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ORIGINAL ARTICLE

Randomized trial to assess worsening renal function by adding dapagliflozin for acute decompensated heart failure

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Abstract

Aims Dapagliflozin (DAPA), a sodium-glucose co-transporter 2 inhibitor, has been shown to reduce cardiovascular mortality among patients with chronic heart failure. We aimed to evaluate the impact on a worsening renal function (WRF) by adding DAPA as compared to standard decongestive therapy with loop diuretics alone.

Methods and results We enrolled 114 consecutive acute decompensated heart failure (ADHF) patients with a left ventricular ejection fraction (LVEF) of less than 50%. The patients were prospectively randomized to be assigned either to DAPA group who received DAPA at a dose of 10 mg once daily within 24 h after admission or conventional therapy group (CON group) who received loop diuretics alone. All patients were adjusted by increasing or decreasing the loop diuretic by 10 mg to maintain a 1–2 mL/kg/h urine output. The primary endpoint was the incidence of WRF, which was defined as an increase in the serum creatinine of ≥0.3 mg/dL from baseline. The median age of the patients was 77 [interquartile range (IQR): 64, 85] years, 35% were female and the median LVEF was 33 [IQR: 28, 38] %. There was no significant difference in the incidence of WRF between the two groups (16.1%, *n* = 9 vs. 12.1%, *n* = 7, *P* value = 0.54). The total dose of loop diuretics through day 7 was lower in the DAPA group than CON group (184 ± 79.5 mg vs. 214 ± 66.5 mg, *P* value = 0.03).

Conclusions This randomized prospective trial revealed the addition of DAPA within 24 h after admission reduced the diuretic dose without WRF.

Keywords acute decompensated heart failure; dapagliflozin; diuretics; worsening renal function

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Introduction

Congestion is the major reason for hospitalizations in patients with acute decompensated heart failure (ADHF) and is an important target for therapy.[1] Furthermore, residual congestion is associated with a greater risk of death and heart failure readmission.[2] Therefore, diuretics are essential for fluid management in ADHF. However, diuretic use, especially loop diuretics, is a predictor of a worsening renal function (WRF), which is associated with a poor outcome.[3]

Dapagliflozin (DAPA), a sodium-glucose co-transporter 2 (SGLT2) inhibitor, has been shown to reduce readmissions for heart failure and cardiovascular mortality among patients with chronic heart failure (CHF) regardless of the left ventricular ejection fraction (LVEF).[4,5] In patients with CHF, the SGLT2 inhibitor causes a significant increase in the 24-h urine volume when used in combination with a loop diuretic.[6] On the other hand, SGLT2 inhibitors cause an initial decline in the estimated glomerular filtration rate (eGFR), which is called an initial dip.[7] A few reports on early initiation of SGLT2 inhibitors in ADHF have evaluated the diuretic efficiency or clinical benefit.[8,9] However, it has not been well investigated whether early administration of SGLT2 inhibitors for ADHF patients reduces WRF under a controlled diuretic strategy. Therefore, we aimed to evaluate the impact on the WRF by adding DAPA as compared to standard deconges-

tive therapy with loop diuretics alone. Furthermore, the SGLT2 inhibitors for CHF caused changes in biomarkers relating to iron metabolism consistent with an increase in iron mobilization and use in previous reports.[10] The impact of SGLT2 inhibitors on iron kinetics in ADHF is not well investigated. Therefore, the effect of DAPA on iron metabolism was observed in patients with ADHF in this study.

Methods

Study design

The ROAD-ADHF (Randomized trial to assess worsening renal function by adding dapagliflozin for acute decompensated heart failure) was a single-centre, prospective, randomized trial. This study protocol was approved by the Institutional Review Board and was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. Informed consent was signed by all study participants. This study was registered on the University Hospital Medical Information Network under the identifier (UMIN000044342).

Patient population

Eligible patients were males or females aged >18 years who were hospitalized for ADHF with an LVEF of less than 50%. The diagnosis of ADHF was defined using the Framingham criteria.[11] Exclusion criteria included recent treatment with SGLT2 inhibitors or unacceptable side effects associated with the SGLT2 inhibitors, recent diuretic medications other than loop diuretics such as thiazide diuretics or tolvaptan, type 1 diabetes mellitus, acute coronary syndrome, an eGFR below 20 mL per minute per 1.73 m^2 of body surface area, and cardiogenic shock requiring catecholamine or ventilatory management.

Trial procedure

All eligible patients were randomly assigned in a 1:1 fashion to the DAPA group which received DAPA at a dose of 10 mg once daily within 24 h after admission or the conventional therapy group (CON group) which received only loop diuretics, along with the initial therapy such as oxygen therapy including non-invasive positive pressure ventilation or medical therapy including nitroglycerin. DAPA was discontinued at the physician's discretion if there were adverse events.

Standard decongestive therapy

All patients were adjusted by increasing or decreasing the loop diuretic by 10 mg to maintain 1–2 mL/kg/h urine output every 12 h.[12,13] In addition, we did not use other diuretics such as acetazolamide, thiazide-like diuretics, tolvaptan and amiloride. Conditions for switching to an oral loop diuretic were (1) no need for oxygen and (2) no evidence of congestion on the chest X-ray. After determining the maintenance dose of the oral loop diuretics and confirming that the patient had not gained weight for more than 24 h, the patient could be discharged.

