Original Article

Prognostic Value of Nighttime Blood Pressure in the Elderly: A Prospective Study of 24-Hour Blood Pressure

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Although it has been suggested in several reports that 24-h ambulatory blood pressure (BP) is a better predicter than casual BP measured in a clinician's office of the incidence of cardiovascular (CV) events, little information is available concerning the prognostic value of nighttime BP in the elderly population. Therefore, to evaluate the clinical implications of the nighttime BP in the elderly, we prospectively followed-up 324 elderly individuals (mean age, 77.2±7.0 years) who had undergone ambulatory BP monitoring at an annual health examination over a mean follow-up period of 51.5±22.0 months, and the relationship between BP and CV events was analyzed using Cox's proportional hazard model. For the analysis, 310 participants, excluding 14 subjects who were withdrawn due to non-CV events, were classed into two groups, one consisting of 134 individuals who were undergoing treatment with an anti-hypertensive drug (medicated group) and another consisting of 176 who were not medicated (nonmedicated group). New cardiovascular events developed in 43 cases in the medicated group and in 14 cases in the non-medicated group during the follow-up period. In the medicated group, a linear relationship was observed between BP and the event rates. The hazard ratio for CV events adjusted for age, sex, and other cardiovascular risks was 1.28 (95% confidence interval [CI], 1.05 to 1.54, $p<0.05$) for a 10 mmHg increase of 24-h systolic BP. Corresponding values in 24-h diastolic BP, nighttime systolic BP, and nighttime diastolic BP were 1.71 (1.19 to 2.46, $p<0.01$), 1.34 (1.13 to 1.58, $p<0.01$), and 1.67 (1.20 to 2.31, $p<0.01$), respectively. In the non-medicated group, the event rate was least in the subgroup in the second-lowest quartile for nighttime systolic BP, with a slight non-significant increase in the subgroup of the lowest quartile. It was shown that insufficient control of nighttime BP in the elderly with hypertension is associated with the development of CV complications. (*Hypertens Res* 2000; 23: 323-330)

***Key Words*: nighttime blood pressure, cardiovascular disease**

Intoroduction

The prognosis for hypertensive patients depends on the level of blood pressure (BP) and the degree of target-organ damage (*1-4*). It has been shown that the target-organ damage is more closely related to 24-h ambulatory BP readings than to office BP (*5-8*). Several studies have suggested a 24-h ambulatory BP or home BP is a better predictor of future cardiovascular (CV) events (*9-15*). However, little information is available concerning the prognostic value of nighttime BP in the elderly population with or without hypertension. Although clinical trials of antihypertensive treatment have demonstrated the overall benefits of BP reduction (*16, 17*), there is considerable controversy regarding the optimal BP in hypertensive elderly patients during antihypertensive treatment. Some population-based surveys have suggested that a curvi-

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linear (J-shape) relation is present between office BP and the occurrence of CV disease (*17-21*). However, some investigators have argued that an excessive office BP reduction is not a cause of poor prognosis but merely a result of associated exhausting illness, such as a malignant disease, noting the positive linear relationship between BP level and prognosis in longer follow-up studies (*22-24*). With respect to the nighttime BP, there is a dispute as to whether low blood pressure during the night is associated with the development of CV events. To determine the prognostic significance of ambulatory BP, and especially of nighttime BP, we conducted a prospective follow-up study in elderly subjects who had undergone ambulatory BP monitoring at annual health examinations.

Subjects and Methods

The study was carried out using 324 elderly residents of a community home who underwent ambulatory BP monitoring at annual health examinations conducted between May 1990 and July 1992. The age of the subjects ranged from 60 to 92 years old, and the mean age was 77.2 years old. All subjects having autonomic dysfunction or a physical disability that could possibly affect the circadian BP pattern were excluded from the study.

