Practical efficacy of olmesartan versus azilsartan in patients with hypertension: a multicenter randomized-controlled trial (MUSCAT-4 study)

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

Methods **Eighty-four patients treated with the conventional ARBs for more than 3 months were assigned randomly to receive either 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 the OL and AZ groups.**

Results **Office blood pressure of both groups decreased significantly (OL group: 152/86–141/79 mmHg, $P < 0.05$, AZ group: 149/83–135/75 mmHg; $P < 0.05$). Diastolic home blood pressure in the AZ group decreased significantly (79 ± 9–74 ± 7 mmHg; $P < 0.05$), but not in the OL group (79 ± 11–75 ± 10 mmHg; $P = 0.068$). However, there were no significant differences between the groups. The dosage of olmesartan and azilsartan increased significantly and slightly for 16 weeks (OL group: 20.3–23.1 mg; $P < 0.05$, AZ group: 20.5–23.2 mg; $P < 0.05$), without a significant difference between groups. Furthermore, there were no significant differences in renal function, lipid profiles, brain natriuretic peptide, soluble fms-like tyrosine kinase-1, and urinary L-type fatty acid-binding protein between the two groups.**

Conclusion **Both olmesartan and azilsartan equally reduced blood pressures. Both olmesartan and azilsartan showed a renoprotective effect and were well tolerated without any major adverse events.** ***Blood Press Monit*** **22:59–67**

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Keywords: angiotensin II receptor blocker, azilsartan, hypertension, olmesartan, renoprotective effect

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Introduction

Angiotensin II induces arterial constriction and the secretion of aldosterone, leading to hypertension. Angiotensin II produces reactive oxygen species and an inflammatory response [1,2]. These effects cause and lead to progression of various diseases such as hypertension, diabetes mellitus (DM), and kidney disease. Angiotensin II receptor blocker (ARB) is one of the safest and most effective antihypertensive agents; therefore, it has been used widely in many countries, including in Japan. Furthermore, ARBs reduce oxidative stress and inflammation [3], leading to an organ-protective effect beyond a 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 DM [10,11].

Several studies have reported that olmesartan (olmesartan medoxomil) has a strong antihypertensive effect superior to that of other conventional ARBs [12–14]. Increasing the dosage of olmesartan leads to a greater reduction in blood pressure than the other ARBs [14]. Furthermore, olmesartan showed a renal protective effect as it was associated with a delayed onset of albuminuria in patients 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 patients with stable angina pectoris (AP) [19]. In patients with essential hypertension after

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cardiac surgery, olmesartan inhibited left ventricular hypertrophy and improved arterial compliance by a decrease in plasma angiotensin II and plasma aldosterone levels [20]. In a mouse model, olmesartan attenuated cardiac remodeling [21] and suppressed adipocyte hypertrophy [22]. These evidences indicate the protective effect of olmesartan on the cerebrocardiovascular events. Meanwhile, azilsartan [azilsartan itself, not azilsartan medoxomil (AZL-M)] is the latest ARB launched in Japan. Azilsartan is expected to show an excellent hypotensive effect than the other ARBs partially because of the high binding affinity to the angiotensin II type 1 receptor [23]. In an experimental model, besides an antihypertensive effect, azilsartan was reported to improve salt sensitivity [24] and decrease renal and cardiovascular injury [25]. There is a report showing that the antihypertensive effect of olmesartan is equivalent to that of AZL-M [26]. However, there is no report of a direct comparison of olmesartan with azilsartan in terms of a potential antihypertensive effect in Japanese hypertensive patients.

The aim of the present study is to compare the 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] study carried out at multiple hospitals and clinics, comparing the effects of angiotensin II type 1 receptor blockers 4 (MUSCAT-4).

Inclusion criteria

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

Exclusion criteria

Patients with severe renal dysfunction [serum creatinine (Cr) > 2.0 mg/dl], liver dysfunction (serum aspartate transaminase or alanine transaminase > 100 IU/l), a history of clinically significant adverse reactions with ARB, possible pregnancy, and a disease with a poor prognosis such as the malignant tumor were excluded. If the attending physician expected that switching ARB might be disadvantageous to the patients, they were also excluded.

Study protocol

An overview of the protocol is described in Fig. 1. All participants were assigned randomly to two groups and received 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 could be increased up to 40 mg if the target blood pressure level in each patient was not achieved.

