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ORIGINAL ARTICLE
Heart Failure

Comparison of Canagliflozin, Dapagliflozin and Empagliflozin Added to Heart Failure Treatment in Decompensated Heart Failure Patients With Type 2 Diabetes Mellitus

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Background: Three sodium-glucose cotransporter-2 inhibitors (SGLT2i), canagliflozin, dapagliflozin and empagliflozin, successfully reduced hospitalization for heart failure (HF) in patients with type 2 diabetes mellitus (T2DM). It remains unclear, however, whether the efficacy of the 3 SGLT2i for HF in T2DM patients is similar.

Methods and Results: Eighty-one T2DM patients hospitalized due to decompensated HF were enrolled. After treatment for HF, one of the 3 SGLT2i was non-randomly used, and clinical parameters for HF and T2DM were followed for 7 days. The attending physician was allowed to adjust the dose of furosemide. No differences were observed between the 3 groups in the increase of glycosuria, or in the decreases of body weight and blood pressure 7 days after SGLT2i (interaction $P>0.05$). Urine volume was similarly increased on day 1, and returned to the baseline on day 7 in each group. Decrease in B-type natriuretic peptide and increase in plasma renin activity were significant in each group. Plasma aldosterone concentration, however, was significantly increased in the empagliflozin and canagliflozin groups ($P<0.01$, respectively), but not in the dapagliflozin group. Additionally, plasma noradrenaline was significantly increased in the empagliflozin group ($P<0.01$), but not in the canagliflozin and dapagliflozin groups.

Conclusions: The neurohumoral responses to the 3 SGLT2i are different under similar volume correction in HF patients with T2DM.

Key Words: Diabetes mellitus; Heart failure; SGLT2 inhibitor

Type 2 diabetes mellitus (T2DM) is closely associated with the onset and progression of cardiovascular disease and heart failure (HF).[1,2] Pharmacological and non-pharmacological treatments that improve the outcome for HF have been established, but T2DM as a comorbidity further worsens the prognosis in patients with HF.[3–5] Thus, intensive treatment for T2DM is considered to be beneficial for prevention of cardiovascular morbidity. Contrary to expectation, however, intensive treatment for T2DM including insulin, thiazolidine and dipeptidylpeptidase-4 inhibitors failed to improve the onset of cardiovascular events.[6–9]

Sodium glucose co-transporter-2 inhibitors (SGLT2i) reduce hyperglycemia by decreasing renal glucose reabsorption, thereby increasing urinary glucose excretion. To date, several large placebo-controlled cardiovascular outcome trials using 3 SGLT2i (canagliflozin, dapagliflozin and empagliflozin) have demonstrated significant reductions in mortality and HF hospitalization in patients with T2DM.[10–12] Given that SGLT2i could reduce blood pressure and body weight in addition to the original action of improving glycemic control, the 3 SGLT2i might exert a beneficial effect as a class effect on HF condition.[13,14] It remains unclear, however, whether the 3 SGLT2i are similarly effective for HF itself in patients with T2DM.

As a preliminary step in the observation of the long-term effectiveness of SGLT2i, it is necessary to confirm the efficacy and safety in the short term. Therefore, the goal of this study was to compare the short-term efficacy and safety of the 3 SGLT2i, canagliflozin, dapagliflozin and empagliflozin in acute decompensated HF patients with T2DM.

Methods

Subjects

This was a single-center, non-randomized, open-label study. This study involved 81 patients who were hospitalized due to decompensated HF complicated with T2DM at Toyama University Hospital. The inclusion criteria were as follows: (1) chronic HF with guideline-directed medical therapy including angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), β-blockers and diuretics; (2) glycated hemoglobin (HbA1c) before study intervention ≥6.1% in patients with T2DM; (3) age ≥20

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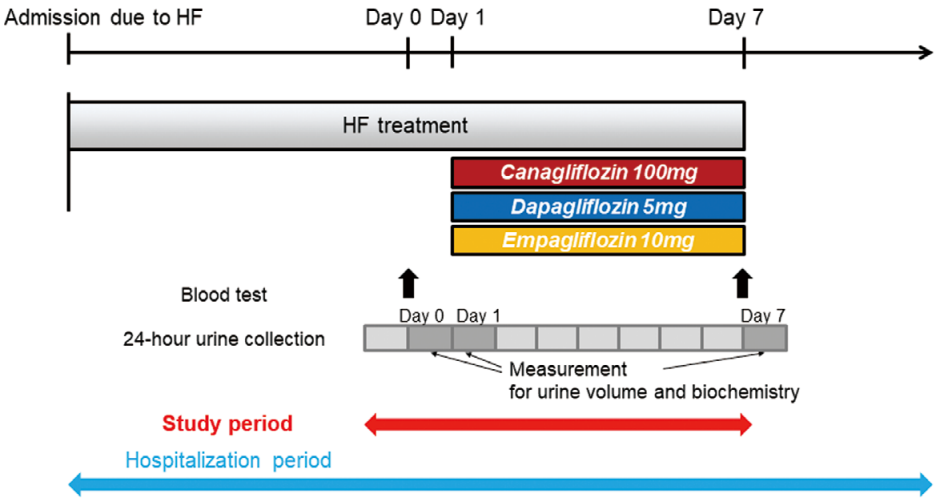