Data collection

The vital signs and body weight were measured over 7 days after randomization. In addition, blood samples including for the sodium, creatinine and plasma osmolality and urine samples such as for the spot urinary sodium, spot urinary glucose and urine osmolality were collected on day 1 (initiation of DAPA), day 2 (24 h after the initiation), day 3 (48 h after the initiation), day 5 (96 h after the initiation) and day 7 (144 h after the initiation). Moreover, the haemoglobin (Hb), haematocrit (Ht), serum iron, total iron binding capacity (TIBC), ferritin, N-terminal pro-brain natriuretic peptide (NT-pro BNP) and high-sensitive troponin I (hs-TnI) were measured upon admission and at discharge. An iron deficiency was defined as a ferritin level <100 ng/mL or a TSAT <20% and a ferritin level <300 ng/mL.[10] Transthoracic echocardiography (TTE) was performed at baseline and pre-discharge according to the standard techniques using a commercially available machine as previously reported.[14] Right heart catheterization (RHC) was performed using a 7Fr Swan-Ganz catheter (Edwards Lifesciences GmbH, Vienna, Austria) before discharge if consent was obtained. The mean pulmonary artery wedge pressure, systolic and diastolic pulmonary artery pressures, mean pulmonary artery pressure, right ventricular end-diastolic pressure and mean right arterial pressure were documented. The cardiac index was measured by thermodilution and Fick's method.

Study endpoints

The primary endpoint of this study was the incidence of WRF. WRF was defined as an increase in the serum creatinine of ≥0.3 mg/dL from baseline within 7 days from admission,[15] based on evidence that most WRF occurs within that period.[16] The secondary endpoints included the urine volume, total amount of loop diuretics through day 7, diuretic response through day 7, blood and urinary measurements including the plasma osmolality and urine osmolality, and pre-discharge TTE data and RHC data before discharge. The

diuretic response was defined as Δ weight kg/[(total intravenous dose)/40 mg] + [(total oral dose)/80 mg] furosemide or equivalent loop diuretic dose) through day 7.[17] The safety endpoints were as follows: (1) a blood glucose less than 70 mg/dL with or without symptoms, ketoacidosis, fractures, amputations or urinary tract infections and (2) adverse events that led to treatment discontinuation including hepatic injury (an elevation of aspartate aminotransferase or alanine aminotransferase ≥3 times the upper limit of normal), severe kidney injury (eGFR < 20 mL/min/1.73 m^2) and physician's decision.

Statistical analysis

Continuous variables with a normal distribution were presented as the mean standard deviation (SD) and were compared by a Student's *t*-test. Continuous data without a normal distribution were shown as the median (interquartile range [IQR]) and the difference between the two segments was calculated by the Wilcoxon rank sum test. Categorical variables are presented as the number and percentage. They were compared by either a chi-square test or Fisher's exact test as appropriate. A value of $P < 0.05$ was considered to be statistically significant. Statistical analyses were performed using JMP version 17.0.0 software (SAS Institute). In addition, a post-hoc subgroup analysis based on eGFR and diabetes was conducted to evaluate the consistency of the treatment effect. Furthermore, propensity score matching was applied to control for confounding factors such as systolic blood pressure at admission, renal function at admission, diabetes mellitus and medications other than dapagliflozin as much as possible.

The power calculation was based on the previous report, which showed that the incidence of WRF during 7 days was 57.7% for conventional treatment with furosemide.[15] There has been little data about the rate of WRF over 7 days with a DAPA additional therapy. Therefore, we assumed the incidence of WRF was 15% in the DAPA group and 40% in the CON group. A sample size of 114 patients was calculated to provide a power of 80% at a two-sided alpha level of 0.05.

Results

Patients

From May 2021 through May 2023, 117 patients were randomized (58 patients to the DAPA group and 59 to the CON group). *Figure 1* shows the flow chart of this study. In the DAPA group, one patient who withdrew informed consent and one who developed cardiogenic shock were excluded. In the CON group, one patient who had a myocardial infarction within 24 h of randomization was also excluded. Finally, we analysed a total of 114 patients (56 patients in the DAPA group and 58 in the CON group). *Table 1* shows the baseline characteristics of the two groups. The mean age of the patients was 73 years, 35% were female, 68% had de novo acute HF, and the mean LVEF was 32.5% and the median NT-pro BNP was 6902 pg/mL. The baseline characteristics between the two groups were well balanced; however, the LVEF was higher and Hb lower in the DAPA group than in the CON group. In addition, 45 patients were assigned to each group after propensity score matching with systolic blood pressure, creatinine, diabetes mellitus, renin-angiotensin system inhibitor, beta-blocker and mineralocorticoid receptor antagonist at admission. There were no significant differences in baseline characteristics including the LVEF and Hb.

Primary endpoint

Figure 2A shows the rate of WRF. There was no significant difference in the incidence of WRF between the two groups (16.1%, *n* = 9 vs. 12.1%, *n* = 7, *P* = 0.54). In addition, the incidence of WRF were similar between the two groups after

Figure 1 CONSORT diagram.

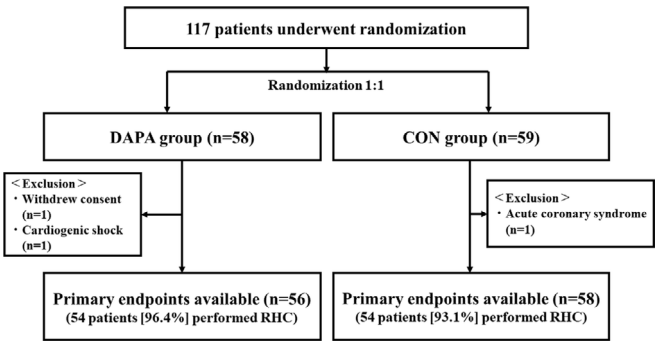


Table 1 Baseline characteristics.