The initial evaluation included a detailed medical history, physical examination, chest X-ray, 12-lead electrocardiogram, and screening laboratory tests. Trained nurses took two sets of BP measurements at intervals of 2 min while the subject was seated. The average for each of the two systolic and diastolic measurements was calculated to give the clinical blood pressure. Of the 324 participants, 140 were receiving antihypertensive treatments due to hypertension, and the remaining 184 were not taking antihypertensive medication, primarily due to normotension. Ambulatory BP measurements were recorded using oscillometric methods every 30 min using an ABPM630 (Cohlin Medical Co. Ltd., Komaki, Japan) for 24 h on a week day. Systolic readings greater than 250 mmHg or less than 70 mmHg, diastolic readings greater than 130 mmHg or less than 30 mmHg, and pulse pressure readings greater than 160 mmHg or less than 20 mmHg were automatically discarded. Before starting the study, the reliability of BP values measured with the monitor were checked against simultaneous measurements with a mercury sphygmomanometer. Differences of less than 5 mmHg were allowed. Subjects with recordings showing an error rate of $>25\%$ of the total readings were also excluded from the study. For the analysis, 24-h BP was separated into daytime and nighttime periods. The daytime period was defined as the interval between 6 AM and 10 PM, and the nighttime period as that between 10 PM and 6 AM.

All subjects gave informed consent to participate in the study, which was conducted in accordance with the declarations of Helsinki and Tokyo.

Clinical Follow-up

After the initial evaluation, which included ambulatory BP measurements, all subjects were followed-up in the outpatient clinic of the hospital or by their home nurses. The therapeutic strategy for BP had been left to the judgement of the doctors of individual patients throughout the study period. Although ambulatory BP data had been accessible to patients and their doctor, it is unlikely that those data significant influenced the therapeutic decisions because the clinical implications of 24-h BP had not been established at the time of the present study.

The end point of follow-up was defined as the development of any fatal or nonfatal cardiovascular event. The CV events included myocardial infarction, angina pectoris, cerebral infarction, cerebral hemorrhage, transient cerebral ischemic attack, sudden death, and progressive congestive heart failure or renal failure. For subjects who experienced two or more events during the follow-up period, only the first event was included in the analysis. The clinical diagnosis of outcome was confirmed by brain CT, ECG, echocardiogram, or the laboratory findings in addition to the clinical findings.

Statistical Analysis

The characteristics of those with CV events and those free of events were expressed as mean $\pm$ SD values and as incidence percentages. Group means were compared using the Student's t test and χ-square test. In two-tailed tests, probability values of less than 0.05 were considered statistically significant.

Event rates are presented as the number of events per 1,000 patient-years based on the ratio of the observed number of events to the total number of patient-years of exposure. Survival curves were estimated using the Kaplan-Meier product-limit method and compared using the log-rank test.

The statistical test of the relationship between quartiles of BP and the incidence of CV events was carried out using Cox's proportional hazards model. Variables that have been linked to cardiovascular events were selected as covariates in the multivariate analysis. These factors were age (in years), gender (female, 0; male, 1), current smoker (no, 0; yes, 1), diabetes (no, 0; yes, 1), electrocardiographical left ventricular hypertrophy, diagnosed according to the Sokolow-Lyon criteria (LVH: no, 0; yes, 1), and prior cardiovascular events (no, 0; yes, 1).

Results

During the mean follow-up period of 51.5 ± 22.0 months, 14 subjects were withdrawn due to death from malignant

Table 1. Clinical Outcome of Medicated and Non-Medicated Groups

	Medicated (n=134)	Non-medicated (n=176)	Total (n=310)
Total	43	14	57
	8*	4*	12*
CVD	21 (46.7%)	8 (57.1%)	30 (9.7%)
	1*	2*	3*
IHD	8 (17.8%)	2 (14.2%)	10 (3.2%)
	1*	1*	2*
CHF	7 (15.6%)	4 (28.5%)	11 (3.6%)
	2*	1*	3*
SD	2 (4.4%)	0	2 (0.7%)
	2*	0*	0*
Others	5 (11.1%)	0	5 (1.6%)
	2*	0*	2*

CVD: cerebrovascular disease, IHD: ischemic heart disease, CHF: congestive heart failure, SD: sudden death. *Number of death.

disease, pneumonia, or for the sake of leaving their community home. A remaining 310 subjects, (mean age 78.2 years) were separated into 176 medicated and 134 non-medicated subjects for the analysis according to whether or not the subject had received antihypertensive medication at the time of entry.

