A Randomized Trial of Empagliflozin to Increase Plasma Sodium Levels in Patients with the Syndrome of Inappropriate Antidiuresis

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ABSTRACT

Background Treatment options to address the hyponatremia induced by the syndrome of inappropriate antidiuresis (SIAD) are inadequate. The sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin promotes osmotic diuresis *via* urinary glucose excretion and therefore, might offer a novel treatment option for SIAD.

Methods In this double-blind, randomized trial, we recruited 88 hospitalized patients with SIAD-induced hyponatremia <130 mmol/L at the University Hospital Basel from September 2016 until January 2019 and assigned patients to receive, in addition to standard fluid restriction of <1000 ml/24 h, a once-daily dose of oral empagliflozin or placebo for 4 days. The primary end point was the absolute change in plasma sodium concentration after 4 days of treatment. Secondary end points included predisposing factors for treatment response and safety of the intervention.

Results Of the 87 patients who completed the trial, 43 (49%) received treatment with empagliflozin, and 44 (51%) received placebo. Baseline plasma sodium concentrations were similar for the two groups (median 125.5 mmol/L for the empaflozin group and median 126 mmol/L for the placebo group). Patients treated with empagliflozin had a significantly higher increase of median plasma sodium concentration compared with those receiving placebo (10 versus 7 mmol/L, respectively; $P=0.04$). Profound hyponatremia (<125 mmol/L) and lower baseline osmolality levels increased the likelihood of response to treatment with empagliflozin. Treatment was well tolerated, and no events of hypoglycemia or hypotension occurred among those receiving empagliflozin.

Conclusions Among hospitalized patients with SIAD treated with fluid restriction, those who received empagliflozin had a larger increase in plasma sodium levels compared with those who received placebo. This finding indicates that empagliflozin warrants further study as a treatment for the disorder.

JASN 31: 615–624, 2020. doi: https://doi.org/10.1681/ASN.2019090944

The syndrome of inappropriate antidiuresis (SIAD) is the predominant cause of hyponatremia,[1–3] with the impaired antidiuretic hormone regulation leading to a reduction of free water excretion with consecutive hypotonic hyponatremia.[4,5] There is a wide variety of causes inducing SIAD, like central nervous system and pulmonary disorders, cancer, drugs, pain, or stress of any etiology.[6]

Received September 21, 2019. Accepted November 25, 2019.

Published online ahead of print. Publication date available at www.jasn.org.

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Despite its high prevalence, treatment options for SIAD other than treating the underlying cause are limited.[7,8] The recommended first-line treatment for SIAD-induced hyponatremia is fluid restriction, which is often not successful.[9] Other treatment options, such as vasopressin receptor antagonists (vaptans), are very costly and bear the risk of plasma sodium overcorrection,[8,10,11] or they are poorly tolerated, resulting in low compliance, such as urea.[12] Accordingly, treatment often remains inadequate,[13] and additional treatment options are needed.

Empagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor, which is used as an antidiabetic drug due to its induction of pronounced glucosuria.[14,15] Glucosuria leads to osmotic diuresis with consequent increased excretion of free water,[16,17] which might also be of interest to patients with SIAD who suffer from retention of free water. In fact, in a recent small proof of concept study in 14 healthy volunteers with desmopressin-induced SIAD, empagliflozin led to a significant increase in urinary free water excretion.[17] Because empagliflozin has a favorable safety profile with beneficial effects on cardiovascular and renal outcomes,[18,19] it further recommends itself as a treatment option for the often elderly and polymorbid patients with SIAD.[20]

The aim of this prospective study was, therefore, to investigate whether treatment with the SGLT2 inhibitor empagliflozin for 4 days compared with placebo in addition to standard fluid restriction results in a greater increase in plasma sodium concentration in hospitalized hyponatremic patients with SIAD.

Significance Statement

Treatment options for the syndrome of inappropriate antidiuresis (SIAD), the predominant cause of hyponatremia, are inadequate. The authors studied the effects of the sodium glucose cotransporter 2 inhibitor empagliflozin, which promotes osmotic diuresis *via* urinary glucose excretion, in a randomized trial of 87 hospitalized patients with SIAD-induced hyponatremia who were also treated with standard fluid restriction. Patients who received 4 days of empagliflozin had a significantly larger increase in plasma sodium compared with those who received placebo (10 versus 7 mmol/L, respectively). Profound hyponatremia (<125 mmol/L) and lower baseline osmolality levels increased the likelihood of response to treatment with empagliflozin. These findings suggest that further investigation of empagliflozin as a treatment option for hospitalized patients with SIAD-induced hyponatremia is warranted.

METHODS

Study Design and Participants

This prospective, double-blind, placebo-controlled, randomized, proof of concept study was performed at the University Hospital Basel, Switzerland from September 2016 to January 2019. The local ethics committee (EKNZ 2015–00131) as well as the national agency for the authorization and supervision of therapeutic products (2016DR2099; swissmedics) approved the study protocol and study medication. The trial was registered at ClinicalTrials.gov (NCT02874807). Written informed consent was obtained from all patients.

