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Original Article

Changeover Trial of Azilsartan and Olmesartan Comparing Effects on the Renin-Angiotensin-Aldosterone System in Patients with Essential Hypertension after Cardiac Surgery (CHAOS Study)

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Background: Angiotensin II receptor blockers (ARBs) have been widely used to treat hypertension and large-scale clinical studies have shown various benefits. In this study, we compared olmesartan with azilsartan, the newest ARB.
Methods: The subjects were outpatients who were clinically stable after cardiac surgery. Sixty patients were randomized to receive either azilsartan or olmesartan for 1 year and were switched to the other drug for the following 1 year. The primary endpoints were the levels of plasma renin activity, angiotensin II, and aldosterone.
Results: Home blood pressure exceeded 140/90 mmHg and additional antihypertensive medication was administered to 12 patients (20 episodes) in the azilsartan group versus 4 patients (4 episodes) in the olmesartan group, with the number being significantly higher in the azilsartan group. After 1 year of treatment, both angiotensin II and aldosterone levels were significantly lower in the olmesartan group than the azilsartan group. Left ventricular mass index was also significantly lower in the olmesartan group than the azilsartan group.
Conclusion: This study showed that olmesartan reduces angiotensin II and aldosterone levels more effectively than azilsartan. Accordingly, it may be effective in patients with increased renin-angiotensin-aldosterone system activity after cardiac surgery or patients with severe cardiac hypertrophy.

Keywords: angiotensin, aldosterone, angiotensin II receptor blocker, hypertension

Introduction

Eight (8) angiotensin II receptor blockers (ARBs) are currently available for clinical use internationally. Losartan was launched in Japan in 1998 and seven other ARBs have been marketed since then. Large-scale clinical studies have demonstrated various benefits of ARBs, including both antihypertensive and organ protective effects. Each of the eight ARBs also has its own unique characteristics.[1] Azilsartan was released in 2012 and is the newest ARB in Japan. Basic research comparing its antihypertensive effect with other ARBs has shown a stronger effect of azilsartan, but sufficient clinical data have not yet been obtained.[2] An in vitro study demonstrated that azilsartan had a higher affinity for the angiotensin II type 1 (AT1) receptor than other ARBs and that its dissociation from the receptor was slower. It was also reported that azilsartan demonstrates strong and persistent blocking of the actions of angiotensin II.[1]

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The renin-angiotensin-aldosterone system (RAAS) is activated after cardiac surgery. We previously reported that RAAS activity was suppressed by carperitide after cardiac surgery, inhibiting target organ damage and improving the long-term prognosis.[3–6] In order to maintain effective suppression of the RAAS over the long-term, we previously conducted a comparative study and demonstrated that switching from candesartan to olmesartan significantly reduced angiotensin II and aldosterone levels, as well as significantly reducing the left ventricular mass index (LVMI) after 6 months and 1 year of treatment.[7]

The RAAS plays an important role in hypertension. Its main component is the angiotensin-converting enzyme (ACE)/angiotensin II/AT1 receptor axis, which induces blood pressure elevation and is related to cardiovascular complications. Recently, the ACE2/angiotensin-(1–7)/Mass receptor axis was also identified as part of the RAAS. It was reported to show antagonistic activity against the ACE/angiotensin II/AT1 receptor axis, thus lowering the blood pressure and having anti-arteriosclerotic and organ protective effects.[8] Azilsartan and olmesartan have both been shown to increase angiotensin-(1–7) in animal experiments.[8,9] Accordingly, we compared the effects of these two drugs on the RAAS, in the present study.

Methods

Study protocol

The CHangeover trial of Azilsartan and Olmesartan comparing effects on the renin-angiotensin-aldosterone System in patients with essential hypertension after cardiac surgery (CHAOS study) was a prospective, open-label, blinded end-point study performed in patients with essential hypertension. The subjects were outpatients with essential hypertension who were clinically stable after cardiac surgery and whose blood pressure had been well controlled by olmesartan for at least 1 year. Home blood pressure was stable at ≤140/90 mmHg and their antihypertensive therapy had not been changed for at least 1 year.

The details of the study were explained to the patients and informed consent was obtained. This study was registered with the University Hospital Medical Information Network (UMIN) (study ID: UMIN000011006).

