Effects of Telmisartan on Arterial Stiffness Assessed by the Cardio-Ankle Vascular Index in Hypertensive Patients

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Key Words

Albuminuria • Telmisartan • Arterial stiffness • Blood pressure • Cardio-ankle vascular index

Abstract

Background/Aims: This study was conducted to determine the effect of telmisartan on the cardio-ankle vascular index (CAVI), a novel blood pressure (BP)-independent marker for arterial stiffness in hypertensive patients. **Methods:** One hundred consecutive hypertensive patients were randomly assigned either to a group treated with calcium channel blocker (CCB)-based therapy or a group treated with telmisartan-based therapy. Clinical and biological parameters were then measured before and 12 months after the start of this study. **Results:** CAVI, the logarithm of urinary albumin excretion, and BP were reduced significantly after telmisartan-based therapy. The decreases in 24-hour diastolic BP and daytime systolic BP associated with telmisartan-based therapy were significantly greater than those associated with CCB-based therapy. Both therapies significantly and similarly decreased the clinical BP, 24-hour systolic BP, daytime diastolic BP and serum levels of low-density lipoprotein cholesterol. No significant differences in the metabolic parameters were observed between the two therapies. **Conclusion:**

Telmisartan-based therapy had beneficial effects on arterial stiffness assessed by CAVI, albuminuria, 24-hour BP and metabolism compared with CCB-based therapy. Since these markers are known to influence the future risk of cardiovascular events, telmisartan could be a useful drug for hypertensive patients.

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Introduction

Arterial stiffness is a powerful independent marker of vascular target organ damage and an independent prognostic predictor for cardiovascular morbidity and mortality [1]. In addition, arterial stiffness has been implicated as a marker for vasculature aging [2]. Its prevention and control are important in light of the growing number of patients with diabetes and hypertension. Arterial stiffness has been assessed using several methods, including pulse pressure, the augmentation index (AI) and pulse wave velocity (PWV). These parameters can easily be measured in the clinic in a matter of minutes using relatively inexpensive technology and a simple reproducible method. Each of these simple measures of arterial aging is correlated with the risk of cardiac, cerebral and vascu-

lar events [1, 3, 4]. However, these measures cannot be used to determine whether the improvement in arterial stiffness is caused by a blood pressure (BP)-dependent effect or a BP-independent mechanism. The cardio-ankle vascular index (CAVI) is a new marker of arterial stiffness that is calculated from the PWV and adjusted according to the BP value [5]. CAVI has been shown to be closely correlated with other markers contributing to arterial stiffness, such as the carotid intima-media thickness (IMT) [6].

Several lines of experimental and clinical evidence have documented that the renin-angiotensin system (RAS) plays a key role in the pathophysiology of a number of cardiovascular diseases. Angiotensin II type 1 receptor blocker (ARB) is currently one of the most widely used first-line antihypertensive drugs. Evidence shows that it not only reduces BP, but also has some ancillary effects on cardiovascular properties, such as the protection of heart and kidney function beyond the mere lowering of elevated BP [7]. In particular, ARB telmisartan is reported to have an agonistic activity on peroxisome proliferator-activated receptor gamma (PPAR- γ), thereby ameliorating progression or even causing the regression of arterial stiffness [8]. In fact, treatment with telmisartan (40 mg/day for 3 months) in hypertensive patients decreased both BP and PWV [9]. However, whether telmisartan improves CAVI, which is less dependent on BP [5], remains uncertain.

The aim of this study was to assess the effects of an ARB telmisartan on markers of arterial stiffness using CAVI, AI and the maximum of the carotid intima-media thickness (MAX-IMT), along with urinary albumin excretion (UAE) and brain natriuretic peptide (BNP), which are known surrogate markers for cardiovascular morbidity and mortality in hypertensive patients [10].

Patients and Methods

Study Population and Design

The subjects of the present study were comprised of 100 consecutive patients with untreated hypertension or uncontrollable hypertension treated with medications other than RAS inhibitors. Hypertension was defined as follows. In patients without comorbid illness, hypertension was defined as a clinical systolic BP of >140 mm Hg and/or a clinical diastolic BP of >90 mm Hg at any time, and/or a systolic ambulatory BP of >130 mm Hg and/or a diastolic ambulatory BP of >85 mm Hg in the morning. In patients with diabetes mellitus, hypertension was defined as a clinical systolic BP of >130 mm Hg and/or a clinical diastolic BP of >80 mm Hg at any time.

