Original Article

Renal and Vascular Protective Effects of Telmisartan in Patients with Essential Hypertension

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It is known that the angiotensin receptor blockers (ARBs) have organ protective effects in patients with heart failure or renal impairment. Several studies have revealed that the ARB telmisartan has an organ protective effect, but there have been few studies directly comparing the effects of telmisartan and calcium antagonists, since most clinical studies on telmisartan have been conducted in treated patients or patients on combination therapy. The present study was conducted to compare the renal and vascular protective effects of telmisartan monotherapy and calcium antagonist monotherapy in untreated hypertensive patients. Forty-three patients with untreated essential hypertension were randomized to receive amlodipine (*n*=22) or telmisartan (*n*=21), which were respectively administered at doses of 5 mg and 40 mg once daily in the morning for 24 weeks. The patients were examined before and after treatment to assess changes of renal function, flow-mediated dilation (a parameter of vascular endothelial function), and brachial-ankle pulse wave velocity (baPWV; a parameter of arteriosclerosis). Before treatment, there were no significant differences in these parameters between groups. The decreases of urinary albumin excretion and baPWV, and the increase of flow-mediated dilation were significantly greater in the telmisartan group than the amlodipine group, while the antihypertensive effects were not significantly different between the two groups. In conclusion, these results suggest that telmisartan is more effective at protecting renal function and vascular endothelial function, and at improving arteriosclerosis than the calcium channel blocker in patients with essential hypertension. (*Hypertens Res* 2006; 29: 567–572)

***Key Words*: essential hypertension, antihypertensive drug, renal dysfunction, endothelial dysfunction, arteriosclerosis**

Introduction

Since antihypertensive therapy has the objective of preventing cardiovascular complications, the organ protective effect of antihypertensive drugs is very important. It has been shown by many clinical studies that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are effective for protecting against hypertension-related organ damages (*1*). Angiotensin II not only causes target organ damage indirectly due to its hypertensive action, but also directly promotes myocardial and vascular hypertrophy as well as renal dysfunction (*2*). Therefore, it is reasonable to presume that ACE inhibitors and ARBs will protect target organs without the benefit of an antihypertensive action.

Telmisartan is an ARB that exhibits a strong and sustained antihypertensive effect (*3*) over 24 h and is secreted into the bile. There are scattered reports indicating that telmisartan has an organ protective effect, but there have been few studies directly comparing telmisartan and calcium antagonists, since most clinical studies on telmisartan have been conducted in treated patients or patients on combination therapy. There-

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Table 1. Characteristics of the Subjects

	A group (n=22)	T group (n=21)
Age (years)	58±2	56±2
Sex (male/female)	9/13	9/12
Family history of hypertension (yes/no)	13/9	15/6
History of hypertension (years)	5±1	7±1
Smoking (yes/no)	6/16	5/16
Body mass index (kg/m^2)	24.0±0.7	24.8±0.9
Fasting glucose (mg/dl)	112±5	114±7
HbA1c (%)	5.3±0.2	5.5±0.4

Average values are expressed as mean±SEM. A, amlodipine; T, telmisartan.

Table 2. Baseline Data

	A group (n=22)	T group (n=21)
Systolic blood pressure (mmHg)	163±3	162±5
Diastolic blood pressure (mmHg)	93±1	95±4
Heart rate (bpm)	75±2	78±3
Blood urea nitrogen (mg/dl)	20.3±2.8	19.8±2.6
Serum creatinine (mg/dl)	0.6±0.4	0.6±0.2
Urinary albumin excretion (mg/day)	38.4±4.5	32.3±3.7
Urinary protein excretion (mg/day)	188.4±14.1	165.7±16.2
Creatinine clearance (ml/min)	94.9±3.7	90.3±5.7
%FMD (%)	4.2±0.7	2.7±0.8
%NTG (%)	9.4±1.1	10.2±1.1
baPWV (cm/s)	1,611±56	1,699±70

Values are expressed as the mean±SEM. A, amlodipine; T, telmisartan; FMD, flow-mediated dilatation; NTG, nitroglycerin; baPWV, brachial-ankle pulse wave velocity.

fore, the present study was conducted to compare the renal and vascular protecting effects of telmisartan monotherapy and calcium antagonist monotherapy in untreated hypertensive patients.

