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Valsartan Dosage on Ventriculo-Vascular Coupling Index Dose-Dependency in Heart Failure Patients

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Purpose: Heart failure (HF) poses significant morbidity and mortality. Recently, the ventriculo-vascular coupling index (VVI) was introduced as an independent prognostic factor reflective of the overall cardiovascular performance index in HF. We aimed to determine the effectiveness of force-titration of valsartan on VVI values in HF patients.
Materials and Methods: In this multicenter and prospective observational trial, the effect of valsartan was stratified according to dosages [non-ceiling dose (NCD) vs. ceiling dose (CD)] in HF patients with left ventricular ejection fraction (LVEF) <55%. Biochemical studies, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), echocardiography with VVI, the treadmill test, and the activity scale index were assessed at baseline and after 24 weeks of treatment.
Results: One-hundred thirty-eight patients were force-titrated to either a CD group (n=81) or a NCD group (n=57). The mean age of the study participants was 59 years and 66% were male. After 6 months of follow up, left ventricular mass index (LVMI) values had significantly improved in the CD group but not in the NCD group. Intriguingly, in HF patients with a reduced ejection fraction (HFrEF) (n=52, LVEF <40%), a significant improvement in VVI was only observed in the CD group (from 2.4±0.6 to 1.8±0.5, p<0.001).
Conclusion: CDs of valsartan for 6 months showed better improvement in VVI, as well as LVMI, in patients with HFrEF, compared with NCDs.

Key Words: Heart failure, ventricular ejection fraction, valsartan, dosage, ventriculo-vascular coupling index

INTRODUCTION

Heart failure (HF) is a clinical syndrome associated with serious morbidity and mortality that has become a major public health concern worldwide.[1] Although various classes of medications are used for the management of HF, for decades, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been the most commonly used drugs in patients with HF patients with a reduced ejection fraction (HFrEF).[2,3] Many trials, including VAL-HeFT and VALIANT, have shown that valsartan is effective in managing HF,[4-6] and several studies have demonstrated that the ceiling dose (CD) (160 mg twice a day) of valsartan is effective in patients with HF. However, the exact beneficial effects of force-titration to the CD of valsartan in clinical situations remain unclear.[7,8]

The ventriculo-vascular coupling index (VVI) reflects interactions between the left ventricle and the arterial system, indicating overall cardiovascular performance.[9] An abnormal ventriculo-vascular coupling (Ea/Ees) value may be a sign of the development of HF.[10] Ky, et al.[11] reported that ventriculo-vascular coupling can be an independent prognostic factor in HFrEF. Meanwhile, although ACEIs and ARBs are commonly used in HF management, studies of these drugs and their ac-

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tions on VVI in HF patients are scarce.

We performed a clinical trial to assess the effect of the CD of valsartan in patients with chronic stable HF, focusing primarily on VVI. Overall, our objective was to evaluate the effect of valsartan at the CD (160 mg twice a day) and non-ceiling dose (NCD) (<320 mg a day) after force-titration in HF patients using biochemical markers, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), echocardiographic data, the treadmill test, the activity scale index [Korea Activity Scale Index (KASI) score], and VVI.

MATERIALS AND METHODS

Study population

This trial was conducted as a multi-institutional, prospective, and open-label trial. One-hundred sventy patients at two hospitals in Incheon, South Korea were screened: among these patients, 145 patients were enrolled, and 138 patients were finally force-titrated on valsartan (Fig. 1). The study protocol was approved by the Institutional Review Board. Appropriate ethics committees confirmed that the investigation conformed to the principles outlined in the Declaration of Helsinki. The primary inclusion criterion was a clinical diagnosis of stable HF. We included patients aged 18 years or older who were diagnosed with congestive HF at least 3 months prior to an initial visit. We performed echocardiography and screened the patients who had ejection fractions of <55% and an indexed end-diastolic left ventricular (LV) diameter of >2.9 cm/m^2 during the wash-out period after the initial visit. We included patients on stable maintenance doses of HF medications throughout at least 2 weeks prior to the initial visit and during wash-out period. Female patients had to be post-menopausal for over 1, surgically sterile, or using effective contraception with a negative pregnancy test. All the patients provided written informed consent for study participation.

