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Left Ventricular Reverse Remodeling Following Initiation of Sacubitril/Valsartan for Heart Failure with Reduced Ejection Fraction and Low Blood Pressure

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Abstract

Sacubitril/valsartan has become an important first-line drug for symptomatic heart failure (HF) patients, especially with left ventricular (LV) ejection fraction (LVEF) < 50%. However, the impact of sacubitril/valsartan on cardiovascular outcomes, especially LV reverse remodeling for such patients with low blood pressure, remains uncertain. We retrospectively studied 164 HF patients with LVEF < 50% who were treated with sacubitril/valsartan from two institutions. Echocardiography was performed before and 9.5 ± 5.1 months after initiation of maximum tolerated dose of sacubitril/valsartan. The maximum tolerated dose of sacubitril/valsartan was lower for the low blood pressure group (≤ 100 mmHg in systole) than for the non-low blood pressure group (> 100 mmHg in systole) (165 ± 106 mg vs. 238 ± 124 mg, P=0.017). As expected, significant LV reverse remodeling was observed in the non-low blood pressure group after initiation of sacubitril/valsartan. It was noteworthy that significant LV reverse remodeling was also observed in the low blood pressure group after initiation of sacubitril/valsartan (LV end-diastolic volume: 177.3 ± 66.0 mL vs. 137.7 ± 56.1 mL, P<0.001, LV end-systolic volume: 131.6 ± 60.3 mL vs. 94.6 ± 55.7 mL, P<0.001, LVEF: 26.8 ± 10.3% vs. 33.8 ± 13.6%, P=0.015). Relative changes in LV volumes and LVEF after initiation of sacubitril/valsartan were similar for the two groups. In conclusion, significant LV reverse remodeling occurred after initiation of sacubitril/valsartan, even in HF patients with LVEF < 50% and systolic blood pressure ≤ 100 mmHg.

Key words: sacubitril/valsartan, left ventricular reverse remodeling, heart failure, low blood pressure, echocardiography

Introduction

The recent increase in the number of heart failure (HF) patients, known as the HF pandemic, has led to a major health and economic burden worldwide. The PARADIGM-HF trial has found that sacubitril/valsartan, the first-in-class of dual neprilysin and angiotensin receptor inhibitors, is superior to angiotensin converting enzyme (ACE) inhibitor enalapril for reducing hospitalizations for worsening HF, cardiovascular mortality, and all-cause mortality in symptomatic HF patients with reduced ejection fraction (HFrEF) [1]. Since then, various large clinical studies have demonstrated the effectiveness of sacubitril/valsartan for HF patients in various ways, such as reducing cardiovascular mortality [2-6], left ventricular (LV) reverse remodeling [7, 8], lowering high blood pressure [9], reducing ventricular arrythmias [10, 11] and safety[1, 5, 12] so that guidelines have recommended that an ACE inhibitor or angiotensin receptor blocker (ARB) should be replaced by sacubitril/valsartan for symptomatic patients with HFrEF, who remain symptomatic despite optimal treatment [13-15]. Thus, sacubitril/valsartan has become an important first-line drug for HF, especially LV ejection fraction (LVEF) < 50%. Since sacubitril/valsartan was reported to be more potent than renin-angiotensin-aldosterone system (RAAS) inhibitors for lowering blood pressure [9], HF patients with systolic blood pressure < 100 mmHg were not included in most clinical studies as a result of sacubitril/valsartan administration, and average systolic blood pressure of most enrolled patients was around 120 mmHg. Thus, the effect of sacubitril/valsartan on cardiovascular outcomes, especially LV reverse remodeling for HF patients with LVEF < 50% and low blood pressure, remains uncertain. The aim of this study was therefore to examine the effect of sacubitril/valsartan on LV reverse remodeling after initiation of the maximum tolerated dose of sacubitril/valsartan for HF patients with LVEF < 50% and systolic blood pressure ≤ 100 mmHg, and a comparison of its efficacy with that for patients with systolic blood pressure > 100 mmHg.

Methods

Study population

For this study, 164 patients with HFrEF and HF with mildly reduced ejection fraction (HFmrEF) who were treated with sacubitril/valsartan at two centers of Kobe University Hospital and the National Hospital Organization Kobe Medical Center between June 2020 and July 2022 were retrospectively enrolled. Not included were patients who were: (1) 18 years of age and younger, with: (2) symptomatic hypotension; (3) history of angioedema; (4) unacceptable side effects when receiving ACE inhibitors or ARBs. The criterion for the low blood pressure group was defined as baseline systolic blood pressure ≤ 100 mmHg, and for the non-low blood pressure group as baseline systolic blood pressure > 100 mmHg. Blood pressure measurements were obtained using office blood pressure. This study was approved by the local ethics committee of our institution in conformity with the Declaration of Helsinki (No. B220138).

Echocardiographic examination

Echocardiographic studies were performed before and 9.5 ± 5.1 months after initiation of the maximum tolerated dose of sacubitril/valsartan by using a commercially available echocardiographic system (Aplio Artida, Aplio 400 and Xario, Canon Medical Systems, Tochigi, Japan; Vivid 7 and E9, GE-Vingmed, Horten, Norway; iE33, Philips Medical Systems, Andover, MA). Standard echocardiographic measurements were obtained in accordance with the current guidelines of the American Society of Echocardiography[16]. The time interval from the baseline echocardiography to the initiation of sacubitril/valsartan was 33 days (2-119 days).

Definition of study endpoint

The primary endpoint was defined as a comparison of LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LVEF at baseline and after initiation of the maximum tolerated dose of sacubitril/valsartan for each group. The secondary endpoint was defined as a comparison of relative changes in LVEDV, LVESV and LVEF at baseline and after initiation of the maximum tolerated dose of sacubitril/valsartan for the two groups.

