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ORIGINAL ARTICLE

Uptitration of Sacubitril/Valsartan and Outcomes in Patients With Heart Failure

— Insight From the REVIEW-HF Registry —

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Background: Guideline-directed medical therapy has become an important component of heart failure (HF) therapy, with sacubitril/valsartan as one of the recommended drugs; however, the real-world prognostic implications of sacubitril/valsartan uptitration are unclear.

Methods and Results: Patients with HF newly initiated on sacubitril/valsartan were registered in a retrospective multicenter study (REVIEW-HF). In all, 995 patients were divided into 3 groups according to the maximum dose achieved: high dose, sacubitril/valsartan 400 mg; intermediate dose, sacubitril/valsartan 200–<400 mg; and low dose, sacubitril/valsartan <200 mg. A total of 397 (39.9%) patients received high-dose sacubitril/valsartan; they had a significantly lower risk of mortality or HF hospitalization than patients in the low-dose (hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.29–0.53; P<0.001) and intermediate-dose (HR 0.64; 95% CI 0.45–0.94; P=0.03) groups. In the multivariable Cox regression model, higher systolic blood pressure and maintained geriatric nutritional risk index were significantly associated with a higher incidence of achieving a high dose of sacubitril/valsartan. Patients who did not receive high-dose sacubitril/valsartan experienced more hypotension during the follow-up period, whereas hyperkalemia, severe renal events, and angioedema did not differ across the achieved dose classifications.

Conclusions: Patients who achieved sacubitril/valsartan uptitration had a better prognosis than those who did not. Before sacubitril/valsartan uptitration, patients need to monitor blood pressure closely to prevent worsening events.

Key Words: Heart failure; REVIEW-HF registry; Sacubitril/valsartan; Titration

Heart failure (HF) is a global health issue associated with increased morbidity, mortality, and economic burden in older patients.[1,2] Guideline-directed medical therapy (GDMT) is an important component of HF drug therapy.[3–5] The guidelines recommend sacubitril/valsartan as one of the GDMT drugs to be prescribed and advise titrating it to a high dose.[6–9] The tolerability through early titration of sacubitril/valsartan, based on a combination of patient groups in randomized controlled trials (RCTs) for HF,[10] and the safety of early titration of sacubitril/valsartan have been proven.[11] However, real-world prognostic data of sacubitril/valsartan uptitration for HF are insufficient. Approximately 20% of patients screened for PARADIGM-HF (Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine

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Impact on Global Mortality and Morbidity in Heart Failure Trial) were unable to complete the run-in period, which required patients to tolerate a maximum dose of 10 mg twice daily of enalapril for 2 weeks, followed by a 4- to 6-week treatment with up to 97 mg/103 mg of sacubitril/valsartan twice daily.[12] The prognostic implications of uptitrating sacubitril/valsartan through real-world dose achievement, including in patients who cannot participate in an RCT, are unclear. Moreover, the factors involved in sacubitril/valsartan uptitration, including comorbidities, other medications, disease severity, and malnutrition, are unknown. Therefore, we investigated the association between titrations using data from the introduction of sacubitril/valsartan in Japan.

Methods

Study Design

The Real-world Evidence of Angiotensin Receptor-Neprilysin Inhibitor in Patients with Heart Failure (REVIEW-HF) registry is a nationwide, multicenter study in Japan designed to evaluate the features and outcomes of patients with HF who were newly prescribed sacubitril/valsartan during the first year after its approval by the government, from August 2020 to August 2021.[11] During this period, the Japanese government, under its insurance system, required patients to be treated with sacubitril/valsartan and visit hospitals every 2 weeks for close monitoring. All patients who were initiated on sacubitril/valsartan for HF management were enrolled in the REVIEW-HF registry from 17 large-scale hospitals. Patients <20 years of age were excluded from the study.

The present study adhered to the principles set forth in the Declaration of Helsinki. The study protocol, including the use of an opt-out consent method, was approved by the Ethics Committee of Toho University Omori Medical Center (No. M21257) and the local ethics committees of all participating institutions. Furthermore, the study was registered with the University Hospital Medical Information Network Clinical Trial Registry (UMIN000047636) before the first patient was enrolled, in accordance with the International Committee of Medical Journal Editors.

From the REVIEW-HF registry data, we classified patients according to whether they reached the defined doses of sacubitril/valsartan and confirmed the correlation between the dose classification in patients who underwent titration. The uptitration protocol was at the discretion of individual physicians. Patients were divided into 3 groups according to the maximum dose of sacubitril/valsartan achieved at least once during the follow-up period: high dose, 400 mg; intermediate dose, 200–<400 mg; and low dose, <200 mg.

Data Collection

In this study, data were retrospectively collected from patient records using an electronic data capture system. Baseline characteristics and prespecified longitudinal timepoint data were collected, including laboratory findings (at 2 weeks and 1, 3, 6, and 12 months). To assess the risk of malnutrition, the Geriatric Nutritional Risk Index (GNRI), which is commonly used to assess nutritional status in patients with HF, was calculated with albumin (g/dL) and body mass index (BMI) (kg/m^2) as follows.[13–15]

$$\mathrm{GNRI} = 14.89 \times \mathrm{albumin} + 41.7 \times \mathrm{BMI}/22$$

Outcomes

The primary outcome was a composite endpoint of all-cause death and HF hospitalization. The time to the first occurrence of the composite endpoint of all-cause death or HF hospitalization and each component of the composite outcome or cardiovascular mortality was also examined. Cardiovascular mortality included death that resulted from acute coronary syndrome, heart failure, stroke, sudden death, and other cardiac causes. In addition, we assessed the discontinuation of sacubitril/valsartan during the follow-up period. Death was not included as a reason for drug discontinuation.