Variable	Before matching			After matching		
	DAPA group (n = 56)	CON group (n = 58)	P value	DAPA group (n = 45)	CON group (n = 45)	P value
Age, years	74 [63, 85]	78 [70, 85]	0.44	74 [62, 83]	78 [72, 85]	0.12
Female sex, n (%)	21 (37.5)	19 (32.8)	0.60	19 (42.2)	15 (33.3)	0.38
Body weight, kg	60 [48, 71]	63 [54, 67]	0.50	62 [48, 76]	59 [51, 67]	0.70
BMI, kg/m^2	24.0 [19.9, 27.5]	23.6 [21.7, 26.1]	0.72	24.2 [20.0, 29.1]	22.7 [21.6, 25.7]	0.34
HR, bpm	104 [90, 122]	113 [92, 135]	0.10	105 [90, 127]	112 [88, 126]	0.52
SBP, mmHg	140 [123, 168]	137 [124, 165]	0.80	142 [124, 168]	141 [127, 166]	0.95
DBP, mmHg	100 [85, 116]	98 [77, 111]	0.37	104 [91, 118]	98 [77, 109]	0.16
NYHAIII/IV, n (%)	35 (62.5)	41 (70.7)	0.35	30 (66.7)	31 (68.9)	0.82
De novo acute HF[a], n (%)	36 (64.3)	41 (70.7)	0.47	31 (68.9)	30 (66.7)	0.82
Ischaemic aetiology[b], n (%)	23 (43.3)	23 (41.8)	0.87	16 (38.1)	20 (46.5)	0.43
Hypertension, n (%)	34 (60.7)	36 (62.1)	0.88	28 (62.2)	28 (62.2)	1.00
Diabetes mellitus, n (%)	15 (26.8)	9 (15.5)	0.14	6 (13.3)	9 (20.0)	0.40
Atrial fibrillation, n (%)	17 (30.4)	24 (41.4)	0.22	17 (37.8)	16 (35.6)	0.83
Previous PCI or CABG, n (%)	11 (19.6)	6 (10.3)	0.16	6 (13.3)	5 (11.1)	0.75
CRT, n (%)	1 (1.8)	0 (0.0)	0.23	1 (2.2)	0 (0.0)	0.24
ICD, n (%)	2 (3.6)	0 (0.0)	0.09	1 (2.2)	0 (0.0)	0.24
Medications at admission						
ACEi and/or ARB and/or ARNi, n (%)	17 (30.4)	13 (22.4)	0.34	12 (26.7)	10 (22.2)	0.62
Beta-blocker, n (%)	14 (25.0)	10 (17.2)	0.31	11 (24.4)	9 (20.0)	0.61
MRA, n (%)	3 (5.4)	2 (3.5)	0.62	2 (4.4)	1 (2.2)	0.55
Loop diuretic, n (%)	8 (14.3)	6 (10.3)	0.52	6 (13.3)	4 (8.89)	0.50
Oxygen therapy, n (%)	35 (62.5)	41 (70.7)	0.35	28 (62.2)	33 (73.3)	0.26
NPPV, n (%)	12 (21.4)	15 (25.9)	0.58	8 (17.8)	13 (28.9)	0.21
Intravenous vasodilator, n (%)	15 (26.8)	23 (39.7)	0.14	13 (28.9)	17 (37.8)	0.37
Examination findings at admission						
LVEF, %	35 [29, 39]	30 [25, 36]	<0.01	35 [29, 40]	32 [28, 37]	0.08
LVEF < 40%, n (%)	44 (78.6)	53 (91.4)	0.06	34 (75.6)	40 (8.9)	0.10
Serum sodium, mmol/L	140 [138, 142]	140 [137, 142]	0.92	140 [139, 142]	140 [137, 142]	0.76
Serum glucose, mmol/L	7.5 [6.2, 11]	7.6 [6.4, 9.5]	0.86	7.3 [5.8, 8.6]	7.5 [6.3, 9.6]	0.25
Serum creatinine, μmol/L	88.4 [69.2, 113]	88.4 [73.8, 115]	0.64	88.4 [68.5, 114]	87.5 [72.5, 113]	0.75
NT-pro BNP, pg/mL	6983 [3610, 14 840]	6854 [4034, 10 720]	0.69	7124 [3992, 14 400]	6902 [4002, 11 580]	0.78
Hb, g/dL	12.7 [11.2, 14.2]	13.6 [12.3, 14.6]	0.02	12.9 [11.7, 14.5]	13.5 [12.2, 14.2]	0.45
Ht, %	39 [35, 43]	41 [37, 44]	0.06	39 [36, 44]	41 [37, 43]	0.54
Iron, μg/dL	48 [35, 62]	52 [33, 71]	0.39	49 [36, 64]	52 [33, 70]	0.51
TIBC, μg/dL	280 [245, 338]	286 [244, 329]	0.67	282 [247, 349]	273 [240, 317]	0.16
TSAT, %	16 [12, 22]	18 [11, 26]	0.25	16 [12, 22]	19 [13, 26]	0.18
Ferritin, ng/mL	104 [44.1, 252]	118 [66.9, 211]	0.63	108 [40.8, 320]	120 [73.0, 210]	0.73
Iron deficiency, n (%)	36 (64.3)	38 (66.7)	0.79	27 (60.0)	29 (65.9)	0.56
HbA1c, %	6.2 [5.8, 6.6]	5.9 [5.7, 6.3]	0.24	6.0 [5.6, 6.4]	5.9 [5.7, 6.3]	0.80
Plasma osmolality, mOsm/kg	288 [284, 294]	289 [283, 295]	0.74	288 [284, 294]	290 [283, 295]	0.86
Urine osmolality, mOsm/kg	401 [325, 577]	407 [345, 673]	0.47	380 [322, 569]	398 [338, 617]	0.59

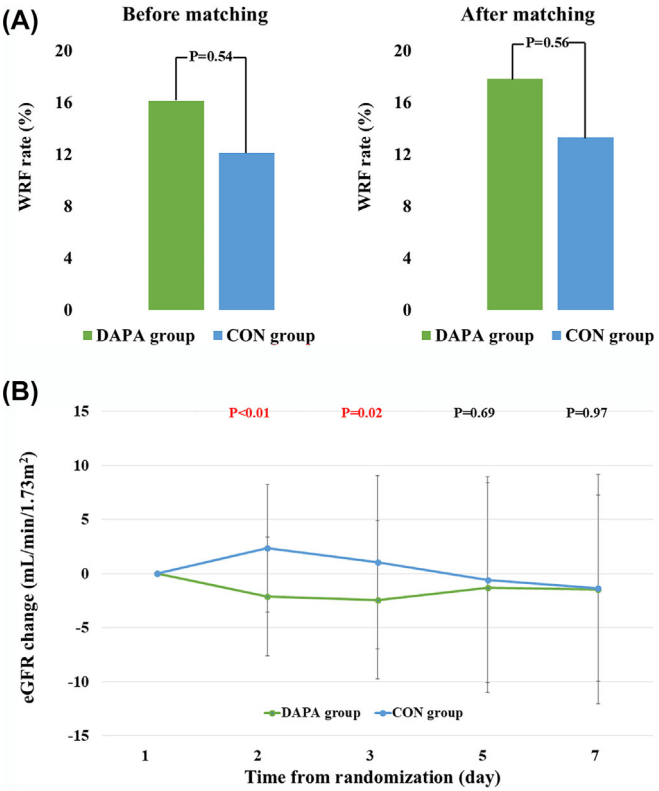
Note: Values are median [IQR] or n (%).

