ORIGINAL ARTICLE

Practical efficacy of Olmesartan versus Azilsartan in patients with hypertension ~ multicenter randomized control trial ~ MUSCAT-4 Study

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Comparison of OL vs AZ in BP lowering effect (45 characters)

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Conflicts of interest
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Practical efficacy of olmesartan versus azilsartan in patients with hypertension ~ multicenter randomized control trial ~ MUSCAT-4 Study

Abstract

**Background** Olmesartan and azilsartan, angiotensin II receptor blockers (ARBs), are expected to decrease blood pressure more than the other ARBs. We conducted the randomized controlled trials to compare the practical efficacy of olmesartan with azilsartan.

**Methods** Eighty-four patients treated with the conventional ARBs more than 3 months were randomly assigned either to receive 20 mg of olmesartan (olmesartan medoxomil, OL group) or 20 mg of azilsartan (azilsartan, not azilsartan medoxomil, AZ group) once daily for 16 weeks. The practical efficacy on blood pressure was compared between OL and AZ group.

**Result** Office blood pressure of both group significantly decreased (OL group; 152/86 to 141/79 mmHg, P < 0.05, AZ group; 149/83 to 135/75 mmHg; P < 0.05). Diastolic home blood pressure in AZ group significantly decreased (79 ± 9 to 74 ± 7 mmHg; P < 0.05) but not in OL group (79 ± 11 to 75 ± 10 mmHg; P = 0.068). However, there were no significant difference between groups. The dosage of olmesartan and azilsartan increased significantly and slightly for 16 weeks (OL group; 20.3 to 23.1 mg; P < 0.05, AZ group; 20.5 to 23.2 mg; P < 0.05), without a significant difference between groups. Furthermore, there were no significant differences in renal function, lipid profiles, BNP, sFlt-1 and U-L-FABP between two groups.

**Conclusion** Both olmesartan and azilsartan equally reduced blood pressures. Both olmesartan and azilsartan demonstrated the renoprotective effect and were well-tolerated without any major adverse events.

**KEYWORDS** angiotensin II receptor blocker, azilsartan, hypertension, olmesartan, renoprotective effect
Introduction

Angiotensin II induces the arterial constriction and the secretion of aldosterone, leading to hypertension. Angiotensin II produces reactive oxygen species and inflammatory response [1,2]. These effects cause and deteriorate various diseases such as hypertension, diabetes mellitus (DM) and kidney disease. Angiotensin II receptor blocker (ARB) is one of the safe and effective antihypertensive agents, therefore, it has been widely used in many countries, including in Japan. Furthermore, ARBs reduce oxidative stress and inflammation [3] leading to the organ protective effect beyond blood pressure lowering effect. ARBs suppress the deterioration of renal function by dilatation of efferent arterioles and attenuate albuminuria [4-7]. ARBs reduce cardiovascular morbidity and mortality [8,9]. Furthermore, ARBs improve insulin resistance and decrease the incidence of diabetes mellitus [10,11].

Several studies have reported that olmesartan (olmesartan medoxomil) has a strong antihypertensive effect superior to other conventional ARBs [12-14]. Increasing dosage of olmesartan leads to the greater reduction in blood pressure than the other ARBs [14]. Furthermore, olmesartan demonstrated a renal protective effect since it was associated with a delayed onset of albuminuria in patient with type 2 diabetes [15,16]. Olmesartan attenuated atherosclerosis [17] improved endothelium-dependent coronary dilation in hypertensive patients [18] and played a favorable role against progression of coronary atheroma in the patients with stable angina pectoris [19]. In patients with essential hypertension after cardiac surgery, olmesartan inhibited left ventricular hypertrophy and improved arterial compliance by a decrease in plasma angiotensin II and plasma aldosterone levels [20]. In mouse model, olmesartan attenuates cardiac remodeling [21] and suppress adipocyte hypertrophy [22]. These evidence indicate the protective effect of olmesartan on the cerebro-cardiovascular events. Meanwhile, azilsartan (azilsartan itself, not azilsartan medoxomil) is the latest ARB launched in Japan. Azilsartan is expected to show excellent hypotensive effect than the other ARBs partially because of the high binding affinity to angiotensin II type 1 receptor [23]. In experimental model, besides the antihypertensive effect, azilsartan was reported to improve salt sensitivity [24] and decrease renal and cardiovascular injury [25]. There is a report demonstrating that antihypertensive effect of olmesartan is equivalent to azilsartan medoxomil (AZL-M) [26]. However, there is no report of the direct comparison of olmesartan with azilsartan in the potential of antihypertensive effect in the Japanese hypertensive patients.

