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# Real-World Usage of Sacubitril/Valsartan in Korea: A Multi-Center, Retrospective Study

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## ABSTRACT

**Background and Objectives:** Differences in drug prescriptions exist between clinical trials and real-world practice. We evaluated the real-world treatment patterns of sacubitril/valsartan in Korean patients with heart failure (HF).
**Methods:** In this retrospective, multicenter cohort study, 600 patients with HF with reduced left-ventricular ejection fraction (LVEF <40%) with ≥1 sacubitril/valsartan prescription were identified by reviewing patient-level medical records at six academic tertiary hospitals in Korea between February 2017 and April 2019.
**Results:** At baseline, 59.2%, 28.3%, 4.8%, and 7.7% of the patients received low (50 mg bid), moderate (100 mg bid), target (200 mg bid), and unconventional dose of sacubitril/valsartan, respectively. Patients with low and moderate doses experienced either 'no-titration' (39.8%) or 'stable up-titration' (41.5%). At 12 months, 31.7%, 28.5%, 24.8%, and 15% received low, moderate, target doses, and unconventional dose, respectively. On follow-up, 31 (5.2%) patients discontinued sacubitril/valsartan. The time-averaged N-terminal pro-B-type natriuretic peptide (NT-proBNP) level decreased from 879.6 to 406 pg/mL (ratio, 0.5; 95% confidence interval, 0.4–0.5). The mean LVEF increased by 10.4±12.2% from 27.2±5.8 to 36.3±11.1%, whereas LV end-diastolic volume index decreased by 18.7±26.1 mL/m$^2$ from 114.5±37.7 mL/m$^2$ to 98.9±42.3 mL/m$^2$ at baseline and follow-up, respectively.
**Conclusions:** In real-world practice, 95% patients started with low and moderate doses of sacubitril/valsartan. Many patients experienced dose up-titration during follow-up; 30% reached the target dose. Cardiac reverse remodelling was reflected by a profound NT-proBNP level and LV size reduction, and LVEF increment. This study confirms the gap in treatment patterns between clinical trials and real-world practice.

**Keywords:** Heart failure; Treatment pattern; Dosage; Remodeling

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**Conflict of Interest**
The authors have no financial conflicts of interest.

**Author Contributions**
Conceptualization: Park JJ, Choi DJ; Data curation: Park JJ, Lee SE, Cho HJ, Choi JO, Yoo BS, Kang SM, Wang HC, Sue Lee, Choi DJ; Formal analysis: Park JJ, Wang HC, Sue Lee; Funding acquisition: Choi DJ; Methodology: Choi DJ; Project administration: Choi DJ; Resources: Choi DJ; Software: Wang HC; Supervision: Park JJ; Validation: Park JJ, Choi DJ; Writing - original draft: Park JJ; Writing - review & editing: Park JJ, Lee SE, Cho HJ, Choi JO, Yoo BS, Kang SM, Wang HC, Sue Lee, Choi DJ.

## INTRODUCTION

Heart failure (HF) is associated with high mortality rates, frequent hospitalizations, and poor quality of life.[1-3] Neurohumoral modulation, including the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS), and natriuretic peptide (NP) system plays a crucial role in the initiation and progression of HF.[4-6]

NPs are vasoactive peptides that promote natriuresis and vasodilation, inhibit the SNS, and exert anti-fibrotic and anti-hypertrophic effects, resulting in beneficial structural and hemodynamic changes in the failing heart.[6,7] Sacubitril/valsartan is the first-in-class angiotensin-receptor neprilysin inhibitor (ARNI), which inhibits RAAS and enhances the NP system. In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) study,[8] sacubitril/valsartan was superior to enalapril in patients with HF and reduced ejection fraction (HFrEF), and is recommended in HF treatment guidelines.[9,11]

NPs lower blood pressure[12] and patients receiving sacubitril/valsartan experience more hypotension.[8] Initiation and up-titration of the ARNI encounter physicians' inertia due to physicians being concerned with prescribing medications that lower blood pressure in HF patients.[13] Consequently, in the real world, most patients do not receive the recommended target dose of sacubitril/valsartan.[13,14]

Patient characteristics differ among ethnicities and countries. Compared to Caucasians, Korean patients with HF have a lower blood pressure and less hypertensive cardiomyopathy.[2] The prescription patterns and dosing strategies also differ among countries.

Understanding the dosing strategy is important for achieving maximal tolerance and persistence of HF drugs. Therefore, in this study, we aimed to characterize the dosing strategy of sacubitril/valsartan in real clinical practice in Korea.

## METHODS

### Study design and population

REal-world usAge of Sacubitril/valsartan in adult Korean heart failURE patients with reduced ejection fraction (REASSURE) was a retrospective, multicenter cohort study to evaluate the real-world usage of sacubitril/valsartan in adult HFrEF patients in Korea. A total of 600 HFrEF patients with ≥1 sacubitril/valsartan prescription were identified by reviewing patient-level electronic medical records at six academic tertiary hospitals in Korea between February 1, 2017 and April 29, 2019.

