Original Article

Renal Protective Effect in Hypertensive Patients: The High Doses of Angiotensin II Receptor Blocker (HARB) Study

Mitsuru OHISHI[1)], Takashi TAKAGI[1)], Norihisa ITO[1)], Yuji TATARA[1)], Norihiro HAYASHI[1)], Atsushi SHIOTA[1)], Yoshihiro IWAMOTO[1)], Tomohiro KATSUYA[1)], Hiromi RAKUGI[1)], and Toshio OGIHARA[1)]

Angiotensin receptor blockers (ARBs) are the recommended first-line antihypertensive treatment for managing chronic kidney disease, and strict blood pressure (BP) regulation is crucial for the reduction of proteinuria. Valsartan and candesartan are commonly used ARBs in Japan, with maximum permissible doses of 160 mg/day and 12 mg/day, respectively. We evaluated BP and proteinuria after changeover from the maximum dose of candesartan to the maximum dose of valsartan, in 55 poorly controlled hypertensive patients undergoing candesartan treatment who were unable to achieve optimal BP according to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). We measured BP and pulse rate and assessed urinary protein excretion (UPE) before and after changeover. Changeover was associated with decreases in systolic BP and diastolic BP from 158/89 mmHg to 150/86 mmHg ($p<0.01$). Changeover was also associated with a reduction in UPE adjusted to urinary creatinine from 0.35±0.19 g/g creatinine to 0.19±0.37 g/g creatinine ($p=0.0271$) in patients who had high urinary protein levels prior to changeover without significant decreases in BP ($p=0.0184$). According to multiple regression analysis, higher UPE ($p<0.0001$) and a lower glomerular filtration rate (GFR) ($p=0.0011$) prior to changeover were independently correlated with reduction in UPE. Our results suggest that the maximum dose of valsartan is more effective than the maximum dose of candesartan for reducing BP and proteinuria. (*Hypertens Res* 2007; 30: 1187–1192)

***Key Words*: valsartan, high dosage, changeover, Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004), urinary protein excretion**

Introduction

Chronic kidney disease (CKD) has received considerable attention in the management of hypertension (*1*) and is an independent risk factor for cardiovascular disease in patients with hypertension (*2*). Proteinuria is one of the clinical parameters for diagnosing renal damage, especially glomerular hypertension, and is a risk factor and predictor for cardiovascular events (*3*). Reducing glomerular pressure is a principal strategy for reducing proteinuria in hypertensive patients (*4*). To decrease glomerular pressure, blood pressure (BP) must be lowered, and arteriolar resistance in efferent arterioles must be reduced (*5*, *6*). Angiotensin II type 1 receptors are localized to afferent and efferent arterioles (*7*), and angiotensin II receptor blockers (ARBs) (*8*) and angiotensin-converting enzyme inhibitors (ACEIs) (*9*) have reduced proteinuria in several multicenter randomized clinical trials. Based on these results, ARBs and ACEIs are first-choice drugs for managing hypertensive patients with CKD, accord-

From the [1)]Department of Geriatric Medicine, Osaka University Graduate School of Medicine, Suita, Japan.

Address for Reprints: Hiromi Rakugi, M.D., Ph.D., Department of Geriatric Medicine, Osaka University Graduate School of Medicine, 2–2 Yamadaoka, Suita 565–0871, Japan. E-mail: rakugi@geriat.med.osaka-u.ac.jp

Received May 2, 2007; Accepted in revised form July 8, 2007.

ing to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004), and the recommended BP for such patients is lower than that for hypertensive patients with no complications or that for elderly hypertensive patients.

