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ORIGINAL ARTICLE
Heart Failure

Early Initiation of Sodium-Glucose Cotransporter 2 Inhibitor Leads to a Shorter Hospital Stay in Patients With Acute Decompensated Heart Failure

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Background: The efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in patients with acute chronic heart failure (HF) is increasingly being reported. However, it is not clear when SGLT2i should be initiated in patients with acute decompensated HF (ADHF) after hospitalization. We retrospectively analyzed ADHF patients with newly prescribed SGLT2i.

Methods and Results: Among the 694 patients hospitalized due to HF between May 2019 and May 2022, data were extracted for 168 patients with newly prescribed SGLT2i during the index hospitalization. These patients were divided into 2 groups: and early group (92 patients who started SGLT2i within 2 days of admission) and a late group (76 patients who started SGLT2i after 3 days). Clinical characteristics were comparable between the 2 groups. The date of cardiac rehabilitation initiation was significantly earlier in the early than late group (2.5±1.2 vs. 3.8±2.2 days; P<0.001). Hospital stay was significantly shorter in the early group (16.4±6.5 vs. 24.2±16.0 days; P<0.001). Although there were significantly fewer HF readmissions within 3 months in the early group (2.1% vs. 10.5%; P=0.044), the association disappeared in a multivariate analysis including clinical confounders.

Conclusions: Early initiation of SGLT2i may shorten hospital stays.

Key Words: Early initiation of SGLT2 inhibitor; Heart failure; Shorter hospital stay

The number of patients with heart failure (HF) in Japan continues to increase due to the increase in lifestyle-related diseases and population aging.[1–3] Most patients with HF are elderly, which is related to a poor prognosis and increased hospitalization costs.[4,5] The in-hospital mortality rate for patients hospitalized with acute HF in Japan is approximately 5%, and the number of readmissions for HF in Japan has not decreased at all in the past decade.[6]

Pharmacotherapy for HF has changed dramatically in recent years, and the efficacy of guideline-directed medical therapy (GDMT), known as 'the Fantastic 4', for HF with reduced ejection fraction (HFrEF) seems to be well established.[7–9] Among GDMT, sodium-glucose cotransporter 2 inhibitors (SGLT2i) may hold a particularly important position, and their prognostic benefit for HFrEF was demonstrated in the Dapagliflozin and Prevention of Adverse outcomes in heart failure (DAPA-HF) and the Empagliflozin Outcome trial in Patients with Chronic Heart Failure and a Reduced Ejection Draction (EMPA-reduced) trials for patients with chronic HF.[10,11] Furthermore, the EMPEROR-preserved and DELIVER trials have demonstrated the prognostic benefits of SGLT2i for HF with mildly reduced ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF).[12,13] These trials demonstrated the efficacy of SGLT2i regardless of ejection fraction (EF).[14,15] These trials were conducted in patients with chronic HF.

There are a few studies examining the effect of SGLT2i in patients hospitalized for acute decompensated HF (ADHF). Sotagliflozin was shown to improve the prognosis of patients with type 2 diabetes who were hospitalized for exacerbation of HF in the Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure (SOLOIST-WHF) trial.[16] However, in that study, only 48.8% of patients had received sotagliflozin or a placebo before discharge. The pilot study of the SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized (EMPULSE) trial, the Randomized, double-blind, placebo-controlled, multicentre

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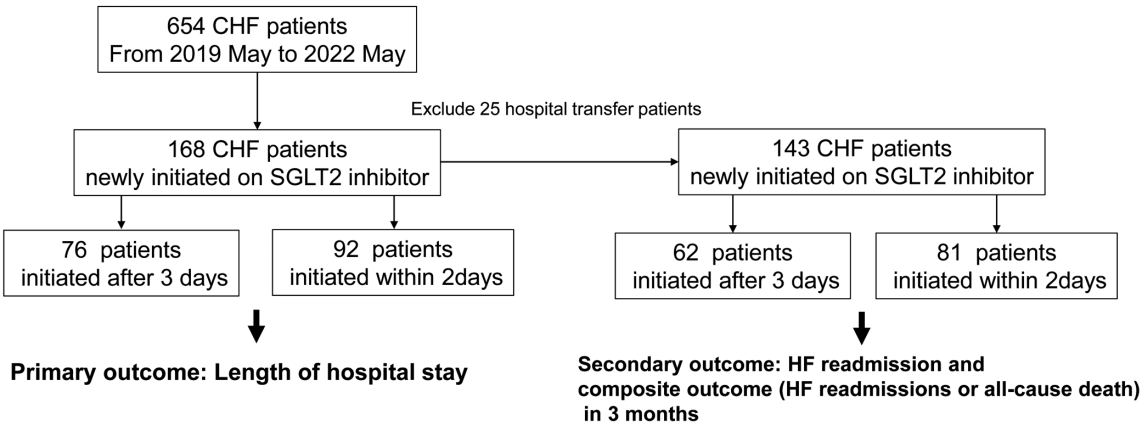

Figure 1. Study protocol. CHF, congestive heart failure; HF, heart failure; SGLT2, sodium-glucose cotransporter 2.

pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF) trial, was a study of the clinical outcomes of empagliflozin initiated within 24 h of hospitalization in patients with ADHF and found significantly fewer HF readmissions in the empagliflozin group at 2 months.[17] The EMPULSE trial started empagliflozin or placebo during hospitalization for acute de novo or decompensated chronic HF regardless of EF and continued for 90 days, with a median time to drug start of 3 days. Clinical benefits were observed for both acute de novo and decompensated chronic HF, and were observed regardless of EF or the presence or absence of diabetes.[18]

However, there have been no studies examining the timing of initiation of SGLT2i in patients hospitalized for ADHF. Thus, the aim of the present study was to determine whether there is a difference in clinical outcomes between patients hospitalized for ADHF who receive SGLT2i early after admission and those who received them later.

