Clinical Considerations When Introducing Sodium-Glucose Co-Transporter 2 Inhibition in Patients With Heart Failure

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Background: In patients with heart failure (HF), discontinued medical therapy because of adverse events (AE) is associated with high mortality. Patients with type 2 diabetes mellitus (T2DM) treated with sodium-glucose co-transporter 2 inhibitors (SGLT2i) have a lower risk of HF, but AE sometimes occur with the introduction of SGLT2i. In order to use SGLT2i safely in patients with HF, we investigated factors associated with AE following the introduction of SGLT2i.

Methods and Results: AE were defined as hypotension or an increase in serum creatinine ≥0.3 mg/dL by the fifth day after SGLT2i introduction. Sixty-four hospitalized patients with HF and T2DM treated with an SGLT2i were enrolled in this study. Patients were divided into 2 groups: with AE (n=13, 20.3%) and without (n=51, 79.7%). On logistic regression analysis, female sex, hemoglobin ≥15.2 g/dL, serum creatinine ≥1.05 mg/dL, and cardiac index on echocardiography ≤2.15 L/min/m², were significantly associated with AE. A scoring system was constructed to predict AE according to significant variables (area under the receiver operating characteristic curve, 0.83; P<0.001) and the cut-off point was 2 points.

Conclusions: Female sex, hemoconcentration, kidney injury, and low cardiac output were associated with AE at SGLT2i initiation in patients with HF. Using this scoring system, introduction of SGLT2i could be done safely in patients with HF.

Key Words: Heart failure; Hemoconcentration; Kidney injury; Low cardiac output; Sodium-glucose co-transporter 2 inhibitor

Cardiovascular risk and mortality in patients with diabetes mellitus (DM) are higher than in those without DM. Heart failure (HF) is a rapidly increasing cardiovascular disease. DM is closely associated with poor prognosis in patients with HF. Therefore, an appropriate therapeutic approach is needed in patients with DM and HF. In large randomized trials, patients with type 2 DM (T2DM) treated with sodium-glucose co-transporter 2 inhibitors (SGLT2i) had a lower risk of cardiovascular events than those treated with placebo. These effects of SGLT2i treatment on cardiovascular outcomes were similar in patients with HF at baseline. Therefore, major guidelines have recommended the use of SGLT2i in patients with T2DM and cardiovascular disease including HF.

In patients hospitalized due to HF, hypotension after the introduction of medical therapy is a risk factor for adverse outcomes. Similarly, worsening renal function (WRF) during treatment in patients with congestive HF is also associated with poor prognosis. Hospitalized patients with HF who have discontinued and/or decreased guideline-directed medications (GDMT) because of adverse events (AE), such as hypotension and/or WRF, have higher rates of post-discharge mortality. Therefore, it is very important to begin GDMT without AE in patients with HF. Also, decreased blood pressure (BP) and renal function have been observed following the initiation of SGLT2i treatment. In addition, severe hypotension and/or renal dysfunction have been reported to occur occasionally following initiation of SGLT2i. In order to continue SGLT2i, it is necessary to avoid and reduce AE at the time of introduction, but, because there are few data on the introduction of SGLT2i treatment, clinical background and factors associated with AE following SGLT2i introduction are still unknown. Thus, the aim of the present study was to investigate factors related to AE and transition of clinical parameters after initiation of SGLT2i in patients with HF.
Methods

Subjects
This was a single-center observational study of patients admitted to Kitasato University Hospital in Japan between September 2014 and November 2018. Eighty-eight hospitalized patients with HF and T2DM defined as hemoglobin A1c ≥6.5% or fasting blood glucose ≥126 mg/dL who were started on SGLT2i were enrolled in this study. All patients received conventional HF treatment and dietary support.

