepato-renal Regulation of Water Conservation in Heart Failure Patients With SGLT-2 Inhibitor Treatment) was a single-center, double-blind, randomized, placebo-controlled trial, in which patients with chronic heart failure NYHA functional classes I/II and reduced ejection fraction were randomly assigned to receive dapagliflozin 10 mg daily or placebo (1:1) for 4 weeks. The primary endpoint was change from baseline in urine osmolyte concentration. Secondary endpoints included changes in copeptin levels and solute free water clearance.

RESULTS Thirty-three randomized, sodium-glucose cotransporter 2 inhibitor–naïve participants completed the study, 29 of whom (placebo: n = 14; dapagliflozin: n = 15) provided accurate 24-hour urine collections (mean age 59 ± 14 years; left ventricular ejection fraction 31% ± 9%). Dapagliflozin treatment led to an isolated increase in urine glucose excretion by 3.3 mmol/kg/d (95% CI: 2.51–4.04; $P < 0.0001$) within 48 hours (early) which persisted after 4 weeks (late; 2.7 mmol/kg/d [95% CI: 1.98–3.51]; $P < 0.0001$). Dapagliflozin treatment increased serum copeptin early (5.5 pmol/L [95% CI: 0.45-10.5]; $P < 0.05$) and late (7.8 pmol/L [95% CI: 2.77–12.81]; $P < 0.01$), leading to proportional reductions in free water clearance (early: −9.1 mL/kg/d [95% CI: −14 to −4.12; $P < 0.001$]; late: −11.0 mL/kg/d [95% CI: −15.94 to −6.07; $P < 0.0001$]) and elevated urine concentrations (late: 134 mmol/L [95% CI: 39.28–229.12]; $P < 0.01$). Therefore, urine volume did not significantly increase with dapagliflozin (mean difference early: 2.8 mL/kg/d [95% CI: −1.97 to 7.48; $P = 0.25$]; mean difference late: 0.9 mL/kg/d [95% CI: −3.83 to 5.62]; $P = 0.70$).

CONCLUSIONS Physiological-adaptive water conservation eliminated the expected osmotic diuretic potential of dapagliflozin and thereby prevented a glucose-driven increase in urine volume of approximately 10 mL/kg/d · 75 kg = 750 mL/kg/d. (Hepato-renal Regulation of Water Conservation in Heart Failure Patients With SGLT-2 Inhibitor Treatment [DAPA-Shuttle1]; NCT04080518). (J Am Coll Cardiol 2024;83:1386–1398) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Sodium-glucose cotransporter 2 inhibitors (SGLT2i) block sodium and glucose reabsorption in the renal proximal tubule, which leads to glucosuria and thereby lowers blood glucose levels. Although SGLT2i were initially developed for the treatment of type 2 diabetes mellitus, outcome trials have shown that the clinical benefits of these inhibitors go beyond glycemic control.[1-4] Treatment with SGLT2i reduces cardiovascular mortality and heart failure hospitalizations for patients with reduced and preserved ejection fraction[5-7] and improves renal outcomes in patients with chronic kidney disease[8,9] regardless of diabetes status.[10]

SEE PAGE 1399

Although the cardioprotective and renoprotective effects of pharmacologic SGLTi are an undisputable success of pragmatic clinical outcome trial performance, the pathophysiological basis of this success story is elusive.[4,11,12] Lifestyle intervention studies with comparable reductions in glycated hemoglobin levels or body weight had no effect on cardiovascular outcomes,[13] indicating that the favorable pathophysiological features of SGLT2i consist of more than glycemic control. Furthermore, the beneficial effects of SGLT2i on cardiovascular outcomes occur within several weeks and without any changes in atherosclerosis-related endpoints, making it difficult to conclude that the blood pressure–lowering effect plays a major role in the observed reductions in cardiovascular mortality.[2,3,14,15]

Many investigators attribute the beneficial effects of SGLT2i to the drugs' natriuretic diuretic or osmotic diuretic effects.[16-18] The underlying assumption is that, similar to diuretics, SGLT2i increase urine volume and thereby exert beneficial effects on cardiac workload and myocardial energy expenditure, especially in states of cardiac congestion.[4,19] However, the effects of SGLT2i on solute-driven urine volume formation are different from those of traditional diuretics.[20] The observed natriuretic, osmotic diuretic effects[16,21] of SGLT2i are often short-lasting,[22-27] modest,[28-30] or absent.[31-33] Retrospective analysis of the currently available data suggests that SGLT2 inhibition does not produce durable decongestion.[34,35] It is thus unclear how, and how fast, patients receiving therapeutic SGLT2i overcome the osmotic driving force of elevated urine solute excretion and prevent osmotic diuresis.

To address this knowledge gap, we designed and conducted a mechanistic, randomized, placebo-controlled trial in patients with chronic, stable heart failure and reduced ejection fraction (DAPA-Shuttle1 [Hepato-renal Regulation of Water Conservation in Heart Failure Patients With SGLT-2 Inhibitor Treatment]) and prospectively tested the hypotheses that a standard dose of dapagliflozin increases glucose excretion with or without parallel increases in urine Na^+ excretion but causes an immediate and chronically sustained physiological-adaptive water conservation response, which counterbalances the osmotic diuretic effect of glucosuria by strengthening the renal urine concentration mechanism.

ABBREVIATIONS AND ACRONYMS

^{23}Na MRI = sodium magnetic resonance imaging

FWC = solute-free water clearance

SGLT2i = sodium-glucose cotransporter 2 inhibitors

METHODS

STUDY DESIGN AND PARTICIPANTS. DAPA-Shuttle1 was an investigator-initiated, 4-week, double-blind, placebo-controlled, randomized, phase 4 clinical trial, designed to compare the effects of dapagliflozin 10 mg vs matching placebo on the renal water and electrolyte handling and the mobilization of tissue Na^+ stores in patients with heart failure.

From November 2019 until September 2021, we enrolled 40 participants with chronic heart failure NYHA functional classes I and II, with or without type 2 diabetes, from the National Heart Centre, Singapore. Participants with type 2 diabetes had received stable treatment for at least 6 weeks before recruitment; antihypertensive treatment (including diuretics) and all other background treatment was required to be stable for at least 4 weeks before randomization. Patients with impaired renal function with an estimated glomerular filtration rate <45 mL/min/1.73 m^2, type 1 diabetes mellitus, and those with uncontrolled type 2 diabetes (glycated

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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.