The aim of the present study is to compare blood pressure lowering effect between olmesartan and azilsartan in hypertensive patients. Further, we assessed the
effect of each ARB on kidney function, oxidative stress and inflammatory markers.
Methods

Study design

This was a multicenter prospective randomized open-label, blinded endpoint evaluation (Probe) design [27] at multiple hospitals and clinics, comparing the effects of angiotensin II type 1 receptor blockers 4 (MUSCAT-4).

Inclusion criteria

Outpatients with hypertension who didn’t achieve the target blood pressure levels with the conventional ARBs (losartan, candesartan, irbesartan, valsartan or telmisartan) in the accordance with The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [28] more than 3 months were recruited in the study. All participants were 20 years old or more and less than 85 years old.

Exclusion criteria

Patients with severe renal dysfunction (serum Cr > 2.0 mg/dL), liver dysfunction (serum AST or ALT > 100 IU/L), a history of clinically significant adverse reactions with ARB, possible pregnancy and a disease of poor prognosis such as the malignant tumor were excluded. The patients who the attending physician recognized inappropriate were also excluded.

Study protocol

Overview of the protocol was described in the Fig 1. All participants were randomly assigned into the two groups; to receive either olmesartan (OL group) or azilsartan (AZ group) once daily for 16 weeks instead of the current ARB. The dosage conversion formula from an ARB to the assigned ARB was as follows: olmesartan or azilsartan 20 mg was equivalent to candesartan 8 mg, valsartan 80 mg, losartan 50 mg, telmisartan 40 mg, and irbesartan 100 mg. The dosage of assigned ARB was allowed to increase up to 40 mg if the target blood pressure level in each patient was not achieved.

Blood pressure measurement

The method of blood pressure measurement followed JSH 2009 [28]. In brief, office blood pressure (OBP) was measured at out-patient clinics after 5 min of resting in a sitting position [29-31]. Home blood pressure (HBP) was determined by an electronically automated manometer. The average value taken in the morning at least
five consecutive days before visiting a physician’s office was considered as the patient’s HBP.

Clinical efficacy and outcomes

The primary outcome in this study was the reduction of OBP and HBP under the treatments with olmesartan versus azilsartan. Secondary outcomes were the effects on renal function such as estimated glomerular filtration rate (eGFR), serum potassium level, soluble fms-like tyrosine kinase-1 (sFlt-1), urinary Alb/Cr ratio (U-Alb) and urinary L-type fatty acid-binding protein (U-L-FABP), serum lipid profiles such as total cholesterol, LDL-cholesterol and HDL-cholesterol levels, brain natriuretic peptide (BNP), hemoglobin A1c (HbA1c) and the dosage of each ARB. Patients’ complications such as DM, dyslipidemia (DLP), chronic kidney disease (CKD), a history of myocardial infarction (MI), angina pectoris (AP) and stroke were also investigated along with the physicians’ chart. The definition of each disease was as follows; DM was defined by receiving medication for DM or fulfilling the diagnostic criteria [32]: fasting plasma glucose levels ≥ 126 mg/dL (7.0 mmol/L), a random plasma glucose levels ≥ 200 mg/dL or plasma glucose ≥ 200 mg/dL 2 hours after a 75 g glucose load, or HbA1c ≥ 6.5 %. DLP was defined by receiving medication for DLP or fulfilling the diagnostic criteria [33]: LDL-cholesterol ≥ 140 mg/dL, HDL-cholesterol < 40 mg/dL, triglycerides ≥ 150 mg/dL. CKD was defined as follows [34,35]. 1) Structural or functional abnormalities, defined as abnormal findings on histological examination, urinalysis, biochemical examination, or imaging studies for a duration of 3 months or longer regardless of eGFR. 2) eGFR < 60 mL/min/1.73m² regardless of the primary disease, using the Modification of Diet in Renal Disease Study equation [36]. MI and AP were defined as the previous symptomatic chest pain and a diagnosed history of angina or previous myocardial infarction by the coronary angiography. Stroke was defined as the previous or current symptomatic paralysis or headache and a diagnosed history of cerebral infarction, cerebral hemorrhage by CT or MRI imaging.