Sixty patients were randomized by the envelop method to receive treatment with either azilsartan or olmesartan for 1 year, after which they switched to the other medication and for another 1-year period. The dosages of azilsartan and olmesartan were fixed and the test drug was administered once a day in the morning. Adding another antihypertensive drug was avoided during the study period, if possible. However, if the early morning home blood pressure exceeded 140/90 mmHg, a calcium antagonist was used as add-on therapy. In this study, assessors were blinded to the medications at each time of measurement. Patients were excluded if they required treatment for cardiac-related events within one year or if they had poorly-controlled diabetes (hemoglobin A_{1C} >6.5%), renal insufficiency (serum creatinine (sCr) >2.0 mg/dl), arteriosclerosis obliterans, or left ventricular dysfunction (left ventricular ejection fraction <35%).

Endpoints

The primary endpoints were plasma renin activity, plasma angiotensin II, and plasma aldosterone.

The secondary endpoints were as follows: (1) blood pressure (early morning home blood pressure and nighttime home blood pressure, and office blood pressure) and heart rate, (2) sCr and estimated glomerular filtration rate (eGFR), (3) urinary albumin, (4) cystatin-C, (5) oxidized low density lipoprotein (Ox-LDL), (6) eicosapentaenoic acid/arachidonic acid ratio (EPA/AA ratio), (7) remnant like particles-cholesterol (RLP-cho), (8) standard lipid profile (total cholesterol (T-cho), triglycerides (TG), low density lipoprotein (LDL), and high density lipoprotein (HDL)), (9) high-sensitivity C-reactive protein (hs-CRP), (10) atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), and (11) left ventricular mass index (LVMI). The LVMI was evaluated by echocardiography (VIVID 7, GE Yokokawa Medical Systems Co., Tokyo, Japan), which was performed by a specialist echocardiographer. The echocardiographer was blinded to the medication information of the patients when conducting an examination. The BP, HR, sCr, eGFR, T-cho, TG, LDL, HDL and hs-CRP were measured every month, while U-Alb, cystatin-C, Ox-LDL, EPA/AA ratio, RLP-cho, ANP and BNP were every 3 months. LVMI was measured after 6 and 12 months of treatment. In this study, 12-month data were used for comparison.

Statistical analysis

Measured values were expressed as the mean ± standard error of the mean (SEM). Two-way analysis of variance (ANOVA) was used to compare parameters between the azilsatran and olmesartan groups and a p value of less than 0.05 was considered statistically significant.

Results

Patients

Sixty patients were enrolled in this trial. During the 2-year study period, two patients died while taking

Table 1 Patient characteristics

Number	60
Age (years)	68.8 ± 8.8
Gender (male: female)	39:21
Body surface area (m^2)	1.65 ± 0.17
Main diagnosis	
Ischemic heart disease	20
Aortic valve disease	11
Mitral valve disease	2
Thoracic aortic disease	26
Congenital heart disease	1
Surgical procedure	
CABG	19
AVR	9
MVR	2
Bentall	2
Asc-Ao replacement	17
Total arch replacement	1
Desc-Ao replacement	4
ASD patch closure	1
CABG + AVR	2
CABG + Asc Ao replacement	2
CABG + AVR + Asc Ao replacement	1
Post-operative period (years)	3.3 ± 0.6 (1.7–4.5)
Risk factors	
Diabetes mellitus	14 (23%)
Dyslipidemia	26 (43%)
Hyperuricemia	10 (17%)
Obesity	11 (18%)
Smoking	15 (25%)
Chronic kidney disease <60	33 (55%)
Chronic kidney disease <30	4 (7%)
Daily dose of olmesartan before the study	
10 mg	4
20 mg	30
40 mg	26
Concomitant medications	
ACE inhibitor	5 (8%)
Calcium antagonist	39 (65%)
Beta blocker	25 (42%)
Alpha blocker	11 (18%)
Renin antagonist	13 (22%)

CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MVR: mitral valve replacement; Asc-Ao: Ascending aorta; Desc-Ao: Descending aorta; ASD: atrial septal defect; ACE: angiotensin-converting enzyme inhibitor

azilsartan (hematemesis and heart failure in one case each) and one patient died of cancer while taking olmesartan. The other 57 patients completed the 2-year study observation period.

