Table 1. Baseline characteristics of subjects with and without future stroke events

Measures	Total Population (n = 811)	Stroke Events	
		No Events (n = 752)	Events (n = 59)
Age (yr)	72 (9.8)	72 (9.9)	78 (7.1)*
Male (%)	49	37	51‡
Body mass index (kg/m^2)	23.9 (3.5)	24.0 (3.5)	23.0 (3.6)‡
Clinic systolic BP (mm Hg)	164 (18)	164 (18)	171 (19)*
Clinic diastolic BP (mm Hg)	90 (14)	90 (93)	93 (14)
Clinic mean BP (mm Hg)	115 (13)	115 (13)	119 (14)‡
Clinic pulse pressure (mm Hg)	74 (16)	73 (16)	78 (15)‡
Smoker (%)	20	19	41*
Diabetes mellitus (%)	12	12	17
Hyperlipidemia (%)	19	19	17
Ambulatory BP parameters (mm Hg)			
24-h systolic BP	138 (16)	137 (16)	148 (16)*
24-h diastolic BP	78 (9.7)	78 (9.7)	82 (9.7)*
24-h mean BP	98 (12)	98 (11)	104 (11)*
24-h pulse pressure	60 (9.3)	59 (9.0)	66 (11)*
Awake systolic BP	145 (18)	144 (18)	153 (17)*
Awake diastolic BP	82 (11)	81 (11)	85 (10)‡
Awake mean BP	103 (13)	102 (13)	108 (12)*
Awake pulse pressure	63 (10)	63 (9.8)	68 (11)*
Sleep systolic BP	127 (18)	126 (18)	138 (20)*
Sleep diastolic BP	72 (11)	72 (11)	76 (12)†
Sleep mean BP	90 (13)	90 (12)	97 (14)*
Sleep pulse pressure	55 (11)	54 (10)	61 (12)*

Data are shown as means (SD) or percentages.
* $P < .001$, † $P < .01$, ‡ $P < .05$ v no event group.

tensin-converting enzyme inhibitors). Strokes occurred in 32 (8.3%) of 385 untreated hypertensives, and in 27 (6.3%) of 426 treated hypertensives ($\chi^2 = 1.2$, $P = .28$).

Baseline Characteristics

Table 1 lists baseline characteristics of studied hypertensives with and without future stroke events. The mean age and clinic and ambulatory BP and PP levels and the prevalences of men and smokers were significantly higher, and body mass index (BMI) was significantly lower in the hypertensives who developed future stroke event (stroke group), than in those who did not develop stroke (nonstroke group; Table 1). The prevalences of SCI and multiple SCI were significantly higher in the stroke group (n = 43) than in the nonstroke group (n = 472) (86% v 47%, $P < .0001$; 31% v 77%, $P < .0001$, respectively).

Stroke Risk and Pulse Pressure and Mean BP

Figs. 1A and C depict the association between PP tertiles and stroke risk unadjusted and adjusted for covariates (age, gender, BMI, diabetes, hyperlipidemia, antihypertensive medication, and MBP) using Cox regression analysis, separated for clinic, 24-h, awake, and sleep BPs. There were marked positive associations between all PP parameters and unadjusted stroke risk; however, after adjustment for covariates, only the clinic and sleep PPs remained significant. Table 2 shows the results of Cox regression analysis, in which the same covariates as in Fig. 1C were included and PP and MBP parameters were considered as continuous variables. For each 10 mm Hg increase in sleep PP, there was an independent 43% (95% CI:16%–75%, P = .001) increase in the stroke risk, and sleep MBP did not yield significance after controlling for sleep PP. On the other hand, for each 10 mm Hg increase in awake MBP, there was an independent 48% (95% CI:21%–81%, P = .0002) increase in the stroke risk, and awake PP did not yield significance after adjusting for awake MBP.

Fig. 2 shows the stroke incidence in the subjects separated according to sleep PP and awake MBP. The stroke incidence was 8.7 times higher in the highest risk hypertensives with awake MBP ≥110 mm Hg (the highest tertile) and sleep PP ≥60 mm Hg (the highest tertile) than in the lowest risk hypertensives with low awake MBP <95 mm Hg (the lowest tertile) and low sleep PP <50 mm Hg (the lowest tertile). When both sleep PP and awake MBP were entered into the same model including covariates (age, gender, BMI, diabetes, hyperlipidemia, antihypertensive medication), both sleep PP (RR = 1.32, P = .04) and awake MBP (RR = 1.35, P = .01) were associated with stroke risk independently of each other (Table 3).

Fatal Cardiovascular Events

Fig. 1B shows the association between PP tertiles and fatal cardiovascular event risk unadjusted. After adjusting for the covariates listed in Table 2 (age, gender, BMI, diabe-

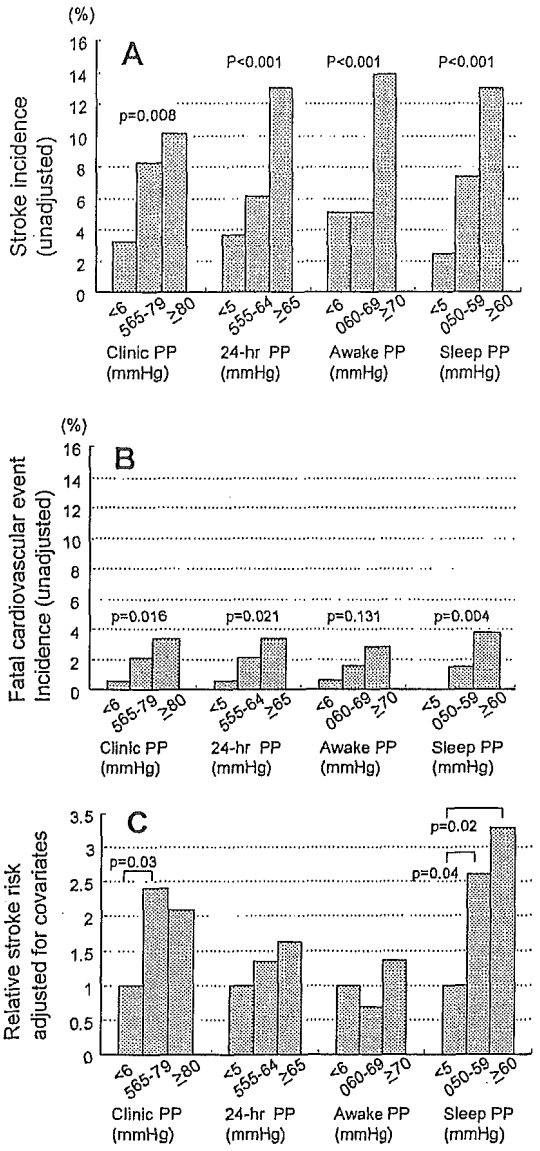

FIG. 1. A) Stroke incidence (unadjusted). **B)** Fatal cardiovascular event incidence (unadjusted). **C)** Relative risk for stroke event (adjusted for age, gender, body mass index, diabetes, hyperlipidemia, antihypertensive medication, and mean blood pressure) in each tertile of pulse pressure (PP) parameter.

tes, hyperlipidemia, antihypertensive medication) using Cox regression analysis, all APP parameters (clinic, 24-h, awake, and sleep) were predictors for fatal cardiovascular events (fatal stroke and cardiac events), independently of MBP parameters. For each 10 mm Hg increase in PP, there was an independent 41% (95% CI: 10%–81%, $P = .007$) increase for clinic BP, 71% (95% CI: 21%–141%, $P = .003$) increase for 24-h BP, 64% (95% CI:13–137%, p=0.01) increase for awake BP, and 63% (95% CI: 21%–121%, $P = .002$) for sleep BP in the stroke risk, whereas clinic, 24-h, awake, and sleep MBPs did not yield significance after controlling for PP parameters.

Table 2. Results of stepwise Cox regression analysis for clinical stroke event ($n = 811$)

Covariates	Relative Risk (95% CI)	P
Clinic BP		
Age (10 yr)	1.91 (1.46–2.51)	.0000
Current smoker	2.69 (1.59–4.53)	.0004
Clinic mean BP (10 mm Hg)	1.26 (1.07–1.49)	.0084
24-h BP		
Age (10 yr)	1.94 (1.48–2.53)	.0000
Current smoker	2.39 (1.42–4.03)	.0016
24-h mean BP (10 mm Hg)	1.56 (1.27–1.91)	.0000
Awake BP		
Age (10 yr)	2.01 (1.53–2.64)	.0000
Current smoker	2.55 (1.52–1.81)	.0007
Awake mean BP (10 mm Hg)	1.48 (1.21–1.81)	.0002
Sleep BP		
Age (10 yr)	1.68 (1.26–2.24)	.0003
Current smoker	2.38 (1.40–4.03)	.0020
Sleep pulse pressure (10 mm Hg)	1.43 (1.16–1.75)	.0012

CI = confidence interval. Age, gender (women = 0, men = 1), body mass index, smoking status (absence = 0, presence = 1), diabetes (absence = 0, presence = 1), hyperlipidemia (absence = 0, presence = 1), antihypertensive medication (absence = 0, presence = 1), and clinic, 24-h, awake, and sleep mean BP and pulse pressure were selected for the stepwise Cox regression analysis.

Impact of Silent Cerebral Infarct

Then we grouped the 515 subjects who had both ABPM and brain MRI into 258 subjects without SCI and 257 with SCI. There was a positive association between all PP parameters (clinic, 24-h, awake, and sleep) and SCI (data not shown). However, after adjusting for covariates (age, gender, BMI, diabetes, hyperlipidemia, antihypertensive medication) using stepwise multiple logistic regression

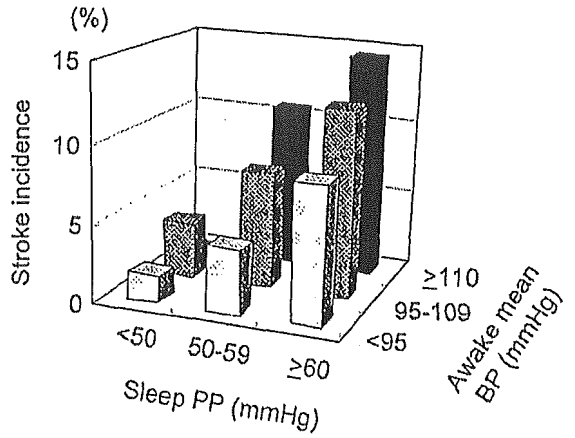

FIG. 2. Stroke incidence from the first to the third tertile of the distribution of pulse pressure (PP) parameters and awake mean blood pressure (BP).