Moreover, we evaluated the occurrence of adverse events potentially related to sacubitril/valsartan administration within 3 months of drug initiation, defined as a composite of hypotension, hyperkalemia, renal events, or angioedema. Referring to our previous study,[12] the adverse events were defined as follows.

Hypotension was classified as moderate, severe or symptomatic. Moderate hypotension was defined as a reduction in systolic blood pressure (SBP) to <90 mmHg if baseline SBP was ≥100 mmHg, or a reduction in SBP >10% if baseline SBP was <100 mmHg. Severe hypotension was defined as a reduction in SBP to <80 mmHg if baseline SBP was ≥100 mmHg or a reduction in SBP >20% if baseline SBP was <100 mmHg. Symptomatic hypotension was defined as a reduction in SBP reduction to <95 mmHg if baseline SBP was ≥100 mmHg or a reduction in SBP >5% if baseline SBP was <100 mmHg.

Hyperkalemia was defined as a potassium level ≥5.6 mmol/L. Worsening kidney function was defined as a reduction in the estimated glomerular filtration rate (eGFR) ≥50% from baseline, an absolute reduction in eGFR >30 mL/min/1.73 m^2 from baseline, or the initiation of hemodialysis. Angioedema was defined as clinically determined angioedema by a physician.

Statistical Analysis

Patient characteristics are presented as numbers and percentages for categorical variables, and as the mean±SD or median value with interquartile range for continuous variables. For continuous variables, differences between the 3 dose groups (high, intermediate, and low) were assessed using 1-way analysis of variance (ANOVA) and the Kruskal-Wallis test. Student's t-test or the Mann-Whitney U test was used for comparisons between 2 groups. Differences in categorical variables were compared using the Chi-squared test. Two-way ANOVA followed the Dunnett post hoc test or Steel–Dwass post hoc test was used to compare variables between the dose group and the intermediate- or low-dose group individually. Statistical significance was defined as 2-sided $P<0.05$.

Associations between dose classification and outcomes during the follow-up period were estimated using logistic regression analysis to compute odds ratios, hazard ratios (HR), and 95% confidence intervals (CIs) for each outcome. The cumulative incidence of the outcome was estimated using Kaplan-Meier curves, and a log-rank test was performed to assess differences between the sacubitril/valsartan dose groups. Individual curves were compared post hoc using the Holm–Bonferroni method.

To account for potential immortal time bias, we assessed the association between sacubitril/valsartan dose achievement and the development of outcomes using time-updated Cox proportional hazard models.[16] Patients

were initially considered in a low-dose window before reaching their maximum dose of sacubitril/valsartan; if the patient subsequently uptitrated to their maximum dose, then the patient was reclassified at that point in time. Using the same time-updated models, we then assessed the potential modification of the treatment effect on clinical outcomes before or after uptitration. To estimate the predictors of reaching a high dose of sacubitril/valsartan, the following variables were used in a multivariable analysis model: age, sex, New York Heart Association (NYHA) functional class, SBP, eGFR <30 mL/min/1.73 m^2, GNRI, prior hospitalization for HF, and left ventricular ejection fraction phenotype. Statistical analyses were performed using JMP Pro 16 software (SAS Institute Inc., Cary, NC, USA) and R version 4.3.2 Windows.

Results

Overall, 995 patients were enrolled in the REVIEW-HF registry, with 397 (39.9%) receiving a high dose, 239 (24.0%) receiving an intermediate dose, and 359 (36.1%) receiving a low dose of sacubitril/valsartan. The median duration of achieved high-dose sacubitril/valsartan treatment was 64 days. The mean follow-up duration was 403±170 days. Of the 995 patients included, 94 (9.4%) died and 180 (18.1%) were hospitalized for HF after being prescribed sacubitril/valsartan.

Baseline Characteristics According to Sacubitril/Valsartan Dose Classification

The baseline characteristics according to sacubitril/valsartan dose classification are presented in **Table 1**. Overall, 291 (29.2%) participants were female, and the mean age was 69.6 years, with 56.8% of participants aged >70 years and 24.8% aged >80 years (**Table 1**). Of the patients who achieved high doses of sacubitril/valsartan, approximately half were aged >70 years, and one-quarter were aged >80 years. Three-quarters of patients (76.7%) had NYHA classes II and III. Baseline SBP and diastolic blood pressure were significantly higher in patients receiving a high dose of sacubitril/valsartan than in those receiving low and intermediate doses, and 20.9% of patients receiving a high dose of sacubitril/valsartan had SBP >140 mmHg at baseline (**Table 1**). Patients in the high-dose group had higher BMI, albumin levels, and GNRI, and lower N-terminal pro B-type natriuretic peptide (NT-proBNP) levels than those in the low- and intermediate-dose groups at baseline (**Table 1**). Regarding the proportion of comorbidities, hypertension was more prevalent in patients receiving a high dose of sacubitril/valsartan, whereas other comorbidities did not differ across the sacubitril/valsartan dose classifications (**Table 1**).