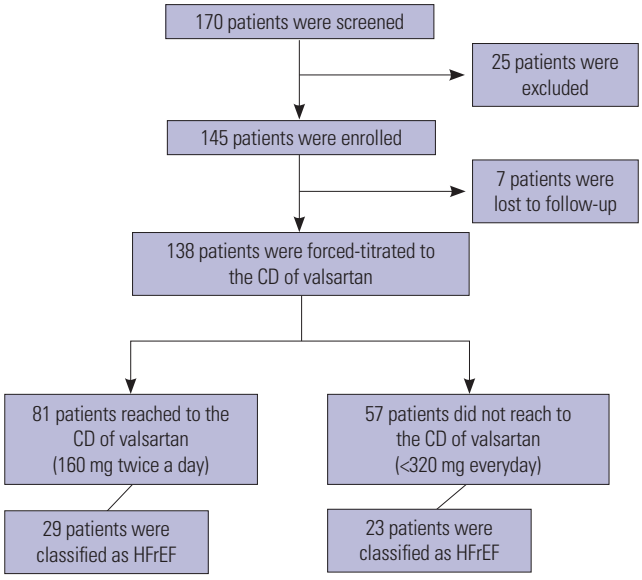

Fig. 1. Flowchart of patient enrollment and patient grouping according to the titrated dose of valsartan. CD, ceiling dose; HFrEF, HF patients with a reduced ejection fraction.

Participants were excluded if they had contraindication to ARBs, decompensated HF, acute coronary syndrome, persistent orthostatic hypotension, recent stroke and other major non-cardiac conditions (serum creatinine >1.8 mg/dL, major hepatic disease, malignant tumors that limited 5-year survival rates), or if they were unable or unwilling to provide informed consent. Pregnant or lactating females were also excluded. We excluded patients who had right HF secondary to pulmonary disease. Patients who had a history of cardiac transplantation or were on the transplantation list or who had significant mitral valve disease were also excluded. Subjects who had prolonged ventricular arrhythmia with a history of syncope within the last 3 months without treatment or who took class Ic antiarrhythmic medications, such as flecainide or propafenone, within 2 weeks prior to the initial visit were excluded. For the subjects, biochemical markers, such as NT-proBNP, transthoracic echocardiography, the treadmill test, and the KASI were measured at baseline and after 24 weeks of treatment.

Dose titration

After a 2-week washout period, we started valsartan at a dose of 40 mg twice a day and doubled the dose every 4 weeks when the patients were tolerating the therapy. The requirements for increasing the drug dose were systolic blood pressure over 90 mm Hg in the standing position, no symptoms of hypotension, and a serum creatinine level within the normal range. If standing systolic blood pressure was consistently below 80 mm Hg or there were symptoms of hypotension or elevated serum creatinine levels over 50% from baseline, the dose was reduced by half. With a standing systolic blood pressure of ≥80 mm Hg and <90 mm Hg, no symptoms of hypotension, and a serum creatinine increase of <50%, the drug dose was maintained at the same level.

Laboratory analysis

Laboratory tests for hematologic values and blood chemistry were evaluated at baseline and 24 weeks after treatment. NT-proBNP was assessed with an electrochemiluminescence sandwich immunoassay using a Cobas 4000 analyzer (Roche Diagnostics, Mannheim, Germany).

