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Effects of a changeover from other angiotensin II receptor blockers to olmesartan on left ventricular hypertrophy in heart failure patients

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Abstract

Left ventricular (LV) hypertrophy (LVH) is an independent cardiovascular risk factor for heart failure (HF) patients. The renin-angiotensin system plays a key role in LVH, and since olmesartan increases plasma angiotensin-(1-7) through an increase in angiotensin-converting enzyme-related carboxypeptidase (ACE2) expression, it was hypothesized to reduce LVH, unlike other angiotensin II receptor blockers (ARBs). The objective of this study was therefore to investigate the effects of a changeover from other ARBs to olmesartan on LVH in HF patients. Participants enrolled in this prospective trial were 64 outpatients with stable HF who had received ARBs other than olmesartan for more than one year (age: 59 ± 13 years). Transthoracic echocardiography and laboratory tests were performed before and 6 months after administration of olmesartan. Other drugs were not changed during follow-up. The primary end point was defined as a change in LV mass index (LVMI) from baseline up to 6 months after administration of olmesartan. No significant changes were observed in blood pressures and heart rate after administration of olmesartan. LVMI showed a significant decrease from 119 ± 38 g/m^2 to 110 ± 24 g/m^2 (p= 0.007) 6 months after administration of olmesartan, and further decreased from 110 ± 24 g/m2 to 103 ± 35 g/m2 (p=0.0003) after 12 months. Moreover, this reduction tended to be more prominent in patients with LVH. In conclusions, LVH in HF patients was reduced by the changeover to olmesartan. This finding may well have clinical implications for better management of HF patients.

Key Words: left ventricular hypertrophy; echocardiography; heart failure; olmesartan; renin angiotensin aldosterone system

Introduction

Left ventricular (LV) hypertrophy (LVH) is an independent cardiovascular risk factor in the general population, and occurs in various types of heart failure (HF) patients such as those with HF with reduced ejection fraction (EF) (HFrEF) and HF with preserved EF (HFpEF)[1-3]. Since the development of LVH was found to be associated with progression to HF, interest has been high in treatment to reduce LVH in HF patients. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that angiotensin (Ang) II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers reduced LV mass by approximately 10-13%[4]. ARBs are widely used in the treatment of hypertension, and large-scale clinical studies have shown that they have a variety of effects, not only their anti-hypertensive effect but also prevention of the progression of HF[5]. The renin-angiotensin system (RAS) plays a key role in LVH, and Ang II is a major determinant in this process[6]. Ang II stimulates LVH and fibrosis in HF patients, whereas Ang II blockade prevents development of LVH [7-10]. An ACE-related carboxypeptidase, known as ACE 2, was identified in the human heart, and ACE 2 degrades Ang I into Ang-(1-9) and Ang II into Ang-(1-7)[11-13]. Characterization of the actions of Ang-(1-7) has demonstrated that the RAS consists of an important biochemical arm which generates Ang II via the action of ACE on Ang I. In addition, the RAS possesses another important biochemical arm which generates Ang-(1-7) from either Ang I or Ang II via enzymes other

than ACE[14, 15]. The discovery of ACE 2 and the demonstration that its catalytic efficiency is approximately 400-fold higher with Ang II as a substrate than with Ang I[16], as well as the report that the ARB olmesartan is associated with high activity of ACE2 and increases Ang-(1-7) via ACE2[17-21], suggests that olmesartan may have the capability to reduce LVH in HF patients more than other ARBs.

The objective of this study was therefore to investigate the effects on LVH in HF patients of a change-over from other ARBs to olmesartan.