Statistical Analysis

Continuous variables were expressed as mean values and standard deviation for normally distributed data, and as the median and interquartile range for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The parameters of the two subgroups were compared by using the Student *t* test or paired *t* test as appropriate. Proportional differences were evaluated with Fisher's exact test or the χ^2 test as appropriate. Relative change in LVESV between different three groups of maximum tolerated dose of sacubitril/valsartan was evaluated with Tukey-Kramer test. All the analyses were performed with commercially available software (MedCalc software version 20.109; MedCalc Software, Mariakerke, Belgium).

Results

Baseline characteristics

Of the 164 patients initially enrolled, sacubitril/valsartan was discontinued for 17 (10.4%) as decided by the attending physician mainly due to symptomatic hypotension. The prevalence of discontinuation of sacubitril/valsartan for the low blood pressure group was higher than that for the non-low blood pressure group, but the difference was not statistically significant [4/25 (16.0%) vs. 13/139 (9.4%), P=0.320)]. No serious adverse events occurred during this study. Patients with discontinuation of sacubitril/valsartan were more likely to be older (72.6 ± 10.6 years vs. 65.6 ± 13.3 years, P=0.04), lower systolic blood pressure (111.5 ± 19.9 mmHg vs. 122.8 ± 20.2 mmHg, P=0.03), higher prevalence of New York Heart Association functional class III/VI (41% vs. 12%. P=0.002), lower hemoglobin level (11.6 ± 2.2 g/dL vs. 13.7 ± 1.9 g/dL, P<0.001), and higher brain natriuretic peptide [597 mg/dL (350-894) vs. 167 mg/dL (43-645), P=0.025] compared to those without discontinuation of sacubitril/valsartan. In addition, 40 patients were excluded because neither baseline nor follow-up echocardiograms were available, and two patients were also excluded because follow-up echocardiograms were not available due to cardiovascular death (Figure 1). Therefore, 105

patients were finally enrolled in this study to investigate the impact of sacubitril/valsartan on LV reverse remodeling (Table 1). Twenty patients were assigned to the low blood pressure group, and the remaining 85 to the non-low blood pressure group.

Baseline characteristics of the two groups

The baseline clinical findings and characteristics of the two groups are summarized and compared in Table 1. Patients with low blood pressure were likely to have higher brain natriuretic peptide / N-terminal prohormone of brain natriuretic peptide [603 pg/mL (237-883) vs. 108 pg/mL (35-449), P=0.015, 5892 pg/mL (3250-8852) vs. 860 pg/mL (504-2909), P=0.003, respectively], higher prevalence of New York Heart Association functional class III/VI (35% vs. 12%, P=0.011), larger LV volumes (LVEDV: 177.3 ± 66.0 mL vs. 143.4 ± 51.3 mL, P=0.015, LVESV: 131.6 ± 60.3 mL vs. 94.0 ± 40.5 mL, P=0.001) and lower LVEF (26.8 ± 10.3% vs. 35.4 ± 8.1%, P<0.001).

Furthermore, Table 2 shows the results of association baseline dose of RAAS inhibitors with systolic blood pressure at baseline and after initiation of maximum tolerated dose of sacubitril/valsartan in both groups.

LV reverse remodeling following initiation of sacubitril/valsartan

The duration between initiation of maximum tolerated dose of sacubitril/valsartan and follow-up echocardiogram between low blood pressure group and non-low blood pressure group were similar (9.1 ± 4.9 months vs. 8.8 ± 5.1 months, p=0.835; Table 3). In addition, the maximum tolerated dose of sacubitril/valsartan for the low blood pressure group was significantly smaller than that for the non-low blood pressure group (165 ± 106 mg vs. 238 ± 124 mg, P=0.017; Table 2). As expected, significant LV reverse remodeling was observed in the non-low blood pressure group after initiation of sacubitril/valsartan (LVEDV: 143.4 ± 51.3 mL vs. 127.1 ± 49.5 mL, P<0.001, LVESV: 94.0 ± 40.5 mL vs. 77.2 ± 40.1 mL, P<0.001, LVEF: 35.4 ± 8.1% vs. 41.2 ± 10.6%, P<0.001; Figure 2). It was noteworthy, however, that significant LV reverse remodeling after initiation of sacubitril/valsartan was also observed in the low blood pressure group (LVEDV: 177.3 ± 66.0 mL

vs. 137.7 ± 56.1 mL, P<0.001, LVESV: 131.6 ± 60.3 mL vs. 94.6 ± 55.7 mL, P<0.001, LVEF: 26.8 ± 10.3% vs. 33.8 ± 13.6%, P=0.015; Figure 3). Characteristics of patients after initiation of sacubitril/valsartan is shown in Table 3. Significant LV reverse remodeling after initiation of sacubitril/valsartan was also observed in the low blood pressure group with New York Heart Association functional class III/VI (LVEDV: 151.6 ± 49.6 mL vs. 126.7 ± 42.8mL, P= 0.034, LVESV: 110.6 ± 43.8 mL vs. 81.0 ± 37.9 mL, P=0.008, LVEF: 27.7 ± 8.4 % vs. 37.6 ± 13.1 %, P=0.004). Moreover, the prevalence of cardiovascular events was similar between low blood pressure group and non-low blood pressure group (HF hospitalization: 4.0% vs. 4.3%, P=0.345; cardiac death: 8.0% vs. 2.2%, P=0.685) during mean follow-up period of 8.4 months.

Comparison of LV reverse remodeling in the two groups following initiation of sacubitril/valsartan

LV reverse remodeling after initiation of sacubitril/valsartan in the two groups is compared in Figure 4, showing that relative changes in LVEDV, LVESV and LVEF after initiation of sacubitril/valsartan were similar for the two groups (LVEDV: 80.7 ± 26.0% vs. 90.3 ± 24.0%, P=0.125, LVESV: 75.5 ± 33.6% vs. 82.9 ± 26.2%, P=0.293, LVEF: 137.9 ± 79.9% vs. 119.9 ± 35.8%, P=0.128; Figure 4). When using a reduction of 15% or more in LVESV as the cutoff for LV reverse remodeling, there was no significant difference of the prevalence of LV reverse remodeling between the low blood pressure group and the non-low blood pressure group (reverse remodeling occurrence rate: 68% vs. 54%, P=0.26). In addition, relative change in LVESV between different three groups of maximum tolerated dose of sacubitril/valsartan of 50-100mg, 101-200mg and 201-400mg in entire patients were similar (76.8 ±28.2%, 87.2±30.8%, and 79.6±22.0%, respectively, P= 0.264; Figure 5).