AE were classified as hypotension (decrease in systolic BP [SBP] ≥10 mmHg and SBP ≤90 mmHg or symptomatic hypotension) or an increase in serum creatinine ≥0.3 mg/dL by the fifth day after SGLT2i introduction. Exclusion criteria included treatment with infusion therapy and a change in medication 2 days before and 5 days after SGLT2i initiation. Patients who were unable to be followed for 5 days were also excluded from the study. The study protocol was approved by the institution committee on human investigations, and written informed consent was obtained from all patients prior to study initiation.
Predictors for AE on SGLT2i Use in HF

On echocardiography, left ventricular (LV) volumes were...
calculated using the biplane method of disk summation (modified Simpson’s rule), and the LV ejection fraction (LVEF) was measured as the difference between the end-diastolic volume and end-systolic volume.\textsuperscript{16} LV outflow tract (LVOT) diameter data were obtained at mid-systole at the point of entry of aortic valve cusps. LVOT peak velocity and velocity-time integral (VTI) measurements were obtained from the apical 5-chamber view with pulsed wave Doppler sample placed in the LVOT immediately below the hinge points of the aortic valve leaflets. Stroke volume (SV), cardiac output, and cardiac index were calculated as follows: \( SV = VTI \times \text{LVOT area} \), where \( \text{LVOT area} = \pi \left( \frac{\text{LVOT diameter}}{2} \right)^2 \); cardiac output = \( SV \times \text{heart rate} \); cardiac index = cardiac output/body surface area.\textsuperscript{17}

Pulmonary congestion score and plasma volume status (PVS) were used as indicators of change in body fluid volume during the study period. Pulmonary congestion score was measured on chest X-ray. The lower, middle, and upper segments of each lung were scored in the upright position. The grades of congestion were defined as follows: 0, normal; 1, perihilar haze, peribronchial cuffing, or septal lines only; 2, localized or mild confluent density increase; and 3, intense confluent density increase. These values were then summed into the pulmonary congestion score.\textsuperscript{18} Conversely, PVS was calculated using body weight and hematocrit. Actual PV (aPV) was calculated using hematocrit and weight: \( aPV = (1 - \text{hematocrit}) \times (a + bx\text{weight in kg}) \) where hematocrit is a fraction, and \( a = 1,530 \) and 864, while \( b = 41 \) and 47.9 in male and female patients, respectively. Ideal PV (iPV) was calculated using weight: \( iPV = c \times \text{weight} \) where \( c = 39 \) in male patients and \( c = 40 \) in female patients. Relative PVS, an index of the degree of deviation from iPV, was subsequently calculated from the following equation: \( \text{PVS} = \left[ \frac{aPV - iPV}{iPV} \right] \times 100 \% . \textsuperscript{19} \)

Statistical Analysis
Data are presented as mean±SD or as frequency (percentage). Intergroup comparison was done using the Student’s t-test. Pearson’s chi-squared test was used to evaluate categorical variables. The paired-sample t-test was used to compare continuous variables at day −2 and day 5 of SGLT2\textsuperscript{i} introduction. McNemar test was used to compare categorical variables before–after SGLT2\textsuperscript{i} introduction.
Predictors for AE on SGLT2i Use in HF

Baseline Characteristics Before Initiation of SGLT2i

Sixty-four patients met the inclusion criteria for this study. Enrolled patients were divided into 2 groups: those with AE (AE group; n=13, 20.3%) and those without AE (non-AE group, n=51, 79.7%; Figure 2). AE included in the study were SBP ≤90 mmHg (n=4), symptomatic hypotension (n=1), and an increase in serum creatinine ≥0.3 mg/dL (n=9; including duplication). Baseline characteristics are listed in Table 1. BP, heart rate, 24-h urine volume, and medication including diuretics at baseline were not significantly different between the 2 groups. There were more female patients in the AE group than in the non-AE group. Hemoglobin and serum creatinine were higher in the AE group than in the non-AE group. On echocardiography, LVEF and LV dimensions were not significantly different between the 2 groups, but both the cardiac output and cardiac index were lower in the AE group than in the non-AE group.

Change in Laboratory and Urinary Parameters

Absolute change in laboratory and urinary parameters from day 0 (or day −2) to day 4 are shown in Figure 3. In both groups, blood glucose level decreased (Figure 3A) and 24-h urinary glucose significantly increased (Figure 3B) after introduction of SGLT2i. Hemoglobin level was significantly increased after introduction of SGLT2i (Figure 3C). Serum creatinine was significantly higher after introduction of SGLT2i (Figure 3D). The increase in creatinine was significantly larger in the AE group than in the non-AE group from day 0 to day 4. The median decrease in estimated glomerular filtration rate (eGFR) was 13.0% (IQR, 3.62–19.1) following introduction of SGLT2i. The 24-h urine volume was significantly larger only in the non-AE group on day 1 and day 2 (Figure 3E). Brain natriuretic peptide

Two-tailed P<0.05 was considered to indicate statistical significance.