Table 3. Results of forced Cox regression analysis for clinical stroke event

Covariates	Model 1 (n = 811) Relative Risk (95% CI)	P	Model 2 (n = 515) Relative Risk (95% CI)	P
Age (10 yr)	1.82 (1.33–2.48)	.0002	1.72 (1.13–2.61)	.01
Male	1.45 (0.81–2.59)	.21	1.19 (0.58–2.43)	.64
Body mass index (kg/m^2)	0.99 (0.92–1.08)	.87	1.01 (0.92–1.11)	.79
Current smoker	2.14 (1.18–3.87)	.01	2.06 (1.03–4.13)	.04
Diabetes	1.03 (0.51–2.10)	.93	0.91 (0.42–1.99)	.81
Hyperlipidemia	1.56 (0.76–3.20)	.23	1.14 (0.50–2.56)	.76
Antihypertensive medication	0.71 (0.41–1.24)	.23	0.51 (0.26–0.98)	.04
Silent cerebral infarct	Not included		4.49 (1.85–10.9)	.0009
Awake mean BP (10 mm Hg)	1.35 (1.07–1.69)	.01	1.30 (1.00–1.69)	.048
Sleep pulse pressure (10 mm Hg)	1.32 (1.02–1.72)	.04	1.30 (0.98–1.72)	.066

CI = confidence interval. Age, gender (women = 0, men = 1), body mass index, smoking status (absence = 0, presence = 1), diabetes (absence = 0, presence = 1), hyperlipidemia (absence = 0, presence = 1), antihypertensive medication (absence = 0, presence = 1), awake mean BP, and sleep pulse pressure were selected for the Model 1 of the forced Cox regression analysis. The silent cerebral infarct (absence = 0, presence = 1) was added in Model 2.

analysis, MBP parameters (clinic, 24-h, awake, sleep) significantly were associated with SCI (0 = absent, 1 = present); however, none of the PP parameters yielded statistical significance (Table 4).

Stroke occurred in 6 (2.3%) of the non-SCI group, and in 37 (14%) of the SCI group, indicating that SCI is a strong predictor of clinical stroke (RR = 7.1, $P < .0001$). The association between SCI (0 = absent, 1 = present) and stroke risk remained significant independently of all parameters of PP and MBP. Fig. 3 shows the positive associations between PP parameters and stroke risk in both the SCI group and non-SCI group. To study the potential mediating role of SCI in the association between PP, MBP, and stroke risk, we added SCI (0 = absent, 1 = present) into the same model as used for the results shown in Table 2. The impacts of clinic MBP (RR = 1.23, P = .03), awake MBP (RR = 1.38, P = .007), and sleep PP (RR = 1.32, P = .016) on stroke risk remained significant independently of SCI. Instead of 24-h mean BP (independent predictor for stroke event in Table 2), 24-h PP appeared to be a significant predictor for stroke event (RR = 1.41, P = .015) in this model that included SCI.

Table 4. Results of stepwise multiple logistic analysis for silent cerebral infarct detected by brain MRI (n = 515)

Covariates	Odds Ratio (95% CI)	P
Clinic BP		
Age (10 yr)	1.98 (1.59–2.49)	.0000
Male	1.80 (1.24–2.64)	.0021
Clinic mean BP (10 mm Hg)	1.19 (1.04–1.36)	.0092
24-h BP		
Age (10 yr)	2.03 (1.62–2.55)	.0000
Male	1.62 (1.10–2.39)	.0136
24-h mean BP (10 mm Hg)	1.28 (1.09–1.51)	.0021
Awake BP		
Age (10 yr)	2.07 (1.65–2.60)	.0000
Male	1.63 (1.11–2.39)	.0130
Awake mean BP (10 mm Hg)	1.31 (1.13–1.52)	.0003
Sleep BP		
Age (10 yr)	1.99 (1.59–2.49)	.0000
Male	1.67 (1.14–2.45)	.0087
Sleep mean BP (10 mm Hg)	1.20 (1.04–1.39)	.0138

Abbreviations as in Table 2.

Discussion

This study has first demonstrated that in older hypertensives, the impacts of PP and MBP on stroke risk are different during sleep and awake periods. Sleep PP and awake mean BP were independent predictors for stroke events. These associations were independent of other cardiovascular risk factors and SCI.

Sleep Pulse Pressure

All PP parameters (clinic, 24-h, awake, and sleep) were positively associated with stroke risk. However, after adjusting for covariates, only sleep PP remained significant independently of MBP. Previous studies have not studied the association of PP and MBP with cardiovascular events separately for awake and sleep periods. To consider the possible mechanism for the difference in the association of the PP and MBP with stroke events between the sleep and awake periods, we have to consider diurnal changes of neurohumoral factors. Although PP is totally considered as a global indicator of arterial stiffness, various factors such as stroke volume, rapidity of ventricular ejection, viscoelastic properties of large arteries, and timing of reflected pulse waves from the peripheral sites determine PP.[1–3] In an acute human study, pulse wave velocity was

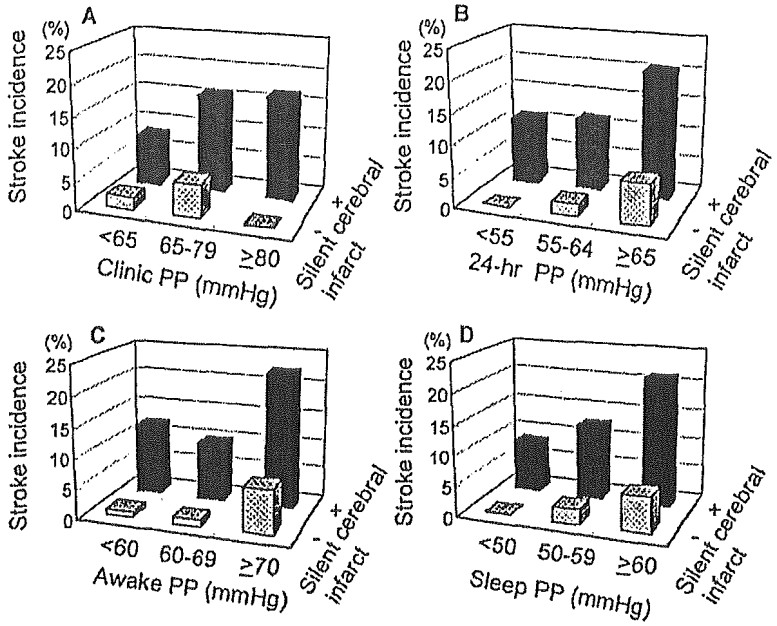

FIG. 3. Stroke incidence from the first to the third tertile of the distribution of pulse pressure (PP) parameters in the groups with and without baseline silent cerebral infarct detected by brain magnetic resonance imaging. (**A**: clinic PP; **B**: 24-h PP; **C**: awake PP; **D**: sleep PP).

unaffected by β-adrenergic blockade, but was reduced by combined α- and β-adrenergic blockade, indicating that sympathetic nervous activity affects the functional stiffness of the large artery.[14] In addition, infusion of angiotensin II increases augmentation index, which implies an augmentation of pressure during the late systolic phase, resulting in increased PP.[15] Thus, it is possible that the diurnal variation in these neurohumoral activities will change the PP during different diurnal periods. During the sleep period, parasympathetic activity increases with diminished sympathetic activity. The activity of the renin-angiotensin system also decreases during the sleep period. Thus, sleep PP may more closely reflect structural arterial stiffness with less effect on the neurohumoral factors, whereas awake PP may reflect not only structural stiffness but also functional stiffness, which is also affected by diurnal neurohumoral activation. The results of our study indicate that structural arterial stiffness might be a more powerful determinant of stroke event in the elderly hypertensives.

In addition, the marked dilatation of all peripheral arteriole, which usually occurs during night, might lead to a greater decrease in diastolic BP than systolic BP, which consequently discloses the predictive value of sleep PP (superior to that of sleep MBP) for stroke. This phenomenon might be particularly relevant in the elderly. Furthermore, an increased PP itself may be a causal mechanism for plaque disruption. A recent study (European Carotid Surgery Trial) demonstrated that PP is independently associated with carotid plaque ulceration in patients with carotid stenosis, suggesting that pulsatile hemodynamic forces are an important cause of plaque rupture leading to cardiovascular events.[16]

Awake, Twenty-four-hour, and Clinic Pulse Pressure

On the other hand, after adjusting for covariates, awake, 24-h, and clinic PPs were not associated with stroke independently of MBP. Instead, awake, 24-h, and clinic MBPs were independent predictors for future stroke. In previous prospective studies, contradictory results were obtained regarding the association between clinic PP and stroke risk.[4] In the Systolic Hypertension in the Elderly Program (SHEP), both PP and MBP were independent predictors of stroke.[17] In the recent analysis of the Medical Research Council (MRC) Mild Hypertension Trial, stroke risk was best predicted by MBP,[18] and in the European Working Party on Hypertension in the Elderly (EWPHE), MBP was a predictor for stroke even after adjusting for PP, whereas PP did not significantly predict stroke after adjusting for MBP.[4,19] In contrast, in the Systolic Hypertension in Elderly in Europe (Syst-Eur) and Systolic Hypertension in Elderly in Chinese (Syst-China) studies of elderly patients with isolated systolic hypertension, PP was a stronger predictor of stroke than MBP.[4] One prospective study using ABPM found an independent positive association between 24-h PP and cardiac events, but did not find an independent association between 24-h PP and stroke.[9] However, that study did not analyze separately for sleep and awake periods. In addition, their study population was much younger (mean age, 51 years) than our population (mean age, 72 years). In study populations with different ages, PP seems to have a different impact on stroke, because in another prospective study using ABPM, an independent impact of PP on cardiovascular events was only found in older patients aged 65 years or more. How-

ever, MBP was an independent determinant for cardiovascular events in younger adults aged <65 years.[8] It appears that when the stroke risk is analyzed separately for sleep and awake periods in older hypertensive patients, the association between APP and stroke risk might be significant, even after adjusting for MBP. The impacts of awake MBP and sleep PP on stroke risk were independent of each other, even after adjusting for covariates.