All the patients were randomly assigned to either a group treated with calcium channel blocker (CCB)-based therapy or a group treated with telmisartan-based therapy. The randomization was performed by the envelop method. The target BP was defined as <130/85 mm Hg in patients without any complications and <130/80 mm Hg in patients with diabetes mellitus, chronic kidney disease or metabolic syndrome. Patients treated with CCB-based therapy were first treated with 20 mg/day of nifedipine, 2.5 mg/day of amlodipine, 5 mg/day of cilnidipine or 2 mg/day of benidipine for 4 weeks, and the doses of the CCBs were subsequently increased every 4 weeks until the target BP was attained (up to 60 mg/day of nifedipine, 10 mg/day of amlodipine, 20 mg/day of cilnidipine and 8 mg/day of benidipine). If the target BP was not achieved, ARBs, β -blockers, diuretics and ACE inhibitors were subsequently added. Patients treated with telmisartan-based therapy were first treated with 20 mg/day of telmisartan for 4 weeks, and the telmisartan dose was subsequently increased every 4 weeks until the target BP was attained (up to a maximum dose of 80 mg/day). The CCBs and diuretics were subsequently added unless the BP fell below the target BP. Clinical and biological parameters were measured before and 12 months after the start of this study. During the study period, previous medications and therapies other than antihypertensive drugs were continued. The subjects were not blinded to the treatment, although all measurements were performed under blind conditions.

The study was approved by the review board of Keio University Medical School Hospital and written informed consent was obtained from every subject.

Serum levels of creatinine, potassium, uric acid, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), glucose and glycoalbumin, and plasma levels of BNP, the active renin concentrations (ARC) and aldosterone (PAC) were measured in venous blood samples. The logarithm of urinary albumin excretion (log UAE) was measured in urinary samples drawn on the morning after an overnight fast on the same days as the ankle-brachial index (ABI), CAVI, AI, BP and MAX-IMT measurements were performed.

Ambulatory BP Monitoring

An oscillometric-based device (TM-2431; A&D Co., Tokyo, Japan) was used to perform 24-hour ambulatory BP monitoring. BP was measured every 30 min during the day (between 6:00 a.m. and 10:00 p.m.) and every 60 min during the night (between 10:00 p.m. and 6:00 a.m.). The mean values and the standard deviations of the ambulatory BP for each subject were calculated for a 24-hour period. The standard deviation of the ambulatory BP values was recorded as the variability of ambulatory BP in this study. The nocturnal decrease in BP was calculated as the average systolic BP during the day minus the average systolic BP during the night. The morning BP surge was calculated as the highest systolic BP during the first 2 hours after waking minus the lowest systolic BP during the night.

Cardio-Ankle Vascular Index

CAVI was measured using a VaSera VS-1000 vascular screening system (Fukuda Denshi Co. Ltd., Tokyo, Japan), as described previously [11]. Cuffs were applied to bilateral upper arms and ankles, with the subjects lying in a supine position with their heads held along the midline. ECG electrodes were placed on both

wrists and a microphone for detecting heart sounds was placed over the sternum. The patients rested in this supine position for at least 10 min before the start of monitoring. CAVI was calculated using the following formula:

$$\text{CAVI} = a \{ (2\rho/\Delta P) \times \ln (P_s/P_d) \text{PWV}^2 \} + b,$$

where P_s is the systolic BP, P_d is the diastolic BP, ΔP is $P_s - P_d$, ρ is blood density, and a and b are constants.

Augmentation Index

AI was measured using an automated tonometric device (HEM-9000AI; Omron Healthcare Co. Ltd., Kyoto, Japan), as described previously [12]. Peripheral pressure waveforms were recorded over 30 s from the radial artery at the wrist with the subjects in a sitting position after resting for at least 5 min. AI was calculated using the following formula:

$$\text{AI} = (\text{late systolic BP} - \text{diastolic BP}) / (\text{systolic BP} - \text{diastolic BP}) \times 100 (\%).$$

Urinary Albumin Excretion

UAE was evaluated on the basis of the mean albumin-to-creatinine ratio in three nonconsecutive overnight urine samples. The urinary concentrations of albumin and creatinine were determined using a turbidimetric immunoassay with a Superior-Microalbumin kit (DPC Co., Tokyo, Japan) and with the Jaffé reaction using an autoanalyzer.