Eligible patients were 18 years of age or older and had SIAD-induced hyponatremia <130 mmol/L defined as clinically assessed euvolemia, plasma osmolality <275 mmol/kg, urine osmolality >100 mmol/kg, urine sodium >30 mmol/L, exclusion of hypothyroidism, and hypocortisolism.[21] Hyponatremic patients with severe symptoms in need of treatment with 3% NaCl solution; renal impairment; hepatic impairment; systolic BP <90 mm Hg; diabetes mellitus type 1; current treatment with SGLT2 inhibitors, lithium chloride, or urea; a contraindication for lowering BP (*e.g.*, subarachnoid bleeding); severe immunosuppression (leukocytes <2 G/L); peripheral arteriovascular disease stage 3 or 4; fasting or other reasons preventing medication intake; participation in another study; pregnancy or breastfeeding; or end of life care were ineligible.

Plasma sodium values of all hospitalized patients in the University Hospital Basel were screened daily using an electronic screening alert. Patients meeting the eligibility requirements were randomly assigned in a 1:1 ratio to receive either oral empagliflozin (25 mg) or matching placebo once daily for 4 days in addition to standard fluid restriction of <1000 ml/d. Further treatment of the concomitant conditions was otherwise at the discretion of the treating physician who was not involved in the study.

Study Assessments

Study assessments, including clinical parameters and blood and urine sampling, were performed at baseline (day 0) and then once daily until 4 days (day 4) after administration of the first study drug (empagliflozin 25 mg or placebo). For safety reasons, additional plasma sodium and glucose measurements were taken 12 and 36 hours after the start of the study. Plasma sodium values were again checked at discharge and at the follow-up visit scheduled 30 days after inclusion.

At baseline, on day 4, and at the follow-up visit, patients were asked to rate their general wellbeing on a visual analog scale reaching from zero (no wellbeing) to ten (excellent wellbeing). Furthermore, they were asked if they experienced thirst, vertigo, headache, and nausea on a yes or no basis.

The primary end point was the absolute change in plasma sodium concentration from baseline (day 0) to day 4 (*i.e.*, 4 days after administration of the first study drug). Prespecified secondary end points included plasma sodium concentration at the other time points (absolute changes from baseline to 24 hours, 48 hours, discharge, and 30 days and area under the curve [AUC] from 12 hours to 4 days); plasma and urinary values: urea, uric acid and osmolality (absolute change from baseline to day 4), glucose, and urinary sodium (AUC 12/24 hours to 4 days); weight (AUC 24 hours to 4 days); change of general wellbeing; and symptoms of hyponatremia (change from baseline to day 4 and 30 days).

Profound hyponatremia was defined as <125 mmol/L, moderate hyponatremia was defined as between 125

and 129 mmol/L, and normonatremia was defined as 135–145 mmol/L. Plasma sodium overcorrection was defined as an increase of >12 mmol/L within 24 hours or >18 mmol/L within 48 hours according to guidelines.[8]

Adverse events were defined as any new medical problem or exacerbation of an existing medical problem in a patient enrolled in the study. All adverse events of category 3 or more according to Common Terminology Criteria for Adverse Events v4.0 were recorded. Seriousness and severity of each event were documented, and its relation to the study intervention was assessed. The investigators reported the events to the appropriate regulatory authorities.

Laboratory Measurements

Plasma and urine concentrations of sodium, glucose, creatinine, urea, uric acid, and osmolality were measured by the central laboratory of the University Hospital Basel. Plasma and urinary osmolality levels were measured using the freezing point depression osmometric method. To ensure the double-blind design of the study, results from the urinary diagnostics after administration of the first study drug were blinded until the end of the study.

Sample Size Estimation

Sample size was estimated to be able to show the superiority of empagliflozin as add on compared with the standard fluid restriction with regard to the primary end point. Sample size was set to ensure at least 90% power ($1-\beta = 0.9$) at a significance level $\alpha = 5\%$. Assuming an estimated difference of 2 mmol/L between the trial arms, a total of 83 evaluable patients were needed. Additional details are in Supplemental Material.

Analysis Sets

A total of 88 patients were enrolled and randomized. In one patient, blinded postrandomization exclusion was performed due to erroneous enrolment (wrong diagnosis). The full analysis set included all 87 randomized patients with confirmed diagnosis of SIAD (43 empagliflozin and 44 placebo). Patients were analyzed according to the intention-to-treat principle. Three patients withdrew consent during the treatment phase of the study, and one patient only received 50% of the study medication (all in the empagliflozin group). Because these data were not per protocol, they were excluded from the per protocol analysis set, which included 83 patients (39 empagliflozin and 44 placebo) (Figure 1).

The main analysis was performed on the full analysis set using multiple imputation of missing values (details are in Supplemental Material). A two-sided Wilcoxon rank sum test was performed to test whether the primary end point differs between the empagliflozin and placebo groups using a significance level of 0.05. Results from multiple imputations were pooled applying Rubin rules. Sensitivity analyses were performed on (*1*) the per protocol set using the last observation carried forward approach in case of missing plasma sodium at day 4 and (*2*) all patients with the primary end point available (complete patient analysis). Auxiliary analyses were performed to further investigate whether the primary end point was associated with different patient characteristics (covariates). Separate linear regression models were fitted, each including the respective covariate, trial arm, and the interaction term as predictors.