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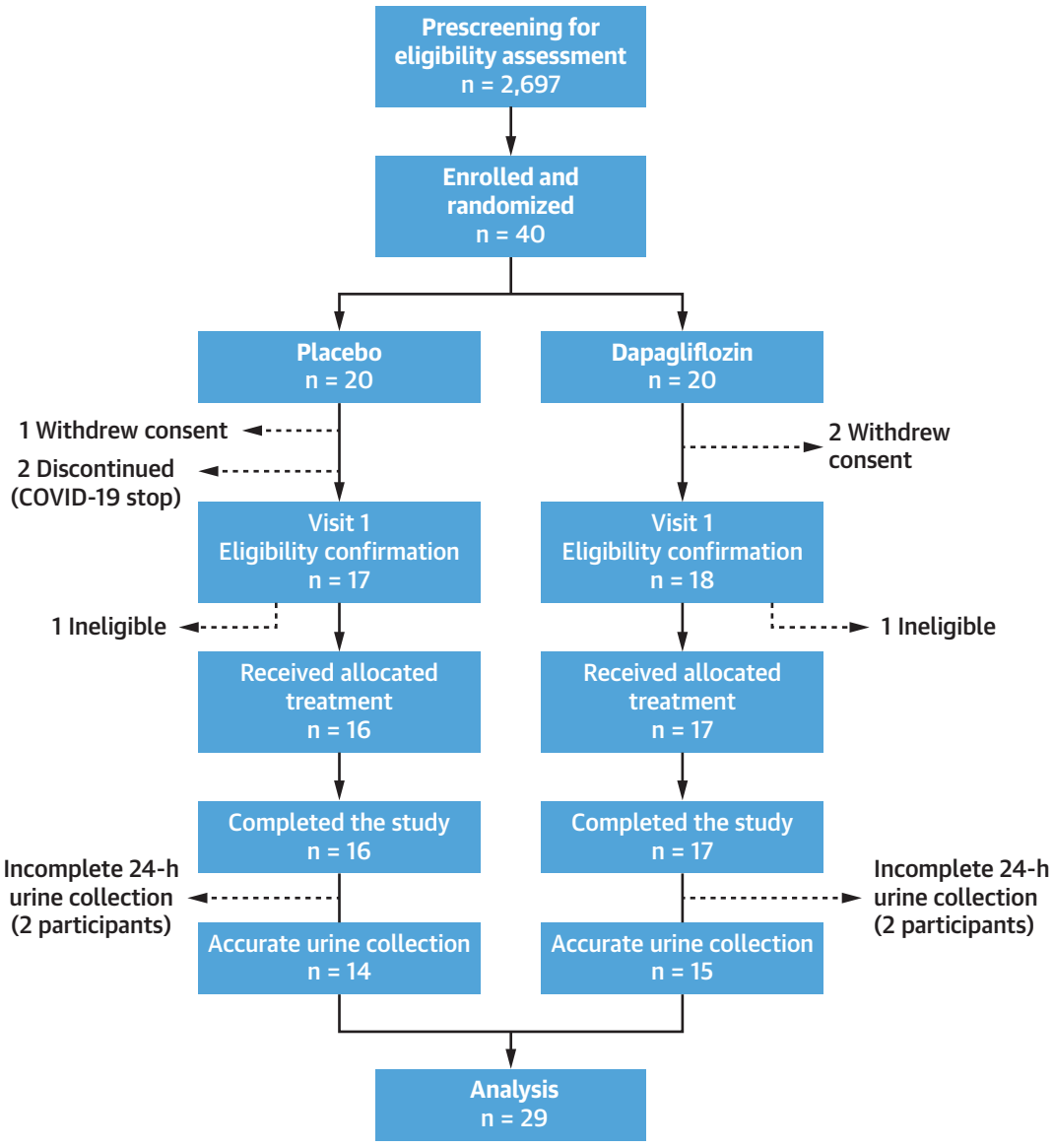
FIGURE 1 Participant Flow Through the DAPA-Shuttle1 Trial



Consolidated Standards of Reporting Trials diagram of participant flow from enrollment to analysis in the DAPA-Shuttle1 (Hepato-renal Regulation of Water Conservation in Heart Failure Patients With SGLT-2 Inhibitor Treatment) trial.

hemoglobin level >10.5%) were excluded. The medication regimen, including diuretics, remained unchanged throughout the study.

The trial was approved by the SingHealth Centralised Institutional Review Board, Singapore, and by the National University of Singapore (NUS) Institutional Review Board. It was registered on ClinicalTrials.gov (NCT04080518). To evaluate the baseline hydration status of our patients with heart failure, their body water and solute conservation profile was compared to that of healthy participants from the ongoing cohort study Sodium Storage in Singaporeans (SSIS), which was approved by the same review boards and is registered on ClinicalTrials.gov (NCT04319068). All study participants provided written informed consent. The study was designed, conducted, and reported in accordance with Good Clinical Practice standards.

RANDOMIZATION AND STUDY PROCEDURES. After consent and screening, eligible subjects were

randomized to receive dapagliflozin 10 mg, or matching placebo, in a 1:1 ratio according to the randomization plan. The assignment occurred in a blinded fashion using codes assigned to the kit number by a block randomization scheme. The codes were generated by an independent statistician using a computerized random number generator. Investigators and participants were blinded to the treatment group assignment.

The treatment duration was 4 weeks, during which all participants attended 3 study visits: at baseline (before treatment initiation, morning visit; fasted), after 48 hours (morning visit on day 3; fasted) to investigate the early effects of dapagliflozin, and after 4 weeks (morning visit; fasted) to investigate the late treatment effects. Participants were told to take the study medication daily, in the morning, in addition to background medication. Treatment adherence was assessed via pill count.

At each visit, participants underwent a physical examination, including measurements of height and weight, blood pressure, and heart rate. Ambulatory blood pressure was measured 3 times, at 2-minute intervals, and the average of the 3 measurements was used for analysis. For each visit, the participants were required to bring a complete 24-hour urine collection from the previous day, and urine volume was measured gravimetrically. Total urine/serum solute concentration was calculated as: $2 \cdot [Na^+] + 2 \cdot [K^+] + [Urea] + [Glucose]$, as reported previously.[36] Free water clearance was calculated using the formula: free water clearance = UVol × (1 - eUOsm/ePOsm), where UVol = urine volume, eUOsm = calculated urine solute concentration, and ePOsm = calculated serum solute concentration. All 24-hour urine excretion parameters were normalized per body weight. A sodium magnetic resonance imaging (^{23}Na MRI) scan of the lower leg for the quantification of skin and muscle Na^+ stores was performed on a 3T MRI scanner (Biograph mMR, Siemens Healthineers AG) equipped with a frequency-adapted mono-resonant transmit/receive birdcage knee coil (32.6 MHz, Stark-Contrast). The ^{23}Na MRI scan protocol and tissue sodium quantification have been described in detail previously.[37]

MECHANISTIC ENDPOINTS. The primary endpoint was the change from baseline in 24-hour urine solute concentration. Secondary endpoints included changes from baseline at day 3 and day 28 in plasma copeptin and solute free water clearance.

STATISTICAL ANALYSIS. Study data were collected and managed by using REDCap electronic data capture tools hosted at Duke-NUS Medical School, Singapore.[38,39] Demographic and baseline patient characteristics and clinical features are reported for control and intervention groups as mean ± SD and frequency (%) for continuous and categorical variables, respectively. No baseline comparison is made, following the Consolidated Standards of Reporting Trials statement for randomized trials.[40]

Study participants with heart failure were compared vs healthy SSIS individuals to investigate potential differences in baseline characteristics of body water and solute conservation profile by using the Mann-Whitney *U* test. Early and late effects of placebo and dapagliflozin treatment on markers of water and electrolyte handling were assessed via linear mixed model analysis, in which within-group changes over time were examined as the overall trend followed by testing the differences in within-group changes at visits 2 and 3 adjusted for baseline levels; the results are reported as least squares mean

TABLE 1 Participants' Characteristics at Baseline

	Control (n = 14)	Intervention (n = 15)
Age, y	62.9 ± 10.5	55.8 ± 15.7
Male	14 (100.0)	12 (80.0)
Chinese ethnicity	11 (78.6)	12 (80.0)
Body weight, kg	74.3 ± 17.8	78.4 ± 18.7
BMI, kg/m^2	26.4 ± 5.22	29.1 ± 5.91
NYHA functional class		
I	2 (14.3)	5 (33.3)
II	12 (85.7)	10 (66.7)
LVEF, %	27.4 ± 8.5	33.4 ± 8.0
Systolic blood pressure, mm Hg	119 ± 14.3	128 ± 19.9
Diastolic blood pressure, mm Hg	70.4 ± 10.1	73.9 ± 10.3
Hypertension	5 (35.7)	8 (53.3)
Atrial fibrillation/atrial flutter	6 (42.9)	6 (40.0)
Type 2 diabetes	6 (42.9)	8 (53.3)
HbA_{1c} (previously collected), %	6.32 ± 0.7	6.54 ± 0.9
Glucosuria (>1 mmol/L)	5 (35.7)	6 (40.0)
NT-proBNP, pg/mL	1,440 ± 2,310	468 ± 490
24-hour creatinine clearance, mL/min	75.5 ± 43.6	89.0 ± 38.9
Medication		
ACEI/ARB/ARNI	14 (100.0)	15 (100.0)
Beta-blockers	13 (92.9)	15 (100.0)
Loop diuretics	11 (78.6)	7 (46.7)
Mineralocorticoid receptor antagonists	13 (92.9)	9 (60.0)
Metformin	3 (21.4)	4 (26.7)
Sulfonylureas	1 (7.1)	2 (13.3)
Gliptins	1 (7.1)	0 (0.0)
Anticoagulants	5 (35.7)	9 (60.0)
Statins	13 (92.9)	11 (73.3)
Previous treatment with SGLT2i	0 (0.0)	0 (0.0)

Values are mean ± SD or n (%).

