Circulation Reports
Circ Rep 2020; 2: 51–59
doi:10.1253/circrep.CR-19-0080

ORIGINAL ARTICLE
Heart Failure

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

Mayu Yazaki, MD; Takeru Nabeta, MD, PhD; Takayuki Inomata, MD, PhD; Kenji Maemura, MD; Takumi Ooki, MD; Teppei Fujita, MD, PhD; Yuichiro Iida, MD, PhD; Yuki Ikeda, MD, PhD; Shunsuke Ishii, MD, PhD; Takashi Naruke, MD, PhD; Junya Ako, MD, PhD

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/m^2, 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.[1] Heart failure (HF) is a rapidly increasing cardiovascular disease.[2] DM is closely associated with poor prognosis in patients with HF.[3] 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.[4–6] These effects of SGLT2i treatment on cardiovascular outcomes were similar in patients with HF at baseline.[7] Therefore, major guidelines have recommended the use of SGLT2i in patients with T2DM and cardiovascular disease including HF.[8,9]

In patients hospitalized due to HF, hypotension after the introduction of medical therapy is a risk factor for adverse outcomes.[10] Similarly, worsening renal function (WRF) during treatment in patients with congestive HF is also associated with poor prognosis.[11] 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.[12] 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,[13,14] 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.

Received September 4, 2019; accepted November 14, 2019; J-STAGE Advance Publication released online December 14, 2019 Time for primary review: 25 days

Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara (M.Y., T. Nabeta, K.M., T.O., T.F., Y. Iida, Y. Ikeda, S.I., T. Naruke, J.A.); Department of Cardiovascular Medicine, Kitasato University Kitasato Institute Hospital, Tokyo (T.I.), Japan

J.A., T.I. are members of *Circulation Reports*' Editorial Team.

Mailing address: Takeru Nabeta, MD, PhD, Department of Cardiovascular Medicine, Kitasato University School of Medicine, 1-15-1 Kitasato, Minami-ku, Sagamihara 252-0329, Japan. E-mail: nabetake@med.kitasato-u.ac.jp

ISSN-2434-0790

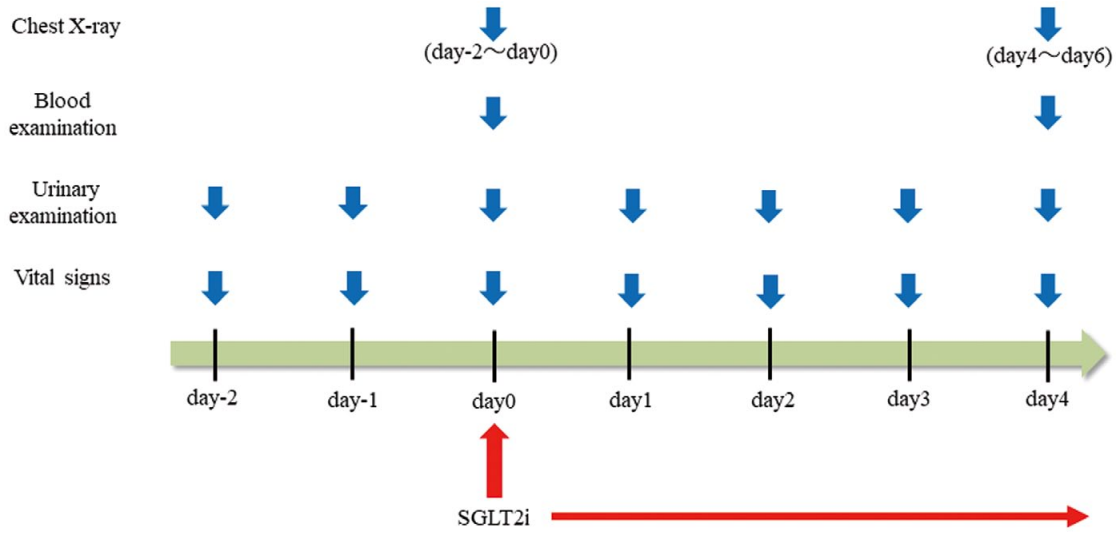

Figure 1. Time line of patient interventions and treatment. Chest X-ray was done once, between day −2 and day 0, and again between day 4 and day 6. SGLT2i, sodium-glucose co-transporter 2 inhibitors.