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; Hb, haemoglobin; HbA1c, haemoglobin A1c; HR, heart rate; Ht, haematocrit; ICD, Implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NPPV, non-invasive positive pressure ventilation; NT-pro BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIBC, total iron binding capacity; TSAT, transferrin saturation.

[a]Patients with the first diagnosis of heart failure at admission.

[b]Patients with ischaemia-positive coronary stenosis on coronary angiography.

Figure 2 The incidence of WRF and the eGFR change through day 7. (A) The incidence of worsening renal function (WRF) before and after propensity score matching. (B) The change in the eGFR from day 1 through day 7.



propensity score matching (17.8%, *n* = 8, 13.3%, *n* = 6, *P* = 0.56). Subgroup analysis based on eGFR or diabetes showed no significant differences in the incidence of WRF between two groups (*Table S1*). In patients with diabetes mellitus, the incidence of WRF was similar between two groups (20.0%, *n* = 3 vs. 0.0%, *n* = 0, *P* = 0.15).

Furthermore, we analysed the change in the eGFR from day 1 as shown in *Figure 2B*. The decline in the eGFR was significantly greater in the DAPA group than CON group up to 3 days, but there was no significant difference in the eGFR change between the two groups at day 5 and day 7.

Impact of DAPA on the urine volume and cumulative dose of loop diuretics

Figure 3 demonstrates the urine volume and urine volume per body weight per hour. There were no significant differences in urine volume over 7 days and the urine volume per body weight per hour over 7 days. Moreover, the urine volume per body weight per hour was regulated at 1–2 mL/kg/h according to the standard decongestive therapy.[11,12] *Figure 4* shows the cumulative dose of loop diuretics. The total dose of intravenous or oral loop diuretics after day 3 was lower in the DAPA group than CON group (184 ± 79.5 mg over 7 days vs. 214 ± 66.5 mg over 7 days, *P* = 0.03).

Impact of DAPA on the diuretic response and blood and urinary measurements

There were no significant differences in the body weight through day 7 (−3.2 kg [−5.2, −1.6] vs. −3.5 [−4.5, −2.0], *P* = 0.72). In addition, there were no significant differences in the diuretic response through day 7 (−0.88 kg/40 mg furosemide equivalent [−1.5, −0.53] vs. -0.80 kg/40 mg furosemide equivalent [−1.4, −0.37], *P* = 0.32). *Table 2* shows the plasma and urinary electrolytes in both groups. In the DAPA group, the serum sodium was significantly higher on days 2 and 3 than in the CON group. However, the spot urinary sodium and fractional excretion of sodium (FENa) did not significantly differ between the two groups over 7 days. The spot urinary glucose was significantly higher in the DAPA group than CON group after 2 days. In addition, the plasma osmolality was significantly higher from day 1 to day 3, and the urine osmolality tended to be higher after day 2 in the DAPA group than in the CON group.

Figure 3 Urine volume and urine volume per body weight. (A) Urine volume through day 7. (B) Urine volume per body weight per kilogram through day 7.

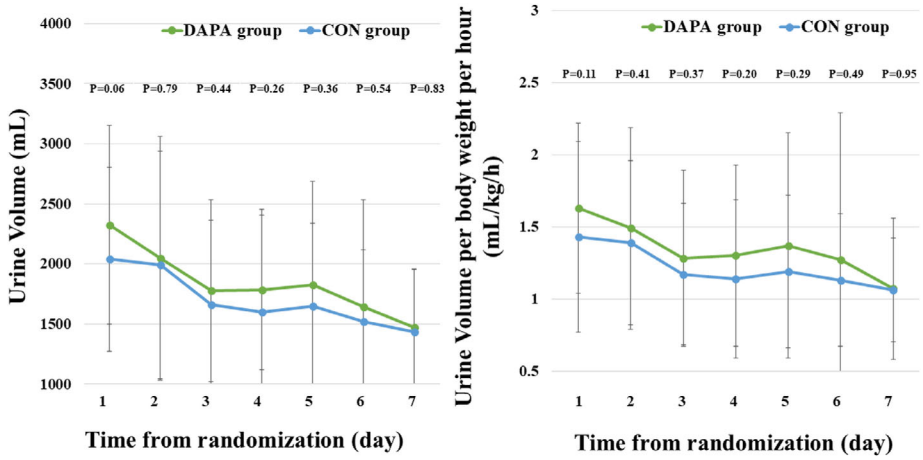
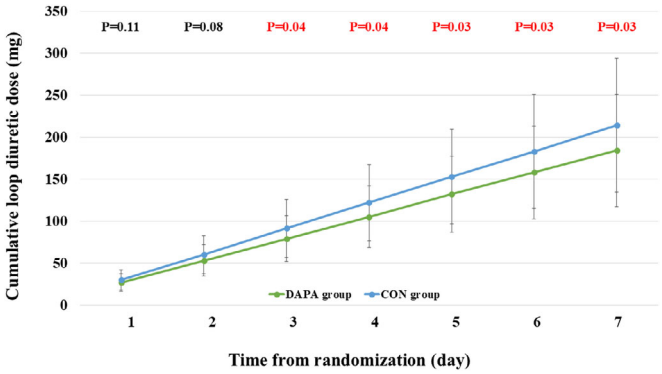


Figure 4 Cumulative loop diuretic dose through day 7.