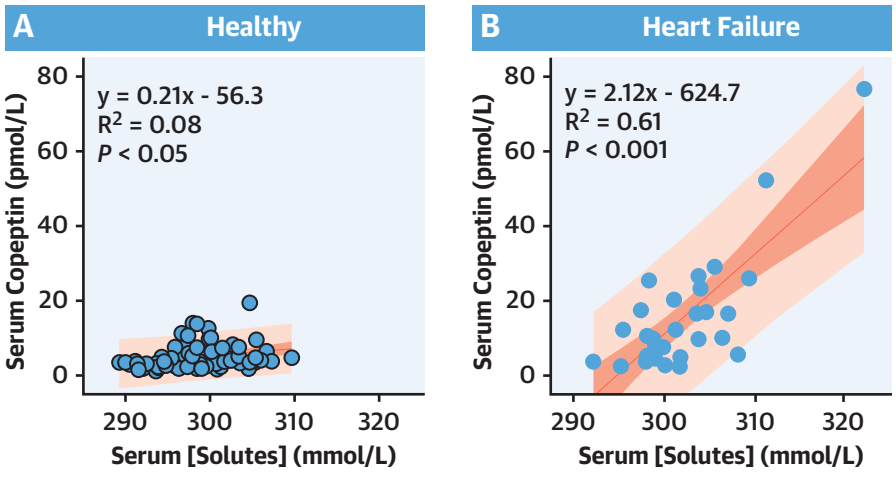
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blockers; ARNI = angiotensin receptor–neprilysin inhibitor; BMI = body mass index; $HbA1_c$ = glycated hemoglobin; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

TABLE 2 Baseline Characteristics of Body Solute and Water Status in Study Participants With Heart Failure Compared With Healthy Individuals

	Participants With Heart Failure (n = 29)	Healthy Control Subjects (n = 77)	Beta (95% CI)	*P* Value	Interpretation
Age, y	59.2 ± 13.7	49.1 ± 10.8	-	**<0.001**	Subsequent baseline characteristics are adjusted for age, sex, and BMI
Male	26 (89.7)	40 (51.9)	-	**<0.001**	
SBP, mm Hg	124 ± 17.8	121 ± 12.6	-	0.815	
DBP, mm Hg	72.2 ± 10.2	72.9 ± 9	-	0.898	
BMI, kg/m^2	27.8 ± 5.67	23.7 ± 4.10	-	**<0.001**	
24-hour urine solute and water excretion[a]					Water conservation in heart failure via increased renal water reabsorption
UNaV, mmol/kg/d	1.87 ± 0.757	1.98 ± 0.771	−0.05 (−0.47 to 0.36)	0.8032	
UKV, mmol/kg/d	0.553 ± 0.259	0.633 ± 0.267	0.002 (−0.14 to 0.14)	0.9796	
UUreaV, mmol/kg/d	3.52 ± 1.03	4.24 ± 1.59	0.002 (−0.74 to 0.74)	0.9947	
UGlucV, mmol/kg/d	0.124 ± 0.324	0.0854 ± 0.575	0.07 (−0.21 to 0.35)	0.6233	
USolutesV, mmol/kg/d	8.49 ± 2.40	9.56 ± 3.10	−0.03 (−1.57 to 1.51)	0.9697	
Urine volume, mL/kg/d	18.6 ± 8.47	28.9 ± 11.6	7.51 (2.20 to 12.8)	**0.0060**	
FWC, mL/kg/d	−9.51 ± 6.42	−3.12 ± 13.5	7.45 (1.26 to 13.6)	**0.0188**	
Hormone profile[a]					
Copeptin, pmol/L	16.0 ± 16.0	4.93 ± 3.33	−8.72 (−13.4 to −4.08)	**0.0003**	
Urine solute concentrations[a]					Water conservation in heart failure via increased urine concentration
Na^+, mmol/L	112 ± 46.7	78.2 ± 37.9	−37.2 (−57.7 to −16.7)	**0.0005**	
K^+, mmol/L	31.9 ± 14.0	25.0 ± 14.2	−7.71 (−15.2 to −0.22)	**0.0437**	
Glucose, mmol/L	6.92 ± 18.1	3.61 ± 21.6	1.31 (−9.59 to 12.2)	0.8126	
Urea, mmol/L	220 ± 101	168 ± 86.6	−73.8 (−119 to −28.5)	**0.0016**	
eUOsmo, mmol/L	515 ± 189	378 ± 174	−162 (−251 to −73.7)	**0.0004**	
Plasma solute concentrations[a]					Increased organic osmolyte production for water conservation in heart failure
Na^+, mmol/L	140 ± 1.82	140 ± 1.94	−0.03 (−1.01 to 0.95)	0.9548	
K^+, mmol/L	4.17 ± 0.357	3.92 ± 0.260	−0.21 (−0.37 to −0.05)	**0.0098**	
Urea, mmol/L	6.50 ± 2.82	4.77 ± 1.36	−1.45 (−2.38 to −0.52)	**0.0024**	
Glucose, mmol/L	6.55 ± 1.32	5.63 ± 1.89	−0.23 (−1.16 to 0.7)	0.6232	
ePOsmo, mmol/L	302 ± 5.89	298 ± 4.58	−2.16 (−4.6 to 0.29)	0.0831	
^{23}Na MRI tissue Na^+ content[a]					No baseline elevation in tissue Na^+ in participants with heart failure
Skin Na^+, mmol/L tissue volume	20.4 ± 3.80	16.9 ± 3.95	−0.33 (−2.11 to −1.45)	0.7152	
Muscle Na^+, mmol/L tissue volume	23.1 ± 3.52	21.9 ± 2.61	0.02 (−1.41 to 1.45)	0.9811	