Discussion

The findings of our study demonstrate that significant LV reverse remodeling was observed in HF patients with LVEF < 50% and systolic blood pressure ≤ 100 mmHg after initiation of sacubitril/valsartan, although the prevalence of discontinuation of sacubitril/valsartan tended to be higher and the maximum tolerated dose of sacubitril/valsartan to be significantly smaller than that for HF patients with LVEF < 50% and systolic blood pressure > 100 mmHg. Interestingly, similar LV reverse remodeling after initiation of sacubitril/valsartan was also observed in HF patients with LVEF < 50% and systolic blood pressure ≤ 100 mmHg and > 100 mmHg.

LV reverse remodeling after initiation of sacubitril/valsartan

Sacubitril/valsartan, which consists of the neprilysin inhibitor sacubitril and the ARB valsartan, was shown in the PARADIGM-HF trial to be superior to the ACE inhibitor enalapril for reducing hospitalizations for worsening HF, cardiovascular mortality, and all-cause mortality for symptomatic HF patients with LVEF ≤ 40% [1]. Although lowering total HF hospitalizations and cardiovascular death combined by sacubitril/valsartan was non-significant in comparison with that by ARB valsartan for symptomatic HF patients with LVEF ≥ 45% [5], the efficacy of sacubitril/valsartan as seen in outcomes for HF patients varied depending on LVEF, and treatment benefits were greatest for those with LVEF below normal compared with the benefits for those treated with RAAS inhibitors as demonstrated by pooled patient-level data for the 13,195 HF patients enrolled in the PARADIGM-HF and PARAGON-HF trials [2]. Thus, sacubitril/valsartan should now be considered an essential drug in the pharmacological treatment of HF, especially LVEF < 50%, and the use of sacubitril/valsartan deserves to be recommended for reducing morbidity and mortality for symptomatic patients with HFrEF as a class I recommendation and evidence level A, and may also be considered for reducing the risk of HF hospitalization and cardiovascular mortality for symptomatic patients with HFmrEF. In particular, the use of sacubitril/valsartan for patients with LVEF at the lower end of this spectrum deserves to be viewed as a class IIb recommendation and evidence level B based on the most recent HF guideline from American Heart

Association / American College of Cardiology [13]. On the other hand, the efficacy of sacubitril/valsartan in terms of outcomes for HF patients with low blood pressure, especially those with systolic blood pressure < 100 mmHg, remains uncertain because patients with systolic blood pressure < 100 mmHg at screening or < 95 mmHg at randomization were not included in the PARADIGM-HF trials (mean systolic blood pressure was 122 ± 15 mmHg for the sacubitril/valsartan group and 121 ± 15 mmHg for the enalapril group) [1].

LV remodeling is crucial for the progression of HFrEF [17, 18], and occurs in response to injury, hemodynamic changes, or neurohormonal activation. Remodeling consists of changes in cardiac geometry, function, or both, as reflected by a reduction in LVEF and an increase in LV volume. However, LV remodeling is associated with risks of cardiovascular events, including hospitalization for HF and death, and represents an important target for HF therapy. The PROVE-HF study, a prospective, single-group, open-label study using 794 HF patients with LVEF < 40%, that LVEF increased from 28.2% to 37.8% ($P < 0.001$), the LVEDV index decreased from 86.93 mL/m^2 to 74.15 mL/m^2 ($P < 0.001$) and the LVESV index decreased from 61.68 mL/m^2 to 45.46 mL/m^2 ($P < 0.001$) 12 months after initiation of sacubitril/valsartan [7]. However, the impact of sacubitril/valsartan on LV reverse remodeling for HF patients with LVEF < 50% and low blood pressure, especially systolic blood pressure ≤ 100 mmHg, remains uncertain since the mean systolic blood pressure for patients in this study was 125 ± 16 mmHg.

Sacubitril/valsartan for patients with low blood pressure

Sacubitril/valsartan is more potent than RAAS inhibitors for lowering blood pressure. The reduction in systolic blood pressure for the sacubitril/valsartan group was greater than for the ARB olmesartan group from baseline to 12 weeks (-25.7 mmHg vs. -22.8 mmHg; P=0.31) and from baseline to 52 weeks (-26.1 mmHg vs. -20.8 mmHg; P=0.28) for patients with hypertension [9]. In some countries, sacubitril/valsartan is indicated for patients with essential hypertension as well as for those with HF in response to its excellent antihypertensive effect. However, this effect may also

induce adverse events including symptomatic hypotension for HFrEF patients. In the PARADIGM - HF trial, symptomatic hypotension (systolic blood pressure < 90 mmHg) occurred in 2.7% of patients in the sacubitril/valsartan group, a prevalence significantly higher than for the enalapril group (2.7% vs. 1.4%, P<0.001) [1]. In the PARAGON-HF trial, hypotension (systolic blood pressure < 100 mmHg) occurred in 15.8% of the patients in the sacubitril/valsartan group, significantly higher than in the valsartan group (15.8% vs. 10.8%, P<0.001) [5]. However, since baseline systolic blood pressure of the sacubitril/valsartan group in both trials was not low (122 ± 15 mmHg and 131 ± 16 mmHg, respectively), the prevalence of the adverse effects of sacubitril/valsartan, especially hypotension-related adverse effects on HF patients with systolic blood pressure ≤ 100 mmHg remains unclear.

In addition, the maximum tolerated dose of sacubitril/valsartan for the low blood pressure group was significantly smaller than that for the non-low blood pressure group in our study (165 ± 106 mg vs. 238 ± 124 mg, P=0.017). However, the magnitude of benefit for patients on lower doses of sacubitril/valsartan relative to those on lower doses of enalapril was similar to that for patients who remained on target doses of both drugs in a post-hoc analysis of PARADIGM-HF [4].