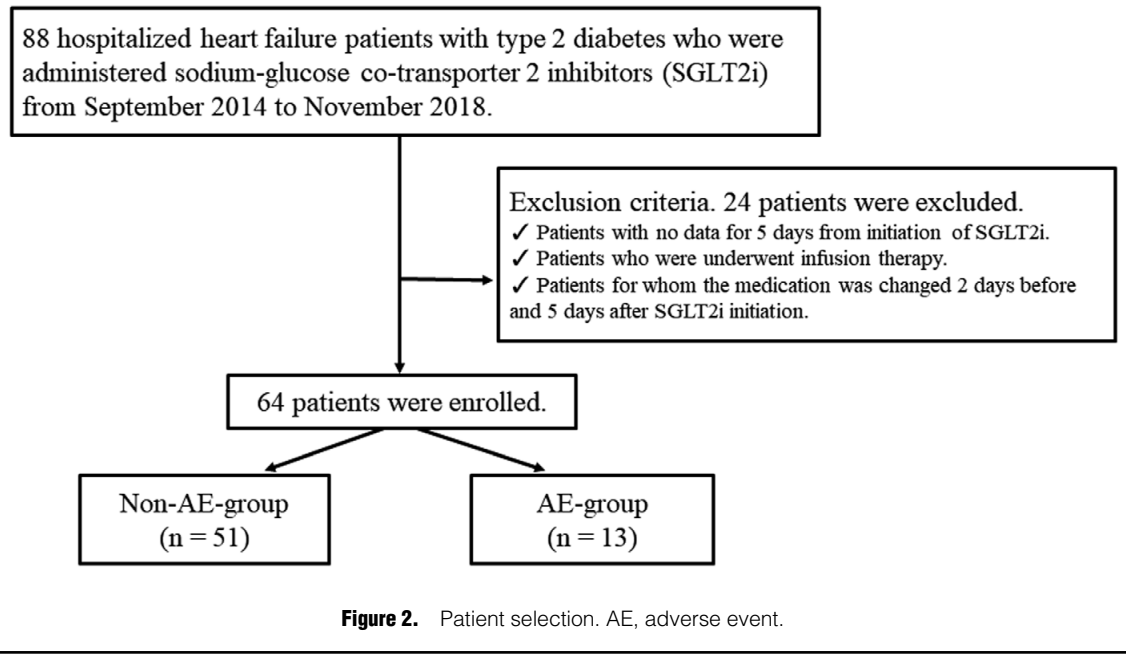

Figure 2. Patient selection. AE, adverse event.

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)[10,15] or an increase in serum creatinine ≥0.3 mg/dL[11] 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.

