

Original Article

Proposal of a Risk-Stratification System for the Japanese Population Based on Blood Pressure Levels: The Ohasama Study

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The aim of the present study was to propose a risk-stratification system based on self-measurement of home blood pressure (HBP) as well as casual-screening BP (CBP) in relation to Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). For 4 weeks, the subjects measured their HBP while seated every morning within 1 h after awaking, after having rested for at least 2 min. The subjects included 2,368 Ohasama residents aged 35 years, with no history of stroke. CBP was measured twice consecutively at baseline. Among all subjects, there were 174 incidences of stroke or transient ischemic attack (TIA) observed during 9.4 years (interquartile 7.0–12.4) of follow-up. The analysis revealed statistically significant linear increases in stroke or TIA risk in both the CBP-based and HBP-based classifications. The risk for high-normal blood pressure (BP) was not significantly high according to the CBP-based classification (relative hazard [RH] 1.52; 95% confidence interval [CI] 0.89–2.60), whereas it was significantly high by the HBP-based classification (RH 1.91; 95% CI 1.04–3.51). On the basis of the data in the absolute risk table, the risks of first stroke or TIA for the 4 groups in the CBP-based and HBP-based classifications were proposed. Stroke or TIA risk increased linearly with the increase in the stage of stratified risk, regardless of BP information (trend $p < 0.0001$). Risks for non-hypertensive individuals should be assessed in the next version of the Japanese BP guidelines. Furthermore, the importance of HBP should be emphasized in order to accurately evaluate BP risks for individuals. (*Hypertens Res* 2008; 31: 1315–1322)

Key Words: home blood pressure, stroke, general population, Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004)

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Introduction

Hypertension is a leading cause of cardiovascular disease. The utility of self-measurement of blood pressure (BP) at home (HBP) has been recognized in the accurate diagnosis and treatment of hypertension. We previously reported that risk stratification based on HBP is a valuable tool for predicting the incidence of stroke, and this finding supported the assertion that BP management should be based on HBP information (1, 2). However, recent guidelines for BP management are based on casual-screening BP (CBP) only, even in Japan, where HBP devices have been widely accepted and used in clinical practice (3).

Thus far, researchers have focused on the cardiovascular risks in high-normal (4) or prehypertensive (5) individuals with several risk factors. In the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004), hypertensive patients were stratified into three risk groups according to BP levels and complications (3). However, little attention has been paid to normal or high-normal individuals with risk factors other than BP. Accurate evaluation of normal or high-normal individuals is important in the formulation of strategies that address the needs of the overall population.

The present study proposes a risk-stratification system based on HBP as well as CBP in relation to the JSH 2004, and evaluates whether or not normal and high-normal BP values are harmful to individuals with other risk factors.

Methods

Study Population

The present study is part of a longitudinal observational study of subjects who have participated in our HBP measurement project in Ohasama, a rural community in northern Japan, since 1987. The socioeconomic and demographic characteristics of the Ohasama study have been described previously (1, 2, 6–10). From 1988 to 1995, we contacted 4,969 subjects, aged 35 years or older, living in 4 districts of Ohasama. Subjects who were not at home during the study nurses' normal working hours ($n=1,057$) and those hospitalized ($n=166$) or incapacitated ($n=94$) were ineligible. Of the remaining 3,652 residents, 2,933 (80%) participated in baseline examinations and underwent follow-up. We excluded 454 subjects who did not measure their HBP in the morning or in the evening ≥ 3 times (3 d).

To examine the risk of the first onset of stroke, 111 individuals who had a history of stroke were further excluded from the present analysis. Therefore, the study population consisted of 2,368 individuals. 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. Informed consent was obtained

from each subject.

BP Measurements

At annual health check-ups, the subjects were seated at rest for at least 2 min, and then CBP was measured twice consecutively by well-trained nurses or technicians. We used a semi-automatic CBP measuring device (USM700F; Ueda Electronic Works, Tokyo, Japan) based on the microphone method.

