Stroke Risk in Systolic and Combined Systolic and Diastolic Hypertension Determined Using Ambulatory Blood Pressure

The Ohasama Study

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Background: To investigate the risk of stroke in subjects with isolated systolic hypertension (ISH), isolated diastolic hypertension (IDH), and combined systolic and diastolic hypertension (SDH) in a Japanese general population, we used 24-h ambulatory blood pressure (ABP) and casual-screening blood-pressure (CBP) readings.

Methods: Subtypes of hypertension were defined based on systolic blood pressure (SBP) >135 mm Hg or diastolic blood pressure (DBP) >80 mm Hg for 24-h ABP, and SBP >140 mm Hg or DBP >90 mm Hg for CBP. We obtained 24-h ABP and CBP data for 1271 (40% male) subjects aged ≥40 years (mean age, 61 years) without a history of symptomatic stroke; their stroke-free survival was then determined. The prognostic significance of each subtype of hypertension was determined by Cox proportional hazard analysis.

Results: There were 113 symptomatic strokes during follow-up (mean time, 11 years). Compared with normo-tension, among the hypertension subtypes determined by 24-h ABP, the adjusted relative hazards (RHs) of stroke were 2.24 for ISH ($P = .002$) and 2.39 for SDH ($P = .0004$). The association was less marked among subtypes determined by CBP (RH = 1.40 and $P = .13$ for ISH; RH = 2.07 and $P = .017$ for SDH). The IDH group was excluded from the Cox analysis because both the prevalence and the number of events were low in this group.

Conclusions: Isolated systolic hypertension, as determined by 24-h ABP measurements, was associated with a high risk of stroke, similar to that found in SDH subjects; this suggests that the prognosis of hypertensive patients would be improved by focusing treatment on 24-h systolic ABP. Am J Hypertens 2007;20:1125–1131 © 2007 American Journal of Hypertension, Ltd.

Key Words: Systolic hypertension, ambulatory blood pressure, stroke.

The relative prognostic significance of blood pressure (BP) components depends on age.[1] Isolated systolic hypertension (ISH), which is more prevalent among elderly patients, as well as combined systolic and diastolic hypertension (SDH), is a strong risk factor of cardiovascular diseases.[2–7] In contrast, the cardiovascular risk of isolated diastolic hypertension (IDH), which is more common among younger patients, is considered to be

only slightly higher than that of normotension.[6,7] However, these studies were based on data obtained by casual-screening blood pressure (CBP), which is biased and therefore unreliable.[8–10] In our previous study, using data derived from home BP measurement, which was shown to be superior to CBP for predicting cardiovascular disease,[11] we found that systolic hypertension was a stronger risk factor for cardiovascular diseases than IDH.[12] However, only one previous study investigated the relationship between systolic or diastolic hypertension and the risk of target-organ damage, using data derived from 24-h ambulatory BP (ABP) monitoring (ABPM).[13] In the present study, we analyzed the stroke risk of each subtype of hypertension using data derived from ABPM, which was shown to be superior to CBP for predicting cardiovascular events in the general population.[14–18] In addition, we assessed the stroke risk of each subtype of hypertension using CBP data.

Methods
Design

The background rationale, study population, and BP measurements used in the Ohasama Study were presented in detail elsewhere.[14–16,19] The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government.

Study Population

The present study is part of a longitudinal observational study of subjects who have participated in the BP measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. The characteristics of this cohort were described previously.[14–16] Also, the representativeness of the study participants has been fully described in a previous paper.[14] In the present study of Ohasama inhabitants who were ≥40 years old (n = 2716), subjects who were hospitalized (n = 121), demented or bedridden (n = 31), or working outside of Ohasama (n = 575) were excluded. Thus, 1989 eligible individuals were initially identified, and 1542 subjects gave written, informed consent and participated in this study. Of the 1542 subjects, 78 had a previous history of stroke or transient ischemic attack (TIA). These subjects were therefore excluded from the present study dealing with stroke/TIA and BP. Another 193 subjects were also excluded because of a lack of CBP data. Data from the remaining 1271 subjects were analyzed.

