The effectiveness of dapagliflozin versus furosemide in controlling blood pressure in resistant hypertension with subclinical fluid retention in chronic kidney disease

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Background

Resistant hypertension (RHT) in chronic kidney disease (CKD) patients is caused by excess salt and water retention. Reduction of overhydration results in better blood pressure (BP) control. This study aims to evaluate the efficacy of dapagliflozin compared to furosemide for controlling BP in these patients.

Method

A prospective randomized, open-label study on 16 patients with RHT and CKD who underwent bioimpedance spectroscopy (BIS). Patients were allocated to the dapagliflozin group and the furosemide group. No dose adjustment of baseline antihypertensive agents. Assessment of the change in BP and fluid status.

Results

The mean age was 72.6±8.3 years, 56.3% were male and 50% were diabetic. Baseline BP was 143.9±8.5/77.1±9.1 mmHg. In the sixth month, there was a statistically significant greater reduction in systolic blood pressure in the dapagliflozin group compared to the furosemide group, with a decline of SBP of 18.0±9.4 mmHg vs. 7.0±7.4 mmHg (P=0.02).

Conclusions

Dapagliflozin was effective in controlling blood pressure comparable to furosemide in CKD patients with RHT and fluid retention.

Keywords: CKD, resistant hypertension, fluid retention

Research Objectives

Primary objectives

To compare blood pressure change between dapagliflozin and furosemide in controlling blood pressure.

Secondary objectives

To compare the achieving target of blood pressure, fluid status, renal function, and incidence of hospitalized heart failure between dapagliflozin and furosemide.

Materials and methods

Study design and participants

This single-center, non-inferior prospective randomized, open-label study was conducted at Bhumibol Adulyadej hospital. The study protocol was approved by the Institutional Review Board of Bhumibol Adulyadej hospital, Directorate of medical service, Royal Thai Air Force. Written informed consent was obtained from all patients or their legally authorized representatives before participation.

Eligible participants were adults aged $\geq$ 18 years with CKD (GFR-EPI 20-60 ml/min/1.73m^2) with resistant hypertension with fluid retention detected by bioimpedance. Exclusion criteria included patients receiving diuretics or SGLT2i, resistant hypertension with euvolemic status, life expectancy < 12 months (principal investigator's judgement), living-donor transplant scheduled within the next 12 months, cardiovascular disease (dilated cardiomyopathy, valvular heart disease), active infection, current active malignancy, known HIV or active hepatitis B or C, chronic liver disease and/or screening alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range, pregnancy or breastfeeding and subject has any kind of disorder that compromises their ability to informed consent and/or to comply with study procedures.

Sample size

From the study by V lase et al., it was found that furosemide can reduce SBP in resistant hypertension patients by 32 mmHg, and from the study by Micheal A Weber et al. , SGLT2i (dapagliflozin) can reduce SBP in hypertension patients by 11.9 mmHg.

Calculation of non-inferiority in continuous data using a significance level of 0.05, a power of the test of 0.8, the standard deviation of the outcome of 7 mmHg, the non-inferiority limit of 7 mmHg, and a dropout rate of 10%, with a minimum sample size of at least 15 participants per group, totaling at least 30 participants.

Technical note

Calculation based on the formula:

$$n = f(\alpha, \beta) \times 2 \times \sigma^2 / d^2$$

where σ is the standard deviation, and

$$f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$$

Φ^{-1} is the cumulative distribution function of a standardised normal deviate.

Reference: Julious SA. Sample sizes for clinical trials with Normal data. *Statist. Med.* 2004; **23**:1921-1986.

Materials

The Body Composition Monitor (BCM; Fresenius Medical Care, Deutschland GmbH Schweinfurt Plant, Hafenstrasse 9, 97424 Schweinfurt/Germany) utilizes the principle of Bioimpedance spectroscopy technique, which involves using frequencies in the range of 5kHz-1MHz and calculating the electrical resistance values of Extracellular water (ECW) and Intracellular water (ICW) using a combination of Cole-Cole plot and Hanai formulae along with a physiologic tissue model, dividing the body composition into three components: extracellular fluid overload, normohydrated lean tissue, and normohydrated adipose tissue, assuming the proportions of normohydrated lean and adipose tissue remain constant. Then, the program calculates the volume of water in these compartments, with reference values being the 10th-90th percentile of body water volume in the normal population matching the patient's gender and age. This can indicate excess water volume in the studied patients. The value indicating fluid retention in patients is determined by overhydration (OH) exceeding 1 liter.