Ethics

This study followed the Declaration of Helsinki (seventh revision, 2013) on medical protocol and ethics. The ethics committees of Okayama University Institutional Review Board (accredited ISO9001/2000), Okayama, Japan and Institutional Review Board in the related facilities approved the protocol (UMIN ID:000012768). Written informed consents were obtained from all patients.
Statistics

All data are presented as the mean ± standard deviation unless otherwise noted. Differences were analyzed by paired or unpaired t-test where appropriate. Differences in urinary data, BNP, HbA1c, and sFlt-1 were analyzed by Rank sum-test or Signed Rank-test where appropriate. Differences in the presence of complications, gender ratio, and smoking ratio between two groups were analyzed by Fisher Exact test. A $P$ value was calculated with the log converted value only for U-Alb and U-L-FABP. Statistical analysis was carried out using SigmaPlot 12.5 (Systat Software, Inc., San Jose, CA). A $P$ value less than 0.05 was considered to be statistically significant.
Results

Characteristics of the patients and safety

Eighty-eight patients were enrolled from Sep. 2013 to Dec. 2014. Three of 88 patients withdrew after the agreement, and one patient was excluded in accordance with the exclusion criteria. Forty of 84 patients were assigned into the OL group and 44 into the AZ group. Five patients of the OL group and 6 patients of the AZ group were excluded by several reasons (Fig 2). As a result, 73 patients completed the study. Baseline clinical characteristics and parameters of participants did not differ between the two groups (Table 1). There were no significant differences in the prevalence of complications between the two groups. There was no significant difference in just prior treatment with ARBs between the two groups. Both olmesartan and azilsartan were well-tolerated without any major adverse events during the study period.

Changes in blood pressure

Both systolic and diastolic OBP significantly decreased in both groups by 16-week treatment (OL group; 152 ± 14 / 86 ± 11 mmHg to 141 ± 13 / 79 ± 11 mmHg; \( P < 0.001 \), AZ group; 149 ± 14 / 83 ± 10 mmHg to 135 ± 16 / 75 ± 11 mmHg; \( P < 0.001 \), Fig 3). Systolic HBP significantly decreased in both groups after 16-week treatment (OL group; 145 ± 17 mmHg to 133 ± 11 mmHg; \( P < 0.050 \), AZ group; 136 ± 15 mmHg to 129 ± 11 mmHg; \( P < 0.050 \), Fig 3). However, diastolic HBP decreased significantly in only AZ group (OL group; 79 ± 9 mmHg to 74 ± 7 mmHg; \( P < 0.050 \), Fig 3). (See Figure and Supplemental Digital Content 1, in which the Intention-To-Treat analysis of the above contents are shown). There were no significant differences between the two groups in any OBPs and HBPs. The dosage of ARB significantly increased after 16 weeks in both groups (OL group; 20.3 ± 3.8 mg/day to 23.1 ± 8.0 mg/day; \( P < 0.050 \), AZ group; 20 ± 0 mg/day to 23.2 ± 7.4 mg/day; \( P < 0.050 \); Table 2).