Eligible were HFrEF patients aged ≥18 years with a minimum of 12 months follow-up from the index date, defined as the date of the patient's first sacubitril/valsartan prescription. Patients who had received a heart transplant, or hospice or palliative care or were deceased were enrolled with a follow-up duration of less than 12 months. HFrEF was defined as a left-ventricular ejection fraction (LVEF) <40%.[9,11] An electronic case report form was used to document the data of the enrolled patients.

The study protocol was approved by the ethics committee at each participating center and was conducted according to the principles of the 2013 Declaration of Helsinki. The requirement for informed consent was waived by the institutional review board of Seoul National University Bundang Hospital (IRB No: B2003/600-107).

## Sacubitril/valsartan dosage and titration pattern

For the conventional dosing regimen, low, moderate, and target doses were defined as 50 mg bid, 100 mg bid, and 200 mg bid, respectively. For the unconventional dosing regimen, that is, different doses in the morning and in the evening, the average dosage within a day was recorded. However, when the drug was taken only once a day, it was recorded as is (**Supplementary Table 1**).

The titration pattern of sacubitril/valsartan was evaluated during the 12 months from the index date and defined as follows: no titration (patients who remained on the same dose of sacubitril/valsartan throughout the follow-up period); up/down titration (patients who experienced initial increase in sacubitril/valsartan dose followed by subsequent down-titration of dose); stable up-titration (patients who experienced initial increase in sacubitril/valsartan dose without subsequent decrease in dose); down/up titration (patients who experienced initial decrease in sacubitril/valsartan dose followed by subsequent up-titration of dose); and stable down-titration (patients who experienced initial decrease in sacubitril/valsartan dose without subsequent increase in dose).

## Study variables and endpoints

The duration of HF was calculated using the following formula: ([the nearest recorded date before index date – date of initial HF diagnosis + 1]/365.25).

The mean daily dosage of each cardiovascular (CV) medication before the index date was calculated using the following formula:

$$Mean\ Daily\ Dosage\ Pre\ Index = \frac{Total\ Dose\ Prescribed\ Before\ Index\ Date}{Total\ Prescription\ Days\ Before\ Index\ Date}$$

The same formula was applied to the mean daily dosage of each CV medication after the index date. If the end date of CV medication was missing, the study end date, which was defined as the index date plus 365 days, was applied for calculation.

### *Primary endpoint*

The primary endpoint was the final dose of sacubitril/valsartan at 12 months from the index date.

### *Secondary endpoints*

The key secondary endpoint was the titration pattern during the 12 months from the index date. Other secondary endpoints included changes in blood pressure, time-averaged changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and changes in echocardiographic parameters from baseline to follow-up.

Regarding the dose of guideline-directed medical therapy (GDMT), i.e., RAAS inhibitors and beta-blockers, the patients were categorized as being drug-naive or as having low (<50% target dose), medium (≥50% target dose <100%), or target dose according to the treatment guideline.[9-11]


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### Sample size calculation

An assumption of 50% of patients reaching sacubitril/valsartan 100 mg bid or higher (≥50% target dose) was implemented in the analyses, which was based on observations from a study regarding the real-world treatment patterns of sacubitril/valsartan use in Germany.[13] A sample size determination of precision was applied to the study. Considering the width, that is, the distance from the lower to the upper limit, less than 8% as good precision, 600 eligible patients were sufficient when the sample proportion was 50% and two-sided simple asymptotic 95% confidence interval (CI) was considered.

### Statistical analysis

Data are presented as numbers and frequencies for categorical variables and as means ± standard deviation for continuous variables. For comparison among groups, the $\chi^2$ test (or the Fisher exact test when any expected count was <5 for a 2×2 table) for categorical variables, and the unpaired Student's t-test or one-way analysis of variance for continuous variables were applied. A two-sided p value of less than 0.05 was considered to estimate statistically significant differences. All analyses were performed by a professional biostatistician (H.C. Wang) using SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Patients' characteristics

In this study, 600 patients with HFrEF and ≥1 sacubitril/valsartan prescription were included. The mean age was 69.9±13.7 years, 74.2% were male, 37.5% had hypertension, 22.8% had atrial fibrillation, and 33.2% had diabetes. The mean duration of HF was 3.1±4.3 years and the baseline LVEF was 27.2±5.8% (**Table 1**).

Regarding GDMT, before the index date, 73%, 44.3%, 16.7%, and 65.5% received beta-blockers, MRAs, ivabradine, and diuretics, respectively. At 12 months, 89.8%, 52.5%, 26.3%, and 78.2% received beta-blockers, MRAs, ivabradine, and diuretics, respectively.