Methods

Study Design

This was a single-center retrospective cohort study to evaluate the effects of the early initiation of SGLT2i in patients with ADHF. All patients in the study were taking 10 mg empagliflozin or 10 mg dapagliflozin, with a median start date of 2 days after admission. Thus, we defined early initiation of SGLT2i as initiation within 2 days of admission and late initiation as initiation after 3 days of admission. We retrospectively analyzed 654 consecutive patients with ADHF at the Japanese Red Cross Fukuoka Hospital between May 2019 and May 2022. ADHF was independently diagnosed by each attending physician according to the Framingham HF criteria.[19] Data were extracted for 168 patients with newly initiated SGLT2i during hospitalization and analyzed. Patients were followed up for 3 months after discharge. Clinical outcomes, including the length of hospital stay, HF readmissions, and a composite of death from any cause or HF readmission, were investigated. The design of the study is shown in **Figure 1**. In addition, changes in urine output, time to rehabilitation initiation, hemodynamic changes, changes in estimated glomerular filtration rate (eGFR) and changes in B-type natriuretic peptide (BNP) concentrations were examined. The date of HF readmission and death from any cause after discharge was confirmed from the follow-up records in the Japanese Red Cross Fukuoka Hospital or through direct telephone contact with each patient or their family members. The number of days from the date of discharge to the date of the event was used in analyses.

Statistical Analyses

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[20]

Continuous variables in the early and late groups were compared using the unpaired t-test or Mann-Whitney test, as appropriate. Categorical variables were compared between the early and late groups using the Chi-squared test or Fisher's exact test, as appropriate. Changes in clinical parameters were analyzed by repeated-measures analysis of variance (ANOVA). Multiple linear regression was calculated to predict the length of hospital stay based on age, New York Heart Association (NYHA) class, EF, systolic blood pressure (SBP), BNP, albumin, eGFR, the use of non-invasive positive pressure ventilation (NPPV), the use of catecholamines, hospital transfer, and days to initiation of SGLT2i. Independent variables were selected that seemed likely to be associated with the length of hospital stay. Because the length of hospital stay was not normally distributed, log-transformed values were used in the analysis. A significant regression equation was found ($F_{11,154}=7.182$, $P<0.001$), with an R^2 of 0.3339. Multicollinearity was assessed using the variance inflation factor (VIF). A VIF >10 is regarded as indicating serious multicollinearity, and values >4.0 may be a cause for concern; however, evidence for multicollinearity was absent because the VIF for independent variables in the model in this study was <2.0.

Freedom from HF readmissions and the composite outcome were analyzed using Kaplan-Meier curves with the log-rank test. Because some variables associated with HF

readmission and the composite outcome remained significantly different, multivariate analysis using a Cox proportional hazards regression model was added. Several models were used in the analysis: Model 0, univariate analysis of all variables; Model 1, confounding factors that may affect early initiation of SGLT2i were included in the model, excluding those that interact (age, EF, SBP, and eGFR); Model 2, all confounders included in Model 1 were incorporated into the model plus other confounders and mediators, such as medications at discharge (age, EF, whether de novo HF hospitalization, SBP, diastolic blood pressure [DBP], eGFR, early SGLT2i start, angiotensin-converting enzyme inhibitor [ACEi]/angiotensin-receptor blocker [ARB], angiotensin receptor-neprilysin inhibitor [ARNI], β-blocker, mineralocorticoid receptor antagonist [MRA], the dose of loop diuretics, and tolvaptan).

Unless specified otherwise, all data are expressed as the mean±SD or median with interquartile range. All probabilities are 2-tailed, P<0.05 being regarded as statistically significant.

Ethical Considerations

This study was approved by the Ethics Committee of Japanese Red Cross Fukuoka Hospital and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Table 1. Characteristics of the Early and Late Groups

	Early group (n=92)	Late group (n=76)	P value
On admission			
Age (years)	71.4±13.3	72.0±14.2	0.771
Male sex	66 (71.7)	53 (69.7)	0.865
EF (%)	36.0±15.2	36.2±16.7	0.932
HFrEF	61 (66.3)	45 (59.2)	0.422
HFmrEF	12 (13.0)	13 (17.1)	0.517
HFpEF	19 (20.7)	18 (23.7)	0.71
NYHA functional classification			
2	17 (18.5)	9 (11.8)	0.287
3	54 (58.7)	47 (61.8)	0.752
4	21 (22.8)	20 (26.3)	0.718
ICM	27 (29.3)	25 (32.9)	0.738
De novo HF hospitalization	53 (69.7)	66 (71.7)	0.865
Body weight (kg)	64.7±19.4	63.6±17.1	0.705
BMI (kg/m^2)	24.1±6.3	24.1±5.2	0.976
SBP (mmHg)	149.2±35.4	145.9±32.5	0.529
DBP (mmHg)	90.3±24.7	87.6±28.0	0.511
Heart rate (beats/min)	101.0±25.0	93.5±25.1	0.056
BNP (pg/mL)	868.5±930.7	851.0±1,400.9	0.923
Hb (g/dL)	13.0±2.5	12.3±2.7	0.108
BUN (mg/dL)	20.8 [7.3–79.6]	20.3 [10.4–116.1]	0.89
Cr (mg/dL)	1.05 [0.46–3.76]	1.02 [0.51–7.27]	0.754
eGFR (mL/min/1.73 m^2)	52.83±22.40	49.8±19.42	0.356
UA (mg/dL)	6.4±2.2	6.9±2.4	0.23
Na (mEq/L)	138.8±4.3	139.3±3.8	0.397
K (mEq/L)	4.27±0.56	4.23±0.59	0.633
Albumin (g/dL)	3.5±0.5	3.5±0.4	0.901
Treatments in hospital			
SGLT2i start (days)	1.7±0.4	6.9±7.8	<0.001
Empagliflozin	39 (42.4)	41 (53.9)	0.163
Dapagliflozin	53 (57.6)	35 (46.1)	
Loop diuretics	76 (82.6)	68 (89.5)	0.269
Loop diuretic dose on first 2 days (mg/day)	27.0±10.2	24.4±9.0	0.109
Tolvaptan	34 (37.0)	30 (39.5)	0.752
TLV dose on first 2 days (mg/day)	7.6±1.5	6.9±2.0	0.151
NPPV	13 (14.1)	13 (17.1)	0.67
Catecholamine	9 (9.8)	14 (18.4)	0.119
Vasodilator	29 (31.5)	29 (38.2)	0.416
MCS	0 (0.0)	0 (0.0)	1
Carperitide	14 (15.2)	6 (7.9)	0.16

(**Table 1** continued the next page.)