ABPM

Well-trained public health nurses visited each participant on a weekday morning to attach the ABPM device, and then revisited the participants to detach the device the next morning. Participants were asked to keep a diary in which they recorded their daily activities, including the time at which they went to bed and when they arose. Ambulatory BP data were included in the analysis when the monitoring period was >8 h awake (daytime) and >4 h in bed (nighttime). These periods were estimated from the subjects' diaries. The mean duration ± SD of monitoring was 22.6 ± 2.4 h; the mean number of measurements ± SD was 45.2 ± 4.9.[19] Artifactual readings during ABPM were defined according to previously described criteria,[20] and were omitted from the analysis. The averages of 24-h, daytime, and nighttime BP values were calculated for each subject.

CBP Measurements

Annual health checkups, including BP measurement and hematological examination, are available to all Japanese citizens aged ≥40 years. During these checkups, BP is measured twice consecutively in the sitting position, after a rest of at least 2 min, by nurses or technicians using a semiautomated device. The average of the two readings, defined as the CBP, was used in the present analysis.

BP Monitoring Devices

Ambulatory BP was monitored using the ABPM-630 (Nippon Colin, Komaki, Japan), a fully automatic device that was preset to measure BP every 30 min.[20] Although systolic BP (SBP) and diastolic BP (DBP) were measured by both the cuff-oscillometric method and the microphone method, only data obtained by the cuff-oscillometric method were used in the analysis. Casual-screening blood pressure was measured with the USM-700F (UEDA Electronic Works Co. Ltd., Tokyo, Japan), an automatic device based on the Korotkoff sound technique (microphone method). Because almost all subjects' arm circumferences were <34 cm, a standard arm cuff was used for both ABP and CBP measurements. Both the ABPM device and the CBP measuring device used in the present study were previously validated,[19,21] and meet the criteria of the Association for the Advancement of Medical Instrumentation.[22]

Definition of Hypertension Subtypes

Hypertension subtypes derived from 24-h ABPM were defined according to the criteria of the Japanese Society of Hypertension Guidelines for the Management of Hypertension, 2004.[23] Isolated systolic hypertension was defined as SBP ≥135 mm Hg and DBP <80 mm Hg; IDH was defined as SBP <135 mm Hg and DBP ≥80 mm Hg; SDH was defined as SBP ≥135 mm Hg and DBP ≥80 mm Hg; and normotension was defined as SBP <135 mm Hg and DBP <80 mm Hg.

Hypertension subtypes derived from daytime ABPM were defined according to the criteria of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).[24] Isolated systolic hypertension was defined as SBP ≥135 mm Hg and DBP <85 mm Hg; IDH was defined as SBP <135 mm Hg and DBP ≥85 mm Hg; SDH was defined as SBP ≥135 mm Hg and DBP ≥85 mm Hg;

Table 1. Baseline mean age and blood pressure values

| Variables | Overall | Stroke | | Type of stroke | |
		Did not Develop	Developed	Ischemic	Hemorrhagic
n	1271	1158	113	74	34
Age	61 ± 10	61 ± 10	68 ± 9*	68 ± 9	67 ± 9
24-h					
SBP	123 ± 13	122 ± 13	132 ± 13*	131 ± 13	134 ± 15
DBP	72 ± 8	72 ± 8	76 ± 8*	76 ± 8	77 ± 8
Daytime					
SBP	129 ± 14	128 ± 14	137 ± 15*	136 ± 13	141 ± 17
DBP	76 ± 8	76 ± 8	80 ± 9*	80 ± 8	82 ± 10
Nighttime					
SBP	112 ± 14	111 ± 14	121 ± 15*	121 ± 16	121 ± 16
DBP	64 ± 8	64 ± 8	68 ± 8*	68 ± 8	68 ± 9
CBP					
SBP	131 ± 19	130 ± 18	140 ± 20*	140 ± 19	138 ± 22
DBP	74 ± 11	74 ± 11	77 ± 11*	78 ± 11	77 ± 12

CBP = casual blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
  Data are presented as means ± SD. Hemorrhagic stroke included intracerebral hemorrhage and subarachnoid hemorrhage.
  * $P < .001$.

and normotension was defined as SBP <135 mm Hg and DBP <85 mm Hg.