Impact of Silent Cerebral Infarcts

Silent cerebral infarct are predominantly small lacunar infarcts with various types of pathogenesis including microathoeroembolism, hemodynamic infarction, and arteriosclerosis of small penetrating arteries. In the present study, the presence of SCI was a powerful predictor of future stroke. This association was independent of all parameters of PP and MBP. On the other hand, the positive association between sleep and 24-h PPs and stroke risk was independent of the presence or absence of SCI. Thus, our study indicates that in the elderly hypertensive patients, both large vessel disease (increase in PP) and small vessel disease (SCI) determine the risk of future stroke independently of each other.

There was a positive association between all PP parameters (clinic, 24-h, awake, and sleep) and SCI. However, after adjusting for covariates, this association was not independent of MBP. In contrast, all MBP parameters were determinants for SCI independently of PP parameters. These results may imply that the steady BP overload (MBP) is main determinant for the progression of arteriosclerosis of small cerebral arteries resulting in the formation of small lacunar infarcts than the pulsatile component (PP) in hypertensive patients.

Fatal Cardiovascular Events

Because of the small number of fatal stroke events in this study, we combined the fatal stroke and cardiac events as fatal cardiovascular events. All PP parameters (clinic, 24-h, awake, and sleep) had stronger effects on the fatal cardiovascular events than MBP parameters. The impact of PP may be greater on fatal events than nonfatal cardiovascular events in elderly hypertensives.

In conclusion, in older hypertensive patients, APP, particularly during the sleep period, is an important predictor for future stroke risk, independent of age and ambulatory MBP. Antihypertensive therapy targeting the reduction of the pulsatile component of BP in addition to reducing the steady component may achieve more effective reduction of stroke risk.

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AJH 2004; 17:112–117

Comparison of Valsartan and Amlodipine on Ambulatory and Morning Blood Pressure in Hypertensive Patients

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Background: Cardiovascular events occur most frequently in the morning. We aimed to study the effects of monotherapy with the long-acting angiotensin II receptor blocker valsartan compared with the long-acting calcium antagonist amlodipine on ambulatory and morning blood pressure (BP).

Methods: We performed ambulatory BP monitoring before and after once-daily dose of valsartan (valsartan group, $n = 38$) and amlodipine (amlodipine group, $n = 38$) therapy in 76 hypertensive patients. To achieve the target BP of ≤140/90 mm Hg, valsartan was titrated from 40 mg/day to 160 mg/day (mean dose 124 mg/day) and amlodipine was titrated from 2.5 mg/day to 10 mg/day (mean dose 6.4 mg/day).

Results: Both drugs significantly reduced clinic and 24-h systolic BP (SBP) and diastolic BP (DBP) ($P < .002$). However, the antihypertensive effect of amlodipine was superior to that of valsartan in clinical SBP (−26 mm Hg *v* −13 mm Hg, $P = .001$) and 24-h SBP (−14 mm Hg *v* −7 mm Hg, $P = .008$). In addition, morning SBP was significantly reduced by amlodipine from 156 to 142 mm Hg ($P < .001$) but not by valsartan. Both agents reduced lowest night SBP to a similar extent (amlodipine 121 to 112 mm Hg, $P < .001$; valsartan 123 to 114 mm Hg, $P < .002$). Reduction in morning SBP surge (morning SBP minus lowest night SBP) was significantly greater in patients treated with amlodipine compared with those treated with valsartan (−6.1 mm Hg *v* +4.5 mm Hg, $P < .02$).

Conclusions: Amlodipine monotherapy was more effective than valsartan monotherapy in controlling 24-h ambulatory BP and morning BP in hypertensive patients. Am J Hypertens 2004;17:112–117 © 2004 American Journal of Hypertension, Ltd.

Key Words: Valsartan, amlodipine, ambulatory blood pressure, morning blood pressure surge.

Ambulatory blood pressure (BP) levels are closely associated with target organ damage and clinical cardiovascular events in hypertensive patients.[1–5] Cardiovascular events occur more frequently in the morning, and ambulatory BP exhibits a diurnal variation with increases in the morning (morning BP surge).[6,7] The morning BP surge was previously reported to be associated with cardiac hypertrophy in hypertensive patients.[8] Recently we have shown that the morning BP surge was significantly associated with an increased risk of stroke in hypertensive patients.[9] This association was independent of age and 24-h BP level. Thus, antihypertensive medication more specific for morning BP in addition to 24-h BP would be useful for the prevention of cardiovascular events in hypertensive patients.

The renin-angiotensin-aldosterone system (RAAS) is activated in the morning, and may contribute to morning BP surge[7] and to morning increase in cardiovascular risk. Valsartan, a long-acting angiotensin receptor blocker (ARB), has been reported to have a BP lowering effect similar to that of amlodipine, a long-acting calcium antagonist, for controlling ambulatory BP level without disruption of its diurnal variation in hypertensive patients.[10] However, specific comparison of the BP lowering effect on ambulatory BP, morning BP, and morning BP surge between valsartan and amlodipine has not been conducted with each single-drug therapy in hypertensive patients.

Methods

Study Patients

This study was a multicenter, open-label, randomized study of the effects of once-daily morning administration of amlodipine and valsartan on ambulatory BP, including

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Table 1. Patient baseline characteristics

Characteristics	Amlodipine Group (n = 38)	Valsartan Group (n = 38)
Age (yr)	65.7 (8.2)	65.5 (13)
Male gender (%)	32	37
BMI (kg/m^2)	25.2 (4.0)	23.7 (3.7)
Duration of HT (yr)	4.7 (3.2)	6.4 (7.0)
Hyperlipidemia (%)	29	39
Clinic SBP (mm Hg)	164 (8.4)	163 (16)
Clinic DBP (mm Hg)	93 (14)	91 (11)
Clinic PR (mm Hg)	71 (15)	72 (12)
24-h SBP (mm Hg)	147 (12)	148 (12)
24-h DBP (mm Hg)	83 (8.4)	86 (7.7)
24-h PR (mm Hg)	66 (8.4)	68 (8.3)
Awake SBP (mm Hg)	155 (12)	155 (12)
Awake DBP (mm Hg)	88 (9.2)	90 (7.7)
Awake PR (mm Hg)	70 (9.9)	72 (8.8)
Sleep SBP (mm Hg)	131 (16)	135 (19)
Sleep DBP (mm Hg)	75 (9.2)	77 (10)
Sleep PR (mm Hg)	60 (6.5)	59 (7.2)
Morning SBP (mm Hg)	156 (16)	154 (19)
Morning DBP (mm Hg)	89 (9.8)	90 (13)
Morning PR (mm Hg)	68 (10)	72 (8.6)
Lowest night SBP (mm Hg)	121 (14)	123 (19)
Lowest night DBP (mm Hg)	68 (9.1)	69 (10)
Lowest night PR (mm Hg)	59 (6.5)	60 (9.0)

Data did not show any statistical significance between the amlodipine and the valsartan group.

BMI = body mass index; DBP = diastolic blood pressure; PR = pulse rate; SBP = systolic blood pressure.

morning BP. The subjects included older Japanese hypertensive patients at four Japanese hospital clinics. The entry period was May 2002 to May 2003. A total of 76 patients (26 men and 50 women, mean age 65.6 years) with average seated clinic systolic BP (SBP) ≥140 mm Hg and < 180 mm Hg, or diastolic BP (DBP) ≥90 mm Hg and <110 mm Hg during the follow-up period (1 to 2 weeks) were recruited for this study. To be included in the study, patients were required to be ≥40 years of age, to have a diagnosis of essential hypertension, and to have no history of other significant medical disorders including diabetes, renal failure (serum creatinine ≥2.0 mg/dL), atrial fibrillation, or any clinically overt cardiovascular disease. All patients were fully ambulant. Body mass index was calculated as weight (killograms)/height (meters)^2.

Study Design

Each patient was studied for a maximum of 18 weeks, with a run-in period of 1 to 2 weeks and a treatment period of up to 8 to 16 weeks. After the run-in period, the valsartan group (n = 38) was started on 40 to 80 mg of valsartan just after breakfast, subsequently increasing the dose by 40-mg increments with an interval of 4 weeks (maximal dose 160 mg). The amlodipine group was started on 2.5 to 5 mg of amlodipine, increasing by 2.5 mg, unless the patient's BP had already been reduced to <140 mm Hg for SBP and <90 mm Hg for DBP or unless adverse events had occurred. Informed consent was obtained from all study participants, and the study was approved by the Research Ethics Committee of the Department of Cardiology, Jichi Medical School.

Ambulatory BP Monitoring

Noninvasive ambulatory BP monitoring (ABPM) was carried out twice on two separate weekdays with one of two automatic ABPM devices (TM-2421 or TM-2430, A&D Co., Tokyo, Japan), which recorded BP and pulse rate by the oscillometric method every 30 min for 24 hours. The first ABPM was performed at the end of the run-in period and the second ABPM at the end of the treatment period of 8 to 16 weeks.

Twenty-four-hour BP was defined as the average of all BP readings throughout 24 hours.[5] The subjects were all ambulant during the day, and no subjects reported staying in bed after waking. Sleep BP was defined as the average of BP from the time when patients went to bed until the time they got out of bed; awake BP was defined as the average of BP recorded during the rest of the day.[11] Morning BP was defined as the average of BP during the first 2 h after waking (four BP readings).[9] The lowest night BP was defined as the average BP of three readings centered on the lowest nighttime reading. The morning BP surge was calculated as the morning SBP minus the lowest night SBP.[9] No participants complained of sleep disturbance due to ABPM.

Statistical Analysis

All statistical analyses were carried out with SPSS software package, version 11.0 (SPSS Inc., Chicago, IL). A two-tailed paired t test was used to compare the mean values before and after each drug therapy. The χ^2 test was applied to examine differences between the prevalence in the two groups. Data are expressed as the mean ± SD or prevalence. A value of $P < .05$ was considered to be significant.

Results

All but one patient completed the study protocol. The clinic BP of this patient was 152/93 mm Hg at baseline and remained elevated even after valsartan was titrated to 160 mg/day, resulting in the patient discontinuing the study. However, 40 days after starting valsartan therapy, this patient's second ABPM was performed and the data were included in the analysis. Three adverse reactions were noted in the valsartan group (general fatigue in one patient, slight facial edema in one, and oral dysesthesia in one) and one adverse reaction (general fatigue) in the amlodipine group. All patients in the amlodipine group completed the study.