	Early group (n=92)	Late group (n=76)	P value
Comorbidities			
AF	37 (40.2)	39 (51.3)	0.164
COPD	5 (5.4)	9 (11.8)	0.166
Diabetes	49 (53.3)	37 (48.7)	0.642
Cancer	8 (8.7)	5 (6.6)	0.774
CVD	15 (16.3)	9 (11.8)	0.508
Sleep disorder	3 (3.3)	5 (6.6)	0.47
Dialysis	0 (0.0)	0 (0.0)	1
At discharge			
In-hospital death	0 (0.0)	0 (0.0)	1
Hospital transfer	11 (12.0)	14 (18.4)	0.280
NYHA class	1.9±0.4	2.0±0.4	0.602
BNP (pg/mL)	251.4±292.4	226.3±197.6	0.553
Hb (g/dL)	13.3±2.0	12.9±2.2	0.227
BUN (mg/dL)	23.9 [9.6–72.6]	23.4 [10.3–127.6]	0.838
Cr (mg/dL)	1.17 [0.57–3.44]	1.08 [0.51–3.65]	0.758
eGFR (mL/min/1.73 m^2)	47.26±17.31	47.20±19.25	0.982
UA (mg/dL)	5.8±1.7	5.9±1.8	0.764
Na (mEq/L)	138.0 [126.2–154.3]	138.2 [130.9–144.4]	0.660
K (mEq/L)	4.52±0.52	4.46±0.51	0.47
Albumin (g/dL)	3.4±0.4	3.4±0.4	0.496
SBP (mmHg)	112.7±17.5	112.9±15.2	0.92
DBP (mmHg)	64.6±12.7	65.2±13.2	0.764
Heart rate (beats/min)	70.7±13.0	69.2±10.4	0.423
ACEi/ARB	37 (40.2)	49 (64.5)	0.002
ARNI	43 (46.7)	19 (25.0)	0.004
β-blocker	73 (79.3)	57 (75.0)	0.579
MRA	81 (88.0)	64 (84.2)	0.505
PDE3i	8 (8.7)	11 (14.5)	0.328
Loop diuretics	46 (50.0)	50 (65.8)	0.738
Loop diuretics dose (mg)	10.5±13.8	14.7±15.0	0.062
Tolvaptan	18 (19.6)	23 (30.3)	0.148

Unless indicated otherwise, data are given as the mean±SD, median [interquartile range] or n (%). ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CVD, cerebrovascular disease; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICM, ischemic cardiomyopathy; MCS, mechanical circulatory support; MRA, mineralocorticoid receptor antagonist; NPPV, non-invasive positive pressure ventilation; NYHA, New York Heart Association; PDE3i, phosphodiesterase 3 inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UA, uric acid.

Informed consent for data handling was obtained from patients at the time of admission, and informed consent for the study was obtained via an opt-out method.

Results

Patient Characteristics

The study design is presented in **Figure 1**. We retrospectively analyzed data for 654 consecutive patients with ADHF at Japanese Red Cross Fukuoka Hospital. Of these 654 patients, 168 with newly initiated SGLT2i during hospitalization were investigated. Patients were divided into 2 groups: an early group (those who started SGLT2i within 2 days of admission) and a late group (those who started SGLT2i after 3 days). The characteristics of patients in the 2 groups are presented in **Table 1**. There were no significant differences between the early and late groups in EF (36.0±15.2% vs. 36.2±16.7%, respectively; P=0.932), NYHA Class 3 (58.7% vs. 61.8%, respectively; P=0.752), NYHA Class 4 (22.8% vs. 26.3%, respectively; P=0.718), BNP (868.5±930.7 vs. 851.0±1,400.9 pg/mL, respectively; P=0.923), or eGFR (52.8±22.4 vs. 49.8±19.4 mL/min/1.73 m^2, respectively; P=0.356). Other parameters were also comparable between the 2 groups at the time of admission.

Length of Hospital Stay

Length of hospital stay was significantly shorter in the early than late group (16.4±6.5 vs. 24.2±16.0 days; P<0.001; **Figure 2A**). When the analysis was stratified by EF, the length of hospital stay was significantly shorter in the early group for patients with HFrEF (17.2±6.6 vs. 26.9±19.2 days; P=0.002; **Figure 2B**) or HFmrEF (14.5±6.8 vs. 20.8±8.2 days; P=0.048; **Figure 2C**), and tended to be shorter in the early group for patients with HFpEF, although the difference was not statistically significant (15.0±5.6 vs. 19.8±9.2 days; P=0.06; **Figure 2D**). Further-

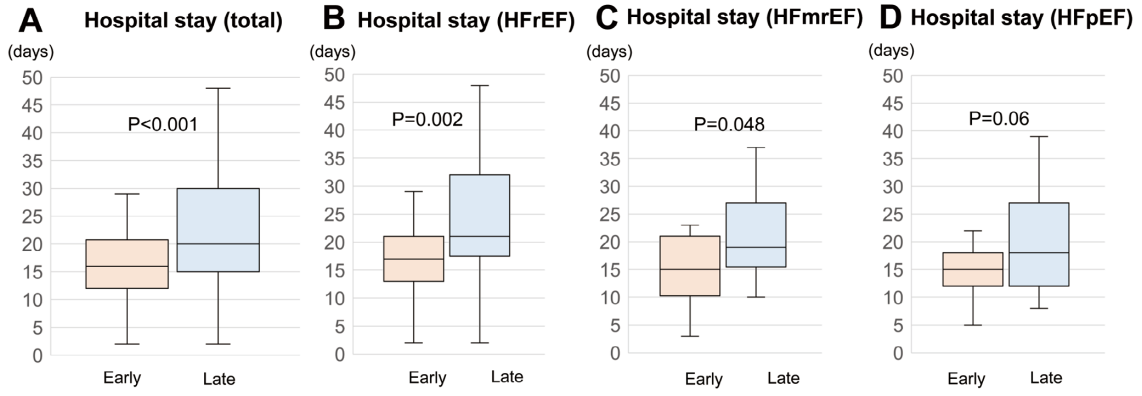

Figure 2. Comparisons of the length of hospital stay between the early and late groups in (**A**) all patients and in those with (**B**) heart failure with reduced ejection fraction (HFrEF), (**C**) heart failure with mildly reduced ejection fraction (HFmrEF), and (**D**) heart failure with preserved ejection fraction (HFpEF). Data were analyzed using t-tests. Data are given as median with interquartile range.