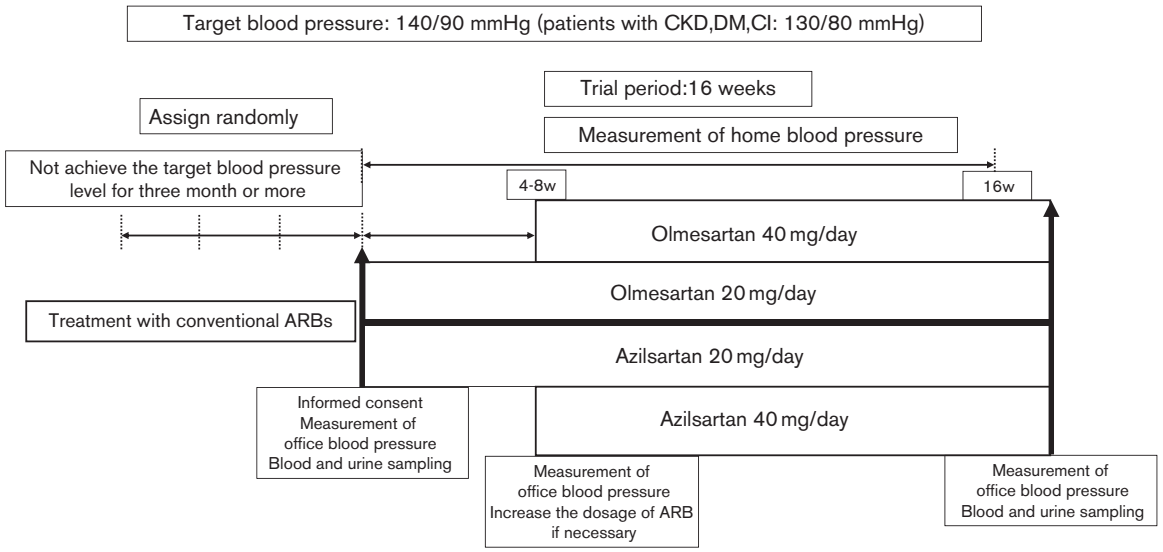
Blood pressure measurement

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

Clinical efficacy and outcomes

The primary outcome in this study was the reduction of OBP and HBP under treatment with olmesartan versus azilsartan. The 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 albumin (U-Alb)/Cr ratio and urinary L-type fatty acid-binding protein (U-L-FABP), serum lipid profiles such as total cholesterol, low-density lipoprotein-cholesterol, and high-density lipoprotein (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), AP, and stroke were also investigated along with the physicians' chart. The definition of each disease was as follows: DM was defined when a patient was on medication for DM or fulfilled the diagnostic criteria [32]: fasting plasma glucose levels more than or equal to 126 mg/dl (7.0 mmol/l), random plasma glucose levels more than or equal to 200 mg/dl or plasma glucose more than or equal to 200 mg/dl 2 h after a 75 g glucose load, or HbA1c of 6.5% or more. DLP was defined when a patient was on medication for DLP or fulfilled the diagnostic criteria [33]: low-density lipoprotein-cholesterol more than or equal to 140 mg/dl, HDL-cholesterol less than 40 mg/dl, and triglycerides more than or equal to 150 mg/dl. CKD was defined as follows: (a) 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 irrespective of eGFR [34,35]; (b) eGFR less than 60 ml/min/1.73 m^2 irrespective of the primary disease using the Modification of Diet in Renal

Fig. 1



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

Disease Study equation [36]. MI and AP were defined as the previous symptomatic chest pain and a diagnosed history of angina or previous MI by coronary angiography. Stroke was defined as previous or current symptomatic paralysis or headache and a diagnosed history of cerebral infarction, cerebral hemorrhage by computed tomography or MRI.

Ethical statement

This study followed the Declaration of Helsinki (7th revision, 2013) on medical protocol and ethics. The ethics committees of the Okayama University Institutional Review Board (accredited ISO9001/2000), Okayama, Japan, and the Institutional Review Board in the related facilities approved the protocol (UMIN ID: 000012768). Written informed consents were obtained from all patients.

Statistical analysis

All data are presented as the mean ± SD unless otherwise noted. Differences were analyzed using a paired or an unpaired *t*-test where appropriate. Differences in urinary data, BNP, HbA1c, and sFlt-1 were analyzed using the rank sum-test or the signed rank-test where appropriate. Differences in the presence of complications, sex ratio, and smoking ratio between two groups were analyzed using Fisher's 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, California, USA). A *P* value less than 0.05 was considered to be statistically significant.

Results

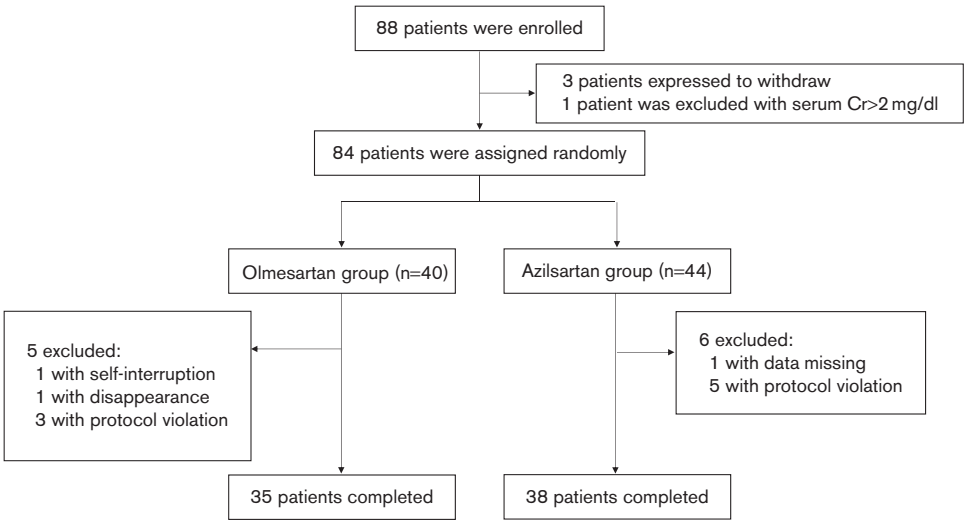
Characteristics of the patients and safety