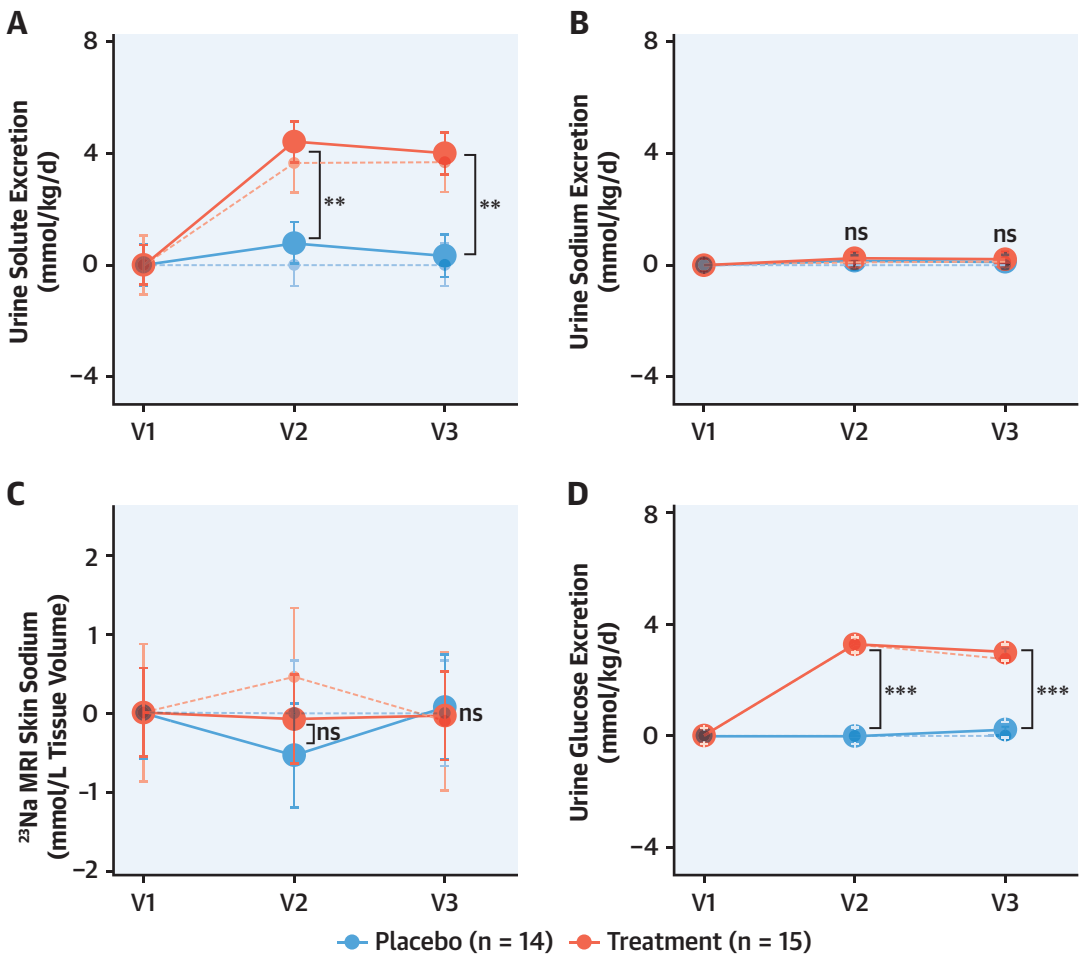
Values are mean ± SD or n (%), unless otherwise indicated. [a]Comparisons between the 2 groups after adjusting for age, sex, and BMI using generalized linear models. **Bold** indicates values of $P < 0.05$. ^{23}Na MRI = sodium magnetic resonance imaging; DBP = diastolic blood pressure; eUOsmo = calculated urine osmolality; ePOsmo = calculated plasma osmolality; FWC = solute-free water clearance; SBP = systolic blood pressure; UGlucV = 24-hour urine glucose excretion; UKV = 24-hour urine K^+ excretion; UNaV = 24-hour urine Na^+ excretion; UUreaV = 24-hour urine urea excretion; USolutesV = 24-hour urine solute excretion; other abbreviations as in Table 1.

FIGURE 2 Participants With Heart Failure Exhibit Underhydration With Elevated Copeptin/Vasopressin Levels



Serum copeptin levels in response to serum solute concentration, calculated as: 2 • [Na^+] + 2 • [K^+] + [Urea] + [Glucose], in healthy participants (A) and in participants with heart failure (B).

FIGURE 3 Dapagliflozin Treatment Causes Glucosuria Without Increasing Natriuresis



(A) 24-hour urine solute excretion. (B) 24-hour urine Na^+ excretion. (C) Skin Na^+ content measured with sodium magnetic resonance imaging (^{23}Na MRI). (D) 24-hour urine glucose excretion. The study participants received either placebo (blue line) or dapagliflozin (red line). Data were analyzed via linear mixed model and depicted as modeled difference from baseline, in which the error bars represent SEM. $^{**}P < 0.01$; $^{***}P < 0.001$. ns = not significant; V1 = baseline (Visit 1); V2 = 48 hours after treatment initiation with 24-hour urine collected between hours 24 and 48 (Visit 2, early treatment effect); V3 = 4 weeks after treatment initiation (Visit 3, late treatment effect).

(95% CI). In this random-intercept linear mixed model analysis, the interactions of visit and treatment arm were included as fixed effects. An unstructured covariance matrix and a restricted maximum likelihood estimation technique were used while containment method was set as the denominator degrees of freedom. Statistical significance was set at $P < 0.05$, and statistical analysis was performed by using SAS version 9.4 for Windows (SAS Institute, Inc).

RESULTS

Forty patients with chronic heart failure and reduced ejection fraction on stable background treatment were enrolled. Given the mechanistic nature of this study, only SGLT2i naïve participants were randomized, although enrollment of patients who had previously received SGLT2i therapy was formally allowed in the inclusion criteria. COVID-19 pandemic disruptions led to 3 participant withdrawals and 2 study discontinuations. Two participants were declared ineligible before starting the drug intervention. Thirty-three randomized participants were confirmed eligible at visit 1 and started treatment, all of whom completed the study (Figure 1). In 4 study participants who completed the trial, 24-hour urine collections were classified as under-collection based on the 24-hour creatinine excretion levels and

TABLE 3 Early and Late Effects of Placebo (n = 14) and Dapagliflozin (n = 15) Treatment on Markers of Water and Electrolyte Handling