### Sacubitril/valsartan dosage at index date and 12 months

At baseline, 554 (92.3%) and 46 (7.7%) patients received conventional and unconventional dosing regimens, respectively. Among patients receiving the conventional dosing regimen, 355 (59.2%), 170 (28.3%), and 46 (4.8%) patients started with 50 mg bid, 100 mg bid, and 200 mg bid, respectively (**Table 2**).

At 12 months, 510 (85%) and 90 (15%) patients received conventional and unconventional dosing, respectively. Among patients receiving the conventional dosing regimen, 31.7% received low (50 mg bid) dose, 28.5% received moderate (100 mg bid) dose, and 24.8% received the target dose of 200 mg bid Among the patients receiving an unconventional dosing regimen, 50 (8.3%) received doses of less than 100 mg/day. The most common unconventional dosing was 25 mg bid observed in 40 patients, followed by 100/200 mg bid observed in 20 patients. Four patients received 25 mg q.d.

### Titration patterns of sacubitril/valsartan

**Figure 1** shows the titration patterns from the index date to 12 months. Overall, most patients experienced either no-titration (39.8%) or stable up-titration (41.5%). When stratifying according to the initial sacubitril/valsartan dose, there was a significant difference in the

**Table 1.** Patients' characteristics

| Variables | REASSURE (n=600) | PARADIGM-HF (n=4,187) | PROVE-HF (n=794) |
|---|---|---|---|
| Demographics | | | |
| Age (years) | 69.9±13.7 | 63.8±11.5 | 65.1±12.4 |
| Male (%) | 74.2% | 79% | 71.5% |
| Weight (kg) | 69.3±14.5 | n.a. | n.a. |
| Height (cm) | 164.5±9.0 | n.a. | n.a. |
| Comorbidities | | | |
| Hypertension (%) | 37.5 | 70.9 | 88 |
| Atrial fibrillation (%) | 22.8 | 36.2 | 35.3 |
| Dyslipidemia (%) | 15.7 | n.a. | n.a. |
| Diabetes (%) | 33.2 | 34.7 | 45.5 |
| COPD (%) | 3.2 | n.a. | n.a. |
| Myocardial infarction (%) | 13.8 | 43.4 | 41.4 |
| Heart failure duration (years) | 3.1±4.3/1.1 (0.2–4.9) | | |
| NYHA classification (%) | | | |
| Class I | 9.8 | 4.3 | 0 |
| Class II | 48.5 | 71.6 | 70.3 |
| Class III | 11.0 | 23.1 | 28.0 |
| Class IV | 1.2 | 0.8 | 1.8 |
| Missing | 29.5 | 0.2 | 0 |
| Physical features | | | |
| Sitting SBP (mmHg) | 116.5±17.1 | 122±15 | 124.5±15.9 |
| Sitting DBP (mmHg) | 69.3±12.6 | n.a. | 75.9±10.36 |
| Heart rate (beats/min) | 76.6±14.4 | 72±12 | 72.2±11.3 |
| Laboratory findings | | | |
| Potassium (mmol/L) | 4.5±0.5 | | |
| Chloride (mmol/L) | 103.2±4.7 | | |
| Hemoglobin (g/dL) | 13.8±2.0 | | |
| Blood urea nitrogen (mg/dL) | 20.8±9.7/19.3 (14.8–24.0) | | |
| Creatinine (mg/dL) | 1.2±1.26/1.0 (0.9–1.3) | | |
| eGFR (mL/min/1.72m$^2$) | 70.6±23.5 | | |
| NT-proBNP (pg/mL) | 2,235.5±4,347.8/773 (356–2,206) | 1,631 (885–3,154) | |
| Echocardiography – baseline | | | |
| LVEF (n=422) (%) | 27.2±5.8 | 29.5±6.2 | 28.2 (24.5–32.7) |
| LVEDD (n=462) (mm) | 64.1±7.6 | | |
| LVEDV (n=383) (mL) | 196.8±67.9 | | 86.9 (76.2–100.4) |
| HF therapies | | | |
| Beta-blocker (%) | 73.0 | 93.1 | 95.3 |
| MRA (%) | 44.3 | 54.2 | 35.4 |
| Diuretics (%) | 65.5 | 80.3 | n.a. |
| ICD (%) | n.a. | 14.9 | 28.5 |
| CRT/CRT-D (%) | n.a. | 7.0 | 15.4 |

REASSURE = REal-world usAge of Sacubitril/valsartan in adult Korean heart failURE patients with reduced ejection fraction; PARADIGM-HF = Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PROVE-HF = Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure; COPD = chronic obstructive pulmonary disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; LVEF = left ventricular ejection fraction; LVEDD = left-ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; HF = heart failure; MRA = mineralocorticoid receptor antagonists; ICD = implantable cardioverter-defibrillator; CRT-D = cardiac-resynchronization therapy defibrillator.

dosing strategies (p<0.001). Most patients with a starting dose of 50 mg bid and 100 mg bid experienced either no-titration or stable up-titration. For patients starting with 200 mg bid, 83% of the patients did not experience a dose change during the 12-months follow-up, whereas only 17% experienced a stable-down titration.