Echocardiography

Echocardiographic exams were performed blindly at the beginning of the study and at the 24th week of the study period. VVI [Ea/Ees=(Pes/SV)/(Pes/ESV)=ESV/SV], left ventricular mass index (LVMI), and the systolic and diastolic parameters were measured using the echocardiographic data. VVI, known as ventricular arterial coupling, was calculated as the ratio of

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effective arterial elastance, which is a component of arterial load, and ventricular stiffness at end-systole. In an apical 4-chamber view, LV end-diastolic and end-systolic volume were computed based on Simpson's method, as recommended by the American Society of Echocardiography. Stroke volume was measured from the velocity time integral of the aortic valve area obtained by pulsed-wave Doppler signals were obtained in an apical 5-chamber view, and LV outflow diameter were obtained in a parasternal long axis view. We also compared VVI in HFrEF, as a subgroup of HF patients with left ventricular ejection fraction (LVEF) <40%.

Treadmill tests

Treadmill tests were performed at the second visit (4th week) and the sixth visit (24th week) using the Naughton protocol. Exercise capacity, including exercise duration and metabolic equivalents, was measured.

Activity Scale Index

We identified the symptoms and signs of HF according to the KASI through history taking and physical examinations in the outpatient clinic every 4 weeks.[12] The KASI score is known for its accuracy in the assessment of functional status, and it is convenient for patients.

Statistical analysis

Continuous variables are presented as means and standard errors of the means, and the significances of intergroup differences were determined using Student's t-test. Categorical variables are expressed in absolute numbers and percentages and were analyzed using the chi-square test or Fisher's exact test. The analysis was performed using a computer-based statistical software package [Statistical Package for Social Sciences (SPSS), Ver. 18.0 for Windows; SPSS, Chicago, IL, USA]. Two-sided p values<0.05 were considered statistically significant.

The Institutional Review Board for Clinical Research at Gachon University Gil Medical Center approved the use of medical records for this study (GIRBA 1506).

RESULTS

Baseline characteristics

A total of 138 patients were force-titrated with valsartan. Eight-one patients were classified into the CD group, while 57 patients were classified into the NCD group. There were no meaningful differences between the groups in terms of sex, body mass index, and age (Table 1). More than half of the patients in both groups presented with cardiomegaly (61.2% in the CD group and 55.8% in the NCD group). In the CD group, more patients had high blood pressure than those in the NCD group (40.7%

Table 1. Baseline Characteristics of Patients Overall and according to Subgroups of Titrated Dosages of Valsartan

	Total (n=138)	NCD group (n=57)	CD group (n=81)	p value‡
Sex				
Male	91 (65.94)	39 (68.42)	52 (64.20)	0.606
Female	47 (34.06)	18 (31.58)	29 (35.80)	0.606
Baseline characteristics				
Age (yr)	59.30±12.38	60.60±10.65	58.40±13.46	0.350
BMI (kg/m^2)	24.29±3.14	24.57±2.93	24.09±3.28	0.377
Medical history				
Hypertension	45 (32.60)	12 (21.05)	33 (40.74)	0.015*
IHD	61 (44.86)	24 (42.11)	37 (46.83)	0.677
Atrial fibrillation	7 (5.15)	2 (3.51)	5 (6.33)	0.483
Diabetes mellitus	26 (19.12)	12 (21.05)	14 (17.72)	0.577
Dyslipidemia	5 (3.68)	2 (3.51)	3 (3.80)	0.952
Medications				
Beta blocking agents	97 (70.29)	32 (56.14)	65 (80.25)	0.002†
Diuretics	92 (66.67)	42 (73.68)	50 (61.73)	0.142
HMG-CoA-reductase inhibitors	60 (43.48)	22 (38.60)	38 (46.91)	0.332
Aldosterone antagonists	57 (41.30)	27 (47.37)	30 (37.04)	0.225
ACEIs, alone	51 (36.96)	26 (45.61)	25 (30.86)	0.077
Digitalis glycosides	31 (22.46)	11 (19.30)	20 (24.69)	0.455

NCD, non-ceiling dose; CD, ceiling dose; BMI, body mass index; IHD, ischemic heart disease; HMG-CoA-reductase, 3-hydroxy-3-methyl-glutaryl-coenzyme A-reductase; ACEIs, angiotensin-converting enzyme inhibitors.
Values are expressed as percentages for categorical variables and as mean±standard deviations for continuous variables.
*p<0.05, †p<0.01, ‡p values are based on Fisher's exact tests for sex, arterial hypertension, coronary artery disease, atrial fibrillation, diabetes mellitus, and dyslipidemia and on Kruskal-Wallis tests for other baseline characteristics.