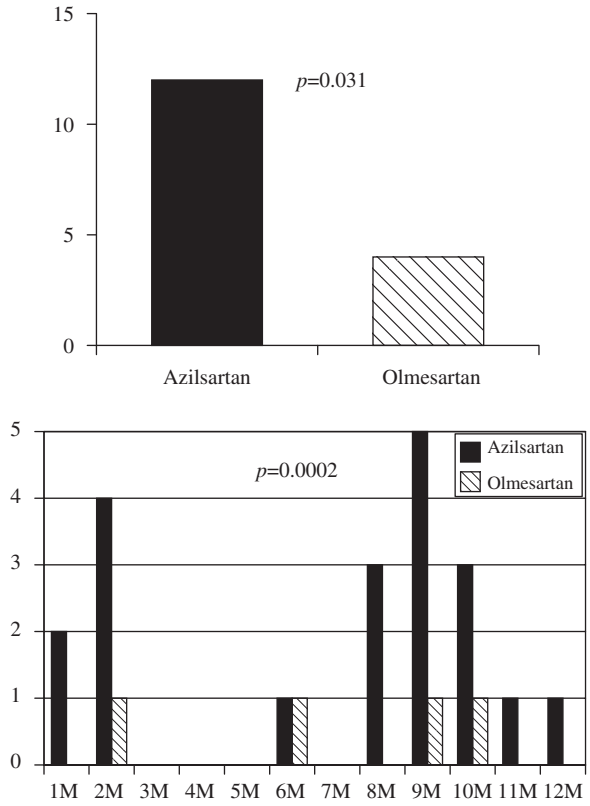

Fig. 1 Number of patients receiving add-on antihypertensive therapy (upper). Timing of the addition of add-on antihypertensive therapy and the number of patients (lower).

Baseline characteristics (Table 1)

The baseline characteristics of the subjects are shown in **Table 1**. During the study period, home blood pressure exceeded 140/90 mmHg in 12 patients (20 episodes) from the azilsartan group versus four patients (4 episodes) from the olmesartan group, with the number being significantly higher in the azilsartan group ($p = 0.031$ ($p = 0.0002$)). (**Fig. 1**) Concerning the timing of add-on therapy, seven patients (14 episodes) received add-on therapy from 6 months onward in the azilsartan group versus three patients (3 episodes) in the olmesartan group (**Fig. 1**).

Primary endpoints

(1) Plasma renin activity, angiotensin II, and aldosterone (**Fig. 2**): There was no difference of plasma renin activity between the two groups after 12 months ($p = 0.209$). However, angiotensin II and aldosterone levels were significantly lower in the olmesartan group than the azilsartan group ($p = 0.011$ and $p = 0028$, respectively).