	Visit	Placebo	Dapagliflozin	Placebo Change (95% CI)	Dapagliflozin Change (95% CI)	*P* Value Overall	Dapagliflozin vs Placebo Change (95% CI)	*P* Value (Visit)
Body weight, kg	1	74.3 ± 17.8	78.4 ± 18.7	0.000 (−0.48 to 0.48)	0.000 (−0.46 to 0.46)	**0.0329**		
	2	74.1 ± 17.6	78.2 ± 18.6	−0.189 (−0.67 to 0.29)	−0.293 (−0.75 to 0.17)		−0.103 (−0.77 to 0.56)	0.7562
	3	74.8 ± 17.9	77.9 ± 18.9	0.429 (−0.05 to 0.91)	−0.556 (−1.02 to −0.09)		−0.985 (−1.65 to −0.32)	**0.0044**
BMI, kg/m^2	1	26.4 ± 5.22	29.1 ± 5.91	0.000 (−0.17 to 0.17)	0.000 (−0.17 to 0.17)	**0.0328**		
	2	26.3 ± 5.14	29.0 ± 5.90	−0.065 (−0.24 to 0.11)	−0.104 (−0.27 to 0.06)		−0.039 (−0.28 to 0.2)	0.7422
	3	26.5 ± 5.23	28.9 ± 6.07	0.154 (−0.02 to 0.32)	−0.198 (−0.36 to −0.03)		−0.351 (−0.59 to −0.11)	**0.0046**
SBP, mm Hg	1	119 ± 14.3	128 ± 19.9	0.000 (−5.31 to 5.31)	0.000 (−5.13 to 5.13)	0.5073		
	2	116 ± 19.0	121 ± 14.4	−3.214 (−8.53 to 2.1)	−7.511 (−12.64 to −2.38)		−4.297 (−11.68 to 3.09)	0.2486
	3	115 ± 24.6	120 ± 16.2	−4.119 (−9.43 to 1.19)	−8.333 (−13.47 to −3.2)		−4.214 (−11.6 to 3.17)	0.2577
DBP, mm Hg	1	70.4 ± 10.1	73.9 ± 10.3	0.000 (−2.81 to 2.81)	0.000 (−2.71 to 2.71)	0.8211		
	2	66.7 ± 9.42	71.4 ± 7.74	−3.667 (−6.47 to −0.86)	−2.467 (−5.18 to 0.24)		1.200 (−2.7 to 5.1)	0.5402
	3	66.4 ± 12.9	71.1 ± 7.83	−3.976 (−6.78 to −1.17)	−2.778 (−5.49 to −0.07)		1.198 (−2.7 to 5.1)	0.5407
Heart rate, beats/min	1	67.4 ± 12.2	69.0 ± 10.6	0.000 (−2.53 to 2.53)	0.000 (−2.44 to 2.44)	0.4783		
	2	66.5 ± 12.4	70.4 ± 9.68	−0.976 (−3.51 to 1.55)	1.422 (−1.02 to 3.87)		2.398 (−1.12 to 5.91)	0.1771
	3	66.1 ± 13.4	69.9 ± 11.0	−1.286 (−3.81 to 1.24)	0.889 (−1.55 to 3.33)		2.175 (−1.34 to 5.69)	0.2204
Skin Na^+, mmol/L tissue volume	1	21.8 ± 2.72	19.3 ± 4.20	0.000 (−1.14 to 1.14)	0.000 (−1.1 to 1.1)	0.8693		
	2	21.3 ± 2.56	19.2 ± 4.25	−0.538 (−1.88 to 0.8)	−0.084 (−1.22 to 1.06)		0.455 (−1.31 to 2.21)	0.6211
	3	21.9 ± 3.72	19.3 ± 2.88	0.072 (−1.27 to 1.41)	−0.035 (−1.17 to 1.1)		−0.107 (−1.87 to 1.65)	0.9076
Muscle Na^+, mmol/L tissue volume	1	24.3 ± 2.75	22.3 ± 3.84	0.000 (−0.71 to 0.71)	0.000 (−0.69 to 0.69)	0.7164		
	2	23.8 ± 3.13	22.1 ± 3.77	−0.568 (−1.4 to 0.27)	−0.171 (−0.88 to 0.54)		0.397 (−0.7 to 1.49)	0.4886
	3	24.2 ± 3.22	22.0 ± 3.68	−0.111 (−0.95 to 0.73)	−0.276 (−0.99 to 0.43)		−0.165 (−1.26 to 0.93)	0.7733
Fasting blood glucose, mmol/L	1	6.78 ± 1.13	6.34 ± 1.47	0.000 (−0.42 to 0.42)	0.000 (−0.41 to 0.41)	**0.0292**		
	2	6.31 ± 1.15	6.19 ± 0.947	−0.471 (−0.89 to −0.05)	−0.147 (−0.55 to 0.26)		0.325 (−0.26 to 0.91)	0.2692
	3	6.88 ± 1.45	5.85 ± 0.693	0.100 (−0.32 to 0.52)	−0.487 (−0.89 to −0.08)		−0.587 (−1.17 to 0)	**0.0487**
Serum Na^+ , mmol/L	1	141 ± 1.86	140 ± 1.67	0.000 (−0.67 to 0.67)	0.000 (−0.65 to 0.65)	**0.0268**		
	2	140 ± 2.26	140 ± 2.02	−0.857 (−1.53 to −0.18)	0.000 (−0.65 to 0.65)		0.857 (−0.08 to 1.79)	**0.0724**
	3	139 ± 2.02	140 ± 1.74	−1.714 (−2.39 to −1.04)	−0.133 (−0.78 to 0.52)		1.581 (0.64 to 2.52)	**0.0014**
Serum K^+, mmol/L	1	4.26 ± 0.424	4.08 ± 0.265	0.000 (−0.12 to 0.12)	0.000 (−0.12 to 0.12)	0.3353		
	2	4.12 ± 0.487	4.11 ± 0.294	−0.143 (−0.26 to −0.02)	0.027 (−0.09 to 0.14)		0.170 (0 to 0.34)	**0.0487**
	3	4.23 ± 0.270	4.11 ± 0.308	−0.036 (−0.16 to 0.09)	0.027 (−0.09 to 0.14)		0.062 (−0.11 to 0.23)	0.4613
Serum urea, mmol/L	1	7.59 ± 3.49	5.47 ± 1.51	0.000 (−0.7 to 0.7)	0.000 (−0.67 to 0.67)	0.0944		
	2	7.32 ± 3.19	6.21 ± 1.42	−0.271 (−0.97 to 0.43)	0.733 (0.06 to 1.41)		1.005 (0.03 to 1.97)	**0.0426**
	3	6.96 ± 2.45	6.13 ± 1.98	−0.629 (−1.33 to 0.07)	0.653 (−0.02 to 1.33)		1.282 (0.31 to 2.25)	**0.0105**
ePOsmo, mmol/L	1	305 ± 6.66	300 ± 3.76	0.000 (−1.6 to 1.6)	0.000 (−1.54 to 1.54)	**0.0116**		
	2	302 ± 7.47	300 ± 4.61	−2.743 (−4.34 to −1.15)	0.640 (−0.9 to 2.18)		3.383 (1.16 to 5.6)	**0.0035**
	3	301 ± 6.25	300 ± 3.88	−4.029 (−5.62 to −2.43)	−0.047 (−1.59 to 1.5)		3.982 (1.76 to 6.2)	**0.0007**
Serum copeptin, pmol/L	1	20.5 ± 20.2	11.8 ± 9.60	0.000 (−3.61 to 3.61)	0.000 (−3.49 to 3.49)	**0.0230**		
	2	20.2 ± 18.8	17.0 ± 14.1	−0.279 (−3.89 to 3.33)	5.193 (1.7 to 8.68)		5.472 (0.45 to 10.5)	**0.0333**
	3	17.2 ± 12.2	16.2 ± 13.1	−3.364 (−6.98 to 0.25)	4.427 (0.94 to 7.92)		7.791 (2.77 to 12.81)	**0.003**
NT-proBNP, pg/mL	1	1,440 ± 2,310	468 ± 490	0.000 (−151.12 to 151.12)	0.000 (−146 to 146)	0.2675		
	2	1,220 ± 2,100	438 ± 445	−220.429 (−371.55 to −69.3)	−29.067 (−175.07 to 116.93)		191.362 (−18.77 to 401.49)	0.0734
	3	1,370 ± 2,220	411 ± 338	−69.214 (−220.34 to 81.91)	−56.267 (−202.27 to 89.73)		12.948 (−197.18 to 223.08)	0.9021
Hematocrit, %	1	44.7 ± 4.94	45.0 ± 4.30	0.000 (−0.73 to 0.73)	0.000 (−0.7 to 0.7)	0.7680		
	2	44.2 ± 5.22	44.5 ± 4.61	−0.443 (−1.17 to 0.28)	−0.440 (−1.14 to 0.26)		0.003 (−1.01 to 1.01)	0.9955
	3	44.4 ± 4.95	44.3 ± 4.20	−0.257 (−0.98 to 0.47)	−0.653 (−1.36 to 0.05)		−0.396 (−1.41 to 0.61)	0.4355
Urine volume, mL/kg/d	1	16.7 ± 5.92	20.3 ± 10.2	0.000 (−3.4 to 3.4)	0.000 (−3.28 to 3.28)	0.6199		
	2	19.4 ± 6.76	25.7 ± 6.59	2.649 (−0.75 to 6.05)	5.403 (2.12 to 8.68)		2.754 (−1.97 to 7.48)	0.2474
	3	19.9 ± 6.94	24.4 ± 7.68	3.200 (−0.2 to 6.6)	4.097 (0.82 to 7.38)		0.897 (−3.83 to 5.62)	0.7049