Similarly, hypertension subtypes derived from nighttime ABPM were defined according to the criteria of JNC7. Isolated systolic hypertension was defined as SBP ≥120 mm Hg and DBP <75 mm Hg; IDH was defined as SBP <120 mm Hg and DBP ≥75 mm Hg; SDH was defined as ≥120 mm Hg and DBP ≥75 mm Hg; and normotension was defined as SBP <120 mm Hg and DBP <75 mm Hg.

Hypertension subtypes derived from CBP were defined as follows. Isolated systolic hypertension was defined as SBP ≥140 mm Hg and DBP <90 mm Hg; IDH was defined as SBP <140 mm Hg and DBP ≥90 mm Hg; SDH was defined as SBP ≥140 mm Hg and DBP ≥90 mm Hg; and normotension was defined as SBP <140 mm Hg and DBP <90 mm Hg.

Follow-Up and Outcome

Residence in Ohasama (as of December 31, 2001) was confirmed by residents' registration cards. In Japan, these cards are considered accurate and reliable because they are used for pensions and social security benefits. The incidence of stroke and TIA until December 31, 2001 was determined by reviewing the Stroke Registration System of Iwate Prefecture, death certificates, National Health Insurance receipts, and questionnaires sent to each household at the time of ABPM. This information was then confirmed by checking the medical records of Ohasama Hospital, which is the only hospital located in the town, and it is where >90% of the subjects have their regular checkups. Almost all stroke cases were admitted to Ohasama Hospital, where the diagnosis was confirmed by computed tomography or magnetic resonance imaging of

the brain. The diagnoses of subjects who were admitted elsewhere were determined by reviewing case information provided by the Stroke Registration System of Iwate Prefecture. Less than 2% of subjects were admitted elsewhere. The diagnostic criteria of stroke subtypes were based on the Classification of Cerebrovascular Disease III of the United States National Institute of Neurological Disorders and Stroke.[25] We defined cerebral infarction as ischemic stroke, and we defined intracerebral hemorrhage and subarachnoid hemorrhage as hemorrhagic stroke.

Data Collection and Analysis

Information on smoking status, the use of antihypertensive medication at baseline, and past history of heart disease, diabetes mellitus (DM), and hypercholesterolemia was obtained from questionnaires sent to each household at the time of ABPM and from Ohasama Hospital's medical records, which included the results of laboratory investigations performed at the time of annual health checkups. Subjects using lipid-lowering drugs, or those with serum cholesterol levels ≥5.68 mmol/L, were considered to have hypercholesterolemia. Subjects with a fasting glucose level of ≥7.0 mmol/L or a nonfasting glucose level of ≥11.1 mmol/L, or those using insulin or oral antihyperglycemic drugs, were defined as having DM. A past history of heart disease included a history of myocardial infarction, angina pectoris, atrial fibrillation, or cardiac failure. The association between hypertension subtypes and the incidence of first stroke or TIA was examined using Cox proportional hazards regression,[26] adjusted for age, gender, smoking status, the use of antihypertensive medication, and history of heart disease, DM, or hypercholesterolemia. The dependent variable in these analyses was the number of days from date of ABPM to date of

Table 2. Baseline mean age and blood pressure values for each hypertension subtype