Table 2. Multivariate Analysis About Factors Associated With Length of Hospital Stay

	Estimate	95% CI	SE	t value	P value
Intercept	1.591	1.202, 1.980	0.197	8.077	<0.001
Age	0.0004	−0.002, 0.003	0.001	0.334	0.738
NYHA functional classification	0.012	−0.047, 0.149	0.030	0.411	0.681
EF	−0.001	−0.003, 0.001	0.001	−0.820	0.413
SBP	−0.0004	−0.001, 0.0006	0.0005	−0.830	0.407
BNP	0.00001	−0.00001, 0.00004	0.00001	0.919	0.359
Albumin	−0.095	−0.163, −0.027	0.034	−2.780	0.006
eGFR	0.0003	−0.001, 0.002	0.0008	0.448	0.654
NPPV use	0.037	−0.062, 0.137	0.050	0.746	0.456
Catecholamine use	0.245	0.142, 0.348	0.052	4.709	<0.01
Hospital transfer	0.051	−0.046, 0.149	0.049	1.041	0.299
Early SGLT2i start	−0.116	−0.182, −0.049	0.033	−3.449	<0.001

CI, confidence interval; SE, standard error. Other abbreviations as in Table 1.

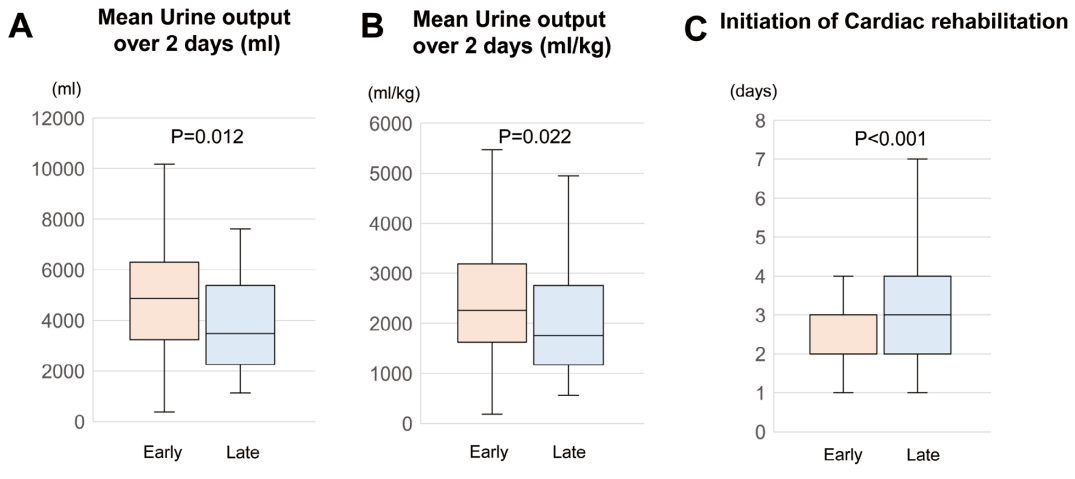

Figure 3. Comparisons of (**A**) mean 2-day urine output, (**B**) mean 2-day urine output corrected for body weight, and (**C**) time to initiation of cardiac rehabilitation between the early and late groups. Data were analyzed using t-tests. Data are given as median with interquartile range.