Methods

Study Subjects

The subjects were selected from among patients with untreated essential hypertension who visited our center between April 2003 and March 2004, excluding patients who had suffered from ischemic heart disease, acute coronary syndrome, congestive heart failure (New York Heart Association class II or greater) or stroke within 6 months of study initiation, had impaired renal function (serum creatinine ≥1.5 mg/dl), or were pregnant. The subjects were randomly assigned to the amlodipine group or telmisartan group, and the drugs were respectively administered to the 2 groups at doses of 5 and 40 mg, once daily in the morning for 24 weeks.

Blood Pressure/Heart Rate

Blood pressure (BP) and heart rate (HR) were measured at baseline, and at 8 weeks, 16 weeks, and 24 weeks of treatment. Parameters to assess the protective effect of the drugs were measured at baseline and after 24 weeks of treatment. Outpatient BP measurements were obtained twice in the sitting position after 2 to 3 min of rest at 2 to 5 h after administration of the test drug, and the mean of 2 values was determined.

Renal Function

Creatinine clearance (CCr), urinary protein excretion, and urinary albumin excretion were determined using 24-h urine samples as parameters of the renal protective effect of the study drugs.

Vasodilation

Endothelium-dependent and -independent dilation were assessed as parameters of vasodilation according to the guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery (*4*). Using high-resolution ultrasound (Logiq 500; GE Yokogawa Medical Systems, Tokyo, Japan) with a 7.5-MHz linear array transducer, diameter measurements of the brachial artery were taken after supine rest for at least 5 min, after cuff deflation completing suprasystolic compression (30 mmHg above systolic pressure) of the upper arm for 2 min and after sublingual application of 0.3 mg nitroglycerin. A stereotactical arm was used for optimal transducer positioning on the brachial artery proximal to the bifurcation of the radial and ulnar arteries. The longitudinal image of the artery was recorded at baseline, continuously from 30 s before to 2 min after cuff deflation, and for 5 min after nitroglycerin administration. The diameter of the artery was measured from one media-adventitia interface to the other. Vasodilation was then evaluated from the change of artery diameter after release of occlusion (%FMD) and the change of artery diameter after administration of nitroglycerin (%NTG), respectively.

Arteriosclerosis

The brachial-ankle pulse wave velocity (baPWV) was measured bilaterally using a volume-plethysmographic apparatus PWV/ABI device (Colin Medical Technology Company, Komaki, Japan) in accordance with a methodology described elsewhere (*5*), and the mean value was calculated as a parameter of arteriosclerosis.

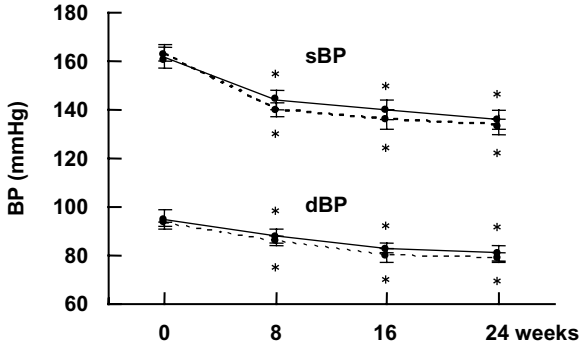

Fig. 1. *Time course of blood pressure changes by treatment with amlodipine or telmisartan. Dotted line, amlodipine group; solid line, telmisartan group. BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure.* n = *22 for the amlodipine group and* n = *21 for the telmisartan group.* *p < *0.01 compared with before treatment.*

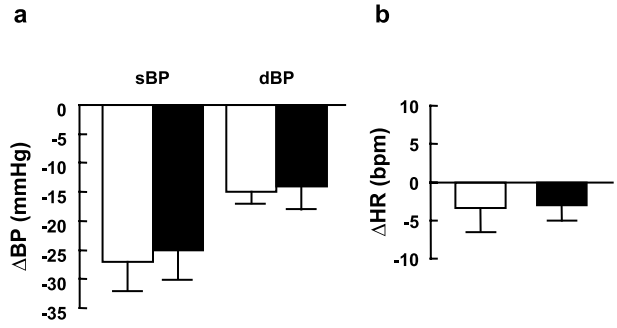

Fig. 2. *Changes of blood pressure (a) and heart rate (b) 24 weeks after treatment with amlodipine or telmisartan. Open bars, amlodipine group; closed bars, telmisartan group. BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate.* n = *22 for the amlodipine group and* n = *21 for the telmisartan group.*