Physicians and well-trained public health nurses conducted health education classes to instruct the subjects on how to perform HBP. After their ability to measure HBP was verified, the subjects measured their own BPs once in the morning, in the sitting position after at least 2 min of rest, within 1 h after awaking. Patients were asked to record their measurements for 4 weeks. Individuals taking antihypertensive medications measured their HBP before taking the medication. We allowed subjects to measure their own BP two or more times on each occasion; however, the first measurement value from each occasion was used for analysis to exclude subjects' selection bias. All subjects were instructed to hold their cuff-covered arm at heart level during HBP measurements. These procedures were described in detail in our previous report (9), and they followed the Japanese guidelines for self-monitoring of BP at home (11). HBP was measured using the HEM 401C (Omron Healthcare, Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric principle, that generates a digital display of both systolic and diastolic BP (12). The devices for measuring CBP and HBP were calibrated before the start of the study (12). The devices met the criteria set by the Association for the Advancement of Medical Instrumentation (13). We used a standard arm cuff for HBP measurements, since none of the subjects had an arm circumference of 34 cm or more.

Classification of Groups in Relation to JSH 2004

Based on the JSH 2004 risk-stratification system (3), the subjects were first classified into 6 BP categories as shown in Table 1. The HBP-based and CBP-based criteria were defined as follows: Optimal (HBP < 115/75, CBP < 120/80 mmHg); Normal (HBP 115/75–124/79, CBP 120/80–129/84 mmHg); High-normal (HBP 125/80–134/84, CBP 130/85–139/89 mmHg); Stage 1 HT (mild hypertension: HBP 135/85–149/94, CBP 140/90–159/99 mmHg); Stage 2 HT (moderate hypertension: HBP 150/95–164/104, CBP 160/100–179/109 mmHg); and Stage 3 HT (severe hypertension: HBP $\geq 165/105$, CBP $\geq 180/110$ mmHg). When a subject's systolic and diastolic BPs were in different categories, the subject was assigned to the higher category. The classification based on CBP was equal to the JSH 2004 criteria, and classification based on HBP was in accordance with our previous report (1, 2). Briefly, HBP of 135/85 mmHg is equivalent to CBP of 140/90 mmHg according to several guidelines (3–5). To

Table 1. Stratification of Risk to Quantify Prognosis

Category definition	Optimal	Normal	High-normal	Stage 1 HT	Stage 2 HT	Stage 3 HT
CBP-based	≤120/80	120/80–129/84	130/85–139/89	140/90–159/99	160/100–179/109	≥180/110
HBP-based	≤115/75	115/75–124/79	125/80–134/84	135/85–149/94	150/95–164/104	≥165/105

HT, hypertension; CBP, casual-screening blood pressure; HBP, home blood pressure.