Table 1. Baseline Characteristics Before SGLT2i Therapy

	Non-AE group (n=51)	AE group (n=13)	P-value
Age (years)	65.8±12.0	65.0±10.0	0.833
Female	10 (19.6)	6 (46.2)	0.049
History of IHD	38 (74.5)	9 (69.2)	0.701
Body weight (kg)	65.6±13.6	63.5±18.0	0.651
BMI (kg/m^2)	24.4±3.9	24.0±3.7	0.743
BSA (m^2)	1.7±0.2	1.7±0.3	0.532
24-h urine volume (mL)	1,475.0±601.4	1,357.5±648.0	0.557
SBP (mmHg)	118.0±17.6	117.2±17.0	0.891
DBP (mmHg)	68.3±11.0	72.4±15.0	0.277
Heart rate (beats/min)	71.7±12.2	67.8±10.8	0.299
AF rhythm	3 (5.9)	3 (23.1)	0.058
Drug therapy			
Calcium channel blocker	4 (7.8)	2 (15.4)	0.405
RAAS inhibitor	48 (94.1)	13 (100.0)	0.370
β-blocker	46 (90.2)	11 (84.6)	0.565
Furosemide	24 (47.1)	6 (46.2)	0.954
Furosemide dose (mg)	20.0±8.8	20.0±11.0	1.000
Insulin	8 (15.7)	0 (0.0)	0.127
Laboratory data			
HbA1c (%)	7.9±1.3	8.2±1.3	0.444
Blood glucose (mg/dL)	150.6±50.1	152.4±41.8	0.907
Hematocrit (%)	39.0±6.5	42.5±7.8	0.097
Hemoglobin (g/dL)	12.9±2.1	14.3±2.8	0.040
Urea nitrogen (mg/dL)	17.0±6.3	19.0±6.3	0.293
Serum creatinine (mg/dL)	0.9±0.2	1.1±0.3	0.001
eGFR (mL/min/1.73 m^2)	65.7±15.8	50.8±22.5	0.007
BNP (pg/mL)	448.7±573.7	331.8±343.4	0.486
Urinary indices			
24-h glucose (mg)	2,776.5±5,405.1	793.3±1,484.0	0.287
Creatinine (mg/dL)	75.6±41.0	69.8±38.7	0.715
Sodium (mmol/L)	67.7±24.0	71.0±25.0	0.731
Echocardiography			
LVEF (%)	47.2±18.5	42.3±15.7	0.391
LVDd (mm)	52.5±12.3	52.1±7.5	0.903
LVDs (mm)	40.2±14.5	39.7±7.8	0.909
IVC (mm)	16.2±4.6	16.7±6.1	0.777
E wave (m/s)	80.5±24.5	75.0±21.8	0.476
E/e'	15.4±7.1	19.4±12.8	0.158
TRPG (mmHg)	28.0±13.0	27.4±19.8	0.906
VTI (cm)	17.2±5.8	14.1±4.2	0.118
Stroke volume (mL)	59.9±22.1	47.6±20.3	0.157
Cardiac output (L/min)	4.6±1.1	3.4±1.1	0.008
Cardiac index (L/min/m^2)	2.6±0.6	2.1±0.6	0.026
Pulmonary congestion score (points)	2.1±2.9	0.7±1.5	0.096
Plasma volume status (%)	0.1±13.0	−5.2±19.2	0.238

Data given as n (%) or mean±SD. AF, atrial fibrillation; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IHD, ischemic heart disease; IVC, inferior vena cava; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter 2 inhibitors; TRPG, trans-tricuspid pressure gradient; VTI, velocity time integral.

Measurements

BP, heart rate, body weight, blood glucose, and urinary indices were measured daily from 2 days before introduction of SGLT2i until the end of the observation period. Laboratory data were obtained before and at the fourth day after introduction of SGLT2i; chest X-ray was obtained from day −2 to day 0 and from day 4 to day 6, and echocardiography was performed before the start of SGLT2i treatment (**Figure 1**).