Continued on the next page

TABLE 3 Continued

	Visit	Placebo	Dapagliflozin	Placebo Change (95% CI)	Dapagliflozin Change (95% CI)	*P* Value Overall	Dapagliflozin vs Placebo Change (95% CI)	*P* Value (Visit)
USolutesV, mmol/kg/d	1	8.30 ± 2.27	8.66 ± 2.59	0.000 (−1.53 to 1.53)	0.000 (−1.48 to 1.48)	**0.0045**		
	2	9.09 ± 2.42	13.1 ± 3.69	0.786 (−0.74 to 2.32)	4.432 (2.95 to 5.91)		3.646 (1.52 to 5.77)	**0.0011**
	3	8.64 ± 2.78	12.7 ± 3.40	0.340 (−1.19 to 1.87)	4.009 (2.53 to 5.49)		3.669 (1.54 to 5.8)	**0.0011**
eUOsmo, mmol/L	1	544 ± 208	489 ± 173	0.000 (−68.27 to 68.27)	0.000 (−65.95 to 65.95)	0.0850		
	2	503 ± 164	522 ± 138	−40.393 (−108.66 to 27.87)	32.785 (−33.17 to 98.74)		73.178 (−21.74 to 168.1)	0.128
	3	464 ± 179	543 ± 169	−80.223 (−148.49 to −11.96)	53.975 (−11.98 to 119.93)		134.198 (39.28 to 229.12)	**0.0064**
FWC, mL/kg/d	1	−10.5 ± 7.40	−8.58 ± 5.46	0.000 (−3.55 to 3.55)	0.000 (−3.43 to 3.43)	**0.0017**		
	2	−10.7 ± 8.10	−17.8 ± 10.7	−0.188 (−3.74 to 3.36)	−9.248 (−12.68 to −5.82)		−9.061 (−14 to −4.12)	**0.0005**
	3	−8.75 ± 8.16	−17.8 ± 9.66	1.760 (−1.79 to 5.31)	−9.244 (−12.67 to −5.81)		−11.004 (−15.94 to −6.07)	**<0.0001**
UNaV, mmol/kg/d	1	1.78 ± 0.603	1.95 ± 0.891	0.000 (−0.37 to 0.37)	0.000 (−0.36 to 0.36)	0.9089		
	2	1.92 ± 0.564	2.20 ± 0.949	0.145 (−0.22 to 0.51)	0.248 (−0.11 to 0.6)		0.103 (−0.41 to 0.61)	0.6874
	3	1.87 ± 0.585	2.17 ± 0.959	0.096 (−0.27 to 0.46)	0.216 (−0.14 to 0.57)		0.121 (−0.39 to 0.63)	0.6381
UKV, mmol/kg/d	1	0.562 ± 0.292	0.544 ± 0.235	0.000 (−0.08 to 0.08)	0.000 (−0.08 to 0.08)	0.9237		
	2	0.599 ± 0.281	0.605 ± 0.181	0.037 (−0.05 to 0.12)	0.061 (−0.02 to 0.14)		0.024 (−0.09 to 0.14)	0.6855
	3	0.584 ± 0.323	0.567 ± 0.189	0.022 (−0.06 to 0.11)	0.023 (−0.06 to 0.1)		0.001 (−0.12 to 0.12)	0.992
UUreaV, mmol/kg/d	1	3.53 ± 1.18	3.51 ± 0.915	0.000 (−0.58 to 0.58)	0.000 (−0.56 to 0.56)	0.2895		
	2	3.95 ± 1.23	4.05 ± 1.03	0.423 (−0.15 to 1)	0.539 (−0.02 to 1.1)		0.116 (−0.68 to 0.92)	0.7726
	3	3.40 ± 1.13	4.07 ± 1.28	−0.130 (−0.71 to 0.45)	0.553 (0 to 1.11)		0.682 (−0.12 to 1.48)	0.0933
UGlucV, mmol/kg/d	1	0.0957 ± 0.237	0.151 ± 0.395	0.000 (−0.55 to 0.55)	0.000 (−0.53 to 0.53)	**<0.0001**		
	2	0.0960 ± 0.257	3.43 ± 1.99	0.000 (−0.55 to 0.55)	3.276 (2.74 to 3.81)		3.276 (2.51 to 4.04)	**<0.0001**
	3	0.330 ± 1.12	3.13 ± 1.63	0.234 (−0.32 to 0.79)	2.978 (2.44 to 3.51)		2.744 (1.98 to 3.51)	**<0.0001**

Values are mean ± SD unless otherwise indicated. Placebo and dapagliflozin changes from baseline and the group differences are reported as delta change (95% CI) adjusted for baseline levels, using linear mixed model analysis. **Bold** indicates values of $P < 0.05$.

Visit 1 = baseline visit, before treatment; Visit 2 = after 48 hours of treatment; Visit 3 = after 28 days of treatment; other abbreviations as in Tables 1 and 2.

excluded from statistical analysis. The resulting information from 29 study participants (mean age 59 ± 14 years; left ventricular ejection fraction 31% ± 9%) was included for data analysis (placebo: n = 14; dapagliflozin: n = 15).

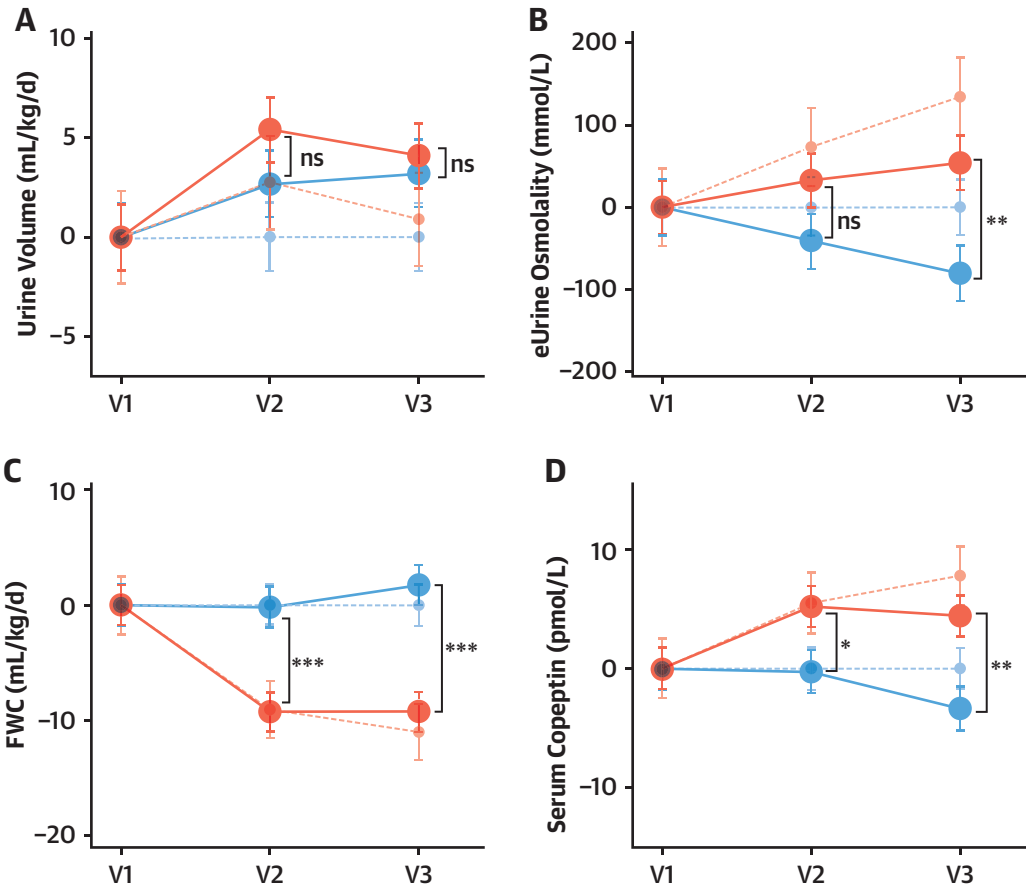
Baseline characteristics, including demographic characteristics, clinical laboratory data, and background medication of the participants, are summarized in Table 1. Six participants (42.9%) from the placebo group and 8 participants (53.3%) from the treatment group had a diagnosis of type 2 diabetes mellitus. All participants were on stable doses of renin-angiotensin-aldosterone-system inhibitors, and all but 1 had beta-blockers as part of their routine treatment regimens. Diuretic treatment was stable in the 4 weeks previous to starting the intervention and was not changed during the study. Baseline N-terminal pro-B-type natriuretic peptide levels did not differ between the 2 groups ($P = 0.36$). Overall, treatment with dapagliflozin was well tolerated, and treatment adherence was 98.6%.