Clinical implications

Sacubitril/valsartan is no longer a drug exclusively for patients with HFrEF and has become a first-line standard of care in response to the HF pandemic. However, HF patients with low blood pressure are usually hesitant to receive sacubitril/valsartan for fear of hypotension-related adverse effects. However, there are patients with HFrEF and low blood pressure who need to consider switching to sacubitril/valsartan from RAAS inhibitors. Since there were sicker patients in low blood pressure group in this study (i.e. patients with low blood pressure were likely to have higher brain natriuretic peptide / N-terminal prohormone of brain natriuretic peptide, higher prevalence of New York Heart Association functional class III/VI, larger LV volumes and lower LVEF, we dared to switch to sacubitril/valsartan from RAAS inhibitors in patients with low blood pressure.

We were able to demonstrate that significant LV reverse remodeling occurred after initiation of sacubitril/valsartan even in HF patients with LVEF < 50% and systolic blood pressure ≤ 100 mmHg, and that similar LV reverse remodeling occurred in those with systolic blood pressure > 100 mmHg. Although the prevalence of discontinuation of sacubitril/valsartan tended to be higher than that for HF patients with LVEF < 50% and systolic blood pressure > 100 mmHg, the administration of sacubitril/valsartan should be considered in the hope of generating LV reverse remodeling.

Study limitations

This study was retrospective and comprised a small number of patients with a short follow-up period, so that future prospective studies with larger patient populations and a longer follow-up period will be needed to validate our findings. Furthermore, baseline characteristics between low blood pressure group and non-low blood pressure group were different, especially LVEF and LV volumes. This can affect on LV reverse remodeling after initiation of sacubitril/valsartan.

Conclusion

Significant LV reverse remodeling can occur after initiation of sacubitril/valsartan even in HF patients with LVEF < 50% and systolic blood pressure ≤ 100 mmHg if tolerated. This finding is expected to offer new insights for better management of HF patients.

Conflict of interest

H.T. is a consultant for AstraZeneca plc, Ono Pharmaceutical Company, Limited. Pfizer Inc, Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Company, Limited, and Novartis International AG.

H.O is a consultant for Abbott Vascular Japan and Terumo Co.

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The remaining authors have no conflicts of interest to declare.

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Figure Legends

Figure 1: Flowchart of patients recruited for this study.

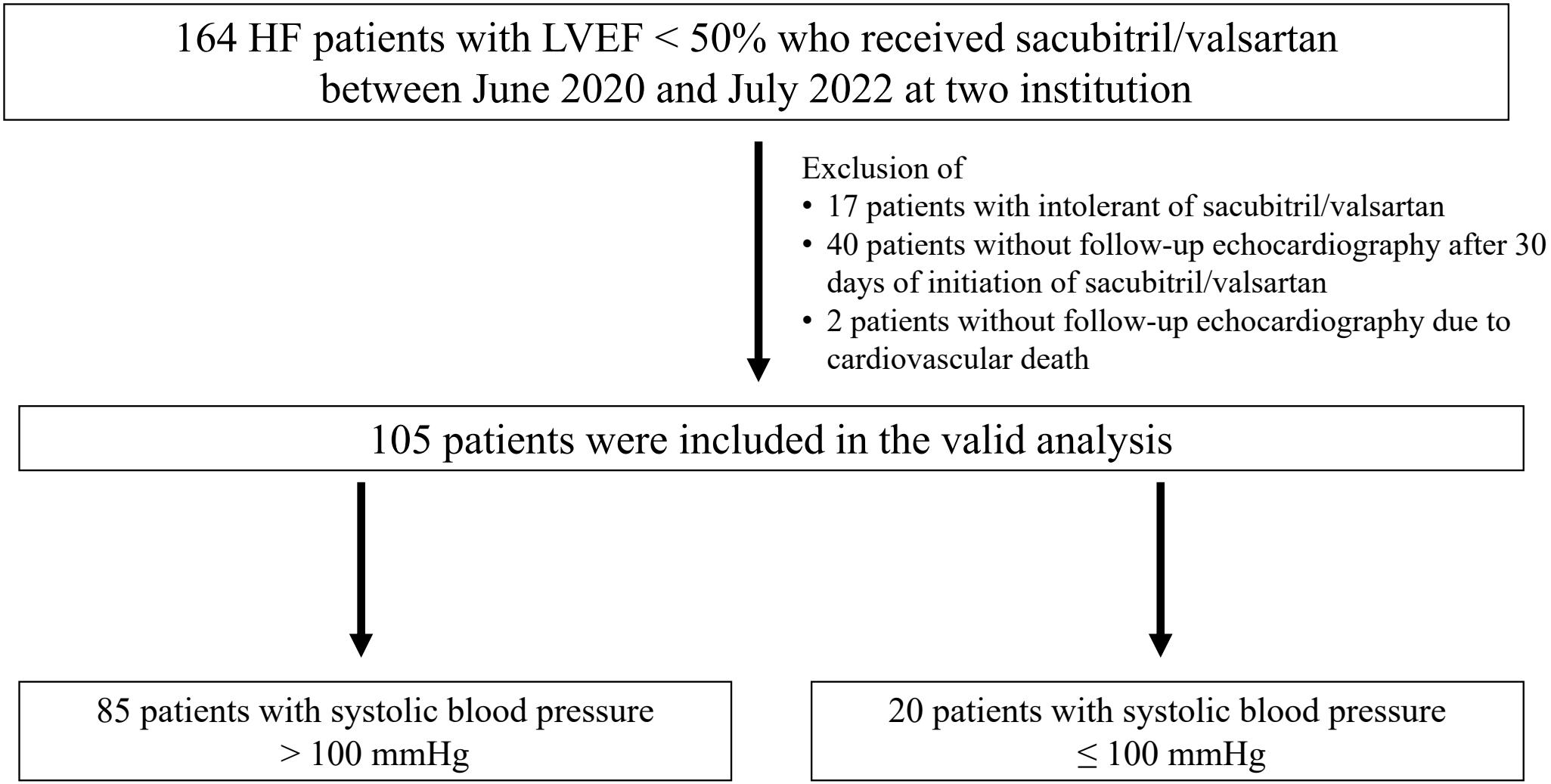
HF, heart failure; LVEF, left ventricular ejection fraction