Other laboratory data, medications, TTE and RHC before discharge

The results of the laboratory data, TTE data, RHC data and medications before discharge are shown in *Table 3*. The Hb, serum iron and transferrin saturation (TSAT) were significantly lower in the DAPA group than CON group. However, the Ht, TIBC and ferritin were similar between the two groups. The rate of an iron deficiency was similar between the two groups. Transfusions were performed in four patients in the DAPA group and in three in the CON group (7.1% vs. 5.2%, *P* value = 0.66). Oral or intravenous iron supplementations were used in three patients in the DAPA group and in two in the CON group (5.4% vs. 3.5%, *P* value = 0.62). After excluding nine patients with transfusions and oral or intravenous iron supplementation, the serum iron and TSAT were significantly lower in the DAPA group than the CON group, and the TIBC, ferritin and rate of an iron deficiency were similar between the two groups. Furthermore, the serum iron and TSAT were significantly lower in the DAPA group compared to the CON group after propensity score matching (65 [46, 85] vs. 78 [61, 99], *P* value = 0.047 and 19.5 [15.8, 29.5] vs. 27.7 [21.2, 36.7], *P* value$<$0.01). Additionally, there were no significant differences in the high-sensitive troponin I and NT-pro BNP levels. Regarding medications, the furosemide equivalent loop diuretic doses at discharge were significantly lower in the DAPA group than CON group (21.8 ± 12.5 mg vs. 27.2 ± 15.5 mg, *P* = 0.04). There were no significant differences in the renin-angiotensin system inhibitors, beta-blockers and mineralocorticoid receptor antagonists at 7 days and before discharge. TTE before discharge was performed in 55 patients (98.2%) in the DAPA group and in 58 (100%) in the CON group. The left ventricular diameter at end-diastole, change in the LVEF, left atrial dimension

Table 2 Blood and urine measurements over the 7 days.

Variable	DAPA group (n = 56)	Conventional therapy group (n = 58)	P value
Serum sodium, mmol/L			
Day 1	141 [139, 143]	141 [138, 142]	0.36
Day 2	141 [140, 143]	140 [138, 141]	<0.01
Day 3	141 [139, 143]	140 [138, 142]	<0.01
Day 5	140 [138, 142]	140 [137, 142]	0.38
Day 7	139 [138, 142]	140 [137, 142]	0.38
Spot urinary sodium, mmol/L			
Day 1	129 [101, 149]	121 [97,.4, 145]	0.58
Day 2	118 [91.9, 141]	116 [92.8, 146]	0.92
Day 3	99.0 [81.4, 130]	113 [79.3, 132]	0.48
Day 5	88.1 [60.1, 114]	82.8 [56.5, 111]	0.93
Day 7	80.6 [57.0, 105]	80.6 [50.5, 105]	0.95
Fractional excretion of sodium, %			
Day 1	1.9 [0.88, 3.6]	1.5 [0.84, 2.3]	0.19
Day 2	1.6 [0.72, 3.0]	1.5 [0.79, 3.0]	0.76
Day 3	1.1 [0.50, 1.8]	1.3 [0.65, 2.1]	0.57
Day 5	0.70 [0.40, 1.3]	0.72 [0.40, 1.4]	0.94
Day 7	0.62 [0.42, 1.3]	0.60 [0.41, 1.0]	0.50
Spot urinary glucose, mmol/L			
Day 1	0.22 [0.056, 1.1]	0.22 [0.11, 0.39]	0.61
Day 2	40 [19, 96]	0.17 [0.11, 0.42]	<0.01
Day 3	62 [18, 140]	0.17 [0.11, 0.42]	<0.01
Day 5	53 [23, 130]	0.22 [0.056, 0.39]	<0.01
Day 7	55 [12, 120]	0.22 [0.010, 0.39]	<0.01
Plasma osmolality, mOsm/kg			
Day 1	291 [286, 294]	287 [283, 291]	0.02
Day 2	289 [286, 294]	286 [281, 291]	<0.01
Day 3	291 [287, 296]	287 [283, 292]	<0.01
Day 5	290 [284, 295]	289 [285, 294]	0.42
Day 7	292 [286, 297]	290 [287, 294]	0.46
Urinary osmolality, mOsm/kg			
Day 1	445 [381, 527]	480 [389, 575]	0.37
Day 2	494 [417, 680]	458 [354, 575]	0.09
Day 3	540 [439, 693]	440 [387, 584]	<0.01
Day 5	560 [424, 714]	494 [369, 612]	0.03
Day 7	564 [441, 687]	502 [401, 616]	0.09

Note: Values are median [IQR].

and inferior vena cava diameter were similar between the two groups. RHC before discharge was performed in 54 patients (96.4%) in the DAPA group and in 54 (93.1%) in the CON group. There were no significant differences in the pulmonary artery wedge pressure, pulmonary artery pressure, right atrial pressure and cardiac index by the thermodilution method or the Fick method.

Safety

The safety data are presented in *Table 4*. The length of stay was similar between the two groups. In addition, there were no significant differences in hypoglycaemia with or without symptoms, ketoacidosis, fractures, amputations and urinary tract infections. Three patients (5.4%) discontinued DAPA during the hospitalization. The reasons for the discontinuation were elevated liver enzymes, a urinary tract infection and decreased appetite, respectively.

Discussion

Main findings

This prospective randomized trial, the ROAD-ADHF trial, had three major findings. (1) The incidence of WRF was not reduced by adding DAPA within 24 h after admission. (2) The total dose of intravenous or oral loop diuretics was significantly lower in the DAPA group than in the CON group according to the standard decongestive therapy. (3) Despite the reduction in the loop diuretics, the RHC or TTE data before discharge were similar between the two groups.