Randomization

The patients were randomly assigned in a 1:1 ratio to receive either dapagliflozin or furosemide. The allocation sequence used random numbers in a block of fours.

Procedures

Participants were selected for the research study based on inclusion and exclusion criteria. Patients were informed about the study details and provided consent to participate. Basic data of research participants were collected through interviews, echocardiograms, Bioelectrical Impedance Analysis (BIS), and dietary sodium restriction guidance of less than 2 grams per day. Patients were randomly assigned into two groups. The experimental group received a daily dose of 10 milligrams of dapagliflozin, while the control group received an initial dose of 20 mg/day of furosemide with dosage adjustment based on BIS assessment. Blood samples were collected, and variables related to the research outcomes were recorded over 6 months. Body fluid status was assessed using BIS monthly during months 1-3 and month 6. Outcomes at 6 months were evaluated through echocardiograms and laboratory tests. Statistical analysis was conducted on the obtained results, shown in Figure 1.

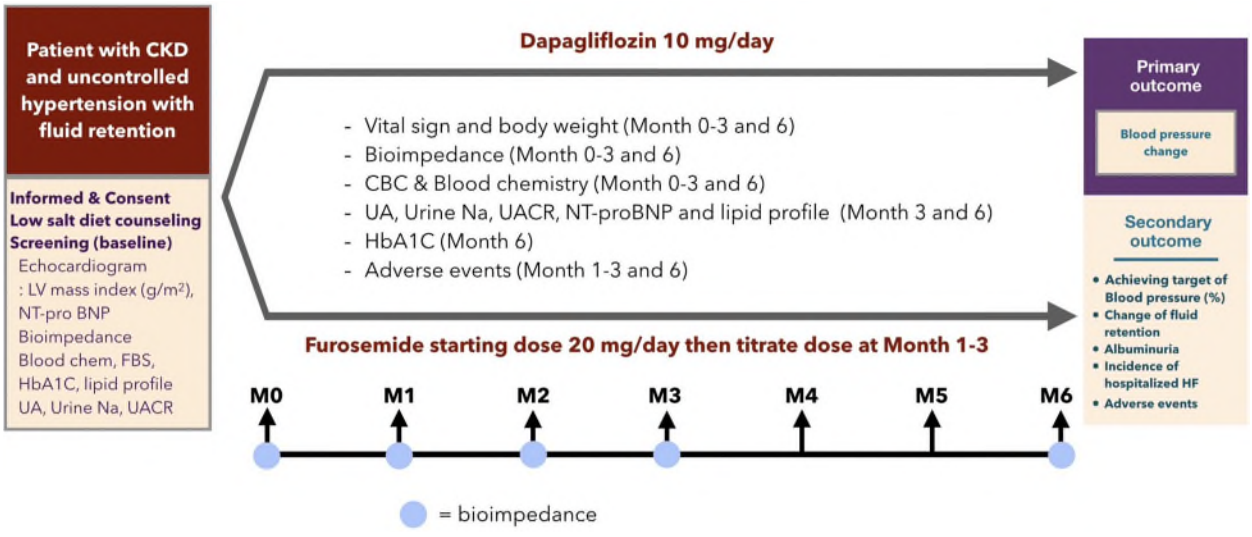

Figure 1. Research protocol.

Outcomes

The primary outcome was to compare blood pressure change between dapagliflozin and furosemide in controlling blood pressure.

The secondary outcome was to compare the achieving target of blood pressure, fluid status (assessed by ECW, ICW, and ECW/Total body water), renal function (eGFR, UACR), cardiac function (change in LVEF, LV mass index, NT-pro BNP), and incidence of hospitalized heart failure between dapagliflozin and furosemide.