Figure 1. Study design. HF, heart failure

Table 1. Patient Demographic and Disease Characteristics

	Total (n=81)	Canagliflozin (n=34)	Dapagliflozin (n=24)	Empagliflozin (n=23)	P-value
Age (years)	72.6±13.2	74.2±10.7	71.6±15.6	71.4±14.1	0.810
Male	50 (62)	24 (71)	12 (50)	14 (61)	0.282
Body weight (kg)	59.1±14.8	58.7±14.4	61.4±14.0	57.4±16.5	0.702
BMI (kg/m^2)	23.3±4.3	22.9±4.0	24.8±4.3	22.5±4.7	0.092
HbA1c (%)	7.3±1.2	7.1±1.0	7.4±1.3	7.5±1.5	0.629
FBG (mg/dL)	134±55	133±53	144±64	124±49	0.501
LVEF (%)	43±18	44±19	44±17	41±18	0.811
IHD	34 (42)	15 (44)	9 (38)	10 (44)	0.868
DCM	11 (14)	5 (15)	5 (21)	1 (4)	0.249
VHD	11 (14)	6 (18)	2 (8)	3 (13)	0.592
HF treatment period (days)†	8.8±6.2	7.6±5.7	8.3±5.3	11.2±7.4	0.101
HF treatment					
β-blockers	71 (88)	31 (91)	19 (79)	21 (91)	0.321
ACEI/ARB	70 (86)	25 (74)	24 (100)	21 (91)	0.011
Loop diuretics	56 (69)	24 (71)	17 (71)	15 (65)	0.891
MRA	56 (69)	21 (62)	18 (75)	17 (74)	0.473
Thiazides	3 (4)	2 (6)	1 (4)	0 (0)	0.509
Tolvaptan	20 (25)	8 (24)	6 (25)	6 (26)	0.975
Anti-diabetic agents					
Sulfonylureas	7 (9)	2 (6)	4 (17)	1 (4)	0.244
DPP-4i	45 (56)	19 (56)	16 (67)	10 (44)	0.278
Biguanides	10 (12)	4 (12)	4 (17)	2 (9)	0.702
Insulin	10 (12)	4 (12)	3 (13)	3 (13)	0.989

Data given as mean±SD or n (%). †Time from hospitalization to the day before starting SGLT2i (baseline). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; DCM, dilated cardiomyopathy; DPP-4i, dipeptidyl peptidase-4 inhibitor; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium glucose co-transporter-2 inhibitor; VHD, valvular heart disease.

years at the time of obtaining consent; (4) oral meal intake; and (5) consent given, with sufficient understanding of the documents. Before enrollment, patients were also required to be hemodynamically stable, which was defined as (1) systolic blood pressure (SBP) ≥90 mmHg before the study; (2) no cardiogenic shock; (3) no dehydration; and (4) no use of i.v. vasodilators or inotropes during the preceding 24 h. Exclusion criteria were as follows: (1) previous use of SGLT2i; (2) severe infection, scheduled surgery, or recent serious trauma; (3) serious renal failure (estimated glomerular filtration rate <20 mL/min/1.73 m^2); (4) pregnancy or breastfeeding in the study period; (5) urinary tract

Table 2. Change in Clinical Parameters After 7 Days of SGLT2i Treatment

(n=81)	Baseline	Day 7	P-value
Vital signs			
SBP (mmHg)	112±14	108±15	0.004
DBP (mmHg)	64±11	61±10	0.057
Heart rate (beats/min)	73±13	70±12	0.003
Body weight (kg)	59.1±14.8	57.7±14.7	<0.001
Blood parameters			
Hemoglobin (g/dL)	12.6±2.4	13.0±2.3	<0.001
Hematocrit (%)	38.0±6.6	38.9±6.6	0.001
Serum albumin (g/dL)	3.3±0.4	3.6±0.4	<0.001
Total bilirubin (mg/dL)	0.7±0.4	0.8±1.3	0.397
Serum sodium (mEq/L)	138±3	137±3	<0.001
Serum potassium (mEq/L)	4.3±0.5	4.5±0.5	0.002
Serum creatinine (mg/dL)	1.07±0.40	1.20±0.49	<0.001
eGFR (mL/min/1.73 m^2)	55.6±24.2	49.9±22.4	<0.001
Serum insulin (μU/mL)	11.0±13.1	8.2±5.3	0.048
Plasma BNP (pg/mL)	324±280	228±242	<0.001
Plasma NT-proBNP (pg/mL)	2,778±3,456	2,339±3,505	<0.001
Plasma renin activity (ng/mL/h)	7.5±9.5	13.5±14.5	<0.001
Plasma aldosterone (pmol/L)	121±81	172±129	<0.001
Plasma noradrenaline (pg/mL)	371±206	426±243	0.016
24-h urine test			
Urine volume (mL/24 h)	1,270±604	1,330±461	0.358
Urine glucose (g/24 h)	2.6±9.4	25.5±25.9	<0.001
Loop diuretics dose (mg/day)	22±21	20±21	<0.001