Incidence of WRF

WRF was reported to occur in 20% to 30% of the patients with ADHF in the previous studies.[18] In addition, the incidence of WRF within 7 days was reported to be approximately 20% by adding empagliflozin for ADHF patients.[19] In our study, the incidence of WRF was approximately 15% and that result was similar to the previous reports.[18,19] WRF is a common reason for withholding or reducting a guideline-directed medical therapy in the management of heart failure patients.[20] Therefore, it is a very important finding that WRF was not increased by adding DAPA within 24 h after admission.

Lower total dose of loop diuretics over 7 days in the DAPA group

The use of DAPA was reported to reduce the increase of the diuretic therapy during hospitalization in the previous study.[21] However, in the previous studies, the diuretic strategy was left to the discretion of the physicians, and other types of diuretics such as thiazides or acetazolamide could be added.[17,21] On the other hand, in our study, we adjusted the intravenous furosemide by 10 mg to maintain a urine output of 1–2 mL/kg/h according to the guidelines.[11,12] In addition, no other types of diuretics were used during the hospitalization in this study. The protocol for adjusting loop diuretics and excluding the use of other diuretics is considered novel. In fact, *Figure 3* demonstrates that most of the patients maintained a urine output of 1–2 mL/kg/h according to the standard decongestive therapy. Moreover, there were no differences in the congestion at discharge observed by the NT-pro BNP level, TTE data and RHC. Residual congestion can worsen the outcomes in ADHF patients.[2] The guidelines recommend that euvolemia should be achieved with the lowest dose of diuretics.[12] Therefore, it was proved to be able to reduce the use of loop diuretics and the amount of loop diuretics at discharge by adding DAPA within 24 h after the ADHF admission in this study. A reduction in the loop diuretic

Table 3 Examination findings and medication.

Variable	DAPA group (n = 56)	CON group (n = 58)	P value
Vital sign at discharge			
Body weight change, kg	−3.7 [−5.5, −1.6]	−4.3 [−7.0, −2.1]	0.31
HR, bpm	72 [62, 79]	75 [66, 81]	0.19
SBP, mmHg	115 [98, 123]	115 [97, 131]	0.57
DBP, mmHg	65 [59, 76]	73 [57, 81]	0.42
Laboratory data at discharge			
Serum creatinine, μmol/L	94.6 [75.1, 114]	89.7 [76.0, 109]	0.64
Hb, g/dL	12.5 [11.4, 14.1]	13.3 [12.3, 14.6]	0.046
Ht, %	38 [35, 42]	41 [36, 44]	0.08
Iron, μg/dL	66 [46, 83]	82 [63, 101]	0.02
TIBC, μg/dL	301 [258, 348]	301 [258, 332]	0.45
TSAT, %	20 [15, 30]	28 [21, 35]	<0.01
Ferritin, ng/mL	172 [87.6, 378]	202 [94.5, 380]	0.51
Iron deficiency, n (%)	23 (41.8)	20 (35.1)	0.46
Reticulocyte, ‰	12 [9.0, 16]	11 [8.0, 16]	0.45
Erythropoietin, mIU/mL	11 [6.7, 17]	10 [6.5, 16]	0.59
hs-TnI, pg/mL	0.03 [0.02, 0.2]	0.03 [0.02, 0.1]	0.14
NT-pro BNP, pg/mL	1925 [788.4, 5064]	1822 [915.6, 3426]	0.61
Total cholesterol, mg/dL	157 [136, 188]	164 [138, 182]	0.64
Triglyceride, mg/dL	105 [83.5, 142]	106 [80, 131]	0.80
LDL cholesterol, mg/dL	94 [70, 117]	101 [73.5, 118]	0.63
HbA1c, %	6.2 [5.7, 6.7]	6.0 [5.8, 6.4]	0.50
Medication at 7 days			
ACEi or ARB or ARNi during 7 days, n (%)	43 (76.8)	45 (77.6)	0.92
ACEi at 7 days, n (%)	21 (37.5)	20 (34.5)	0.74
ARB at 7 days, n (%)	10 (17.9)	19 (32.8)	0.07
ARNi at 7 days, n (%)	12 (21.4)	6 (10.3)	0.10
Beta-blocker at 7 days, n (%)	32 (57.1)	28 (48.3)	0.34
MRA at 7 days, n (%)	39 (69.6)	47 (81.0)	0.16
Medication before discharge			
ACEi and/or ARB and/or ARNi, n (%)	42 (75.0)	47 (81.0)	0.44
ACEi, n (%)	24 (42.9)	20 (34.5)	0.36
ARB, n (%)	4 (7.1)	12 (20.7)	0.03
ARNi, n (%)	14 (25.0)	15 (25.9)	0.92
Beta-blocker, n (%)	48 (85.7)	55 (94.8)	0.09
MRA, n (%)	39 (70.0)	47 (81.0)	0.16
Furosemide equivalent loop diuretic dose, mg/day	21.8 ± 12.5	27.2 ± 15.5	0.04
Echocardiographic data before discharge	**DAPA group (n = 55)**	**CON group (n = 58)**	**P value**
LVDD, mm	57 [51, 62]	56 [50, 62]	0.49
LVDS, mm	47 [40, 53]	45 [40, 54]	0.86
LVEF, %	38 [32, 45]	35 [28, 39]	0.03
Change in LVEF from admission, %	2.0 [0.0, 7.0]	2.0 [0.0, 7.3]	0.62
LAD, mm	47 [43, 50]	46 [43, 50]	0.62
IVCD, mm	13 [11, 15]	14 [12, 16]	0.11
IVC collapse > 50% with sniff, n (%)	48 (87.3)	54 (93.1)	0.29
TRPG, mmHg	28 [21, 34]	25 [23, 32]	0.79
Right heart catheterization	**DAPA group (n = 54)**	**CON group (n = 54)**	**P value**
Mean PAWP, mmHg	11 [6.0, 15]	9.5 [6.0, 17]	0.74
Systolic PAP, mmHg	25 [21, 35]	25 [21, 31]	0.39
Diastolic PAP, mmHg	12 [8.0, 18]	12 [8.0. 18]	0.81
Mean PAP, mmHg	17 [13, 24]	17 [14, 23]	0.68
RVEDP, mmHg	5.0 [3.0, 8.5]	4.5 [3.0, 7.8]	0.24
Mean RAP, mmHg	3.5 [2.0, 6.0]	4.0 [1.5, 6.0]	0.66
CI by thermodilution method, L/min/m^2	2.6 [2.3, 3.2]	2.51 [1.9, 3.0]	0.11
CI by Fick method, L/min/m^2	1.9 [1.6, 2.4]	2.0 [1.6, 2.3]	0.87