Because we hypothesize that hypertensive patients with CKD would benefit from treatment with an ARB that sufficiently reduces BP, based on meta-analyses (*10*), and the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA2) multicenter clinical trial (*11*), the initial, standard, and maximum doses of ARBs in Japan are under government regulation. Candesartan and valsartan are frequently used ARBs and have demonstrated clinical efficacy at doses of 12 mg/day (*12*) and 160 mg/day (*10*), respectively. The large Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) clinical trial (*13*) revealed that 32 mg/day candesartan reduced mortality and morbidity in patients with chronic heart failure. The Valsartan Heart Failure Trial (Val-HeFT) (*14*) and Valsartan in Acute Myocardial Infarction Trial (VALIANT) (*15*) trials revealed that 320 mg/day valsartan had beneficial effects on prognosis in chronic heart failure and ischemic heart disease. The permitted maximum doses of candesartan and valsartan are low compared to the doses used in those clinical trials. Although higher doses of those ARBs may have clinical benefits in hypertensive patients, the BP-lowering and renal-protective effects of the permitted maximum doses of ARBs in Japan have not been compared. In the present study, the High Dose of ARB (HARB) study, we evaluated BP and urinary protein excretion (UPE) in hypertensive patients who were switched from the maximum permitted dose of candesartan to the maximum permitted dose of valsartan.

Table 1. Patient Characteristics

	Before changeover	After changeover	*p* value
Male/female	32/23		
Age (years)	66.0±11.7		
Diabetes (*n* (%))	18 (33)		
Hyperlipidemia (*n* (%))	28 (51)		
Number taking antihypertensive drugs	2.2±1.0		
Candesartan onlys (*n* (%))	12 (22)		
+ACE inhibitor	7 (13)		
+β-Blockers (*n* (%))	7 (13)		
+CCBs (*n* (%))	41 (75)		
+Diuretics (*n* (%))	8 (15)		
+α-Blockers (*n* (%))	3 (5)		
TC (mg/dL)	207±28	206±22	n.s.
TG (mg/dL)	157±106	143±94	n.s.
HDL-C (mg/dL)	55±15	57±14	n.s.
UA (mg/dL)	5.6±1.2	5.7±1.5	n.s.
Creatinine (mg/dL)	1.0±0.6	1.0±0.6	n.s.
AST (IU/L)	24±11	27±12	n.s.
ALT (IU/L)	25±21	28±22	n.s.
γ-GTP (U/L)	41±40	53±58	n.s.
FBG (mg/dL)	112±22	119±38	n.s.

ACE, angiotensin converting enzyme; CCBs, calcium channel blockers; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; UA, uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyltranspeptidase; FBG, fasting blood glucose; n.s., not significant.

Methods

Study Population and Protocol

Sixty hypertensive outpatients at Osaka University Hospital who had been receiving 12 mg candesartan/day for at least 3 months were recruited for the study. At the onset of the study, the patients had not achieved the JSH 2004–recommended optimal BP. JSH 2004 defines optimal BP for the management of hypertensive patients with diabetes or chronic kidney disease as <130/80 mmHg; of patients <65 years of age and without major complications as <130/85 mmHg; of elderly patients as <140/90 mmHg; and of patients with proteinuria or >1.0 g/day UPE as <125/75 mmHg. Patients who had suffered a stroke or cardiovascular event during the previous year; had congestive heart failure of grade 2 or higher, according to the New York Heart Association scale; and/or had >3.0 mg/dL of serum creatinine were excluded from the study. Use of other antihypertensive drugs was permitted, and the doses of those drugs were not changed during the study. Our protocol was approved by the hospital ethics committee, and informed consent was obtained from all patients 2 months prior to switching from candesartan to valsartan (*i.e.*, changeover). Three patients whose average BP was lower than optimal at changeover were excluded. Thus, at changeover, 57 hypertensive patients were switched from 12 mg/day candesartan to 160 mg/day valsartan and other antihypertensive drugs were not modified. Two patients left the study due to headache, leaving 55 hypertensive patients for analysis.

BP and Renal Function Measurements

A total of five BP and pulse rate (PR) measurements were obtained for each patient during hospital visits at −1 month and −2 months before changeover, at changeover, and at +1 month and +2 months after changeover. Two measurements were taken while the patient was seated after 10 min of rest using a BP-103iII (Nippon Colin Co., Ltd., Tokyo, Japan). The averages of the two BP and PR measurements were automatically calculated, recorded, and used for analysis. All subjects took candesartan or valsartan on the mornings of the hospital visits −2 months before changeover, at changeover, and +1 month after changeover. Patients did not take cande-