Table 1. Baseline Characteristics According to the Maximum Dose of Sacubitril/Valsartan

	Overall (n=995)	Sacubitril/valsartan			P value
		Low (<200 mg) dose (n=359)	Intermediate (200–<400 mg) dose (n=239)	High (400 mg) dose (n=397)	
Age (years)	69.6±14.5	71.4±13.9	70.0±14.5	67.7±14.8*	0.01
Age >70 years	565 (56.8)	219 (61.0)	135 (56.5)	211 (53.1)	0.09
Age >80 years	247 (24.8)	99 (27.6)	65 (27.2)	83 (20.9)	0.07
Female sex	291 (29.2)	123 (34.3)	72 (30.1)	96 (24.2)*	0.01
BMI (kg/m^2)	23.4±4.7	22.3±4.3	23.3±4.7	24.4±4.9*,†	<0.001
NYHA functional class					<0.001
I	149 (15.0)	39 (10.9)	41 (17.2)	69 (17.4)	
II	481 (48.3)	142 (39.6)	119 (49.8)	220 (55.4)	
III	282 (28.3)	136 (37.9)	60 (25.1)	86 (21.7)	
IV	71 (7.1)	39 (10.9)	14 (5.9)	18 (4.5)	
Ischemic etiology of HF	361 (36.3)	118 (32.9)	86 (36.0)	157 (39.5)	0.16
Heart rate (beats/min)	74.4±14.4	76.0±14.3	73.7±15.5	73.2±13.7*	0.01
SBP (mmHg)	116.4±20.4	109.6±19.6	115.1±19.0	123.7±19.5*,†	<0.001
SBP category					<0.001
<100 mmHg	200 (20.1)	116 (32.3)	48 (20.1)	36 (9.1)	
100–<120 mmHg	359 (36.1)	139 (38.7)	90 (37.7)	130 (32.7)	
120–<140 mmHg	270 (27.1)	72 (20.1)	71 (29.7)	127 (32.0)	
≥140 mmHg	135 (13.6)	30 (8.4)	22 (9.2)	83 (20.9)	
DBP (mmHg)	68.2±13.9	65.6±13.3	66.3±13.2	72±14.1*,†	<0.001
Hemoglobin (g/dL)	12.7±2.3	12.3±2.2	12.6±2.4	13.0±2.4*	0.001
Potassium (mEq/L)	4.3±0.5	4.3±0.5	4.3±0.5	4.3±0.5	0.75
Albumin (g/dL)	3.7±0.6	3.5±0.7	3.7±0.6	3.8±0.6*,†	<0.001
GNRI	98.6±13.8	94.0±14.0	98.6±12.7	103.0±12.9*,†	<0.001
eGFR (mL/min/1.73 m^2)	48.5±22.7	48.3±27.3	48.5±20.7	48.6±19.0*	0.97
eGFR <60 mL/min/1.73 m^2	737 (74.1)	268 (74.7)	173 (72.4)	296 (74.6)	0.79
eGFR <30 mL/min/1.73 m^2	194 (19.5)	84 (23.4)	50 (20.9)	60 (15.1)	0.01
NT-proBNP (pg/mL)	2,118 [982–4,463]	2,984 [1,617–6,450]	1985 [885–4,773]	1,724 [645–3,269]*,†	<0.001
LVEF (%)	39.1±14.9	37.9±15.0	40.3±15.4	39.4±14.4	0.13

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

	Overall (n=995)	Sacubitril/valsartan			P value
		Low (<200 mg) dose (n=359)	Intermediate (200–<400 mg) dose (n=239)	High (400 mg) dose (n=397)	
Medical history					
Prior hospitalization for HF	641 (64.4)	259 (72.1)	153 (64.0)	229 (57.7)*	<0.001
Diabetes	348 (35.0)	117 (32.6)	87 (36.4)	144 (36.3)	0.50
Hypertension	644 (64.9)	199 (55.4)	153 (64.6)	292 (73.6)*,†	<0.001
Coronary artery disease	362 (36.4)	115 (32.0)	90 (37.7)	157 (39.6)	0.09
Myocardial infarction	210 (21.1)	77 (19.8)	55 (23.0)	84 (21.2)	0.64
CABG	86 (8.6)	31 (8.6)	16 (6.7)	39 (9.8)	0.40
PCI	291 (29.2)	89 (76.1)	75 (86.2)	127 (88.2)	0.07
Atrial fibrillation	440 (44.2)	162 (45.1)	110 (46.0)	168 (42.3)	0.60
Hyperkalemia	62 (6.2)	16 (20.8)	14 (22.2)	32 (34.4)	0.12
VT/VF	115 (11.6)	50 (13.9)	24 (10.0)	41 (10.3)	0.21
Angioedema	33 (3.3)	13 (5.0)	9 (5.3)	11 (4.5)	0.73
COPD	64 (6.4)	27 (7.5)	17 (7.1)	20 (5.0)	0.34
Stroke	86 (8.6)	36 (10.0)	17 (7.1)	33 (8.3)	0.44
Dyslipidemia	518 (52.1)	173 (48.2)	124 (52.3)	221 (55.7)	0.12
Treatments					
ACEi	365 (36.7)	156 (43.5)	84 (35.1)	125 (31.5)*	0.01
ARB	595 (59.8)	189 (52.6)	146 (61.1)	260 (65.5)*	0.01
ACEi or ARB	942 (94.7)	336 (93.6)	225 (94.1)	381 (96.0)	0.32
β-blocker	827 (83.1)	297 (82.7)	196 (82.0)	334 (84.1)	0.76
MRA	679 (68.2)	260 (72.4)	158 (66.1)	261 (65.7)	0.10
Loop diuretics	772 (77.6)	295 (82.2)	183 (76.6)	294 (74.1)*	0.03
SGLT2i	344 (34.6)	140 (39.0)	77 (32.2)	127 (32.0)	0.09
Digoxin	46 (4.6)	28 (7.8)	7 (2.9)	11 (2.8)*	0.01
Statin	419 (42.1)	130 (36.2)	111 (46.4)	178 (44.8)*	0.02
Ivabradine	66 (6.6)	22 (6.1)	13 (5.4)	31 (7.8)	0.45
Pimobendan	103 (10.4)	53 (14.8)	22 (9.2)	28 (7.1)*	0.01
Pacemaker	95 (9.5)	31 (8.6)	24 (10.0)	40 (10.1)	0.76
CRT-P/CRT-D	111 (11.1)	58 (16.2)	26 (10.9)	27 (6.8)*	<0.001
ICD	154 (15.4)	68 (18.9)	33 (13.8)	53 (13.4)	0.08