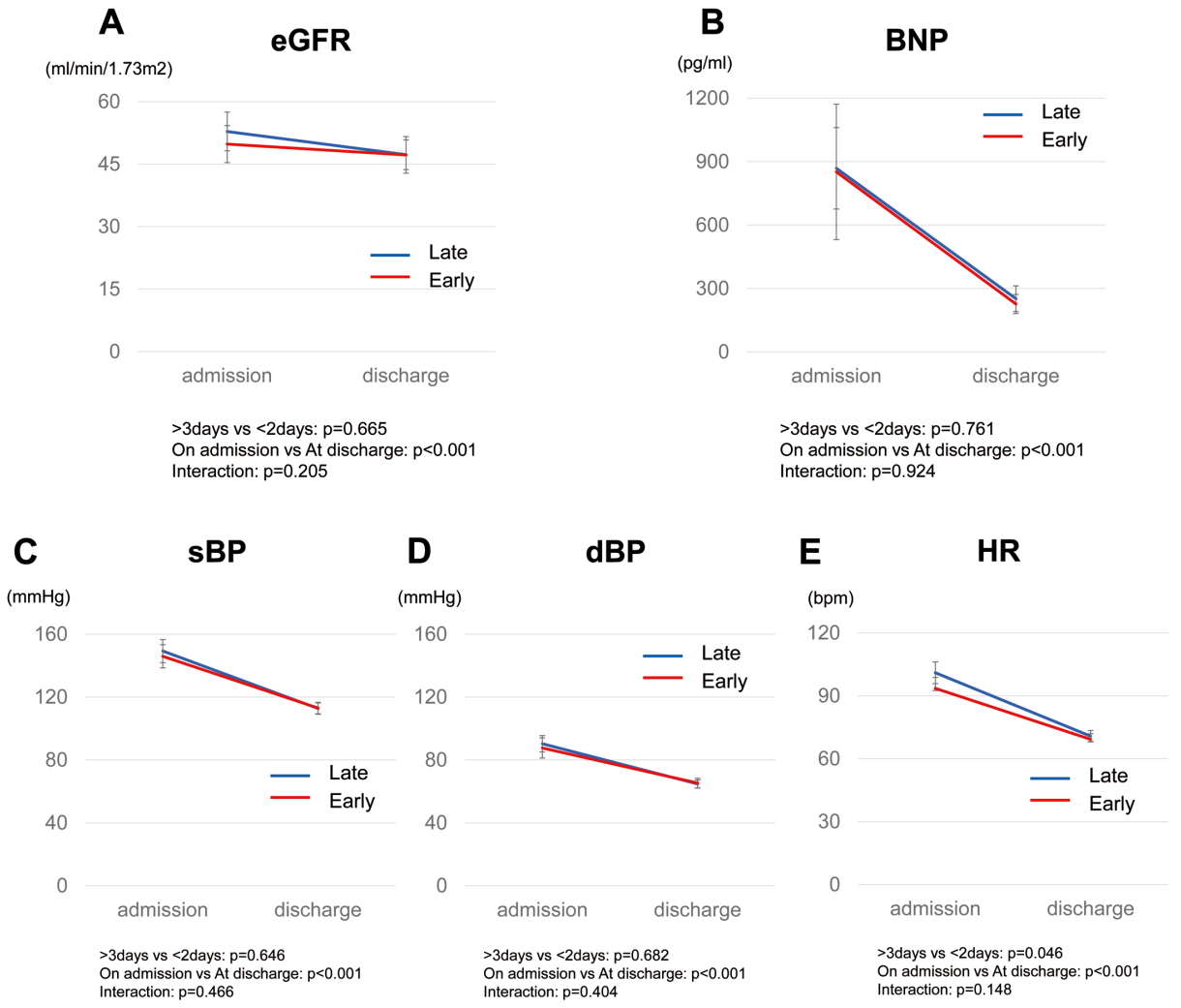

Figure 4. Comparisons of changes in (**A**) estimated glomerular filtration rate (GFR), (**B**) B-type natriuretic peptide (BNP), (**C**) systolic blood pressure (SBP), (**D**) diastolic blood pressure, and (**E**) heart rate (HR) from admission to discharge in the early and late groups. Data were analyzed by repeated-measures ANOVA. Data are given as the mean with standard error.

more, multivariate analysis of factors associated with the length of hospital stay showed that lower albumin concentrations, catecholamine use, and a longer time to initiation of SGLT2i were strongly associated with the length of hospital stay (**Table 2**).

Urine Output and Initiation of Cardiac Rehabilitation

Mean urine output over 2 days after admission was higher in the early than late group (2,582.3±1,498.5 vs. 2,003.1±1,133.9 mL; P=0.012; **Figure 3A**). Similar results were seen after correcting urine volume for body weight (40.0±21.2 vs. 32.0±19.5 mL/kg; P=0.022; **Figure 3B**).

Cardiac rehabilitation was initiated earlier in the early than late group (2.5±1.2 vs. 3.8±2.2 days; P<0.001; **Figure 3C**).

Changes in Renal Function, BNP, and Hemodynamics

Changes in eGFR and BNP were comparable in the 2 groups (**Figure 4A**,**B**). Changes in SBP, DBP, and heart rate were also comparable in the 2 groups (**Figure 4C**–**E**).

Characteristics at Discharge

Characteristics at discharge are presented in **Table 1**. BNP concentrations, eGFR, and other parameters, including blood pressure and heart rate, were comparable between the 2 groups. Conversely, the prescription rate of ACEi/ARBs was lower and that of ARNI was higher in the early than late group, and the dose of loop diuretics tended to be lower in the early group.

HF Readmissions and Composite Outcomes Over 3 Months

We investigated HF readmissions and the composite outcome over a 3-month period from discharge in 143 patients (excluding 25 patients who transferred to other hospitals). Kaplan-Meier curve analysis showed that the early initiation of SGLT2i reduced HF readmissions and the composite outcome in the 3-month period (**Figure 5**). Univariate analysis (Model 0) showed that SGLT2i were strongly associated with HF readmissions and the composite outcome over the 3-month period (HF readmissions: hazard

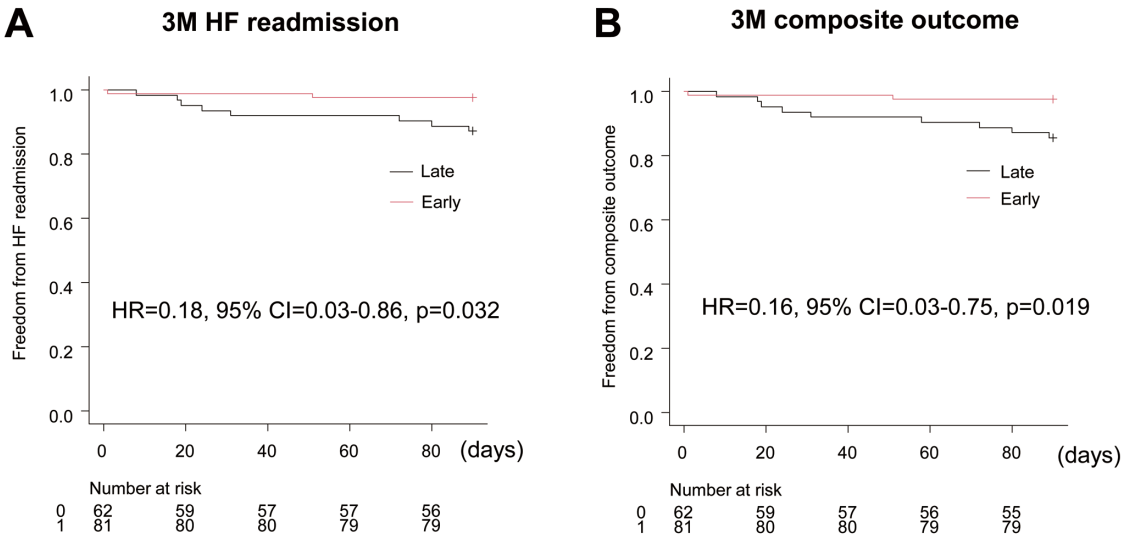

Figure 5. Kaplan-Meier survival curves showing freedom from (**A**) heart failure (HF) readmission and (**B**) the composite outcome (death from any cause or HF readmission) over the 3-month period from discharge between the early and late groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were analyzed by Cox proportional hazards regression analysis.