Table 2. Vital Signs, Echocardiographic Characteristics, and Laboratory Results of Patients Overall and according to Subgroups of the Titrated Dosages of Valsartan

	Total (n=138)	NCD group (n=57)	CD group (n=81)	*p* value
SBP				
Baseline	122.62±20.37	118.56±17.96	126.58±21.97	
24th week	120.49±17.41	118.56±16.72	122.38±18.06	
Difference	-2.13±22.49	0.00±20.82	-4.20±24.09	0.410
p value	0.403	1.000	0.277	
DBP				
Baseline	76.99±10.96	73.44±8.95	80.54±11.72	
24th week	78.41±9.42	76.77±9.32	80.05±9.36	
Difference	1.42±11.11	3.33±11.02	-0.49±11.01	0.130
p value	0.262	0.067	0.784	
LVEF (%)				
Baseline	40.66±10.71	39.86±11.10	41.13±10.53	0.813
24th week	45.06±11.86	44.15±14.17	45.59±10.36	0.498
Difference	4.40±9.62	4.29±10.55	4.46±9.12	0.638
p value	<0.001‡	0.014†	<0.001‡	
LVEDV (mL)				
Baseline	119.57±55.36	139.92±66.19	109.60±46.80	0.332
24th week	112.81±50.87	131.69±60.42	103.55±43.21	0.063
Difference	-6.76±27.17	-8.22±24.13	-6.05±28.75	0.751
p value	0.037†	0.109	0.147	
LVESV (mL)				
Baseline	76.12±48.61	93.70±62.30	67.52±38.14	0.279
24th week	67.60±43.28	82.48±57.95	60.32±32.18	0.129
Difference	-8.52±22.03	-11.22±20.55	-7.20±22.80	0.468
p value	0.002†	0.014†	0.032†	
LVMI (g/m^2)				
Baseline	135.63±45.40	137.22±55.57	134.84±40.01	0.716
24th week	127.65±41.47	135.8±41.60	123.65±41.18	0.178
Difference	-7.98±35.36	-1.43±45.13	-11.19±29.35	0.304
p value	0.041†	0.868	0.006‡	
E/E'				
Baseline	15.30±8.79	14.08±7.99	16.01±9.22	0.451
24th week	9.18±7.99	8.12±7.17	9.79±8.43	0.394
Difference	-6.12±8.51	-5.96±8.02	-6.22±8.85	0.889
p value	<0.001‡	<0.001‡	<0.001‡	
VVI*				
Baseline	1.77±0.94	2.05±1.24	1.63±0.73	0.259
24th week	1.57±1.01	1.77±1.23	1.48±0.87	0.473
Difference	-0.19±0.91	-0.28±0.76	-0.15±0.97	0.569
p value	0.072	0.085	0.282	
NT-proBNP (pg/mL)				
Baseline	992.91±1870.3	1010.18±1820.16	983.45±1909.59	0.943
24th week	795.84±2170.0	694.22±1286.71	850.34±2527.09	0.674
Difference	-35.80±1395.8	-13.70±877.4	-46.85±1599.4	0.895
p value§	0.001	0.035	0.015	

NCD, non-ceiling dose; CD, ceiling dose; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; VVI, ventriculo-vascular coupling index; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Values are expressed as percentages for categorical variables and as mean±standard deviations for continuous variables.
*VVI is calculated with echocardiographic parameters (ESV/SV), †p<0.05, ‡p<0.01, §p value is calculated by substituting log for NT-proBNP.

