

Impact of Dapagliflozin Treatment on Serum Sodium Concentrations in Acute Heart Failure

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Keywords

Acute heart failure · Dapagliflozin · Hyponatremia

Abstract

Introduction: The dynamics of serum sodium are important in acute heart failure (AHF), and hyponatremia is associated with a poor prognosis. The effect of sodium-glucose cotransporter type 2 inhibitors (SGLT2i) on serum sodium concentrations in AHF is unknown. **Methods:** In a single-centre, controlled, randomized study, patients were prescribed dapagliflozin in addition to standard treatment during the first 24 h of hospitalization versus standard treatments. The pre-specified outcome was an absolute change in plasma sodium concentrations between randomization (first 24 h after admission) and discharge. The secondary outcomes were an absolute change in serum sodium concentrations within 48 h of randomization and the persistence of hyponatremia. **Results:** The sample comprised 285 patients (53% males; average age 73.26 ± 13 years); 140 of these were randomized to the dapagliflozin group. The average ejection fraction was $46 \pm 14\%$; 155 patients (54%) had ischaemic heart failure; and 35% had diabetes mellitus. Median N-terminal pro b-type natriuretic peptide was $4,225 [2,120; 9,105]$ pg/mL. The average estimated glomerular filtration rate was 53.9 ± 17.2 mL/min. Hospital mortality was

6.7%. At randomization, serum sodium concentrations were 139.8 ± 4.32 mmol/L in the dapagliflozin group versus 140.85 ± 4.04 mmol/L in the control group; $p = 0.048$. 48 h later, there was an increase in serum sodium in the dapagliflozin group ($2 [-2; 4]$ mmol/L), as compared to the control group ($-1 [-3.75; 2]$); $p < 0.001$. This was accompanied by equilibration of the sodium levels between the groups (141.08 ± 4.08 mmol/L in the dapagliflozin group vs. 140.05 ± 4.82 mmol/L in the control group; $p = 0.096$). At the time of discharge, there was no difference in serum sodium concentrations (140.98 ± 4.77 mmol/L vs. 139.86 ± 4.45 mmol/L; $p = 0.082$). The increase in serum sodium concentrations during the period of observation [randomization; discharge] was small but statistically significant in the dapagliflozin group ($1 [-3; 3.75]$ mmol/L vs. $-2 [-4.5; 2]$ mmol/L; $p = 0.015$). Of 36 patients (21 in the dapagliflozin group and 15 in the control group) with baseline hyponatraemia, this persisted in 6 (16.6%) in the dapagliflozin group and in 11 (73.3%) in the control group ($p = 0.008$). **Conclusion:** The use of dapagliflozin in AHF is associated with a tendency to the increase in serum sodium concentrations and lesser persistence of hyponatremia. This effect occurred within the first 48 h and persisted until discharge. The impact of dapagliflozin on serum sodium was more pronounced in patients with hyponatremia at randomization.

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Published by S. Karger AG, Basel

Introduction

Hyponatremia (defined as a serum sodium concentration of less than 135 mmol/L) is the most common electrolyte disorder in patients with acute heart failure (AHF), and it is associated with a poor prognosis [1]. Hyponatremia in AHF tends to be hypervolemic and dilutional in its nature [2].

Glucosuric agents (inhibitors of the sodium-dependent glucose type 2 cotransporter) (SGLT2i) improve cardiovascular outcomes in patients with chronic heart failure (HF) who have any left ventricular ejection fraction (LVEF), regardless of their diabetes status [3]. The efficacy and safety of SGLT2i have also been demonstrated in several studies with AHF [4]. The potential impact of SGLT2i on sodium homeostasis is worth studying [5], so the aim of this research was to clarify the effect of SGLT2i on serum sodium concentrations in AHF patients.

Methods

The present study is part of an ongoing trial, whose design and inclusion criteria have been published recently [4]. In short, this is a randomized, open-label, parallel-group, controlled, single-centre trial. The ClinicalTrials.gov number is NCT04778787. The protocol was approved by the Local Ethics Committee. Participants gave informed consent to participate in the study before taking part.

Study Design and Participants

The study involved patients over 18 years of age, admitted to hospital with AHF, whose planned treatment was intravenous administration of loop diuretics. Diagnosis was based on the European Society of Cardiology (ESC) HF guidelines [6], and the patients presented with dyspnoea upon minimal exertion and signs of congestion (rales on chest auscultation, peripheral oedema, swelling of the cervical veins, hepatomegaly, ascites, and hepatojugular reflux). Patients were included after signing an informed consent form.