Data given as mean±SD. BNP, b-type natriuretic peptide; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-b-type natriuretic peptide; SBP, systolic blood pressure; SGLT2i, sodium glucose co-transporter-2 inhibitor.

or genital infection; (6) history of hypersensitivity to the study drugs; (7) severe ketosis, diabetic coma or precoma; and (8) otherwise considered unsuitable by the attending physician. The Institutional Ethics Board of Toyama University Hospital approved the study protocol (Rin 29-94), which complied with the Declaration of Helsinki. Written informed consent was obtained from all of the patients in the study.

Study Design

The study design is shown in **Figure 1**. Of canagliflozin (100 mg/day), dapagliflozin (5 mg/day) and empagliflozin (10 mg/day), 1 drug was non-randomly selected and given for 7 days. After clinical stabilization for HF, 24-h urine collection was begun 1 day before the examination date (day 0). Blood pressure and heart rate measured at 10:00, 14:00 and 18:00 hours, body weight before breakfast and physical examination for HF were obtained daily throughout the study. The 3 blood pressure and heart rate measurements were averaged. Data were obtained as follows. Vital signs, body weight and blood test were measured on day 0 (baseline) and day 7. Urine volume and urine biochemistry were measured using the urine sample on the day before initiation of SGLT2i (baseline); and at 1 day and 7 days of SGLT2i treatment (day 1 and day 7). Blood test parameters were as follows: Hb, hematocrit, albumin, total bilirubin, blood urea, creatinine, sodium, potassium, B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), insulin, plasma renin activity, plasma aldosterone concentration and plasma noradrenaline. Blood glucose was measured at 7 different time points on baseline and day 7. Urine glucose was measured using 24-h urine. Treatment for HF was not changed throughout the study period, except for minimal loop diuretic dose adjustment at the discretion of the attending physician to avoid excessive diuretic response after SGLT2i treatment. Chest radiograph was also assessed on baseline and at day 7 for cardiothoracic ratio, the degree of pulmonary congestion and pleural effusion.

Statistical Analysis

Continuous variables are expressed as mean±SD. Considering the skewed data distribution, plasma renin activity, plasma BNP and serum NT-proBNP were log transformed for analysis. Paired t-test was used to compare parameters before and after SGLT2i treatment. One-way repeated-measures analysis of variance was applied to determine whether baseline parameters differed between the 3 SGLT2i. Two-way repeated-measures analysis of variance was applied to determine whether (1) the 3 SGLT2i have a similar effect on clinical parameters during the time course; and (2) all SGLT2i have the same effect on BNP regardless of clinical characteristics before and 7 days after SGLT2i. The Bonferroni-Dunn procedure was used for multiple comparisons. Statistical analysis was performed using SigmaPlot 14.0 (Systat Software, San Jose, CA, USA). Sample size calculation was performed using GPower version 3.1.9.4. To detect significance with an alpha level of 0.05, and a power of 0.80 using 2-way repeated-measures analysis of variance, 22 patients in each group were required. The level of significance was set at $P<0.05$.

Table 3. Change in Clinical Parameters vs. Type of SGLT2i

	Baseline	Day 7	P-value	P interaction
SBP (mmHg)	112±14	108±15	0.004	0.924
Canagliflozin (n=34)	111±15	108±15	0.084	
Dapagliflozin (n=24)	115±15	111±15	0.056	
Empagliflozin (n=23)	108±13	105±14	0.160	
Heart rate (beats/min)	73±13	70±12	0.003	0.136
Canagliflozin (n=34)	72±14	71±12	0.640	
Dapagliflozin (n=24)	73±14	70±12	0.009	
Empagliflozin (n=23)	75±11	70±11	0.014	
Body weight (kg)	59.1±14.8	57.7±14.7	<0.001	0.576
Canagliflozin (n=34)	58.7±14.4	57.2±14.4	<0.001	
Dapagliflozin (n=23)	61.4±14.0	60.2±14.2	<0.001	
Empagliflozin (n=23)	57.4±16.5	56.0±16.1	<0.001	
Hemoglobin (g/dL)	12.6±2.4	13.0±2.3	<0.001	0.548
Canagliflozin (n=34)	12.6±2.2	12.9±2.2	0.082	
Dapagliflozin (n=24)	12.5±2.9	12.8±2.8	0.052	
Empagliflozin (n=23)	12.8±2.1	13.3±2.1	0.005	
Hematocrit (%)	38.0±6.6	38.9±6.6	0.001	0.517
Canagliflozin (n=34)	38.0±6.1	38.7±6.3	0.167	
Dapagliflozin (n=24)	37.7±8.4	38.7±8.1	0.051	
Empagliflozin (n=23)	38.2±5.7	39.6±5.4	0.010	
Serum albumin (g/dL)	3.3±0.4	3.6±0.4	<0.001	0.376
Canagliflozin (n=34)	3.4±0.4	3.6±0.4	<0.001	
Dapagliflozin (n=24)	3.3±0.5	3.5±0.5	<0.001	
Empagliflozin (n=23)	3.3±0.3	3.6±0.4	<0.001	
Serum sodium (mEq/L)	138±3	137±3	<0.001	0.556
Canagliflozin (n=34)	138±3	137±4	0.004	
Dapagliflozin (n=24)	138±4	137±3	0.178	
Empagliflozin (n=23)	139±3	137±3	0.007	
Serum potassium (mEq/L)	4.3±0.5	4.5±0.5	0.002	0.249
Canagliflozin (n=34)	4.2±0.4	4.3±0.4	0.265	
Dapagliflozin (n=24)	4.4±0.4	4.5±0.5	0.117	
Empagliflozin (n=23)	4.3±0.6	4.6±0.6	0.003	
Serum creatinine (mg/dL)	1.07±0.40	1.20±0.49	<0.001	0.909
Canagliflozin (n=34)	1.10±0.45	1.22±0.54	<0.001	
Dapagliflozin (n=24)	1.10±0.34	1.24±0.47	<0.001	
Empagliflozin (n=23)	1.00±0.38	1.12±0.43	0.001	
eGFR (mL/min/1.73 m^2)	55.6±24.2	49.9±22.4	<0.001	0.621
Canagliflozin (n=34)	55.8±22.5	50.7±22.6	<0.001	
Dapagliflozin (n=24)	51.5±24.6	46.5±23.1	0.003	
Empagliflozin (n=23)	59.4±26.4	52.3±21.9	<0.001	