Continuous secondary end points were analyzed with linear regression models, and binary end points were analyzed using logistic regression models. Separate models were fitted, including the corresponding baseline value or status as covariate and the trial arm as predictor.

All secondary analyses were performed on the full analyses set on the basis of available data.

All analyses were predefined and conducted using the statistical software package R (R Core Team, 2018). No adjustments for multiple testing were made.

Data Sharing Statement

The following data will be shared on publication to researchers who provide a methodologically sound proposal to achieve the aims in the approved proposal: deidentified individual participant data that underlie the results reported in this article, study protocol, and statistical analysis plan. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

RESULTS

Baseline Characteristics

Forty-three patients were assigned to receive empagliflozin 25 mg daily, and 44 were assigned to receive placebo for 4 days in addition to standard fluid restriction (Figure 1). Baseline characteristics were similar between the two trial arms as was severity of hyponatremia, with a median plasma sodium concentration of 125.5 mmol/L (interquartile range [IQR], 122–127) in the empagliflozin group and 126 mmol/L (IQR, 123–127) in the placebo group, respectively (Tables 1 and 2). The leading causes for SIAD were central nervous system disorders, nausea/pain, and drug induced.

Efficacy

Four days of treatment resulted in a significantly higher median increase in plasma sodium concentration of 10 mmol/L (IQR, 5–12) with empagliflozin versus 7 mmol/L (IQR, 3–11) with placebo ($P=0.04$) (Figure 2, Supplemental Figure 1). This finding was confirmed when repeating the analysis on the per protocol analysis set (10 mmol/L [IQR, 5–13] empagliflozin versus 7 mmol/L [IQR, 3–11] placebo; $P=0.04$) and on the complete cases (10 mmol/L [IQR, 5–12] empagliflozin versus 7 mmol/L [IQR, 3–10.5] placebo; $n=83$; $P=0.08$).

The first difference in plasma sodium levels between the treatment arms was noted after 24 hours and persisted until day 4. Accordingly, the AUC from 12 hours after start of treat-