Carotid Intima-Media Thickness

Ultrasonography B-mode imaging of the carotid artery was performed using a PowerVision 6000 machine (Toshiba, Tokyo, Japan) at a transducer frequency of 7.5 MHz. Each subject was examined while in a supine position. Up to 4 cm of the common carotid artery and the carotid bulb were scanned bilaterally using longitudinal and transverse projections. The images were focused on the far wall of the artery. IMT was defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall, and the greatest IMT value in the bilateral longitudinal projections was recorded as the maximum IMT. The IMT was measured within plaque-free areas. The mean intraobserver and interobserver coefficients of variation for the maximum IMT were 4.3 and 4.7%, respectively.

Statistical Analyses

Analyses were performed using Microsoft Office Excel 2007 and StatView 5.0. software (SAS Institute Inc., Cary, N.C., USA). Fisher's exact test was used to analyze sex and the frequency of diabetes mellitus, smoking and the use of statins. The Mann-Whitney U test was used to analyze age and body mass index. Changes in biological parameters were analyzed using Student's t test and a two-way analysis of variance for repeated measures combined with Tukey-Kramer post hoc tests. The contributions of changes in variables to changes in CAVI were tested using a regression analysis and an analysis of covariance. A p value < 0.05 was considered significant. Data are presented as the means $\pm$ SD.

Table 1. Patient characteristics at baseline

Characteristics	CCB-based	Telmisartan-based	p
Number	50	50	0.999
Age, years	51.0 $\pm$ 10.0	52.4 $\pm$ 8.7	0.615
Male gender, n	35	39	0.495
BMI	25.4 $\pm$ 4.1	24.1 $\pm$ 3.7	0.412
WC, cm	86.9 $\pm$ 9.9	89.0 $\pm$ 8.1	0.452
DM, n	6	7	0.999
Smoker, n	14	14	0.999
Use of statins, n	12	10	0.810
Serum Cr, mg/dl	0.88 $\pm$ 0.34	0.84 $\pm$ 0.14	0.539
Serum K, mEq/l	4.3 $\pm$ 0.3	4.4 $\pm$ 0.4	0.062
Serum UA, mg/dl	6.2 $\pm$ 1.4	6.1 $\pm$ 1.5	0.626
Serum TG, mg/dl	165 $\pm$ 126	166 $\pm$ 128	0.964
Serum HDL-C, mg/dl	57 $\pm$ 15	53 $\pm$ 13	0.213
Serum LDL-C, mg/dl	130 $\pm$ 34	121 $\pm$ 24	0.142
GA, %	14.5 $\pm$ 1.9	14.7 $\pm$ 1.8	0.609
BNP, pg/ml	11.0 $\pm$ 8.3	11.2 $\pm$ 11.9	0.927
Plasma ARC, pg/ml	12.1 $\pm$ 17.0	9.6 $\pm$ 8.7	0.363
Log UAE	1.16 $\pm$ 0.69	1.03 $\pm$ 0.66	0.445
ABI	1.13 $\pm$ 0.13	1.16 $\pm$ 0.08	0.188
CAVI	7.8 $\pm$ 1.3	8.2 $\pm$ 1.0	0.051
AI, %	80.1 $\pm$ 16.2	83.7 $\pm$ 13.6	0.408
max IMT, mm	1.1 $\pm$ 0.8	1.2 $\pm$ 0.6	0.394

Data are the means $\pm$ SD. WC = Waist circumference; DM = diabetes mellitus; Cr = creatinine; K = potassium; UA = uric acid; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; GA = glycoalbumin.

Results

Table 1 shows that no significant differences in baseline patient characteristics were observed between the group treated with CCB-based therapy and the group treated with telmisartan-based therapy. At the end of the study, the numbers of patients in the group treated with CCB-based therapy who had been prescribed additional antihypertensive medication were as follows: 5 for losartan, 4 for valsartan, 2 for olmesartan, 7 for candesartan, 2 for enalapril, 3 for diuretics, and 10 for β -blockers. In the group treated with telmisartan-based therapy, 3 patients were additionally treated with diuretics and 17 were treated with CCB.