Data given as mean±SD. Abbreviations as in Table 2.

Results

Baseline Patient Characteristics

After a median HF treatment period of 7 days (range, 1–24 days), lower limb edema and dyspnea were improved in most patients. The baseline characteristics of all patients and according to subgroup are listed in **Table 1**. Canagliflozin was used in 34 patients, dapagliflozin in 24 patients and empagliflozin in 23 patients. Patient background did not differ significantly between the 3 SGLT2i groups, except for use of renin-angiotensin system (RAS) inhibitors (P=0.011). Mean fasting blood glucose and HbA1c were 134 mg/dL and 7.3%, respectively. The etiology of HF was ischemic in 42% and non-ischemic in 58%. Reduced left ventricular ejection fraction (<40%) was noted in 40 patients (50%); mid-range ejection fraction (40–49%), in 14 patients (17%); and preserved ejection fraction (≥50%) in 27 patients (33%). Approximately 86% of the patients were treated with RAS inhibitors. Seventy patients (86%) were treated with β-blockers. Mineral corticoid receptor antagonists were used in 56 patients (69%), loop diuretics in 56 patients (69%), and tolvaptan in 20 patients (25%). The use of sulfonylurea, dipeptidase-4 inhibitor, biguanide, and insulin was noted in 9%, 56%, 12%, and 12% of patients, respectively. Thirty-two patients (40%) had no anti-diabetic agents.

Effect of SGLT2i on Clinical Parameters

Total Patient Group Change in clinical parameters after 7 days of SGLT2i treatment is given in **Table 2** (n=81).