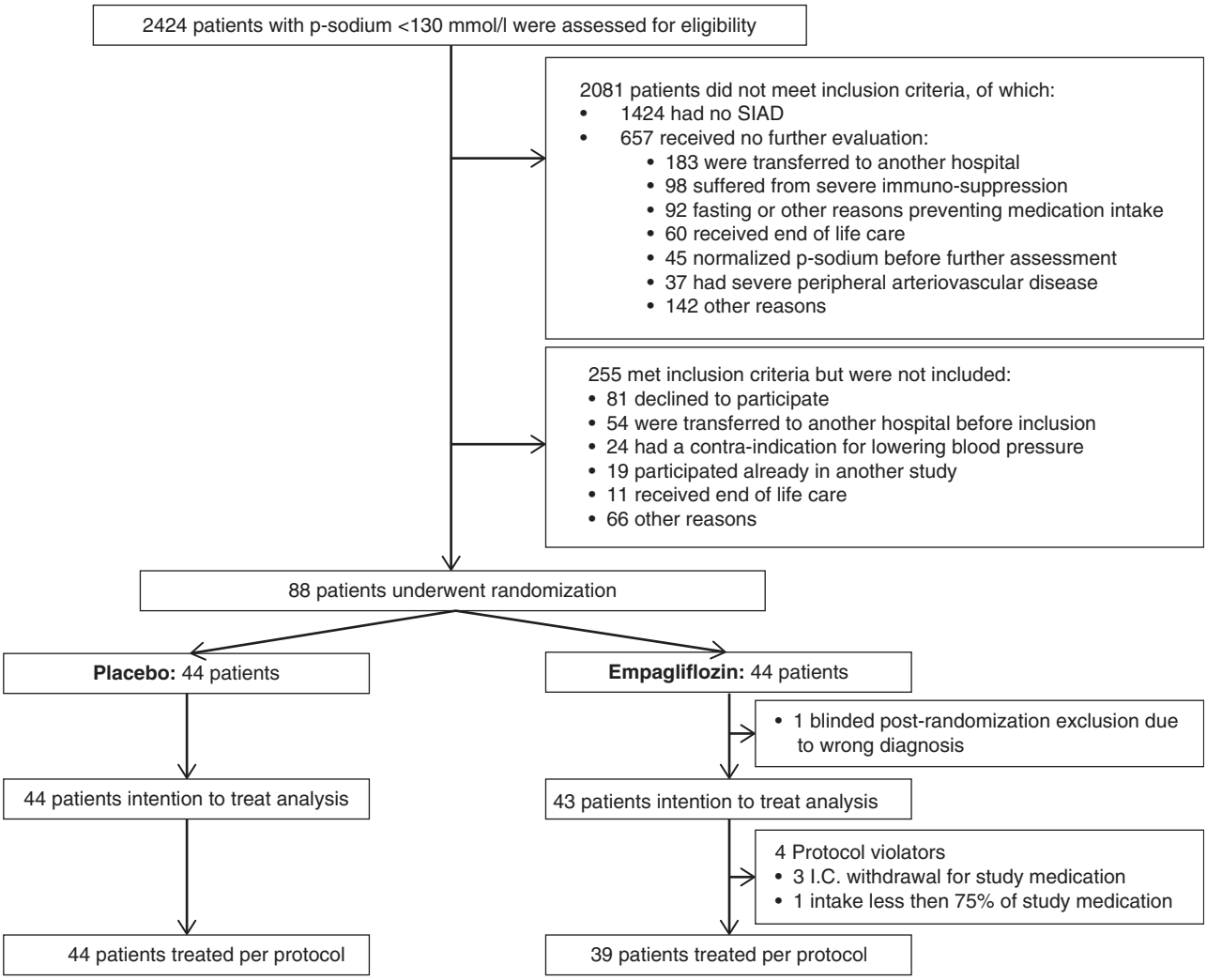

Figure 1. Study flow diagram. I.C., informed consent; p-sodium, plasma sodium; SIAD, syndrome of inappropriate antidiuresis.

ment to day 4 was slightly larger with empagliflozin compared with placebo (linear regression estimate adjusted for baseline plasma sodium: 5.7; 95% confidence interval [95% CI], 0.4 to 11.0; $P=0.04$) (Supplemental Material, Supplemental Table 1).

The proportion of patients reaching a plasma sodium level of 130 mmol/L or above was higher in the empagliflozin arm with 87% (34 of 39 patients) compared with the placebo arm with 68% (30 of 44 patients). A similar picture emerged when looking at minimal plasma sodium increases of 4, 5, or 6 mmol/L, which were reached in proportionally more patients in the empagliflozin arm compared with the placebo arm (82%, 77%, and 69% compared with 70%, 66%, and 57%, respectively).

Plasma sodium levels at discharge were similar to the ones at the end of the treatment period, with 48% ($n=20$ of 42) being discharged normonatremic in the empagliflozin arm compared with 36% ($n=16$ of 44) in the placebo treatment arm. At the 30-day follow-up visit, 37% ($n=13$ of 35) from the empagliflozin group and 47% ($n=18$ of 38) from the placebo group showed persistent hyponatremia.

The change in plasma sodium concentration was negatively correlated with plasma sodium and plasma osmolality levels at baseline (Figure 3, A and B). These two associations differed between patients taking empagliflozin compared with placebo (P value for interaction "trial arm × baseline level" plasma sodium: 0.05; plasma osmolality: 0.018). For both plasma sodium and plasma osmolality, the inhibiting effect of a high baseline level was stronger in patients taking empagliflozin compared with placebo (in Figure 3, A and B, the slopes for empagliflozin have a steeper decline). This was further supported by a strong positive correlation between baseline plasma sodium and baseline plasma osmolality concentration (Pearson correlation coefficient β, 0.75; 95% CI, 0.64 to 0.83).

A similar association was found when treatment response according to severity of hyponatremia was evaluated. Change in plasma sodium concentration was larger in patients with profound hyponatremia (plasma sodium <125 mmol/L),

Table 1. Baseline characteristics

	Empagliflozin, *n*=43	Placebo, *n*=44
Age, yr (SD)	74 (14)	76 (12)
Sex, women (%)	27 (63)	28 (64)
BMI, kg/m^2 (SD)	24.0 (4.1)	23.1 (4.9)
Systolic BP, mm Hg (SD)	138 (17)	142 (21)
Diastolic BP, mm Hg (SD)	69 (15)	75 (14)
Heart rate, (bpm)	73 (10)	75 (16)
Comorbidities, *n* (%)		
Cardiovascular disease	31 (72)	33 (75)
Cerebrovascular disease	6 (14)	10 (23)
Pulmonary disease	6 (14)	9 (21)
Diabetes mellitus type 2	6 (14)	6 (14)
Psychiatric disease	9 (21)	11 (25)
Causes of SIAD, *n* (%)		
Central nervous system disorders	5 (12)	10 (23)
Nausea/pain	6 (14)	9 (21)
Trauma/postoperative	3 (7)	6 (14)
Drug induced (primarily antipsychotic/antiepileptic drugs)	9 (21)	5 (11)
Pulmonal disease	4 (9)	6 (14)
Infectious diseases	4 (9)	3 (7)
Malignant disease	7 (16)	1 (2)
Idiopathic	5 (12)	4 (9)

Summary statistics of patient characteristics according to the full analysis set. Categorical variables are shown as frequencies (percentage), and numerical variables are shown as mean (SD). BMI, body mass index.

with a trend toward a more pronounced effect in the empagliflozin group (P=0.08) (Figure 3C). No association between the primary end point and other electrolytes, age, sex, or etiology of SIAD was found (Supplemental Material, Supplemental Table 2).