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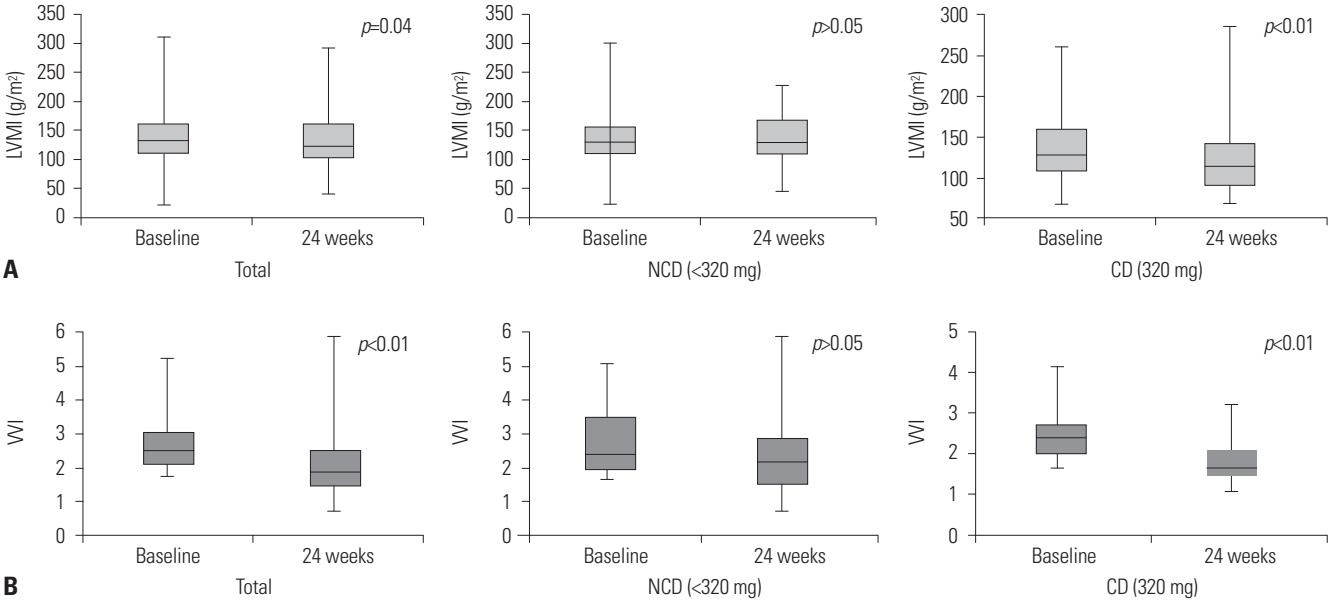

Fig. 2. Changes in parameters at baseline and 24 weeks after treatment. (A) Changes in LVMI according to the dosage of valsartan. (B) Changes in VVI according to the dosage of valsartan in the HFrEF group. NCD, non-ceiling dose; CD, ceiling dose; LVMI, left ventricular mass index; VVI, ventriculo-vascular coupling index; HFrEF, HF patients with a reduced ejection fraction.

vs. 21.1%, p=0.015), and among antihypertensive medications, the proportion of patients using β-blocking agents was higher in the CD group (80% in the CD group, 56% in the NCD group, p=0.002).

Laboratory analysis

In both groups, NT-proBNP levels were improved meaningfully (in the CD group, from 983.5±1909.6 pg/mL to 850.3± 2527.1 pg/mL, p=0.015; in the NCD group, from 1010.2±1820.2 pg/mL to 694.2±1286.7 pg/mL, p=0.036).

Echocardiography

There were significant improvements in echocardiographic indices, such as the LVEF and E/E' ratios, in both the CD group (n=81) and the NCD group (n=57) (p<0.05) (Table 2). LVEF was improved significantly overall (from 40.7±10.7% to 45.1±11.9%, p<0.001), in the CD group (from 41.1±10.5% to 45.6±10.4%, p<0.001), and in the NCD group (from 39.9±11.1% to 44.2± 14.2%, p=0.014). E/E' ratios were improved meaningfully overall (from 15.3±8.8 to 9.2±8.0, p<0.001), in the CD group (from 16.0±9.2 to 9.8±8.4, p<0.001) and in the NCD group (from 14.1±8.0 to 8.1±7.2, p<0.001). LVMI was improved significantly overall (from 135.6±45.4 g/m^2 to 127.7±41.5 g/m^2, p=0.041) and in the CD group (from 134.8±40.0 g/m^2 to 123.7±41.2 g/m^2, p=0.006), but not in the NCD group (from 137.2± 55.6 g/m^2 to 135.8±41.6 g/m^2, p=0.868) (Fig. 2).