Table 2. Clinical Characteristics among Groups*

Variables	Optimal	Normal	High-normal	Stage 1 HT	Stage 2 HT	Stage 3 HT
Home blood pressure–based groups						
Number of subjects	679	551	513	458	141	26
Age (years)	52.7±11.5	58.4±11.0	61.3±11.2	64.7±10.6	66.7±10.7	68.2±11.8
Men (%)	23.3	40.1	39.4	46.1	64.5	73.1
Body mass index (kg/m ²)	22.7±2.8	23.6±3.0	23.8±3.1	24.0±3.2	24.2±3.3	24.2±4.7
Past history of CVD (%)	0.0	1.1	0.6	1.1	0.7	0.0
Diabetes mellitus (%)	7.1	9.4	9.4	12.2	13.5	15.4
Smoking (%)	12.8	22.5	19.3	21.4	29.8	42.3
Hypercholesterolemia (%)	19.3	29.8	31.8	30.1	33.3	30.8
Use of antihypertensive medication (%)	7.5	16.7	35.9	54.1	67.4	65.4
Home SBP (mmHg)	107.2±5.6	119.3±3.2	128.6±3.7	139.0±6.0	152.6±7.1	164.8±11.7
Home DBP (mmHg)	65.0±5.7	72.2±4.8	76.9±5.5	82.8±7.1	89.7±9.3	97.0±11.6
Casual SBP (mmHg)	119.9±14.6	127.6±13.9	134.8±15.4	141.0±18.0	145.7±17.0	154.4±23.5
Casual DBP (mmHg)	69.0±9.4	73.2±9.5	75.3±10.3	79.7±11.6	82.4±12.6	86.2±14.7
Casual-screening blood pressure–based groups						
Number of subjects	598	544	531	521	137	37
Age (years)	55.0±11.4	58.2±11.6	60.2±12.0	62.5±11.7	64.2±12.0	63.6±13.3
Men (%)	27.6	36.0	42.6	43.2	50.4	56.8
Body mass index (kg/m ²)	22.6±2.8	23.5±3.0	23.7±3.1	24.0±3.2	24.1±3.1	24.4±3.4
Past history of CVD (%)	0.7	0.4	0.8	0.8	0.0	2.7
Diabetes mellitus (%)	7.7	9.6	10.7	10.6	9.5	10.8
Smoking (%)	17.9	20.0	20.3	19.2	21.2	21.6
Hypercholesterolemia (%)	20.1	28.7	29.9	30.9	28.5	43.2
Use of antihypertensive medication (%)	12.5	24.4	29.6	44.3	52.6	51.4
Home SBP (mmHg)	113.6±11.7	121.6±12.6	125.9±13.0	131.9±13.7	138.7±15.1	142.4±14.7
Home DBP (mmHg)	69.1±8.6	73.7±8.9	75.5±9.1	78.2±9.4	81.2±11.1	82.8±12.5
Casual SBP (mmHg)	110.0±6.9	124.1±3.5	133.8±4.0	146.5±6.4	163.6±9.3	186.1±15.2
Casual DBP (mmHg)	64.7±6.8	71.0±6.6	75.7±8.0	82.0±9.1	90.3±10.8	97.8±14.8

*See Table 1 for the definitions of groups. Values are expressed as mean±SD. CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HT, hypertension.

define other BP levels based on HBP, we postulated that 75, 80, 95, and 105 mmHg of diastolic HBP were equivalent to 80, 85, 100, and 110 mmHg of diastolic CBP, respectively. Then systolic BP levels for HBP were introduced based on the proportion of subjects in each CBP classification. In the present analysis, we did not include the concept of pure systolic hypertension.

The study subjects were then stratified into three classes based on the extent of cardiovascular risks: first class (no risk factors), second class (one or two risk factors except diabetes mellitus), and third class (three or more risk factors, diabetes mellitus, or past history of cardiovascular disease). Risk fac-

tors were defined as follows: age ≥60 for men, age ≥65 for women, body mass index (BMI) ≥25 kg/m², habitual smoking, and hypercholesterolemia. Finally, individuals were assigned to one of four risk groups: No, Low, Moderate, or High. The assignment to a group was based on a combination of JSH 2004 criteria, cardiovascular risk factors, and absolute risk for stroke or transient ischemic attack (TIA) incidence.

Follow-Up and Risk Assessment

We accumulated follow-up data from 1987 through 2001. The subjects' residence status in Ohasama was confirmed by