## Discontinuation of sacubitril/valsartan and adverse events

A total of 31 patients (5.2%) discontinued sacubitril/valsartan during follow-up: 12 patients discontinued due to adverse events, 11 patients at the physician's discretion, three patients died, three patients were lost to follow-up, and two patients refused sacubitril/valsartan.


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**Table 2.** The proportion of conventional sacubitril-valsartan dosing regimen at baseline and month

| Sacubitril-valsartan dosing regimen | Sacubitril-valsartan (n=600) | |
|---|---|---|
| | Baseline | Month 12 |
| Conventional | 554 (92.3) | 510 (85) |
| 50 mg bid | 355 (59.2) | 190 (31.7) |
| 100 mg bid | 170 (28.3) | 171 (28.5) |
| 200 mg bid | 29 (4.8) | 149 (24.8) |
| Unconventional | 46 (7.7) | 90 (15) |
| Lower than 100 mg/day | 43 (7.2) | 50 (8.3) |
| 100 mg/day to <200 mg/day | 3 (0.5) | 17 (2.8) |
| 200 mg/day to <400 mg/day | 0 (0) | 22 (3.7) |
| ≥400 mg/day | 0 (0) | 1 (0.2) |
| Conventional and unconventional | 600 (100) | 600 (100) |
| <100 mg/day | 398 (66.3) | 240 (40) |
| ≥400 mg/day | 29 (4.8) | 150 (25) |

Values are presented as number (%).