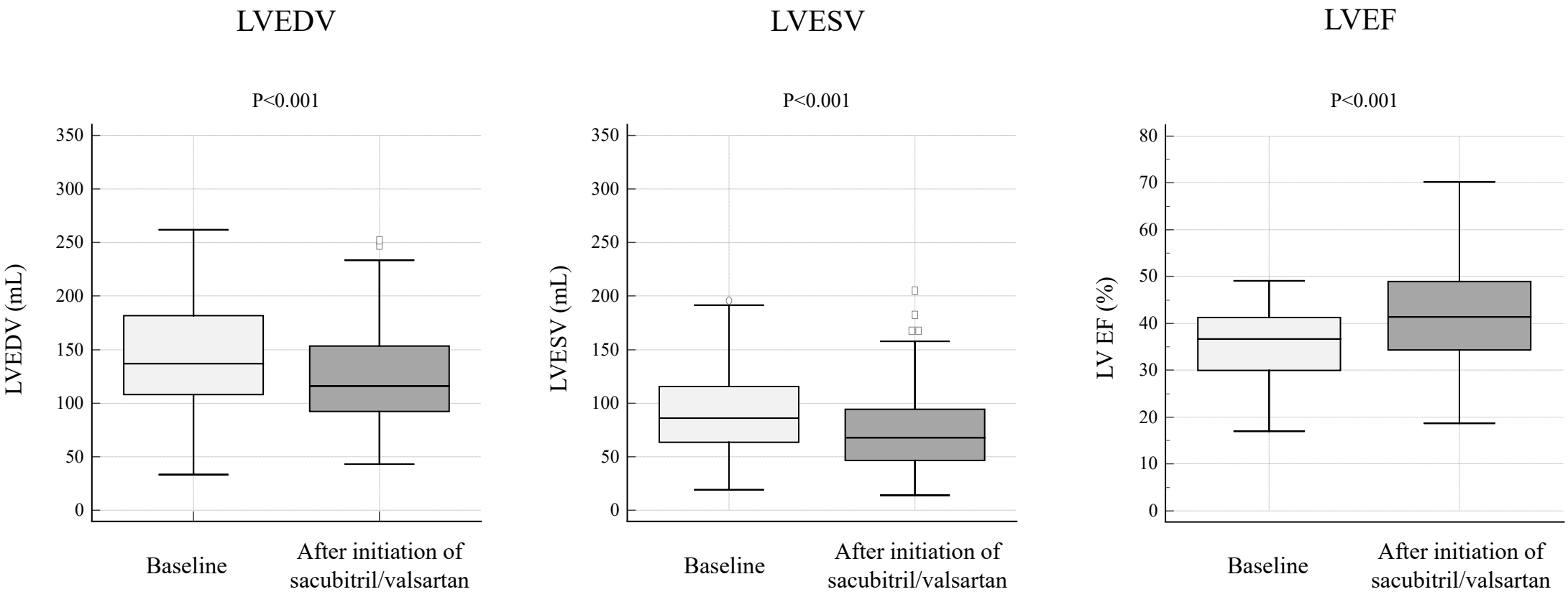
Figure 2: Bar graphs showing changes in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) after initiation of sacubitril/valsartan for the non-low blood pressure group, indicating occurrence of significant LV reverse remodeling.

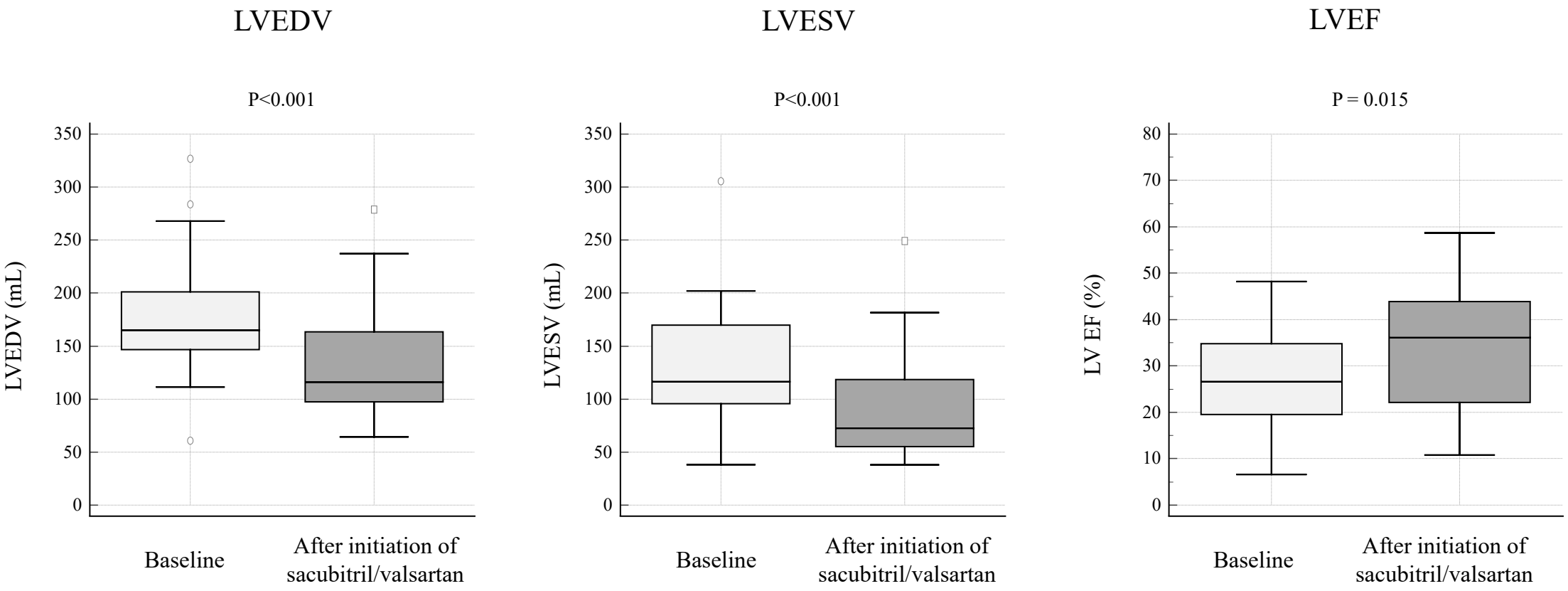
Figure 3: Bar graphs showing changes in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) after initiation of sacubitril/valsartan for the low blood pressure group, indicating occurrence of significant LV reverse remodeling.