Baseline characteristics, including ambulatory BP of the study subjects, were comparable between the amlodip-

Table 2. Blood pressure before and after treatment

	Amlodipine Group (n = 38)			Valsartan Group (n = 38)		
	Baseline	Amlodipine	P	Baseline	Valsartan	P
Clinic SBP (mm Hg)	164 (8.4)	138 (7.3)	< .001	163 (16)	150 (19)	< .001
Clinic DBP (mm Hg)	93 (14)	83 (7.2)	< .001	91 (11)	84 (12)	.001
Clinic PR (mm Hg)	71 (15)	67 (11)	.11	72 (12)	71 (11)	.445
24-h SBP (mm Hg)	147 (12)	133 (10)	< .001	148 (12)	141 (14)	.001
24-h DBP (mm Hg)	83 (8.4)	78 (7.8)	< .001	86 (7.7)	83 (8.8)	.002
24-h PR (mm Hg)	66 (8.4)	69 (7.5)	.007	68 (8.3)	68 (8.4)	.861
Awake SBP (mm Hg)	155 (12)	140 (12)	< .001	155 (12)	148 (15)	.001
Awake DBP (mm Hg)	88 (9.2)	82 (8.1)	< .001	90 (7.7)	87 (9.0)	.005
Awake PR (mm Hg)	70 (9.9)	73 (8.8)	.004	72 (8.8)	71 (9.0)	.653
Sleep SBP (mm Hg)	131 (16)	119 (12)	< .001	135 (19)	128 (18)	.015
Sleep DBP (mm Hg)	75 (9.2)	70 (8.3)	< .001	77 (10)	73 (9.8)	.016
Sleep PR (mm Hg)	59 (6.5)	60 (7.0)	.04	59 (7.2)	60 (8.3)	.707
Morning SBP (mm Hg)	156 (16)	142 (11)	< .001	154 (19)	151 (19)	.396
Morning DBP (mm Hg)	89 (9.8)	85 (10)	.006	90 (13)	88 (13)	.437
Morning PR (mm Hg)	68 (10)	72 (9.9)	.006	72 (8.6)	70 (9.9)	.226
Lowest night SBP (mm Hg)	121 (14)	112 (11)	< .001	123 (19)	114 (18)	.002
Lowest night DBP (mm Hg)	68 (9.1)	66 (8.7)	.053	69 (10)	66 (11)	.078
Lowest night PR (mm Hg)	59 (6.5)	61 (7.8)	.218	60 (9.0)	59 (8.7)	.473

Paired t test was used for comparison between baseline and posttreatment values.
Abbreviations as in Table 1.

ine and valsartan groups (Table 1). Clinic BP, 24-h BP, awake BP, and sleep BP decreased significantly in both groups (Table 2). However, the reduction in all BP parameters (clinic SBP −26 mm Hg v −13 mm Hg, P = .001), 24-h SBP (−14 mm Hg v −7 mm Hg, P = .008), and awake SBP (−15 mm Hg v −7 mm Hg, P = .007) were significantly greater in the amlodipine group than in the valsartan group (Fig. 1).

Valsartan did not significantly reduce morning SBP, although it reduced the lowest night SBP (P = .002; Table 2). In contrast, amlodipine reduced both morning SBP and the lowest night SBP (both P < .001). The reduction of morning SBP surge (morning SBP minus lowest night SBP) was significantly greater in the amlodipine group than in the valsartan group (−6.1 mm Hg v +4.5 mm Hg, P = .02; Fig. 1).

There were no significant differences in reduction of 24-h SBP (7.7 mm Hg v 6.4 mm Hg) and morning SBP (3.0 mm Hg v 2.8 mm Hg) between the lower dose (40 to 80 mg/day) and the higher dose (120 to 160 mg/day) valsartan groups. There was no significant difference in the BP reduction of 24-h SBP (12 mm Hg v 16 mm Hg) and morning SBP (14 mm Hg v 15 mm Hg) between the lower dose (2.5 to 5.0 mg/day) and the higher dose (7.5 to 10 mg/day) amlodipine groups. With regard to both the lower and higher doses, the BP lowering effect was significantly

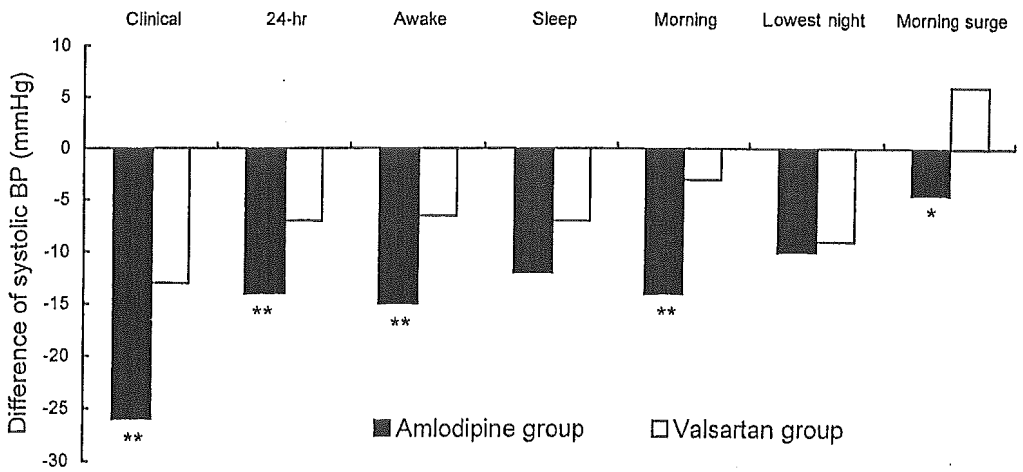

FIG. 1. Differences in clinic systolic blood pressure and ambulatory systolic blood pressure before and after amlodipine and valsartan treatment. **Black bars**, amlodipine group; **white bars**, valsartan group. BP = blood pressure. *P < .05 v valsartan group by ANOVA (between groups); **P < .01 v valsartan group by ANOVA.

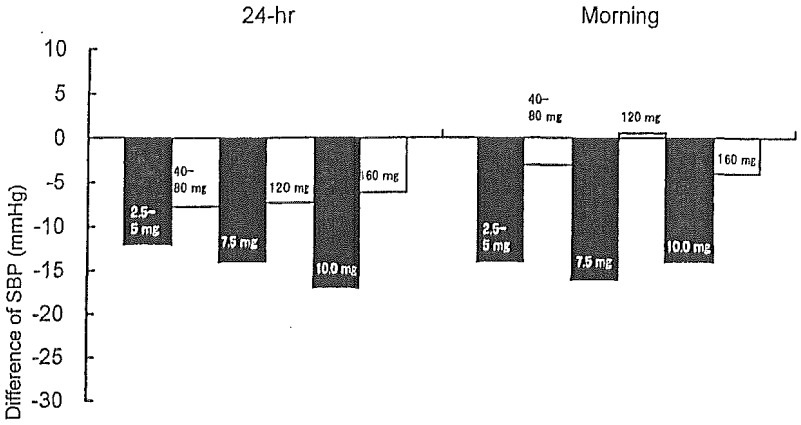

FIG. 2. Effects of amlodipine and valsartan on 24-hour and morning systolic blood pressure (SBP) by each dose. **Black bars,** amlodipine group; dose (**from left to right**): 2.5 to 5 mg (n = 21), 7.5 mg (n = 8), 10.0 mg (n = 9). **White bars,** valsartan group; dose (**from left to right**): 40 to 80 mg (n = 12), 120 mg (n = 7), and 160 mg (n = 19).

greater for amlodipine than for valsartan (both $P < .01$; Fig. 2).

To study the effect of age on the BP lowering effect, we separated the study patients into a younger age group (<65 years) and older group (≥65 years). The BP lowering characteristics of valsartan and amlodipine were essentially the same in each age group. In addition, there were no gender differences in the BP lowering effect of the two drugs.

To study the BP lowering characteristics of BP in relation to baseline BP, we graphed the scatter plot of the baseline and the reduction of 24-h BP for each group (Fig. 3). A baseline BP-dependent BP reduction was found in the amlodipine group but was not found in the valsartan group for 24-h and morning SBP.

Discussion

In this study, a once-daily morning dose of amlodipine significantly reduced morning BP and morning BP surge. In comparison, a once-daily morning dose of the long-acting ARB valsartan did not significantly reduce morning BP and morning BP surge in hypertensive patients, and its BP lowering effect on 24-h ambulatory BP was weaker and more heterogeneous independent of baseline BP level than was amlodipine. This difference was significant independent of the dose of each drug.

Twenty-four-hour BP (mean of BP throughout a 24-h period) is the most important predictor of hypertensive target organ damage (brain, heart, and kidney) and subsequent fatal and nonfatal cardiovascular events (stroke and coronary artery disease). In a recent prospective study on treated hypertensive patients, 24-h BP was an independent predictor of cardiovascular events independent of clinic BP.[12] A significant BP lowering effect as indicated by 24-h BP and morning BP is well established from our previous study in hypertensive patients.[13] In one recent study using ABPM, the BP lowering effect of valsartan 80 mg/day was comparable to that of amlodipine 5 mg in hypertensive patients.[10] However, in our study, the mean doses were 6.4 mg/day for amlodipine and 124 mg/day for valsartan, and the BP lowering effect was clearly less effective in the valsartan group than in the amlodipine group. Ethnic char-

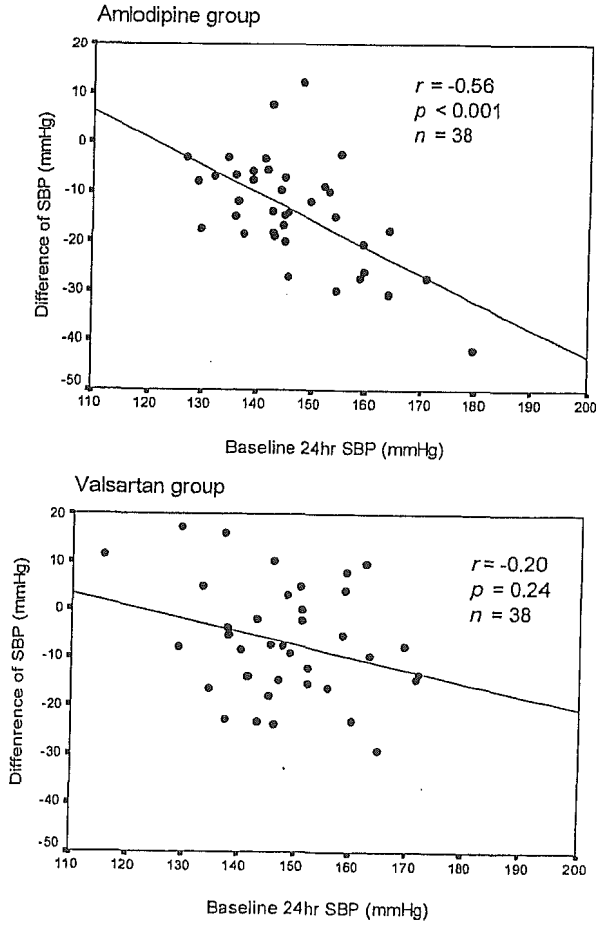

FIG. 3. Effects of amlodipine and valsartan on 24-h and morning systolic blood pressure (SBP) by each dose. **Solid lines** indicate linear regression lines.