The exclusion criteria were as follows: (1) cardiogenic shock (systolic blood pressure <90 mm Hg; signs of hypoperfusion [altered mental status, cold skin, diuresis <30 mL/h, and blood lactate >2.0 mmol/L]); (2) patients requiring mechanical ventilation; (3) use of intravenous inotropes or vasopressors; (4) urinary tract infection; (5) type 1 diabetes mellitus and episodes of diabetic ketoacidosis or hypoglycemia; (6) use of drugs from the SGLT2i group in the previous 4 weeks; (7) estimated glomerular filtrate rate (eGFR) <30 mL/min/1.73 m² (Chronic Kidney Disease Epidemiology Collaboration); (8) individual SGLT2i intolerance; (9) Child-Pugh class C liver failure; (10) mental illness (inability to sign an informed consent form; lack of comprehension of the possible consequences); (11) patients already hospitalized for AHF triggered by an acute myocardial infarction or pulmonary

embolism; (12) pregnant or breastfeeding patients; and (13) refusal to sign an informed consent form.

Within 24 h of hospital admission, the patients were randomized 1:1, either to 10 mg daily of dapagliflozin in addition to standard therapy or to the control group (standard therapy for AHF). The treatment was carried out in accordance with current clinical recommendations [6]. The basis of therapy was use of loop diuretics. Laboratory data were obtained at the randomization, 48 h later and on discharge.

Serum sodium levels were corrected in cases of severe hyperglycemia using the following formula: [7]

$$\text{Corrected Na} = \text{Serum Na} + 1.6 \times \{[\text{Glucose} - 5.6] / 5.6\}$$

In the case of hypertriglyceridemia, sodium levels were corrected using the following formula: [8]

$$\begin{aligned} \text{Corrected Na} = & \text{Serum Na} \\ & + \{[0.21 \times \text{triglycerides (g/L)}] - 0.6\} \times (\text{NA}^+ / 100) \end{aligned}$$

Study Endpoints

The primary endpoint was an absolute change in plasma sodium concentrations between randomization (first 24 h after admission) and discharge.

Secondary endpoints included the following.

- 1 An absolute change in serum sodium concentrations within 48 h of randomization;
- 2 Persistence of hyponatremia (defined as discharge serum sodium levels <135 mmol/L in patients with hyponatremia at the randomization [1]).

Statistical Analysis

The Student's *t* test (in a normal distribution) or the Mann-Whitney test (abnormal distribution) was used. Categorical variables were presented in the form of absolute and relative values, and the χ^2 criterion or the exact Fisher criterion was used. Normally distributed continuous variables were presented as mean \pm standard deviation and non-normally distributed variables as median and 25th–75th percentile. For statistical analysis, we used SPSS 22.0 for Windows (SPSS Inc., Chicago, USA). The differences were considered significant at $p < 0.05$.

Results

Trial Population

Between December 2020 and April 2022, 430 patients with a clinical diagnosis of AHF were screened; 145 of these were excluded because they did not meet the inclusion criteria or refused to sign an informed consent form; 285 patients were randomized, of whom 140 were assigned to receive dapagliflozin in addition to standard therapy; 145 were assigned to standard therapy.

The median enrolment point for the trial was 11 h [9, 10] after admission. Dapagliflozin was started 11.5 h [9, 11] after admission.

Table 1. Baseline characteristics

Variable	Dapagliflozin group (n = 140)	Control group (n = 145)	p value
Age, years	72±12	75±13	0.1
Male	78 (56)	73 (50)	0.36
De novo acute HF	47 (34)	50 (34.5)	0.87
Myocardial infarction	73 (52)	67 (46)	0.51
PCI	41	35	0.33
CABG	8 (5.7)	7 (4.8)	0.76
TD2M	44 (31)	56 (38)	0.2
Arterial hypertension	120 (86)	126 (87)	0.77
Atrial fibrillation	92 (66)	96 (66)	0.93
NYHA class IV	39 (28)	44 (30)	0.64
Average eGFR, mL/min	55.6±20	52±19	0.25
CKD ^a	49 (35)	52 (36)	0.88
NT-proBNP at randomization, pg/mL	5,100 [2,120; 9,107]	4,191 [2,117; 9,154]	0.67
Pretreatment time, hours	11 [8.5; 17]	10 [7.25; 17]	0.32
Blood glucose, mmol/L	6.7 [5.4; 7.9]	6.6 [5.6; 8.2]	0.94
Troponin, ng/mL	0.04 [0.02; 0.17]	0.04 [0.02; 0.16]	0.23
Haemoglobin, g/L	127±21	122±25	0.15
Pleural effusion	95 (68)	97 (67)	0.86
Edema	133 (95)	138 (95)	0.95
Ascites	27 (19)	28 (19)	0.95
SBP, mm Hg	130±16	128±17	0.36
DBP, mm Hg	78.5±8	78.9±9	0.73
HR, bpm	94.2±20	96±21	0.4
Average LVEF	44±14	47±13	0.064
LVEF <45%	74 (53)	60 (41)	0.052