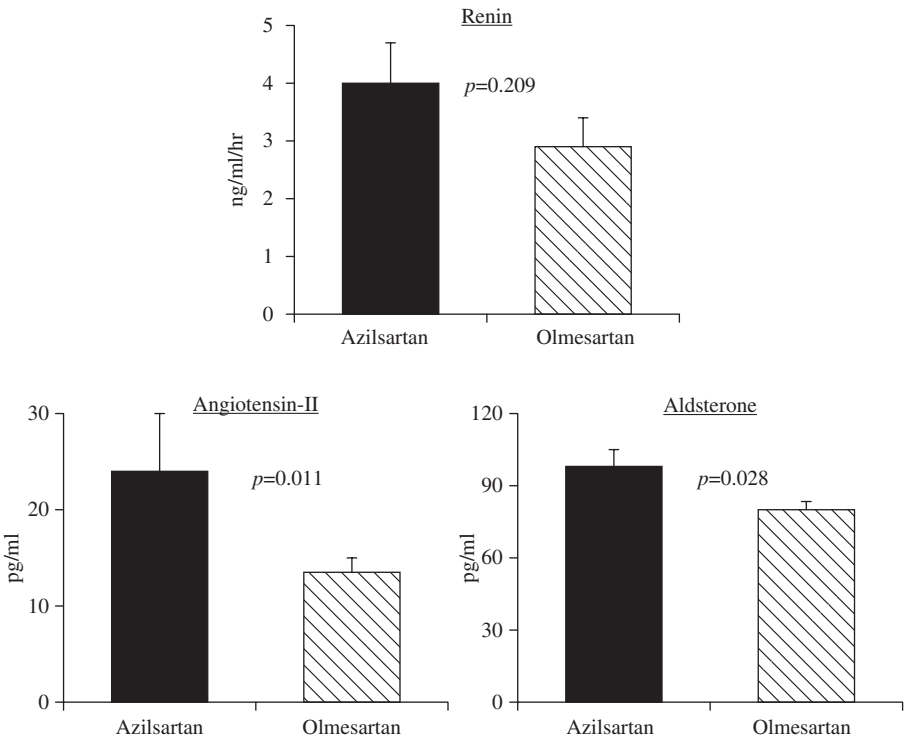

Fig. 2 Renin-angiotensin-aldosterone system parameters after 1 year.

Table 2 Laboratory parameters at baseline and after 1 year

	Baseline	Azilsartan	Olmesartan	p value (Azilsartan vs. Olmesartan)
serum Creatinine (mg/dL)	1.01 ± 0.29	1.03 ± 0.04	1.06 ± 0.05	0.496
eGFR (mL/min/1.73m^2)	55.4 ± 1.6	53.8 ± 2.1	52.7 ± 2.4	0.715
Urinary-albumin (mg/g · CRE)	59.3 ± 14.5	49.1 ± 17.1	41.8 ± 13.5	0.491
Cystatin-C (mg/L)	1.17 ± 0.31	1.18 ± 0.04	1.20 ± 0.05	0.469
Ox-LDL (U/L)	91.1 ± 2.6	97.6 ± 7.2	79.6 ± 3.4	0.096
EPA/AA	0.55 ± 0.03	0.50 ± 0.05	0.57 ± 0.05	0.290
RLP-cho (mg/dL)	5.00 ± 0.34	5.12 ± 0.52	4.28 ± 0.34	0.185
Total cholesterol (mg/dL)	166.8 ± 3.1	168.3 ± 4.2	163.9 ± 3.3	0.414
Triglycerides (mg/dL)	129.1 ± 7.7	130.6 ± 12.1	115.8 ± 8.9	0.330
Low density lipoprotein (mg/dL)	91.9 ± 2.6	94.5 ± 3.7	89.7 ± 2.8	0.305
High density lipoprotein (mg/dL)	57.5 ± 1.3	58.7 ± 1.9	60.9 ± 1.9	0.410
hs-CRP (mg/ dl)	0.20 ± 0.03	0.23 ± 0.05	0.45 ± 0.25	0.350
ANP (pg/mL)	48.0 ± 2.5	48.3 ± 4.1	48.3 ± 4.0	0.996
BNP (pg/mL)	67.4 ± 5.0	67.0 ± 7.6	62.9 ± 9.5	0.623

eGFR: estimated glomerular filtration rate; CRE: cretinine; Ox-LDL: oxidized low density lipoprotein; EPA/AA: eicosapentaenoic acid/arachidonic acid; RLP-cho: remnant like particles-cholesterol; hs-CRP: high-sensitivity C-reactive protein; ANP: atrial natriuretic peptide; BNP: brain natriuretic peptide

Secondary endpoints

(1) Blood pressure and pulse rate: With respect to the early morning home blood pressure, the systolic pressure was 126.3 ± 0.8 mmHg at baseline, 127.3 ± 1.3 mmHg after 12 months in the azilsartan group, and 128.6 ± 1.2 mmHg after 12 months in the olmesartan group (p = 0.454), while the diastolic pressure was 69.3 ± 0.8 mmHg at baseline, 69.3 ± 1.1 mmHg in the azilsartan group, and 69.8 ± 1.3 mmHg in the olmesartan group (p = 0.743). The daytime pulse rate was 66.6 ± 0.9/min at baseline, while it was 68.3 ± 1.3/min after 12 months in the azilsartan group and 66.8 ± 1.2/min in the olmesartan group (p = 0.410).