Unless indicated otherwise, data are presented as the mean±SD or median [interquartile range] for continuous measures and as n (%) for categorical measures. *P<0.05 compared with low-dose group; †P<0.05 compared with intermediate-dose group. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; VF, ventricular fibrillation; VT, ventricular tachycardia.

Although patients receiving a high dose of sacubitril/valsartan were younger, predominantly male, were not in NYHA class III or IV, had a lower heart rate, higher hemoglobin levels, and were more likely to have an eGFR of ≥30 mL/min/1.73 m^2 and no prior HF hospitalizations compared with those in the intermediate-dose group, no significant differences were found between the intermediate- and high-dose groups (**Table 1**).

In terms of treatment at baseline, the prescription rates of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), loop diuretics, digoxin, statins, and pimobendan, and the prevalence of cardiac resynchronization therapy with a defibrillator or cardiac resynchronization therapy were significantly lower among patients receiving a high dose of sacubitril/valsartan compared with those on a low dose. No differences were observed between the intermediate- and high-dose groups (**Table 1**). The dosages of each ACEi and ARB are summarized in the **Supplementary Table**.

Outcomes in the Sacubitril/Valsartan According to Dose Classification and Kaplan-Meier Curves Adjusting Landmarked Time to the First Event

In the high-, intermediate-, and low-dose sacubitril/valsartan groups, the composite outcome (allcause death or HF hospitalization) occurred in 62 (15.6%), 51 (21.3%), and 129 (35.9%) patients, respectively. The overall clinical outcomes, with Kaplan-Meier curves adjusting the landmark time to the first event, are shown in the **Figure**. Patients who achieved a high dose of sacubitril/valsartan had a significantly lower risk of the composite outcome than those who reached low and intermediate doses (high vs. low dose: HR 0.39, 95% CI 0.29–0.53, P<0.001; high vs. intermediate dose: HR 0.64, 95% CI 0.45–0.94, P=0.03; **Figure A**).

All-cause death occurred in 18 (4.5%), 16 (6.7%), and 60 (16.7%) patients who reached a high, intermediate, and low dose of sacubitril/valsartan, respectively. The overall effect of titration with sacubitril/valsartan on the survival rate was significant (P<0.001; **Figure B**). Patients who

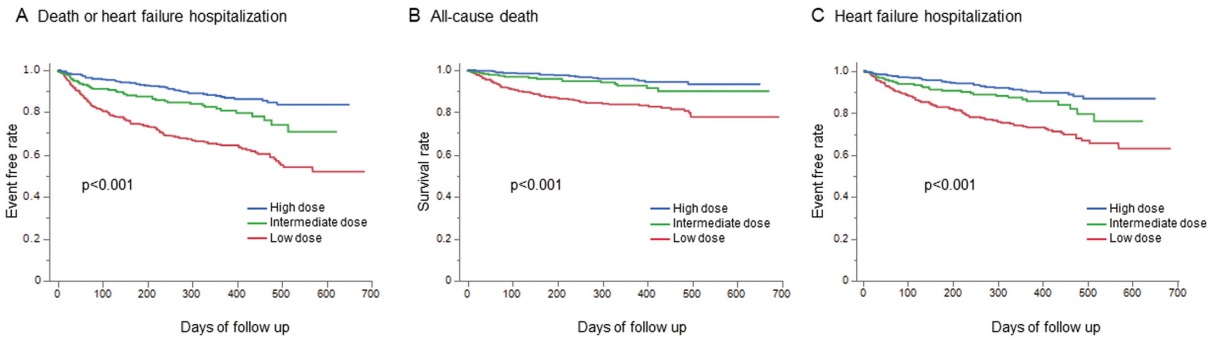

Figure. Kaplan-Meier curves for clinical outcomes according to dose classification of sacubitril/valsartan using time-updated Cox proportional hazard models. (**A**) Composite outcome (death or heart failure [HF] hospitalization); (**B**) all-cause death; (**C**) HF hospitalization. The high-, intermediate, and low-dose groups comprised patients who could tolerate sacubitril/valsartan up to 400, 200–<400 mg, and <200 mg, respectively, reaching the dose at least once during the follow-up period.