Statistics

Data were analyzed by the paired or unpaired Student's *t*-test to detect significant differences between before and after treatment or between the groups. Values are shown as the means±SEM, and differences were considered statistically significant at $p<0.05$.

This study was approved by the Ethical Committee of Ohmihachiman City Hospital. Before enrollment, the subjects were given complete information about the study and their consent was obtained.

Results

The subjects comprised 43 patients (18 men and 25 women), of whom 22 were assigned to the amlodipine group and 21 to the telmisartan group. There were no differences of baseline characteristics, such as sex, age, or biochemical parameters, between the 2 groups (Table 1). No subjects changed their smoking status during the study period. Body mass index (23.9±0.7 and 24.7±0.8 kg/m^2 in the amlodipine and telmisartan group, respectively), fasting glucose (110±6 and 112±6 mg/dl), and hemoglobin A1c (5.3±0.2 and 5.4±0.3%) were not significantly changed by the treatment for 24 weeks.

BP/HR

There was no difference in the baseline BP between the 2 groups (Table 2). After the start of treatment, BP showed a similar gradual and significant decrease with time in both groups (Fig. 1). After 24 weeks of treatment, BP was 137±4/79±2 mmHg in the amlodipine group and 136±4/81±3 mmHg in the telmisartan group, and there was no difference in the extent of change between the 2 groups (Fig. 2a). There was no difference in the baseline HR between the 2 groups (Table 2), HR was not significantly changed in either group, and there was no difference in the change of HR between the 2 groups (Fig. 2b).

Renal Function

There were no differences of the baseline CCr, urinary protein excretion, or urinary albumin excretion between the 2 groups (Table 2). Neither CCr (105.1±4.0 ml/min in the amlodipine group and 111.1±4.2 ml/min in the telmisartan group after treatment) nor urinary protein excretion (172.4±14.5 mg/day in the amlodipine group and 141.7±16.6 mg/day in the telmisartan group) significantly changed in either group, and the changes were not significantly different between groups (Fig. 3). Although urinary albumin excretion also showed no significant change in the amlodipine group, it was significantly decreased in the telmisartan group (43.5±5.0 mg/day in the amlodipine group and 20.1±4.6 mg/day in the telmisartan group after treatment) (Fig. 4a). Urinary albumin excretion showed a significantly greater decline in the telmisartan group than in the amlodipine group (Fig. 4b).

Vasodilation

There were no differences in baseline %FMD or %NTG between the 2 groups (Table 2). %FMD showed no significant change after treatment with amlodipine (3.1±0.9% after treatment), but treatment with telmisartan caused a significant increase (5.7±1.0% after treatment, $p<0.05$) (Fig. 5a). The telmisartan group showed a significantly greater increase of %FMD than the amlodipine group (Fig. 5b). On the other hand, %NTG showed no significant changes in either group (post-treatment %NTG was 9.7±1.4% in the amlodipine group and 12.3±1.7% in the telmisartan group). There was no difference in the extent of change between the 2 groups.

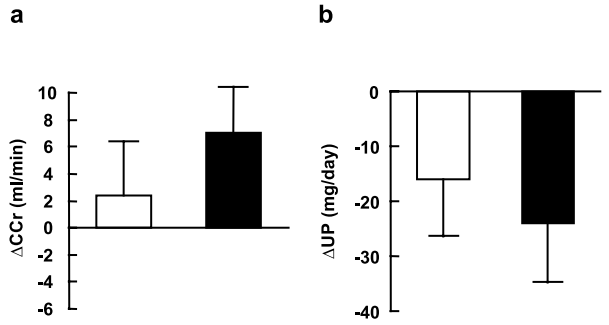

Fig. 3. *Effect of amlodipine and telmisartan on creatinine clearance (a) and urinary protein excretion (b). Open bars, amlodipine group; closed bars, telmisartan group. CCr, creatinine clearance; UP, urinary protein excretion.* n = *22 for the amlodipine group and* n = *21 for the telmisartan group.*