On echocardiography, left ventricular (LV) volumes were

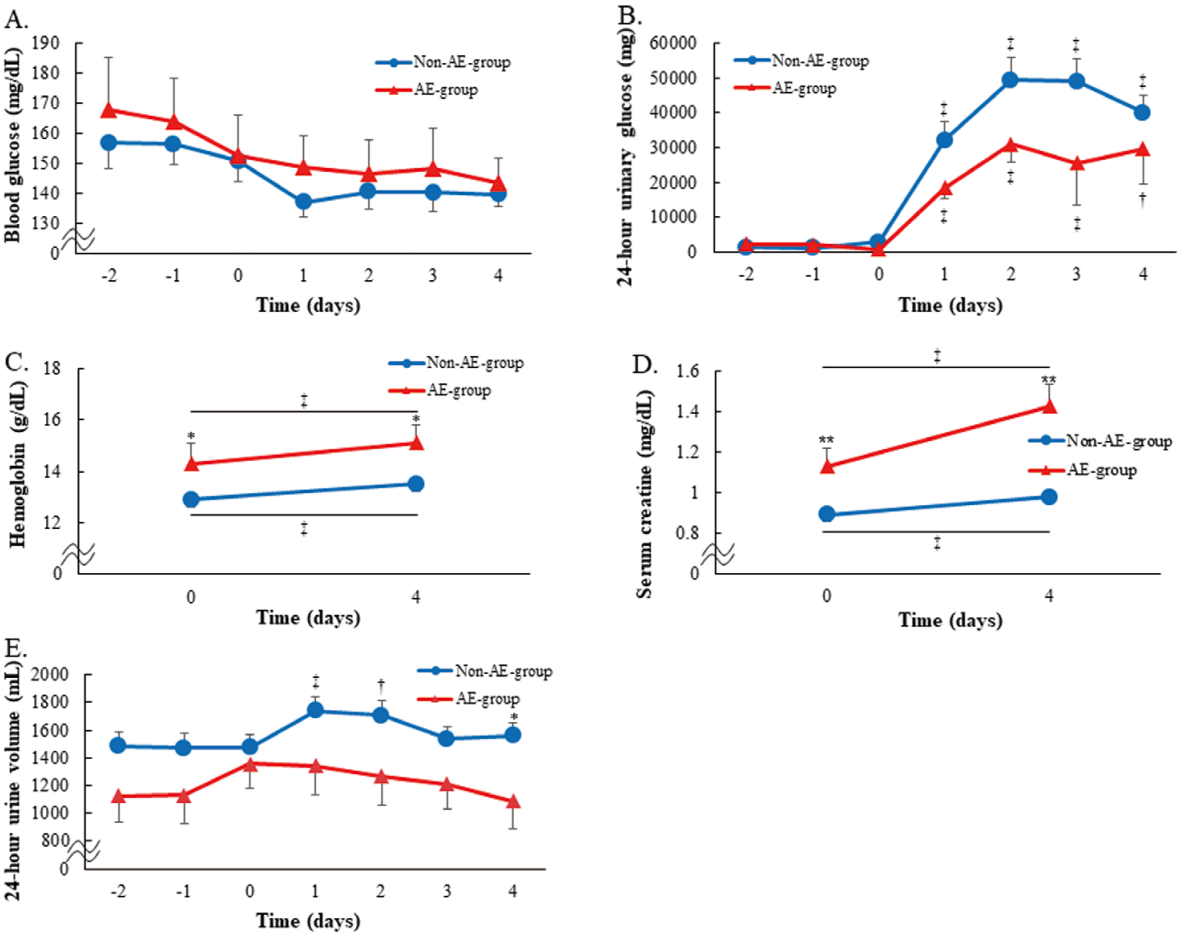

Figure 3. Change in (**A**) blood glucose, (**B**) 24-h urinary glucose, (**C**) hemoglobin, (**D**) serum creatinine, and (**E**) 24-h urinary volume in hospitalized patients with heart failure and type 2 diabetes mellitus treated with sodium-glucose co-transporter 2 inhibitors, according to adverse 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.

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 divided by the end-diastolic volume.[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× LVOT area, where LVOT area=π (LVOT diameter/2)^2; cardiac output=SV×heart rate; cardiac index=cardiac output/body surface area.[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.[18] Conversely, PVS was calculated using body weight and hematocrit. Actual PV (aPV) was calculated using hematocrit and weight: aPV=(1−hematocrit)×[a+(b×weight in kg)] where hematocrit is a fraction, and a=1,530 and 864, while b=41 and 47.9 in male in female patients, respectively. Ideal PV (iPV) was calculated using weight: iPV=c×weight (kg) 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: PVS=[(aPV−iPV)/iPV]×100%.[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 SGLT2i introduction. McNemar test was used to compare categorical variables before–after SGLT2i introduction.