BASELINE CHARACTERIZATION OF HYDRATION STATUS. Compared with healthy SSIS participants, our trial participants with heart failure exhibited reduced urine volume generation (18.6 ± 8.5 mL/kg/d vs 28.9 ± 11.6 mL/kg/d; $P < 0.01$), reduced renal solute free water excretion (−9.5 ± 6.4 mL/kg/d vs −3.1 ± 13.5 mL/kg/d; $P < 0.05$), increased urine concentration (515 ± 189 mmol/L vs 378 ± 174 mmol/L; $P < 0.001$), and elevated copeptin levels (16.0 ± 16.0 pmol/L vs 4.9 ± 3.3 pmol/L; $P < 0.001$) (Table 2). We conclude that, compared with a healthy study population, these study participants with heart failure showed augmented water conservation at baseline. The predisposition to renal water conservation was not accompanied by increased Na^+, K^+, urea, or glucose excretion into the urine, and ^{23}Na MRI showed no differences in tissue Na^+ content between patients with heart failure and healthy cohort participants.

We also characterized the physiological-adaptive nature of vasopressin release. With increasing serum solute concentration, which marks underhydration, both the healthy participants from the SSIS cohort (Figure 2A) and the trial participants with heart failure (Figure 2B) exhibited increasing copeptin levels. This finding indicates that at baseline, the neuroendocrine vasopressin response that limits renal water excretion during states of underhydration was intact in our study participants.

EFFECT OF DAPAGLIFLOZIN ON RENAL NA^+ AND GLUCOSE EXCRETION. Dapagliflozin-treated participants exhibited a steep and persisting increase in

FIGURE 4 Physiological-Adaptive Water Conservation Overrides the Osmotic Diuretic Effect of Dapagliflozin-Driven Glucosuria



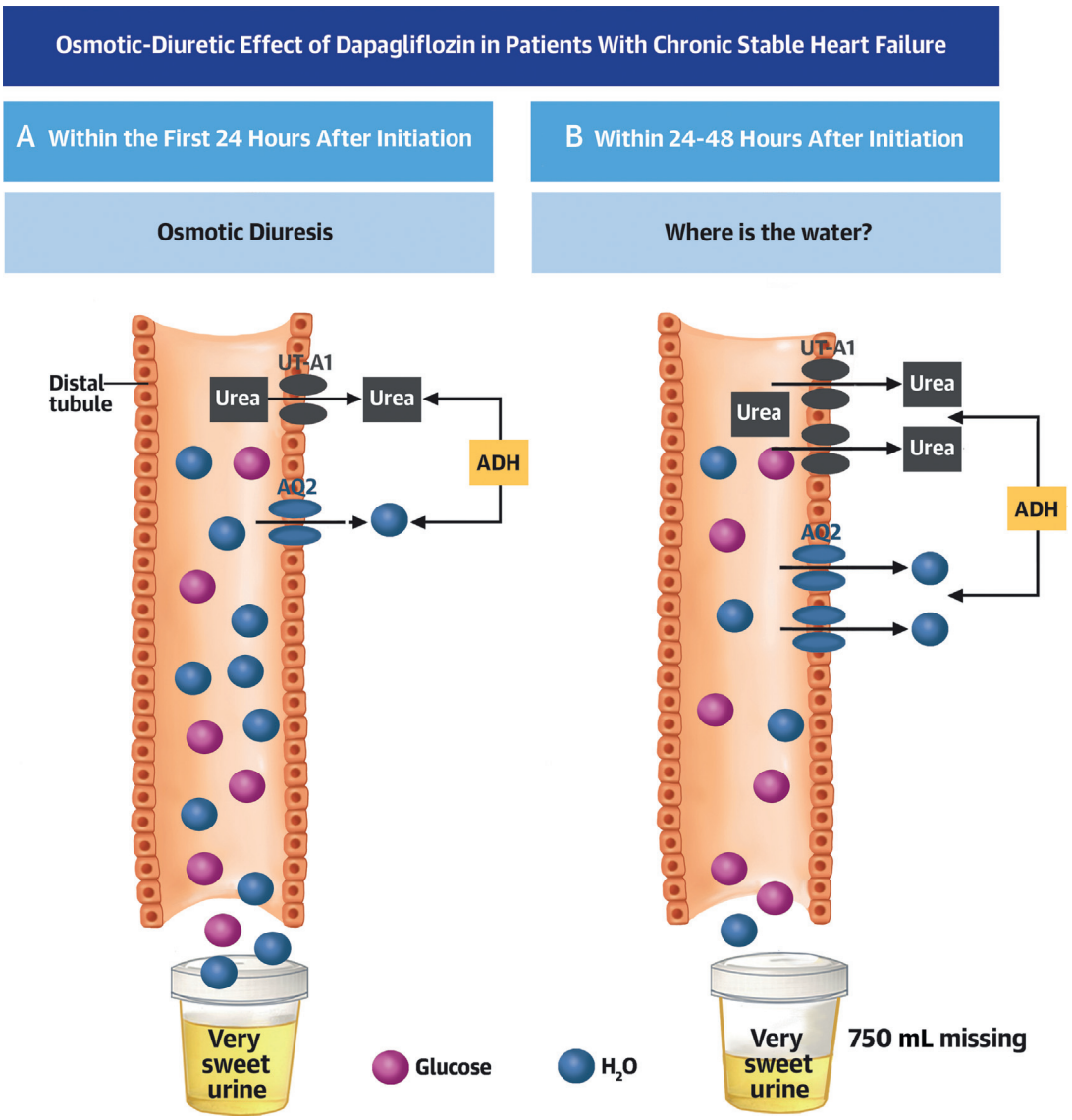
(A) 24-hour urine volume excretion. (B) 24-hour urine osmolality, calculated as $2 \cdot [Na^+] + 2 \cdot [K^+] + [Urea] + [Glucose]$. (C) 24-hour urine solute-free water clearance (FWC). (D) Serum copeptin levels. Treatment groups, other abbreviations, and data analysis as in Figure 3. $^{**}P < 0.01$; $^{***}P < 0.001$.

total 24-hour solute excretion with treatment initiation (Figure 3A, Table 3); however, SGLT2i had no effect on 24-hour urine Na^+ excretion (Figure 3B, Table 3). In line with this observation, treatment with dapagliflozin did not change tissue Na^+ content, neither after 48 hours nor after 4 weeks (Figure 3C, Table 3). In the absence of an increase in 24-hour urine Na^+ excretion, the observed early and late increases in 24-hour urine solute excretion in the dapagliflozin group was almost entirely explainable by glucosuria (Figure 3D, Table 3), which predisposed to renal water loss by osmotic diuresis.

PHYSIOLOGICAL-ADAPTIVE WATER CONSERVATION OVERRIDES THE OSMOTIC DIURETIC EFFECT OF DAPAGLIFLOZIN-DRIVEN GLUCOSURIA. Despite the significant early and persistent increase in urine solutes (Figure 3A) and glucose (Figure 3D) excretion, treatment with dapagliflozin resulted in a statistically nonsignificant early increase in urine volume (mean difference 2.8 mL/kg/d; 95% CI: −1.97 to 7.48; $P = 0.25$), which diminished after 4 weeks (0.9 mL/kg/d; 95% CI: −3.83 to 5.62; $P = 0.7$) (Figure 4A, Table 3).

Urine solute concentration increased by 134.2 mmol/L (95% CI: 39.28-229.12; $P < 0.01$) (Figure 4B, Table 3) after 4 weeks, indicating that participants treated with dapagliflozin had successfully prevented glucose-driven water loss by renal water conservation. The early and late effect of dapagliflozin on renal water conservation was a ≈10 mL/kg/d reduction in renal free water clearance (Figure 4C, Table 3); this indicates that the strengthening of the urine concentration mechanism prevented a glucose solute-driven increase in urine

CENTRAL ILLUSTRATION **Glucosuria, Osmotic Diuresis, and Secondary Water Conservation With Sodium-Glucose Cotransporter 2 Inhibition**



Marton A, et al. J Am Coll Cardiol. 2024;83(15):1386–1398.