Fatal and Non-Fatal Outcome (Table 1)

Of the medicated group, 43 subjects experienced fatal or non-fatal CV events, including 8 deaths during the follow-up period, while only 14 subject, including 4 deaths occurring as a result of these events, were observed in the non-medicated group.

Comparison of clinical findings between the medicated and non-medicated groups (Tables 2 and 3): The mean ages of the two group were similar, but the office systolic BP in the medicated group was significantly higher than that in the non-medicated group ($p<0.02$) (although there was no difference in diastolic BP (153.6/71.8 mmHg *vs.* 137.2/66.2 mmHg). Twenty-four hour systolic and diastolic BPs in the medicated group were significantly higher than in the non-medicated group ($p<0.02$, 141.6/76.9 mmHg *vs.* 131.0/72.2 mmHg), as shown in Table 2.

Although total cholesterol and serum creatinine levels in the two groups were comparable, the incidence of electrographical left ventricular hypertrophy in the medicated group was significantly higher than that in the non-medicated group (29.1 *vs.* 9.0%, $p<0.05$). Smoking, diabetes mellitus, prior strokes, prior ischemic heart disease, and congestive heart failure were more frequently observed in the medicated group.

Comparison of the clinical background between the event (+) and event (−) group (Tables 2 and 3): In the medicated group, the mean age of the subjects experiencing events was not significantly different from that of those who were free from events. The subgroup that experienced CV events had significantly higher 24-h and nighttime BPs for both SBP and DBP than the subgroup that was free from such events, although the office BP and daytime BP were similar in the two subgroups. The levels of serum creatinine and the incidence of LVH were significantly higher in individuals with events than in those without in the medicated group. There was no significant difference in the frequency distribution for antihypertensive drugs between subjects with and without subsequent CV events, as shown in Fig. 1.

In the non-medicated group, only the incidence of atrial fibrillation in the subgroup with events was significantly different from that in the subgroup without events. There was no significant difference in BP values between the subjects with and without CV events. Figure 2 shows the event rates per 1,000 patient-years in each quartile of BP in the medicated group. A linear relationship was observed between the event rates and 24-h systolic BP and nighttime BP, both systolic and diastolic, in this group. The hazard ratio, after adjusting for age, sex, smoking habits, diabetes, LVH, and prior CV events, was 1.28 (95% confidence interval [CI], 1.05 to 1.54; $p<0.05$), with a 10-mmHg increase in 24-h SBP. Corresponding values in nighttime SBP and nighttime DBP were 1.34 (CI, 1.13 to 1.58; $p<0.01$) and 1.67 (CI, 1.20 to 2.31; $p<0.01$), respectively.

Figure 3 shows the event rate for the non-medicated group. In this group, the event rate was lowest in the subgroup of the second lowest quartile of 24-h systolic BP and nighttime systolic BP. A slight but not significant increase in event rates was observed in the lowest quartile of BP.

Discussion

In this prospective follow-up study, higher 24-h and nighttime BP for both SBP and DBP were associated with a higher incidence of CV events among hypertensive patients who were taking antihypertensive medication. In contrast, a curvilinear relationship was suggested between ambulatory BP and the incidence of CV events in non-medicated subjects.