Secondary Outcomes

Courses of body weight, plasma and urinary electrolytes, osmolality, and glucose are shown in Table 2. All changes were negatively associated with the respective baseline values, irrespective of the trial arm. Patients allocated to empagliflozin showed a larger increase in urine osmolality compared with the placebo group (estimate, 164; 95% CI, 88 to 239; P<0.001), with a corresponding markedly increased AUC for urinary glucose (median empagliflozin, 250 [IQR, 157–458] versus placebo, 0.45 [IQR, −60.0–1.7]; P<0.001). Furthermore, slightly lower increases of plasma uric acid and

Table 2. Study measures

	Empagliflozin		Placebo	
	Day 0	Day 4	Day 0	Day 4
Weight, kg	68.7 (56.2–76.9)	65.5 (53.3–75.6)	59.0 (50.2–70.4)	60.1 (49.2–67.4)
P-sodium, mmol/L	125.5 (122–127)	134 (132–136)	126 (123–127)	133 (129–136)
Absolut change p-sodium levels, mmol/L		10 (5–14)		7 (3–13)
Patients achieving normonatremia, *n* (%)		18 (42)		13 (30)
P-potassium, mmol/L	4.0 (3.7–4.3)	4.2 (4.0–4.4)	4.0 (3.6–4.2)	4.2 (4.0–4.5)
P-glucose, mmol/L	6.3 (5.3–6.9)	5.2 (4.8–5.7)	6.2 (5.3–7.5)	5.2 (4.8–6.2)
P-urea, mmol/L	4.4 (2.9–5.5)	4.9 (3.8–6.8)	3.7 (3.1–5.2)	4.2 (3.6–5.1)
P-uric acid, mmol/L	214 (139–287)	185 (134–241)	181 (131–252)	207 (154–259)
P-osmolality, mosm/kg	260 (253–268)	281 (273–285)	259 (254–268)	274 (268–281)
U-sodium, mmol/L	68 (54–99)	81 (57–125)	71 (62–100)	81 (52–129)
U-glucose, mmol/L	0.0 (0–0)	111.2 (56–162)	0.0 (0–0)	0.3 (0.2–0.5)
U-urea, mmol/L	127 (81–169)	180 (121–247)	125 (84–171)	159 (100–216)
U-uric acid, μmol/L	1131 (608–2350)	2126 (1501–2922)	1277 (637–1932)	1623 (1158–2719)
U-osmolality, mosm/kg	419 (297–488)	634 (490–759)	418 (291–514)	448 (357–545)
FE sodium	0.97 (0.5–1.51)	0.64 (0.43–1.34)	0.79 (0.45–1.26)	0.67 (0.40–1.19)
FE urea	46.5 (35.4–55.8)	39.6 (32.7–46.7)	42.0 (35.9–54.0)	41.8 (30.6–50.0)
FE uric acid	11.2 (8.8–14.8)	12.9 (9.2–18.2)	10.9 (5.9–13.9)	9.7 (8.0–12.6)

Summary statistics of study measures according to the full analysis set. Categorical variables are shown as frequencies (percentage), and numerical variables are shown as median (IQR). P, plasma; U, urinary; FE, fractional excretion.

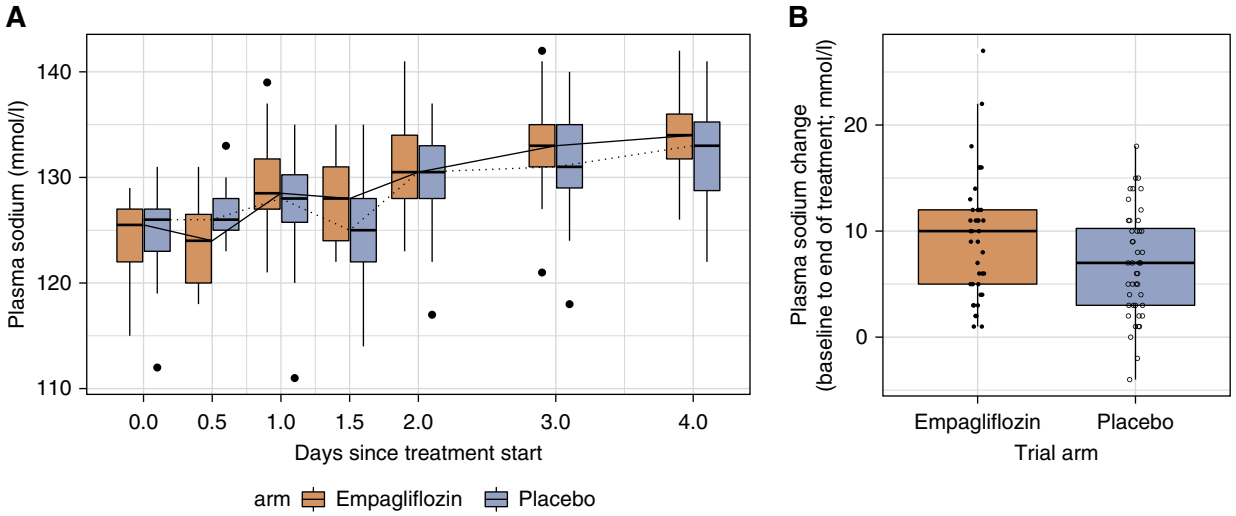

Figure 2. Course of plasma sodium concentration from baseline to end of treatment. (A) Course of plasma sodium from baseline to end of treatment according to trial arm. (B) Absolute change in plasma sodium from baseline to end of treatment according to trial arm. Boxes contain the 25% through 75% quantiles (spanning the IQR), and the thick horizontal line is the median. Whiskers indicate the most extreme values lying within the box edge and 1.5 times the IQR. All eventual further values are plotted as individual points (outliers).