VVI was not improved significantly overall (from 1.8±0.9 to 1.6±1.0, p=0.072), in the CD group (from 1.6±0.7 to 1.5± 0.9, p=0.282), or in the NCD group (from 2.1±1.2 to 1.8±1.2, p=0.085). Intriguingly, a significant improvement in VVI was observed in the participants in the CD group with LVEF <40% (from 2.4±0.6 to 1.8±0.5, p<0.001) (Table 3), but not in the NCD group (from 2.8±1.2 to 2.3±1.3, p=0.059) (Fig. 2). Additionally, participants receiving the CD of valsartan showed greater improvements in symptoms, as well as LVMI, compared with those receiving NCDs. However, there were no significant differences between the CD group and the NCD group in regards to improvements in other echocardiographic parameters and in HF with preserved ejection fraction (HFpEF).

Treadmill test

Total exercise time measured through the treadmill test was improved significantly overall (from 16.7±7.9 minutes to 18.2± 10.7 minutes, p=0.031), but not in the CD group (from 17.2± 8.3 minutes to 18.4±10.3 minutes, p=0.174) or the NCD group (from 15.8±7.1 minutes to 18.0±11.5 minutes, p=0.092).

Activity Scale Index

KASI scores significantly improved overall (from 40.17±14.87 to 44.22±14.74, p<0.001), in the CD group (from 42.9± 16.28 to 46.2±15.42, p=0.017), and in the NCD group (from 36.66±12.15 to 41.64±13.57, p<0.001).

Adverse events

There were no major adverse events reported during this study (Table 4). The most common adverse event was dizziness, and it was more common in the NCD group (17.54% vs. 7.41%). The frequency of adverse events was not significantly different between the CD group and the NCD group. Serum potassium levels were not significantly different between the CD group and the NCD group. Additionally, potassium levels were not significantly elevated after taking valsartan in any group (overall

group: 4.5±0.4 mEq/L to 4.6±0.5 mEq/L, p=0.241; CD group: 4.5±0.5 mEq/L to 4.5±0.5 mEq/L, p=0.856; NCD group: 4.5± 0.3 mEq/L to 4.6±0.4 mEq/L, p=0.095).

DISCUSSION

Our study was designed to assess the effect of the CD of the valsartan on VVI in patients with HF. LVMI was meaningfully improved in the CD group, but no significant difference was

Table 3. Echocardiographic Characteristics in a Subgroup of Patients with Reduced Ejection Fraction (LVEF <40%) according to Titrated Dosages of Valsartan