Table 2 shows the changes in BP during the 12-month treatment period. No significant differences in the baseline BP were observed between the group treated with CCB-based therapy and the group treated with telmisartan-based therapy. The clinical systolic BP decreased significantly after the CCB-based therapy and also de-

Table 2. Changes in blood pressure during the study period

Therapy	CCB-based		Telmisartan-based		p (between therapies)
	baseline	12 months	baseline	12 months	
Clinical SBP	155 ± 19	134 ± 12*	156 ± 14	136 ± 13*	0.935
Clinical DBP	95 ± 11	85 ± 10*	101 ± 10	87 ± 11*	0.232
24-hour SBP	138 ± 18	130 ± 13	144 ± 11	128 ± 11*	0.053
24-hour DBP	88 ± 9	80 ± 8*	91 ± 9	81 ± 7*	0.045
Daytime SBP	142 ± 20	135 ± 14	148 ± 10	132 ± 11*	0.045
Daytime DBP	88 ± 12	83 ± 9*	94 ± 7	84 ± 8*	0.050
Nighttime SBP	125 ± 20	116 ± 12	131 ± 17	113 ± 13*	0.124
Nighttime DBP	76 ± 11	71 ± 9	83 ± 11	72 ± 9*	0.076
Nocturnal decrease	18 ± 16	19 ± 12	17 ± 13	18 ± 12	0.994
Morning surge	44 ± 12	47 ± 20	47 ± 20	43 ± 17	0.317
SBP variability	20 ± 4	20 ± 5	19 ± 5	19 ± 5	0.763

Units are mm Hg. Data are the means ± SD. SBP = Systolic blood pressure; DBP = diastolic blood pressure.
 * p < 0.05 vs. the baseline value.

creased significantly after the telmisartan-based therapy, although no significant difference was observed between the two groups. The clinical diastolic BP decreased significantly after the CCB-based therapy, and also declined significantly after the telmisartan-based therapy, although no significant difference was observed between the two groups. The 24-hour ambulatory systolic BP decreased significantly after the telmisartan-based therapy, whereas it did not change significantly after the CCB-based therapy. The 24-hour ambulatory diastolic BP decreased significantly after both the CCB-based therapy and the telmisartan-based therapy. The reduction in the 24-hour ambulatory diastolic BP after the telmisartan-based therapy was significantly greater than that after the CCB-based therapy. The daytime systolic BP decreased significantly after the telmisartan-based therapy, whereas it did not change significantly after the CCB-based therapy. The reduction in the daytime systolic BP after the telmisartan-based therapy was significantly greater than that after the CCB-based therapy. The daytime diastolic BP decreased significantly after the CCB-based therapy and also decreased significantly after the telmisartan-based therapy, although no significant difference was observed between the two groups. The nighttime systolic BP decreased significantly after the telmisartan-based therapy, but did not change significantly after the CCB-based therapy. The nighttime diastolic BP decreased significantly after the telmisartan-based therapy, but did not change significantly after the CCB-based therapy. The reduction in the nighttime diastolic pres-

sure after the telmisartan-based therapy was significantly greater than that after the CCB-based therapy. No significant changes in the nocturnal decrease in systolic BP, the morning systolic BP surge or the systolic BP variability were seen during the 12-month observation period in either group.

Figure 1 shows the change in the BNP, UAE and arterial stiffness as assessed by CAVI, AI and MAX-IMT in both groups. The log UAE level decreased significantly from 1.03 ± 0.66 to 0.57 ± 0.52 after the telmisartan-based therapy, whereas it did not change significantly after the CCB-based therapy. CAVI decreased significantly from 8.2 ± 1.0 to 7.7 ± 0.9 after the telmisartan-based therapy, whereas it did not change significantly after the CCB-based therapy. CAVI also decreased significantly from 100 to $93.7 \pm 9.8\%$ after the telmisartan-based therapy when the baseline values of CAVI were adjusted, but did not change significantly after the CCB-based therapy. No significant changes in the levels of BNP, AI or MAX-IMT were observed in either group.

Figure 2 shows the changes in the metabolic parameters in both groups. During the 12-month observation period, the serum LDL-C level decreased significantly from 130 ± 34 to 119 ± 32 mg/dl after the CCB-based treatment and also decreased significantly from 121 ± 24 to 115 ± 29 mg/dl after the telmisartan-based therapy. However, no significant difference was observed between the two groups. The plasma ARC increased significantly from 9.6 ± 8.7 to 46.7 ± 84.7 pg/ml after the telmisartan-based therapy, whereas no significant change was seen af-

Fig. 1. Serum BNP, log UAE, AI, CAVI, the baseline adjusted CAVI and MAX-IMT at baseline and after 12 months of treatment in the CCB-based therapy (open circles) and the telmisartan-based therapy (closed circles) groups. * $p < 0.05$ vs. the baseline value.