The medicated and non-medicated groups in the present study can be considered to be equivalent to hypertensive and normotensive groups, respectively, because the community home where the participants lived was located within easy access of our hospital. Most elderly subjects who were diagnosed as hypertensive at their annual examination expected to receive antihypertensive treatment from their doctors. However, systolic BP in the medicated group was significantly higher than that in the

Table 2. Clinical Background of Medicated and Non-Medicated Groups

	Medicated			Non-medicated		
	Event (−)	Event (+)	Total	Event (−)	Event (+)	Total
n	91	43	134	162	14	176
Age	77.3±6.7	79.6±8.0	78.5±7.0	76.4±6.9	77.9±5.2	77.2±6.2
Male (%)	44 (49.4)	23 (51.1)	67 (50)	85 (52.4)	7 (50)	92 (52.3)
BMI (kg/m^2)	22.0±4.0	22.1±3.3	22.0±3.8	20.9±3.4	19.4±2.2	20.2±2.8
TC (mmol/l)	5.02±0.99	4.93±1.10	5.01±1.1	4.68±1.04	4.45±1.09	4.51±1.05
Cr (μmol/l)	90.3±19.4	117.5±62.1*	102.5±38.2	90.3±68.0	87.4±29.1	88.2±42.3
LVH	15 (16.8)	24 (53.3)*	39 (29.1)§	13 (8.0)	3 (21.4)	16 (9.0)
Af	4 (4.5)	3 (6.7)	7 (5.2)	8 (5.0)	5 (35.7)*	13 (7.4)
Smoking	41 (46.1)	16 (35.5)	57 (42.5)§	26 (16.1)	5 (35.7)	31 (17.6)
DM	7 (7.9)	4 (8.9)	11 (14.7)§	9 (5.6)	0	9 (5.1)
Prior CVD	13 (14.6)	20 (44.4)	33 (24.6)§	12 (7.4)	2 (14.3)	14 (8.0)
IHD	7 (7.9)	7 (15.6)	14 (10.4)§	3 (1.9)	1 (7.1)	4 (2.2)
CHF	4 (4.5)	3 (6.7)	7 (5.2)§	1 (0.6)	2 (14.3)	3 (1.7)

( ): percentage, *: In comparison between event (+) and (−) group, $p<0.05$, §: in comparison between the medicate and the non-medicate group, $p<0.05$, BMI: body mass index, TC: total cholesterol, Cr: serum creatinin, LVH: left ventricular hypertrophy, AF: atrial fibrillation, DM: diabetes mellitus.

Table 3. The Office and Ambulatory Blood Pressure Measurements in Each Subgroup

		Medicated		Non-medicated	
		Event (−)	Event (+)	Event (−)	Event (+)
Office	SBP	152.9±24.1	154.8±22.0	137.7±22.8	136.7±29.6
	DBP	71.0±16.0	72.9±13.4	67.3±14.1	65.0±15.0
24-h	SBP	138.3±15.5	144.9±14.4*	130.4±16.4	132.1±15.7
	DBP	75.4±9.3	78.7±7.8*	72.7±9.2	71.9±8.3
Daytime	SBP	140.4±15.7	143.0±14.5	132.3±15.3	133.1±14.6
	DBP	77.3±9.4	78.8±8.1	74.0±9.0	72.8±8.8
Nighttime	SBP	129.1±21.2	142.0±18.0*	125.3±18.9	128.1±18.7
	DBP	70.2±9.5	75.2±8.9*	68.7±10.4	67.7±10.1

* Indicates significant ($p<0.05$) difference compared to subjects without cardiovascular events within the same group.