ratio [HR] 0.200 [95% CI 0.042–0.942]; composite outcome: HR 0.265 [95% CI 0.071–0.980]; **Table 3A**). After adjusting for confounders (Model 1), SGLT2i remained strongly associated with HF rehospitalization and the composite outcome in the 3-month period (HF readmissions: HR 0.205 [95% CI 0.043–0.968]; composite outcome: HR 0.264 [95% CI 0.071–0.982]; **Table 3B**). The association disappeared in Model 2, in which other confounders and mediators (medications at discharge) were added to the analysis (HF readmissions: HR 0.382 [95% CI 0.064–2.274]; composite outcome: HR 0.543 [95% CI 0.117–2.526]; **Table 3B**).

Discussion

The present study demonstrated the possible efficacy of early initiation of SGLT2i in terms of length of hospital stay in patients with ADHF. This is the first report to compare the timing of initiation of SGLT2i. First, hospital stay was significantly shorter in the group in which SGLT2i were initiated early. When stratified by EF, patients with HFrEF and HFmrEF in the early group had a significantly shorter hospital stay than those in the late group, whereas patients with HFpEF in the early group tended to have a shorter hospital stay, although the difference did not reach statistical significance. The length of hospital stay is greatly influenced by the severity of HF, comorbidities, treatment during hospitalization, and transfer to other hospitals. However, in the present study, there were no differences between the 2 groups in terms of the severity of HF, comorbidities, treatment during hospitalization, or rate of hospital transfer. Furthermore, in a multivariate analysis including these factors, early initiation of SGLT2i was a factor strongly associated with a shorter hospital stay.

The early group had a significantly higher 2-day urine output. The higher urine output in the early group during the first 2 days may be due purely to the additional SGLT2i, which is consistent with the findings of a previous report,[16] because there was no difference in treatment, including other diuretics, between the 2 groups.

Further, the time to start rehabilitation was significantly earlier in the early than late group. The high urinary output during the first 2 days may indicate early improvement of HF symptoms, and, consequently, early initiation of rehabilitation. Early initiation of rehabilitation would directly lead to a shorter hospital stay.

Conversely, there were no differences in blood pressure changes, renal function, or BNP at the time of both admission and discharge between the 2 groups, whereas reductions in heart rate were greater in the early group. Blood pressure, heart rate, renal function, and BNP at discharge did not differ at all between the 2 groups. However, the rate of HF readmissions and composite outcomes at 3 months were significantly lower in the early than late group. Multivariate analysis in a model adjusted for age, EF, blood pressure, and renal function showed the association, but the association disappeared in a model including other confounders and mediators. This may be due, in large part, to the small sample size and the presence of mediators such as HF drugs that directly affect prognosis. The effects of loop diuretic dose may have been too large to mask the association between early initiation of SGLT2i and prognosis. Patients in the early group tended to receive lower doses of loop diuretics at discharge (10.5±13.8 vs. 14.7±15.0 mg). Early initiation of SGLT2i may indirectly affect prognosis by reducing the dose of loop diuretics. Further, prescription rates of β-blockers and MRA were high in both groups, but the prescription rate of ARNI was significantly higher in the early than late group. It is possible that differences in sacubitril/valsartan prescription rates may have influenced to differences in HF readmission rates in the present study. Sacubitril/valsartan has been shown to have beneficial effects on HF readmission and prognosis in the Angiotensin-Neprilysin Inhibition versus Enalapril

Table 3. (A) Univariate Analysis (Model 0) of Factors Associated With HF Readmission and the Composite Outcome in the 3-Month Period After Discharge, (B) Multivariate Analysis (Models 1 and 2) of Factors Associated With HF Readmission and the Composite Outcome in the 3-Month Period From Discharge

(A) Variables	HR	95% CI	P value
HF readmission within 3 months			
On admission			
Age	1.047	0.988–1.108	0.115
Male sex	0.562	0.158–1.995	0.373
EF	1.004	0.967–1.042	0.842
NYHA	1.771	0.640–4.900	0.271
ICM	1.037	0.268–4.010	0.958
De novo HF hospitalization	0.770	0.199–2.981	0.706
Body weight	0.995	0.960–1.032	0.797
BMI	0.990	0.889–1.104	0.868
SBP	0.978	0.956–1.001	0.055
DBP	0.968	0.937–1.000	0.051
Heart rate	0.994	0.969–1.020	0.667
BNP	0.998	0.996–1.000	0.097
Hb	1.080	0.846–1.377	0.537
BUN	1.016	0.992–1.044	0.166
eGFR	0.987	0.956–1.019	0.442
UA	1.059	0.772–1.452	0.723
Na	0.960	0.830–1.110	0.581
K	0.524	0.168–1.635	0.266
Albumin	2.406	0.585–9.906	0.223
Treatments in hospital			
Early SGLT2i start	0.183	0.039–0.865	0.032
NPPV	2.836	0.733–10.97	0.131
Catecholamine	3.046	0.787–11.79	0.106
Vasodilator	0.422	0.089–1.988	0.275
Carperitide	0.838	0.106–6.620	0.867
Comorbidities			
AF	2.976	0.769–11.51	0.114
COPD	–	0–Inf	0.998
Diabetes	0.758	0.213–2.686	0.667
Cancer	–	0–Inf	0.998
CVD	–	0–Inf	0.998
Sleep disorder	–	0–Inf	0.998
At discharge			
NYHA	1.183	0.264–5.288	0.825
BNP	0.996	0.991–1.002	0.228
Hb	1.014	0.763–1.346	0.925
BUN	1.022	0.998–1.045	0.066
eGFR	0.984	0.947–1.022	0.409
UA	1.199	0.864–1.665	0.277
Na	0.960	0.830–1.110	0.581
K	0.870	0.248–3.044	0.827
Albumin	2.408	0.585–9.906	0.223
SBP	0.973	0.935–1.012	0.176
DBP	0.959	0.910–1.011	0.119
Heart rate	0.985	0.934–1.040	0.601
ACEi/ARB	1.022	0.295–3.530	0.972
ARNI	0.605	0.156–2.341	0.467
β-blocker	0.119	0.030–0.461	0.002
MRA	0.310	0.080–1.203	0.090
PDE3i	1.707	0.362–8.040	0.498
Loop diuretics	–	0–Inf	0.998
Loop diuretic dose	1.044	1.018–1.071	<0.001
Tolvaptan	3.237	0.937–11.18	0.063

(**Table 3** continued the next page.)