Eighty-eight patients were enrolled from September 2013 to December 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 to the OL group and 44 patients were assigned to the AZ group. Five patients of the OL group and six patients of the AZ group were excluded for several reasons (Fig. 2). As a result, 73 patients completed the study. Baseline clinical characteristics and parameters of the 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 previous treatment with only 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 decreased significantly in both groups with a 16-week treatment (OL group:

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 to the olmesartan group and 44 patients were assigned to the azilsartan group. Five patients of the olmesartan group and six patients of the azilsartan group were excluded for several reasons. As a result, 73 patients completed the study. Cr, creatinine.

Table 1 Baseline clinical characteristics of each group

	OL group ($n=40$) [n (%)]	AZ group ($n=44$) [n (%)]	P
Age (years)	66.6 ± 11.8	68.7 ± 10.1	0.373
Sex (male)	18 (45)	22 (50)	0.668
BMI (kg/m²)	25.9 ± 3.9	25.2 ± 3.3	0.396
Smoking (mmHg) (%)	66.7	71.4	0.794
Systolic OBP	150.1 ± 14.1	150.4 ± 15.4	0.935
Diastolic OBP	83.2 ± 11.8	83.0 ± 9.8	0.948
Systolic HBP	145.8 ± 17.0	137.4 ± 13.5	0.068
Diastolic HBP	82.2 ± 12.5	80.8 ± 8.6	0.663
Prevalence of complications			
Diabetes mellitus	19 (47.5)	19 (43.2)	0.827
Dyslipidemia	22 (55)	20 (45.4)	0.512
Renal dysfunction	9 (22.5)	8 (18.2)	0.786
Liver dysfunction	6 (15.0)	3 (6.8)	0.298
Myocardial infarction	2 (5.0)	3 (7.5)	1.000
Angina pectoris	4 (10)	4 (9.1)	1.000
Cerebral infarction	3 (7.5)	2 (4.5)	0.665
Cerebral hemorrhage	1 (2.5)	0 (0)	1.000
Preuse of ARB			
Candesartan	12 (30.0)	14 (31.8)	1.000
Valsartan	11 (27.5)	7 (15.9)	0.287
Losartan	8 (20.0)	10 (22.7)	0.796
Telmisartan	9 (22.5)	9 (20.5)	1.000
Irbesartan	0 (0)	4 (9.1)	0.117

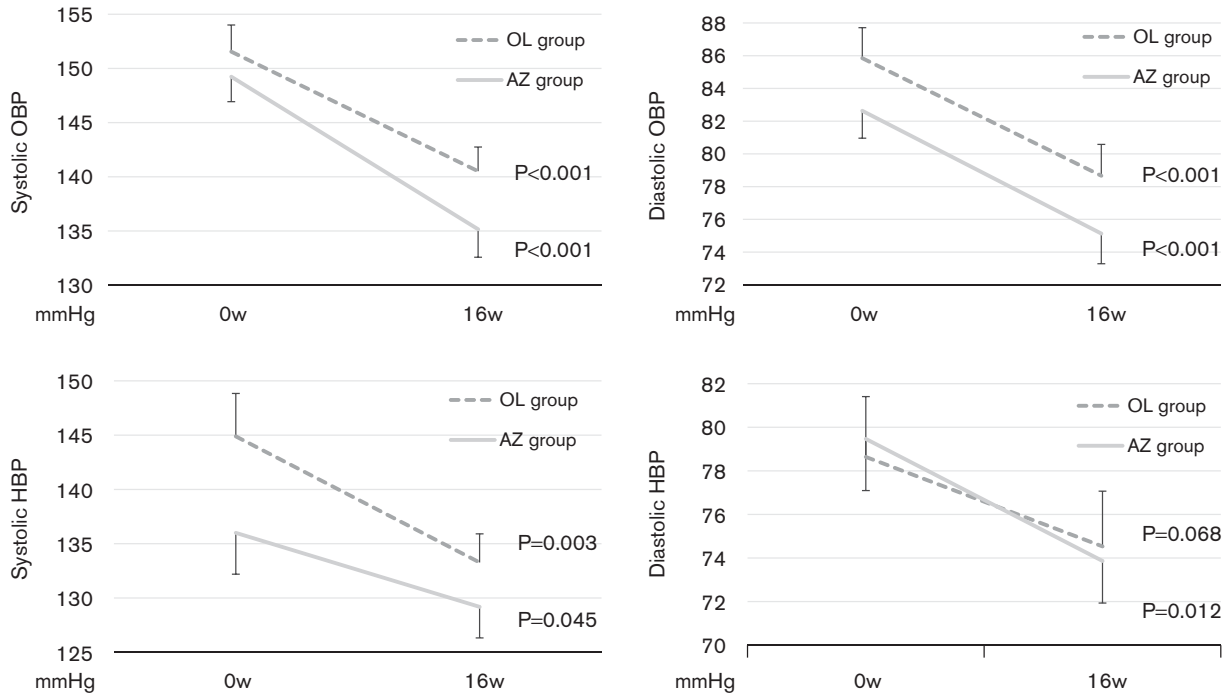
P values were obtained using a t-test for the parameters of age and BMI; for the others, P values were obtained using Fisher's exact test.
ARB, angiotensin II receptor blocker; AZ, azilsartan; HBP, home blood pressure; OBP, office blood pressure; OL, olmesartan.