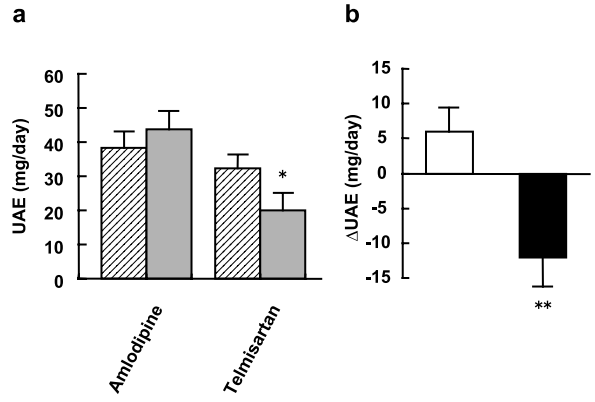

Fig. 4. *Effect of amlodipine and telmisartan on urinary albumin excretion. Hatched bars, before treatment; gray bars, after treatment; open bar, amlodipine group; closed bar, telmisartan group. UAE, urinary albumin excretion.* n = *22 for the amlodipine group and* n = *21 for the telmisartan group.* *p < *0.05 compared with before treatment,* **p < *0.05 compared with amlodipine.*

Arteriosclerosis

There was no difference in baseline baPWV between the 2 groups (Table 2). Although baPWV showed a significant decrease after treatment in both groups (1,540±61 cm/s in the amlodipine group and 1,432±62 cm/s in the telmisartan group) (Fig. 6a), the change was significantly greater in the telmisartan group compared with the amlodipine group (Fig. 6b).

Discussion

Since antihypertensive therapy has the objective of preventing the development of cardiovascular complications, the organ protective effect of antihypertensive agents is very important. This study was undertaken to compare the antihypertensive effects and renal and vascular protective effects of the ARB telmisartan and the calcium antagonist amlodipine, which both exhibit a long-acting profile (*3*, *6*). In this study, the test drugs were administered as monotherapy to 2 groups of patients with untreated essential hypertension, unlike in many other large-scale studies that have been conducted in treated patients or patients on combination therapy. Therefore, the present study may be considered to allow direct comparison of the renal and vascular protective effect between this ARB and calcium antagonist.

In this study, amlodipine and telmisartan exhibited a similar antihypertensive effect. These findings are in agreement with another report (*6*) that compared amlodipine and telmisartan by ambulatory BP monitoring. Despite both drugs having a similar antihypertensive effect, there was a clearly different renal and vascular protective effect.

Urinary albumin excretion (measured as a parameter of the renoprotective effect) was clearly decreased in the telmisartan group, while the amlodipine group showed no change. Like the present study, many previous studies have also indicated that ARBs exhibit a renoprotective effect. The RENAAL study showed that the ARB losartan could prevent diabetic nephropathy from progressing to renal failure and decrease the initiation of dialysis (*7*). The JLIGHT study revealed that losartan causes a significantly greater decrease of urinary protein excretion than amlodipine (*8*). The decrease of urinary protein excretion observed after treatment with telmisartan may also be considered as evidence of the renoprotective effect of ARBs. Our study was small, being conducted in 2 groups of about 20 subjects each, but the difference between the telmisartan and amlodipine groups obtained statistical significance. The reason why amlodipine did not show a decrease, or rather, showed a slight insignificant increase, in urinary albumin excretion remains unclear. However, this finding may have been due to the inadequate BP reduction in this study; that is, the BP was 136/81 mmHg 24 weeks after monotherapy with amlodipine. In contrast, telmisartan achieved a significant reduction of urinary albumin excretion, although this monotherapy also failed to achieve an adequate BP reduction (the BP by telmisartan was 137/79 mmHg 24 weeks after treatment). These results suggest that telmisartan has a powerful renoprotective effect. The lowering of urinary albumin levels seems to slow the rate of aggravation of renal dysfunction. These findings also suggest that ARBs such as telmisartan are more suitable than calcium antagonists as antihypertensive therapy for patients with nephropathy.