	ISH	IDH	SDH	NT	*P* (ANOVA)
24-h					
n	88	37	146	1000	
Total stroke	22	4	24	63	
Ischemic	12	4	14	44	
Hemorrhagic	9	0	9	16	
Age	71 ± 8	58 ± 8*	63 ± 9	60 ± 10*	<.001
SBP	140 ± 5	132 ± 2	146 ± 8	118 ± 9	<.001
DBP	76 ± 3	82 ± 2	86 ± 5	69 ± 6	<.001
Daytime					
n	214	5	178	874	
Total stroke	33	0	32	48	
Ischemic	21	0	18	35	
Hemorrhagic	10	0	13	11	
Age	66 ± 10	56 ± 7§	62 ± 9	60 ± 10	<.001
SBP	141 ± 5	133§	150 ± 10	121 ± 8	<.001
DBP	81 ± 4	86§	90 ± 5	72 ± 6	<.001
Nighttime					
n	210	1	118	942	
Total stroke	34	0	21	58	
Ischemic	23	0	13	38	
Hemorrhagic	9	0	8	17	
Age	68 ± 9	74§	63 ± 9	60 ± 9	<.001
SBP	128 ± 7	119§	138 ± 10	105 ± 8	<.001
DBP	69 ± 4	76§	80 ± 5	61 ± 6	<.001
CBP					
n	238	18	91	924	
Total stroke	36	1	14	62	
Ischemic	22	1	9	42	
Hemorrhagic	12	0	4	18	
Age	67 ± 9	63 ± 11*	61 ± 9*	60 ± 10*	<.001
SBP	153 ± 13	135 ± 4	161 ± 14	122 ± 11	<.001
DBP	78 ± 8	93 ± 4	97 ± 7	70 ± 9	<.001

ABP = ambulatory blood pressure; CBP = casual blood pressure; DBP = diastolic blood pressure; IDH = isolated diastolic hypertension; ISH = isolated systolic hypertension; SBP = systolic blood pressure; SDH = systolic and diastolic hypertension; NT = normotension.

Data are presented as means ± SD. Unit of each blood pressure value is mm Hg.

* Not significantly different.

§ Excluded from analysis because of small numbers of subjects.

stroke/TIA or censoring. Stroke/TIA-free survivors were censored as of December 31, 2001. When examining the incidence of stroke/TIA, death from causes other than fatal stroke events was censored. The analysis included only the first event in those subjects who had multiple nonfatal events.

The estimated relative hazard (RH) and 95% confidence interval (95% CI) of variables were derived from the coefficient and its standard error, as determined by the Cox proportional hazards model.

Results
Subjects' Characteristics

The overall mean age of subjects was 61 years, and the male:female ratio was 40:60. There were 1271 study subjects, and at baseline, 245 (19%) were classified as current or ex-smokers, 350 (28%) were being treated with antihypertensive medication, 14 (1.1%) were classified as having a history of heart disease, 220 (17%) had a history of DM, and 202 (16%) had a history of hypercholesterolemia.

Follow-Up and Outcome

The mean duration of follow-up ± SD was 11.1 ± 2.7 years. Of 1271 subjects, 192 died and 25 moved out of the region during the follow-up period. A first stroke or TIA occurred in 113 subjects, including cerebral infarction in 74 (65%), intracerebral hemorrhage in 24 (21%), subarachnoid hemorrhage in 10 (9%), TIA in 3 (2.6%), and unknown cause in 2 (1.8%). The mean time period ± SD between the 24-h ABPM and stroke was 5.6 ± 3.4 years.