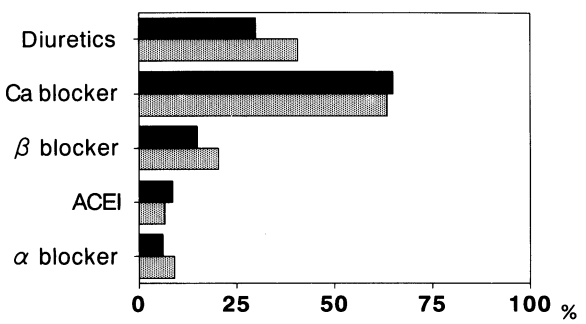

Fig. 1. *Frequency distribution of antihypertensive drugs taken by medicated subjects with and without subsequent CV events. Combination therapy was observed in 38% and 41% of subjects, respectively (n.s.). Black column: Subjects without subsequent CV events, Stipple column: Subjects with subsequent CV events.*

non-medicated group despite the antihypertensive treatment. The incidence of events in the medicated group reached nearly three fold that of the non-medicated group ($p<0.01$). The present study clearly demonstrates that the higher the nighttime BP, the higher the incidence of CV complications in the hypertensive elderly undergoing antihypertensive treatment.

Several previous studies have suggested the better prognostic predictive value of ambulatory BP over office BP in long-term prospective studies (*9-12*). Perloff *et al.* (*10*) first demonstrated that the long-term incidence of CV disease is highly associated with the mean levels of ambulatory BP recorded during daytime hours but not with clinical BP. However, nighttime BP monitoring was not carried out in their study because they used the manually manipulated cuff inflation system in the measurement of 24-h BP. More recently, Staessen *et al.* (*15*) have reported that ambulatory systolic BP is a significant predictor of cardiovascular risk over and above conventional BP

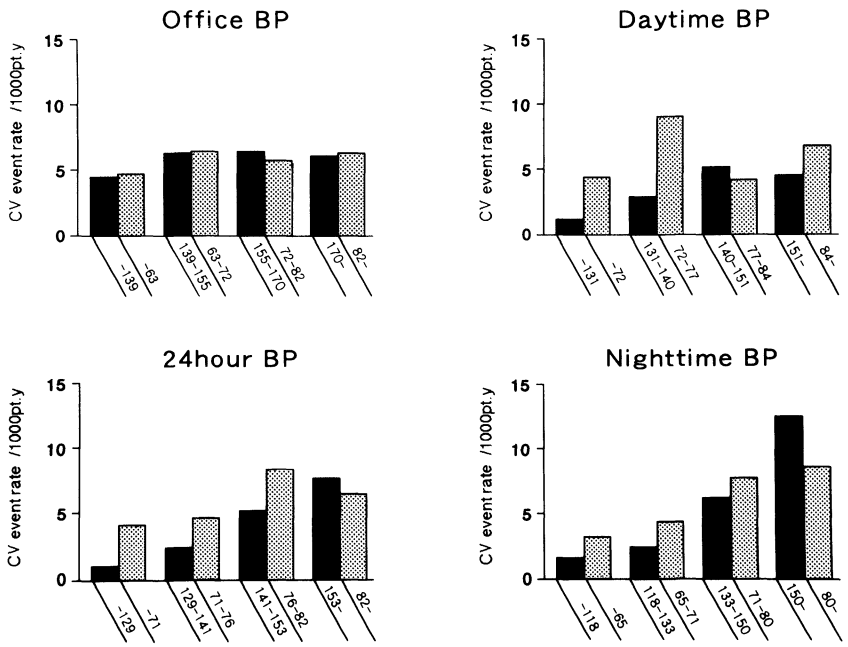

Fig. 2. *For the medicated group, the cardiovascular event rates per 1,000 patient-years in each quartile for BP. Black column: systolic BP, Stipple column: diastolic BP.*