plasma urea levels (estimate, 29; 95% CI, 0.9 to 57; $P=0.05$ and −0.9; 95% CI, −1.7 to 0.01; $P=0.06$, respectively) as well as a lower AUC for plasma glucose from baseline to the end of treatment (estimate, 1.9; 95% CI, 0.4 to 3.3; $P=0.01$) were observed in the empagliflozin treatment arm. Median plasma osmolality levels increased to 281 mosm/kg (IQR, 273–286) in the empagliflozin group and 274 mosm/kg (IQR, 268–281) in the placebo group (estimate, −3.5; 95% CI, −8.8 to 1.7; $P=0.19$). No between-group differences were found for urinary sodium levels and body weight (Supplemental Figure 2) during the treatment period. Fractional excretions of sodium and urea decreased under treatment irrespectively of the treatment arm (Table 2).

Tolerability and Safety

General wellbeing and symptoms improved over the treatment period, but no difference was seen between the two groups (Table 3). Data for the three patients who discontinued the study are missing; however, no adverse event or specific reasons for discontinuing were recorded for those participants.

No events of hypoglycemia (Figure 3D) or hypotension occurred during the observation period under empagliflozin. Six adverse events were potentially study related in the empagliflozin treatment arm. Four patients showed a decrease in their renal function (maximal plasma creatinine level 2.5-fold upper limit), which required loosening of the fluid restriction. In two patients, study medication was stopped early; one patient was unblinded and therefore, reported as a serious adverse event. Renal impairment was transient in all patients. In two patients, plasma sodium overcorrection (15 and 17 mmol/L within 24 hours) occurred, leading to lowering of the concomitant fluid restriction. Neither of the events resulted in neurologic complications as assessed clinically.

In the placebo treatment arm, three potentially study-related (fluid restriction) events were reported. Two patients had an orthostatic collapse, and one patient required additional hydration due to plasma sodium overcorrection of 14 mmol/L within 12 hours. Follow-up of this patient also showed no adverse effect of the overcorrection.

All other adverse and serious adverse events were associated with the corresponding comorbidities, including one death during the follow-up period that was due to progressive malignant disease.

DISCUSSION

We here show for the first time that short-term treatment with the SGLT2 inhibitor empagliflozin in addition to standard fluid restriction leads to a stronger increase in plasma sodium concentration compared with placebo in hospitalized patients with SIAD. This treatment effect was more pronounced in patients with lower baseline plasma sodium and osmolality levels. A similar association between plasma sodium levels and treatment response has previously been noted in the hyponatremia registry outcome study.[6]

A new treatment option for SIAD—the prevalent cause of hyponatremia—is of great importance because current options are limited, and the existing ones have limitations.[7–9] In contrast to other reports,[13] fluid restriction *per se* was quite effective as a therapeutic measure in our study. This may be partly explained by the often observed better patient compliance in study settings.[22] Furthermore, the majority of patients