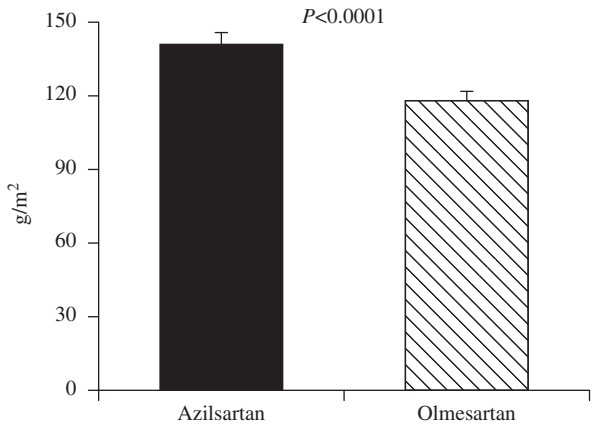

Fig. 3 Left ventricular mass index after 1 year.

Concerning the nighttime home blood pressure, the systolic pressure was 122.4 ± 1.0 mmHg at baseline, 123.9 ± 1.5 mmHg after 12 months in the azilsartan group, and 123.4 ± 1.6 mmHg after 12 months in the olmesartan group (p = 0.803), while the diastolic pressure was 66.2 ± 0.8 mmHg at baseline, 66.2 ± 1.2 mmHg in the azilsartan group, and 65.5 ± 0.8 mmHg in the olmesartan group (p = 0.728). The nighttime pulse rate was 67.2 ± 0.9/min at baseline, while it was 67.7 ± 1.3/min after 12 months in the azilsartan group and 65.8 ± 1.1/min in the olmesartan group (p = 0.264). Regarding the office blood pressure, the systolic pressure was 133.0 ± 1.7 mmHg at baseline, 132.8 ± 2.4 mmHg after 12 months in the azilsartan group, and 131.4 ± 2.3 mmHg after 12 months in the olmesartan group (p = 0.678), while the diastolic pressure was 74.8 ± 1.0 mmHg at baseline, 73.3 ± 1.4 mmHg in the azilsartan group, and 72.8 ± 1.4 mmHg in the olmesartan group (p = 0.824). The office pulse rate was 64.9 ± 0.9/min at baseline, while it was 64.1 ± 1.3/min after 12 months in the azilsartan group and 64.8 ± 1.3/min in the olmesartan group (p = 0.698). No significant differences of these parameters were observed between the two groups.

(2) Laboratory parameters: As shown in **Table 2**, there were no significant differences between the two groups with regard to the results of blood tests and urinalysis.

(3) LVMI (**Fig. 3**): LVMI was significantly lower in the olmesartan group than in the azilsartan group (p <0.0001).

Discussion

The Japanese Treatment Guideline recommends to control the systolic pressure below 130–140 mmHg depending on the nature of complications. (https://www.jpnsh.jp/data/jsh2009digest.pdf, http://www.jpnsh.jp/data/jsh2014/jsh2014v1_1.pdf) This is because of the fact that many studies indicated the incidence of cardiovascular events by controlling the systolic blood below 140 mmHg. Since the number of patients in this study is limited and the duration of the follow-up period is short, it is difficult to discuss the incidence of cardiovascular events. However, patients who underwent cardiac surgery is associated with a higher risk of cardiovascular events after hear surgery than non-surgical patients, strict blood pressure control should be performed. Accordingly, in this study, the protocol requested the addition of an anti-hypertensive drug in case the systolic pressure increased above 140 mmHg.

This study demonstrated that significantly fewer patients required add-on antihypertensive therapy during the study period in the olmesartan group than in the azilsartan group. Also, more patients received add-on antihypertensive therapy in the azilsartan group was common after 6 months. Patient recruitment for this study, was conducted in May–July and 6 months corresponded to the winter in Japan. Accordingly, olmesartan was found to be an ARB that exerted a stable antihypertensive effect throughout the year. In addition, it appears that result in aldosterone breakthrough is less likely to occur with olmesartan, since angiotensin II and aldosterone levels were significantly lower in the olmesartan group compared to the azilsartan group. In general, ARB treatment results in an increase of angiotensin II due to cancellation of negative feedback on the RAAS. However, our previous comparative study of olmesartan versus candesartan showed that treatment with olmesartan resulted in a significant decrease of both angiotensin II and aldosterone. Tsutamoto et al. also compared olmesartan with candesartan and reported that the angiotensin II level was significantly lower in patients treated with olmesartan.[10] Thus, olmesartan is an ARB that reduces angiotensin II levels, thereby lowering the aldosterone concentration, which suggests that aldosterone breakthrough is less likely to occur during olmesartan therapy. In animal studies, both azilsartan and olmesartan increased angiotensin-(1–7) via an effect on ACE2.8,9) However, olmesartan has a stronger influence on the ACE2/angiotensin-(1–7)/Mass receptor axis and this may explain why it does not increase angiotensin II. Unfortunately, Ang-(1–7) was not measured in the present study, so this point cannot be clarified. There have not been many clinical studies that have investigated the ACE2/angiotensin-(1–7)/Mass receptor axis. Furuhashi et al. measured urinary ACE2 levels in patients on treatment with various antihypertensive drugs and reported that the ACE2 level was significantly higher with olmesartan compared to calcium antagonists (amlodipine or long-acting