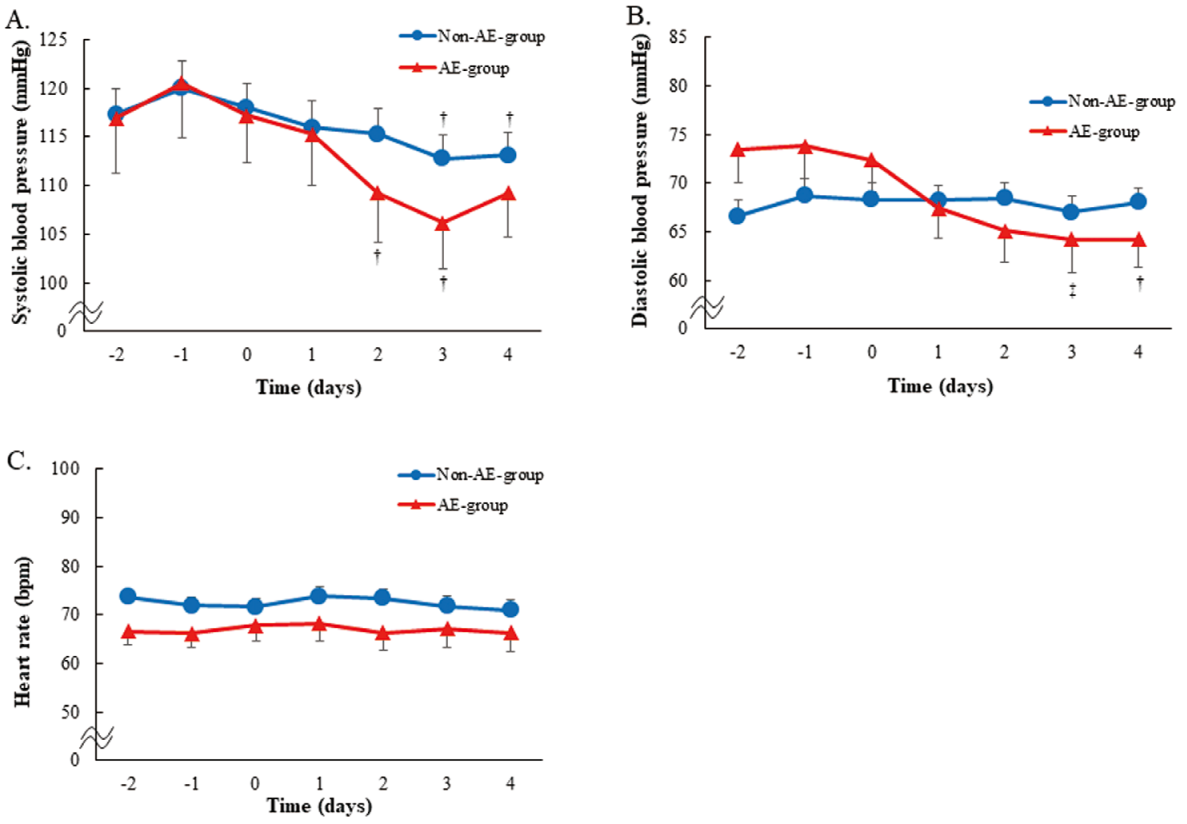

Figure 4. Change in (**A**) systolic blood pressure, (**B**) diastolic blood pressure, and (**C**) heart rate in hospitalized patients with heart failure and type 2 diabetes mellitus treated with sodium-glucose co-transporter 2 inhibitors, according to adverse event (AE) status. Data given as mean±SE. *P<0.05, **P<0.01, non-AE group vs. AE group; †P<0.05, ‡P<0.01, vs. day 0. bpm, beats/min.