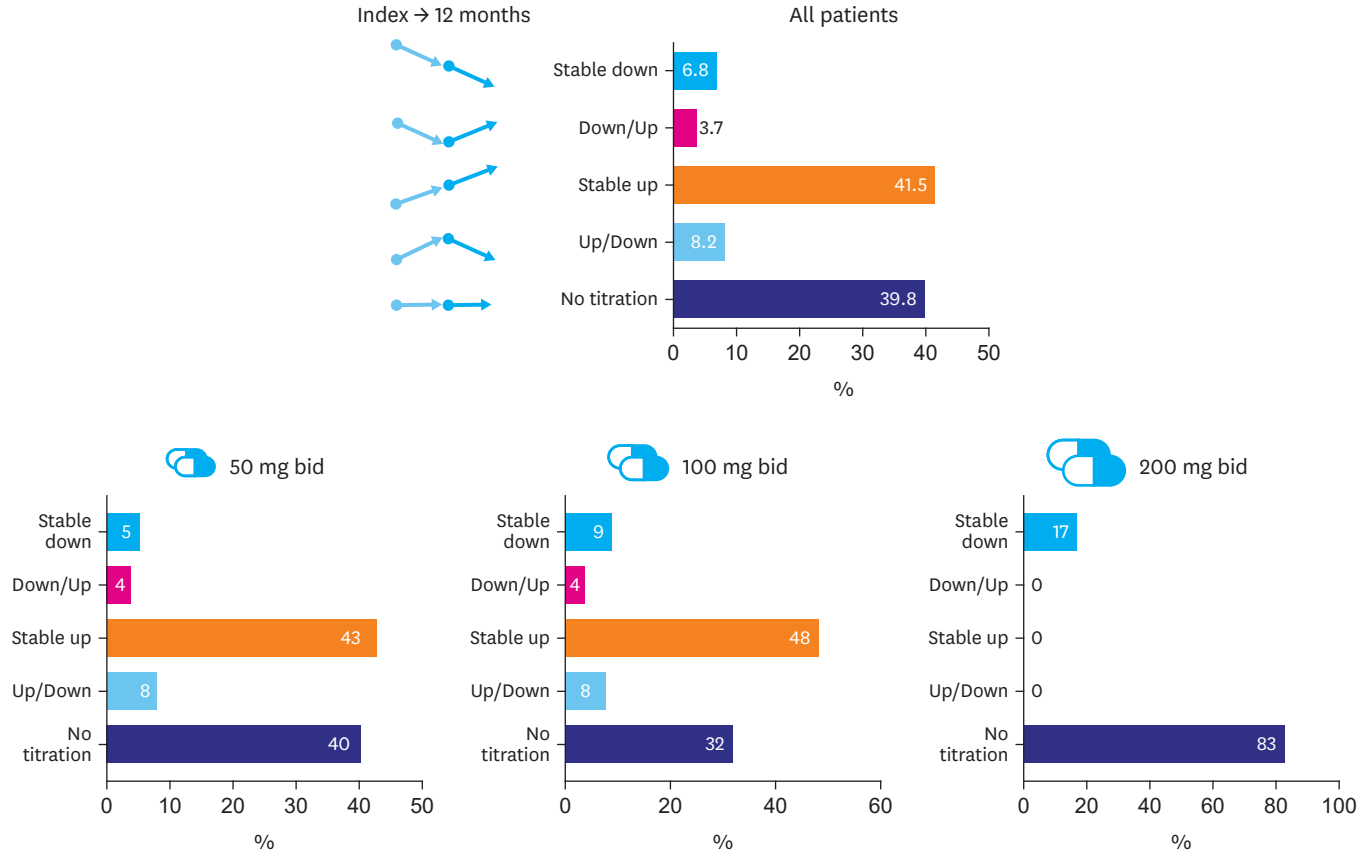


**Figure 1.** Titration patterns during the 12 months. Upper panel: all patients enrolled in the study. Lower panel: patient data stratified by sacubitril/valsartan index date. No titration (patients who remained on the same dose of sacubitril/valsartan throughout the follow-up period); up/down titration (patients who experienced initial increase in sacubitril/valsartan dose followed by subsequent down-titration of dose); stable up-titration (patients who experienced initial increase in sacubitril/valsartan dose without subsequent decrease in dose); down/up titration (patients who experienced initial decrease in sacubitril/valsartan dose followed by subsequent up-titration of dose); and stable down-titration (patients who experienced initial decrease in sacubitril/valsartan dose without subsequent increase in dose).

Overall, 125 (20.8%) patients experienced at least one adverse event, of which 63 (10.5%) were treatment related. Forty (6.7%) patients experienced severe adverse events, of which six (1.0%) were treatment related. The most common adverse event was dizziness observed in 34 patients (5.7%), followed by hypotension observed in 15 patients (2.5%) (**Table 3**).


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**Table 3.** Adverse events during follow-up

| Events | Values |
|---|---|
| Number of subjects with at least one event | 125 (20.8) |
| Hypotension | 15 (2.5) |
| Orthostatic hypotension | 4 (0.7) |
| Dizziness | 34 (5.7) |
| Syncope | 1 (0.2) |
| Peripheral edema | 3 (0.5) |
| Generalized edema | 1 (0.2) |
| Cough | 4 (0.7) |
| Hyperkalemia | 2 (0.3) |

Values are presented as number (%).

## Changes of blood pressure, echocardiography and NT-proBNP during follow-up

The sitting systolic blood pressure and eGFR decreased by 2.2±19.8 mmHg and 2.1±14.5 mL/min/1.73 m$^2$ from index date to follow-up (**Figure 2A**). However, patients who experienced down titration (up/down and stable down titration pattern) displayed a greater drop in blood pressure whereas patients with other titration patterns did not show meaningful drop in blood pressure during follow-up (**Table 4**).

LVEF data were available for 422, 344, and 250 patients at baseline, follow-up, and both at baseline and follow-up, respectively (**Table 5**). The mean LVEF increased by 10.4±12.2% from 27.2±5.8 to 36.3±11.1%, whereas LV end-diastolic volume index (LVEDVI) decreased by 18.7±26.1 mL/m$^2$ from 114.5±37.7 mL/m$^2$ to 98.9±42.3 mL/m$^2$ at baseline and follow-up, respectively (**Figure 2B**).

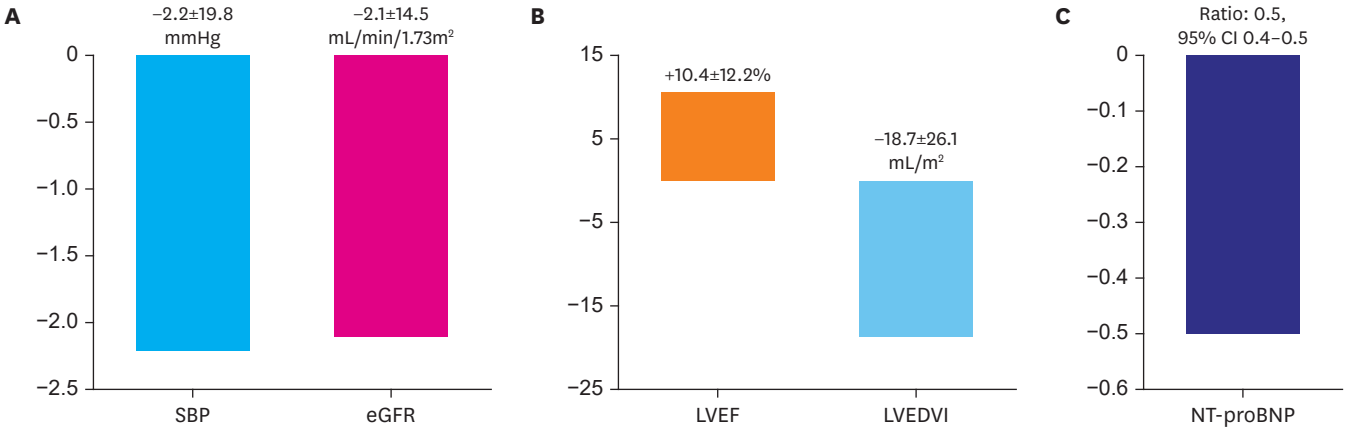


**Figure 2.** Changes in clinical and laboratory parameters from baseline to 12 months. (A) Change in systolic blood pressure and estimated glomerular filtration rate. (B) Changes in echocardiographic parameters. (C) Change in NT-proBNP level.
SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; NT-proBNP = N-terminal B-type pro-natriuretic peptide.