nifedipine), ACE inhibitors (enalapril), and other ARBs (losartan, candesartan, valsartan, and telmisartan).[11] Moreover, Tada et al. reported significant increase of Ang-(1–7) after switching to olmesartan from other ARBs.[12]

In comparative studies, it is usual to switch the treatment regimen after 8 or 12 weeks. However, aldosterone breakthrough does not occur in such a short period and more than 6 months of treatment is needed in order to clarify the influence of medications on aldosterone. Therefore, the present study employed a 1-year treatment period before switching. Aldosterone breakthrough occurs because of angiotensin II generation via pathways such as chymase that do not depend on ACE, which means that ACE inhibitors cannot completely block the generation of angiotensin II. As a result of angiotensin II generation via alternate pathways, inhibition of the secretion of aldosterone is reduced and aldosterone breakthrough follows with the organ protective effect of therapy being reduced. While aldosterone breakthrough was originally considered to be a phenomenon that only occurred with ACE inhibitors,[13] it has also been shown to occur with ARBs.[14] The present study was not a large-scale investigation with a long follow-up period. However, this study demonstrated that olmesartan inhibited aldosterone and also inhibited myocardial hypertrophy, suggesting that reduction of the incidence of cardiac events and an organ protective effect may have been demonstrated by a longer investigation.

Although there was no statistical difference of oxidative markers (Ox-LDL and RLP-cho), these were lower in the olmesartan group (Ox-LDL: $p = 0.096$, RLP-cho: $p = 0.185$). However, there was no difference of renal function between the two groups. A long-term observational study may reveal further characteristics of each drug, suggesting that a large-scale, long-term study is warranted.

There are many elderly patients who undergo cardiac surgery and they are complicated by CKD. In this study, 55% of patients were complicated by CKD. The number of patients is too small to compare between patients with or without CKD in this study and the limitation is that we cannot make a definitive conclusion. In the future, a study in CKD patients alone or a sub-analysis of this study on CKD patients alone may provide us some insights and we will carefully consider such a possibility.

Up to now, there has not been much clinical research on azilsartan or comparative studies using azilsartan and olmesartan. Bakris et al. compared the influence of these two drugs on 24-h ambulatory systolic blood pressure, finding no differences between azilsartan medoxomil (40 mg) and olmesartan medoxomil (40 mg). However, azilsartan medoxomil (80 mg) significantly reduced 24-h ambulatory mean systolic blood pressure compared with olmesartan medoxomil (40 mg).[15] Rakuji et al. compared azilsartan with candesartan and reported that 24-h ambulatory blood pressure was significantly lower with the former drug.[16] In addition, White et al. reported that azilsartan medoxomil (80 mg) significantly reduced 24-h mean systolic BP compared to olmesartan (40 mg) and valsartan (320 mg).[17] Thus, the antihypertensive effect of azilsartan may be comparable to or even stronger than that of olmesartan, but its blood pressure-lowering mechanisms and characteristics need to be elucidated further.

Conclusion

This study demonstrated that olmesartan reduced angiotensin II and aldosterone levels more effectively than azilsartan, resulting in a stable antihypertensive effect. Olmesartan also had an inhibitory effect on cardiac hypertrophy. Accordingly, it may be effective for patients with increased RAAS activity after cardiac surgery or patients with severe cardiac hypertrophy.

Limitations

The subjects of this study had good blood pressure control by olmesartan for at least 1 year. Accordingly, they might have been patients who were more responsive to olmesartan, suggesting that a comparative study in patients with untreated hypertension is needed. In addition, Ang-(1–7) was not measured, but its measurement could help to clarify the mechanism underlying inhibition of angiotensin II and aldosterone secretion.

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