Neither drugs changed %NTG, a parameter of vascular endothelium-independent dilation. On the other hand, telmisartan clearly improved %FMD, a parameter of vascular endothelium-dependent dilation, while amlodipine showed no effect on %FMD. The vascular endothelium releases various vasoactive substances that exhibit a vasoprotective effect (*9*, *10*). Considering that endothelial damage is known to acti-

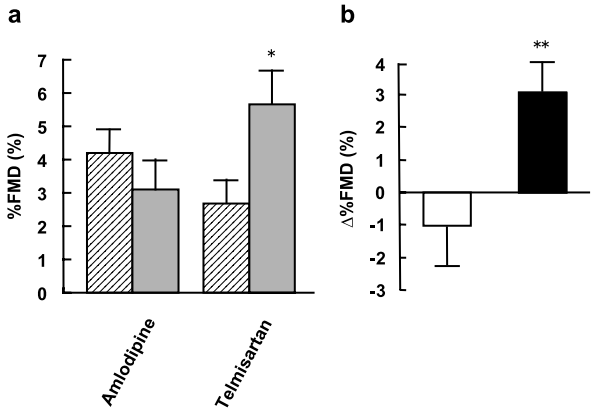

Fig. 5. *Effect of amlodipine and telmisartan on flow-mediated dilatation. Hatched bars, before treatment; gray bars, after treatment; open bar, amlodipine group; closed bar, telmisartan group. FMD, flow-mediated dilatation.* n = *22 for the amlodipine group and* n = *21 for the telmisartan group.* *p < *0.05 compared with before treatment,* **p < *0.01 compared with amlodipine.*

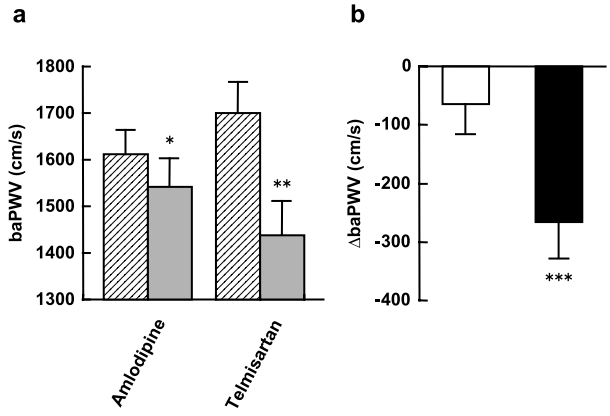

Fig. 6. *Effect of amlodipine and telmisartan on the brachial-ankle pulse wave velocity. Hatched bars, before treatment; gray bars, after treatment; open bar, amlodipine group; closed bar, telmisartan group. baPWV, brachial-ankle pulse wave velocity.* n = *22 for the amlodipine group and* n = *21 for the telmisartan group.* *p < *0.05 and* **p < *0.01 compared with before treatment,* ***p < *0.05 compared with amlodipine.*

vate smooth muscle cells and cause intimal hypertrophy leading to arteriosclerosis (*11*), the effect of telmisartan on the intima is very important. Several lines of evidence indicate that ACE inhibitors and ARBs improve vascular endothelial dysfunction (*12–15*), while calcium channel blockers do not change it (*13–15*). These reports are in agreement with our finding that telmisartan was more effective than amlodipine for improvement of vascular endothelial dysfunction.

Furthermore, telmisartan improved baPWV more markedly than amlodipine. It has already been reported that telmisartan decreases PWV (*16*). Our present study provides new evidence that telmisartan is more effective at preventing arteriosclerosis than calcium antagonists.