**Table 4.** Blood pressure change according to the titration pattern

| Titration pattern | Baseline | Last measurement | Change from Baseline |
|---|---|---|---|
| All patients | 116.5±17.1 | 114.4±19.0 | −2.1±19.8 |
| Titration pattern | | | |
| No titration | 114.3±16.8 | 112.3±18.3 | −2.0±18.8 |
| UP/Down | 114.9±14.5 | 106.8±16.8 | −7.3±18.2 |
| Stable up | 118.9±17.0 | 118.2±19.0 | −0.9±20.7 |
| Down/Up | 112.7±16.7 | 114.6±15.5 | 0.7±15.4 |
| Stable down | 118.3±20.6 | 112.4±23.0 | −6.3±22.9 |


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**Table 5.** Echocardiographic parameters

| Time point statistics | Baseline | | Last measurement during post-index | | Change from baseline | | |
|---|---|---|---|---|---|---|---|
| | No. | Mean±SD | No. | Mean±SD | No. | Mean±SD | Min, Max |
| LVEF | 422 | 27.22±5.779 | 344 | 36.31±11.064 | 250 | 10.39±12.212 | −17.0, 51.0 |
| LVEDD | 462 | 64.09±7.616 | 378 | 60.48±9.385 | 286 | −4.51±5.887 | −27.0, 11.0 |
| LVEDV | 383 | 196.80±67.846 | 309 | 172.66±76.811 | 233 | −31.54±44.330 | −187.0, 136.0 |
| LVEDVI | 370 | 114.51±37.658 | 294 | 98.89±42.338 | 228 | −18.70±26.143 | −118.2, 77.6 |
| LVESV | 384 | 143.40±56.011 | 309 | 114.61±66.713 | 233 | −36.46±44.807 | −185.8, 107.0 |
| LVESVI | 370 | 83.54±31.050 | 294 | 65.52±36.811 | 228 | −21.77±26.651 | −115.4, 61.1 |

LVEF = left ventricular ejection fraction; LVEDD = left-ventricular end-diastolic diameter; LVEDV = left-ventricular end-diastolic volume; LVEDVI = left-ventricular end-diastolic volume index; LVESV = left-ventricular end-systolic volume; LVESVI = left-ventricular end-systolic volume index.

**Table 6.** Time-averaged N-terminal pro-B-type natriuretic peptide change

| Biomarker | Sac/Val (n=600) | | | | | |
|---|---|---|---|---|---|---|
| | Number of patients | Baseline geometric mean | Post-index geometric mean | Ratio E/B: geometric mean | 95% CI | p value |
| All patients | 184 | 879.6 | 406.2 | 0.5 | 0.4–0.5 | <0.0001 |
| Titration pattern | | | | | | |
| No titration | 55 | 639.2 | 456.6 | 0.7 | 0.6–0.9 | 0.0057 |
| UP/Down | 19 | 1,025.9 | 460.5 | 0.4 | 0.3–0.7 | 0.0014 |
| Stable up | 87 | 928.0 | 337.9 | 0.4 | 0.3–0.5 | <0.0001 |
| Down/Up | 7 | 688.4 | 367.3 | 0.5 | 0.3–0.8 | 0.0148 |
| Stable down | 16 | 1,826.5 | 665.7 | 0.4 | 0.2–0.6 | 0.0016 |

CI = confidence interval.

Data on NT-proBNP levels were available for 184 patients. Overall, the time-averaged NT-proBNP level decreased from 879.6 to 406 pg/mL (ratio, 0.5; 95% CI, 0.4–0.5) (**Figure 2C**). When stratified by titration pattern, a decrease in NT-proBNP level was observed across all titration patterns (**Table 6**).

### Changes of furosemide dose according to titration pattern

In this study 393 (65.5%) patients received diuretics at baseline and 469 (78.2%) at 12 months. Regarding the dose change, the mean equivalent dose of furosemide was 38.1±26.8 mg, (median 40 mg, IQR 20–40 mg) and 36.5±26.8mg (median 26.6 mg, IQR 20–40 mg) at 12 months, suggesting a minimal dose reduction. When stratifying according to the sacubitril/valsartan titration pattern, there was also a numerical decrease in furosemide dose from the baseline to 12-months follow-up (**Supplementary Table 2**).