Table 2. Blood Pressure and Pulse Rate at Each Visit

	−2 months	−1 month	Changeover	+1 month	+2 months
SBP (mmHg)	156±17	156±19	159±20	149±20**,##,$$$	151±20*,#,$$
DBP (mmHg)	90±11	88±13	90±11	86±11*,$$$	86±10*,$$
MBP (mmHg)	112±12	111±14	113±13	107±12*,###,$$	108±13#,$
PP (mmHg)	66±14	68±14	68±15	63±15**,#,$$$	64±16*,$$
PR (bpm)	78±15	76±13	76±12	76±12	76±12

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; PR, pulse rate; bpm, beats per minute. *$p<0.05$, **$p<0.01$, ***$p<0.001$ *vs*. −2 months; #$p<0.05$, ##$p<0.01$, ###$p<0.001$ *vs*. −1 month; $$p<0.05$, $$$p<0.01$, $$$$p<0.001$ *vs*. changeover.

sartan or valsartan on the mornings of hospital visits −1 month before changeover and +2 months after changeover.

To evaluate the effects of changeover on renal function, we measured fasting levels of serum and urinary creatinine and urinary protein −1 month prior to changeover and +2 months after changeover. We calculated UPE adjusted by urinary creatinine and estimated the glomerular filtration rate (GFR) using the modified Modification of Diet in Renal Disease (MDRD) equation (*16*):

$$\text{GFR (mL/min/1.73 m}^2) = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.741 \ (\times 0.742 \text{ if female}).$$

Statistical Analysis

Data were analyzed with commercially available statistical software (JMP version 5.1.1; SAS Institute Inc., Cary, USA). Differences in results between treatment with candesartan and valsartan were assessed using paired *t*-tests. Differences in low and high UPE were assessed by one-factor ANOVA and Fisher's test. We used multiple regression analysis to evaluate influential factors for reducing UPE. *p* values <0.05 were considered statistically significant.

Results

Results are expressed as the means±SD.

Patient Characteristics

Table 1 summarizes the characteristics of the 55 patients who completed the changeover study. Twenty-two patients took only candesartan, and 43 took candesartan in combination with additional antihypertensive drugs, such as calcium channel blockers ($n=41$, 75%), angiotensin converting enzyme inhibitors ($n=7$, 13%), β-blockers ($n=7$, 13%), diuretics ($n=8$, 15%), and α-blockers ($n=3$, 5%). The common risk factors and liver functions described in Table 1 were not modified during the study.

BP and PR before and after Changeover

BP and PR did not differ between administration of candesartan (measured at −2 months, −1 month, and at changeover) and valsartan (+1 month, +2 months) (Table 2). Systolic BP (SBP), diastolic BP (DBP), and mean BP were significantly lower when patients took valsartan. To compare BP and PR before and after changeover, we used the average of the −1 month and changeover measurements as the before-changeover BP and PR (*i.e.*, the candesartan BP and PR) and the average of the +1 and +2 month measurements as the after-changeover BP and PR (*i.e.*, the valsartan BP and PR). As shown in Table 3, the after-changeover SBP (149.8±10.9 mmHg) and DBP (86.4±9.6 mmHg) were significantly reduced compared to the before changeover values (SBP, 157.5±19.2, $p=0.0001$; DBP, 89.4±10.9 mmHg, $p=0.0063$). The after-changeover PR (76.1±11.5 bpm) was not significantly different from the before-changeover PR (76.3±12.0 bpm, $p=0.8425$). The after-changeover pulse pressure (63.5±14.6 mmHg) and mean BP (107.5±11.1 mmHg) were significantly reduced compared to the before-changeover values (pulse pressure, 68.1±13.8, $p=0.0006$; mean BP, 112.1±12.6 mmHg, $p=0.0005$). By a histogram analysis according to SBP reduction, 15 (27%) patients had increased SBP, 18 (33%) had <10 mmHg decreases in SBP, 12 (22%) had 10–20 mmHg decreases in SBP, and 10 (18%) had >20 mmHg decreases in SBP after changeover (data not shown). We also evaluated the percentage of patients achieving optimal BP after changeover, as recommended by the JSH 2004 (data not shown). Overall, 10/55 (18%) patients achieved optimal BP, including 1/21 (4.8%) patients with diabetes (<130/80 mmHg); 3/9 (33%) patients <65 years of age and without major complications (<130/85 mmHg); and 6/18 (33%) elderly patients (<140/90 mmHg). None of the 7 (0%) patients with proteinuria or >1.0 g/day UPE (<125/75 mmHg) achieved optimal BP.