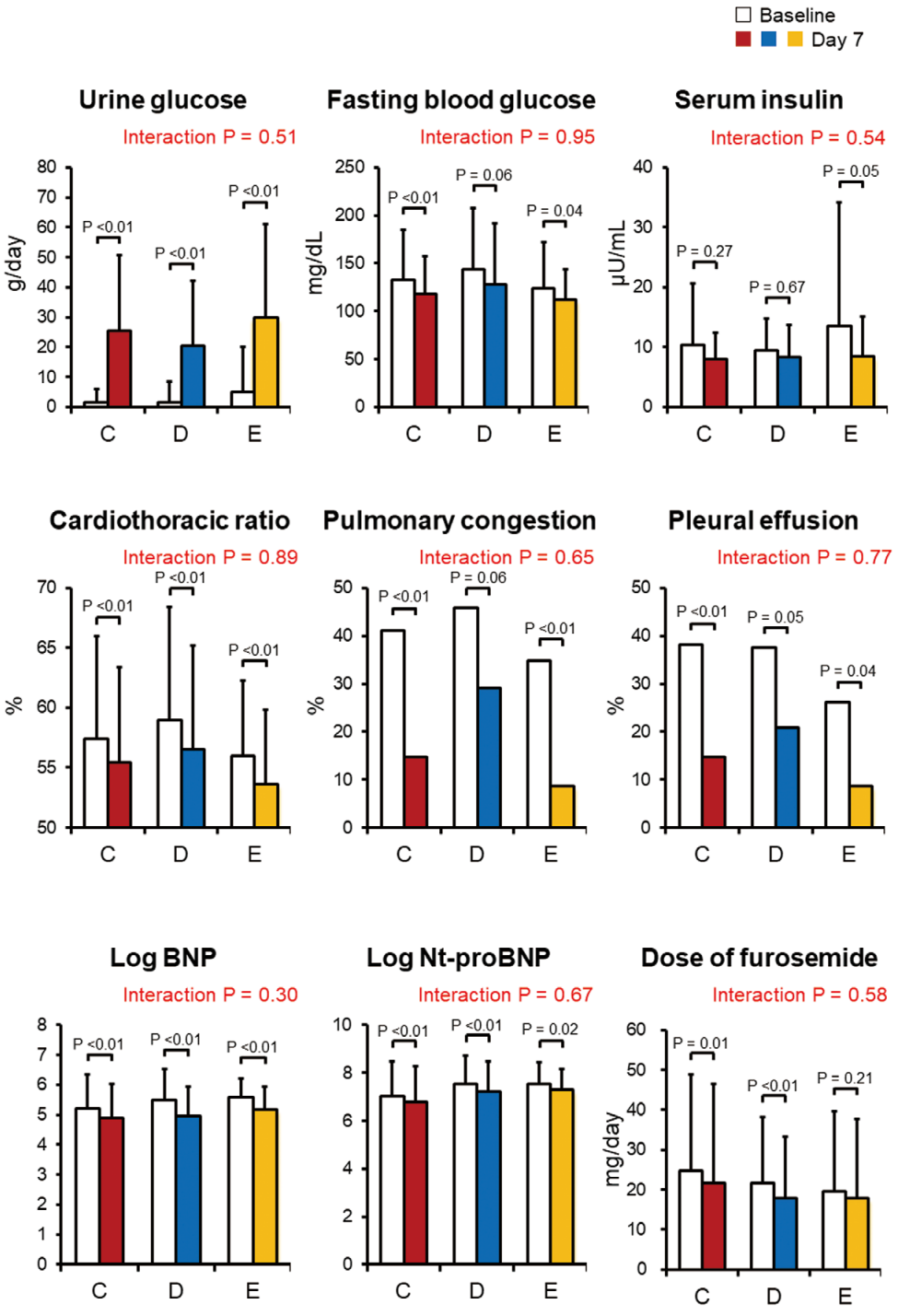

Figure 2. Clinical parameters and chest radiograph before and after 7 days of canagliflozin (C), dapagliflozin (D) and empagliflozin (E) treatment. BNP, b-type natriuretic peptide; NT-proBNP, N-terminal pro-b-type natriuretic peptide.

After SGLT2i, urine glucose excretion was increased, and average blood glucose and fasting blood glucose were decreased significantly (193±63 to 178±61 mg/dL, P=0.01; 134±55 to 119±46 mg/dL, P<0.01, respectively). SBP, body weight and body mass index were also decreased significantly. Importantly, heart rate was also decreased significantly in spite of reduced blood pressure.

SGLT2i Subgroups Clinical parameters at baseline and at day 7 are listed separately for each SGLT2i group (**Table 3**; **Figures 2–4**). No differences were observed between the 3 groups in the increase of glycosuria, or in the decreases of body weight and blood pressure 7 days after SGLT2i. Fasting blood glucose decreased in the canagliflozin and empagliflozin groups and tended to decrease

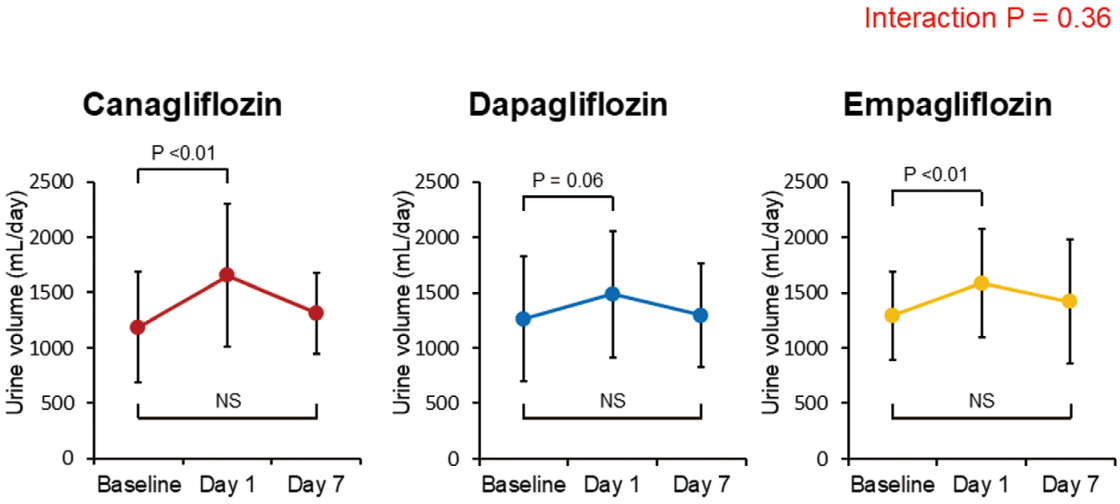

Figure 3. Time course of urine volume in canagliflozin, dapagliflozin and empagliflozin groups during 7 days of treatment.