Achievement ratio on target levels of OBP and HBP

Next, we assessed the antihypertensive effect of the two drugs regarding the achievement ratio on the target level. The percentage of patients who achieved a systolic OBP of < 140 mmHg at the end of study didn’t differ significantly between the two groups (OL group; 48.5 %, AZ group; 63.2 %; \( P = 0.239 \)). Similarly, there were no significant differences in the percentage of patients who achieved a diastolic OBP of < 90 mmHg (OL group; 75.8 %, AZ group; 86.9 %; \( P = 0.357 \), a systolic HBP of < 135 mmHg (OL group; 50.0 %, AZ group; 75.0 %; \( P = 0.172 \) and a diastolic HBP of < 85
mmHg (OL group; 80.0 %, AZ group; 86.7 %; \( P = 1.000 \)) at the end of study between the two groups. Likewise, there were no significant difference in the percentage of patients who achieved > 10 mmHg reduction after the treatment in a systolic OBP (OL group; 54.5 %, AZ group; 57.9 %; \( P = 0.814 \)), a diastolic OBP (OL group; 42.4 %, AZ group; 57.6 %; \( P = 0.814 \)), a systolic HBP (OL group; 38.9 %, AZ group; 31.3 %; \( P = 0.729 \)) and a diastolic HBP (OL group; 13.3 %, AZ group; 40.0 %; \( P = 0.215 \)).

**Secondary outcomes**

The parameters such as serum potassium, sFlt-1 and U-L-FABP, significantly decreased in OL group (serum potassium; 4.38 ± 0.41 mmol/L to 4.24 ± 0.36 mmol/L; \( P < 0.050 \), sFlt-1; 72.17 ± 9.02 pg/mL to 69.84 ± 9.24 pg/mL; \( P < 0.050 \), U-L-FABP; 12.07 ± 13.66 ug/gCr to 5.28 ± 4.90 ug/gCr; \( P < 0.050 \); Table 2). In AZ group, serum Cr levels significantly increased (serum Cr; 0.79 ± 0.20 mg/dL to 0.83 ± 0.21 mg/dL; \( P < 0.050 \); Table 2). In contrast, eGFR, HDL-C and U-Alb significantly decreased after 16-week treatment (eGFR; 69.0 ± 16.7 mL/min/1.73m² to 65.5 ± 16.5 mL/min/1.73m²; \( P < 0.050 \), HDL-C; 62.8 ± 24.7 mg/dL to 58.9 ± 21.9 mg/dL; \( P < 0.050 \), U-Alb; 228.49 ± 543.90 ug/gCr to 137.11 ± 384.41 ug/gCr; \( P < 0.050 \); Table 2). However, there were no significant differences between the two groups in the other parameters.
Discussion

We compared the practical efficacy of olmesartan versus azilsartan. In western countries, azilsartan medoxomil (AZL-M), "the prodrug of azilsartan", is widely used in clinical practice. The titer of dosage of AZL-M is different from that of azilsartan (20mg of azilsartan is equivalent to 40mg of AZL-M). In western countries, the main dosages used in clinical practice of AZL-M are 40 or 80 mg once daily. In a similar way, the typical dose of azilsartan is defined as 20mg once daily, and the highest dose of azilsartan is defined as 40 mg once daily in Japan. In addition, the typical dose used in clinical practice of olmesartan are 20 mg once daily, and the highest dose of olmesartan is 40mg once daily in Japan and several countries, at least 93 countries. Bakris GL, et al., [26] reported that reduction in 24-hour mean SBP was greater with AZL-M 80 mg than olmesartan 40 mg, while AZL-M 40 mg was non-inferior to olmesartan 40 mg. Therefore, we compared olmesartan 20mg with azilsartan 20mg once daily. Further, we allowed that the dosage of assigned ARB increased up to 40mg if the target blood pressure level in each patient was not achieved. Both olmesartan and azilsartan exerted a similar blood pressure lowering effect. In addition, both olmesartan and azilsartan demonstrated the protective effect on renal function; olmesartan decreased sFlt-1 and U-L-FABP, whereas, azilsartan decreased significantly U-Alb and eGFR. Both olmesartan and azilsartan were well-tolerated without any major adverse events.