	Total (n=52)	NCD group (n=23)	CD group (n=29)	*p* value
LVEF (%)				
Baseline	29.94±5.88	29.91±6.69	29.96±5.33	0.643
24th week	37.04±10.76	36.20±13.08	37.68±8.84	0.658
Difference	7.10±9.77	6.29±10.07	7.72±9.70	0.639
p value	<0.001‡	0.014†	<0.001‡	
LVEDV (mL)				
Baseline	154.08±64.84	172.29±69.18	139.91±59.34	0.464
24th week	138.75±61.73	157.17±64.06	124.41±57.57	0.118
Difference	-15.33±31.41	-15.11±23.81	-15.50±36.95	0.973
p value	0.009†	0.034†	0.093	
LVESV (mL)				
Baseline	110.61±55.03	126.40±63.37	98.33±45.67	0.352
24th week	92.32±52.40	108.75±60.99	79.54±42.04	0.098
Difference	-18.29±24.75	-17.65±17.42	-18.79±29.73	0.900
p value	<0.001‡	0.002†	0.016†	
LVMI (g/m^2)				
Baseline	155.76±51.43	159.11±58.84	153.52±47.26	0.526
24th week	143.32±38.46	145.89±39.59	141.60±38.58	0.694
Difference	-12.44±35.13	-13.22±33.43	-11.92±37.03	0.917
p value	0.044†	0.163	0.156	
E/E'				
Baseline	18.22±11.32	15.02±8.10	20.55±12.85	0.232
24th week	11.48±11.55	9.40±10.01	12.99±12.56	0.397
Difference	-6.74±11.69	-5.62±9.69	-7.56±13.11	0.620
p value	0.001‡	0.035†	0.013†	
RVsPr				
Baseline	33.83±15.59	36.00±18.32	32.92±14.75	0.580
24th week	29.59±13.58	32.78±15.79	28.24±12.77	0.370
Difference	-4.25±15.37	-3.22±12.94	-4.68±16.60	0.827
p value	0.163	0.504	0.235	
LA vol index				
Baseline	3.95±19.70	3.97±26.59	3.93±11.52	0.330
24th week	4.33±23.24	4.16±31.93	4.49±12.44	0.998
Difference	0.39±6.13	0.19±8.83	0.55±2.17	0.853
p value	0.690	0.926	0.245	
VVI*				
Baseline	2.56±0.91	2.77±1.15	2.40±0.64	0.186
24th week	1.99±0.98	2.31±1.32	1.75±0.54	0.138
Difference	-0.57±0.68	-0.47±0.85	-0.65±0.53	0.462
p value	<0.001‡	0.059	<0.001‡	

NCD, non-ceiling dose; CD, ceiling dose; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; RVsPr, right ventricular systolic pressure; LA vol index, left atrial volume index; VVI, ventriculo-vascular coupling index. Values are expressed as percentages for categorical variables and as mean±standard deviations for continuous variables.
*VVI is calculated with echocardiographic parameters (ESV/SV), †p<0.05, ‡p<0.01.

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Table 4. Major Adverse Events Overall and in Subgroups of Titrated Dosages of Valsartan

Event	Total (n=138)	NCD group (n=57)	CD group (n=81)
Dizziness	16 (11.59)	10 (17.54)	6 (7.41)
Headache	6 (4.35)	0 (0.00)	6 (7.41)
Cough	4 (2.90)	3 (5.26)	1 (1.23)
Dyspnea	2 (1.45)	2 (3.51)	0 (0.00)
Elevated serum creatinine	2 (1.45)	1 (1.75)	1 (1.23)

NCD, non-ceiling dose; CD, ceiling dose.
Values are expressed as n (%).
p=0.7011.

noted in the NCD group. Interestingly, the CD of valsartan significantly improved VVI only in patients with HFrEF. Valsartan also improved the systolic and diastolic function and symptoms in patients with stable HF, regardless of valsartan dosage. To date, our study is the first to report that an ARB improved VVI in patients with HFrEF, although there have been many reports that have shown improvements in HF with ARBs.

Although the target dose of valsartan was 160 mg twice a day in large, randomized controlled trials, such as Val-HeFT and VALIANT, which was the same as the CD of our study, the optimal dosage of valsartan for HF treatment has not been standardized clinically. When prescribing valsartan in HF patients in actual clinical practice, it is common not to reach to the target dose (CD) because of various obstacles, including drug side effects. There have not been meaningful studies to directly compare the effect of dosage differences of valsartan; in other words, the effect of lower doses of valsartan has not been well researched. Additionally, the mechanism by which the CD of valsartan improved clinical outcomes in these large studies is still unclear.