Table 2. Relevant Adverse Events and Discontinuation of Sacubitril/Valsartan According to Dose Classification Adjusting Landmarked Time to the First Event

	Overall (n=995)	Sacubitril/valsartan			P value
		Low (<200 mg) dose (n=359)	Intermediate (200–<400 mg) dose (n=239)	High (400 mg) dose (n=397)	
Relevant adverse events[A]	203 (20.4)	135 (37.6)	41 (17.2)	27 (6.8)	<0.001
Hypotension					
Any hypotension[B]	177 (17.8)	122 (34.0)	36 (15.1)	19 (4.8)	<0.001
Moderate hypotension[C]	95 (9.5)	65 (18.1)	22 (9.2)	8 (2.0)	<0.001
Severe hypotension[D]	68 (6.8)	51 (14.2)	11 (4.6)	6 (1.5)	<0.001
Symptomatic hypotension[E]	78 (7.8)	51 (14.2)	16 (6.7)	11 (2.8)	<0.001
Hyperkalemia					
Potassium ≥5.6 mmol/L	16 (1.6)	7 (1.9)	4 (1.7)	5 (1.3)	0.75
Potassium ≥6.0 mmol/L	9 (0.9)	6 (1.7)	0	3 (0.8)	0.10
Worsening kidney function					
eGFR reduction ≥50%	10 (1.0)	7 (1.9)	3 (1.3)	0	0.02
eGFR absolute reduction >30 mL/min/1.73 m^2	8 (0.8)	5 (1.4)	1 (0.4)	1 (0.3)	0.29
Initiation of dialysis	3 (0.3)	3 (0.8)	0	0	0.07
Other adverse events					
Angioedema	4 (0.4)	3 (0.8)	2 (0.8)	0	0.19
Discontinuation of sacubitril/valsartan					
Any discontinuation	160 (16.1)	121 (12.2)	29 (2.9)	10 (8.3)	<0.001
Due to relevant adverse events	85 (8.5)	70 (19.6)	12 (5.0)	3 (0.8)	<0.001

Unless indicated otherwise, data are given as n (%). [A]Defined as any of hypotension, hyperkalemia, renal events, or angioedema. [B]Hypotension or symptomatic hypotension events. [C]Systolic blood pressure (SBP) reduction to <90 mmHg if baseline SBP ≥100 mmHg or SBP reduction >10% if baseline SBP <100 mmHg. [D]SBP reduction to <80 mmHg if baseline SBP ≥100 mmHg or SBP reduction >20% if baseline SBP <100 mmHg. [E]SBP reduction to <95 mmHg if baseline SBP ≥100 mmHg or SBP reduction >5% if baseline SBP <100 mmHg. eGFR, estimated glomerular filtration rate.

achieved a high dose of sacubitril/valsartan had significantly lower mortality rates than patients who reached a low dose, whereas no difference in survival rates was observed between the high- and intermediate-dose groups (high vs. low dose: HR 0.25, 95% CI 0.15–0.43, P<0.001; high vs. intermediate dose: HR 0.61, 95% CI 0.31–1.20, P=0.14; **Figure B**).

HF hospitalization occurred in 51 (12.8%), 40 (16.7%), and 89 (24.8%) patients who reached a high, intermediate, and low dose of sacubitril/valsartan, respectively. The overall effect of sacubitril/valsartan titration on the hospitalization rate for HF was significant (P<0.001; **Figure C**). Patients who achieved a high dose of sacubitril/valsartan had a significantly lower risk of HF hospitalization than those on a low dose, whereas no difference in HF hospitalization rates was observed between the high- and intermediate-dose groups (high vs. low dose: HR 0.47, 95% CI 0.33–0.66, P<0.001; high vs. intermediate dose: HR 0.68, 95% CI 0.45–1.03, P=0.09; **Figure C**).

Cardiovascular mortality occurred in 13 (3.3%), 11

Table 3. Univariate and Multivariable Analysis Models of Factors Related to Achieving a High Dose of Sacubitril/Valsartan

	Univariate analysis model		Multivariable analysis model	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.99 (0.98–0.99)	<0.001	1.00 (0.98–1.01)	0.48
Female sex	0.66 (0.50–0.88)	0.01	0.68 (0.48–0.95)	0.02
NYHA Class III or IV	0.49 (0.37–0.65)	<0.001	0.60 (0.43–0.82)	0.01
SBP ≥140 mmHg (vs. <140 mmHg)	2.92 (2.01–4.25)	<0.001	3.26 (2.11–5.04)	<0.001
eGFR <30 mL/min/1.73 m^2 (vs. ≥30 mL/min/1.73 m^2)	0.61 (0.44–0.86)	0.01	0.60 (0.40–0.89)	0.01
GNRI ≥98 (vs. <98)	2.28 (1.72–3.01)	<0.001	1.88 (1.38–2.57)	<0.001
Prior hospitalization for HF	0.62 (0.47–0.80)	<0.001	0.75 (0.55–1.02)	0.07
HFrEF (vs. HFmrEF/HFpEF)	0.92 (0.71–1.19)	0.52	0.92 (0.67–1.27)	0.61

CI, confidence interval; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; OR, odds ratio. Other abbreviations as in Table 1.

(4.6%), and 47 (13.1%) patients who reached high, intermediate, and low doses of sacubitril/valsartan, respectively. Patients who achieved a high dose of sacubitril/valsartan had significantly lower cardiovascular mortality rates than patients who achieved a low dose. However, no difference in survival rates was observed between the high- and intermediate-dose groups (high vs. low dose: HR 0.23, 95% CI 0.13–0.43, P<0.001; high vs. intermediate dose: HR 0.64, 95% CI 0.29–1.43, P=0.28; **Supplementary Figure**).