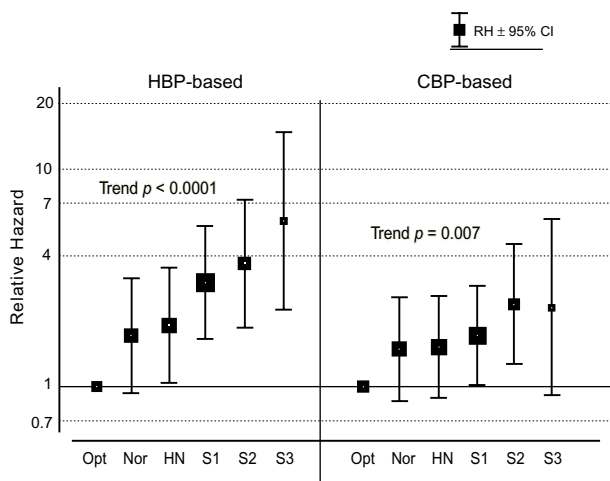


Fig. 1. Risk of first stroke or TIA among 6 categories defined on the basis of BP levels. Relative hazard (RH) and 95% confidence intervals (CI) for classifications based on BP levels are displayed. Criteria are shown in Table 1. The optimal BP category was treated as the reference category. Solid squares indicate the RH point and are sized in proportion to the number of events observed. Trend p -value expresses the linearity among groups. Adjusted factors were age, sex, body mass index, smoking status, drinking habit, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease. HBP, home blood pressure; CBP, casual-screening blood pressure; Opt, Optimal; Nor, Normal; HN, High-normal; S1, Stage 1 hypertension; S2, Stage 2 hypertension; S3, Stage 3 hypertension.

registration cards. These cards are accurate and reliable because they are used for pensions and social security benefits in Japan.

The incidence and history of stroke and TIA were investigated through the Stroke Registration System of Iwate Prefecture, death certificates, National Health Insurance receipts, and a questionnaire sent to each household at the time of home BP measurement. The information was then confirmed by checking the medical records of Ohasama Hospital, where more than 90% of the subjects received their regular health check-ups. We used CT scans and MRI to determine the clinical definition of stroke. For 3% of stroke cases, death certificates were the only source of information. In those who had multiple nonfatal events, the analysis included only the first event. The diagnostic criteria of stroke, TIA, and their subtypes were based on the system for the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke (14).

Other information about individuals, such as height, weight, smoking status, drinking habit, use of antihypertensive medication at baseline, history of heart disease, hypercholesterolemia, or diabetes mellitus, was obtained from the questionnaire sent to each household at the time of HBP mea-

surements, from records of annual health check-ups, and from medical records at Ohasama Hospital. Subjects using lipid-lowering drugs or those with serum cholesterol levels of ≥ 5.68 mmol/L (220 mg/dL) were considered to have hypercholesterolemia. Subjects with a fasting glucose level of ≥ 7.0 mmol/L (126 mg/dL) or a non-fasting glucose level of ≥ 11.1 mmol/L (200 mg/dL), or those using insulin or oral antihyperglycemic drugs, were defined as having diabetes mellitus. A past history of cardiovascular disease included a history of myocardial infarction, angina pectoris, atrial fibrillation, and cardiac failure.

Data Analysis

The HBP values were averaged separately in individuals, *e.g.*, the HBP value for an individual who measured his or her BP for 20 d was the average of those 20 measurements. The CBP of each subject was the average of the two consecutive CBP readings taken at the beginning of the study.

The Cox proportional hazards model was used for examining the risk of a first stroke. The dependent variable was the number of days from the measurement of the first HBP to the event or to the censoring of survivors at the end of the study period (December 31, 2001). The independent variables were the risk-stratification groups in which the factors of age and sex were included. The relative hazard (RH) is expressed relative to the reference group (RH=1). Separate models were used for HBP classification and CBP classification after verification of the proportionality assumption for the Cox model. We calculated the absolute risks for stroke or TIA incidence. All data are shown as mean \pm SD unless otherwise stated. A p value < 0.05 (two-sided test) was accepted as indicative of statistical significance. The SAS software package version 9.13 (SAS Institute, Cary, USA) was used for all statistical analyses.

Results

The characteristics of the subjects are shown in Table 2. They were followed up for a median of 9.4 years (interquartile 7.0–12.4) with a maximum of 13.9 years. We obtained 174 incident cases of first stroke or TIA among the 2,368 individuals: 118 (67.8%) cerebral infarction, 35 (20.1%) intracerebral hemorrhage, 12 (6.9%) subarachnoid hemorrhage, and 9 (5.2%) TIA.