Note: Values are mean±SD, median [IQR] or n (%).
Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; CI, cardiac index; DBP, diastolic blood pressure; Hb, haemoglobin; HbA1c, haemoglobin A1c; HR, heart rate; hs-TnI, high-sensitive troponin I; Ht, haematocrit; IVC, inferior vena cava; IVCD, inferior vena cava diameter; LAD, left atrial dimension; LVDD, left ventricular diameter at end diastole; LVDS, left ventricular diameter at end systole; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-pro BNP, N-terminal pro-brain natriuretic peptide; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; RVEDP, right ventricular end-diastolic pressure; SBP, systolic blood pressure; TIBC, total iron binding capacity; TRPG, tricuspid regurgitation pressure gradient; TSAT, transferrin saturation.

Table 4 Safety endpoint.

Variable	DAPA group (n = 56)	Conventional therapy group (n = 58)	P value
Length of stay, days	14 [11, 18]	15 [13, 19]	0.18
Hypoglycaemia without symptom, n (%)	0 (0.0)	1 (1.7)	0.24
Hypoglycaemia with symptom, n (%)	0 (0.0)	0 (0.0)	-
Ketoacidosis, n (%)	0 (0.0)	0 (0.0)	-
Fracture, n (%)	0 (0.0)	0 (0.0)	-
Amputation, n (%)	0 (0.0)	0 (0.0)	-
Urinary tract infection, n (%)	2 (3.6)	3 (5.2)	0.68

Note: Values are median [IQR] or n (%).

dose might be associated with a lack of a difference in the renal function decline after 3 days. In addition, high diuretic doses during HF hospitalizations have been associated with an increased mortality in a previous report.[22] A reduction in the diuretic dose with the addition of DAPA may be beneficial with respect to the long-term prognosis as well as the long-term renal function.

Decline in the eGFR up to 3 days by adding DAPA

There were two possible mechanisms with regard to the decrease in the eGFR after initiating the SGLT2 inhibitor. One was the 'initial dip' and the second was 'osmotic diuresis'.

SGLT2 inhibitors are reported to cause an initial dip by augmenting the tubuloglomerular feedback.[23] The action of SGLT2 inhibitors in the proximal convoluted tubules results in an increased concentration of Na^+ in the macula densa. This leads to an adenosine-mediated signal cascade and, in turn, vasoconstriction of the afferent arterioles, which causes the initial dip. This study revealed that an initial dip might be observed when treating ADHF in combination with loop diuretics.

The osmotic diuretic effect of SGLT2 inhibitors was reported in the EMPA-RESPONSE-AHF study.[24] The serum sodium, plasma and urinary osmolality, and urinary glucose level increased over 3 days by adding DAPA without affecting the diuretic response or FENa as shown in *Table 2*. As more glucose is excreted by adding DAPA, more water is drawn to the urine keeping the osmolality constant. The serum sodium and plasma osmolality are increased as a result of an increased electrolyte-free water excretion. Our study revealed that osmotic diuresis was one of the mechanisms of DAPA when treating ADHF in combination with loop diuretics.

Impact of DAPA on the iron metabolism for ADHF

There is little knowledge about how the addition of DAPA to ADHF affects iron metabolism. This study revealed serum iron and TSAT were significantly lower in the DAPA group than CON group among the ADHF patients after excluding patients with transfusions and oral or intravenous iron supplementation. The TSAT was significantly reduced in the DAPA group as compared to that in CHF patients with a placebo.[10] The cytosolic iron repletion hypothesis has been proposed.[25] The effect of SGLT2 inhibitors on decreasing the hepcidin and ferritin and increasing the transferrin represents a direct effect mediated by an increase in the sirtuin-1 signalling, and those changes lead to an increase in the iron utilization. That effect of DAPA might be applicable to ADHF patients, but further studies are needed on the impact of DAPA on the iron metabolism in ADHF.

Study limitations

This study had several limitations. First, this study was not a placebo-controlled trial and the participants were not blinded. The investigators knew the treatment allocation, which might have affected the dosages of the drugs. However, there were no differences in the congestion upon discharge observed in the NT-pro BNP level, TTEs and RHC data. In addition, the amount of loop diuretics was lower than that in other countries. The dose of furosemide in Japan was less than half of the dose of furosemide administered in the USA in a previous report.[26] In fact, the average dose of loop diuretics in this study was 26.3 ± 9.5 mg/day in the DAPA group and 30.6 ± 11.4 mg/day in the conventional therapy group, however, Charaya et al. reported an average dose of loop diuretics of 78.46 ± 38.95 mg/day in the group who received DAPA and 102.82 ± 31.26 mg/day in the control group.[21] However, there might have been fewer differences in the dosage of loop diuretics among the attending physicians due to the standardized diuretic treatment protocol in this study. Finally, this study lacked the statistical power to demonstrate a significant difference, as the incidence of WRF was lower than anticipated in both groups. One possible reason for the lower-than-expected incidence of WRF could be that excessive diuretic use was avoided owing to the standardized diuretic treatment protocol. Larger scale studies with longer follow-up are deemed necessary.

Conclusions

This prospective randomized trial, the ROAD-ADHF, revealed that the addition of DAPA within 24 h after admission resulted in a reduction in the diuretic dose in those without WRF over 7 days. The conclusions are limited by the small sample size and the absence of a placebo group. Larger scale studies with longer follow-up are needed to confirm these findings.

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Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Subgroup analysis of WRF stratified by eGFR and diabetes mellitus.

