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ORIGINAL ARTICLE
Heart Failure

Initial Real-World Practical Experience of Sacubitril/Valsartan Treatment in Japanese Patients With Chronic Heart Failure

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Background: Sacubitril/valsartan, an angiotensin receptor-neprilysin inhibitor, has demonstrated survival benefit and reduces heart failure hospitalization compared with enalapril in patients with heart failure and reduced ejection fraction. However, its efficacy in real-world practice in Japan remains unknown.

Methods and Results: We initiated sacubitril/valsartan treatment for 37 patients (median age 68 years; median left ventricular ejection fraction 37%) between August and November 2020. Within 3 months, sacubitril/valsartan was discontinued in 3 patients due to symptomatic hypotension or worsening heart failure. Two patients were hospitalized due to worsening heart failure, with one of these patients undergoing percutaneous mitral valve repair. Three patients received scheduled non-pharmacological treatment: 1 received cardiac resynchronization therapy (CRT), 1 received CRT and underwent transcatheter aortic valve implantation, and 1 underwent left ventricular assist device implantation. Of the 30 patients who continued sacubitril/valsartan for 3–6 months without additional non-pharmacological therapy, there was a tendency for a decrease in N-terminal pro B-type natriuretic peptide concentrations (baseline vs. after 3–6 months ARNI treatment; median 733 vs. 596 pg/mL; P=0.097) and an increase in left ventricular ejection fraction (median 37% vs. 39%; P=0097).

Conclusions: Sacubitril/valsartan therapy with a lower initial dose was safe and may be effective in Japanese heart failure patients in a real-world setting. Further evaluation of optimal patient selection and clinical management using sacubitril/valsartan is warranted.

Key Words: Congestive heart failure; Heart failure with reduced ejection fraction (HFrEF); Japanese

Sacubitril/valsartan, a complex containing the neprilysin inhibitor sacubitril and the angiotensin II receptor blocker valsartan, augments endogenous compensatory vasoactive peptides by inhibiting their breakdown and blocks the renin-angiotensin system.[1] The PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial demonstrated advantages in survival and reductions in heart failure recurrence with sacubitril/valsartan therapy over enalapril in patients with heart failure with reduced ejection fraction (HFrEF).[2] A pooled analysis of 2 clinical trials (i.e., PARADIGM-HF and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trial) showed therapeutic benefits of sacubitril/valsartan among patients with an ejection fraction (EF) below the normal range.[3]

However, patients with systolic blood pressure (SBP) <100 mmHg at screening or <95 mmHg at randomization were excluded in the PARADIGM-HF trial, and those with SBP <110 mmHg at screening were excluded in the PARAGON-HF trial. A prospective comparison study of sacubitril/valsartan with enalapril in Japanese HFrEF patients (PARALLEL-HF (Prospective comparison of ARNI with ACE inhibitor to determine the noveL beneficiaL trEatment vaLue in Japanese Heart Failure patients) study) also excluded patients with SBP <100 mmHg at screening or <95 mmHg at the end of the run-in period.[4,5]

Many patients encountered in real-world practice often do not satisfy the inclusion criteria of these formal trials. The efficacy of sacubitril/valsartan in relatively more sick patients, especially those with relatively lower blood pressure, warrants further investigation. In the present study we investigated, for the first time in Japan, the safety and efficacy of sacubitril/valsartan in heart failure patients, including those with relatively lower blood pressure, in real-word daily practice.

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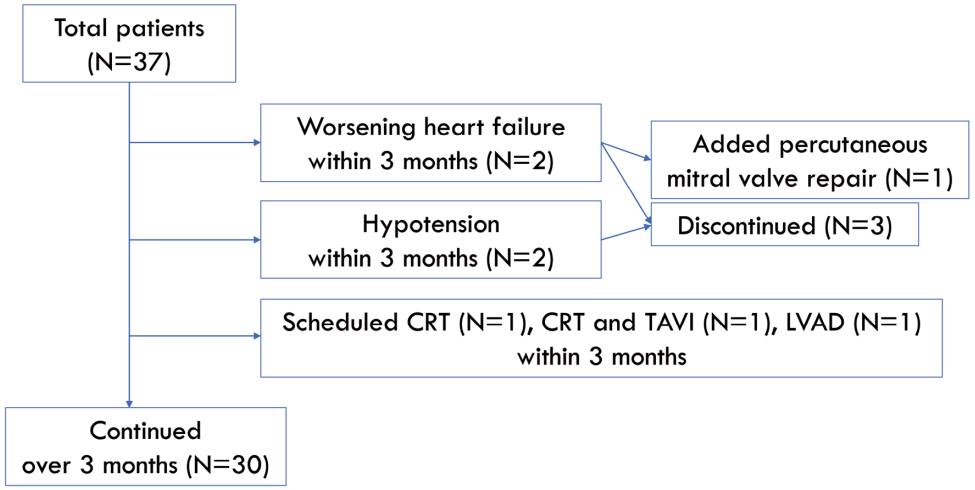