Methods

Study Population

Participants enrolled in this prospective trial were 64 outpatients with stable HF who had been treated with ARBs other than olmesartan for more than one year at Kobe University Hospital between December 2013 and March 2016. We excluded patients with (1) development of HF within 3 months; (2) hypotension <90/50 mmHg; (3) severe types of renal dysfunction defined as serum creatinine level (Cr) > 3mg/dl; (4) atrial fibrillation; and (5) administration of ACE inhibitors. At the time of enrollment, all patients were in clinically stable condition. The trial was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registration number UMIN000011807), conformed to the principles outlined in the Declaration of Helsinki and was performed with the approval

of the Ethics Committee of Kobe University Hospital. Written informed consent was obtained from all patients.

Study Protocol

Patients who had consented to their participation in the present study switched from other ARBs to olmesartan on the basis of the findings of their most recent late phase II dose-finding studies to maintain blood pressure[22-26] (Table 1). Other drugs were not changed after the change to olmesartan. The physical examinations, blood tests, and echocardiography were performed on the same day at baseline and 6 months after administration of olmesartan. Blood pressure was measured after at least 15 minutes of rest in a supine position and before echocardiography by a physician (H.S.), and was determined by averaging two consecutive measurements (Terumo Elemano Blood Pressure Monitor; Terumo, Tokyo, Japan).

Echocardiographic Examination

Two-dimensional echocardiography was performed using a commercially available ultrasound system (Aplio Artida; Toshiba Medical Systems, Tochigi, Japan). Digital routine grayscale two-dimensional cine loops from three consecutive heartbeats were obtained at end-expiratory apnea from the standard parasternal views and three apical views. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. LV measurements were obtained in accordance with the current guidelines of the

American Society of Echocardiography/European Association of Cardiovascular Imaging[27]. The early diastolic (E) and atrial wave velocities (A) and the E-wave deceleration time were measured using the pulsed-wave Doppler recording from the apical four-chamber view. Spectral pulsed-wave Doppler-derived early diastolic velocity (e') was obtained from the septal mitral annulus, and the E/e' ratio was calculated to obtain an estimate of LV filling pressure[28]. LV mass was estimated from the formula proposed by Devereux et al and LV mass index (LVMI) was calculated for each subject by dividing LV mass by body surface area[29]. LVH was defined as LVMI >95 g/m^2 for females and >115 g/m^2 for males[27].

Definitions of End Point

The primary end point was defined as a change in LVMI between baseline and 6 months after the start of administration of olmesartan. The secondary end points comprised a change in brain natriuretic peptide (BNP), e', E/e', and E/A between baseline and 6 months after the start of administration of olmesartan.

Statistical Analysis

Continuous variables were expressed as mean ± SD or percentages, while categorical data were summarized as frequencies and percentages. The parameters of the two subgroups were compared by means of Student t test or Wilcoxon rank sum test as appropriate. Assuming 30% of patients with decreased LVMI 6 months after administration of olmesartan, an alpha error of 0.05, a be-ta error of 0.2, and statistical power of 80 %, and the sample size

requirement was 44 patients. However, considering a potential 25 % dropout or loss to follow-up rate, 58 will be considered. Statistical significance was basically defined as p value < 0.05 for each step. MedCalc version 15.11.4 (MedCalc Software, Mariakerke, Belgium) was used for all analyses.

Results

Three initially eligible patients (4.7%) were excluded from all subsequent analyses because of lost follow-up, so that the final study group consisted of 61 patients. There were no cardiac events or deaths during follow-up. The baseline clinical and echocardiographic characteristics of the 61 HF patients are summarized in Table 2 and 3. Their mean age was 59 ± 13 years, LVEF was 46 ± 12 %, and 24 patients (39 %) were female. HFpEF was observed in 23 patients (38%), and the remaining 38 patients (62%) were classified as HFrEF.

No significant changes were observed in systolic and diastolic blood pressures and heart rate 6 months after administration of olmesartan (120 ± 20 mmHg vs. 121 ± 21 mmHg, p=0.92; 70 ± 11 mmHg vs. 72 ± 13 mmHg, p=0.08; 67 ± 11 bpm vs. 67 ± 12 bpm, p=0.86, respectively, Table 3).