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

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

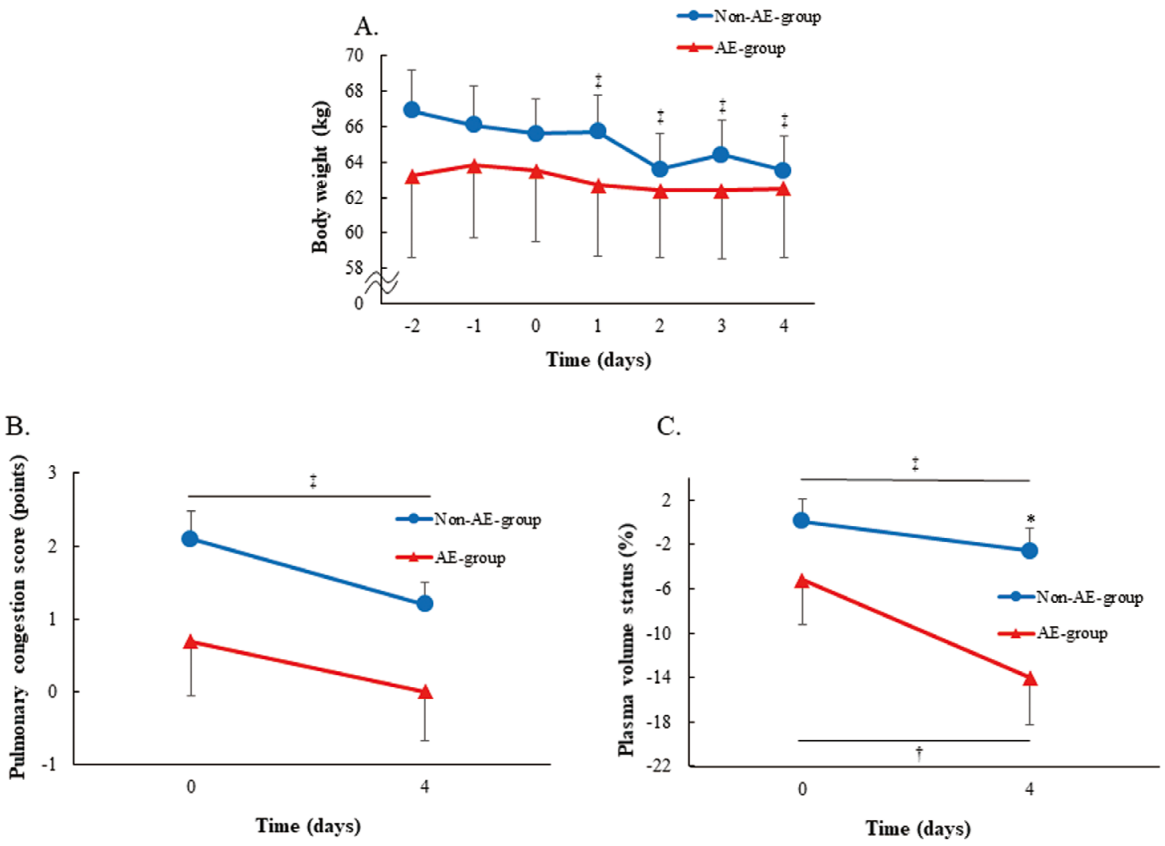

Figure 5. Change in (**A**) body weight, (**B**) pulmonary congestion score, and (**C**) plasma volume status in hospitalized patients with heart failure and type 2 diabetes mellitus treated with sodium-glucose co-transporter 2 inhibitors, according to adverse event (AE) status. Data given as mean±SE.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

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/m^2)			9.04 (1.19–68.74)	0.033

(BNP) was obtained on day 4 in 44/64 patients (69%). The change in BNP (−94.0±166.7 vs. −188.5±400.5; P=0.496) and in BNP on day 4 (330.2±354.8 vs. 399.6±493.2; P=0.695) were not significantly different between the AE group and non-AE group.

Change in BP and Heart Rate

Absolute changes in BP and heart rate from day −2 to day 4 are shown in **Figure 4**. In both groups, SBP significantly decreased after introduction of SGLT2i (**Figure 4A**). A reduction of SBP >10 mmHg was observed in 22 patients (34%). Diastolic BP (DBP) significantly decreased in the AE group, but not in the non-AE group (**Figure 4B**). In both groups, heart rate did not significantly change after introduction of SGLT2i (**Figure 4C**). In patients experiencing AE, 6/13 patients (46%) discontinued SGLT2i after the study period because of AE.

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

A.

Parameters	values	score
Sex	Female	1
Hemoglobin (g/dL)	≥15.2	1
Serum creatinine (mg/dL)	≥1.05	1
Cardiac index (L/min/m^2)	≤2.15	1

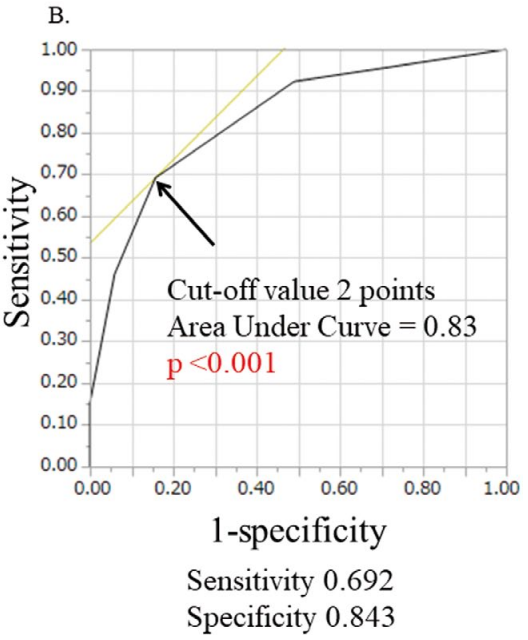

Figure 6. (**A**) Scoring system developed to predict adverse events (AE) on sodium-glucose co-transporter 2 inhibitor treatment, based on significant variables from the multivariate analysis. (**B**) Receiver operating characteristic curve for AE score.