Statistical analysis

Continuous data were presented as means with standard deviation (SD) or medians with interquartile range (IQR) and compared using the Student's t-test or Wilcoxon Rank-Sum test, as appropriate. Categorical data were presented as proportions and compared using Fisher's exact test. An alpha level of $\leq$ 0. 05 was deemed statistically significant for all tests. This study used program R version 4.1.1 for data analysis.

Results

Patient enrollment and baseline characteristics

The study enrolled a total of 17 CKD patients who underwent follow-up at the outpatient clinic between 2022 and 2023, with 9 patients randomly assigned to receive dapagliflozin and 8 patients to receive furosemide. During the study period, one patient withdrew from the study due to poor compliance. The patients had a mean age of 72.6 (SD 8.3) years, 56.3% were male, 50% were diabetic, and a mean BMI of 27.1 (SD 6.5) kg/m^2. The mean initial SBP was 143.9 (SD 8.5) mmHg and DBP was 77.1 (SD 9.1) mmHg. In terms of fluid status, the median initial value of overhydration (OH) was 1.55 (IQR 1.4, 2.275), and the mean initial value of ICW was 17.7 (SD 4.5), ECW was 17.5 (SD 3.9), and ECW/TBW was 0.498 (SD 0.024). Left ventricular hypertrophy was found in 62.5% of patients, with a mean LV mass index of 123.7 (SD 25.4) g/m^2. However, there was a significant difference in LVEF between the two groups; the dapagliflozin group had a mean LVEF of 70.2 (SD 4.9) %, while the furosemide group had a mean

LVEF of 63.0 (SD 4.3) %, (p=0.007). The mean initial serum eGFR level was 40.0 (SD 10.2) mL/min/1.73 m^2, the median UACR level was 42.0 (IQR 27.0,99.3) mg/g, and the median NT-pro BNP level was 314.5 (IQR 159.0,422.3). The patients received an average of 4 types of medication. Both the dapagliflozin and furosemide groups received ACEi or ARB in 93.8% (7 vs 8), CCB in 100%, and beta-blocker in 87.5% (6 vs 8). The mean Baseline characteristics were well-balanced between the two groups (accept LVEF), as shown in Table 1.

Table 1. Baseline characteristics.

Characteristics	Dapagliflozin (n=8)	Furosemide (n=8)	P-value
Age - year (SD)	74.5 (6.2)	70.6 (10.0)	0.367
Male sex - no. (%)	5 (62.5)	4 (50.0)	1.000
Diabetes - no. (%)	5 (62.5)	3 (37.5)	0.619
Smoking status - no. (%)			1.000
Former smoking	2 (25.0)	3 (37.5)	
Never smoked	6 (75.0)	5 (62.5)	
Weight - kg (SD)	71.2 (17.5)	75 (25.1)	0.729
Body-mass index - kg/m^2(SD)	26.1 (5.5)	28.1 (7.6)	0.570
Blood pressure - mmHg (SD)			
Systolic - mmHg (SD)	146.4 (6.4)	141.4 (9.9)	0.251
Diastolic - mmHg (SD)	74 (10.1)	80.3 (7.4)	0.179
LVEF - % (SD)	70 (4.9)	63 (4.3)	0.007
LV mass index - g/m^2 (SD)	114.1 (21.8)	133.2 (26.5)	0.137
Left ventricular hypertrophy - no. (%)	4 (50.0)	6 (75.0)	0.608