Primary Endpoint

LVMI showed significant decreases from 119 ± 38 g/m^2 to 110 ± 24 g/m^2 (p= 0.007) 6 months after administration of olmesartan (Figure 1). In addition, LVMI showed

significantly further decreased from 110 ± 24 g/m^2 to 103 ± 35 g/m^2 (p=0.0003) of 51 patients 12 months after administration of olmesartan available (Figure 1). Patients with LVH, defined as an LVMI >95 g/m^2 for female and >115 g/m^2 for male was observed in 34 patients (56%), and the remaining 27 patients (44%) were classified as without LVH (Figure 2). Reduction of LVMI for patients with LVH was significantly higher than that for patients without LVH both between baseline and 6 months after the start of administration of olmesartan (-24.1±29.3 g/m^2 vs. 1.6±26.9 g/m^2, p<0.001), and between baseline and 12 months after the start of administration of olmesartan (-41.0±44.0 g/m^2 vs. -7.2±23.3 g/m^2, p<0.001).

Secondary Endpoint

The results of using the secondary endpoint are shown in Figure 3. BNP tended to decrease 6 months after the start of administration of olmesartan from 52 pg/mL (17-182) to 40pg/mL (19-129) (p=0.2), but the difference was not statistically significant. No significant changes were observed in E/A, e' and E/e' 6 months after administration of olmesartan.

Other Echocardiographic Parameters

Other echocardiographic parameters, such as LV end-diastolic diameter, intra-ventricular septal thickness, and LV end-diastolic and end-systolic volumes were also significantly rerduced6 months after the start of administration of olmesartan (Table 3).

Discussion

The findings of our study indicate that LVMI for HF patients, who had received other ARBs, significantly decreased 6 months after the change-over to olmesartan despite similar blood pressures and further decreased after 12 months. This reduction tended to be more prominent in patients with LVH. This is the first study to demonstrate the further reduction in LVH attainable with olmesartan as compared with that attained with ARBs.

Effect of Olmesartan on of LV Hypertrophy Reduction

LVH is an independent cardiovascular risk factor in the general population and occurs in various types of HF patients[1-3]. The development of LVH has been associated with progression to HF as characterized by increased LV end-diastolic pressure and diminished LV contractility. A meta-analysis of the effects of treatment on LV mass in essential hypertension reported that ARBs, ACE inhibitors, and calcium channel blockers reduced LV mass by approximately 10% to 13%[4]. The RAS plays a key role in LVH, and Ang II is a major determinant in this process[6]. Ang II stimulates LVH and fibrosis in HF patients, whereas Ang II blockade prevents development of LVH [7, 8]. Moreover, Ang II also causes LVH independent of its effect on blood pressure, whereas blockade of the RAS attenuates or reverses the cellular adaptations to pressure overload[30, 31]. An ACE-related carboxypeptidase, known as ACE 2 and identified in the human heart degrades Ang I into Ang-(1-9) and Ang II into Ang-(1-7)[11-13]. Characterization of the actions of Ang-(1-7) demonstrated that the RAS consists of two biochemical arms: one generates Ang II via the

action of ACE on Ang I, and the second generates Ang-(1–7) from either Ang I or Ang II via enzymes other than ACE[14, 15]. The discovery of ACE 2 was followed by the demonstration that its catalytic efficiency is approximately 400-fold higher with Ang II as a substrate than with Ang I[16]. In this study, we showed that olmesartan may have the potential to exert a stronger reductive effect on LVH than any other ARBs. The reason for this is that olmesartan features a higher activity of ACE2 than other ARBs, and increases Ang-(1-7) via ACE2 more than do the other ARBs[17-21]. Several previous investigators have reported the use of olmesartan was advantageous for attaining regression of LVH. Agata et al. reported that the long-term administration of olmesartan in an animal study caused an increase in renin activity, no changes in angiotensin II, and a decrease in aldosterone[32]. This resulted in reductions in LVMI, coronary arterial wall lumen ratio and perivascular fibrosis, as well as improvement in cardiovascular remodeling. Igase et al. reported that olmesartan reduced the thickness of the tunica media of the abdominal aorta and that this led to an increase in Ang-(1-7)[33]. Yokoyama et al. found that olmesartan showed definite inhibitory effects on LVH and mesenteric arterial hypertrophy, and that these effects on cardiovascular remodeling were due to factors related to hypotensive effects and also factors not dependent on blood pressure[34].