Fig. 2. Serum creatinine (Cr), serum K, glycoalbumin (GA), serum uric acid (UA), serum triglyceride (TG), serum LDL-C and plasma ARC at baseline and after 12 months of treatment in the CCB-based therapy (open circles) and the telmisartan-based therapy (closed circles) groups. * $p < 0.05$ vs. the baseline value; † $p < 0.05$ vs. the group treated with the CCB-based therapy.

Table 3. Effects of percent changes in LDL, ARC, log UAE, clinical BP, 24-hour BP, daytime BP and nighttime BP on percent changes in CAVI after telmisartan-based therapy

ANCOVA	Coefficient	SE	t test	p
Intercept	-0.058	0.016	-3.640	0.0008
ΔLDL	0.004	0.088	0.046	0.9638
Intercept	-0.044	0.019	-2.281	0.0298
ΔARC	-0.005	0.002	-2.382	0.0238
Intercept	-0.039	0.024	-1.623	0.1151
Δlog UAE	0.064	0.051	1.263	0.2165
Intercept	-0.038	0.024	-1.570	0.1241
Δclinical SBP	0.182	0.157	1.154	0.2552
Intercept	-0.039	0.024	-1.637	0.1093
Δclinical DBP	0.167	0.142	1.181	0.2446
Intercept	-0.027	0.028	-0.963	0.3427
Δ24-hour SBP	0.290	0.204	1.423	0.1645
Intercept	-0.001	0.028	-0.042	0.9671
Δ24-hour DBP	0.449	0.199	2.515	0.0171
Intercept	-0.033	0.028	-1.190	0.2429
Δdaytime SBP	0.246	0.205	1.201	0.2386
Intercept	-0.015	0.027	-0.570	0.5729
Δdaytime DBP	0.397	0.193	2.054	0.0483
Intercept	-0.019	0.024	-0.782	0.4398
Δnighttime SBP	0.320	0.136	2.350	0.0251
Intercept	-0.024	0.021	-1.114	0.2734
Δnighttime DBP	0.305	0.120	2.531	0.0165

SBP = Systolic blood pressure; DBP = diastolic blood pressure.

ter the CCB-based therapy. The increase in the plasma ARC after the telmisartan-based therapy was significantly greater than that after the CCB-based therapy. No significant changes in the serum levels of creatinine, potassium, glycoalbumin, uric acid or triglyceride were seen during the 12-month observation period in either group.

In the present study, serum LDL-C, ARC, log UAE, clinical BP, 24-hour BP, daytime BP and nighttime BP changed significantly after the telmisartan-based therapy. As table 3 shows, we performed ANCOVA (analysis of covariance) to examine whether these variables affected the change in CAVI during telmisartan-based therapy. The changes in the plasma ARC, 24-hour diastolic BP, daytime diastolic BP and nighttime systolic and diastolic BP contributed significantly to the decrease in CAVI after the telmisartan-based therapy.

Table 4. Effects of percent changes in LDL, ARC, CAVI, clinical BP, 24-hour BP, daytime BP and nighttime BP on percent changes in log UAE after telmisartan-based therapy

ANCOVA	Coefficient	SE	t test	p
Intercept	-0.301	0.065	-4.641	<0.0001
ΔLDL	0.041	0.408	0.101	0.9201
Intercept	-0.265	0.085	-3.130	0.0044
ΔARC	-0.013	0.009	-1.438	0.1629
Intercept	-0.265	0.074	-3.571	0.0012
ΔCAVI	0.787	0.624	1.263	0.2165
Intercept	-0.271	0.113	-2.403	0.0227
Δclinical SBP	0.265	0.773	0.342	0.7347
Intercept	-0.282	0.112	-2.522	0.0172
Δclinical DBP	0.150	0.683	0.220	0.8276
Intercept	-0.222	0.121	-1.830	0.0783
Δ24-hour SBP	0.946	0.841	1.125	0.2705
Intercept	-0.224	0.127	-1.761	0.0896
Δ24-hour DBP	0.890	0.870	1.023	0.3152
Intercept	-0.230	0.128	-1.793	0.0842
Δdaytime SBP	0.858	0.898	0.956	0.3475
Intercept	-0.274	0.123	-2.232	0.0341
Δdaytime DBP	0.497	0.843	0.589	0.5606
Intercept	-0.215	0.094	-2.287	0.0302
Δnighttime SBP	0.950	0.525	1.810	0.0815
Intercept	-0.262	0.093	-2.812	0.0091
Δnighttime DBP	0.581	0.506	1.150	0.2602

SBP = Systolic blood pressure; DBP = diastolic blood pressure.