Bioimpedance			
Overhydration (OH) - L (IQR)	1.55 (1.4, 1.2)	1.65 (1.35, 2.275)	0.832
Intracellular water (ICW) - L (SD)	18.4 (4.2)	17.1 (4.9)	0.578
Extracellular water (ECW) - L (SD)	17.7 (3.6)	17.2 (4.4)	0.800
Total body water (TBW) - L (SD)	36.1 (7.7)	34.2 (9.2)	0.671
ECW/TBW - (SD)	0.493 (0.023)	0.504 (0.026)	0.375
NT-pro BNP level - pg/mL (IQR)	314.5 (193.5,979)	268.5 (154.5,394.5)	0.637
Serum sodium - mEq/L (SD)	139.5 (2.88)	140.12 (0.99)	0.571
Urine sodium - mEq/L (SD)	79.4 (27.8)	66.9 (23.6)	0.349
eGFR - mL/min/1.73 m^2 (SD)	41.6 (10.8)	38.4 (10.1)	0.546
UACR - mg/g (IQR)	59.5 (17,99.25)	42.0 (32,93.25)	0.793
Urine volume - ml/day (SD)	1331.2 (518.9)	1421.2 (372.3)	0.696
Antihypertensive drugs - no. (SD)	4 (0.5)	4.1 (0.8)	0.727
Antihypertensive drugs			
ACEI/ARB - no. (%)	7 (87.5)	8 (100)	1.000
CCB - no. (%)	8 (100)	8 (100)	1.000
Beta-blocker - no. (%)	6 (75)	8 (100)	0.467
Others - no. (%)	8 (100)	8 (100)	1.000

Table 2. Primary outcome.

End point	Dapagliflozin	Furosemide	Estimated treatment effect (95% CI)	P Value	
Primary outcome				2 sided	1 sided (margin = 7)
Change of SBP - mmHg (SD)	-18.00 (9.35)	-7.00 (7.39)	-11.00 (-22.76, 0.76)	0.0205	0.9996
Change of DBP - mmHg (SD)	-9.75 (10.11)	-1.25 (9.22)	-8.5 (-17.95, 0.95)	0.1008	0.9968