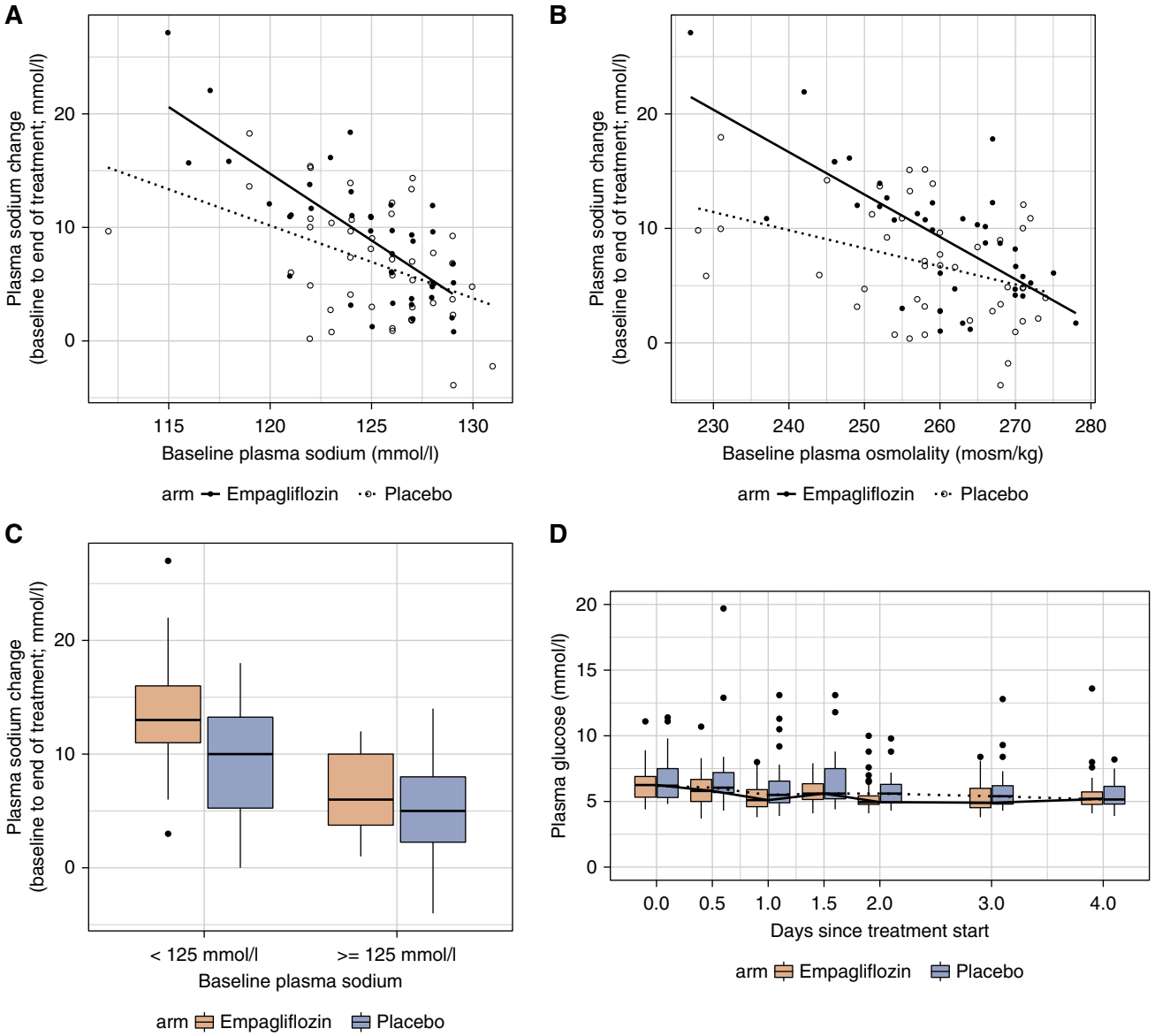

Figure 3. Association of the primary end point (absolute change in plasma sodium concentration) with covariates. (A) baseline plasma sodium concentration, (B) baseline plasma osmolality concentration, (C) severity of hyponatremia. (D) Shows course of plasma glucose levels during intervention. (A and B) Indicated lines are the respective linear regression lines. (C and D) Boxes contain the 25% through 75% quantiles (spanning the IQR), and the thick horizontal line is the median. Whiskers indicate the most extreme values lying within the box edge and 1.5 times the IQR. All eventual further values are plotted as individual points (outliers).

responding well to fluid restriction had a urinary osmolality <500 mosm/kg and urinary sodium <130 mmol/L, which have been previously defined as predictors of treatment response.[9] The fact that treatment with empagliflozin was superior despite successful standard treatment further underlines its efficacy. Also, because long-term compliance to fluid restriction is often limited, empagliflozin may provide here an attractive treatment alternative in the future.

The induction of osmotic diuresis as an effective therapeutic option for SIAD has been shown in several studies evaluating the effect of treatment with urea.[12,23,24] Consequently, the observed treatment effect in our study was similar or slightly higher than that reported in two retrospective analyses in a similar inpatient setting, where treatment with urea led to a plasma sodium increase of 7 mmol/L within 4.5[24] and 3 days,[12] respectively. However, despite the proven efficacy of urea, there is no long-term data evaluating its safety, and adverse effects due to its increase in plasma urea levels might occur.[25] In addition, availability and health coverage are a problem as well as patient compliance with long-term treatment due to its peculiar taste. The other available potent treatment option is vaptans, but controversy remains about their

Table 3. Symptoms and adverse events

	Empagliflozin			Placebo		
	Baseline	Day 4	Day 30	Baseline	Day 4	Day 30
Symptoms						
General wellbeing, VAS	5 (3–7)	6 (5–8)	7 (6–8)	5 (5–6)	7 (5–8)	6 (5–8)
Thirst, *n* (%)	20 (47)	18 (42)	10 (23)	18 (41)	17 (39)	9 (21)
Vertigo, *n* (%)	11 (26)	7 (16)	8 (19)	16 (36)	10 (23)	19 (43)
Headache, *n* (%)	14 (33)	9 (21)	9 (21)	11 (25)	9 (21)	8 (18)
Nausea, *n* (%)	9 (21)	4 (9)	2 (5)	12 (27)	5 (11)	7 (16)
AEs						
All causes		14			10	
Serious AEs		5			5	
Withdrawal because of AE		0			0	
Potentially study related		6			3	
Serious AEs		1			0	
Withdrawal because of AE		0			0	
Specific AEs						
Plasma-sodium overcorrection		2			1	
Potentially study related		2			1	
Neurologic complications		0			0	
Decreased renal function		3			0	
Potentially study related		3				
Persistent impairment		0				
Increased hepatic parameters		0			1	
Potentially study related					0	
Urinary tract infection		3			1	
Potentially study related		0			0	
Gastrointestinal disorders		1			0	
Potentially study related		0				
Orthostatic collapse		0			2	
Potentially study related					2	
Specific severe AEs						
Decreased renal function leading to unblinding		1			0	
Potentially study related		1				
Persistent impairment		0				
Prolongation hospitalization		1			4	
Potentially study related		0			0	
Rehospitalization		2			1	
Potentially study related		0			0	
Death		1			0	
Potentially study related		0				