Figure 1. Patient selection. Seven patients who discontinued sacubitril/valsartan or received non-pharmacological treatment within 3 months after sacubitril/valsartan were excluded, leaving 30 patients who received sacubitril/valsartan for 3–6 months in the study. CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device; TAVI, transcatheter aortic valve implantation.

Methods

Patient Selection

Patients who started sacubitril/valsartan between August and November 2020 and continued sacubitril/valsartan therapy for 3–6 months at Toyama University Hospital were included in the present retrospective study. All patients were included for the safety assessment. Those who discontinued sacubitril/valsartan within 3 months or received non-pharmacological treatment were excluded from the efficacy assessment (**Figure 1**).

This study was approved by the local institutional review board of Toyama University (IRB no. R2015154). The need for written informed consent was waived due to the retrospective nature of this study and the opt-out method of inclusion.

Sacubitril/Valsartan Therapy

Chronic heart failure patients with left ventricular impairment or remaining heart failure symptoms, despite guideline-directed medical therapy in the outpatient clinic or during index hospitalization, were converted from an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker to sacubitril/valsartan at the discretion of their attending cardiologist. Sacubitril/valsartan was initiated at 100 mg/day in principle, and the dose was uptitrated depending on patients' SBP (>110 mmHg). If patients had an SBP <100 mmHg or the dose of enalapril before initiation of sacubitril/valsartan was <2.5 mg/day, the initial dose of sacubitril/valsartan was reduced to 50 mg/day. Then, if SBP increased to >120 mmHg, the dose of sacubitril/valsartan was uptitrated to 100 mg/day. The dose of sacubitril/valsartan was adjusted according to SBP and not according to EF and/or New York Heart Association (NYHA) classification.

Data Collected

Data on baseline characteristics, including SBP, NYHA classification, serum creatinine and N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations, plasma B-type natriuretic peptide (BNP) concentrations, echocardiographic data, concomitant medications, and the rate of implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy (CRT) with cardioverter-defibrillator were collected.

Plasma BNP and serum NT-proBNP and creatinine concentrations, as well as echocardiographic data, were also measured at 3–6 months after the initiation of sacubitril/valsartan for the efficacy analysis. Left ventricular EF (LVEF) was calculated by the modified Simpson method in apical 4- and 2-chamber views.

Endpoints

The primary efficacy endpoint (efficacy analyses) was defined as changes in NT-proBNP and LVEF in patients who continued sacubitril/valsartan for >3 months without additional non-pharmacological treatment. The primary safety endpoint (safety analyses) was defined as drug-related adverse events that led to drug discontinuation, unplanned visits, and hospitalizations, and required unplanned procedures.

Statistical Analysis

Statistical analyses were performed using JMP pro ver.14.0 (SAS Institute, Cary, NC, USA). Two-sided $P<0.05$ was considered significant. Continuous data are presented as the median and interquartile range (IQR) and were compared between 2 groups using the Mann-Whitney U test. Categorical data were compared between 2 groups using the Chi-squared test or Fischer's exact test, as appropriate. In 30 patients who continued sacubitril/valsartan treatment for >3 months, clinical data were compared between at baseline and at 3–6 months using a Wilcoxon signed-rank test.

Results

Baseline Characteristics for Efficacy Assessment (n=30)

The baseline characteristics of the patients included in the efficacy assessment are presented in the **Table**. The median

age was 67 years and 21 (70%) patients were male. The median SBP was 110 mmHg. At baseline, 21 patients (70%) had NYHA Class I–II and 9 patients (30%) had NYHA Class III–IV. The median BNP and NT-proBNP concentrations were 99.0 and 732.5pg/mL, respectively, and the median LVEF was 37%. Most patients had LVEF <50% (87%).

The median initial dose of sacubitril/valsartan was 100 mg (IQR 100–100 mg) and the median maintenance dose was 100 mg (IQR 100–200 mg). Seven (23%) patients were receiving sacubitril/valsartan at a dose of 400 mg. The median duration of sacubitril/valsartan administration was 175 days (IQR 145–183 days). All patients received β-blockers at a dose of 15 mg carvedilol equivalent; 25 patients (83%) received a mineralocorticoid receptor antagonist.