Values are mean ± SD, n (%) or median (25th, 75th interquartile range). bpm, beats per minute; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DBP, diastolic blood pressure; ECHO, echocardiography; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; mg, milligrams; mL/min, milliliters per minute; mm Hg, millimeters of mercury; mmol/L, millimol per liter; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; pg/mL, picograms per milliliter; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TD2M, type 2 diabetes mellitus. ^aeGFR less than 60 mL/min.

The average age was 73 ± 12 years; 53% of the participants were men; 204 (71%) were New York Heart Association (NYHA) class III, and 81 (29%) were NYHA class IV. The mean LVEF was 46 ± 14%; 55% of the patients had LVEF <45%; 155 (54%) of the patients had ischaemic HF; 100 (35%) of the patients had TD2M. Data on N-terminal prohormone of brain natriuretic peptide (NT-proBNP) were available for 51% of the patients; the median NT-proBNP was 4,225 [2,120; 9,105] pg/mL; 76% of the patients had atrial fibrillation. The mean eGFR at randomization was 53.9 ± 17.2 mL/min; 34% had de novo HF. The clinical and functional characteristics of patients at randomization are presented in Table 1.

Outcomes of Hospitalization

The median duration of hospitalization was 5 days [4, 6]. Hospital mortality was 6.7%.

At randomization, serum sodium concentrations in the dapagliflozin group and in the control group were 139.8 ± 4.32 mmol/L and 140.85 ± 4.04 mmol/L, respectively ($p = 0.048$). Forty-eight hours after randomization, there was an increase in serum sodium in the dapagliflozin group (2 [−2; 4] mmol/L), as compared to the control group (−1 [−3.75; 2]; $p < 0.001$), which was accompanied by equilibration of the sodium levels (141.08 ± 4.08 mmol/L in the dapagliflozin group vs. 140.05 ± 4.82 mmol/L in the control group; $p = 0.096$).

At the time of discharge, serum sodium concentrations also did not differ significantly (140.98 ± 4.77 mmol/L vs. 139.86 ± 4.45 mmol/L; $p = 0.082$) (shown in Fig. 1). The increase in serum sodium concentrations during the period of observation [randomization; discharge] was small but statistically significant in the dapagliflozin group (1 [−3; 3.75] mmol/L vs. −2 [−4.5; 2] mmol/L; $p = 0.015$) (Table 2).

Fig. 1. Change in serum sodium levels between randomization and discharge.