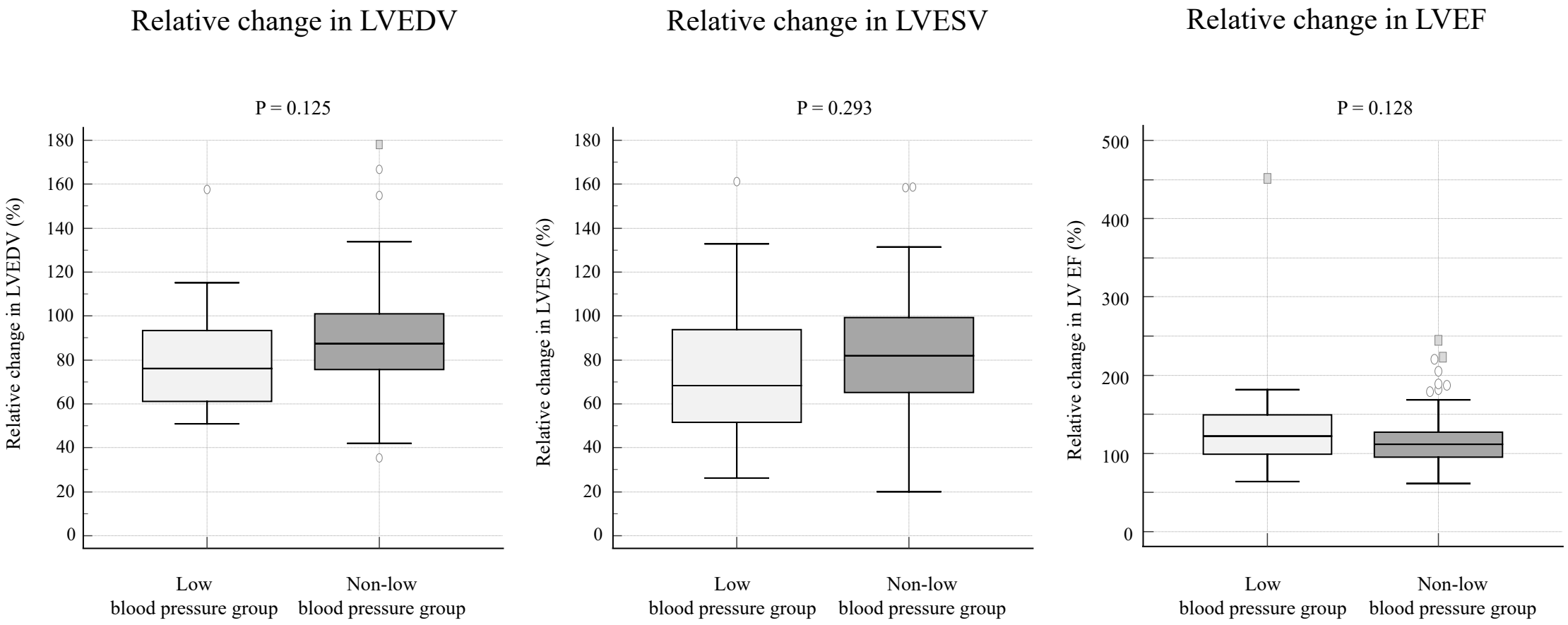
Figure 4: Bar graphs showing comparison of relative changes in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) after initiation of sacubitril/valsartan for the low and non-low blood pressure groups, signifying occurrence of similar LV reverse remodeling.

Figure 5: Bar graphs showing comparison of relative changes in left ventricular end-systolic volume (LVESV) between different three groups of maximum tolerated dose of sacubitril/valsartan of 50-100mg, 101-200mg and 201-400mg in entire patients, signifying occurrence of similar LV reverse remodeling.


164 HF patients with LVEF < 50% who received sacubitril/valsartan between June 2020 and July 2022 at two institution
Exclusion of
• 17 patients with intolerant of sacubitril/valsartan
• 40 patients without follow-up echocardiography after 30 days of initiation of sacubitril/valsartan
• 2 patients without follow-up echocardiography due to cardiovascular death
105 patients were included in the valid analysis
85 patients with systolic blood pressure > 100 mmHg
20 patients with systolic blood pressure ≤ 100 mmHg


LVEDV
P<0.001
LVEDV (mL)
350
300
250
200
150
100
50
0
Baseline
After initiation of sacubitril/valsartan
LVESV
P<0.001
LVESV (mL)
350
300
250
200
150
100
50
0
Baseline
After initiation of sacubitril/valsartan
LVEF
P<0.001
LV EF (%)
80
70
60
50
40
30
20
10
0
Baseline
After initiation of sacubitril/valsartan


LVEDV
P<0.001
LVEDV (mL)
350
300
250
200
150
100
50
0
Baseline
After initiation of sacubitril/valsartan
LVESV
P<0.001
LVESV (mL)
350
300
250
200
150
100
50
0
Baseline
After initiation of sacubitril/valsartan
LVEF
P = 0.015
LV EF (%)
80
70
60
50
40
30
20
10
0
Baseline
After initiation of sacubitril/valsartan