152 ± 14/86 ± 11–141 ± 13/79 ± 11 mmHg; $P<0.001$, AZ group: 149 ± 14/83 ± 10–135 ± 16/75 ± 11 mmHg; $P<0.001$, Fig. 3). Systolic HBP decreased significantly in both groups after a 16-week treatment (OL group: 145 ± 17–133 ± 11 mmHg; $P<0.050$, AZ group: 136 ± 15–129 ± 11 mmHg; $P<0.050$, Fig. 3). However, diastolic HBP decreased significantly only in the AZ group (OL group: 79 ± 11–75 ± 10 mmHg; $P=0.068$, AZ group: 79 ± 9–74 ± 7 mmHg; $P<0.050$, Fig. 3) (see Supplementary Fig., Supplemental digital content 1, *http://links.lww.com/BPMJ/A29*, in which the intention-to-treat analyses of the above contents are shown). There were no significant differences between the two groups in any OBPs and HBPs. The dosage of ARB was increased significantly after 16 weeks in both groups (OL group: 20.3 ± 3.8–23.1 ± 8.0 mg/day; $P<0.050$, AZ group: 20 ± 0–23.2 ± 7.4 mg/day; $P<0.050$; Table 2).

Achievement ratio on target levels of office blood pressure and home blood pressure

Next, we assessed the antihypertensive effect of the two drugs on the achievement ratio on the target level. The percentage of patients who achieved a systolic OBP of less than 140 mmHg at the end of study did not 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 less than 90 mmHg (OL group: 75.8%, AZ group: 86.9%; $P=0.357$), a systolic HBP of less than 135 mmHg (OL group: 50.0%, AZ group: 75.0%; $P=0.172$), and a diastolic HBP of less than 85 mmHg (OL group: 80.0%, AZ group: 86.7%; $P=1.000$) at the end of the study between the two groups. Similarly, there were no significant differences in the percentage of patients who achieved a greater than 10 mmHg reduction after the treatment in systolic OBP (OL group: 54.5%, AZ group: 57.9%; $P=0.814$), diastolic OBP (OL group: 42.4%, AZ group: 57.6%; $P=0.814$), systolic HBP (OL group: 38.9%, AZ group: 31.3%;

Fig. 3



Blood pressure changes after a 16-week treatment with olmesartan or azilsartan. The blood pressure levels were compared between the baseline and the endpoint of study in each group. The dark gray dotted line indicates the mean blood pressure level in the olmesartan group. The light gray solid line indicates the mean blood pressure level in the azilsartan group. *P* values were obtained using a paired *t*-test. AZ, azilsartan; HBP, home blood pressure; OBP, office blood pressure; OL, olmesartan; 0w, 0 week (baseline); 16w, 16 weeks (the endpoint of the study).

Table 2 Baseline parameters and their changes after a 16-week treatment with olmesartan or azilsartan

	OL group ($n=40$)			AZ group ($n=44$)		
	Baseline	16 weeks	*P*	Baseline	16 weeks	*P*
Dosage of ARB (mg/day)	20.3±3.6	23.1±8.0	0.023*	20.5±3.0	23.2±7.5	0.012*
PR (/min)	76.0±12.1	73.8±12.8	0.453	75.6±13.8	75.7±12.9	0.929
K (mmol/l)	4.4±0.4	4.2±0.4	0.017*	4.3±0.4	4.3±0.4	0.622
Cr (mg/dl)	0.8±0.3	0.8±03	0.484	0.8±0.2	0.8±0.2	0.033*
eGFR (ml/min)	68.6±18.1	67.0±18.8	0.605	68.6±16.8	65.5±16.5	0.022*
T-Chol (mg/dl)	193.4±47.5	197.4±80.5	0.753	187.7±49.0	185.5±42.2	0.784
LDL-C (mg/dl)	104.2±30.2	104.5±23.8	0.640	111.5±27.7	110.2±27.4	0.309
HDL-C (mg/dl)	61.4±15.6	57.7±12.6	0.083	61.1±23.3	58.9±21.9	0.001**
HbA1c (%)	6.1±0.8	6.1±0.8	0.132	6.0 ±0.7	6.11±0.8	0.867
BNP (pq/ml)	37.7±48.6	37.6±43.3	0.067	30.2±27.0	32.0±31.6	0.971
sFlt-1 (pg/ml)	72.9±9.3	69.4±9.6	0.034*	74.7±12.9	74.2±12.8	0.182
U-Alb (mg/gCr)	114.0±239.6	133.1±316.5	0.642	211.5±512.2	137.1±384.4	0.047*
U-L-FABP (μg/gCr)	11.2±12.7	4.9±4.0	0.019*	8.8±7.4	7.56±12.1	0.547

ARB, angiotensin receptor blocker, AZ, azilsartan; BNP, brain natriuretic peptide; Cr, serum creatinine concentration; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol concentration; K, serum potassium concentration; LDL-C, low-density lipoprotein cholesterol concentration; OL, olmesartan; PR, pulse rate; sFlt-1, soluble fms-like tyrosine kinase-1; T-chol, total cholesterol concentration; U-Alb, urinary albumin/creatinine ratio; U-L-FABP, urinary L-type fatty acid-binding protein/creatinine ratio.
*$P<0.05$.
**$P<0.01$.