Multivariable logistic regressions analysis was performed to identify variables related to AE from among the baseline variables. To select the optimal subset of covariates for the multivariate analysis, a stepwise variable selection approach was adopted with forward selection that optimized Akaike information criterion. Considering the variables that were significantly different between patients with and without AE at baseline, we defined a risk scoring system based on the summation of scores. In constructing categorical variables from continuous data, a cut-off point was obtained using receiver operating characteristic (ROC) analysis. The ROC curve of the new score was used to predict AE, and the area under the curve for the new score was calculated. JMP version 13 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

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Change in Body Fluid Volume

Absolute changes observed in body fluid volume are shown in Figure 5. Body weight significantly decreased in the non-AE group after introduction of SGLT2i (Figure 5A). Pulmonary congestion scores significantly decreased in the non-AE group from day 0 to day 4 (Figure 5B). In both groups, PVS significantly decreased from day 0 to day 4 (Figure 5C).

Factors Associated With AE

On multivariate analysis, female sex (OR, 6.62; 95% CI: 1.30–33.64; P=0.023) and serum creatinine (per 0.2-mg/dL increase: OR, 2.75; 95% CI: 1.39–5.43; P=0.004) were independent factors associated with AE. We constructed a

Table 2. Multivariate Indicators of Adverse Events

| Variables                          | Model 1 |       |       | Model 2 |       |       |
|------------------------------------|---------|-------|-------|---------|-------|-------|
|                                    | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Female sex                         | 6.62 (1.30–33.64) | 0.023 | 14.62 (1.36–157.50) | 0.027 |
| Serum creatinine (per 0.2-mg/dL increase) | 2.75 (1.39–5.43) | 0.004 |         |       |
| Cardiac index (L/min/m²)           | 9.04 (1.19–68.74) | 0.033 |         |       |

Figure 5. Change in (A) body weight, (B) pulmonary congestion score, and (C) plasma volume status in hospitalized patients with heart failure and type 2 diabetes mellitus treated with sodium-glucose co-transporter 2 inhibitors, according to adverse event (AE) status. Data given as mean±SE. *P<0.05, **P<0.01, non-AE group vs. AE group; †P<0.05, ‡P<0.01, vs. day 0.
Predictors for AE on SGLT2i Use in HF

Mechanism of Decreasing BP and WRF
In a previously published meta-analysis, treatment with SGLT2i agents reduced SBP by 3.9 mmHg and DBP by 1.6 mmHg. The mechanisms by which SGLT2i reduces BP are not fully understood. Chronic osmotic diuresis due to increase urinary glucose and/or weight loss may be related to the decrease in BP. Additionally, SGLT2i may suppress sympathetic nerve activity in a rat model. Therefore, reduced sympathetic nerve activity may affect reduced BP.

SGLT2i induced a rapid increase in serum creatinine during the first week of treatment. Reduction in intraglomerular pressure through reduced systemic BP has been reported to produce an initial rise in serum creatinine. Fluid volume depletion is a common factor related to acute kidney injury, and thus, hypovolemia due to osmotic diuresis by SGLT2i may also result in WRF. Furthermore, in patients with DM, increased filtration pressure has been reported due to glomerular hypertension and hyperfiltration. Treatment with SGLT2i agents has been reported to normalize filtration pressure through the activation of a tubule-glomerular feedback process, which acts as a nephron-protective mechanism in the long term. Acute decline of eGFR, however, can occur in some patients in the short term.

Discussion
We report 2 main findings in this study. First, AE, such as low BP and WRF, occurred in 20.3% of patients with HF following introduction of SGLT2i treatment. Female sex, high hemoglobin, high serum creatinine, and low cardiac index were associated with AE. Therefore, frequent monitoring is needed in such patients. Second, weight loss and improved pulmonary congestion were observed in the non-AE group after the introduction of SGLT2i.

Cautions for Initiating SGLT2i in HF Patients
The risk of severe hypotension and of acute kidney injury is not high following the introduction of SGLT2i. Further, an initial drop in eGFR at introduction of SGLT2i does not affect long-term kidney function, but only 10–15% of patients with HF were included in these studies. Additionally, the collection of key data reflecting HF status (e.g., LVEF) was incomplete. Therefore, the safety and evalu-
ation of factors associated with AE due to SGLT2i are still currently unknown in patients with hospitalized HF. Indeed, the reduction in BP and eGFR following introduction of SGLT2i in the present study was substantial when compared with previous studies.\textsuperscript{38,39}

AE might occur not only due to SGLT2i but also due to common medical therapy for HF. The present study, however, excluded patients who changed or increased medication other than SGLT2i during the observation period. In addition, the type of medication (e.g., diuretics) was not significantly different between the AE group and the non-AE group. Therefore, we considered that AE in this study were mainly caused by SGLT2i introduction.