## DISCUSSION

In this study of real-world HFrEF patients prescribed with sacubitril/valsartan at six centres in Korea, 92% and 8% started with conventional and unconventional dosing regimens, respectively. Two-thirds of patients started with a daily dose of <100 mg, but many patients experienced dose up-titration. At 12 months, the proportion of patients with target dose increased from 4.8% at baseline to 24.8% at follow-up. Only 31 (5.2%) patients discontinued sacubitril/valsartan. The systolic blood pressure decreased by 2.1 mmHg, whereas LVEF increased by 10.4%, and the geometric mean NT-proBNP level decreased by 50% from baseline to follow-up (**Figure 3**).

NPs increase cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells and kidneys, and cause vasodilation and natriuresis, among others, leading to blood pressure reduction.[5] In the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) study,[12] omapatrilat, an ACE-neprilysin inhibitor, could reduce blood pressure more than enalapril alone in hypertensive patients. Similarly, in the PARADIGM-HF study,[8]

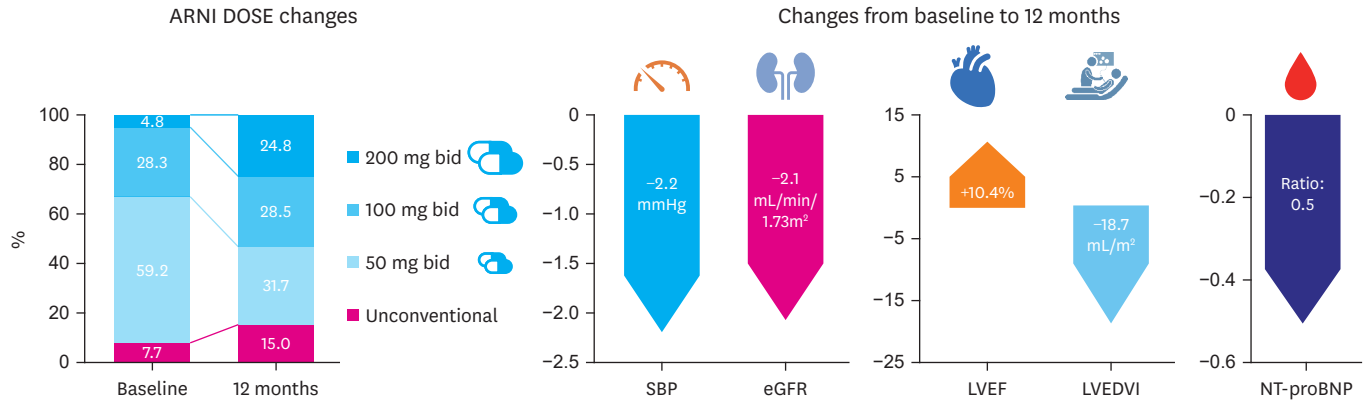


**Figure 3.** Real world use of angiotensin-neprilysin receptor inhibitor in Korea. In the real-world with 600 heart failure and reduced ejection fraction patients prescribed with sacubitril/valsartan, the proportion of patients with target dose increased from 4.8% to 24.8%, whereas the proportion of patients with low dose decreased from 59.2% to 31.7%, at baseline and at follow-up, respectively. During follow-up, the systolic blood pressure decreased only by 2.1 mmHg, and that of estimated glomerular fraction rate by 2.1 ml/min/1.73m$^2$. Many patients experienced cardiac reverse remodelling reflected by a profound decrease in NT-proBNP level, LV size, and an increase in LVEF.
SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; LVEDVI = left ventricular end-diastolic volume index; NT-proBNP = N-terminal B-type pro-natriuretic peptide.

more patients with sacubitril/valsartan had hypotension than those with enalapril. Therefore, many physicians are concerned about initiating and up-titrating sacubitril/valsartan in HF patients, especially in those with low blood pressure.

In this study, 398 (66.3%) and 29 (4.8%) patients started with a daily dose of <100 mg and ≥400 mg, respectively. During the follow-up, physicians increased the sacubitril/valsartan dose in patients taking below the target dose. At 12 months, 240 (40%) and 150 (25%) patients received daily doses of <100 mg/day and ≥400 mg/day, respectively. In the PARADIGM-HF study, nearly all patients received the target dose at randomization; however, the dose was reduced in 42% of patients in the sacubitril/valsartan arm during follow-up, of whom 37% subsequently returned to the target dose. In that study, the dose reduction was lowest in the Asian region, which was at 35%.[15] In the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) study,[16] 81.7% started with sacubitril/valsartan 50 mg twice daily. By the end of the study, 13.9%, 21.2%, and 65% received 50 mg bid, 100 mg bid, and 200 mg bid, respectively. Symptomatic hypotension (5.0%) was the main reason for the inability to reach the target dose. In the TITRATION study,[17] 76% of patients were able to be titrated to 200 mg bid within 12 weeks. In clinical trials, the investigated drugs were rigorously up-titrated according to the dosing schedule. In contrast, the prescribed dose of sacubitril/valsartan was lower in real-world studies. In a cohort study using data from a pharmacy database in Germany, 64%, 32%, and 4% of patients received 50 mg bid, 100 mg bid, and 200 mg as the initial dose, respectively, which is similar to our data.[13] It is of note that the prevalence of hypertension and myocardial infarction was lower in this study. Generally, East Asian HF patient have lower prevalence of hypertension and ischemic heart disease compared to Caucasians.[2] The relatively low prevalence of hypertension is important because patients with high blood pressure are more likely to tolerate higher dose of sacubitril/valsartan. The ESC-HF long-term registry showed that almost two-thirds of HF patients did not receive the target dose.[18] In the ASIAN-HF registry, the guideline-recommended dose was achieved in only 17% of cases for ACE inhibitors or ARB, 13% for beta-blockers, and 29% for MRAs.[19] These observations imply that the lack of up-titration of disease-modifying HF drugs to the target dose is not a drug-specific problem for sacubitril/valsartan, but for all HF drugs.