Adverse Events and Discontinuation of Sacubitril/Valsartan According to Dose Classification, Adjusting Landmarked Time to the First Event

After adjusting for time to the first event with sacubitril/valsartan, 203 (20.4%) patients had a composite of hypotension, hyperkalemia, worsening kidney function, or angioedema (**Table 2**). The rate of relevant adverse events was significantly lower among patients receiving a high dose of sacubitril/valsartan than those receiving low and intermediate doses (high vs. low dose, P<0.001; high vs. intermediate dose, P=0.01). Hypotension was the most common adverse event. The high-dose group had a lower incidence of hypotension than the low- and intermediate-dose groups (high vs. low dose, P<0.001; high vs. intermediate dose, P=0.01). The rates of hyperkalemia, severe renal events, and angioedema did not differ across the dose classifications. **Table 2** presents the sacubitril/valsartan discontinuation rates according to achieved dose classification. Drug discontinuation was significantly less frequent among patients receiving a high dose of sacubitril/valsartan than among those receiving low and intermediate doses (high vs. low dose, P<0.001; high vs. intermediate dose, P<0.001).

Predictors of Achieving High-Dose Sacubitril/Valsartan

In the univariate Cox regression model, lower age, male sex, lower NYHA classification, higher SBP, higher eGFR, higher GNRI, and no prior hospitalization for HF were associated with a higher likelihood of achieving a high dose of sacubitril/valsartan (**Table 3**). In the multivariable Cox regression model, male sex, lower NYHA classification, higher SBP, higher eGFR, and higher GNRI were significantly associated with a higher likelihood of achieving a high dose of sacubitril/valsartan (**Table 3**).

Discussion

This study found that, in a Japanese cohort, patients who received a high dose of sacubitril/valsartan had better clinical outcomes than those who did not. We determined that approximately 40% of patients achieved a high dose of sacubitril/valsartan at least once. Predictors of achieving a high dose of sacubitril/valsartan included male sex, hypertension, maintained GNRI score, non-severe kidney dysfunction, and low NYHA class. The tolerability of uptitration, measured as the incidence rate of adverse events, was significantly higher in the high-dose group because of the lower incidence of hypotension.

According to the guidelines, in patients with HF with reduced ejection fraction, titration of GDMT to achieve high doses is recommended to reduce cardiovascular mortality and HF hospitalizations unless not well tolerated.[5,9] Post hoc analysis of RCTs has revealed the prognostic benefit associated with a high dose of sacubitril/valsartan.[17,18] However, a few small studies have explored the prognostic implications of uptitrating sacubitril/valsartan in real-world clinical trials.[19,20] Moreover, RCTs are limited to a subset of patients who are not fully representative of an unselected real-world population by design.[21] Thus, the findings of the present study demonstrate that sacubitril/valsartan uptitration does not compromise its effects in improving prognosis in real-world patients with HF.

Despite more than half the population being aged ≥70 years in our study, approximately 40% of patients received a high dose of sacubitril/valsartan at least once. Retrospective studies in different countries in Europe, as well as China and the US have shown that the rate of achieving a high dose of sacubitril/valsartan is only 2–30%.[22–25] Clinical inertia, which includes patient-, physician-, and system-related factors, was indicated as a prominent factor contributing to underdosing of GDMT.[26,27] Our results may support decisions regarding sacubitril/valsartan uptitration and help avoid clinical inertia in physicians, given the relatively higher titration rate in our study.

The present study identified hypertension and less advanced HF with fewer comorbidities (higher GNRI score and intact renal function) as predictors of sacubitril/valsartan dose uptitration. These findings are consistent with those of previous HF trials involving ACEi, ARBs, and β-blockers.[28,29] Higher baseline blood pressure predicted higher uptitration success. Low blood pressure is often a limitation in the initiation and uptitration of evidence-based medications for HF. To avoid hypotension, slow uptitration to a high dose in the highly vulnerable post-acute decompensated HF phase may be effective.[30] However, we were not able to compare differences in the intermediate dose of sacubitril/valsartan with respect to uptitration,

downtitration, or a maintained intermediate dose because we did not have follow-up data of the sacubitril/valsartan dose after drug discontinuation or downtitration from 400 mg. Thus, future studies of the sacubitril/valsartan intra-integral volume are needed.

The GNRI, which is used as an indicator of nutritional status, is a prognostic predictor in patients with HF, including older adults.[31–33] More comorbidities and fewer physical activities lead to malnutrition in patients with HF and in older adults.[34,35] In malnourished patients, intravascular albumin decreases, making it difficult to maintain intravascular volume and leading to hypotension.[36] In addition, the autonomic nervous system response is diminished, resulting in orthostatic hypotension.[37,38] As a result, malnourished patients likely cannot tolerate the uptitration of sacubitril/valsartan. This study revealed that the GNRI was an independent predictor of sacubitril/valsartan uptitration. Therefore, any other biomarker or physical score related to nutritional status, such as the prediction of HF prognosis, may be a predictor of uptitration with sacubitril/valsartan.[39,40]