acteristics or differences in salt intake between Asian (ie, Japanese) and white patients and may partly account for these inconsistent results. In Japan, stroke is much more common than coronary artery disease as compared the incidence in Western countries,[5] and the benefit of BP reduction for stroke is greater than that for coronary artery disease. In fact, as shown in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), relatively lower BP lowering effect of an angiotensin-converting enzyme (ACE) inhibitor was associated with increased cardiovascular risk, particularly for stroke, when compared with amlodipine.[14] In addition, the protective effect of RAAS blockade on hypertensive target organs seems limited under the BP control and is insufficient. Although a beneficial effect of valsartan in addition to ACE inhibitors on the prognosis of congestive heart failure patients whose BP is only moderately increased has been clearly demonstrated,[15] the insufficient BP lowering effect of valsartan monotherapy seems to be less beneficial than amlodipine for preventing cardiovascular events in hypertensive patients.

Recently we showed that the morning BP surge was significantly associated with clinical stroke risk in hypertensive patients.[9] This association was independent of age, 24-h BP level, and silent cerebral infarcts,[9] which are powerful predictors of clinical stroke events.[5] In addition to morning BP surge, morning BP level is also an important predictor of stroke events in hypertensive patients.[9] Because it has recently been demonstrated that, in addition to circulating factors, tissue RAAS of the cardiovascular system exhibits diurnal variation,[16] possibly in relation to a clock gene,[17] it was unexpected that valsartan did not significantly reduce morning BP level. As both valsartan and amlodipine reduced the lowest night BP to a similar degree, the morning BP surge was slightly increased in the valsartan group. This may be due to the shorter half-life of valsartan than that of amlodipine, particularly in nonresponders.

This lower BP reduction may not be generalized to all ARBs, such as telmisartan and irbesartan, given that the BP lowering effect of valsartan is weaker than that of these drugs.[18,19] However, even in the case of valsartan, when used in combination with diuretics, the BP lowering effects would be increased.[20] In the following large clinical trials in which diuretics have been permitted, benefits of RAAS blockers have been clearly demonstrated. The Perindopril pROtection aGainst Recurrent Stroke Study (PROGRESS) has demonstrated that stroke prognosis has been demonstrated only when the long-acting ACE inhibitor perindopril is used with diuretics in stroke survivors.[21] The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial has also clearly demonstrated that the benefit of ARB losartan was greater than that of β-blockers in high-risk hypertensive patients with left ventricular hypertrophy.[22] In our study, BP reduction is dependent on baseline BP level in the amlodipine group, whereas this BP response is heterogeneous in the valsartan group (as depicted in Fig. 3), indicating that there are responders and nonresponders for RAAS blockers. With regard to nonresponders, combination therapy with diuretics would be initiated or other classes of antihypertensive medication used.

In conclusion, amlodipine monotherapy controlled ambulatory BP throughout a 24-h period including the morning hours, whereas valsartan monotherapy was limited to controlling ambulatory BP, particularly morning BP, in hypertensive patients. Combination therapy with diuretics or other classes of antihypertensive medications would be necessary to achieve target BP levels.

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Short- and Long-Term Incidence of Stroke in White-Coat Hypertension

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Abstract—White-coat hypertension (WCH) has been associated with a low risk for stroke, but long-term data are scanty. We analyzed individual data from 4 prospective cohort studies from the United States, Italy, and Japan that used comparable methodology for 24-hour noninvasive ambulatory blood pressure monitoring (ABPM). Overall, 4406 subjects with essential hypertension and 1549 healthy normotensive controls who were untreated at the time of initial ABPM were followed for a median of 5.4 years up to censoring or occurrence of a first stroke. At entry, mean age of subjects was 56 years (range 18 to 97). Prevalence of WCH was 9%. During follow-up, there were 213 new cases of stroke. Stroke rate (×100 person years) was 0.35 in the normotensive group, 0.59 in the WCH group, and 0.65 in the group with ambulatory hypertension. In a multivariate analysis, the adjusted hazard ratio for stroke was 1.15 (95% confidence interval [CI], 0.61 to 2.16) in the WCH group (P=0.66) and 2.01 (95% CI, 1.31 to 3.08) in the ambulatory hypertension group (P=0.001) compared with the normotensive group. After the sixth year of follow-up, the incidence of stroke tended to increase in the WCH group, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of follow-up. In conclusion, WCH was not associated with a definitely increased risk of stroke during the total follow-up period. However, WCH might not be a benign condition for stroke in the long term. (***Hypertension.* 2005;45:203-208.)**

Key Words: blood pressure monitoring, ambulatory ■ stroke ■ blood pressure

White-coat hypertension (WCH),[1] referred to as office[2] or isolated clinic[3] hypertension, is defined by a persistently elevated clinic blood pressure (BP), with normal BP outside the hospital or doctor's office.[1–4] The prognostic significance of WCH is emerging from some event-based cohort[5–8] and interventional[9] studies, which suggest that individuals with WCH have a risk of major cardiovascular events apparently comparable with that of clinically normotensive subjects and markedly less than that of subjects with elevated daytime BP.

Almost all these studies examined a composite pool of cardiovascular events, so that any specific association between WCH and cerebrovascular or coronary events remains elusive. In a study from Japan,[6] incidence of stroke was comparable between clinically normotensive individuals and subjects with WCH and increased in subjects with higher levels of ambulatory BP.[6] However, conclusions of this study are hardly applicable to different ethnic groups at lower stroke risk.

In the present study, we pooled and analyzed individual data from 4 prospective cohort studies from the United States, Italy, and Japan that used comparable methods for 24-hour noninvasive ambulatory BP monitoring (ABPM).

Methods

The International Collaborative Study of the Prognostic Utility of ABPM was initiated to examine the relationship between ambulatory BP and the risks of cardiovascular disease using individual data from a pooled sample of large observational cohorts that contain ambulatory BP measurements. The aims of the study, the structure of the database, and all analytic and publication aspects were discussed and agreed on in advance. The study from the United States was the New York Prognostic Effects of ABPM (NYPEAP)[10]; the study from Italy was the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA)[5,11]; and the studies from Japan were the Ohasama study[12] and the Jichi Medical School (JMS)-ABPM Study, Wave 1.[6,13] Details regarding inclusion and exclusion criteria in the single studies have been published previously.[5,6,10–13]

The majority of subjects in the NYPEAP (83%), PIUMA (88%), and JMS-ABPM (88%) cohorts had a clinic BP ≥140 mm Hg systolic BP (SBP) or 90 mm Hg diastolic BP (DBP) at entry compared with only 27% in the Ohasama community sample. Subjects on antihypertensive medications in NYPEAP, PIUMA, and Tochigi, but not Ohasama, were withdrawn from medications for a minimum of 2 weeks before ABPM. In NYPEAP, PIUMA, and JMS-ABPM, clinically normotensive subjects (ie, those with office BP <140 mm Hg SBP and 90 mm Hg DBP) were generally healthy volunteers recruited from the hospital staff or asymptomatic subjects without medical problems referred to the hospital facility for various reasons.

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Subjects with overt cardiac or cerebrovascular disease, cancer, or hepatic or renal disease at enrollment were excluded. Subjects with diabetes, defined by a fasting glucose of 7.8 mmol/L or use of an oral hypoglycemic agent or insulin, were included. All subjects provided informed consent to be included in each of the 4 studies, which were approved by local ethical committees.

BP Measurement

Details regarding the procedures for clinic BP and ABPM in the NYPEAP,[10] PIUMA,[5,11] Ohasama,[12] and JMS-ABPM[6,13] cohorts have been published previously. Clinic BP was taken at the time of enrollment into the study. In the NYPEAP study, a BP taken by the physician was available for 85% of participants. When missing, the clinic BP taken by a nurse was substituted.

In all 4 studies, ABPM was carried out at entry. In the PIUMA study, the monitor (SpaceLabs 5200, 90202, or 90207; SpaceLabs) was set to measure BP every 15 minutes during the entire 24-hour period. In the NYPEAP study, readings were taken either: (1) every 15 minutes between 6 AM and 12 PM and at 30-minute intervals between 12 PM and 6 AM using either a Del Mar Avionics P2 or P3 or a SpaceLabs 5200 (first 672 subjects); or (2) every 15 minutes between 8 AM and 10 PM and at 30-minute intervals between 10 PM and 8 AM using a SpaceLabs 90202 monitor (last 341 subjects).

In the Ohasama study, readings were taken at 30-minute intervals. Well-trained public health nurses visited each participant on a weekday morning to attach the ABPM device and to detach it the next morning. The participants kept a diary to record daily activities. Ambulatory BP was monitored using the ABPM-630 (Nippon Colin), preset to measure BP every 30 minutes. In the JMS-ABPM, noninvasive ABPM was performed on a weekday with 1 of 3 automatic devices (ABPM-630; Nippon Colin; TM-2421 or TM-2425, A&D Co., Inc.), which recorded BP and pulse rate every 30 minutes for 24 hours.

Using self-reports of the times participants went to sleep and woke up, ambulatory BP readings were aggregated to create a mean of all readings taken while awake and the mean of all readings taken during sleep. This was done separately for SBP and DBP and for pulse pressure (PP), the difference between SBP and DBP.

White-Coat Hypertension

WCH was defined by an average awake ambulatory BP <130 mm Hg SBP and 80 mm Hg DBP. We also determined the risk of stroke associated with a definition of WCH based on an awake ambulatory BP <135/85 mm Hg.[14,15]

Follow-Up

Follow-up was based on telephone contacts or periodical clinical visits at the referring facility or through the Regional Stroke Registration System. Stroke was defined as a focal central nervous system lesion considered vascular in origin and having clinical sequelae lasting ≥24 hours. Fatal and nonfatal strokes were included. Transient ischemic attacks were excluded from the present analysis.