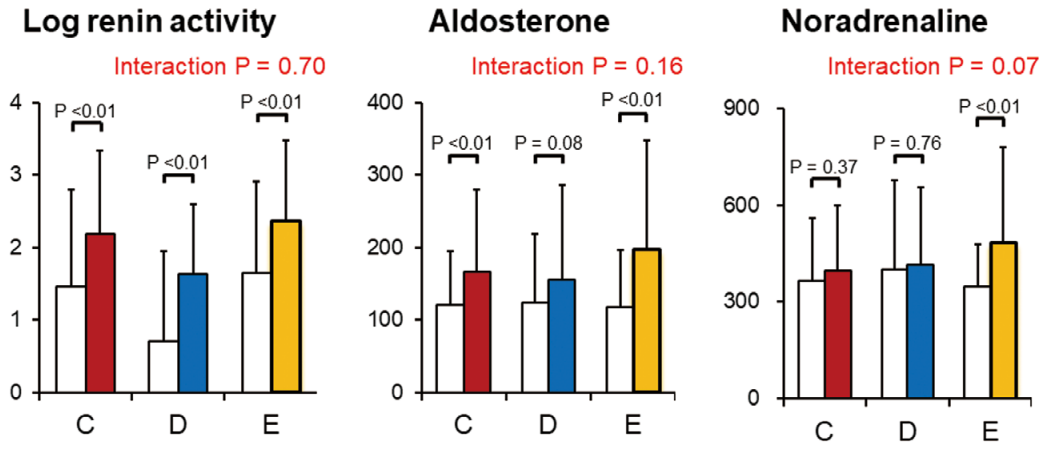

Figure 4. Logarithmic plasma renin activity, plasma aldosterone concentration and plasma noradrenaline level before and after 7 days of canagliflozin (C), dapagliflozin (D) and empagliflozin (E) treatment.

in the dapagliflozin group (**Figure 2**). Change in serum insulin, however, did not reach statistical significance in any group (**Figure 2**). The changes in fasting blood glucose and serum insulin were also not significantly different between the 3 groups (P for interaction=0.95 and 0.54, respectively; **Figure 2**).

The increase in urine volume from baseline to day 1 did not reach statistical significance in the dapagliflozin group (P=0.06), but in each group the urine volume increase on day 1 was similar, and returned to baseline on day 7 in each group (P for interaction=0.36; **Figure 3**). Although the furosemide dose was reduced in 17% of patients, prevalence of pulmonary congestion, and the cardiothoracic ratio and BNP were decreased similarly in the 3 groups (P for interaction=0.30; **Figure 2**). Logarithmic plasma renin activity was also increased similarly in the 3 groups (P for interaction=0.70; **Figure 4**). Plasma aldosterone concentration, however, was significantly increased in the empagliflozin and canagliflozin groups, but not in the dapagliflozin group (P for interaction=0.16). Additionally, plasma noradrenaline was significantly increased in the empagliflozin group, but not in the canagliflozin or dapagliflozin groups (P for interaction=0.07). Importantly, the significant change in plasma noradrenaline level in the empagliflozin group was consistently observed when the analysis was performed in the limited patients in whom furosemide was not changed (n=67, **Supplementary Figure**).

Effect of SGLT2i on Plasma BNP

To determine whether SGLT2i are consistently effective on HF status, effect of SGLT2i on BNP level was compared in several subgroups of patients according to clinical characteristics (**Table 4**). In the total group, SGLT2i reduced BNP by 30% (P<0.01) with similar benefit in the

Table 4. Change in Log BNP After 7 Days of SGLT2i Treatment

	Baseline	Day 7	P-value	P interaction
Age				
≤75 years (n=45)	5.24±1.07	4.74±1.05	<0.001	0.051
>75 years (n=36)	5.56±0.89	5.29±0.87	0.002	
Sex				
Male (n=50)	5.36±1.10	5.00±1.06	<0.001	0.333
Female (n=31)	5.43±0.82	4.96±0.93	<0.001	
HbA1c				
<6.9% (n=40)	5.42±1.18	5.01±1.19	<0.001	0.898
≥6.9% (n=41)	5.35±0.80	4.95±0.80	<0.001	
Fasting blood glucose				
<126 mg/dL (n=46)	5.39±1.08	4.97±1.09	<0.001	0.795
≥126 mg/dL (n=35)	5.38±0.90	5.00±0.90	<0.001	
BMI				
<23 kg/m^2 (n=40)	5.66±0.76	5.23±0.87	<0.001	0.663
≥23 kg/m^2 (n=40)	5.06±1.09	4.68±1.02	<0.001	
LVEF				
<40% (n=40)	5.58±0.99	5.21±1.07	<0.001	0.659
≥40% (n=41)	5.20±0.99	4.77±0.91	<0.001	
Blood pressure				
SBP ≥110 mmHg (n=39)	5.15±1.11	4.65±1.10	<0.001	0.085
SBP <110 mmHg (n=42)	5.60±0.85	5.30±0.81	<0.001	
Baseline eGFR				
<60 mL/min/1.73 m^2 (n=52)	5.60±0.86	5.21±0.92	<0.001	0.860
≥60 mL/min/1.73 m^2 (n=29)	4.99±1.12	4.58±1.04	<0.001	
Baseline urine albumin				
<15 mg/24 h (n=39)	5.28±1.12	4.96±1.00	<0.001	0.197
≥15 mg/24 h (n=39)	5.43±0.84	4.96±1.00	<0.001	
Baseline plasma BNP				
<260 pg/mL (n=41)	4.58±0.79	4.33±0.85	0.001	0.047
≥260 pg/mL (n=40)	6.21±0.40	5.65±0.71	<0.001	
Baseline ACEI/ARB				
Yes (n=70)	5.42±1.01	4.99±1.04	<0.001	0.210
No (n=11)	5.14±0.94	4.92±0.76	0.181	
Baseline β-blockers				
Yes (n=71)	5.32±1.00	4.93±0.99	<0.001	0.563
No (n=10)	5.86±0.89	5.37±1.11	0.004	
Baseline MRA				
Yes (n=56)	5.56±0.91	5.17±0.87	<0.001	0.788
No (n=25)	5.00±1.09	4.57±1.18	<0.001	
Baseline loop diuretics				
Yes (n=56)	5.66±0.88	5.25±0.92	<0.001	0.850
No (n=25)	4.78±1.01	4.40±0.96	<0.001	