In our cohort, the group of patients who could not reach a high dose of sacubitril/valsartan had more hypotension, whereas hyperkalemia, severe renal events, and angioedema did not differ across the achieved dose classifications. These findings could lead to discussions on managing hypotension during sacubitril/valsartan titration. Although initiation of sacubitril/valsartan therapy triggered a reduction in NT-proBNP in Japanese patients hospitalized for acute HF, concerns exist regarding potential differences in drug tolerability and safety between Asian and non-Asian populations.[41] Physical characteristics, such as a lower body weight and smaller size of Asian patients, may contribute to these differences, leading to the advocacy of lower doses of HF drugs for Asian patients.[42] In addition, as seen in the total PARADIGM-HF population, hypotension was more common among Asian patients randomized to sacubitril/valsartan than to enalapril.[12] Therefore, non-Asian patients may be more tolerant of hypotension than Asian patients. However, ongoing monitoring is recommended because the discontinuation rate in the present study was 23% higher than in other RCTs.[10,12] Moreover, we previously reported that patients who experienced adverse events had a higher risk of cardiovascular death or hospitalization for HF than those who did not.[11] Consequently, close monitoring of worsening events, mainly increased blood pressure, is required before sacubitril/valsartan uptitration if patients have high blood pressure.

Study Limitations

Because this was a retrospective study in Japan, the results are not necessarily applicable to prospective cohorts or other countries. Inertia, including the possibility that certain healthcare providers have a negative attitude towards titration, cannot be excluded. Survival bias regarding hypertension in this cohort was not excluded because patients with hypertension might find it easier to uptitration of sacubitril/valsartan. The effects of downtitration were unclear because the "high-dose group" of sacubitril/valsartan was defined as patients who reached the dose at least once during the follow-up period. There was no predefined priority regarding other medications during titration, such as sodium-glucose cotransporter 2 inhibitors or β-blockers. Simultaneous titration of other medications was not performed. Therefore, the observed effects may not be solely attributable to sacubitril or valsartan.

Conclusions

Patients who achieved sacubitril/valsartan uptitration had better prognoses than those who did not. Physicians should closely monitor worsening events, particularly blood pressure. However, physicians should not hesitate to uptitrate when patients have tolerance to titrate sacubitril/valsartan.

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IRB Information

The study protocol, including opt-out consent, was approved by the Ethics Committee of Toho University Omori Medical Center (No. M21257) and local ethics committees. The study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000047636) before patient enrollment.

Data Availability

The data generated in this study will not be shared.

References

1. Kanaoka K, Iwanaga Y, Sumita Y, Nakai M, Miyamoto Y. Management and outcomes of acute heart failure hospitalizations in Japan. *Circ J* 2024; **88:** 1265–1273.
2. Christ M, Störk S, Dörr M, Heppner HJ, Müller C, Wachter R, et al. Heart failure epidemiology 2000–2013: Insights from the German Federal Health Monitoring System. *Eur J Heart Fail* 2016; **18:** 1009–1018.
3. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol* 2015; **12:** 220–229.
4. Matsukawa R, Kabu K, Koga E, Hara A, Kisanuki H, Sada M, et al. Optimizing guideline-directed medical therapy during hospitalization improves prognosis in patients with worsening heart failure requiring readmissions. *Circ J* 2024; **88:** 1416–1424.
5. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022; **145:** e895–e1032, doi:10.1161/CIR.0000000000001142.

6. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2013; **15:** 1173–1184.
7. Tsutsui H, Isobe M, Ito H, Ito H, Okumura K, Ono M, et al. JCS 2017/JHFS 2017 guideline on diagnosis and treatment of acute and chronic heart failure: Digest version. *Circ J* 2019; **83:** 2084–2184.
8. 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. *J Card Fail* 2021; **27:** 1404–1444.
9. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42:** 3599–3726.
10. Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: Results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. *Eur J Heart Fail* 2016; **18:** 1193–1202.
11. Matsumoto S, McMurray JJV, Nasu T, Ishii S, Kagiyama N, Kida K, et al. Relevant adverse events and drug discontinuation of sacubitril/valsartan in a real-world Japanese cohort: REVIEW-HF registry. *J Cardiol* 2024; **84:** 133–140.
12. McMurray JJ, 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.
13. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric Nutritional Risk Index: A new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr* 2005; **82:** 777–783.
14. Sunaga A, Hikoso S, Yamada T, Yasumura Y, Tamaki S, Yano M, et al. Change in nutritional status during hospitalization and prognosis in patients with heart failure with preserved ejection fraction. *Nutrients* 2022; **14:** 4345.
15. Yoshihisa A, Kanno Y, Watanabe S, Yokokawa T, Abe S, Miyata M, et al. Impact of nutritional indices on mortality in patients with heart failure. *Open Heart* 2018; **5:** e000730, doi:10.1136/openhrt-2017-000730.
16. Chatur S, Vaduganathan M, Claggett BL, Mc Causland FR, Desai AS, Jhund PS, et al. Dapagliflozin in patients with heart failure and deterioration in renal function. *J Am Coll Cardiol* 2023; **82:** 1854–1863.
17. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, et al. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: The PARADIGM-HF trial. *Eur J Heart Fail* 2016; **18:** 1228–1234.
18. Shen L, Jhund PS, Docherty KF, Vaduganathan M, Petrie MC, Desai AS, et al. Accelerated and personalized therapy for heart failure with reduced ejection fraction. *Eur Heart J* 2022; **43:** 2573–2587.
19. Wang C, Lin Z, Miao D, Zhang H, Fu K, Zhang X, et al. Dose titration of sacubitril/valsartan for heart failure with reduced ejection fraction: A real-world study. *ESC Heart Fail* 2023; **10:** 1961–1971.
20. Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovasc Ther* 2018; **36:** e12435, doi:10.1111/1755-5922.12435.
21. Camm AJ, Fox KAA. Strengths and weaknesses of "real-world" studies involving non-vitamin K antagonist oral anticoagulants. *Open Heart* 2018; **5:** e000788, doi:10.1136/openhrt-2018-000788.
22. Wachter R, Klebs S, Balas B, Kap E, Engelhard J, Schlienger R, et al. Heart failure signs and symptoms, hospital referrals, and prescription patterns in patients receiving sacubitril/valsartan in primary care and cardiologist settings in Germany. *ESC Heart Fail* 2020; **7:** 2318–2330.
23. Cheang I, Shi S, Lu X, Liao S, Zhu X, Su X, et al. Efficacy and dosage pattern of sacubitril/valsartan in Chinese heart failure with reduced ejection fraction patients. *J Cardiovasc Transl Res* 2022; **15:** 1192–1202.
24. Greene SJ, Fonarow GC, DeVore AD, Sharma PP, Vaduganathan M, Albert NM, et al. Titration of medical therapy for heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019; **73:** 2365–2383.
25. Savarese G, Bodegard J, Norhammar A, Sartipy P, Thuresson M, Cowie MR, et al. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: A multinational observational study (US, UK and Sweden). *Eur J Heart Fail* 2021; **23:** 1499–1511.
26. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. *Ann Intern Med* 2001; **135:** 825–834.
27. Kuwayama T, Okumura T, Kondo T, Oishi H, Kimura Y, Kazama S, et al. Characteristics, treatment, and prognosis in octogenarian and older patients with acute heart failure in Japan: Prospective Observational Study on Acute Pharmacotherapy and Prognosis in Management of Acute Heart Failure (POPEYE-AHF Registry). *Circ J* 2024, doi:10.1253/circj.CJ-24-0299.
28. Straburzynska-Migaj E, Senni M, Wachter R, Fonseca C, Witte KK, Mueller C, et al. Early initiation of sacubitril/valsartan in patients with acute heart failure and renal dysfunction: An analysis of the TRANSITION study. *J Card Fail* 2024; **30:** 425–435.
29. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: A prospective European study. *Eur Heart J* 2017; **38:** 1883–1890.
30. Andries G, Yandrapalli S, Aronow WS. Benefit-risk review of different drug classes used in chronic heart failure. *Expert Opin Drug Saf* 2019; **18:** 37–49.
31. Scotti A, Coisne A, Granada JF, Driggin E, Madhavan MV, Zhou Z, et al. Impact of malnutrition in patients with heart failure and secondary mitral regurgitation: The COAPT trial. *J Am Coll Cardiol* 2023; **82:** 128–138.
32. Minamisawa M, Seidelmann SB, Claggett B, Hegde SM, Shah AM, Desai AS, et al. Impact of malnutrition using geriatric nutritional risk index in heart failure with preserved ejection fraction. *JACC Heart Fail* 2019; **7:** 664–675.
33. Honda Y, Nagai T, Iwakami N, Sugano Y, Honda S, Okada A, et al. Usefulness of Geriatric Nutritional Risk Index for assessing nutritional status and its prognostic impact in patients aged ≥65 years with acute heart failure. *Am J Cardiol* 2016; **118:** 550–555.
34. Ni Lochlainn M, Cox NJ, Wilson T, Hayhoe RPG, Ramsay SE, Granic A, et al. Nutrition and frailty: Opportunities for prevention and treatment. *Nutrients* 2021; **13:** 2349.
35. Jayanama K, Theou O, Blodgett JM, Cahill L, Rockwood K. Frailty, nutrition-related parameters, and mortality across the adult age spectrum. *BMC Med* 2018; **16:** 188.
36. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: From bench to bedside. *Mol Aspects Med* 2012; **33:** 209–290.
37. Keskin K, Çiftçi S, Öncü J, Melike Doğan G, Çetinkal G, Sezai Yıldız S, et al. Orthostatic hypotension and age-related sarcopenia. *Turk J Phys Med Rehabil* 2021; **67:** 25–31.
38. Soysal P, Kocyigit SE, Dokuzlar O, Ates Bulut E, Smith L, Isik AT. Relationship between sarcopenia and orthostatic hypotension. *Age Ageing* 2020; **49:** 959–965.
39. Doi S, Ashikaga K, Kida K, Watanabe M, Yoneyama K, Suzuki N, et al. Prognostic value of Mini Nutritional Assessment-Short Form with aortic valve stenosis following transcatheter aortic valve implantation. *ESC Heart Fail* 2020; **7:** 4024–4031.
40. Suzuki N, Kida K, Suzuki K, Harada T, Akashi YJ. Assessment of transthyretin combined with mini nutritional assessment on admission provides useful prognostic information in patients with acute decompensated heart failure. *Int Heart J* 2015; **56:** 226–233.
41. Tanaka A, Kida K, Matsue Y, Imai T, Suwa S, Taguchi I, et al. In-hospital initiation of angiotensin receptor-neprilysin inhibition in acute heart failure: The PREMIER trial. *Eur Heart J* 2024, doi:10.1093/eurheartj/ehae561.
42. Teng TK, Tromp J, Tay WT, Anand I, Ouwerkerk W, Chopra V, et al. Prescribing patterns of evidence-based heart failure pharmacotherapy and outcomes in the ASIAN-HF registry: A cohort study. *Lancet Glob Health* 2018; **6:** e1008–e1018, doi:10.1016/S2214-109X(18)30306-1.

Supplementary Files

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