It has been suggested that the aldosterone breakthrough is an important risk factor for cardiovascular disease progression including the progression of LVH, despite the use of ACE inhibitors or ARBs[35-37]. Sezai et al evaluated the effects of a change-over from candesartan

to olmesartan on the renin-angiotensin-aldosterone system in 56 patients with essential hypertension found that angiotensin II and aldosterone are reduced by a change-over from candesartan to olmesartan. Furthermore, LVMI and BNP decreased 6 months and 12 months after the change-over[38]. In another clinical study which compared the effects of candesartan and olmesartan[39], Tsutamoto et al. found no difference between the effects of the two drugs on aldosterone but Ang II was significantly lower for the group after 3 months to one year of olmesartan administration. The rate of reduction in the LVMI of the olmesartan group was significantly higher after one year of administration, and the rates for Ang II and LVMI reduction correlated[39]. Thus, olmesartan may be associated with a lower incidence of aldosterone breakthrough than attainable with other ARBs, so that this may be one of the reasons for the more pronounced regression of LVH.

Clinical Implications

As mentioned before, LVH is an independent cardiovascular risk factor for various types of HF patients. The use of ARBs has been highly recommended for HF patients, especially those with HFrEF[5]. On the other hand, there is no established pharmacological treatment for a better prognosis of patients with HFpEF. LVH was found to be present in the majority of patients with HFpEF, and LV mass to be independently associated with an increased risk of morbidity and mortality[40]. Our findings indicate that the use of olmesartan rather than other ARBs may lead to regression of LVH, and may result in a favorable clinical

outcome for patients with HFrEF and HFpEF.

Study Limitations

There were certain limitations to this study. First, ACE2 and Ang-(1-7) were not measured in this study so that we were not sure that LVH was determined by ACE2 and Ang-(1-7) to a greater than other factors such as hemodynamics. Second, the assessment of cardio-pulmonary test, and cardiothoracic ratio in chest X-ray, and 12-lead electrocardiogram to evaluate the effects of a changeover from other ARBs to olmesartan was not part of this study. Finally, we used only echocardiography to assess LVH, and the assessment of LVH by means of cardiac magnetic resonance imaging was not part of this study.

Conclusions

LVH of HF patients was reduced following the change-over from treatment with other ARBs to that with olmesartan. This finding may well have clinical implications for better management of HF patients. This study covered a small number of patients in a single-center study, so that future prospective studies of larger patient populations with randomly assigned to receive olmesartan or other ARBs or cross-over study are necessary to validate our findings.

Conflict of interest: The authors declare that they have no competing interests.