Practical efficacy on office and home blood pressure

Consistent with previous reports [12,13,26,37,38], both olmesartan and azilsartan decreased OBP after switching from conventional ARBs. We found that there was no difference in blood pressure lowering effect between the two drugs. There was a report that the reduction of blood pressure depends on the dosage of olmesartan [14]. In present study, the dosage of olmesartan and azilsartan significantly increased after 16-week treatment. Accordingly, the increment of the dosage of these drugs might lead to the significant reduction of OBP. However, the increased daily dosage in both groups were only 3 mg. Accordingly, it is reasonable that olmesartan and azilsartan are superior to the conventional ARBs in blood pressure reduction. The decrease of systolic OBP in both groups were more than 10 mmHg. In a meta-analysis, every 10 mmHg reduction in systolic blood pressure significantly decreased the risk of major cardiovascular disease events, coronary heart disease, stroke and heart failure led to a significant 13% reduction in all-cause mortality [39]. Therefore, we considered both olmesartan and azilsartan provided the significant clinical impacts. In our study, the percentage of patients who achieved a systolic OBP of <140 mmHg at the end of
study was more than 40% in both OL and AZ group. Regarding to target blood pressure levels, in the ACCORD BP trial [40], both the intensive-therapy group (targeting a systolic blood pressure of less than 120 mmHg) and the standard-therapy group (targeting a systolic blood pressure of less than 140 mmHg) reduce equivalently the rate of a composite outcome of fatal and nonfatal major cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events. On the other hand, in the SPRINT trial [41], the intensive-therapy group (targeting a systolic blood pressure of less than 120 mmHg) resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause compared with the standard-therapy group (targeting a systolic blood pressure of less than 140 mmHg), although significantly higher rates of some adverse events were observed in the intensive-treatment group among non-diabetic patients at high risk for cardiovascular events. Thus, the target level of systolic OBP in the treatment for hypertensive patients still remains controversial. Regarding HBP, in the present study, the reduction of diastolic HBP in AZ group reached statistical significance, whereas, the reduction in OL group did not reach statistical significance. Since the difference of lowering diastolic HBP between the two groups was only 1.5 mmHg, it is likely considered that both olmesartan and azilsartan exerted similar practical efficacy in HBP reduction. Further large clinical trial will be required to evaluate HBP lowering effects of both drugs.

Renoprotective effect

Angiotensin II constricts glomerular efferent arterioles, which leads to the increase of intraglomerular pressure, resulting in glomerular hyperfiltration and albuminuria. Accordingly, the blockade of angiotensin II by ARB decreases intraglomerular pressure, glomerular hyperfiltration, which potentially reduces eGFR, and albuminuria. In the present study, as expected, eGFR and U-Alb significantly decreased after 16-week treatment in AZ group. Therefore, azilsartan could exert more potent angiotensin II receptor blockade than the conventional ARBs. It is reported that the extent of the reduction of albuminuria by therapeutic intervention is correlated with the suppression of the decline of renal function [42]. Further, Japanese clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2012 shows that RAS inhibitors could be continued to administer if the decrease of GFR was less than 30% after three months. In our study, the decrease of eGFR in AZ group was less than 30% (about 4.5%), therefore this reduction was considered a pharmacological effect and safe. These observations led to the suggestion that azilsartan exerted
renoprotective effect.