In the present study, the ARB telmisartan did not differ from the calcium antagonist amlodipine with regard to antihypertensive effect, but it improved both renal and vascular function to a significantly greater extent. In general, it is possible that changes of smoking status, body mass index, and blood sugar levels may affect renal function, vascular endothelial function, and arteriosclerosis. However, this was not the case in the present study, since the smoking status, body mass index, fasting glucose, and hemoglobin A1c were unchanged during the study period. Whether the present results are due to class effects of ARB or specific to telmisartan also remains to be determined. Renal and vascular protective effects of other ARBs have been reported, although our study was the first to focus on both organ protective effects (*7*, *8*, *12*, *15–17*). Accordingly, we suspect that the renal and vascular protective effects of telmisartan observed in this study are common to all ARBs. However, further studies will be needed to confirm this.

In conclusion, the present study indicated that telmisartan is more effective at protecting renal function and vascular endothelial function, and at improving arteriosclerosis than the calcium channel blocker amlodipine in patients with essential hypertension. Further studies are required to determine the underlying mechanism by which this agent achieves its beneficial effects.

References

1. Suzuki H, Kanno Y, Efficacy of Candesartan on Outcome in Saitama Trial (E-COST) Group: Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005; **28**: 307–314.
2. Morgan T: Renin, angiotensin, sodium and organ damage. *Hypertens Res* 2003; **26**: 349–354.
3. White WB, Lacourciere Y, Davidai G: Effects of the angiotensin II receptor blockers telmisartan *versus* valsartan on the circadian variation of blood pressure: impact on the early morning period. *Am J Hypertens* 2004; **17**: 347–353.
4. Corretti MC, Anderson TJ, Benjamin EJ, *et al*: Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilatation of the brachial artery. *J Am Coll Cardiol* 2002; **39**: 257–265.
5. Motobe K, Tomiyama H, Koji Y, *et al*: Cut-off value of the ankle-brachial pressure index at which the accuracy of brachial-ankle pulse wave velocity measurement is diminished. *Circ J* 2005; **69**: 55–60.
6. Lacourciere Y, Lenis J, Orchard R, *et al*: A comparison of the efficacies and duration of action of the angiotensin II receptor blockers telmisartan and amlodipine. *Blood Press Monit* 1998; **3**: 295–302.
7. Brenner BM, Cooper ME, de Zeeuw D, *et al*, RENAAL Study Investigators: Effects of losartan on renal and cardio-

vascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861–869.
8. Iino Y, Hayashi M, Kawamura T, *et al*, Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) Study Investigators: Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension—a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. *Hypertens Res* 2004; **27**: 21–30.
9. Vanhoutte PM, Mombouli JV: Vascular endothelium: vasoactive mediators. *Prog Cardiovasc Dis* 1996; **39**: 229–238.
10. Luscher TF, Barton M: Biology of the endothelium. *Clin Cardiol* 1997; **20** (11 Suppl 2): II-3–II-10.
11. Clowes AW, Reidy MA, Clowes MM: Kinetics of cellular proliferation after arterial injury. I. Smooth muscle growth in the absence of endothelium. *Lab Invest* 1983; **49**: 327–333.
12. Cheetham C, O'Driscoll G, Stanton K, *et al*: Losartan, an angiotensin type I receptor antagonist, improves conduit vessel endothelial function in type II diabetes. *Clin Sci* (*Lond*) 2001; **100**: 13–17.
13. Higashi Y, Sasaki S, Nakagawa K, *et al*: Effect of the angiotensin-converting enzyme inhibitor imidapril on reactive hyperemia in patients with essential hypertension: relationship between treatment periods and resistance artery endothelial function. *J Am Coll Cardiol* 2001; **37**: 863–870.
14. Munakata M, Aihara A, Nunokawa T, *et al*: The influence of one-year treatment by angiotensin converting enzyme inhibitor on baroreflex sensitivity and flow-mediated vasodilation of the brachial artery in essential hypertension—comparison with calcium channel blockers. *Clin Exp Hypertens* 2003; **25**: 169–181.
15. Anderson TJ, Elstein E, Haber H, *et al*: Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study). *J Am Coll Cardiol* 2000; **35**: 60–66.
16. Uchida H, Nakamura Y, Kaihara 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.
17. Munakata M, Nagasaki A, Nunokawa T, *et al*: Effects of valsartan and nifedipine coat-core on systemic arterial stiffness in hypertensive patients. *Am J Hypertens* 2004; **17**: 1050–1055.