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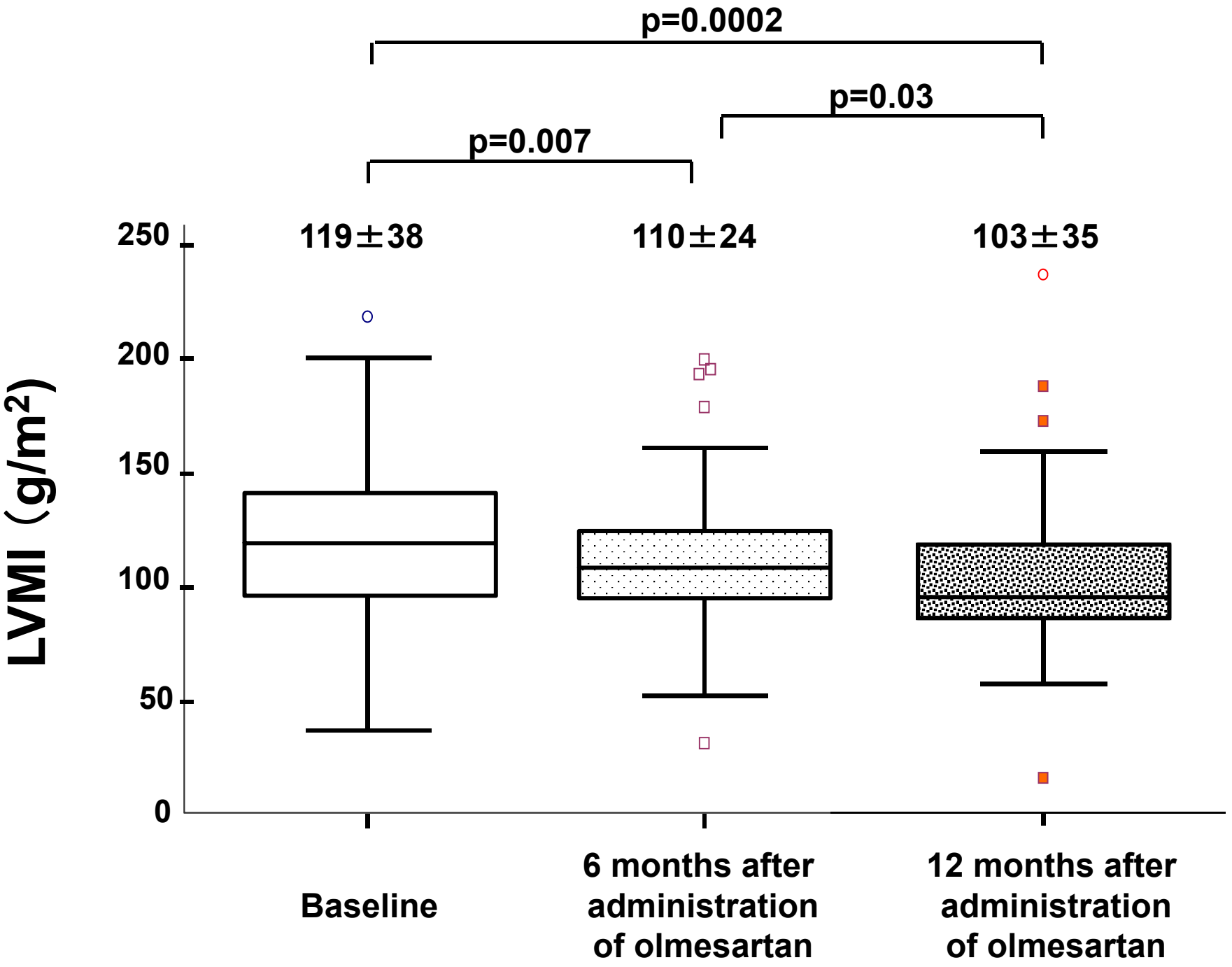