(A) Variables	HR	95% CI	P value
Composite outcome			
On admission			
Age	1.063	1.003–1.128	0.040
Male sex	0.446	0.136–1.464	0.183
EF	1.003	0.968–1.040	0.846
NYHA	1.647	0.627–4.319	0.310
ICM	0.903	0.239–3.407	0.881
De novo HF hospitalization	0.880	0.233–3.320	0.851
Body weight	0.988	0.953–1.025	0.542
BMI	0.986	0.889–1.094	0.793
SBP	0.979	0.958–1.000	0.051
DBP	0.970	0.941–1.000	0.053
Heart rate	0.995	0.972–1.019	0.698
BNP	0.998	0.996–1.000	0.079
Hb	1.045	0.829–1.318	0.707
BUN	1.016	0.990–1.042	0.224
eGFR	0.985	0.958–1.016	0.357
UA	1.059	0.772–1.452	0.723
Na	0.942	0.823–1.078	0.383
K	0.587	0.199–1.728	0.334
Albumin	2.227	0.584–8.481	0.240
Treatments in hospital			
Early SGLT2i start	0.162	0.035–0.750	0.019
NPPV	2.488	0.660–9.382	0.178
Catecholamine	2.673	0.708–10.08	0.146
Vasodilator	0.373	0.080–1.729	0.207
Carperitide	0.752	0.096–5.880	0.786
Comorbidities			
AF	2.228	0.652–7.612	0.201
COPD	–	0–Inf	0.998
Diabetes	0.950	0.290–3.115	0.933
Cancer	–	0–Inf	0.998
CVD	–	0–Inf	0.997
Sleep disorder	–	0–Inf	0.998
At discharge			
NYHA	1.183	0.284–4.919	0.817
BNP	0.997	0.992–1.002	0.294
Hb	0.961	0.731–1.264	0.777
BUN	1.021	0.998–1.044	0.064
eGFR	0.982	0.946–1.019	0.332
UA	1.147	0.833–1.576	0.400
Na	0.934	0.799–1.093	0.397
K	0.726	0.223–2.380	0.600
Albumin	1.900	0.490–7.360	0.352
SBP	0.966	0.929–1.004	0.077
DBP	0.954	0.907–1.004	0.069
Heart rate	0.993	0.945–1.045	0.804
ACEi/ARB	0.848	0.259–2.781	0.786
ARNI	0.526	0.139–1.986	0.343
β-blocker	0.103	0.027–0.388	<0.001
MRA	0.227	0.066–0.777	0.018
PDE3i	1.517	0.327–7.023	0.593
Loop diuretics	–	0–Inf	0.998
Loop diuretic dose	1.040	1.014–1.066	0.002
Tolvaptan	2.691	0.821–8.819	0.102

(**Table 3** continued the next page.)

(B) Variables	Model 1			Variables	Model 2		
	HR	95% CI	P value		HR	95% CI	P value
Association with HF readmission				**Association with HF readmission**			
Early SGLT2i start	0.191	0.040–0.907	0.037	**Early SGLT2i start**	0.342	0.055–2.119	0.249
On admission				**On admission**			
Age	1.052	0.983–1.125	0.142	Age	1.026	0.936–1.123	0.581
EF	1.001	0.962–1.041	0.947	EF	0.953	0.898–1.011	0.113
SBP	0.975	0.950–1.002	0.065	De novo HF hospitalization	0.457	0.075–2.785	0.396
eGFR	1.012	0.974–1.050	0.543	SBP	0.980	0.941–1.022	0.349
				DBP	1.017	0.956–1.082	0.585
				BNP	0.998	0.996–1.001	0.181
				eGFR	1.018	0.980–1.057	0.342
				At discharge			
				ACEi/ARB	0.619	0.076–4.997	0.652
				ARNI	1.265	0.135–11.84	0.837
				β-blocker	0.231	0.023–2.294	0.211
				MRA	0.170	0.024–1.173	0.072
				Loop diuretic dose	1.052	1.008–1.099	0.021
				Tolvaptan	1.450	0.298–7.030	0.644
Association with composite outcome				**Association with composite outcome**			
Early SGLT2i start	0.165	0.035–0.770	0.021	**Early SGLT2i start**	0.291	0.048–1.756	0.178
On admission				**On admission**			
Age	1.075	1.002–1.153	0.044	Age	1.035	0.947–1.131	0.448
EF	0.998	0.961–1.036	0.925	EF	0.945	0.891–1.003	0.063
SBP	0.975	0.951–1.001	0.059	De novo HF hospitalization	0.450	0.075–2.700	0.362
eGFR	1.013	0.976–1.050	0.501	SBP	0.979	0.940–1.020	0.316
				DBP	1.020	0.959–1.086	0.522
				BNP	0.998	0.996–1.001	0.151
				eGFR	1.024	0.985–1.064	0.221
				At discharge			
				ACEi/ARB	0.320	0.047–2.178	0.244
				ARNI	0.719	0.092–5.591	0.753
				β-blocker	0.218	0.020–2.280	0.203
				MRA	0.102	0.016–0.652	0.015
				Loop diuretic dose	1.046	1.003–1.091	0.036
				Tolvaptan	1.391	0.291–6.634	0.679

CI, confidence interval; HF, heart failure; HR, hazard ratio; Inf, infinite. Other abbreviations as in Table 1.