Data Analysis

Statistical analysis was performed using SPSS (SPSS) and SAS-Stat (SAS Institute). One-way ANOVA and multiple comparisons with the Tukey test when appropriate were performed to compare the study sites and the 3 groups with clinical normotension, WCH, and ambulatory hypertension. We report the number of strokes that were recorded in each study, the total number of person years of follow-up for that event, and the unadjusted incidence rate. For survival analyses, event-free curves were estimated using Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. For subjects who experienced multiple events, analysis was restricted to the first event. The independent effect of several prognostic factors on survival was tested by stepwise Cox model.[16]

TABLE 1. Main Characteristics in the Study Population

Variable	Total Cohort (n=5955)	NYPEAP (n=1296)	PIUMA (n=2620)	Ohasama (n=1277)	JMS-ABPM (n=762)	Overall *P*-Value
Age, years	56 (14)	50 (13)	51 (12)	61 (10)	72 (10)	*P*<0.0001
Ethnicity						*P*<0.0001
White, %	64.1	92.2	100	0	0	
Black, %	1.4	6.4	0	0	0	
Asian, %	34.2	0	0	100	100	
Other, %	0.3	1.4	0	0	0	
Sex, % men	50	65	53	34	38	-
Weight, kg	68.2 (16)	75.1 (14)	75.1 (14)	54.0 (9)	56 (10)	*P*<0.0001
Body mass index, kg/m^2	25.3 (3.8)	25.1 (3.5)	26.8 (3.9)	23.4 (3.0)	24.0 (3.5)	*P*<0.0001
Diabetes, %	11.0	not available	7.6	17.5	11.9	-
Cigarette smoking, %	19.7	10.7	23.6	19.3	20.9	-
Total cholesterol, mmol/L	5.43 (1.08)	5.85 (1.11)	5.54 (1.09)	4.98 (0.93)	5.17 (0.88)	*P*<0.0001
Serum creatinine, mmol/L	87.5 (22)	95.5 (23)	87.5 (21)	not available	79.6 (19)	*P*<0.0001
Serum glucose, mmol/L	5.50 (1.35)	5.81 (1.18)	5.63 (1.38)	not available	5.33 (1.39)	*P*<0.0001
Office SBP, mm Hg	149 (23)	150 (21)	154 (20)	131 (18)	160 (22)	*P*<0.0001
Office DBP, mm Hg	90 (14)	94 (11)	95 (11)	74 (11)	91 (14)	*P*<0.0001
Office PP, mm Hg	59 (17)	56 (18)	58 (17)	57 (14)	69 (16)	*P*<0.0001
Awake SBP, mm Hg	139 (17)	141 (17)	141 (16)	129 (14)	145 (18)	*P*<0.0001
Awake DBP, mm Hg	87 (15)	91 (10)	91 (11)	76 (8)	82 (29)	*P*<0.0001
Awake PP, mm Hg	52 (15)	49 (13)	50 (11)	53 (8)	62 (29)	*P*<0.0001
Sleep SBP, mm Hg	121 (18)	122 (18)	124 (17)	112 (15)	127 (18)	*P*<0.0001
Sleep DBP, mm Hg	72 (11)	76 (11)	75 (11)	64 (8)	72 (11)	*P*<0.0001
Sleep PP, mm Hg	49 (11)	46 (13)	49 (11)	48 (8)	55 (11)	*P*<0.0001

TABLE 2. Main Characteristics in the Normotensive Group and in the Groups With WCH and Ambulatory Hypertension

Variable	Normotensive Group (n=1549)	WCH (n=398)	Ambulatory Hypertension (n=4008)	Overall *P*-Value
Age, years	55 (14)	61 (14)*†	55 (14)	0.0001
Sex, % women	60	63†	45	0.0001
Weight, kg	60.7 (15)†	63.2 (14)*†	71.5 (15)	0.0001
Body mass index, kg/m^2	24.1 (3.4)†	24.9 (3.8)*†	25.9 (3.9)	0.0001
Diabetes, %	14.3†	11.7*†	9.5	0.0001
Cigarette smoking, %	19.9	13.9*†	20.2	0.010
Total cholesterol, mmol/L	5.11 (1.01)†	5.42 (1.07)*‡	5.55 (1.08)	0.0001
Serum creatinine, mmol/L	86.0 (19)	82.4 (17)†	87.6 (23)	0.001
Serum glucose, mmol/L	5.59 (1.40)	5.42 (1.12)	5.50 (1.36)	0.23
Office SBP, mm Hg	124 (11)†	150 (12)*†	158 (19)	0.0001
Office DBP, mm Hg	74 (9)†	86 (11)*†	96 (11)	0.0001
Office PP, mm Hg	50 (10)†	65 (16)*‡	62 (18)	0.0001
Awake SBP, mm Hg	126 (12)†	121 (6)*†	146 (15)	0.0001
Awake DBP, mm Hg	78 (21)†	73 (5)*†	92 (10)	0.0001
Awake PP, mm Hg	48(20)†	49 (6)†	54 (12)	0.0001
Sleep SBP, mm Hg	110 (13)†	110 (11)†	127 (17)	0.0001
Sleep DBP, mm Hg	64 (9)†	63 (7)†	76 (11)	0.0001
Sleep PP, mm Hg	45 (8)†	47 (8)†	51 (12)	0.0001

*P<0.01 vs normotensive group; †P<0.01 vs ambulatory hypertension; ‡P<0.05 vs ambulatory hypertension.

Analyses were stratified by study site because of expected differences in stroke rate between the different groups. Several potential confounding variables assessed at entry were considered in the analysis: current smoking status, weight, height, body mass index, total cholesterol, and use of antihypertensive medication, including those titrated off before ABPM. In 2-tailed tests, P values <0.05 were considered statistically significant.

Results

Cohort Features

As shown in Table 1, age of the subjects was higher in the JMS-ABPM cohort than in the other cohorts (all P<0.01). Diabetes was more frequent in the Ohasama sample (P<0.001) compared with each of the others, but information was not available from the NYPEAP cohort. Office SBP and PP were highest in the JMS-ABPM cohort (P<0.01 versus the other cohorts), whereas office DBP was highest in the PIUMA cohort (P<0.01 versus the other cohorts). Comparable differences between the cohorts were found for awake and asleep ambulatory BP.

Differences Between Groups

Age of the subjects (Table 2) was higher in the WCH group than in the other groups. Subjects with WCH tended to be women more frequently, smokers less frequently, and diabetics more frequently when compared with those with ambulatory hypertension (all P<0.01). In the WCH group, office BP was intermediate between the normotensive group and that with ambulatory hypertension. In contrast, awake SBP and DBP were lower in the group with WCH than in the normotensive group (both P<0.01), whereas sleep SBP and DBP were comparable between the 2 group. Prevalence of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up is reported in Figure 1. A similar proportion of subjects included in the normotensive control group or the WCH group at entry were receiving the 5 classes of antihypertensive drugs (all P<NS). In contrast, a greater proportion of subjects belonging to the AH group were receiving diuretics, β-blockers, angiotensin-converting enzyme inhibitors or calcium antagonists (P<0.01 versus each of the other groups). Frequency of treatment with angiotensin II antagonists did not differ between the groups.

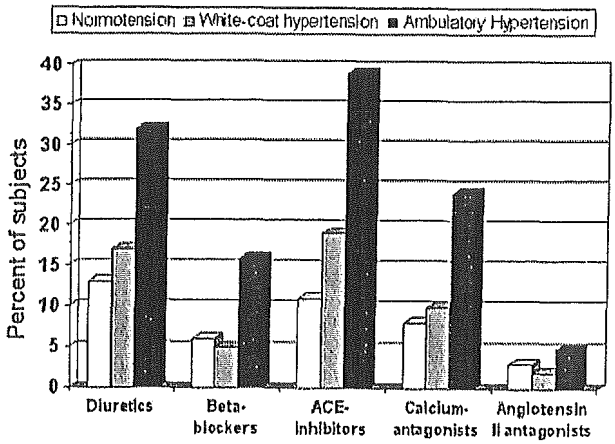

Figure 1. Percentage of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up. ACE indicates angiotensin-converting enzyme.

TABLE 3. Entry Characteristics of Subjects With and Without Future Stroke

Variable	No Future Stroke (n=5742)	Future Stroke (n=213)	*P*-Value
Age, years	55 (14)	68 (12)	0.0001
Sex, % men	49.3	56.3	0.04
Weight, kg	68 (16)	64 (16)	0.0001
Body mass index, kg/m^2	25.3 (3.8)	25.0 (4.0)	0.19
Diabetes, %	10.5	23.5	0.0001
Asian ethnic group, %	33.5	53.5	0.0001
Cigarette smoking, %	19.3	29.7	0.0001
Total cholesterol, mmol/L	5.43 (1.08)	5.35 (1.06)	0.293
Serum creatinine, mmol/L	86.9 (22)	91.1 (20)	0.028
Serum glucose, mmol/L	5.50 (1.3)	5.78 (1.8)	0.021
Office SBP, mm Hg	148 (22)	159 (24)	0.0001
Office DBP, mm Hg	90 (14)	90 (14)	0.95
Office PP, mm Hg	59 (16)	69 (19)	0.0001
Awake SBP, mm Hg	139 (17)	149 (19)	0.0001
Awake DBP, mm Hg	87 (15)	87 (12)	0.657
Awake PP, mm Hg	52 (15)	61 (14)	0.0001
Sleep SBP, mm Hg	121 (17)	134 (21)	0.0001
Sleep DBP, mm Hg	72 (11)	76 (12)	0.0001
Sleep PP, mm Hg	49 (11)	58 (14)	0.0001

Incidence of Stroke

There were 213 new cases of stroke. Overall, the JMS-ABPM cohort showed the highest rate of stroke (6.09×100 person years) followed by the Ohasama cohort (2.12×100 person years), the PIUMA cohort (0.59×100 person years), and the NYPEAP cohort (0.19×100 person years).

At entry (Table 3), subjects with future stroke were older, leaner, and more frequently smokers, diabetics, and of Asian ethnic origin than the subjects without future stroke (all $P<0.01$). Office and awake SBP and PP, but not DBP, were higher in the group with future stroke than in that without future stroke (all $P<0.001$). Sleep SBP, DBP, and PP were higher in the group with future stroke (all $P<0.001$).