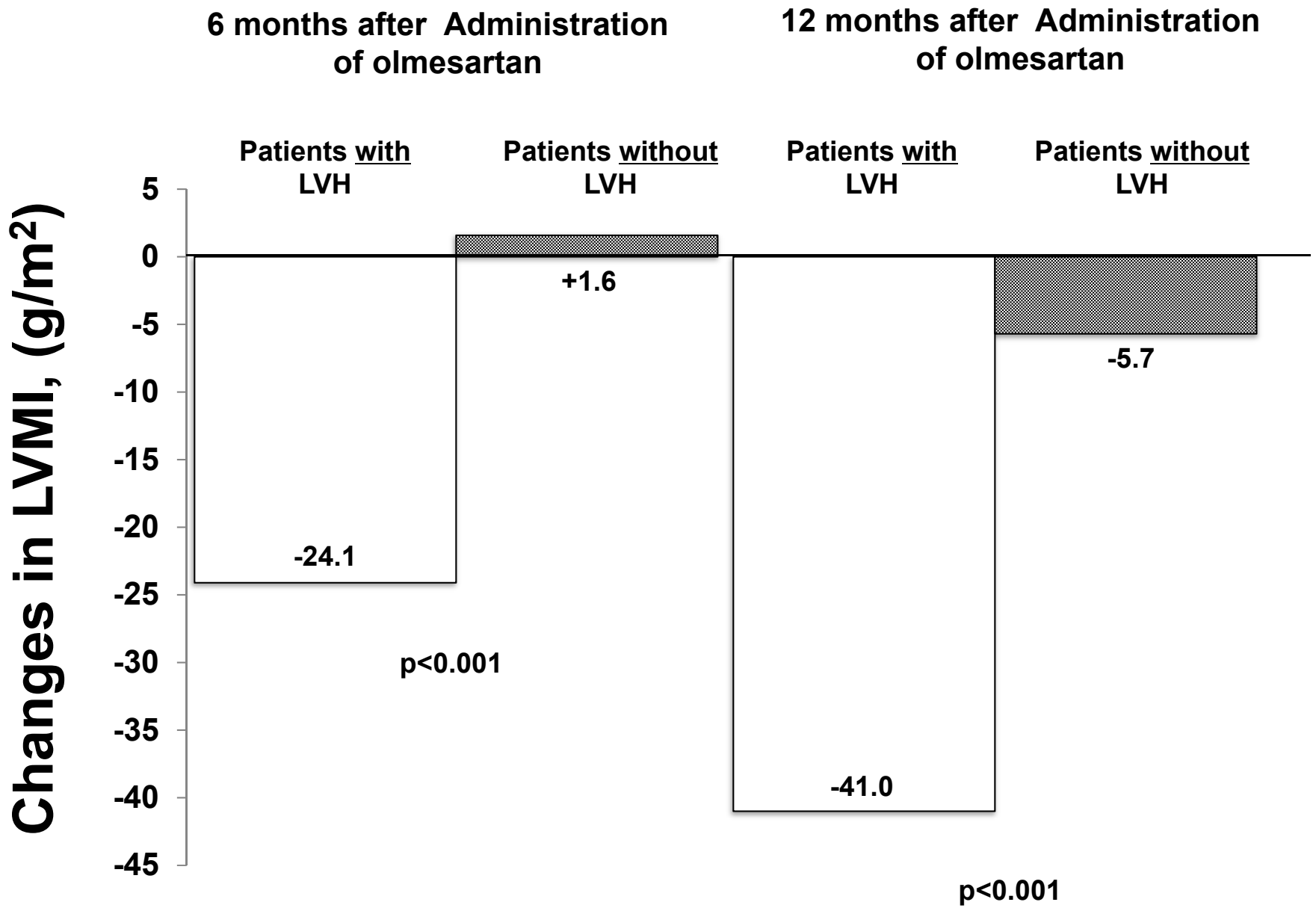
Figure Legends