in Heart Failure (PARADIGM-HF)[21] and Andiontension-Neprilysin Inhibition in Heart Failure with Preseved Ejection Fraction (PARAGON-HF)[22] trials, as well as in their pooled analysis,[23] in HF patients. Combination therapy using multiple drugs is now a common therapeutic strategy for HF. In this context, SGLT2i have been reported to slow the progression of renal dysfunction, are less likely to cause hyperkalemia, and are less likely to affect hemodynamics, making it easier to introduce other drugs. In the present study, symptoms in patients in the early group improved earlier, leading to a stabilization of the hemodynamic status and allowed the prescription of ARNI and other drugs, despite the shorter hospitalization period. This may have resulted in differences between the 2 groups in HF readmission rates and prognosis during the 3-month period from discharge. Differences in HRs for HF rehospitalization and the composite outcome in Model 0 and Model 2 (HR: 0.183 to 0.382 and 0.162 to 0.291, respectively) may reflect the effects of these drugs. Although the sample size was small and statistical significance was not reached, the HRs for the early initiation of SGLT2i were similarly below 1.0 in Model 2, suggesting their efficacy.

The major limitation associated with the present study is its retrospective, observational nature. Another major limitation is that decisions to initiate SGLT2i are left to the attending physician, which may have led to selection bias. However, because there were no differences in patient characteristics between the 2 groups, the influence of selection bias seemed to be minimal.

The GDMT for HF is often introduced during hospitalization in patients admitted with ADHF. Because it has been reported that the effects of SGLT2i and ARNI on clinical outcomes can be seen as early as after 1 month from initiation,[24–27] it is desirable to introduce GDMT as early as possible during ADHF hospitalization. Until now, it has not been clear when SGLT2i should be initiated during

hospitalization, and the criteria for initiation varied from one attending physician to another. The finding of this study suggest that early initiation of SGLT2i after hospitalization leads to a shorter hospital stay and improves the 3-month prognosis. The results of this study may help in to establish routine clinical practice for patients with ADHF in the future.

In conclusion, early initiation of SGLT2i may shorten hospital stays and is associated with reduced short-term HF readmissions and better prognosis.

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IRB Information

The study protocol was approved by the Institutional Review Board of Japanese Red Cross Fukuoka Hospital (Approval no. 404), and informed consent was obtained from patients before participating in the study and the release of study data.

Data Availability

The deidentified participant data will not be shared.

References

1. Okura Y, Ramadan MM, Ohno Y, Mitsuma W, Tanaka K, Ito M, et al. Impending epidemic: Future projection of heart failure in Japan to the year 2055. *Circ J* 2008; **72:** 489–491.
2. Ide T, Kaku H, Matsushima S, Tohyama T, Enzan N, Funakoshi K, et al. Clinical characteristics and outcomes of hospitalized patients with heart failure from the large-scale Japanese Registry Of Acute Decompensated Heart Failure (JROADHF). *Circ J* 2021; **85:** 1438–1450.
3. Kaku H, Funakoshi K, Ide T, Fujino T, Matsushima S, Ohtani K, et al. Impact of hospital practice factors on mortality in patients hospitalized for heart failure in Japan: An analysis of a large number of health records from a nationwide claims-based database, the JROAD-DPC. *Circ J* 2020; **84:** 742–753.
4. Hamaguchi S, Kinugawa S, Goto D, Tsuchihashi-Makaya M, Yokota T, Yamada S, et al. Predictors of long-term adverse outcomes in elderly patients over 80 years hospitalized with heart failure: A report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2011; **75:** 2403–2410.
5. Kanaoka K, Okayama S, Nakai M, Sumita Y, Nishimura K, Kawakami R, et al. Hospitalization costs for patients with acute congestive heart failure in Japan. *Circ J* 2019; **83:** 1025–1031.
6. Shiraishi Y, Kohsaka S, Sato N, Takano T, Kitai T, Yoshikawa T, et al. 9-year trend in the management of acute heart failure in Japan: A report from the national consortium of acute heart failure registries. *J Am Heart Assoc* 2018; **7:** e008687.
7. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Ferreira JP, Zannad F, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: A comparative analysis of three randomized controlled trials. *Lancet* 2020; **396:** 121–128.
8. Tromp J, Ouwerkerk W, Veldhuisen DJ, Hillege HL, Richards AM, Meer P, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC Heart Fail* 2022; **10:** 73–84.
9. Tsutsui H, Ide T, Ito H, Kihara Y, Kinugawa K, Kinugawa S, et al. JCS/JHFS 2021 guideline focused update on diagnosis and treatment of acute and chronic heart failure. *Circ J* 2021; **85:** 2252–2291.
10. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; **381:** 1995–2008.
11. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383:** 1413–1424.
12. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021; **385:** 1451–1461.
13. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022; **387:** 1089–1098, doi:10.1056/NEJMoa2206286.
14. Butler J, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. *Eur Heart J* 2022; **43:** 416–426.
15. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: A patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med* 2022; **28:** 1956–1964, doi:10.1038/s41591-022-01971-4.
16. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med* 2021; **384:** 117–128.
17. Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). *Eur J Heart Fail* 2020; **22:** 713–722.
18. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: A multinational randomized trial. *Nat Med* 2022; **28:** 568–574.
19. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham study. *N Engl J Med* 1971; **285:** 1441–1446.
20. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant* 2013; **48:** 452–458.
21. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371:** 993–1004.
22. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381:** 1609–1620.
23. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation* 2020; **141:** 352–361.
24. Berg DD, Jhund PS, Docherty KF, Murphy SA, Verma S, Inzucchi SE, et al. Time to clinical benefit of dapagliflozin and significance of prior heart failure hospitalization in patients with heart failure with reduced ejection fraction. *JAMA Cardiol* 2021; **6:** 499–507.
25. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction: The EMPEROR-Reduced trial. *Circulation* 2021; **143:** 326–336.
26. Packer M, McMurray JJ, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure. *Circulation* 2015; **131:** 54–61.
27. Morrow DA, Velazquez EJ, DeVore AD, Desai AS, Duffy CI, Ambrosy AP, et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. *Circulation* 2019; **139:** 2285–2288.