Renal Function before and after Changeover

We evaluated the effects of changeover on renal function by analyzing UPE and estimated GFR (Table 3). The after-changeover UPE (0.19±0.37 g/g creatinine) was significantly

Table 3. Blood Pressure, Pulse Rate and Renal Function before and after Changeover

	Before changeover	After changeover	*p* value
SBP (mmHg)			
Total	157.5±19.2	149.8±10.9	0.0001
High UPE	153.0±19.8	147.8±18.4	0.0809
Low UPE	159.4±18.9	150.7±18.0	0.0007
DBP (mmHg)			
Total	89.4±10.9	86.4±9.6	0.0063
High UPE	89.5±12.6	87.9±8.9	0.2947
Low UPE	89.3±10.3	86.0±10.0	0.0113
MBP (mmHg)	112.1±12.6	107.5±11.1	0.0005
PP (mmHg)	68.1±13.8	63.5±14.6	0.0006
PR (bpm)	76.3±12.0	76.1±11.5	0.8425
eGFR (mL/min/1.73 m^2)	58.8±20.2	57.4±18.0	0.2798
UPE (g/g creatinine)			
Total	0.35±0.19	0.19±0.37	0.0271
High UPE	1.16±1.11	0.60±0.48	0.0184
Low UPE	0.02±0.04	0.02±0.09	0.6472
UAE (mg/g creatinine)	26.0±47.0	14.7±28.0	0.0543

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; PR, pulse rate; bpm, beats per minute; eGFR, estimated glomerular infiltration; UPE, urinary protein excretion; UAE, urinary albumin excretion. High UPE: patients with UPE ≥0.2 g/g creatinine (n=16); Low UPE: patients with UPE <0.2 g/g creatinine (n=39).

reduced compared to the before-changeover UPE (0.35±0.19 g/g creatinine, p=0.0271). There was no significant difference in estimated GFR between before (58.8±20.2 mL/min/1.73 m^2) and after (57.4±18.0 mL/min/1.73 m^2) changeover. We also measured urinary albumin excretion (UAE) for 44 patients (80% of the total group). UAE was reduced somewhat after changeover, but not significantly so (p=0.0543).

Influences of UPE before Changeover

To study the influence of UPE on the changeover effects, we analyzed BP changes in patients with UPE ≥0.2 g/g creatinine (n=16) compared to those with UPE <0.2 g/g creatinine (n=39) (Table 3). In patients with low UPE, the after-changeover SBP (159.4±18.9 mmHg) and DBP (89.3±10.3 mmHg) were significantly reduced compared to the before-changeover values (SBP, 150.7±18.0 mmHg, p=0.0007; DBP, 86.0±10.0 mmHg, p=0.0113). However, in patients with high UPE, the after-changeover SBP (147.8±18.4 mmHg) and DBP (87.9±8.9 mmHg) were reduced by a non-significant amount compared to the before-changeover values (SBP, 153.0±19.8, p=0.0809; DBP, 89.5±12.6 mmHg, p=0.2947). UPE was significantly reduced after changeover (0.60±0.48 g/g creatinine) only in patients with high before-changeover UPE (1.16±1.11 g/g creatinine; p=0.0184).

Table 4. Multiple Regression Analysis for Reduction of Urinary Protein Excretion

	F	*p* value
Age	0.0002	0.9892
Sex (male)	3.9708	0.0535
Diabetes	0.2628	0.6112
Dyslipidemia	1.2837	0.2643
Numbers of drugs	3.2092	0.0812
PreSBP	0.9716	0.3305
PreDBP	0.6430	0.4276
PrePR	0.6076	0.2682
SBP reduction	0.1995	0.6576
DBP reduction	0.1703	0.6822
PR reduction	0.0914	0.7640
PreGFR (lower)	12.755	0.0010
PreUPE	279.50	<0.0001

PreSBP, systolic blood pressure before changeover; PreDBP, diastolic blood pressure before changeover; PrePR, pulse rate before changeover; SBP reduction, difference of systolic blood pressure before and after changeover; DBP reduction, difference of diastolic blood pressure before and after changeover; PR reduction, difference of pulse rate before and after changeover; PreGFR, estimated glomerular filtration rate before changeover; PreUPE, urinary protein excretion before changeover.