The cumulative hazard for stroke (Figure 2) differed between the normotensive group, the group with WCH, and the group with ambulatory hypertension (log-rank test; P value for trend=0.0013). Figure 2 shows that the cumulative hazard for stroke was comparable in the WCH and normotensive groups up to the sixth year of follow-up. However, subsequently, there was an increase in the hazard of stroke in the WCH group, with the corresponding curve diverging from that of the normotensive group and crossing that of the ambulatory hypertension group by the ninth year of follow-up.

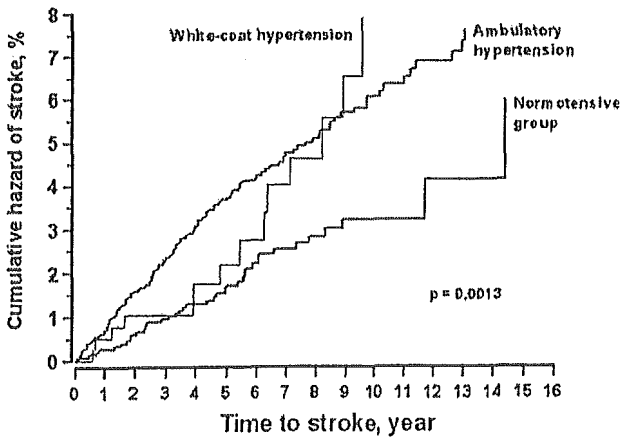

Figure 2. Cumulative hazard for stroke in the 3 groups (normotensive subjects, WCH, and ambulatory hypertension).

The crude rate of stroke (×100 person years) during the entire follow-up period was 0.35 in the normotensive group, 0.59 in the WCH group, and 0.65 in the group with ambulatory hypertension. The corresponding values up to the sixth year of follow-up were 1.06 in the normotensive group, 0.91 in the WCH group, and 1.5 in the ambulatory hypertension group. The unadjusted hazard ratios for stroke, with 95% confidence intervals (CIs), are displayed in Figure 3. Results were comparable using the 130/80 and the 135/85 mm Hg threshold values for definition of WCH.

Multivariate Analysis

In a Cox analysis (Table 4) stratified by center, WCH was associated with a nonsignificant 1.15 hazard ratio for stroke compared with the normotensive group ($P=0.658$). The no-interaction assumption of the stratified model was evaluated according to Kleinbaum[17] and found acceptable at the <0.01 level. The no-interaction assumption implies that the variables being stratified (ie, center) do not interact with the covariates in the model. When office SBP and awake SBP were forced in the same model, office BP did not yield statistical significance ($P=0.322$), and the risk of stroke increased by 2% for any 1 mm Hg increase in the awake SBP (95% CI, 1% to 3%; $P=0.0001$). The 6-year risk factor–adjusted probability of stroke in clinically normotensive individuals and in hypertensive subjects with WCH and ambulatory hypertension is depicted in Figure 4. Estimates have been made in smokers and nonsmokers for either sex.

Discussion

This study is the first to investigate the short- and long-term risk of stroke in subjects with WCH, ambulatory hypertension, and clinical normotension in a large multinational and multiethnic population. WCH was defined by an average daytime ambulatory BP <130 mm Hg SBP and <80 mm Hg DBP because in a previous analysis,[5] the risk of cardiovascular events increased in association with higher ambulatory BP levels. Average daytime levels of BP <130/80 mm Hg have been defined as definitely normotensive.[14]

During the entire follow-up period, the incidence of stroke did not differ between the WCH and the normotensive control groups. However, stroke rate showed a trend to increase after the sixth year of follow-up in the group with WCH, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of observation. Results were consistent among the different cohorts and were independent of age, sex, cigarette smoking, and previous antihypertensive medications.

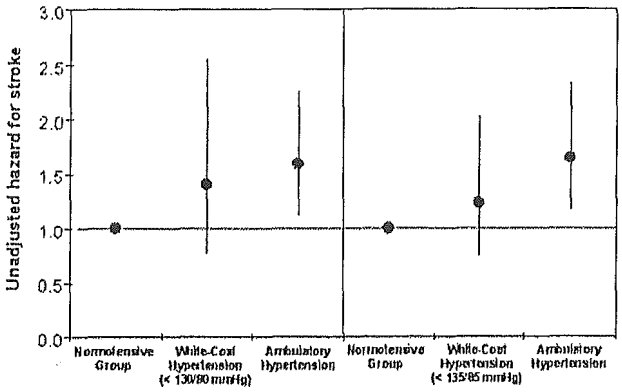

Figure 3. Unadjusted hazard for stroke in the WCH and ambulatory hypertension groups compared with the normotensive group. WCH has been defined by an average awake ambulatory BP <130/80 mm Hg (left panel) or <135/85 mm Hg (right panel).

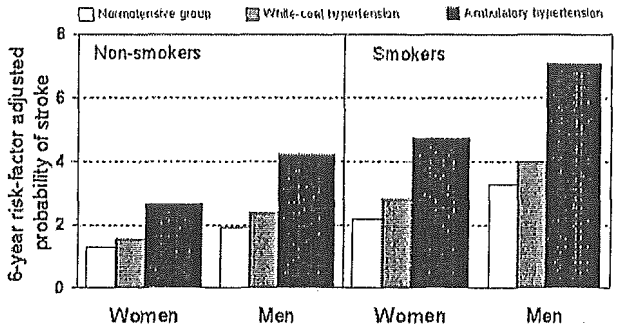

Figure 4. Six-year risk factor adjusted probability of stroke in clinically normotensive subjects and in hypertensive subjects with WCH and ambulatory hypertension. Estimates have been made in smokers and nonsmokers for either sex.

Clinical Relevance and Prognostic Value of WCH

ABPM has been approved by the US Centers for Medicare and Medicaid Services[18] for reimbursement in patients with suspected WCH. Although some outcome-based studies suggested that WCH is associated with a risk of events apparently comparable to that of clinically normotensive subjects and inferior to that of subjects with elevated daytime BP,[5–9] other studies focused on target organ damage suggested that patients with WCH may be at intermediate risk between the clinically normotensive individuals and those with ambulatory hypertension.[7,8,19–21] Therefore, the important issue of whether WCH should be considered an innocent condition remains open and unresolved.[4,22] Unfortunately, only a few data are available on the long-term natural history of WCH. In a longitudinal study, such condition evolved into ambulatory hypertension in 37% of subjects, with an accompanying rise in left ventricular mass.[23] In a study, a comparable proportion of subjects with clinical normotension and WCH evolved toward ambulatory hypertension (15% and 22%, respectively).[24]

In this study, based on 38 100 person years of observation, the highest stroke rate was noted in the clinical-based JMS-ABPM cohort, which included elderly Japanese subjects with hypertension, followed by the Ohasama cohort, which included a general Japanese population, and the PIUMA cohort, which included Italian subjects with essential hypertension. The lowest stroke rate was observed in the NYPEAP cohort, recruited in the New York area. In the absence of a significant center-covariate interaction, our findings can be reliably assumed as consistent across the different cohorts.

An unexpected finding in our study was a distinct trend toward an increased incidence of stroke in the WCH group after the sixth year of follow-up. Although substantiated only by a small number of events, these findings raise some concerns about the long-term safety of WCH. Clearly, further long-term studies are needed to clarify this aspect. In this context, it has been noted that the degree of BP rise during mental stress is a predictor of the long-term growth of atherosclerotic plaque independently of age and initial plaque area[25] Thus, it could be speculated that frequent BP peaks triggered by alerting reactions to stress may contribute to the rise in long-term risk of carotid atherosclerosis and ultimately of stroke in subjects with WCH.

Study Limitations

Because office and ambulatory BP measurements have been obtained only at entry, no information is available on the prognostic impact of serial changes in these parameters over time. In the Office versus Ambulatory Blood Pressure (OvA) study, in-treatment ambulatory BP predicted cardiovascular events independently of traditional risk factors in treated hypertensive patients.[26] However, the OvA study could not compare the predictive value of pretreatment versus in-treatment BP. In the PIUMA study, in-treatment ambulatory BP was more potent

TABLE 4. Independent Predictors of Stroke

Covariate	Comparison	Hazard Ratio	*P*-Value	95% CI
Age	1 year	1.08	0.000	1.07–1.10
Sex	Men vs women	1.57	0.003	1.17–2.12
Smoking status	Yes vs no	1.71	0.001	1.24–2.37
Previous antihypertensive treatment	Yes vs no	1.63	0.001	1.23–2.18
Ambulatory BP category				
	Normotensive group	1		
	WCH	1.15	0.658	0.61–2.16
	Ambulatory hypertension	2.01	0.001	1.31–3.08

Analysis stratified by center. WCH was defined by an average awake BP<130 mm Hg SBP and 80 mm Hg DBP.

than pretreatment ambulatory BP for cardiovascular risk stratification.[27] In the present study, a comparable number of subjects who were clinically normotensive or white-coat hypertensives at entry were receiving antihypertensive drugs during follow-up. These data suggest a comparable evolution toward the need of antihypertensive treatment in subjects with WCH and clinically normotensive controls. Finally, because data on mortality shortly after stroke were not available from all cohorts, no separate analysis could be performed on fatal and nonfatal stroke. Similarly, analyses on the different types of stroke (ie, lacunar, embolic, hemorrhagic, etc) were not possible because of insufficient standardization across the different cohorts. A substantial proportion of strokes in hypertensive subjects are attributable to lacunar infarction at the base of the brain, where short straight arteries transmit a substantial BP load from the large arteries to small resistance arteries over a very short distance.[28]

Perspectives

The long-term prognostic impact of WCH remains uncertain. In this multinational outcome-based study, we failed to detect differences in the risk of stroke between subjects with WCH and clinically normotensive controls. The risk of stroke remained consistently higher among subjects with ambulatory hypertension. However, the incidence of stroke showed a trend to increase in the long run in the group with WCH, with the corresponding hazard curve crossing that of the ambulatory hypertension group by the ninth year of follow-up. These data raise the hypothesis, to be tested in future studies, that WCH might not be a benign condition for stroke in the long term.