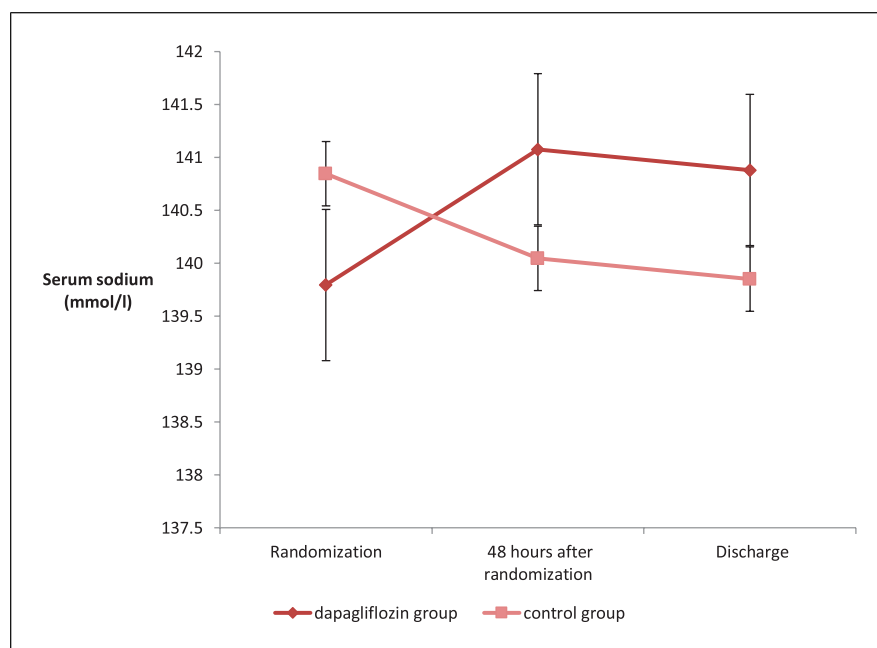


Table 2. Serum sodium dynamics

	Dapagliflozin group (n = 140)	Control group (n = 145)	p value
Serum sodium concentration, mmol/L			
On randomization	139.8±4.32	140.85±4.04	0.048
48 h after randomization	141.08±4.08	140.05±4.82	0.096
On discharge	140.98±4.77	139.86±4.45	0.082
Change in serum sodium concentration, mmol/L			
48 h after randomization; randomization	2 [−2; 4]	−1 [−3.75; 2]	0.000154
Day of discharge; 48 h after randomization	0.5 [−2; 2]	0.5 [−4; 2]	0.31
Day of discharge; randomization	1 [−3; 3.75]	−2 [−4.5; 2]	p = 0.01468

Values are mean ± SD, n (%) or median (25th, 75th interquartile range). mmol/L, millimol per litre.

In the dapagliflozin group, hyponatremia presented in 22 patients (17%) at randomization and in 12 patients (11.8%) upon discharge ($p = 0.27$). In the control group, hyponatremia presented in 14 patients (11.4%) at randomization and in 18 patients (17.1%) upon discharge ($p = 0.22$). Of 36 patients with baseline hyponatremia, this persisted in 6 (17%) in the dapagliflozin group and in 11 (73.3%) in the control group ($p = 0.008$). The amount of de novo hyponatremia (defined as hyponatremia developed during hospitalization and absent on randomization) did not differ (7 [5%] in the dapagliflozin group vs. 14 [9.7%] in the control group; $p = 0.13$).

We also analysed the dynamics of sodium in a subgroup of patients with hyponatremia at randomization ($n = 36$). In the dapagliflozin group, as compared to the

control group, the increase in serum sodium between randomization and discharge was significantly greater (5.5 [2; 11.5] vs. 2 [0; 2.75]; $p = 0.03$). In the subgroup with normonatremia at randomization ($n = 249$), the dynamics of sodium in the dapagliflozin group and the control group also differed (0.5 [−3; 2] vs. −2 [−4; 1]; $p = 0.038$).

In the dapagliflozin group, the increase in sodium concentrations between randomization and discharge was more pronounced in the subgroup with initial hyponatremia than in the subgroup with normonatremia at randomization (5.5 [2; 11.5] vs. 0 [−3; 2]; $p = 0.001$). In the control group, the increase in sodium concentrations between randomization and discharge did not differ between the subgroups of initial hyponatremia

Table 3. Change on serum sodium concentration depending on the presence of hyponatremia

Change in serum sodium concentration in patients with hyponatremia on randomization [day of discharge; randomization], mmol/L		
Dapagliflozin group (n = 22)	Control group (n = 14)	p value
5.5 [2; 11.5]	2 [0; 2.75]	0.03
Change in serum sodium concentration in patients with normonatremia on randomization [day of discharge; randomization], mmol/L		
Dapagliflozin group (n = 118)	Control group (n = 131)	p value
0 [−3; 2]	−2 [−4; 1]	0.038
Change in serum sodium concentration in dapagliflozin group (n = 140) [day of discharge; randomization], mmol/L		
Patients with hyponatremia (n = 22)	Patients with normonatremia (n = 118)	p value
5.5 [2; 11.5]	0 [−3; 2]	0.001
Change in serum sodium concentration in control group (n = 145) [day of discharge; randomization], mmol/L		
Patients with hyponatremia (n = 14)	Patients with normonatremia (n = 131)	p value
2 [0; 2.75]	−2 [−4; 1]	0.15
Values are median (25th, 75th interquartile range). mmol/L, millimol per litre.		

and normonatremia (2 [0; 2.75] vs. −2 [−4; 1]; $p = 0.15$) (Table 3).

The weight loss during hospitalization was more pronounced in the dapagliflozin group (4,450 [3,000; 4,000] g vs. 3,000 [1,500; 4,700] g; $p = 0.001$). Groups of drugs and mean doses of loop diuretics used during hospitalization are summarized in Table 4.