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An unexpected finding was that 10% of the patients had an unconventional dosing regimen, that is, different doses in the morning and evening, reflecting the physicians' concerns and attempts to initiate and up-titrate sacubitril/valsartan.

Regarding the discontinuation rate, when excluding those who died, only 5% discontinued sacubitril/valsartan in our study, whereas in the real-world study from Germany, the persistence at 12 months was estimated to be 71%. In the PARADIGM-HF study, the discontinuation rate due to side effects was lower in Asians.[20]

In this study, the mean reduction in systolic blood pressure was only 2 mmHg. In the PARADIGM-HF study, the mean systolic blood pressure at 8 months was 3.2±0.4 mmHg lower in the LCZ696 group than in the enalapril group.[8] In a substudy of the PARADIGM-HF study, patients with baseline systolic blood pressure <120 mmHg experienced an increase, whereas those with systolic blood pressure >140 mmHg had a decrease in systolic blood pressure from baseline to 4 months,[21] showing a difference between mid- and long-term effect of sacubitril/valsartan on blood pressure according to the baseline blood pressure.

We also observed a decrease in the NT-proBNP level by 50%, decrease in LVEDVI by 18.7 mL/m$^2$, and an increase in LVEF by 10.4±12.2% from baseline to follow-up. These changes are similar to the findings in the PROVE-HF study which also showed a decrease in NT-proBNP concentration by 50% (baseline: 816 pg/mL to follow-up: 455 pg/mL), an increase in LVEF by 9.4% (baseline: 28.2% to follow-up: 37.8%), and a decrease in LVEDVI by 12.25 mL/m$^2$ (baseline: 86.9 mL/m$^2$ to follow-up: 74.1 mL/m$^2$).[16] Our study confirms the findings of the PROVE-HF study in the real world. Since NT-proBNP is secreted from the LV in response to increased wall stress,[22] and according to the law of Laplace, the wall stress is directly proportional to the LV diameter or volume, the changes in NT-proBNP level reflect the reverse cardiac remodelling with sacubitril/valsartan.[16,23,24]

This study has several limitations. First, we included only stable HFrEF who received sacubitril/valsartan at 6 university hospitals with a minimum of 12 months follow-up from the index date. Consequently, the enrolment criteria may lead to selection of patients with more favourable characteristics. In addition, these hospitals have advanced HF treatment program in Korea; therefore, the prescription pattern may deviate from that of physicians in primary and secondary healthcare settings. Wachter and colleagues showed that cardiologists prescribed disease-modifying HF drugs more often than general practitioners in Germany.[13] Consequently, it is unknown whether the study results can be extrapolated to other populations. Second, due to retrospective study design many of the secondary outcome data such as NT-proBNP, echocardiographic data, and NYHA class were not complete in all patients. Third, we did not capture the aetiologies of HF. As a result, it is unknown whether there is difference in sacubitril/valsartan prescription pattern according to the various HF aetiologies e.g., ischemic versus non-ischemic aetiologies. Forth, we did not capture the clinical events, such as cardiovascular deaths or HF hospitalization, so the differential effect of sacubitril/valsartan on these clinical endpoints according to the dosing regimen could not be elucidated.

In conclusion, in this study with real-world HFrEF patients prescribed with sacubitril/valsartan at six centres in Korea, two-thirds of patients started with a daily dose <100 mg, but many patients experienced a dose up-titration, wherein at 12 months, the target dose increased from 4.8% at baseline to 25% at follow-up. The discontinuation rate of sacubitril/valsartan was low. Many patients experienced cardiac reverse remodelling reflected by a profound decrease in NT-

proBNP level, LV size, and an increase in LVEF. This study also confirms the gap in treatment patterns between clinical trials and real-world practice. Identifying the physician's inertia to adopt a guideline-recommended target dose is necessary.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Reference values in eCRF for real world dosage prescription

Click here to view

### Supplementary Table 2

Furosemide equivalent dose by sacubitril/valsartan titration pattern

Click here to view

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