Efficacy Assessment (n=30)

Of the 30 patients who received sacubitril/valsartan therapy for 3–6 months, there was no change in plasma BNP concentrations from baseline to 175 days of sacubitril/valsartan therapy (99 [IQR 55–224] vs.104 [IQR 46–176] pg/mL, respectively; P=0.693; **Figure 2A**), there was a tendency for serum NT-proBNP concentrations to decrease (733 [IQR 360–1,529] vs. 596 [IQR 290–925] pg/mL, respectively; P=0.097; **Figure 2B**), and there was no change in serum creatinine concentrations (1.09 [IQR 0.85–1.24] vs. 0.98 [IQR 0.87–1.24] mg/dL, respectively; P=0.912; **Figure 2C**). There was also no change in the dose of loop diuretics from before to after therapy (10 [IQR 0–20] vs. 10 [IQR 0–20] mg, respectively; P=0.626; **Figure 2D**).

Of the 24 patients in whom echocardiographic measurements were completed at baseline and after 3–6 months of follow-up, LVEF tended to increase from 37% (IQR 29–43%) to 39% (IQR 34–49%; P=0.093; **Figure 2E**), whereas left ventricular end-diastolic diameter remained unchanged (60 [IQR 51–64] vs. 58 [IQR 50–62] mm at baseline and follow-up, respectively; P=0.419; **Figure 2F**).

Safety Analysis for All Participants (n=37)

Of 37 patients who initiated sacubitril/valsartan, 18 patients (49%) had SBP <110 mmHg at the time of initiation, which was an exclusion criterion in the PARAGON-HF trial. Eleven patients (30%) had SBP <100 mmHg at the time of initiation, which was an exclusion criterion in the PARADIGM-HF trial and PARALLEL-HF study.

Seven patients discontinued sacubitril/valsartan within 3 months. Three patients discontinued sacubitril/valsartan due to symptomatic hypotension or worsening heart failure. One patient underwent percutaneous mitral valve repair for worsening heart failure. Three patients received scheduled non-pharmacological therapy: CRT in one, CRT and transcatheter aortic valve replacement in another, and left ventricular assist device implantation in the final patient (**Figure 1**).

Two patients were readmitted unexpectedly for heart failure (on Day 64 and Day 86). Three patients had appropriate electrical defibrillation or antitachycardia pacing. In one of these patients, this was for primary prevention, whereas in the others it was for secondary prevention. In total, there was 1 unplanned procedure, 5 unplanned hospitalizations, 1 unplanned visit, and 3 planned procedures. No patients exhibited worsening renal function or hyperkalemia.

Subgroup Analyses of Participants With Low Blood Pressure (n=18)

Among 18 patients with baseline SBP <110 mmHg, serum NT-proBNP tended to decrease, from 1,254 pg/mL (IQR 645–1,578 pg/mL) to 893 pg/mL (IQR 374–1,292) pg/mL (P=0.221), and LVEF tended to increase, from 35% (IQR 27–44%) to 38% (IQR 31–48%) (P=0.279), with sacubitril/valsartan therapy. Two patients had unplanned hospitalizations and discontinued sacubitril/valsartan due to symptomatic hypotension in one and worsening heart failure in the other. Two patients had unplanned visits due to appropriate ICD therapy.

Table. Baseline Characteristics (n=30 Patients)

Demographics	
Age (years)	67 [55–74]
Male sex	21 (70)
Body mass index (kg/m²)	23.9 [20.8–26.6]
Systolic blood pressure (mmHg)	110 [99–125]
New York Heart Association classification	
Class I–II	21 (70)
Class III–IV	9 (30)
Previous heart failure hospitalization	32 (86)
Atrial fibrillation	9 (30)
Diabetes mellitus	12 (40)
Ischemic etiology	7 (23)
ICD/CRTD	16 (53)
Laboratory data	
Serum creatinine (mg/dL)	1.09 [0.85–1.24]
Plasma BNP (pg/mL)	99.0 [54.6–223.8]
Serum NT-proBNP (pg/mL)	732.5 [360.3–1,528.5]
Echocardiographic data	
LV end-diastolic diameter (mm)	60 [51–64]
LV ejection fraction (%)	37 [29–43]
LV ejection fraction <50%	26 (87)
Medication	
β-blocker	30 (100)
Dose of β-blocker (mg; carvedilol equivalent)	15 [10–20]
Mineralocorticoid receptor antagonist (%)	25 (83)
Diuretics (%)	21 (70)
Dose of loop diuretics (mg; furosemide equivalent)	10 [0–20]
Tolvaptan	11 (34)
SGLT2 inhibitor (%)	10 (33)

Data are given as the median [interquartile range] or n (%). BNP, B-type natriuretic peptide; CRTD, cardiac resynchronization therapy with cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator; LV, left ventricular; NT-proBNP, N-terminal pro B-type natriuretic peptide; SGLT2, sodium-glucose cotransporter 2.