$P=0.729$), and 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 decreased significantly in the OL group (serum potassium: 4.38±0.41–4.24±0.36 mmol/l; $P<0.050$, sFlt-1: 72.17±9.02–69.84±9.24 pg/ml; $P<0.050$, U-L-FABP: 12.07±13.66–5.28±4.90 μg/gCr; $P<0.050$; Table 2). In the AZ group, serum Cr levels increased significantly (serum Cr: 0.79±0.20–0.83±0.21 mg/dl; $P<0.050$; Table 2). In contrast, eGFR, HDL-C, and U-Alb

decreased significantly after a 16-week treatment (eGFR: 69.0 ± 16.7–65.5 ± 16.5 ml/min/1.73 m^2; $P < 0.050$, HDL-C: 62.8 ± 24.7–58.9 ± 21.9 mg/dl; $P < 0.050$, U-Alb: 228.49 ± 543.90 –137.11 ± 384.41 μg/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, AZL-M, 'the prodrug of azilsartan', is used widely in clinical practice. The titer of dosage of AZL-M is different from that of azilsartan (20 mg of azilsartan is equivalent to 40 mg of AZL-M). In western countries, the main dosages used in clinical practice of AZL-M are 40 or 80 mg once daily. Similarly, the typical dose of azilsartan is defined as 20 mg once daily and the highest dose of azilsartan is defined as 40 mg once daily in Japan. In addition, the typical dose used in the clinical practice of olmesartan is 20 mg once daily and the highest dose of olmesartan is 40 mg once daily in Japan and several countries (at least 93 countries). Bakris *et al.* [26] reported that the reduction in 24-h mean systolic blood pressure (SBP) was greater with AZL-M 80 mg than olmesartan 40 mg, whereas AZL-M 40 mg was noninferior to olmesartan 40 mg. Therefore, we compared olmesartan 20 mg with azilsartan 20 mg once daily. Further, we allowed the dosage of assigned ARB to be increased up to 40 mg 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 showed protective effects on renal function; olmesartan decreased sFlt-1 and U-L-FABP, whereas azilsartan decreased U-Alb and eGFR significantly. Both olmesartan and azilsartan were well tolerated without any major adverse events.

Practical efficacy on office and home blood pressures

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 the 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 the present study, the dosage of olmesartan and azilsartan increased significantly after a 16-week treatment. Accordingly, the increment in the dosage of these drugs might have led to a significant reduction in OBP. However, the increased daily dosage in both groups was only 3 mg. Accordingly, it is reasonable that olmesartan and azilsartan are superior to the conventional ARBs in blood pressure reduction. The decreases in systolic OBP in both groups were more than 10 mmHg. In a meta-analysis, every 10 mmHg reduction in SBP significantly decreased the risk of major cardiovascular disease events, coronary heart disease, stroke, and heart failure and led to a significant 13% reduction in all-cause mortality [39]. Therefore, we concluded that both olmesartan and azilsartan exerted significant clinical impacts. In our study, the percentage of patients who achieved a systolic OBP of less than 140 mmHg at the end of study was more than 40% in both the OL and the AZ group. In terms of target blood pressure levels, in the ACCORD BP trial [40], in both the intensive-therapy group (targeting a SBP < 120 mmHg) and the standard-therapy group (targeting a SBP < 140 mmHg), there was an equivalent reduction in 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. However, in the SPRINT trial [41], the intensive-therapy group (targeting a SBP < 120 mmHg) showed lower rates of fatal and nonfatal major cardiovascular events and death from any cause compared with the standard-therapy group (targeting a SBP < 140 mmHg), although significantly higher rates of some adverse events were observed in the intensive-treatment group among nondiabetic patients at high risk for cardiovascular events. Thus, the target level of systolic OBP in the treatment for hypertensive patients still remains controversial. For HBP, in the present study, the reduction in diastolic HBP in the AZ group reached statistical significance, whereas the reduction in the OL group did not reach statistical significance. As the difference in lowering diastolic HBP between the two groups was only 1.5 mmHg, it can likely be considered that both olmesartan and azilsartan exerted similar practical efficacy in HBP reduction. Further large clinical trials will be required to evaluate the HBP-lowering effects of both drugs.