Figure 1: Primary endpoint. Left ventricular mass index (LVMI) showed significant reductions 6 months after the start of administration of olmesartan, and had further decreased significantly 12 months after administration of olmesartan.

Figure 2: Reduction in left ventricular hypertrophy mass index (LVMI) for patients with left ventricular hypertrophy (LVH) was significantly higher than that for patients without LVH both between baseline and 6 months after the start of administration of olmesartan, as well as between baseline and 12 months after the start of administration of olmesartan.

Figure 3: Secondary endpoint. Brain natriuretic peptide (BNP) tended to decrease 6 months after the start of administration of olmesartan, but the difference was not statistically significant. No significant changes were observed either in e', E/A and E/e' at the same point in time.


p=0.0002
p=0.03
p=0.007
119±38
110±24
103±35
250
200
150
100
50
0
LVMI（g/m²）
Baseline
6 months after administration of olmesartan
12 months after administration of olmesartan


6 months after Administration of olmesartan
12 months after Administration of olmesartan
Patients with LVH
Patients without LVH
Patients with LVH
Patients without LVH
Changes in LVMI, (g/m2)
5
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
+1.6
-5.7
-24.1
-41.0
p<0.001
p<0.001

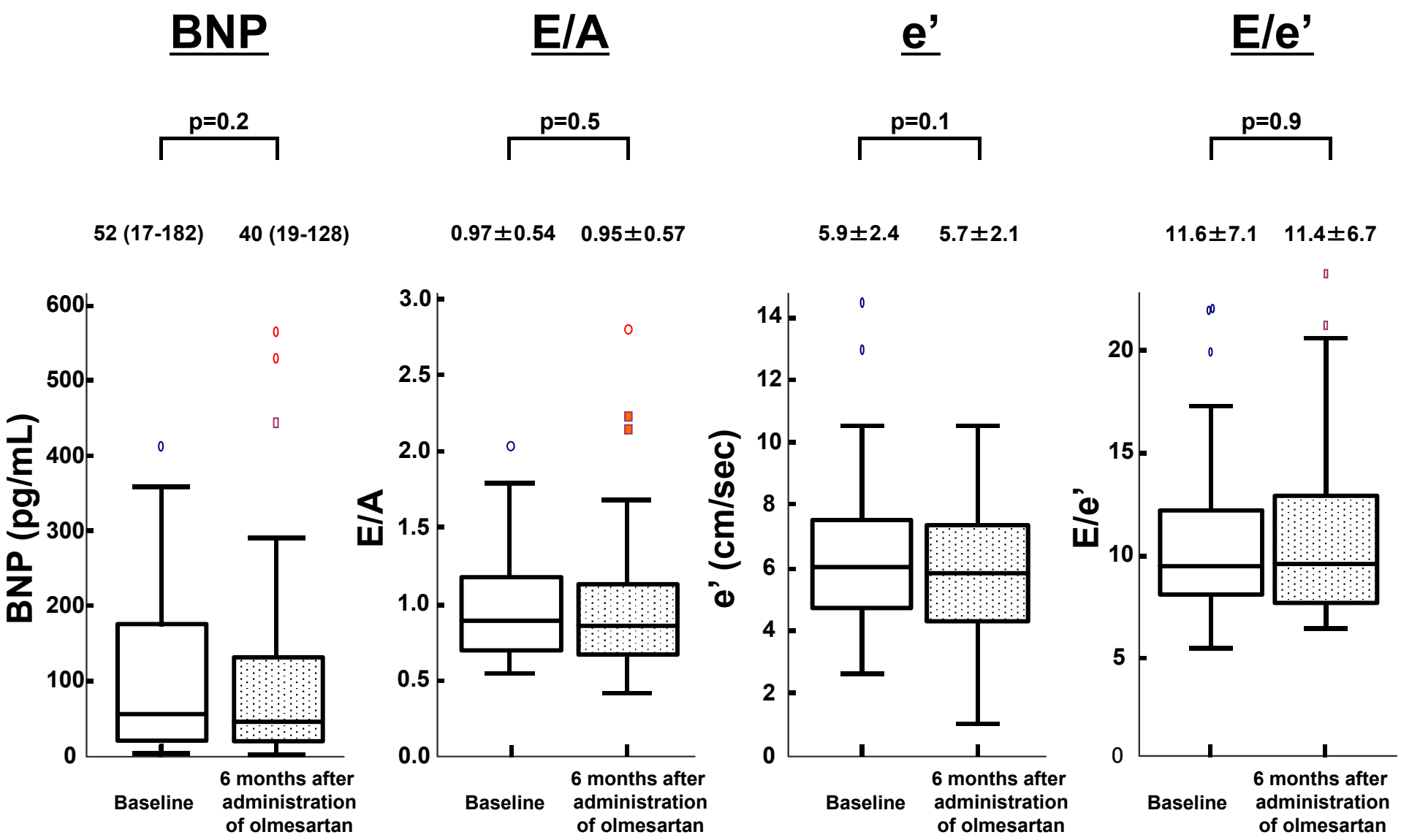

BNP
E/A
e’
E/e’
p=0.2
p=0.5
p=0.1
p=0.9
52 (17-182)
40 (19-128)
0.97±0.54
0.95±0.57
5.9±2.4
5.7±2.1
11.6±7.1
11.4±6.7
BNP (pg/mL)
E/A
e’ (cm/sec)
E/e’
Baseline
6 months after administration of olmesartan

Table 1

The other ARBs-to-olmesartan conversion table

Other ARBs dose (mg/day)					Olmesartan dose (mg/day)
Losartan	Candesartan	Valsartan	Telmisartan	Azilsartan	
25	4	40	20	10	5
50	8	80	40	20	10
100	16	160	80	40	20

ARB; angiotensin II receptor blocker

Table 2
Baseline characteristics of the patients