Acknowledgments

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Original Article

Effects of Bedtime *vs.* Morning Administration of the Long-Acting Lipophilic Angiotensin-Converting Enzyme Inhibitor Trandolapril on Morning Blood Pressure in Hypertensive Patients

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Cardiovascular events occur most frequently in the morning. To study the effects of the long-acting lipophilic angiotensin-converting enzyme (ACE) inhibitor trandolapril on morning blood pressure (BP), we performed ambulatory BP monitoring (ABPM) before and after administration of trandolapril just before going to bed (bedtime-administered group: $n=17$) or in the morning (morning-administered group: $n=20$) in 37 hypertensive patients. Both sets of ABPM data were available in 30 patients. The 24-h systolic BP (SBP) levels were significantly decreased by 7.2 mmHg in the morning-administered group ($p=0.02$) and by 5.2 mmHg in the bedtime-administered group ($p=0.04$). In the bedtime-administered group, prewaking SBP (the average of the 2-h SBP values just before waking) and morning SBP (the average of the 2-h SBP values just after waking) were significantly decreased by 11 mmHg ($p=0.005$) and by 8.4 mmHg ($p=0.03$), respectively. On the other hand, in the morning-administered group, the reduction of prewaking SBP (3.9 mmHg, n.s.) and morning SBP (6.6 mmHg, n.s.) did not reach the level of statistical significance. However, the differences in the reductions of prewaking and morning SBPs between the two groups were not statistically significant. There was no additional reduction of the nighttime lowest BP in either administration group. In conclusion, bedtime administration of the long-acting ACE inhibitor trandolapril seems to be a safe and effective means of controlling morning BP in hypertensive patients without an excessive fall in nocturnal BP. (*Hypertens Res* 2004; 27: 15–20)

***Key Words:* angiotensin-converting enzyme inhibitor, hypertension, morning blood pressure surge, morning hypertension, nocturnal blood pressure**

Introduction

Clinical cardiovascular events and subclinical target organ damage are closely associated with blood pressure (BP) variation independent of BP level (*1–10*). Diurnal BP variation is determined by various genetic (*11*, *12*), and environmental factors, including psychological and physical activities (*13–27*). Cardiovascular events occur more frequently in the morning, and BP also exhibits diurnal variation with increases in the morning (morning surge) (*28–30*). Previously, morning BP surge was reported to be associated with cardiac hypertrophy in hypertensive patients (*31*). Recently, we showed that the morning BP surge was significantly associated with clinical stroke risk in hypertensive patients (*32*). This association was independent of age and 24-h BP level.

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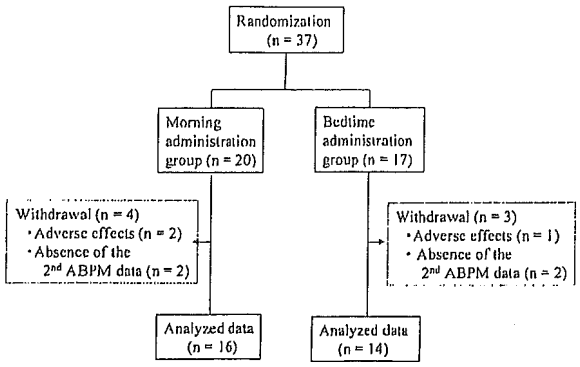

Fig. 1. *Selection of study subjects.*

Thus, an antihypertensive medication that was more specific for morning BP surge would be useful for the prevention of cardiovascular events in hypertensive patients.

The renin-angiotensin-aldosterone system is activated in the morning, and may contribute to morning BP surge (*29*) and morning increase in cardiovascular risk. Long-acting angiotensin-converting enzyme (ACE) inhibitors have been reported to lower the ambulatory BP without disruption of its diurnal variation (*33*). However, a specifically timed administration of the long-acting lipophilic ACE inhibitor trandolapril just before going to bed may achieve a greater reduction of morning BP in hypertensives.

Methods

Patient Selection

This study was a multicenter open-label randomized study of the effects of morning *vs.* evening administration of trandolapril on ambulatory BP. The subjects included older Japanese hypertensive patients at four Japanese hospital clinics. The entry period was February 2001 to January 2003. A total of 37 patients were recruited for this study (Fig. 1). The entry BP criteria were as follows: 1) average seated clinic systolic BP (SBP) $\geq$140 and $<$180 mmHg and/or diastolic BP (DBP) $\geq$90 and $<$110 mmHg during the follow-up period (3–5 weeks); and 2) 24-h SBP $\geq$130 mmHg and/or 24-h DBP $\geq$80 mmHg as shown by baseline first ambulatory BP monitoring (ABPM). To be included in the study, patients had to be $\geq$40 years of age, had to have been diagnosed with essential hypertension, and had to have no history of other significant medical disorders, including diabetes, renal failure (serum creatinine $\geq$2.0 mg/dl), atrial fibrillation, or any clinically overt cardiovascular disease. They were all fully ambulant. The body mass index was calculated as weight (kg)/[height (m)]^2.

Study Design

Each patient was studied for a maximum of 12 weeks, with an observation period of 2–4 weeks, and a treatment period of up to 8 weeks. After the observation period, patients were started on 1 mg of trandolapril, taken at bedtime (bedtime-administration group), or just after breakfast (morning-administration group). After 4 weeks of treatment the dosage was increased to 2 mg of trandolapril unless the patient's BP had already been reduced to below 150 mmHg in systole and 90 mmHg in diastole, or side effects had occurred. Following this dosage adjustment, patients remained on treatment for another 4 weeks. Informed consent was obtained, and the study was approved by the Research Ethics Committee of the Department of Cardiology, Jichi Medical School.

We excluded seven patients for whom the second ABPM recordings were not obtained: four of these patients refused the second ABPM, two developed cough, and one developed dizziness during the titration period (Fig. 1).

ABPM

Noninvasive ABPM was carried out two times on a weekday with one of two automatic ABPM devices (TM-2421 or TM-2425; A&D Co. Inc., Tokyo, Japan), which recorded BP and pulse rate by the oscillometric method every 30 min for 24 h. The first ABPM was performed at the end of the observation period, and the second ABPM at the end of the 8-week treatment period. The interval between the first and second ABPMs was 8 weeks.

Twenty-four hour BP was defined as the average of all BP readings over 24 h (*34*). The subjects were all ambulant during the day, and no subjects reported staying in bed after waking. Sleep BP was defined as the average of BPs from the time when the patient went to bed until the time he/she got out of bed, and awake BP as the average of BPs recorded during the rest of the day (*4*, *7*). Morning BP was defined as the average of BPs during the first 2 h after the wakeup time (four BP readings) (*32*). The nighttime lowest BP was defined as the average BP of three readings centered on the lowest nighttime reading. Evening BP was defined as the average BP during the 2 h before going to bed (four BP readings) (*32*). Preawake BP was defined as the average BP during the 2 h just before wakeup time (four BP readings) (*32*). The morning BP surge (MBPS) was calculated as the morning SBP minus the nighttime lowest SBP (*32*). SBP were used for all these calculations.

Statistical Analysis

The analysis was conducted for the 30 patients for whom the first and second ambulatory BP recordings were successfully obtained. The changes from the baseline values were analyzed statistically using the paired Wilcoxon-test for each subgroup. Two-sided Mann-Whitney *U*-tests and χ^2-tests

Table 1. Patient Characteristics

	Morning administration group (n=16)	Bedtime administration group (n=14)	Total group (n=30)
Age (years)	68±9.0	66±13	67±11
Men/women (n)	7/9	10/4	17/13
Body mass index (kg/m^2)	25.2±5.1	23.8±3.3	24.6±4.3
Other antihypertensives (n)	7	6	13
Calcium antagonist (n)			
Short-acting	0	1	1
Long-acting	5	4	9
α-Blocker	1	1	2
β-Blocker	1	0	1
Dose of trandolapril (mg/day)	1.4±0.5	1.2±0.5	1.3±0.5
Clinic SBP (mmHg)			
Baseline	158±8.7	161±12	160±10
After trandolapril	141±17	143±14	142±15
Reduction	17±16	19±16	18±16
Clinic DBP (mmHg)			
Baseline	93±9.6	92±15	92±12
After trandolapril	83±7.6	84±13	83±11
Reduction	10±7.9	8.3±6.1	9.3±7.1
Sleep time (h)			
Baseline	8.9±1.2	8.7±1.3	8.8±1.2
After trandolapril	8.8±1.4	8.9±1.1	8.9±1.2

BP, blood pressure; SBP, systolic BP; DBP, diastolic BP. Data are shown as the means±SD or the number of patients.

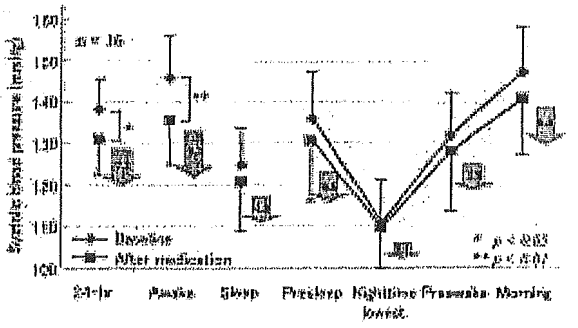

Fig. 2. *Change in ambulatory blood pressure levels in the morning-administration group.*

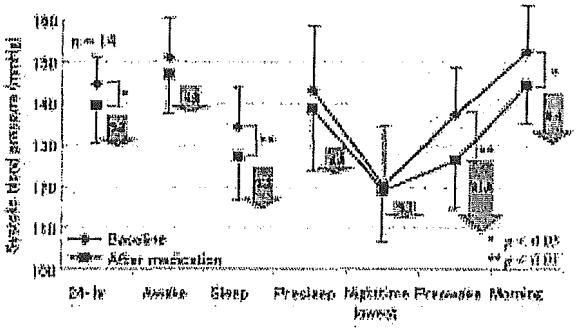

Fig. 3. *Change in ambulatory blood pressure levels in the bedtime-administration group.*

were used to test differences between the two groups in the mean values of continuous measures and prevalence rates, respectively. The criterion for determining statistical significance was $p<0.05$. The results are given as the mean±SD.

Results

The baseline characteristics of the study subjects as well as the baseline BPs and BPs after trandolapril therapy were comparable between the morning- and bedtime-administration groups (Table1). In addition, there were no significant differences in the baseline ABPM-derived BP parameters between the 2 groups. The 24-h BPs were reduced significantly in both groups, and the degrees of the reductions were also comparable between the two groups (Figs. 2, 3). There were no significant differences in the BP-lowering effects on ABPM parameters between subjects taking and those not taking additional antihypertensive medications.

In the morning-administration group, awake BPs were significantly reduced, but the reduction of sleep BPs, morning BPs and preawake BPs did not reach statistical significance (Fig. 2). In the bedtime-administration group, the reduction