Renoprotective effect

Angiotensin II constricts glomerular efferent arterioles, which leads to an increase in intraglomerular pressure, resulting in glomerular hyperfiltration and albuminuria. Accordingly, the blockade of angiotensin II by ARB decreases intraglomerular pressure and glomerular hyperfiltration, which potentially reduces eGFR, and albuminuria. In the present study, as expected, eGFR and U-Alb decreased significantly after a 16-week treatment in the AZ group. Therefore, azilsartan could exert more potent ARB than the conventional ARBs. It is reported that the extent of the reduction of albuminuria by a therapeutic intervention is correlated with the suppression of the decline of renal function [42]. Further, the Japanese clinical practice guidebook for the diagnosis and treatment of chronic kidney disease 2012 shows that renin–angiotensin system inhibitors can be continued if the decrease in glomerular filtration rate is less than 30% after 3 months. In our study, the decrease in eGFR in the 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 a renoprotective effect.

However, eGFR and U-Alb did not decrease significantly in the OL group, suggesting that the suppressive effect of olmesartan on albuminuria was equivalent to that of the conventional ARBs. Therefore, the effect of ARB on glomerular efferent arterioles in the AZ group might be stronger than that in the OL group. With respect to U-L-FABP and sFlt-1, the current study showed that olmesartan significantly decreased both after a 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 diabetic patients with CKD, olmesartan decreased U-L-FABP and increased urinary angiotensin-converting enzyme 2 (ACE2) [45]. Further, changes in urinary ACE2 levels correlated significantly 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 increased ACE2 activity, leading to the suppression of tubulointerstitial damage. sFLT-1 is a potent and selective endogenous inhibitor of vascular endothelial growth factor (VEGF)-mediated angiogenesis [47]. Several reports have shown 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 correlated positively with the urinary Alb/Cr 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 toward endothelial dysfunction in CKD [50]. Kim *et al.* [49] reported that angiotensin II induced a dose-dependent increase in the synthesis of both VEGF and sFLT-1 in cultured human proximal tubule cells. Therefore, it is likely that the reduction in plasma angiotensin II levels caused by olmesartan might decrease sFlt-1 levels in the OL group. Taken together, it is suggested that olmesartan exerts a potent renoprotective effect.

Heart

It is reported that ARB inhibited increasing severity of congestive heart failure (CHF) and cardiovascular events, such as hospitalization and mortality in the patients with CHF [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 patients on hemodialysis [54] and patients with type 2 DM [55]. Therefore, the plasma level of BNP was expected to decrease in the 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 effects on plasma BNP level of olmetsartan and azilsartan were equal to those of the conventional ARBs. It has been reported that eGFR might be correlated negatively with plasma BNP [56]. In our study, the eGFR level decreased in both groups. Thus, the reduction in eGFR might affect, in part, the change in plasma BNP levels. 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 participated in the study were aware of the drug that was prescribed. Therefore, the outcome may include some bias. However, the PROBE design is inexpensive compared with the traditional double-blind design. Further, the PROBE design is similar to a usual clinical practice and the physicians can easily refer to the results of the PROBE study when they devise a therapeutic strategy. Therefore, in this study, we carried out the PROBE study to compare the practical efficacy of olmesartan versus azilsartan.

Limitations

The present study had several limitations. First, the data available were only OBP and HBP, not 24-h ambulatory blood pressure. This might have reduced the opportunity to find a potential contribution of the management of morning surge, nondipper, or riser toward nocturnal blood pressure. Second, the number of patients was relatively small, the age of the patients was relatively older, and the observation period of the study was relatively short compared with previous studies [14,26,36]. Third, we did not measure plasma aldosterone concentration and plasma renin activity. Therefore, the suppressive effect on the renin–angiotensin–aldosterone system in each group was not evaluated. Hence, 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 to drugs vary in each individual. Therefore, we must carefully observe the patients when we apply these findings to clinical practice in other countries.

Conclusion

Our study showed 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 did not achieve the target blood pressure levels. Both olmesartan and azilsartan showed a renoprotective effect by each differential aspect, i.e. olmesartan decreased U-LFABP and sFlt-1 and azilsartan decreased U-Alb. Further long-term clinical studies will

be needed to evaluate the prognosis of the hypertensive patients.

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Conflicts of interest

Haruhito A. Uchida belongs to the Department of Chronic Kidney Disease and Cardiovascular Disease, which is endowed by Chugai Pharmaceutical, MSD, Boehringer Ingelheim, and Kawanishi Holdings. Jun Wada receives speaker honoraria from Astellas, Boehringer Ingelheim, Novartis, Novo Nordisk, and Tanabe Mitsubishi, and receives grant support from Bayer, Daiichi Sankyo, Kyowa Hakko Kirin, MSD, Novo Nordisk, Otsuka, Torii, Pfizer, Takeda, Taisho Toyama, and Tanabe Mitsubishi. For the remaining authors there are no conflicts of interest.