References

1. Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. *Nat Rev Cardiol* 2020;**17**:641–655. doi:10.1038/s41569-020-0379-7
2. Rubio-Gracia J, Demissei BG, Ter Maaten JM, Cleland JG, O'Connor CM, Metra M, et al. Prevalence, predictors and clinical outcome of residual congestion in acute decompensated heart failure. *Int J Cardiol* 2018;**258**:185–191. doi:10.1016/j.ijcard.2018.01.067
3. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014;**35**:455–469. doi:10.1093/eurheartj/eht386
4. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008. doi:10.1056/NEJMoa1911303
5. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;**387**:1089–1098. doi:10.1056/NEJMoa2206286
6. Mordi NA, Mordi IR, Singh JS, McCrimmon RJ, Struthers AD, Lang CC. Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: the RECEDE-CHF trial. *Circulation* 2020;**142**:1713–1724. doi:10.1161/CIRCULATIONAHA.120.048739
7. Adamson C, Docherty KF, Heerspink HJL, de Boer RA, Damman K, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Petrie MC, Ponikowski P, Sabatine MS, Schou M, Solomon SD, Verma S, Bengtsson O, Langkilde AM, Sjöstrand M, Vaduganathan M, Jhund PS, McMurray JJV Initial decline (dip) in estimated glomerular filtration rate after initiation of dapagliflozin in patients with heart failure and reduced ejection fraction: insights from DAPA-HF. *Circulation* 2022;**146**:438–449. doi:10.1161/CIRCULATIONAHA.121.058910
8. Biegus J, Voors AA, Collins SP, Kosiborod MN, Teerlink JR, Angermann CE, Tromp J, Ferreira JP, Nassif ME, Psotka MA, Brueckmann M, Salsali A, Blatchford JP, Ponikowski P Impact of empagliflozin on decongestion in acute heart failure: the EMPULSE trial. *Eur Heart J* 2023;**44**:41–50. doi:10.1093/eurheartj/ehac530
9. Cox ZL, Collins SP, Hernandez GA, McRae AT, 3rd, Davidson BT, Adams K, et al. Efficacy and safety of dapagliflozin in patients with acute heart failure. *J Am Coll Cardiol* 2024;**83**:1295–1306. doi:10.1016/j.jacc.2024.02.009
10. Docherty KF, Welsh P, Verma S, De Boer RA, O'Meara E, Bengtsson O, et al. Iron deficiency in heart failure and effect of dapagliflozin: findings from DAPA-HF. *Circulation* 2022;**146**:980–994. doi:10.1161/CIRCULATIONAHA.122.060511
11. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;**285**:1441–1446. doi:10.1056/nejm197112232852601
12. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155. doi:10.1002/ejhf.1369
13. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;**42**:3599–3726. doi:10.1093/eurheartj/ehab368
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–270. doi:10.1093/ehjci/jev014
15. Kimura K, Momose T, Hasegawa T, Morita T, Misawa T, Motoki H, Izawa A, Ikeda U Early administration of tolvaptan preserves renal function in elderly patients with acute decompensated heart failure. *J Cardiol* 2016;**67**:399–405. doi:10.1016/j.jjcc.2015.09.020
16. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004;**43**:61–67. doi:10.1016/j.jacc.2003.07.031
17. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, van Eck JWM, Heerspink HJL, Voors AA Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail* 2020;**22**:713–722. doi:10.1002/ejhf.1713
18. Emmens JE, Ter Maaten JM, Matsue Y, Figarska SM, Sama IE, Cotter G, et al. Worsening renal function in acute heart failure in the context of diuretic response. *Eur J Heart Fail* 2022;**24**:365–374. doi:10.1002/ejhf.2384
19. Tamaki S, Yamada T, Watanabe T, Morita T, Furukawa Y, Kawasaki M, Kikuchi A, Kawai T, Seo M, Abe M, Nakamura J, Yamamoto K, Kayama K, Kawahira M, Tanabe K, Fujikawa K, Hata M, Fujita Y, Umayahara Y, Taniuchi S, Sanada S, Shintani A, Fukunami M Effect of empagliflozin as an add-on therapy on decongestion and renal function in patients

with diabetes hospitalized for acute decompensated heart failure: a prospective randomized controlled study. *Circ Heart Fail* 2021;**14**:e007048. doi:10.1161/CIRCHEARTFAILURE.120.007048

20. Ibrahim NE, Gaggin HK, Rabideau DJ, Gandhi PU, Mallick A, Januzzi JL, Jr. Worsening renal function during management for chronic heart failure with reduced ejection fraction: results from the pro-BNP outpatient tailored chronic heart failure therapy (PROTECT) study. *J Card Fail* 2017;**23**:121–130. doi:10.1016/j.cardfail.2016.07.440
21. Charaya K, Shchekochikhin D, Andreev D, Dyachuk I, Tarasenko S, Poltavskaya M, Mesitskaya D, Bogdanova A, Ananicheva N, Kuzub A Impact of dapagliflozin treatment on renal function and diuretics use in acute heart failure: a pilot study *Open Heart* 2022;**9**:e001936. doi:10.1136/openhrt-2021-001936
22. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail* 2007;**9**:1064–1069. doi:10.1016/j.ejheart.2007.07.011
23. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:422–434. doi:10.1016/j.jacc.2019.11.031
24. Boorsma EM, Beusekamp JC, Ter Maaten JM, Figarska SM, Danser AHJ, van Veldhuisen DJ, et al. Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. *Eur J Heart Fail* 2021;**23**:68–78. doi:10.1002/ejhf.2066
25. Packer M. Potential interactions when prescribing SGLT2 inhibitors and intravenous iron in combination in heart failure. *JACC Heart Fail* 2023;**11**:106–114. doi:10.1016/j.jchf.2022.10.004
26. Tanaka TD, Sawano M, Ramani R, Friedman M, Kohsaka S. Acute heart failure management in the USA and Japan: overview of practice patterns and review of evidence. *ESC Heart Fail* 2018;**5**:931–947. doi:10.1002/ehf2.12305