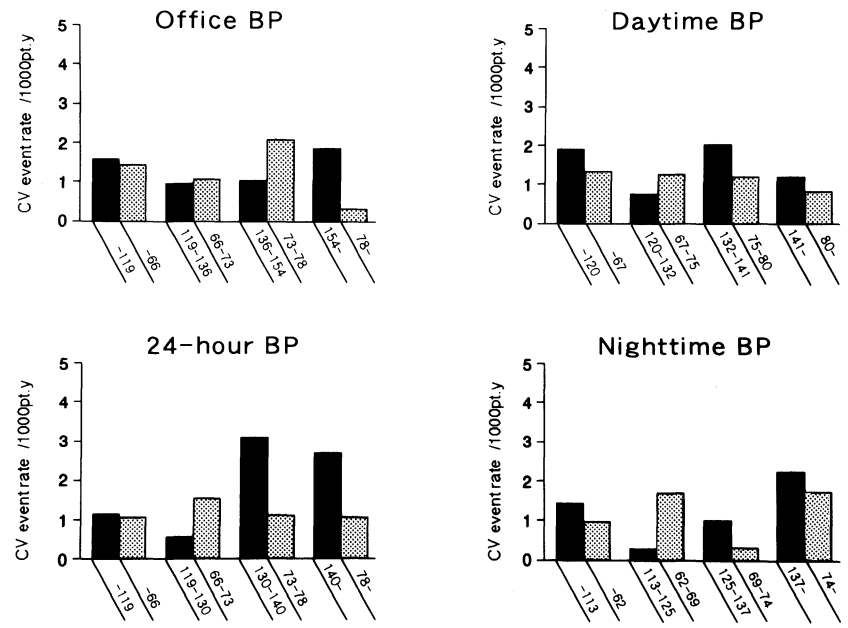

Fig. 3. *For the non-medicated group, the cardiovascular event rates per 1,000 patient-years in each quartile for BP. Black column: systolic BP, Stipple column: diastolic BP.*

in untreated older patients with isolated systolic hypertension. Moreover, they found that nighttime BP was a more consistent predictor of major end points than daytime BP or office BP in their placebo group and in all patients combined. Mann *et al.* (*11*) have observed that BP during the night is significantly more predictive of cardiovascular morbid events than daytime BP in a study of intra-arterial ambulatory BP measurements. Verdecchia *et al.* (*12*) have demonstrated high CV morbidity in hypertensive women, with absent or blunted BP reductions from day to night in

a PIUMA study.

The results of the present study support those of previous studies, suggesting that a high nighttime BP is associated with poor CV prognosis in hypertensive patients receiving antihypertensive treatment. These results are also consistent those of Yamamoto *et al.* (*25*), who demonstrated that a high nighttime BP as well as a reduced nighttime BP fall may have adverse effects on the development of silent ischemic lesions and symptomatic stroke attack in patients with lacunar infarct.

In the present study, the daytime and office BP were not significantly related to subsequent cardiovascular events. The distributions of antihypertensive drugs taken by the subjects, which might have been a confounding effect, did not differ among patients with subsequent cardiovascular events and those without. It is conceivable that differences in the durability of anti-hypertensive effects in subjects in the present study rather than differences in the mechanism of BP lowering may have contributed to our results because at the time when the study began, from 1990 to 1992, short-acting anti-hypertensive agents were still being widely prescribed by many doctors, although several long-acting calcium channel blockers or angiotensin converting enzyme inhibitor were available. The elevated incidence of CV events in patients with higher nighttime BP could reflect an insufficient control of BP during the nighttime, although it could also be accounted for by the abnormal diurnal BP rhythm itself. A suppressed nocturnal reduction of BP, so call non-dipping, has been reported to be more frequent in the elderly (*26*) and is associated with progressed target-organ damage (*27*) and poor CV prognosis (*9, 12*). As previously reported, the incidence of LVH in patients with a non-dipping pattern was higher than in patients with normal nighttime BP reduction (*5*). Other recent studies have disclosed that not only LVH but also peripheral vascular lesions and cerebrovascular diseases, including cognitive dysfunction, are more frequently associated with absent or blunted nighttime BP reduction than with normal nocturnal BP reduction (*6-8*). Since the severity of target organ damage is a strong predictor of future cardiovascular events in hypertensive patients (*1-4*), the abnormal BP rhythm itself could be associated with the higher incidence of these events, although the mechanism of depressed nocturnal BP remains controversial (*28, 29*).