Profiles of BP Values

All ABP and CBP values, as well as age at baseline, were significantly higher in subjects who developed stroke than in those who did not (Table 1) (*P* < .001). There were no differences between the BP values of ischemic stroke patients and hemorrhagic stroke patients. However, hemorrhagic stroke patients had a trend toward higher daytime BP indices than ischemic stroke subjects.
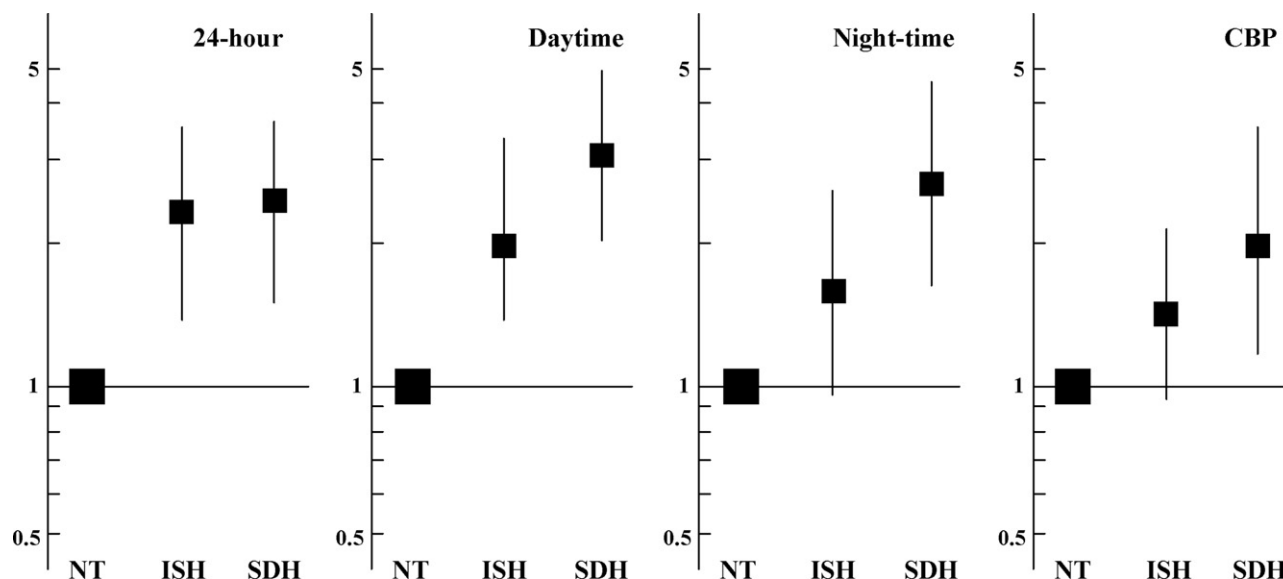
FIG. 1. Adjusted relative hazards (RHs) and 95% confidence intervals (95% CIs) for stroke risk of hypertension subtypes as determined by 24-h ambulatory blood pressure (ABP) monitoring or casual-screening blood-pressure (CBP) measurement. Solid squares represent RHs compared with the reference, adjusted for age, gender, smoking status, use of antihypertensive medication, and history of heart disease, diabetes mellitus, or hypercholesterolemia; they are sized in proportion to the number of events observed. Vertical lines represent 95% CIs. These are plotted on a log scale. NT = normotension; ISH = isolated systolic hypertension; SDH = systolic and diastolic hypertension.

Table 2 shows the BP value and age of each hypertension subtype assessed by ANOVA. Age, SBP, and DBP were all significantly different among the subtypes determined by both ABP and CBP ($P < .001$). However, there was no significant difference between the age of IDH patients and that of normotensive patients determined by 24-h ABP. Also, there were no significant differences in the ages of subjects with IDH, subjects with SDH, and normotensive subjects determined by CBP. Systolic blood pressure and DBP were highest in subjects with SDH determined by both ABP and CBP. The age of ISH subjects was significantly higher than that of patients with other subtypes. Subjects with IDH, as determined by daytime or nighttime ABP, were excluded from the analysis because of the low number of subjects.