Age, years	59 ± 13
Gender (female), n (%)	24 (39)
Body surface area, m^2	1.67 ± 0.21
Medications, n (%)	
Diuretics	21 (35)
β-blockers	54 (89)
Spironolactone	24 (39)
Calcium channel blockers	7 (11)
ARBs, n (%)	61 (100)
Losartan	21 (34)
Candesaltan	24 (39)
Valsartan	11 (18)
Telmisartan	2 (3)
Azilsartan	3 (5)
Etiology of heart failure, n (%)	
HFpEF	23 (38)
EFrEF	38 (62)
Dilated cardiomyopathy	24 (39)
Cardiac sarcoidosis	7 (11)
Valvular heart disease	4 (7)
Ischemic cardiomyopathy	2 (3)
Cardiac amyloidosis	1 (2)

ARB; angiotensin II receptor blocker, HFpEF; heart failure with preserved ejection fraction, HFrEF; heart failure with reduced ejection fraction

Table 3
Changes of after administration of olmesartan

	Baseline	6 months after administration of olmesartan	p value
Systolic blood pressure, mmHg	120 ± 20	121 ± 21	0.9
Diastolic blood pressure, mmHg	70 ± 11	72 ± 13	0.08
Heart rate, bpm	67 ± 11	67 ± 12	0.9
BNP, pg/mL	52, 17-182	40, 19-129	0.2
Echocardiographic parameters			
LV end-diastolic diameter, mm	54 ± 8	52 ± 8	<0.01
LV end-systolic diameter, mm	42± 11	41 ± 11	0.11
Intra ventricular septal thickness, mm	9.8 ± 3.1	9.4 ± 2.6	0.02
LV posterior wall thickness, mm	9.5 ± 2.2	9.8 ± 1.8	0.4
LV end-diastolic volume , mL	124 ± 49	113 ± 39	<0.01
LV end-systolic volume, mL	72 ± 44	65 ± 35	<0.01
LV ejection fraction, %	46 ± 12	45 ± 11	0.8
Left arterial volume index, mL/m^2	40 ± 22	39 ± 20	0.6
Early diastolic wave velocity, cm/sec	61 ± 22	61 ± 23	0.9
Arterial wave velocity, cm/sec	65 ± 18	67 ± 18	0.4
E/A	0.99 ± 0.54	0.95 ± 0.57	0.6
e', cm/sec	6.0 ± 2.4	5.7 ± 2.1	0.1
E/e'	11.6 ± 7.0	11.4 ± 6.66	0.9
LV mass index, g/m^2	119 ± 38	110 ± 24	0.007

LV; left ventricular, E/A; Early diastolic and atrial wave velocities ratio, e'; Early diastolic septal mitral annulus velocity, E/e'; Early diastolic and mitral annulus velocities ratio, BNP; Brain natriuretic peptide.