Data given as mean±SD. Abbreviations as in Tables 1,2.

patients divided into 2 groups according to age, gender, DM control, renal function and ejection fraction (P for interaction >0.05). In contrast, BNP was decreased more significantly in patients with higher baseline BNP compared with patients with lower baseline BNP (P for interaction =0.047).

Adverse Events

All adverse events are listed in **Supplementary Table**. The incidence rate of adverse events was 7% (6/81) in total, including 6% (2/34) in the canagliflozin group, 4% (1/24) in the dapagliflozin group and 13% (3/23) in the empagliflozin group. There was no difference between the 3 groups in the prevalence of adverse effects (P=0.46). No symptomatic hypoglycemia was observed in the study period. Urinary tract infection was observed in only 1 patient using empagliflozin during the study period. Asymptomatic hyperkalemia (potassium >5.5 mEq/L) was observed in 1 patient using empagliflozin.

Discussion

This is the first study to compare the 3 SGLT2i added to HF treatment in decompensated HF patients with T2DM. The major findings were as follows. Urine glucose excretion was increased and blood glucose level was decreased

similarly in the 3 SGLT2i groups. The time course of urine volume was also similar between the 3 groups, as evidenced by the increase on day 1 and the return to baseline on day 7. The signs of HF and levels of BNP and NT-proBNP were also similarly improved on day 7 between the 3 SGLT2i. Plasma renin activity was also significantly increased in the 3 groups. Plasma aldosterone concentration, however, was significantly increased in the empagliflozin and canagliflozin groups, but not in the dapagliflozin group. Additionally, plasma noradrenaline level was increased in the empagliflozin group, but not in the canagliflozin and dapagliflozin groups. Last, the impact of SGLT2i on BNP level was consistent in the HF patient subgroups. This suggests that the neurohumoral responses to the 3 SGLT2i are different under similar volume correction in HF patients with T2DM.

SGLT2i Have Volume-Correcting Effects

In a meta-analysis of 3 large placebo-controlled cardiovascular outcome trials, canagliflozin, dapagliflozin, and empagliflozin were shown to reduce HF hospitalization with or without a history of HF.[15] Several studies have investigated the effects of SGLT2i in HF patients with T2DM. Takeuchi et al investigated the effect of ipragliflozin on HF status in 20 patients with T2DM.[16] Urine volume was increased from day 1 to day 3 and BNP level was decreased on day 3. The present finding of increased urine volume on day 1 was consistent with the Takeuchi et al study, but in the present study it decreased back down to baseline by day 7. Although the increase in urine volume was transient, BNP level was decreased similarly in the 3 SGLT2i groups. Seo et al demonstrated the effect of 3 SGLT2i on HF status in 12 patients with T2DM for 6 months.[17] They showed that the cardiothoracic ratio, the prevalence of pulmonary congestion and BNP were significantly reduced at 1 month and persisted even at 6 months. It was not clear, however, whether the 3 SGLT2i were equally effective. In the present study the 3 SGLT2i patient groups had similarly reduced body weight, cardiothoracic ratio, and prevalence of pulmonary congestion on day 7.

Differing SGLT2i Neurohumoral Effect

Because body weight, BNP and NT-proBNP were decreased after 7 days of drug treatment, fluid loss must have been induced at the same time in the 3 groups. Importantly, fluid loss itself generally leads to neurohumoral activation. Consistently, plasma renin activity and plasma aldosterone concentration were increased in the empagliflozin and canagliflozin groups. Plasma noradrenaline was also increased in the empagliflozin group. Contrary to expectation, plasma aldosterone concentration and plasma noradrenaline level were unchanged in the dapagliflozin group in the present study. In the previous study using ipragliflozin for HF patients with T2DM, plasma renin activity was increased, but plasma aldosterone concentration and plasma noradrenaline level were unchanged.[16] The divergence between the 3 groups is interesting, and we discuss this further here.