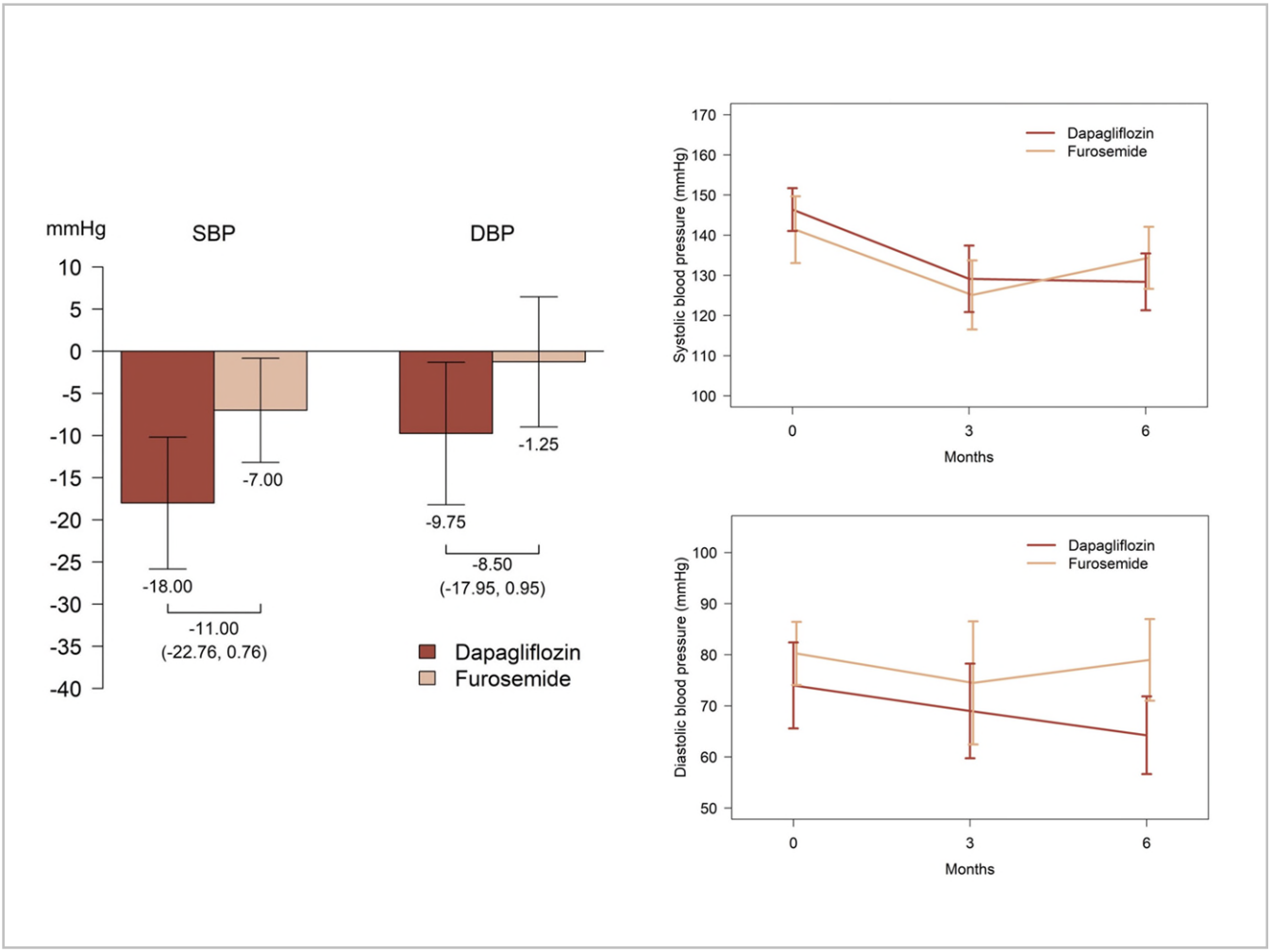

Figure 2. Primary outcomes.

Table 3. Secondary outcomes.

End point	Dapagliflozin	Furosemide	Estimated Treatment Effect (95% CI)	P Value
Achieving target of BP - no. (%)	8 (100)	6 (75)		0.4667
Bioimpedance				
Change of OH - L (SD)	0.20 (0.74)	-0.06 (0.31)	0.26 (-0.37, 0.90)	0.3701
Change of TBW - L (SD)	-0.63 (2.45)	-0.11 (0.88)	-0.52 (-2.60, 1.58)	0.5866
Change of ICW - L (SD)	-0.41 (1.62)	-0.06 (0.36)	-0.35 (-1.74, 1.04)	0.5773
Change of ECW - L (SD)	-0.21 (1.05)	-0.06 (0.36)	-0.15 (-1.05, 0.75)	0.7084
Change of ECW/TBW - (SD)	0.001 (0.021)	-0.001 (0.010)	0.002 (-0.016, 0.021)	0.7773
Changes in cardiac function				
Change of LVEF - % (SD)	-1.25 (8.137)	6.63 (7.15)	-7.88 (-16.10, 0.35)	0.0589
Change of LV mass index - g/m^2 (SD)	6.51 (17.16)	-3.93 (30.47)	10.44 (-16.76, 37.64)	0.4127
Change of NT-pro BNP level - pg/mL (SD)	-83.63 (129.85)	318.63 (889.99)	-402.25 (-1148.00, 343.50)	0.2265
Change of serum Na+ - mEq/L (SD)	1.63 (2.83)	0.63 (1.92)	1.00 (-1.63, 3.63)	0.4218
Change of Urine Na+ - mEq/L (SD)	1.13 (46.23)	-7.50 (24.62)	8.63 (-32.29, 49.54)	0.6486
Change of UACR - mg/g (IQR)	-19.50 (52.06)	-151.75 (383.31)	132.25 (-188.83, 453.33)	0.3499
Change of eGFR - mL/min/1.73 m^2 (SD)	-4.83 (4.83)	-4.07 (4.86)	-0.76 (-5.96, 4.43)	0.7576
Change of body weight - kg (SD)	-1.49 (3.89)	0.45 (1.41)	-1.94 (-5.26, 1.38)	0.2063
Change of urine volume - ml (SD)	217.50 (612.89)	326.88 (970.00)	-109.38 (-995.45, 776.70)	0.7915