References

1 Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res* 1994; **74**:1141–1148.
2 Sahar S, Reddy MA, Wong C, Meng L, Wang M, Natarajan R. Cooperation of SRC-1 and p300 with NF-kappaB and CREB in angiotensin II-induced IL-6 expression in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 2007; **27**:1528–1534.
3 Ogawa S, Mori T, Nako K, Kato T, Takeuchi K, Ito S. Angiotensin II type 1 receptor blockers reduce urinary oxidative stress markers in hypertensive diabetic nephropathy. *Hypertension* 2006; **47**:699–705.
4 Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, *et al*. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; **345**:851–860.
5 Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345**:870–878.
6 Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**:861–869.
7 Makino H, Haneda M, Babazono T, Moriya T, Ito S, Iwamoto Y, *et al*. Prevention of transition from incipient to overt nephropathy with telmisartan in patients with type 2 diabetes. *Diabetes Care* 2007; **30**:1577–1578.
8 Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, *et al*. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**:1004–1010.
9 Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, *et al*. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008; **358**:1547–1559.
10 Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K, *et al*. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008; **51**:393–398.
11 McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, *et al*. Effect of valsartan on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010; **362**:1477–1490.
12 Wang L, Zhao JW, Liu B, Shi D, Zou Z, Shi XY. Antihypertensive effects of olmesartan compared with other angiotensin receptor blockers: a meta-analysis. *Am J Cardiovasc Drugs* 2012; **12**:335–344.
13 Smith DH, Dubiel R, Jones M. Use of 24-h ambulatory blood pressure monitoring to assess antihypertensive efficacy: a comparison of olmesartan medoxomil, losartan potassium, valsartan, and irbesartan. *Am J Cardiovasc Drugs* 2005; **5**:41–50.
14 Giles TD, Oparil S, Silfani TN, Wang A, Walker JF. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. *J Clin Hypertens (Greenwich)* 2007; **9**:187–195.
15 Haller H, Ito S, Izzo JL Jr, Januszewicz A, Katayama S, Menne J, *et al*. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med* 2011; **364**:907–917.
16 Imai E, Ito S, Haneda M, Chan JC, Makino H. Olmesartan reducing incidence of endstage renal disease in diabetic nephropathy trial (ORIENT): rationale and study design. *Hypertens Res* 2006; **29**:703–709.
17 Stumpe KO, Agabiti-Rosei E, Zielinski T, Schremmer D, Scholze J, Laeis P, *et al*. Carotid intima-media thickness and plaque volume changes following 2-year angiotensin II-receptor blockade. The Multicentre Olmesartan atherosclerosis Regression Evaluation (MORE) study. *Ther Adv Cardiovasc Dis* 2007; **1**:97–106.
18 Naya M, Tsukamoto T, Morita K, Katoh C, Furumoto T, Fujii S, *et al*. Olmesartan, but not amlodipine, improves endothelium-dependent coronary dilation in hypertensive patients. *J Am Coll Cardiol* 2007; **50**:1144–1149.
19 Hirohata A, Yamamoto K, Miyoshi T, Hatanaka K, Hirohata S, Yamawaki H, *et al*. Impact of olmesartan on progression of coronary atherosclerosis a serial volumetric intravascular ultrasound analysis from the OLIVUS (impact of OLmesarten on progression of coronary atherosclerosis: evaluation by intravascular ultrasound) trial. *J Am Coll Cardiol* 2010; **55**:976–982.
20 Sezai A, Soma M, Hata M, Yoshitake I, Unosawa S, Wakui S, *et al*. Effects of olmesartan on the renin–angiotensin–aldosterone system for patients with essential hypertension after cardiac surgery – investigation using a candesartan change-over study. *Ann Thorac Cardiovasc Surg* 2011; **17**:487–493.
21 You J, Wu J, Jiang G, Guo J, Wang S, Li L, *et al*. Olmesartan attenuates cardiac remodeling through DLL4/Notch1 pathway activation in pressure overload mice. *J Cardiovasc Pharmacol* 2013; **61**:142–151.
22 Maeda A, Tamura K. Effects of the angiotensin receptor blocker olmesartan on adipocyte hypertrophy and function in mice with metabolic disorders. *BioMed Res Int* 2014; **2014**:946492.
23 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. *Hypertens Res* 2013; **36**:134–139.
24 Hatanaka M, Kaimori JY, Yamamoto S, Matsui I, Hamano T, Takabatake Y, *et al*. Azilsartan improves salt sensitivity by modulating the proximal tubular Na+-H+ exchanger-3 in mice. *PLoS One* 2016; **11**:e0147786.
25 Hye Khan MA, Neckar J, Cummens B, Wahl GM, Imig JD. Azilsartan decreases renal and cardiovascular injury in the spontaneously hypertensive obese rat. *Cardiovasc Drugs Ther* 2014; **28**:313–322.
26 Bakris GL, Sica D, Weber M, White WB, Roberts A, Perez A, *et al*. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. *J Clin Hypertens (Greenwich)* 2011; **13**:81–88.
27 Hansson L, Hedner T, Dahlof B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective randomized open blinded end-point. *Blood Press* 1992; **1**:113–119.
28 Ogihara T, Kikuchi K, Matsuoka H, Fujita T, Higaki J, Horiuchi M, *et al*. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009). *Hypertens Res* 2009; **32**:3–107.
29 Uchida H, Nakamura Y, Kaihara M, Sugimoto T, Norii H, Sasaki M, *et al*. Practical efficacy of telmisartan for decreasing morning home blood pressure and pulse wave velocity in patients with mild-to-moderate hypertension. *Hypertens Res* 2004; **27**:545–550.