Because the 3 agents differ in the selectivity of SGLT1/SGLT2 and the duration of action,[18] the effect of SGLT2i on HF is possibly different. Of the 3 agents, the selectivity of SGLT1/SGLT2 for canagliflozin is relatively low, while the selectivity for empagliflozin is relatively high, and the selectivity for dapagliflozin is intermediate. The selectivity of SGLT1/SGLT2 for ipragliflozin is also relatively low. Urine sugar excretion and urine volume are increased in both SGLT2 and SGLT1 knockout mice compared with SGLT2 alone knockout mice.[19] If the selectivity of SGLT1/SGLT2 inhibition is relatively lower, the fluid reduction effect might be stronger, which might result in a further decrease in BNP. Contrary to such an expectation, however, no clear differences were found between the 3 SGLT2i. This suggests that the differences in SGLT1/SGLT2 selectivity with regard to HF benefit may not be so important between these 3 SGLT2i.

SGLT2i with a longer-acting duration might result in a longer diuretic action via the increase of urinary sugar and urine volume. While dapagliflozin and ipragliflozin are long-acting, canagliflozin and empagliflozin are considered to have an intermediate duration of action.[20] With regard to loop diuretics, long-acting azosemide was useful for the improvement of neurohumoral factors compared with short-acting furosemide in patients with HF.[21] Moreover, azosemide also has a less sympathetic overactivation than furosemide in the experimental setting.[22] The fact that both dapagliflozin and ipragliflozin did not increase the plasma aldosterone and noradrenaline levels suggests that long-acting SGLT2i might be related to the beneficial effect in HF.

Neurohumoral activation is usually detrimental to the long-term prognosis of HF.[23,24] In the present study, plasma noradrenaline level was increased in the empagliflozin group, but not in the canagliflozin and dapagliflozin groups. In contrast, in the previous study, empagliflozin reduced the number of hospitalizations for HF on long-term use.[10] This can be interpreted as meaning that the difference in short-term response to neurohumoral factors does not directly lead to long-term prognosis.

Although SBP tended to be decreased, heart rate decreased significantly in each SGLT2i group in the present study, even though heart rate should be increased in the situation of high pressure receptor unloading in baroreceptors in the aortic arch and carotid receptor. A plausible explanation for this contradictory finding is that SGLT2i might be causing baroreflex resetting. Further study is needed to clarify this point.

Complementary Effect of SGLT2i and HF Treatment

The short-term effect of SGLT2i on clinical parameters with and without 2 types of diuretics (loop diuretics or thiazide) in T2DM patients without HF has been investigated previously.[25] Urinary sodium excretion and urine volume did not change in the SGLT2i or diuretics alone groups, but significantly increased when SGLT2i were given with diuretics. In the present study, urinary sodium excretion was significantly decreased in the patients without loop diuretics. It was unchanged, however, in patients in whom the loop diuretics dose was unchanged during the study period (data not shown). SGLT2i, which act on a different site to that of loop diuretics and thiazides, suppress the co-transport of glucose and sodium from the tubular lumen of the proximal tubules to the blood.[26] Decrease of urinary sodium excretion 7 days after SGLT2i alone might reflect the compensatory absorption of sodium at Henle's loop or in the distal tubules in patients with HF. In contrast, co-treatment of SGLT2i and diuretics might act on diuresis complementarily via double blocking of the proximal tubules and Henle's loop or distal tubules. Because loop diuretics are prescribed to the vast majority of patients with HF, SGLT2i might be effective in DM patients with

HF. In subgroup analyses of CANVAS program, HF hospitalization events were decreased in the group with diuretics, but not in the group without it.[27]

Study Limitations

First, a control group was not used in the present study. Thus, it is not possible to compare the neurohumoral response to the 3 SGLT2i with that of standard diuretics (e.g., furosemide). The differing neurohumoral response, however, was confirmed in this small population study, at least in part. Second, the noradrenaline level was increased in the empagliflozin group, but it is unclear whether the change is fully reflected in the enhancement of sympathetic nerve activity. In a previous study, empagliflozin did not change sympathetic neural activity as determined on microneurography, despite the decrease in blood pressure in T2DM patients without HF.[28] Further study using microneurography is warranted to confirm the differing sympathetic nerve activity among the SGLT2i in T2DM patients with HF. Third, changes in BNP after SGLT2i were not different between the groups with higher and lower HbA1c, but it remains undetermined whether SGLT2i are also effective even in patients without DM. Currently, clinical research on the effectiveness of empagliflozin in HF patients without DM is ongoing. Last, the number of patients was small and the observation period was only 1 week. Further studies are warranted to facilitate definitive conclusions.

Conclusions

The neurohumoral response to the 3 SGLT2i differs under similar volume correction in HF patients with T2DM.

Disclosures

K.K. is a member of *Circulation Reports*' Editorial Team. The other authors declare no conflicts of interest.

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Supplementary Files

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