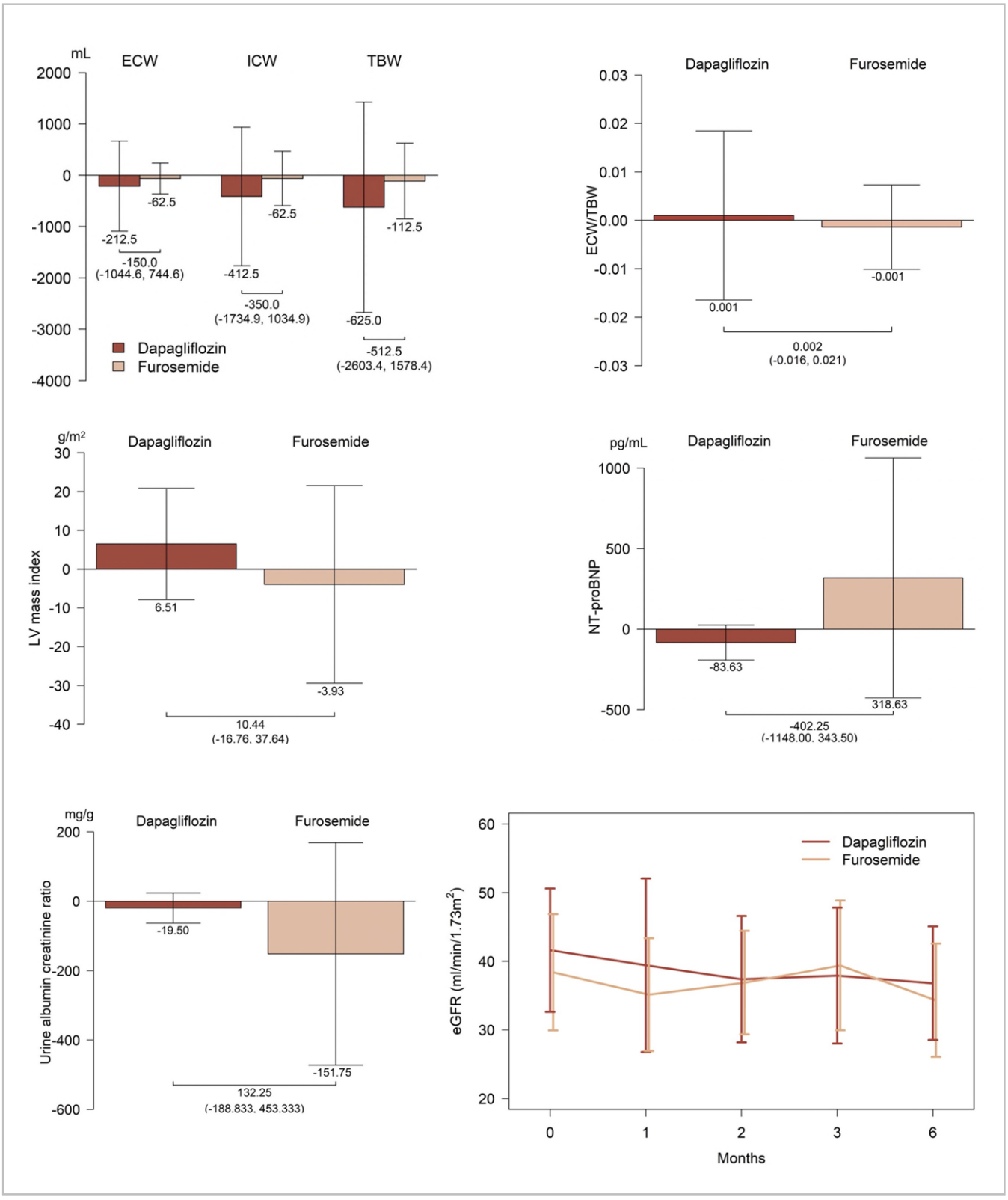

Figure 3. Secondary outcomes.

Primary outcome

In the dapagliflozin group, a reduction of 18 mmHg in SBP was found compared to a reduction of 7 mmHg in the furosemide group, which differ significantly statistically [95% CI -22.76 to 0.76, p = 0.02)]. dapagliflozin also reduced DBP by 9.75 mmHg compared to a reduction of 1.25 mmHg in the furosemide group, which did not differ significantly statistically [95% CI -17.95 to 0.95, (p = 0.99)], with a margin used 7 mmHg, as shown in Table 2.