Discussion

In this study we investigated the efficacy and safety of sacubitril/valsartan in Japanese real-world practice. Most of patients had LVEF <50% and approximately half had SBP <110 mmHg. The main efficacy findings were that NT-proBNP concentrations tended to decrease and LVEF tended to increase after 3–6 months of sacubitril/valsartan therapy. The main safety findings were that the adverse events were symptomatic hypotension and worsening heart

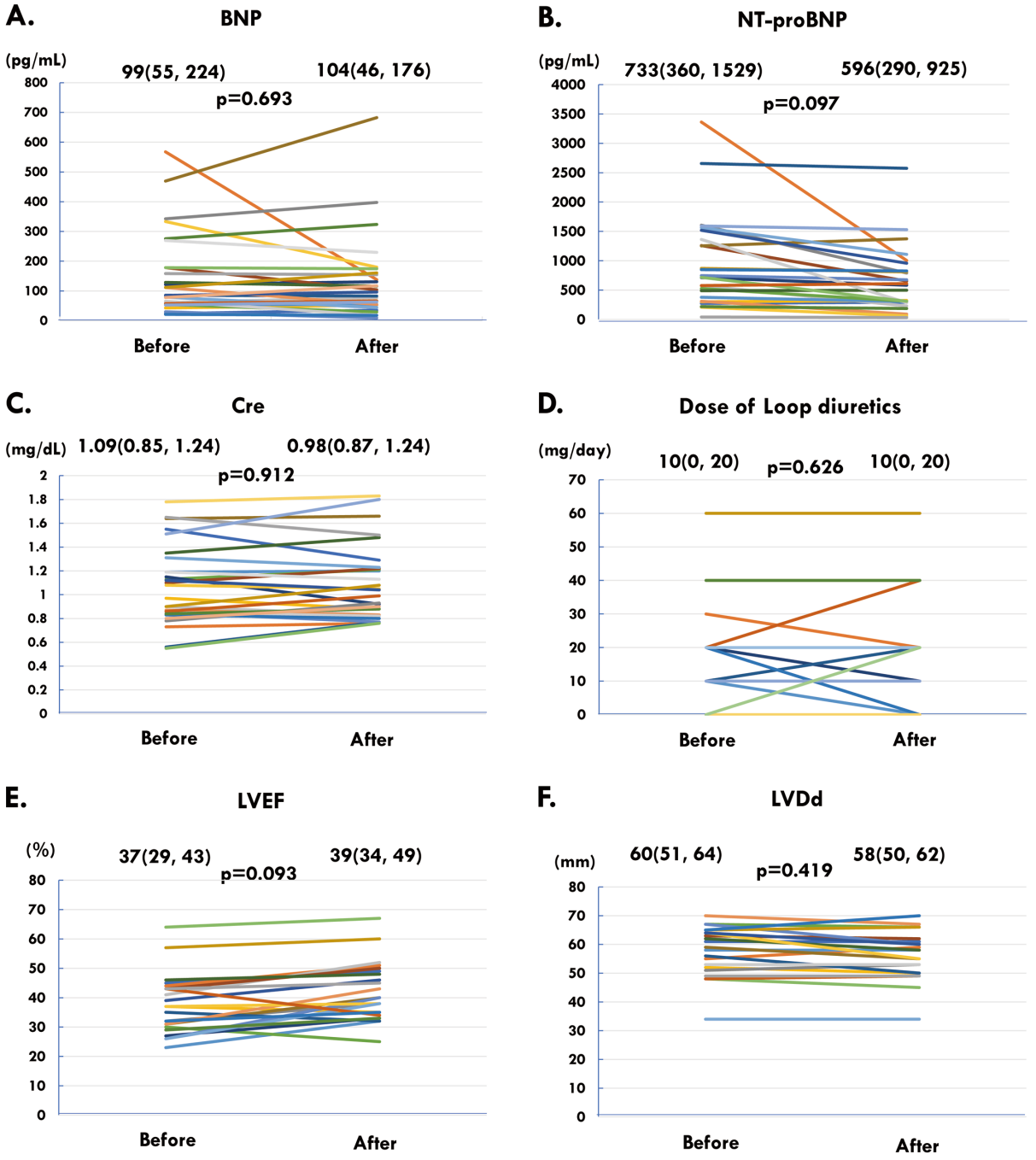

Figure 2. Trends in (**A**) B-type natriuretic peptide (BNP), (**B**) N-terminal pro B-type natriuretic peptide (NT-proBNP), and (**C**) serum creatinine concentrations and (**D**) the dose of loop diuretics in 30 patients from before to 3–6 months after initiation of sacubitril/valsartan. (**E**) Left ventricular end-diastolic diameter (LVDd) and (**F**) left ventricular ejection fraction (LVEF) on echocardiography in 24 patients before and 3–6 months after initiation of sacubitril/valsartan. Median (interquartile range) values are also shown.

failure, with an event rate of 5% each, and there were no cases of worsening renal function or hyperkalemia.

Sacubitril/Valsartan Treatment and SBP

In the PARADIGM-HF trial, symptomatic hypotension, study drug dose reductions, and drug discontinuation were more frequent in patients with lower SBP.[6] In the PARALLEL-HF study, the most frequent adverse event with sacubitril/valsartan was also hypotension.[5]

The median SBP at baseline in this study was 110 mmHg, whereas the mean SBP in the PARADIGM-HF trial and PARALLEL-HF study was 124 and 122 mmHg, respectively.[5,6] In the present study, based on our institutional protocol and these previous results, the initial dose of

sacubitril/valsartan was reduced to 50 mg/day in patients who had SBP <100 mmHg or were receiving <2.5 mg/day enalapril before sacubitril/valsartan initiation.

Sacubitril/Valsartan Dose Adjustment

In the post hoc analysis of the PARADIGM-HF trial, the benefit for patients with lower doses of sacubitril/valsartan was similar to that of patients who remained on target doses.[7] Therefore, in the present study we initiated sacubitril/valsartan at half the dose used in that study in the case of relatively hypotensive patients and up-titrated the dose as needed, taking care to avoid hypotension rather than achieving the maximum dose.

Two patients had symptomatic hypotension (ventricular arrhythmia was suspected in one and the other had an infection), resulting in the discontinuation of sacubitril/valsartan. The hypotension observed in these patients may not be related to sacubitril/valsartan.

Appropriate Patient Selection