Relative change in LVEDV
P = 0.125
Relative change in LVEDV (%)
180
160
140
120
100
80
60
40
20
0
Low
blood pressure group
Non-low
blood pressure group
Relative change in LVESV
P = 0.293
Relative change in LVESV (%)
180
160
140
120
100
80
60
40
20
0
Low
blood pressure group
Non-low
blood pressure group
Relative change in LVEF
P = 0.128
Relative change in LV EF (%)
500
400
300
200
100
0
Low
blood pressure group
Non-low
blood pressure group

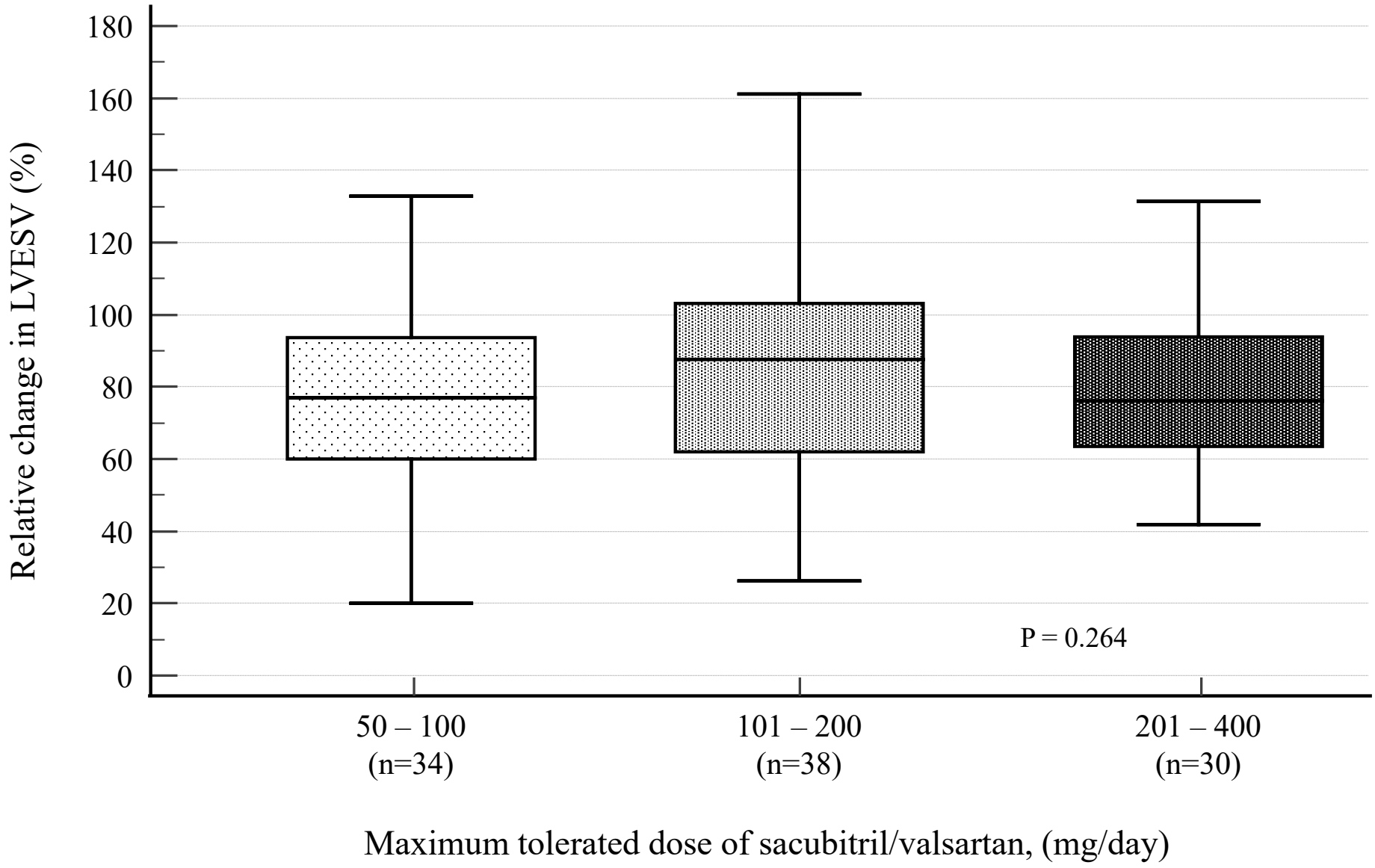

Relative change in LVESV (%)
180
160
140
120
100
80
60
40
20
0
P = 0.264
50 – 100
(n=34)
101 – 200
(n=38)
201 – 400
(n=30)
Maximum tolerated dose of sacubitril/valsartan, (mg/day)

Table1

Baseline characteristics of patients

Variables	Low blood pressure (n=20)	Non-low blood pressure (n=85)	P value
Clinical characteristics			
Age, years	65 ± 11	66 ± 14	0.612
Gender (female), n (%)	8 (40)	20 (24)	0.137
Height	163 ± 9	163 ± 9	0.952
Body weight, kg	54 ± 16	65 ± 14	0.007
Systolic blood pressure, mmHg	93 ± 8	129 ± 17	<0.001
Heart rate, bpm	82 ± 45	70 ± 14	0.040
Previous history of hospitalization for HF	17 (85)	60 (71)	0.193
Blood examination			
Serum creatinine, mg/dL	1.0 ± 0.3	1.2 ± 0.8	0.390
eGFR, mL/min/1.73 m^2	55.9 ± 14.0	56.0 ± 19.5	0.981
BNP, pg/dL	603 (237-883)	108 (35-449)	0.015
NT-proBNP, pg/dL	5892 (3250-8852)	860 (504-2909)	0.003
Clinical features of HF			
Ischemic etiology, n (%)	3 (15)	22 (26)	0.309
NYHA functional class, n (%)			
I	2 (10)	21 (25)	0.155
II	10 (50)	37 (44)	0.605
III-IV	7 (35)	10 (12)	0.011
Unknown	1 (5)	17 (20)	0.111