Volume depletion effects require careful consideration on introduction of SGLT2i.\textsuperscript{3,34} Volume depletion is associated with both hypotension and kidney injury. In the present study, urine volume did not significantly increase after introduction of SGLT2i only in the AE group. We hypothesized that this was because there was little excess body fluid volume in the AE group before introduction of SGLT2i. AE occurred in patients with hemoconcentration and less pulmonary congestion at baseline. Hemoconcentration is a common finding in patients with low body fluid volume. Diuresis induced by SGLT2i in patients with low body fluid volume can lead to AE. Further, there were more female subjects in the AE group than in the non-AE group. Female subjects have lower tolerance to different orthostatic challenges than male subjects.\textsuperscript{33,32} Therefore, female sex might be associated with AE, given that female subjects have greater difficulty in adapting to hypovolemic changes.

Chronic kidney disease (CKD) and low cardiac output should also be carefully considered on introduction of SGLT2i. Baseline serum creatinine concentration is a strong predictor of WRF in patients with HF.\textsuperscript{33,34} Therefore, clinicians need to exercise caution when starting SGLT2i in patients with CKD. Low cardiac output at baseline was associated with AE in the present study. Because fluid volume reduction decreases cardiac output through reduction of preload, diuresis by SGLT2i can decrease cardiac output and result in hypoperfusion of organs such as the kidney.\textsuperscript{38} Suppression of sympathetic nerve activity by SGLT2i might promote reduction of cardiac output due to suppression of sympathetic compensatory mechanisms due to low perfusion. In the present study, the absence of an increase in heart rate following introduction of SGLT2i despite volume reduction, supported this hypothesis.

The optimal timing of introduction of SGLT2i in patients with HF has not been determined. According to the present study, the dehydration state should be avoided. In patients with CKD and/or low cardiac output, close monitoring of symptoms and hemodynamics may be recommended. Dose reduction of diuretics might be appropriate to avoid AE following introduction of SGLT2i in some cases.\textsuperscript{28} Conversely, in patients with pulmonary congestion, fluid volume reduction and improved pulmonary congestion occurred without evidence of AE. Therefore, use of SGLT2i might be safe and effective in patients with residual congestion following HF.

**Clinical Implications**

The efficacy of long-term SGLT2i treatment for the reduction of cardiovascular events is promising. If AE occur, however, following the introduction of an SGLT2i, then SGLT2i might need to be avoided for that patient in the future. Use of the present scoring system to predict AE, accompanied by close patient monitoring in the case of a high score, may be useful when considering introduction of SGLT2i in patients with DM and HF.

**Study Limitations**

Several limitations need to be acknowledged in this study. First, this was a single-center study with a limited number of patients, which resulted in a patient selection bias and lower statistical power due to patient heterogeneity. Second, we used echocardiography to evaluate cardiac output. The accuracy of cardiac output on echocardiography is limited compared with cardiac catheterization. Third, 6/13 patients (46%) in the AE group stopped SGLT2i treatment at the discretion of the physician after the study period. Hence, the long-term effects of AE could not be analyzed. For the same reason, it is difficult to determine whether the scoring system for predicting AE after SGLT2i introduction could also be used to predict long-term AE. We speculate, however, that the scoring system do not affect the long-term effects of SGLT2i, because this scoring system was constructed to predict whether AE occurred after introduction of SGLT2i.

**Conclusions**

Female sex, hemoconcentration, kidney injury, and low cardiac output at baseline were associated with AE, such as hypotension and WRF, at the start of treatment with SGLT2i. Closer monitoring might be important when SGLT2i treatment is started in patients with a high risk of AE according to the present scoring system. SGLT2i treatment could be used to reduce congestion in patients with HF.

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**Disclosures**

J.A., T.I. are members of Circulation Reports’ Editorial Team. The other authors declare no conflicts of interest.

**IRB Information**

This paper has been approved by Kitasato University Medical Ethics Organization. The trial number is KMEO B14-130.

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