Thus, although many investigators have demonstrated that a loss of or suppressed nocturnal BP reduction is associated with the development of CV complications, we did not separate the subjects into dippers and non-dippers because these terms can fundamentally be applied only to untreated hypertensive patients. For instance, hypertensive subjects with a non-dipping pattern can easily be changed into dippers if they take a short-acting calcium channel before bed.

The results of the present study suggest that the persistent burden of high BP throughout the night, which occupies one-third of the 24-h day, could damage the cardiovascular system, Kario *et al.* (*30*) have advocated the concept of the extreme dipper, whose BP is excessively reduced during the nighttime and reported that extreme dippers have a higher incidence of silent lacunar infarction than non-dipping patients. However, daytime BP level in extreme-dippers of their report is very high and it is conceivable that high daytime BP contributed a high incidence of lacunar lesion rather than low nighttime BP caused cerebrovascular damage. In contrast, the event rate in the present study was least in the lowest quartile for 24-h BP. Although so-called extreme dippers, defined by Kario *et al.* (*30*), were observed in 17 cases in the present study, none developed CV events during the follow-up period. The present findings suggest that 24-h BP should be controlled at less than 129/71 mmHg, and nighttime BP at less than 119/65 mmHg. The present study is the first to suggest that poor control of nighttime BP contributes to poor prognosis in elderly patients under medication. However, this study also showed a curvilinear-like relationship between ambulatory BP measurement and the event rate in non-medicated subjects. Some studies have demonstrated U-shaped or J-shaped curves for the SBP or DBP with cardiovascular events (*18-21*), while others have demonstrated a positive linear relation between them (*22-24*). Some suggest that the increased mortality in individuals with lower BP is an artifact of greater co-morbidity in these individuals (*23, 24*). Witteman *et al.* (*31*) have suggested that a decline in DBP indicates vessel wall-stiffening associated with atherosclerotic progression, and that the progression of atherosclerosis may be accompanied by a decrease in DBP rather than the opposing idea, that decreased DBP precipitates the occurrence of atherosclerotic events. Madhavan *et al.* (*32*) have also suggested that the curvilinear relation of diastolic BP fall to myocardial infarction is found only among patients with a wide range of pulse pressure. Glynn *et al.* (*24*) have found a higher mortality in participants with the lowest BP for both SBP and DBP during the first 3 years of follow-up. However, after excluding deaths occurring within the first 3 years of the follow-up period, they identified a positive linear relation between BP and cardiovascular events over an average of 10 years of follow-up. In our study, the mean follow-up period was approximately 52 months, and the relatively short follow-up interval might have contributed to the appearance of the J-shape curves associated with cardiovascular events in non-medicated subjects. Subjects with low SBP might have included subjects in poor condition. This in turn might be associated with the slight elevation in the incidence of these events in the lowest quartile for SBP. The high incidence of atrial fibrillation in the subgroup with events among the non-medicated group may be attributable to more progressed atherosclerotic change in this subgroup

because the incidence of LVH, prior CVD, and IHD also tended be higher in the subgroup with events than the subgroup without events, although the differences were not statistically significant.

The present study had several limitations; the small number of cardiovascular events precluded further differentiation among cardiac, cerebrovascular, and peripheral vascular events. Since hypertensive subjects were treated based on the office BP, those with white coat hypertension, who have been suggested to show a lower incidence of CV events compared with those with sustained hypertension in some studies (*12*), could not be excluded. Further investigations are necessary to examine these issues.

In conclusion, ambulatory BP measurement offers prognostic information in elderly people beyond that provided by age, sex, and other conventional cardiovascular risk factors. The incidence of CV events was least in the lowest quartile for nighttime BP in medicated hypertensive patients, which suggests the benefits of strict therapeutic control of nighttime BP.

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