Comorbidities, n (%)			
Hypertension	12 (60)	71 (84)	0.020
Diabetes mellites	9 (45)	53 (62)	0.159
Dyslipidemia	12 (60)	40 (47)	0.302
Atrial fibrillation	5 (25)	10 (12)	0.131
Mediations, n (%)			
ACE inhibitors / ARBs	18 (90)	77 (91)	0.937
β-blockers	20 (100)	76 (89)	0.131
MRAs	12 (60)	48 (56)	0.777
SGLT2 inhibitors	7 (35)	46 (54)	0.126
Diuretics	14 (70)	41 (48)	0.081
Ivabradine	1 (5)	9 (11)	0.449
Echocardiographic Parameters			
LV end-diastolic volume, mL	177.3 ± 66.0	143.4 ± 51.3	0.015
LV end-systolic volume, mL	131.6 ± 60.3	94.0 ± 40.5	0.001
LVEF, %	26.8 ± 10.3	35.4 ± 8.1	<0.001
Left atrial dimension, mm	37.8 ± 7.6	41.5 ± 7.1	0.011
Interventricular septum thickness, mm	8.7 ± 2.2	9.4 ± 2.4	0.436
LV posterior wall thickness, mm	10.6 ± 8.1	9.6 ± 2.1	0.323
E/e'	14.6 ± 5.0	12.3 ± 5.5	0.428
Mitral regurgitation, n (%)			
none	7 (35)	28 (33)	0.862
mild	5 (25)	43 (51)	0.039
moderate	6 (30)	8 (9)	0.015
severe	2 (10)	6 (7)	0.659

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%)
BNP; brain natriuretic peptide, NT-proBNP; N-terminal prohormone of brain natriuretic peptide, eGFR; estimated glomerular filtration rate, NYHA; New York Heart Association, HF; heart failure, ACE; angiotensin converting enzyme, ARB; angiotensin II receptor blockers, MRA; mineralocorticoid receptor antagonists, LVEF; left ventricular ejection fraction, SGLT2; Sodium–glucose cotransporter 2, E/e'; ratio of early transmitral flow velocity to early diastolic mitral annular velocity

Table 2A

Association baseline dose of RAAS inhibitors with systolic blood pressure after initiation of maximum tolerated dose of sacubitril/valsartan in low blood pressure group

	n (%)	Dose, mg	Systolic blood pressure at baseline, mmHg	Systolic blood pressure after initiation of maximum tolerated dose of sacubitril/valsartan, mmHg
ACE inhibitors				
Enalapril	9 (45)	2.4	95 ± 22	104 ± 27
Perindopril	1 (5)	4.0	82 ± 22	92 ± 27
ARBs				
Losartan	2 (10)	31.3	89 ± 22	75 ± 27
Valsartan	3 (15)	53.3	97 ± 22	87 ± 27
Olmesartan	2 (10)	15.0	85 ± 22	81 ± 27
Candesartan	0 (0)			
Telmisartan	0 (0)			
Irbesartan	1 (5)	100.0	98 ± 22	117 ± 27
Azilsartan	0 (0)			

Table 2B

Association baseline dose of RAAS inhibitors with systolic blood pressure after initiation of maximum tolerated dose of sacubitril/valsartan in non- low blood pressure group

	n (%)	Dose, mg	Systolic blood pressure at baseline, mmHg	Systolic blood pressure after initiation of maximum tolerated dose of sacubitril/valsartan, mmHg
ACE inhibitors				
Enalapril	12 (14)	3.5	122 ± 21	119 ± 23
Perindopril	2 (2)	4.0	141 ± 21	122 ± 23
ARBs				
Losartan	18 (21)	38.2	125 ± 21	118 ± 23
Valsartan	16 (19)	70.0	130 ± 21	124 ± 23
Olmesartan	12 (14)	16.7	119 ± 21	117 ± 23
Candesartan	13 (15)	6.6	136 ± 21	116 ± 23
Telmisartan	2 (2)	40.0	133 ± 21	104 ± 23
Irbesartan	0 (0)			
Azilsartan	2 (2)	40.0	141 ± 21	131 ± 23

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%)
All abbreviations as in Table 1.

Table 3

Characteristics of patients after initiation of sacubitril/valsartan

Variables	Low blood pressure (n=20)	Non-low blood pressure (n=85)	P value
Duration between initiation of maximum tolerated dose of sacubitril/valsartan and follow-up echocardiogram, months	9.1 ± 4.9	8.8 ± 5.1	0.835
Systolic blood pressure, mmHg	96 ± 16	119 ± 19	<0.001
Change in systolic blood pressure after initiation of maximum tolerated dose of sacubitril/valsartan, mmHg	+7 (-10.5 - +11.5)	-7 (-24 - +1)	0.023
Maximum tolerated dose of sacubitril/valsartan, mg	165 ± 106	238 ± 124	0.017
50 mg/day, n (%)	4 (20)	3 (4)	0.008
100 mg/day, n (%)	6 (30)	21 (25)	0.630
200 mg/day, n (%)	7 (35)	31 (36)	0.903
300 mg/day, n (%)	1 (5)	2 (2)	0.527
400 mg/day, n (%)	2 (10)	28 (33)	0.041
Echocardiographic Parameters			
LV end-diastolic volume, mL	137.7 ± 56.1	127.1 ± 49.5	0.413
LV end-systolic volume, mL	94.6 ± 55.7	77.2 ± 40.1	0.118
LVEF, %	33.8 ± 13.6	41.2 ± 10.6	0.009
Left atrial dimension, mm	36.5 ± 9.6	41.5 ± 7.1	0.011
Interventricular septum thickness, mm	8.2 ± 2.8	9.1 ± 2.3	0.048
LV posterior wall thickness, mm	12.2 ± 15.8	9.6 ± 2.3	0.149
E/e'	9.6 ± 3.5	13.3 ± 5.4	0.077
Mitral regurgitation, n (%)			

none	7 (35)	38 (45)	0.435
mild	11 (55)	32 (38)	0.159
moderate	1 (5)	13 (15)	0.227
severe	1 (5)	2 (2)	0.527

Data are mean ± SD for normally distributed data and median and interquartile range for non-normally distributed data, or n (%)
All abbreviations as in Table 1.