As table 4 shows, ANCOVA was also performed to examine whether the changes in the serum LDL-C, ARC, CAVI, clinical BP, 24-hour BP, daytime BP and nighttime BP affected the change in log UAE during the telmisartan-based therapy. However, none of the parameter changes contributed to the decrease in log UAE after the telmisartan-based therapy.

Discussion

This study demonstrated for the first time that telmisartan significantly improves CAVI, which reflects arterial stiffness in a manner that is less dependent on BP, compared with PWV in hypertensive patients [5]. The average coefficient of variation of CAVI is less than 5%,

which is small enough for clinical usage and indicates that CAVI has good reproducibility and validation of the measurement of arterial stiffness [13]. In addition, CAVI is a new marker for arterial stiffness since the previous study has reported that CAVI reflects the fibrosis of arterial walls histologically [5]. In the present study, telmisartan also significantly improved CAVI by 6.3% when the baseline values were adjusted, which was larger than the average coefficient of variation of the CAVI. The results of this study agree with those of previous studies, which showed improvements in vascular compliance after treatment with other ARBs [12]. In fact, previous studies have revealed that the long-term administration of telmisartan improved the PWV in spite of a BP-lowering efficacy comparable to those of other antihypertensive medications [9, 14]. Since angiotensin II stiffens the vascular wall by constricting the vascular smooth muscle and promoting vascular wall remodeling, ARBs might improve arterial stiffness, at least in part, through BP-independent effects [7]. In the present study, ANCOVA showed that the changes in plasma ARC contributed significantly to the decrease in CAVI after the telmisartan-based therapy, although the changes in the 24-hour diastolic BP, daytime diastolic BP and nighttime systolic and diastolic BP also contributed significantly to the decrease in CAVI after the telmisartan-based therapy. Thus, the improvement of CAVI after telmisartan-based therapy might result from RAS blockade as well as antihypertensive effects. In addition, previous studies showed that telmisartan has the unique activity of enhancing PPAR- γ , which plays critical roles in the vasculature [8]. In vascular endothelial cells, PPAR- γ activation inhibits endothelial inflammation by suppressing inflammatory gene expression, leading to endothelial dysfunction [15]. In vascular smooth muscle cells, PPAR- γ activation inhibits proliferation and migration, and promotes apoptosis [15]. Taken together, the properties of telmisartan, such as RAS blockade and PPAR- γ activation, are thought to be involved in the improvement of CAVI. Since arterial stiffness is a powerful and independent risk factor for mortality in cardiovascular events [16], telmisartan could be a first-line antihypertensive drug with additional cardiovascular protective properties.

AI is another marker of arterial stiffness; this marker is associated with the plasma BNP because both markers reflect the central aortic pressure [13, 17]. Vascular stiffening causes an increase in the amplitude and early return of the reflected wave during systole, with augmentation of the central systolic BP and a resultant increase in AI [18]. Furthermore, the carotid IMT represents struc-

tural changes like wall thickening and the formation of atherosclerotic plaques, which are correlated with a greater incidence of atherosclerosis in the coronary circulation and other large arteries [19]. Telmisartan has been shown to cause an insignificant reduction in AI [18] and significant decreases in both BNP [20] and IMT [21]. In the present study, telmisartan-based therapy also tended to decrease the AI and to regress the IMT, consistent with the above-mentioned studies, whereas telmisartan-based therapy did not decrease the BNP. While a previous study demonstrated a significant reduction in BNP after treatment with telmisartan when the initial baseline level was 27.8 ± 21 pg/ml [20], the baseline level of BNP in the present study was 11.2 ± 11.9 pg/ml. Therefore, the plasma BNP level in the subjects in the present study might have been too low to detect any notable changes.