Secondary outcomes

The dapagliflozin group achieved the target blood pressure of 100%, while the furosemide group achieved 75% (8 vs. 6, p = 0.47). In terms of fluid status, there was a decrease in extracellular water (ECW) with dapagliflozin, reducing ECW by 0.21 liter. In comparison, furosemide reduced it by 0.06 liter, with no significant statistical difference [95% CI -1.05 to 0.75, (p = 0.71)]. In terms of cardiac function, it was found that the dapagliflozin group decreased LVEF by 1.25% compared to an increase of 6.63% in the furosemide group, with no statistically significant difference [95% CI -16.10 to 0.35, (p = 0.06)]. Additionally, dapagliflozin increased LV mass index by 6.51 g/m^2 compared to a decrease of 3.93 g/m^2 in the furosemide group, with no statistically significant difference [95% CI -16.76 to 37.64, (p = 0.06)]. However, the dapagliflozin group, decreased NT-pro BNP levels by 83.63 pg/ml compared to an increase of 318.63 pg/ml in the furosemide group, with no statistically significant difference [95% CI -1148.00 to 343.50, (p = 0.23)]. Regarding renal outcomes in the third month, it was found that eGFR decreased by 3.73 mL/min/1.73 m^2 in the dapagliflozin group compared to an increase of 1.01 mL/min/1.73 m^2 in the furosemide group, with a statistically significant difference [95% CI -9.27 to -0.20, (p = 0.04)]. In the sixth month, it was found that eGFR decreased by 4.83 mL/min/1.73 m^2 in the dapagliflozin group compared to a decrease of 4.07 mL/min/1.73 m^2 in the furosemide group, with no statistical significant difference [95% CI -5.96 to 4.43, (p = 0.76)]. Changes in urine Na, UACR, urine volume, and body weight were not statistically significantly different between the two groups, as shown in Table 3. Additionally, there were no occurrences of hospitalized heart failure in either group.

Discussion

In our study, we aimed to compare the change in blood pressure between dapagliflozin and furosemide in patients with CKD with RHT. Both dapagliflozin and furosemide demonstrate the ability to reduce fluid retention and control blood pressure in CKD with RHT. It was found that in the dapagliflozin group, there was a statistically significant greater reduction in blood pressure compared to the furosemide group in the sixth month, which differed from the third month where both medications showed similar reductions in blood pressure. This difference could be due to diuretic resistance to furosemide, which might require an increase in the dosage of furosemide.

Regarding renal outcomes, it was observed that there was a greater decrease in eGFR in the dapagliflozin group compared to the furosemide group in the third month due to GFR dip, likely through the mechanism of reducing glomerular hyperfiltration. In the sixth month, it was observed that the slope of eGFR decline in the dapagliflozin group was lower than that in the furosemide group, as shown in Figure 3. In terms of cardiac outcomes, it was observed that the dapagliflozin group exhibited a trend towards reduced LVEF and increased LV mass index, but decreased NT-pro BNP compared to the furosemide group, although there was no statistically significant difference. These results are not clearly distinguished due to the short duration of follow-up. Additionally, there were no occurrences of hospitalized heart failure during the study period.

The strengths of our study include being the first randomized controlled trial to compare blood pressure reduction between dapagliflozin and furosemide in patients with CKD and resistant hypertension. We also utilized bioimpedance for assessing fluid status in patients and to guide treatment decisions.

However, our study has several limitations. Firstly, it is an unblinded randomized controlled trial because it was not feasible to manufacture identical pills for both treatments. Secondly, it is a small sample size study due to being conducted at a single center and limited research duration, resulting in insufficient power to explain outcomes adequately. The research

team believes that a multicenter study should be conducted to increase the sample size since there are limitations in the study duration.

Conclusions

Dapagliflozin was effective in controlling blood pressure comparable to furosemide in CKD patients with resistant hypertension and fluid retention. However, large-scale studies are warranted to further investigate and establish the comparative effectiveness of both drugs in the future.