Preliminarily, we analyzed the risk of a first onset of stroke or TIA based on BP classification (Fig. 1). Cardiovascular disease risk and drinking habit were used for adjustment of the Cox model instead of risk stratification. This analysis revealed statistically significant linear increases in the risk of stroke or TIA for CBP-based (trend $p=0.007$) and HBP-based (trend $p<0.0001$) classifications. The risk in high-normal subjects was significantly high according to the HBP-based classification (RH 1.91; 95% confidence intervals [CI] 1.04–3.51), although it was not significantly high by the

Table 3. Absolute Risks in Each Categories

Category definition	Optimal	Normal	High-normal	Stage 1 HT	Stage 2 HT	Stage 3 HT
Home blood pressure–based						
First: no risk factors	1.4	4.5	6.3	4.5	N/A	N/A
Second: 1–2 risk factors except DM	2.7	6.9	6.3	14.4	25.2	40.6
Third: >2 risk factors, DM, or PHCVD	6.0	2.4	14.1	20.9	18.9	27.4
Casual-screening blood pressure–based						
First: no risk factors	0.9	4.0	5.1	4.9	5.6	N/A
Second: 1–2 risk factors except DM	3.7	7.6	9.1	10.2	18.5	19.8
Third: >2 risk factors, DM, or PHCVD	14.2	7.5	8.8	18.5	18.8	11.3

The risk indicates per 1,000 person-years. HT, hypertension; DM, diabetes mellitus; PHCVD, past history of cardiovascular disease; N/A, not assessed since no event was observed.

CBP-based classification (RH 1.52; 95% CI 0.89–2.60).

Table 3 indicates the absolute risks that display stroke or TIA incidence per 1,000 person-years. The absolute risk increased with elevation of HBP as well as of CBP, and with the elevation of classes based on the extent of cardiovascular risks.

Mainly on the basis of the absolute risk table (Table 3) and JSH 2004 guidelines, Fig. 2A shows the first stroke or TIA risk for the 4 risk groups (No, Low, Moderate, and High) in each CBP-based and HBP-based classification. Stroke or TIA risk increased linearly with the increase in the stage of stratified risk based on HBP as well as that based on CBP (both trends $p < 0.0001$). The stroke or TIA risk even in the Low risk group was significantly higher than that in the No risk group (HBP: RH 2.39, 95% CI 1.36–4.19; CBP: RH 2.35, 95% CI 1.35–4.10). The High risk group had a very significant risk indeed, regardless of BP information (HBP: RH 5.32, 95% CI 3.21–8.82; CBP: RH 4.12, 95% CI 2.45–6.91). When we designated the Low group as a reference category in the Cox model, the stroke or TIA risk in the Moderate group was significantly higher for HBP (RH 1.71, 95% CI 1.10–2.66); on the other hand, when the CBP classification was used, the Moderate group was not significantly different from the Low group (RH 1.51, 95% CI 0.98–2.32). The risk levels between the Moderate and High groups were not significantly different (both $p > 0.1$). When both classifications were simultaneously included in the model, only the HBP classification was significantly related with stroke or TIA risk (HBP classification: RH 1.61, 95% CI 1.30–2.01; CBP classification: RH 1.09, 95% CI 0.87–1.35).

When based on HBP, the risk of a first stroke or TIA in third class (three or more risk factors, diabetes mellitus, or past history of cardiovascular disease) individuals with high-normal BP was significantly higher than for those with normal BP (RH 5.76, 95% CI 1.28–26.0), whereas there were no significant differences when comparisons were based on CBP (RH 1.17, 95% CI 0.41–3.38). Modified risk classifications in accordance with this result are shown in Fig. 2B; third-class individuals with normal BP were assigned to the Moderate group instead of the High group. The risk of stroke or TIA

was significantly separated into 4 groups when the HBP classification was used (all $p < 0.05$). Although the separation power was similar to that in the former analysis using the CBP classification, the stroke or TIA risk in the High group increased in the magnitude of relative hazard (RH 4.71, 95% CI 2.76–8.06).

Second-class individuals with Stage 2 hypertension had high stroke or TIA risks according to the absolute risk table; therefore, we proposed further modification of the risk classifications (Fig. 2C). The separation power between the Moderate and High groups increased regardless of whether HBP or CBP classification was used.