Two patients who had unexpected readmission for heart failure within 3 months had NYHA Class IV and Stage D heart failure. One patient had a history of heart failure hospitalization 3 times previously and had been listed for heart transplantation. The other patient had a history of 4 heart failure hospitalizations. Patients with advanced heart failure (Stage D or NYHA Class IV) may not be good candidates for sacubitril/valsartan treatment. Optimal patient selection among such a severe cohort is the next concern.

Sacubitril/valsartan reduces the risk of sudden cardiac death.[8] In the present our study, 1 patient had appropriate ICD therapy despite sufficient β-blocker therapy. The effects of sacubitril/valsartan in preventing fatal arrhythmias among patients at high risk should be investigated further.

Efficacy of Sacubitril/Valsartan Treatment

Despite the short study period of 3–6 months and the low rate of target doses achieved, there was a tendency for NT-proBNP concentrations to decrease and LVEF to increase.

Our cohort had a higher rate of non-ischemic etiology, a relatively lower NT-proBNP concentration, and relatively lower SBP compared with participants of previous large-scale trials. Determining the optimal dose with satisfactory safety and efficacy in Japanese patients remains the next concern. Given our findings, a relatively lower dose of sacubitril/valsartan may be sufficient.

Study Limitations

This study had a small sample size, was conducted at a single institute and had a relatively short observation period of 3–6 months. Given the retrospective nature of this study, we did not calculate the sample size in advance to achieve our hypothesis. Despite the relatively small sample size, this study provides comprehensive and detailed data, including initial experiences of sacubitril/valsartan therapy in Japan.

There were no data on echocardiography except for left ventricular end-diastolic diameter and LVEF, and only a few patients underwent follow-up echocardiography at 3–6 months. We also cannot exclude effects of medications that were administered concomitantly.

Conclusions

Sacubitril/valsartan therapy initiated at lower dose was safe and may be effective in Japanese heart failure patients. Further evaluation of optimal patient selection, dose adjustment, and clinical management of sacubitril/valsartan is warranted.

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Disclosures

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IRB Information

This study was approved by the local institutional review board of Toyama University (IRB no. R2015154).

Data Availability

Data are available from the corresponding author upon reasonable request.

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