second multivariate model, given that serum creatinine and cardiac index showed high collinearity. In model 2, female sex (OR, 14.62; 95% CI: 1.36–157.50; P=0.027) and cardiac index (OR, 9.04; 95% CI: 1.19–68.74; P=0.033) were identified as independent factors associated with AE (**Table 2**).

Development of a Scoring System to Predict AE

A score to predict AE was constructed by including variables that differed significantly between the 2 groups at baseline, such as sex, hemoglobin, serum creatinine, and cardiac index. The cut-offs for hemoglobin, serum creatinine, and cardiac index were calculated using ROC analysis. Regarding the scoring system developed in this study, there were 2 categories of gender difference: male (0 points) and female (1 point); hemoglobin level had 2 categories: <15.2 g/dL (0 points) and ≥15.2 g/dL (1 point); serum creatinine had 2 categories: <1.05 mg/dL (0 points) and ≥1.05 mg/dL (1 point); and cardiac index had 2 categories: >2.15 L/min/m^2 (0 points) and ≤2.15 L/min/m^2 (1 point; **Figure 6A**). Therefore, if all the parameters were satisfied, the total sum was 4 points. The area under the curve for predicting AE was 0.83 (P<0.001) using a cut-off of 2 points (**Figure 6B**).

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.

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.[20] The mechanisms by which SGLT2i reduces BP are not fully understood. Chronic osmotic diuresis due to increase urinary glucose[21,22] and/or weight loss[23] may be related to the decrease in BP. Additionally, SGLT2i may suppress sympathetic nerve activity in a rat model.[24,25] Therefore, reduced sympathetic nerve activity may affect reduced BP.

SGLT2i induced a rapid increase in serum creatinine during the first week of treatment.[26] Reduction in intraglomerular pressure through reduced systemic BP has been reported to produce an initial rise in serum creatinine.[27] 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.[26,28] 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,[29] 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.

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.[4,5] Further, an initial drop in eGFR at introduction of SGLT2i does not affect long-term kidney function,[30] 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.[28] 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.[20,30]

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.[26] 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.[31,32] 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.[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.[35] Suppression of sympathetic nerve activity by SGLT2i[24,25] 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.[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 AEs 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.

Acknowledgments

None.

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.

References

1. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **376:** 2215–2222.
2. Yasuda S, Miyamoto Y, Ogawa H. Current status of cardiovascular medicine in the aging society of Japan. *Circulation* 2018; **138:** 965–967.
3. Nasir S, Aguilar D. Congestive heart failure and diabetes mellitus: Balancing glycemic control with heart failure improvement. *Am J Cardiol* 2012; **110:** 50B–57B.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373:** 2117–2128.
5. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. CANVAS Programme Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377:** 644–657.
6. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; **380:** 347–357.
7. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al. Heart failure outcomes with empagliflozin in patients