Discussion

In this randomized, open-label, single-centre trial, we found that the use of dapagliflozin in patients with AHF is associated with an increase in serum sodium concentrations, especially in patients with hyponatremia. Hyponatremia in AHF is a multifactorial condition, the pathogenesis of which involves neurohumoral activation and concomitant medication use. The ESC recommends distinguishing between dilutional and depletion hyponatremia in AHF [9]. Dilutional hyponatremia caused by volume overload is the most common type of hyponatremia in AHF [2]. As a strategy for treatment of dilution hyponatremia in AHF, the ESC suggests temporary

cessation of distal diuretics, water intake restriction, promotion of distal nephron flow, use of vaptans, and correction of concomitant imbalances of serum potassium and magnesium [9]. SGLT2i could be a potential treatment option for hyponatremia in AHF for several reasons.

In AHF, water absorption is associated with an increase in medullary tonicity, which is related to a decrease in flow through the distal parts of the nephron [2]. The mechanism of action of SGLT2i in the kidneys is to block reabsorption of sodium and glucose in the proximal convoluted tubule, and the initial glucosuria is associated with osmotic diuresis and natriuresis [12], increasing flow through distal parts of the nephron [13]. In cases of AHF where combination therapy is an option to promote fluid excretion, this is a reasonable addition to loop diuretics [4]. A specific property of SGLT2i is sodium and fluid mobilization from the interstitium into the vascular space [4]. It is assumed that mobilization of fluid into the vascular space contributes to replenishment of effective intravascular volume and thereby improves renal blood flow [14]. Due to improved renal perfusion, renin secretion may decrease [15].

Table 4. Groups of drugs and mean doses of loop diuretics used during hospitalization

Drugs	Dapagliflozin group (n = 140)	Control group (n = 145)	p value
Mean doses of loop diuretics during hospitalization (in furosemide equivalents), mg	95±35	104±32	0.047
ACE-I/ARBs	115 (82)	120 (83)	0.89
MRAs	73 (52)	78 (54)	0.78
Beta-blockers	84 (60)	84 (58)	0.72
Thiazide diuretics	15 (11)	19 (13)	0.53
Carbonic anhydrase inhibitors	18 (13)	17 (12)	0.77

Values are mean ± SD or n (%). ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor II type 1 receptor blockers; MRAs, mineralocorticoid receptor antagonists.

As a result of a decrease in the effective circulatory volume, activation of baroreceptors and neurohumoral activation (in the sympathetic nervous system and renin-angiotensin-aldosterone system) occurs, the result of which is non-osmotic AVP secretion. It is known that the leading component in the pathogenesis of dilutional hyponatremia in AHF is non-osmotic AVP secretion [2]. Thus, the action of SGLT2i in the interstitium and replenishment of the intravascular volume [4] may also contribute to correction of hyponatraemia. A decrease in renin under the action of SGLT2i also occurs due to an increase in sodium delivery to the macula densa [16]. An increase in chloride delivery to the macula densa lowers the set point for plasma volume [17], thereby affecting volume homeostasis, which may also affect the pathogenesis of hyponatremia in AHF.

In the treatment of hyponatremia, correction of an imbalance of magnesium and potassium is important [2, 9]. The use of SGLT2i has been associated with improvements in hypomagnesemia in patients with diabetes mellitus [18]. It has been shown that use of empagliflozin in AHF does not affect serum potassium concentrations [10].

Although water restriction is one of the options for treatment of hyponatremia [9], it has proven to be ineffective and poorly tolerated [19]. In our study, water intake was not controlled. Stopping distal diuretics is one of the steps in overcoming hyponatremia in AHF [9]. Distally acting diuretics (thiazide or thiazide-like) are often used in combination with loop diuretics in order to overcome resistance to treatment [11]. We have previously shown that use of dapagliflozin in AHF is associated with a lesser need for other classes of diuretics [4]. In this sub-analysis, we did not take into account the need for addition of thiazides, but the previously obtained data [4] support the rationality of using SGLT2i in hyponatremia in AHF.

At one point, vaptans seemed to be a useful group of drugs, but it has been found that they do not improve the prognosis in the case of AHF [20]. In addition, the use of vaptans is associated with overcorrection of sodium levels and liver toxicity [21]. It has been suggested that vaptans cause free water excretion independently of extracellular fluid overload. Thus, extracellular and intracellular fluid volume decreases, leading to dehydration rather than decongestion [20].