On the other hand, eGFR and U-Alb didn’t significantly decrease in OL group, suggesting that the suppressive effect of olmesartan on albuminuria was equivalent to the conventional ARBs. Therefore, the effect of angiotensin II receptor blockade on glomerular efferent arterioles in AZ group might be stronger than OL group. With regard to U-L-FABP and sFlt-1, the current study demonstrated that olmesartan significantly decreased both of them after 16-week treatment but azilsartan did not. Various proximal tubule pathophysiological stresses such as oxidative stress induce the upregulation of human L-FABP gene expression, thereby resulting in increased proximal tubular L-FABP excretion and increased U-L-FABP excretion [43]. The urinary excretion of human L-FABP has been reported to reflect the clinical prognosis in CKD [44]. In diabetes patients with CKD, olmesartan decreased U-L-FABP, and increased urinary angiotensin-converting enzyme 2 (ACE2) [45]. Further, changes in urinary ACE2 levels significantly correlated with changes in U-L-FABP levels [45]. In addition, long-term treatment of hypertensive patients with olmesartan reduces plasma angiotensin II levels [46]. These findings suggest that olmesartan might reduce plasma angiotensin II levels by the increased ACE2 activity, leading to the suppression of tubulointerstitial damage. sFLT-1 is a potent and selective endogenous inhibitor of VEGF-mediated angiogenesis [47]. Several reports have demonstrated that VEGF is a proinflammatory factor [48]. The urinary excretion of VEGF and sFLT-1 increased at a relatively early stage in patients with diabetic nephropathy associated with urinary albumin excretion [49]. The urinary sFLT-1 level appeared to be positively correlated with the urinary albumin to creatinine ratio and plasma sFLT-1 levels in type 2 diabetic patients [49]. Further, plasma sFlt-1 levels were elevated in patients with CKD, and contributed to endothelial dysfunction in CKD [50]. Kim NH, et al. reported that angiotensin II induced a dose-dependent increase in the synthesis of both VEGF and sFLT-1 in cultured human proximal tubule cells [49]. Therefore, it is likely that the reduction of plasma Angiotensin II levels caused by olmesartan might decrease sFlt-1 levels in OL group. Taken together, it is suggested that olmesartan has potent renoprotective effect.

**Heart**

It is reported that ARB inhibited the progression and cardiovascular events, such as hospitalization and mortality in the patients with heart failure [51,52]. The plasma level of BNP is elevated in patients with congestive heart failure and increases in proportion to the degree of left ventricular dysfunction and the severity of symptoms of
heart failure [53]. In previous reports, olmesartan reduced the plasma level of BNP in the patients on hemodialysis [54] and the patients with type 2 diabetes mellitus [55]. Therefore it appeared that the plasma level of BNP was expected to decrease in OL group. Contrary to our expectations, plasma BNP levels did not change in both groups in the current study. This might be because the basal plasma BNP levels in both groups were too low, or, the reducing effect in plasma BNP level of olmetsartan and azilsartan were equal to the conventional ARBs. It has reported that eGFR might be negatively correlated with plasma BNP [56]. In our study, eGFR level decreased in both groups. Thus, the reduction of eGFR might affect, in part, the change of plasma BNP level. Further studies will be needed to investigate the effect of these drugs on plasma BNP levels in patients with hypertension.

Study design
In the Probe study, the physicians and patients who participate in the study are aware of the drug which was prescribed. Therefore, the outcome may include some bias. However, the Probe design is inexpensive compared to the traditional double blind design. Further, the Probe design has similarity to a usual clinical practice and the physicians can easily apply the results in the medical care. Therefore, in this study, we demonstrated the Probe study to compare the practical efficacy of olmesartan versus azilsartan.

Limitation
The present study had several limitations. First, the available data were only OBP and HBP, not 24-h ambulatory blood pressure. This might reduce the opportunity to find a potential contribution for the management of morning surge, non-dipper or riser in nocturnal blood pressure. Second, the number of patients was relative small, the age of patients was relative older, and the observation period of study was relatively short compared with previous studies [14,26,36]. Third, we didn’t measure plasma aldosterone concentration and plasma renin activity. Therefore, the suppressive effect on the renin-angiotensin-aldosterone system in each group was not evaluated. Forth, the prescribed dosage of azilsartan differs from AZL-M. In general, the highest dosage of antihypertensive drugs is often different from country to country. The responses for drugs vary with each individual. Therefore, we must carefully observe the patients when we apply these findings to clinical practice in other countries.