Albuminuria is an important predictor of cardiovascular events and of progression to end-stage renal disease in hypertensive patients [22, 23]. In the present study, telmisartan-based therapy significantly reduced microalbuminuria in hypertensive patients. This result was consistent with those of previous studies showing that ARB treatment inhibits the progression to macroalbuminuria and overt proteinuria in diabetic patients with microalbuminuria [24, 25] and that telmisartan treatment reduces microalbuminuria in hypertensive patients [14]. The renoprotective effects exerted by telmisartan might be partly mediated by BP-independent mechanisms, since ANCOVA showed that the BP changes did not contribute to the decrease in log UAE after the telmisartan-based therapy. Telmisartan, a dual ARB/PPAR- γ agonist, might have a great antiproteinuric effect [26] since treatment with telmisartan enabled a greater reduction in microalbuminuria than treatment with an ARB without any PPAR- γ agonistic action [27]. The present study demonstrated a significant reduction in the log UAE value, even though ACE inhibitors or ARBs other than telmisartan were prescribed for 40% of the patients treated with CCB-based therapy. Thus, ARBs with properties that enhance PPAR- γ might be useful for reducing microalbuminuria in hypertensive patients.

Telmisartan has been shown to be characterized by a balanced antihypertensive efficacy that fully covers a 24-hour period, thereby antagonizing the adverse effects of early morning BP elevations on cardiovascular risk [19]. The beneficial effects of telmisartan on the 24-hour BP values consist not only of lowering the daytime and nighttime BP, but also effectively controlling BP variability [28, 29], which has been shown to be closely correlated with PWV [11], target-organ damage [30] and the incidence of

cardiovascular events and mortality independent of the absolute BP load [31]. Previous studies have shown that the inhibitory effects of telmisartan on BP variability were associated with a reduction in sympathetic nerve activity in hypertensive patients with overt nephropathy [28]. Thus, telmisartan could be beneficial in hypertensive patients with a greater BP variability and/or autonomic dysfunction, such as elderly subjects and diabetic patients. Although reductions in morning surge and BP fluctuations were not observed in the present study, a sustained antihypertensive effect was observed throughout the 24-hour observation period among the subjects treated with telmisartan-based therapy.

ARB has also been shown to have a favorable lipid profile [32]. In the present study, telmisartan significantly decreased the serum level of LDL-C, which was in line with previous studies [33]. However, the reduction in the serum LDL-C levels after telmisartan-based therapy was similar to that observed after CCB-based therapy, probably because of the relatively large proportion of patients with prescriptions for ACE inhibitors or ARBs other than telmisartan among the patients treated with the CCB-based therapy. In the present study, the telmisartan-based therapy did not increase the serum levels of creatinine or potassium, which is consistent with the ONTARGET study (which demonstrated a similar number of patients whose serum creatinine levels and potassium levels increased after telmisartan or ramipril therapy) [34]. Thus, the present study also confirmed the metabolic safety of telmisartan.

In the present study, ARBs and CCBs were added in the group treated with CCBs and telmisartan, respectively, unless the target BP was achieved. The Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trial revealed that BP reduction is important for the cardiovascular protection at an early stage, while the contri-

bution of RAS inhibition to the reduction of the cardiovascular events is apparent in a delayed fashion [35]. Based on the CASE-J trial, one would expect that the early initiation of ARBs will be beneficial for the inhibition of the arterial stiffness. In fact, the current study clearly provided evidence that the arterial stiffness assessed by CAVI significantly improved in the group treated with telmisartan from the start of the study, whereas the improvement of the arterial stiffness in the CCB-based therapy was not as much as that in the telmisartan-based therapy, even after the addition of ARB. Therefore, telmisartan should be the first drug to be initiated in view of the protection from the arterial stiffness.

Some limitations in the interpretation of the results of the present study exist. First, the trial population was comparatively small and the observation period was relatively short. A longer observation with a larger number of subjects might elucidate the beneficial and adverse effects of telmisartan more clearly. In addition, prognostic events were not examined in the present study. Further studies are needed to confirm the benefits and safety of telmisartan-based therapy.

In conclusion, telmisartan-based therapy exerted beneficial effects on arterial stiffness, as assessed using CAVI, albuminuria, 24-hour BP and metabolism compared with CCB-based therapy. Since these markers are known to influence the future risk for cardiovascular events in hypertensive patients, telmisartan could well be a first-line antihypertensive drug for the treatment of hypertensive patients.

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