Acetazolamide, a proximal working diuretic, is also recommended by the ESC for hyponatremia in AHF [9]. The effect of oral acetazolamide on serum sodium concentrations and resistance to diuretics is intriguing. The results of the Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) study may shed light on these issues [22].

In our study, the dynamics of sodium during hospitalization were more significant in the dapagliflozin group. However, this effect was mainly realized due to an increase in concentrations during the first 48 h. The dynamics of sodium over this period [day of discharge; 48 h after randomization] did not differ between the groups. Interestingly, in a study involving tolvaptan (an AVP antagonist that increases serum sodium due to excretion of free water by the kidneys), sodium levels were significantly higher in the tolvaptan group at 6 and 12 h from baseline, and this difference was lost at 48 h from baseline. It was suggested that when assessing the dynamics of sodium only at baseline and 48 h, important differences in the trajectory could have been missed [23]. Since the protocol of our study did not include control of laboratory parameters at time points earlier than 48 h, we have no data on the dynamics of sodium in the earlier period.

We also found that use of dapagliflozin is associated with a decrease in persistence (defined as discharge

serum sodium levels <135 mmol/L in patients with hyponatremia at randomization [1]). It has been shown that the persistence of hyponatremia is associated with an unfavourable prognosis in AHF [1], and recovery from hyponatremia may improve renal outcomes in AHF patients with type I cardiorenal syndrome [24].

In our study, sodium concentrations in the dapagliflozin group were lower than in the control group (139.8 ± 4.32 mmol/L vs. 140.85 ± 4.04 mmol/L, respectively) ($p = 0.048$) during randomization. Forty-eight hours after randomization, the sodium concentrations were equal and remained the same until discharge. The use of dapagliflozin was associated with small but statistically significant increase in sodium concentrations during the time periods studied [48 h after randomization; at randomization] [day of discharge; at randomization], which could improve the prognosis in AHF [23].

Limitations

Firstly, the study included a small number of patients in a single centre. Secondly, this was not a placebo-controlled trial, and the participants were not blinded. The decision with regard to dosages and regimens for diuretic drugs was left to the attending physician. Since physicians were not blinded to the laboratory results, this might have led to bias. Hyponatremia was defined as dilutional based on the clinical picture (signs of volume overload), without confirmation by laboratory parameters (haematocrit, plasma and urine osmolality, urine sodium concentration). Despite the fact that the patients were randomized by the blind method, there was a small but statistically significant difference in serum sodium between the groups at baseline, before any intervention (139.8 vs. 140.85 , $p = 0.048$). However, the difference does not seem to be of clinical significance. We have no data on urine chemistries and urine output. The low prevalence of NT-proBNP levels (51%) makes it more difficult to compare this study to others. We were only able to recruit 36 patients with hyponatremia at randomization. The length of hospitalization was shortened due to the COVID-19 pandemic. Since we excluded patients with $\text{eGFR} < 30$ mL/min and those requiring mechanical ventilation, intravenous use of inotropic drugs and vasodilators, the results cannot be applied to the general AHF population. We did not control water and fluid intake. The present study is a sub-analysis of data collected from a study primarily investigating the effect of dapagliflozin on renal function in AHF. Thus, the results should be

considered as hypothesis-generating until confirmed in larger studies.

Conclusion

The addition of dapagliflozin to the standard treatment of AHF is associated with a tendency to the increase in serum sodium concentrations and lesser persistence of hyponatremia. Its effect of enhancing serum sodium concentrations occurred within 48 h and persisted until discharge. The impact of dapagliflozin was more pronounced in patients with hyponatremia at randomization. Addition of dapagliflozin could be a potentially new therapeutic strategy in AHF.

Acknowledgments

The authors would like to thank the members of the heart team at the participating centre and the study coordinators for their efforts in ensuring the accuracy and completeness of the data.

Statement of Ethics

The protocol was approved by the Local Ethics Committee of the Sechenov First Moscow State Medical University of the Ministry of Health of Russia (Sechenov University), extract from Protocol No. 33–20. Participants gave informed consent to participate in the study before taking part.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

Funding Sources

The authors declare the absence of grants, contracts, foundations, funds, and other forms of financial support.

Author Contributions

Charaya K. and Shchekochikhin D.: wrote and revised manuscript; Agadzhanian A., Chashkina M., Kulikov V., Andreev D., and Vashkevich M.: revised manuscript.

Data Availability Statement

Data are available on request to the corresponding author.

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