In conclusion
Our study demonstrated the practical efficacy of olmesartan versus azilsartan in patients with hypertension. Switching the conventional ARBs to olmesartan or azilsartan significantly reduced the blood pressures in the patients with hypertension who didn’t achieve the target blood pressure levels. Both olmesartan and azilsartan demonstrated renoprotective effect via each specific aspect. Further long-term clinical studies will be needed to evaluate the prognosis of the hypertensive patients.

Appendix
Participants and Participating Centers
Hiroo Hashimoto, Kazuhiko Moriwaki, Kazuhiro Ujike, Innoshima General Hospital;
Fumio Kondo, Kondo Inn Clinic;
Yoshio Kikuchi, Seiyo Municipal Hospital;
Takanobu Nakajima, Kato & Namiki-dori Hospital;
Kosuke Yozai, Okayama Rosai Hospital;
Hiroshi Hirata, Akebono Clinic;
Masashi Muguruma, Misuzu Yamashita, Okayama Kinen Hospital;
Yasuaki Mino, Ochiai Hospital;
Koji Takasugi, Kurashiki Sweet Hospital;
Taro Sugimoto, Sugimoto Clinic;
Keita Ishii, Chugoku Central Hospital;
Kazuyuki Fujino, Kaihara Masanobu, Onomichi Municipal Hospital;
Masami Hashimoto, Hashimoto Kidney Clinic;
Kentaro Inoue, Morimoto Hisanori, Mitoyo General Hospital;
Hidetoshi Kagawa, Tsutomu Hiromasa, Ryutaro Yamanaka, Himeji Red Cross Hospital;
Yoshikazu Hayashi, Tsujii Hayashi Naika Clinic.
Figure Legends

Fig 1. Study design.
Overview of the protocol was described. Outpatients with hypertension who didn’t achieve the target blood pressure levels with the conventional ARBs (losartan, candesartan, irbesartan, valsartan or telmisartan) in the accordance with The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) more than 3 months were recruited in the study. All participants were randomly assigned into the two groups; to receive either olmesartan or azilsartan 20mg once daily for 16 weeks instead of the conventional ARBs. The dosage of assigned ARB was allowed to increase up to 40mg if the target blood pressure level in each patient was not achieved.
Measurement of office blood pressure, blood and urine sampling were demonstrated at the start and end of study.
CKD: chronic kidney disease, DM: diabetes mellitus, CI: cerebral infarction

Fig 2. Trial profile
Eighty-eight patients were enrolled. Three of 88 patients withdrew after the agreement, and one patient was excluded in accordance with the exclusion criteria. Forty of 84 patients were assigned into the olmesartan group and 44 into the azilsartan group. Five patients of the olmesartan group and 6 patients of the azilsartan group were excluded by several reasons. As a result, 73 patients completed the study.

Fig 3. Blood pressure changes after 16-week treatment with olmesartan or azilsartan.
The blood pressure levels were compared between the baseline and the end point of study in each group. Dark gray dotted line indicates the mean blood pressure level in olmesartan group. Light gray solid line indicates the mean blood pressure level in azilsartan group. P-values were obtained by Paired t–test. 0w:0 week (baseline), 16w: 16 weeks (the endpoint of study), OL: olmesartan, AZ: azilsartan, OBP: office blood pressure, HBP: home blood pressure
Reference


Miura S, Okabe A, Matsuo Y, Karnik SS, Saku K. Unique binding behavior of the recently approved angiotensin II receptor blocker azilsartan compared with that of candesartan.


Supplemental Digital Content 1.
the Intention-To-Treat analysis of the blood pressure changes after 16-week treatment with olmesartan or azilsartan are shown. ppt.