Our trial was designed to compare differences in dose effects on HF after force-titration of valsartan to the CD (160 mg twice a day). In the Val-HeFT trial, valsartan was titrated to a target dose of 160 mg twice daily, and the target dose (CD) was achieved in 84% of the patients. The CD of valsartan significantly reduced the morbidity and mortality in this trial.[4] Similarly, in the VALIANT study, valsartan was also titrated to 160 mg twice a day in the valsartan-monotherapy group, but it was titrated to 80 mg twice a day in the valsartan-captopril group.[5] Approximately 55% of the patients reached the target dose in the valsartan-monotherapy group, and only 45% of patients reached the target dose in the valsartan-captopril group. The valsartan-monotherapy group showed similar effects comparable to the captopril-monotherapy group in managing patients who were at high risk of cardiovascular events after myocardial infarction. Recently, in the PARADIGM-HF trial, the dosage was titrated to 200 mg of sacubitril/valsartan in the sacubitril/valsartan group (160 mg of the valsartan component) twice a day. This dose was superior to enalapril in reducing mortality and hospitalizations in patients with HFrEF.[6,13] In our study, 138 patients were force-titrated with valsartan, and 81 patients reached the CD (58.6%). Valsartan markedly improved NT-proBNP levels, symptoms, exercise capacity by treadmill test, and LV systolic and diastolic function in patients with stable HF in both the CD and the NCD groups. These results coincide with the reports of several recent studies.[14-17] Interestingly, however, only the CD of valsartan showed better improvement of VVI, compared to the NCD, in HFrEF patients.

Although no large, randomized studies have directly compared the effects of dosage differences for valsartan, some studies have shown that higher doses of valsartan are more effective. In one trial, a higher dose (160 mg per day) of valsartan exerted a prolonged effect (for approximately 24 hours) on blocking angiotensin II type I receptors.[18] In another study, a higher dose of valsartan (160 mg or 320 mg per day) improved wall motion abnormalities better in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention.[19] We can infer that higher doses, especially the CD, of valsartan are more effective in managing HF through a mechanism possibly involving angiotensin II receptors and the sympathetic nervous system.[18,20,21] In our study, the CD of valsartan improved not only systolic and diastolic parameters as measured by transthoracic echocardiography, but also interactions between the ventricles and arteries (VVI) in patients with HFrEF. There are several reports indicating that VVI is closely associated with the mechanism of development of both HFrEF and HFpEF.[22,23] VVI increased as LV systolic function deteriorated with concomitant peripheral vasoconstriction related to sympathetic stimulation in patients with HFrEF. The study also showed that VVI itself can be an independent prognostic marker in systolic HF.[11] It seems that a longer duration of action of the higher dose of valsartan might be involved in the mechanism undergirding improved VVI in patients with HFrEF. Vasodilator effects of high dose valsartan might optimize mechano-energetic performance in HF patients through lowering peripheral vessel resistance.[24] Expounding on the results of these large randomized controlled studies, we propose that there might be a possibility that VVI improvement can be at least one of the mechanisms affecting prognosis in patients with HFrEF treated with the CD of valsartan.

There were several limitations in our study. First, our study designed an observational study. Secondly, in the CD group, more patients had high blood pressure (41% vs. 21%, p= 0.015) and were also taking β blockers (80% vs. 56%, p=0.002) than in the NCD (<320 mg) group. High blood pressure and β blocker use are factors that can affect VVI.[25-27] Additionally, there have been some trials that have proven the effect of anti-hypertensive drugs on VVI.[28,29] Therefore, there is a possibility that these confounding factors contributed to the improvement of VVI in the HFrEF group in our study. Lastly, we did not set mortality or other major cardiac events as end points.

In conclusion, the CD of valsartan for 6 months elicited better improvement of VVI in patients with HFrEF, compared with

NCDs. Despite a few possible confounding factors, our trial has clinical significance in that it verifies that the CD of valsartan is effective in managing HFrEF, especially in terms of VVI. Additionally, it seems that VVI could be a meaningful and independent parameter of HF, in addition to systolic and diastolic indexes, such as ejection fraction and E/E'. We may need to consider escalating valsartan to the CD for the overall cardiovascular performance index in patients with HFrEF.

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