30 Uchida H, Nakamura Y, Kaihara M, Norii H, Hanayama Y, Makino H. The MUSCAT study: a multicenter PROBE study comparing the effects of angiotensin II type-1 receptor blockers on self-monitored home blood pressure in patients with morning hypertension: study design and background characteristics. *Hypertens Res* 2008; **31**:51–58.
31 Hanayama Y, Uchida HA, Nakamura Y, Makino H. Losartan/hydrochlorothiazide combination therapy surpasses high-dose angiotensin receptor blocker in the reduction of morning home blood pressure in patients with morning hypertension. *Acta Med Okayama* 2012; **66**:449–459.
32 Seino Y, Nanjo K, Tajima N, Kadowaki T, Kashiwagi A, Araki E, *et al*. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Investig* 2010; **1**:212–228.
33 Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, *et al*. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. *J Atheroscler Thromb* 2013; **20**:517–523.
34 Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, *et al*. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**:137–147.
35 KDOQI; National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *Am J Kidney Dis* 2006; **47** (Suppl 3):S11–145.
36 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**:982–992.
37 Rakugi H, Enya K, Sugiura K, Ikeda Y. Comparison of the efficacy and safety of azilsartan with that of candesartan cilexetil in Japanese patients with grade I–II essential hypertension: a randomized, double-blind clinical study. *Hypertens Res* 2012; **35**:552–558.
38 Sica D, White WB, Weber MA, Bakris GL, Perez A, Cao C, *et al*. Comparison of the novel angiotensin II receptor blocker azilsartan medoxomil vs valsartan by ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich)* 2011; **13**:467–472.
39 Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; **387**:957–967.
40 Cushman WC, Evans GW, Byington RP, Goff DC Jr., Grimm RH Jr., Cutler JA, *et al*. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; **362**:1575–1585.
41 Wright JT Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, *et al*. a randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; **373**:2103–2116.
42 Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, *et al*. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. *J Am Soc Nephrol* 2006; **17**:2582–2590.
43 Kamijo A, Kimura K, Sugaya T, Yamanouchi M, Hikawa A, Hirano N, *et al*. Urinary fatty acid-binding protein as a new clinical marker of the progression of chronic renal disease. *J Lab Clin Med* 2004; **143**:23–30.
44 Kamijo A, Sugaya T, Hikawa A, Okada M, Okumura F, Yamanouchi M, *et al*. Urinary excretion of fatty acid-binding protein reflects stress overload on the proximal tubules. *Am J Pathol* 2004; **165**:1243–1255.
45 Abe M, Oikawa O, Okada K, Soma M. Urinary angiotensin-converting enzyme 2 increases in diabetic nephropathy by angiotensin II type 1 receptor blocker olmesartan. *J Renin Angiotensin Aldosterone Syst* 2015; **16**:159–164.
46 Ichikawa S, Takayama Y. Long-term effects of olmesartan, an Ang II receptor antagonist, on blood pressure and the renin–angiotensin–aldosterone system in hypertensive patients. *Hypertens Res* 2001; **24**:641–646.
47 Goldman CK, Kendall RL, Cabrera G, Soroceanu L, Heike Y, Gillespie GY, *et al*. Paracrine expression of a native soluble vascular endothelial growth factor receptor inhibits tumor growth, metastasis, and mortality rate. *Proc Natl Acad Sci USA* 1998; **95**:8795–8800.
48 Marumo T, Schini-Kerth VB, Busse R. Vascular endothelial growth factor activates nuclear factor-kappaB and induces monocyte chemoattractant protein-1 in bovine retinal endothelial cells. *Diabetes* 1999; **48**:1131–1137.
49 Kim NH, Oh JH, Seo JA, Lee KW, Kim SG, Choi KM, *et al*. Vascular endothelial growth factor (VEGF) and soluble VEGF receptor FLT-1 in diabetic nephropathy. *Kidney Int* 2005; **67**:167–177.
50 Di Marco GS, Reuter S, Hillebrand U, Amler S, Konig M, Larger E, *et al*. The soluble VEGF receptor sFlt1 contributes to endothelial dysfunction in CKD. *J Am Soc Nephrol* 2009; **20**:2235–2245.
51 Matsumori A. Efficacy and safety of oral candesartan cilexetil in patients with congestive heart failure. *Eur J Heart Fail* 2003; **5**:669–677.
52 Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, *et al*. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362**:772–776.
53 Yasue H, Yoshimura M, Sumida H, Kikuta K, Kugiyama K, Jougasaki M, *et al*. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. *Circulation* 1994; **90**:195–203.
54 Suzuki R, Honda H, Niikura K, Akizawa T. Olmesartan medoxomil treatment is associated with decreased plasma B-type natriuretic peptide levels in patients on hemodialysis. *Clin Exp Hypertens* 2012; **34**:125–131.
55 Kawai T, Takei I, Shimada A, Hirata T, Tanaka K, Saisho Y, *et al*. Effects of olmesartan medoxomil, an angiotensin II type 1 receptor antagonist, on plasma concentration of B-type natriuretic peptide, in hypertensive patients with type 2 diabetes mellitus: a preliminary, observational, open-label study. *Clin Drug Investig* 2011; **31**:237–245.
56 Tsutamoto T, Wada A, Sakai H, Ishikawa C, Tanaka T, Hayashi M, *et al*. Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2006; **47**:582–586.