(A) The load of glucose that acutely occurs in the most distal parts of the renal tubular system with dapagliflozin treatment initiation cannot be reabsorbed, and osmotic diuresis ensues. (B) Within 24 to 48 hours of treatment initiation, however, a physiological-adaptive, neuroendocrine, antidiuretic response (increased secretion of ADH: antidiuretic hormone, vasopressin) counter-balances the osmotic-diuretic drive of the persisting glucosuria, promotes urea-driven water reabsorption through aquaporin-2 (AQ2) channels, and the urine volume reverts to baseline level. Note that we found no effect of SGLT2 (sodium-glucose cotransporter 2) inhibition on 24h urine Na^+ excretion within 24 to 48 hours of treatment initiation. UT-A1 = urea transporter A1.

volume of ≈10 mL/kg/d · 75 kg = 750 mL/d in the dapagliflozin group.

This renal water conservation process was accompanied by a further increase in copeptin levels (**Figure 4D**, **Table 3**). Osmotic activation of vasopressin release with increasing serum solute concentration remained intact after 2 days and after 4 weeks (Supplemental Figure 1) of dapagliflozin treatment. The dapagliflozin-driven increases in copeptin release compared with placebo (early: 5.5 pmol/L

[95% CI: 0.45-10.50; $P < 0.05$]; late: 7.8 pmol/L [95% CI: 2.77-12.81; $P < 0.01$]) resulted in proportional reductions in solute free water clearance (early: −9.1 mL/kg/d [95% CI: −14.00 to −4.12; $P < 0.001$]; late: −11.0 mL/kg/d [95% CI: −15.94 to −6.07; $P < 0.0001$]), indicating intact vasopressin-driven water conservation.

We interpret these findings to show that physiological-adaptive renal water conservation by urine concentration counterbalanced the osmotic driving force of increased glucosuria, thereby preventing an expected ≈1 L/d osmotic diuretic increase in urine volume.

DISCUSSION

We prospectively studied the activation of the renal water conservation mechanism in response to SGLT2i within 48 hours of treatment initiation and after 4 weeks in patients with chronic, stable heart failure. Our key findings are that dapagliflozin in a standard therapeutic dose increased 24-hour urine glucose excretion without parallel increases in Na^+ excretion; however, parallel vasopressin release and renal water reabsorption quickly counterbalanced the osmotic diuretic force of increased glucosuria by increasing urine concentration, and thereby stabilized the urine volume. Increases in copeptin/vasopressin levels during SGLT2 inhibition have been reported previously in patients with diabetes mellitus and chronic renal failure.[32] We expand this knowledge by showing that dapagliflozin treatment induces renal water conservation in patients with chronic heart failure.

PRACTICAL IMPLICATIONS. Despite increasing urine glucose excretion by ≈225 mmoL/d (**Figure 3A**), daily dapagliflozin treatment did not cause an anticipated ≈750 mL/d increase in urine volume (**Figure 4C**) due to physiological-adaptive strengthening of the urine concentration mechanism. In contrast to this antiparallel movement of glucose solutes and water observed in the dapagliflozin group (**Central Illustration**), treatment with osmotic or loop diuretics is thought to increase renal solute load and dilute the urine, resulting in increased urine volume formation.[41-43] This difference in renal water handling during elevated urine solute excretion explains why a practitioner can expect a significant increase in urine volume with loop diuretics but not with standard-dose SGLT2i.

Patients with severely reduced cardiac ejection fraction and cardiac congestion often exhibit excessive vasopressin release.[44] Such nonosmotic vasopressin release, which marks an effort to maintain the effective circulatory volume by solute free water retention, unsurprisingly predicts poor cardiovascular outcome.[45] In the absence of cardiac congestion, however, our study participants exhibited physiologically intact osmotic vasopressin release at baseline (**Figure 2**) and in response to the additional osmotic diuretic dehydration challenge of SGLT2i-driven glucosuria (**Figure 4D**). It is thus predictable that if appropriately controlled for the nonosmotic effects of cardiac congestion on vasopressin release,[45,46] the beneficial effect of SGLT2i on cardiac health will be associated with increases in plasma copeptin levels.

STUDY LIMITATIONS. Even in controlled environments,[47-49] the role of extrarenal water losses and, perhaps more importantly, the unmeasured variability in endogenous metabolic water production make it impossible to generate reliable long-term information on steady-state body fluid homeostasis.[36] We therefore instead focused on testing the hypothesis that therapeutic SGLT2i causes immediate and powerful physiological-adaptive renal water conservation, and thereby abandons the osmotic diuretic potential of the drug (**Central Illustration**). A limitation of the current study is that due to the experimental design, we missed the immediate, transient, ≈1 L/d osmotic diuretic renal water release that occurs within the first 24 hours of treatment initiation.[23,24] In line with the rigorous day-to-day time series analysis by Wilcox et al,[23] however, our results indicate that it took only 24 to 48 hours to almost completely overcome the osmotic-driving force of sustained glucosuria by vasopressin-driven strengthening of the urine concentration mechanism. This study was not designed to detect the endocrine mechanisms (eg, activation of the renin-angiotensin-aldosterone system) that may have quickly compensated the natriuretic effect of the drug.

Adjusted for the placebo effect, we noticed a nonsignificant 2.8 mL/kg/d (corresponding to ≈210 mL/d) early increase in urine volume in the dapagliflozin group. Comparably mild residual osmotic diuretic effects have been reported in the early, larger powered efficacy trials with various SGLT2i[25,50,51] and in more recent studies in patients with type 2 diabetes[30,52] or heart failure.[29,53] Our study was not designed (and therefore it is most likely underpowered) to detect a true accompanying ≈200 to 250 mL/d residual osmotic diuretic drug effect within the first 24 to 48 hours after dapagliflozin treatment initiation, which disappeared after 4 weeks of treatment (**Figure 4A**). In contrast, this trial was

designed to detect renal water conservation by increased urine concentration in the dapagliflozin treatment group. The prestudy group size estimate predicted that n = 16 per group would suffice to test our primary endpoint. In line with this prediction, the current study was sufficiently powered to detect that early vasopressin-driven water conservation counterbalanced the osmotic diuretic potential of the drug by preventing a daily increase in urine volume of ≈ 750 mL/d (**Figure 4C**).

SUMMARY AND PERSPECTIVES

These findings suggest that SGLT2i may not improve cardiac health status by osmotic diuretic decongestion.[34,35] An alternative "nutrient deprivation signaling/autophagy hypothesis"[54] assigns the beneficial effects of SGLT2i to reprogramming of mitochondrial function. Similar switches in mitochondrial fuel utilization occur in "aestivation," an evolutionary conserved survival strategy in response to combined energy and water deficit.[55] The observed ≈150 kcal/d loss of glucose fuel into the urine (**Figure 3D**) not only requires adaptive energy conservation to prevent an energy deficit but also triggers physiological water conservation to counteract the osmotic diuretic effect of glucosuria and prevent dehydration (**Figure 4C**). As an extension to the "nutrient deprivation signaling/autophagy hypothesis," we suggest that SGLT2 inhibition may result in a biomimicry of aestivation metabolism and thereby improve health span.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with heart failure, dapagliflozin increases glucose excretion without increasing sodium excretion. Vasopressin-driven renal water conservation overcomes osmotic diuresis as the principal mechanism of decongestion.

TRANSLATIONAL OUTLOOK: Further research is needed to clarify the mechanistic relationships between glucose excretion, nutrient deprivation, energy-intense water conservation, and changes in mitochondrial metabolism and how these improve the healthspan in patients with heart failure.

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APPENDIX For a supplemental figure, please see the online version of this paper.