with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME® trial. *Eur Heart J* 2016; **37:** 1526–1534.
8. Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018: A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018; **41:** 2669–2701.
9. Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease. *J Am Coll Cardiol* 2018; **72:** 3200–3223.
10. Patel PA, Heizer G, O'Connor CM, Schulte PJ, Dickstein K, Ezekowitz JA, et al. Hypotension during hospitalization for acute heart failure is independently associated with 30-day mortality: Findings from ASCEND-HF. *Circ Heart Fail* 2014; **7:** 918–925.
11. Metra M, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, et al. Worsening renal function in patients hospitalised for acute heart failure: Clinical implications and prognostic significance. *Eur J Heart Fail* 2008; **10:** 188–195.
12. Abassi ZA, Aronson D, Darawsha W, Azzam ZS, Boulos J. Treatment patterns of patients with acute heart failure who develop acute kidney injury. *ESC Heart Fail* 2018; **6:** 45–52.
13. Heise T, Jordan J, Wanner C, Heer M, Macha S, Mattheus M, et al. Pharmacodynamic effects of single and multiple doses of empagliflozin in patients with type 2 diabetes. *Clin Ther* 2016; **38:** 2265–2276.
14. Tanaka H, Takano K, Iijima H, Kubo H, Maruyama N, Hashimoto T, et al. Factors affecting canagliflozin-induced transient urine volume increase in patients with type 2 diabetes mellitus. *Adv Ther* 2017; **34:** 436–451.
15. Svensson MK, Afghahi H, Franzen S, Björk S, Gudbjörnsdottir S, Svensson AM, et al. Decreased systolic blood pressure is associated with increased risk of all-cause mortality in patients with type 2 diabetes and renal impairment: A nationwide longitudinal observational study of 27,732 patients based on the Swedish National Diabetes Regis. *Diabetes Vasc Dis Res* 2017; **14:** 226–235.
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. 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:** 233–271.
17. Díaz A, Zócalo Y, Cabrera-Fischer E, Bia D. Reference intervals and percentile curve for left ventricular outflow tract (LVOT), velocity time integral (VTI), and LVOT-VTI-derived hemodynamic parameters in healthy children and adolescents: Analysis of echocardiographic methods association and agreement. *Echocardiography* 2018; **35:** 2014–2034.
18. Melenovsky V, Andersen MJ, Andress K, Reddy YN, Borlaug BA. Lung congestion in chronic heart failure: Haemodynamic, clinical, and prognostic implications. *Eur J Heart Fail* 2015; **17:** 1161–1171.
19. Ling HZ, Flint J, Damgaard M, Bonfils PK, Cheng AS, Aggarwal S, et al. Calculated plasma volume status and prognosis in chronic heart failure. *Eur J Heart Fail* 2015; **17:** 35–43.
20. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: A systematic review and meta-analysis. *J Am Soc Hypertens* 2014; **8:** 262–275.
21. Bailey CJ. Renal glucose reabsorption inhibitors to treat diabetes. *Trends Pharmacol Sci* 2011; **32:** 63–71.
22. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, et al. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. *Diabetes Obes Metab* 2015; **17:** 1180–1193.
23. List JF, Whaley JM. Glucose dynamics and mechanistic implications of SGLT2 inhibitors in animals and humans. *Kidney Int* 2011; **79:** S20–S27.
24. Rahman A, Fujisawa Y, Nakano D, Hitomi H, Nishiyama A. Effect of a selective SGLT2 inhibitor, luseogliflozin, on circadian rhythm of sympathetic nervous function and locomotor activities in metabolic syndrome rats. *Clin Exp Pharmacol Physiol* 2017; **44:** 522–525.
25. Chiba Y, Yamada T, Tsukita S, Takahashi K, Munakata Y, Shirai Y, et al. Dapagliflozin, a sodium-glucose co-transporter 2 inhibitor, acutely reduces energy expenditure in BAT via neural signals in mice. *PLoS One* 2016; **11:** e0150756.
26. Van Bommel EJ, Muskiet MH, Tonneijck L, Kramer MH, Nieuwdorp M, van Raalte DH. SGLT2 inhibition in the diabetic kidney: From mechanisms to clinical outcome. *Clin J Am Soc Nephrol* 2017; **12:** 700–710.
27. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345:** 851–860.
28. Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. *JACC Heart Fail* 2019; **7:** 169–172.
29. Anders H, Davis JM, Thurau K. Nephron protection in diabetic kidney disease. *N Engl J Med* 2016; **375:** 2096–2098.
30. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; **377:** 644–657.
31. Convertino VA. Gender differences in autonomic functions associated with blood pressure regulation. *Am J Physiol* 1998; **275:** R1909–R1920.
32. Schlotman TE, Akers KS, Nessen SC, Convertino VA. Differentiating compensatory mechanisms associated to low tolerance to central hypovolemia in females. *Am J Physiol Circ Physiol* 2019; **316:** H609–H616.
33. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; **43:** 61–67.
34. Cowie MR, Komajda M, Murray-Thomas T, Underwood J, Ticho B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: Results of the Prospective Outcomes Study in Heart Failure (POSH). *Eur Heart J* 2006; **27:** 1216–1222.
35. Nieminen MS, Böhm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: The Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; **26:** 384–416.