Predictive Value of Hypertension Subtype

Figure 1 shows the RHs and 95% CIs for the total stroke risk of each hypertension subtype compared with normotension. Among subjects classified by 24-h ABP, the RHs for stroke incidence were significantly higher in SDH subjects (RH = 2.39; 95% CI, 1.48 to 3.87; $P = .0004$) and ISH subjects (RH = 2.24; 95% CI, 1.33 to 3.76; $P = .0024$) than in normotensive subjects. Among subjects classified by daytime ABP, the RHs were significantly higher in ISH subjects (RH = 2.04; 95% CI, 1.29 to 3.22; $P = .0023$) and SDH subjects (RH = 3.16; 95% CI, 2.00 to 5.01; $P < .0001$) than in normotensive subjects. Among subjects classified by nighttime ABP, the RH was significantly higher in SDH subjects (RH = 2.62; 95% CI, 1.55 to 4.41; $P = .0003$) than in normotensive subjects. Isolated systolic hypertension tended to be associated with a higher

RH (RH = 1.52; 95% CI, 0.97 to 2.40; $P = .07$) than normotension. However, the stroke risk was not significantly different between ISH subjects and normotensive subjects.

Among subjects classified by CBP, the RH was significantly higher in SDH subjects (RH = 2.07; 95% CI, 1.14 to 3.76; $P = .017$) than in normotensive subjects. Isolated systolic hypertension tended to be associated with a higher RH (RH = 1.40; 95% CI, 0.91 to 2.14; $P = .13$) than normotension. However, the stroke risk was not significantly different between ISH subjects and normotensive subjects.

In each analysis, the IDH group was excluded from the Cox model because both the prevalence and the number of events were low in this group.

Discussion

The present study involved the longitudinal observation of a representative sample of the general population living in a rural Japanese community. The main findings of this study are that, among a middle-aged to elderly population: 1) SDH had strong predictive value for stroke; and 2) ISH was also a strong risk factor for stroke. Several studies reported that SDH or ISH is a strong risk factor for cardiovascular disease.[2–7]

We previously reported that SBP determined by ABPM is a strong and independent predictor of stroke, and that SBP is more useful in daily practice than other BP indices.[27] In the present analysis, we confirmed that the risk of stroke morbidity was high in subjects with SDH or ISH. Thus, our results indicate that SBP, but not DBP, is a strong predictor of stroke morbidity when hypertension subtypes are determined by ABPM.

Many previous studies concluded that ISH as determined on CBP has a high prognostic value for cardiovascular disease.[2–7] However, in the present study, the predictive power of ISH as determined by CBP was not significant, even though stroke risk associated with ISH tended to be higher than that associated with IDH or normotension. Such inconsistency may be attributed to our study's small sample size and the short observation period compared to previous prospective studies that involved large numbers of subjects and reported a statistically significant association between CBP and stroke risk. However, ABPM detected the stroke risk adequately, despite the short observational period and small sample. It was shown previously that the predictive power for stroke of ABPM is superior to that of CBP.[14–18] The present study again demonstrated the superiority of ABPM.

Isolated diastolic hypertension has not often been studied. Most previous studies found that the risk of IDH is not high.[6,7,12,13] However, several recent studies reported that the risk of IDH is not negligible. Fang et al reported that IDH and ISH were both independent predictors of stroke.[28] Franklin et al reported that IDH is significantly associated with metabolic syndrome,[29] and that younger IDH subjects are likely to develop systolic hypertension.[30] These reports were based on CBP data. Thus, it is necessary to use ABPM data to determine whether the stroke risk of IDH is low. However, in the present study, the number of subjects with IDH was low. There were only 37 subjects with IDH, determined on the basis of 24-h ABP, and only 18 subjects with IDH, determined on the basis of CBP. In addition, IDH subjects might have a lower risk of stroke because they are younger than subjects with ISH or SDH. Thus, it is necessary to follow these subjects until a sufficient number of IDH subjects is gathered and their outcomes are observed.

Conclusions

Isolated systolic hypertension, as determined by 24-h ABP measurements, was associated with a high risk of stroke that was similar to that found in SDH subjects. This suggests that the prognosis of hypertension would be improved by focusing treatment on 24-h systolic ABP.

Acknowledgments

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