Course of symptoms and adverse events (AEs) occurring during observation phase. VAS, visual analog scale; *n*, number of patients.

use because several publications voiced concerns regarding their costs and risk of plasma sodium overcorrection.[10,11,26] Furthermore, long-term safety data as well as prospective studies showing their effect on hyponatremia-associated complications are missing.[21,26] Although treatment with SGLT2 inhibitors also comes with a price, the advantage of empagliflozin over urea and vaptans is its established safety profile with reported long-term cardiovascular and nephroprotective effects,[18,19] its broad availability, and good tolerability. This seems to be particularly important because patients with SIAD are—as also documented in our study—generally older with multiple comorbidities and medications.[20,27,28] Even though plasma sodium overcorrection also occurred in two patients with empagliflozin, this rate is well below the 25% reported by Morris *et al.*[10] for tolvaptan. Another factor to bear in mind is the danger of hyponatremia exacerbation due to nonresponsiveness to vaptan treatment.[26] Empagliflozin in addition to fluid restriction could play an important role here because patients with severe hyponatremia had a better treatment response without experiencing hyponatremia exacerbation.

Although treatment with empagliflozin was generally well tolerated, one safety concern involves the four patients with transient decrease in renal function in the empagliflozin group. Transient decreases in renal function are common according to the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) studies,[19] but in the long-term treatment, empagliflozin ultimately resulted in a nephroprotective effect. However, it cannot be ruled out that the

combination of fluid restriction and increased excretion of free water leads to prerenal stress. In elderly patients treated with empagliflozin, it may, therefore, be necessary to loosen concomitant fluid restriction to avoid this possible renal adverse effect.

It is also noteworthy that three patients in the empagliflozin treatment arm withdrew their consent form. Although no causative adverse event had been identified and no reason was given, treatment with empagliflozin may have reduced their wellbeing.

The strength of our study lies in its prospective, double-blind, randomized design and the novelty of its treatment approach. In evaluating all hyponatremic inpatients, our study cohort represents the typical patients with SIAD. The percentage of patients with SIAD in our study was lower than the previously reported rates of up to 50%.[13,29] However, as shown in the hyponatremia registry study[13] only 21% of patients with SIAD receive all necessary diagnostic measures, pointing to a possible overdiagnosis of SIAD due to inadequate diagnostic workup. Limitations to our study are the unevenly distributed etiologies of SIAD between the two treatment arms. Although our analysis showed no association between treatment response and etiology of SIAD, it is possible that certain diagnoses respond better to the intervention than others. Additionally, with the available urinary measures, we were not able to calculate the electrolyte free water excretion, which would have further strengthened our findings. However, an estimation on the basis of the course of the different fractional excretions (sodium, urea, and uric acid) suggests an increased free water excretion in the empagliflozin arm. This is also in line with our previous findings in healthy volunteers.[17] This proof of principle study aimed at evaluating the efficacy of empagliflozin in addition to the standard treatment fluid restriction in an acute setting. Therefore, the efficacy of empagliflozin without fluid restriction and its use and safety as a long-term treatment in the outpatient setting remain to be investigated in future studies.

In conclusion, empagliflozin in addition to fluid restriction is a promising new treatment option for hospitalized patients with SIAD.

ACKNOWLEDGMENTS

We thank all patients for their participation in our study. In addition, we thank the medical staff and laboratory personnel at the University Hospital Basel for their contribution to the study. A special thanks goes to our study nurses Cemile Bathelt, Nina Hutter, and Joyce Santos de Jesus for their invaluable support.

DISCLOSURES

Prof. Christ-Crain has a patent for sodium glucose cotransporter 2 inhibitors for treatment of syndrome of inappropriate antidiuresis hormone pending. All remaining authors have nothing to disclose.

FUNDING

This study was supported by Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung grant SNF-162608 (to Prof. Christ-Crain) and the University Hospital Basel.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019090944/-/DCSupplemental.

Supplemental Figure 1. Course of plasma sodium levels.

Supplemental Figure 2. Course of urinary sodium levels and body weight.

Supplemental Material. Additional statistical information and supplemental material.

Supplemental Table 1. Changes of plasma sodium levels.

Supplemental Table 2. Effects of covariates on main effect.

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