UPE Reduction and Other Factors

To clarify the influence of other factors on UPE reduction, we analyzed the correlation between UPE and other variables with a multiple regression analysis (Table 4). Higher UPE level before changeover (p<0.0001) and lower estimated GFR before changeover (p=0.0010) were correlated with a significant reduction in UPE after changeover. In contrast, UPE reduction was not correlated with SBP before changeover (*i.e.*, during candesartan treatment), and UPE was not correlated with the SBP reduction between treatment with candesartan and valsartan.

Discussion

In the present study, we first demonstrated that 160 mg/day valsartan resulted in an enhanced reduction of SBP (7.7 mmHg) and DBP (3.0 mmHg) compared to 12 mg/day candesartan. Although no direct comparison has been made of the two maximum dosages of candesartan and valsartan, 80 mg/day valsartan has been shown to be as effective as 8 mg/day candesartan in sufficiently lowering BP as the standard doses (*17*). Based on that evidence, we estimate that the BP-lowering effect of 160 mg valsartan would be equal to that of 16 mg candesartan, which would be greater than that of 12 mg candesartan; however, we have no direct evidence of an advantage of valsartan over candesartan. Several current guidelines for managing essential hypertension (*18*, *19*) and many large

multicenter trials (*12*, *20*) have suggested that strict reduction of BP is the most important factor for preventing cardiovascular mortality and morbidity in hypertensive patients. Patients included in the present study were hypertensive and could not achieve optimal BP with antihypertensive treatment, such as 12 mg/day candesartan. More than 70% of the study participants had reduced BP after the changeover to 160 mg/day valsartan, and 18% achieved optimal BP as defined by the JSH 2004.

Our results also indicate that 160 mg/day valsartan was more effective than 12 mg/day candesartan for reducing UPE. To reduce glomerular pressure, strict reduction of systemic BP and efferent arteriolar dilatation are important, and the MDRD study revealed that reduction of mean BP was useful for decreasing UPE (*21*). Clinical data suggest that high doses of the ARBs candesartan (96 mg/day) (*22*) and irbesartan (640 mg/day (*23*) and 300 mg/day (*10*)) reduce UPE more effectively than low doses of the same drugs. According to these findings, the UPE reduction observed in the present study was not a specific effect of valsartan but rather an effect of high doses of ARBs in general. In evaluating other factors that may have contributed to UPE reduction, we found that overall BP reduction did not influence UPE reduction. Rather, higher UPE levels and lower estimated GFR before changeover were independently correlated with UPE reduction. Although we could not verify efferent arteriolar dilation, dilation may have contributed to the observed UPE reduction, as the reduction of systemic BP and efferent arterioles leads to a reduction in glomerular pressure. This suggests that 160 mg/day valsartan reduces UPE in patients with high levels of UPE, independent of BP reduction, possibly by efferent arteriolar dilation.

In the present study, the maximum permitted dose of valsartan produced a greater reduction in BP and UPE than the maximum allowable dose of candesartan. Moreover, a high dose of valsartan reduced UPE in patients who had higher UPE and lower estimated GFR before changeover. These findings do not negate the efficacy of candesartan in preventing cardiovascular events and total mortality in many multicenter trials (*13*, *24*, *25*). Although government regulations prevented us from comparing 16 mg/day candesartan with 160 mg/day valsartan, increasing the candesartan dosage to 16 mg/day might result in strong and stable BP and a positive prognosis. Together these data suggest that a high dose of valsartan is beneficial for managing hypertensive patients, especially those with impaired renal function.

Study Limitations

The present study had several limitations. The most important of these was the protocol, since only one changeover was performed to compare two antihypertensive drugs. A crossover or randomized study is necessary to properly compare candesartan and valsartan treatment. From an ethical standpoint, we could not switch patients who achieved optimal BP with 160 mg valsartan back to 12 mg candesartan. In the present study, subjects were preferentially selected for poorly controlled hypertension and candesartan treatment. Thus, the study patients did not respond well to candesartan.

Acknowledgements

We are grateful to Ms. Kazuko Iwasa and Ms. Eriko Nagata for their secretarial assistance.

References

1. Peralta CA, Kurella M, Lo JC, Chertow GM: The metabolic syndrome and chronic kidney disease. *Curr Opin Nephrol Hypertens* 2006; **15**: 361–365.
2. Segura J, Campo C, Gil P, *et al*: Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. *J Am Soc Nephrol* 2004; **15**: 1616–1622.
3. De Leeuw PW, Thijs L, Birkenhager WH, *et al*: Prognostic significance of renal function in elderly patients with isolated systolic hypertension: results from the Syst-Eur trial. *J Am Soc Nephrol* 2002; **13**: 2213–2222.
4. Marin R, Gorostidi M, Fernandez-Vega F, Alvarez-Navascues R: Systemic and glomerular hypertension and progression of chronic renal disease: the dilemma of nephrosclerosis. *Kidney Int Suppl* 2005; (99**)**: S52–S56.
5. Hayashi K, Wakino S, Homma K, Sugano N, Saruta T: Pathophysiological significance of T-type Ca^{2+} channels: role of T-type Ca^{2+} channels in renal microcirculation. *J Pharmacol Sci* 2005; **99**: 221–227.
6. Wang T, Takabatake T: Effects of vasopeptidase inhibition on renal function and tubuloglomerular feedback in spontaneously hypertensive rats. *Hypertens Res* 2005; **28**: 611–618.
7. Caldicott WJ, Taub KJ, Margulies SS, Hollenberg NK: Angiotensin receptors in glomeruli differ from those in renal arterioles. *Kidney Int* 1981; **19**: 687–693.
8. Brenner BM, Cooper ME, de Zeeuw D, *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.
9. Ruggenenti P, Perna A, Loriga G, *et al*: Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; **365**: 939–946.
10. Julius S, Kjeldsen SE, Weber M, *et al*: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363**: 2022–2031.
11. Parving HH, Lehnert H, Brochner-Mortensen J, *et al*: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345**: 870–878.
12. Fujikawa K, Hasebe N, Kikuchi K: Cost-effectiveness analysis of hypertension treatment: controlled release nifedipine and candesartan low-dose combination therapy in patients with essential hypertension—the Nifedipine and Candesartan Combination (NICE-Combi) Study. *Hypertens Res*

2005; **28**: 585–591.
13. Pfeffer MA, Swedberg K, Granger CB, *et al*: Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; **362**: 759–766.
14. Cohn JN, Tognoni G: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; **345**: 1667–1675.
15. Pfeffer MA, McMurray JJ, Velazquez EJ, *et al*: Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349**: 1893–1906.
16. Imai E, Horio M, Nitta K, *et al*: Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11**: 41–50.
17. Fogari R, Mugellini A, Zoppi A, *et al*: A double-blind crossover study of the antihypertensive efficacy of angiotensin II–receptor antagonists and their activationof the renin-angiotensin system. *Curr Ther Res Clin Exp* 2000; **61**: 669–679.
18. Guidelines Committee: 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011–1053.
19. Chobanian AV, Bakris GL, Black HR, *et al*: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
20. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *vs* diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981–2997.
21. Peterson JC, Adler S, Burkart JM, *et al*: Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995; **123**: 754–762.
22. Weinberg M, Weinberg A, Cord R, Zappe D: The effect of high-dose angiotensin II receptor blockade beyond maximal recommended doses in reducing urinary protein excretion. *JRAAS* 2001; **2**: S196–S198.
23. Hollenberg NK, Parving HH, Viberti G, Remuzzi G: The Diovan Reduction of Proteinuiria (DROP) Study: albuminuria response to high-doses of valsartan in type 2 diabetes mellitus. *Circulation* 2006; **114**: II-61.
24. Lithell H, Hansson L, Skoog I, *et al*: The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens* 2003; **21**: 875–886.
25. Suzuki H, Kanno Y: Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005; **28**: 307–314.