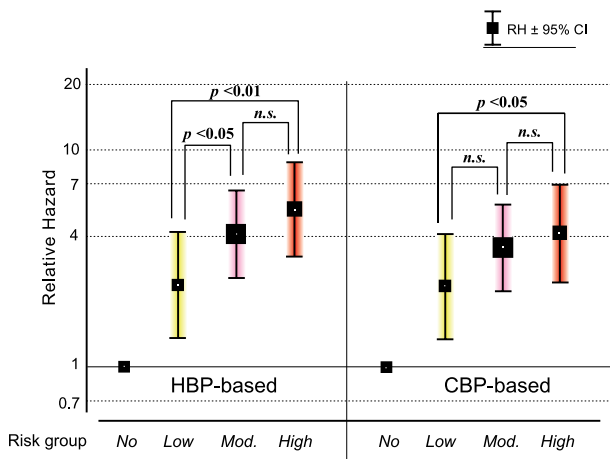
Discussion

In the current prospective cohort study, we have demonstrated that BP classification based on HBP had a stronger predictive power for stroke or TIA risk than that based on CBP. To our knowledge, this is the first report to indicate that individuals with high-normal HBP had a significantly higher stroke or TIA risk than those with optimal HBP in a Japanese population. We also showed that normal or high-normal BP with cardiovascular risk factors was harmful to individuals even when the assessment was based on CBP.

The stroke mortality rates in Eastern Europe, China, the “Stroke Belt” in the southeastern United States, and Japan are approximately 2 to 6 times higher than those in other European countries, the United States excluding the “Stroke Belt,” and Canada (15). Japanese mortality resulting from stroke is 3 times higher than that in the United States (16). Such differences may be explained by differences in environmental and genetic risk factors, and thus guidelines for treating hypertension would depend on the characteristics of each population. Our results demonstrate that the JSH 2004 criteria are valuable for predicting stroke risk in the general Japanese population. In the Hisayama study, a close stepwise relationship was observed between BP and cardiovascular disease, particularly among hypertensive individuals (17). The present study revealed a significantly high stroke or TIA risk in individuals with high-normal BP relative to those with optimal

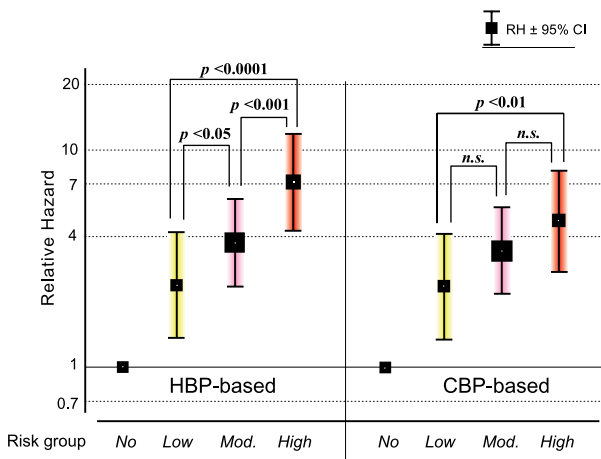
A

BP classification	Optimal	Normal	High normal	Stage 1 HT	Stage 2 HT	Stage 3 HT
No other risk factors	No	No	No	Low	Mod.	High
1–2 risk factors	No	Low	Mod.	Mod.	Mod.	High
≥ 3 risk factors, DM or PHCVD	Mod.	High	High	High	High	High



B

BP classification	Optimal	Normal	High normal	Stage 1 HT	Stage 2 HT	Stage 3 HT
No other risk factors	No	No	No	Low	Mod.	High
1–2 risk factors	No	Low	Mod.	Mod.	Mod.	High
≥ 3 risk factors, DM or PHCVD	Mod.	Mod.	High	High	High	High



C

BP classification	Optimal	Normal	High normal	Stage 1 HT	Stage 2 HT	Stage 3 HT
No other risk factors	No	No	No	Low	Mod.	High
1–2 risk factors	No	Low	Mod.	Mod.	High	High
≥ 3 risk factors, DM or PHCVD	Mod.	Mod.	High	High	High	High

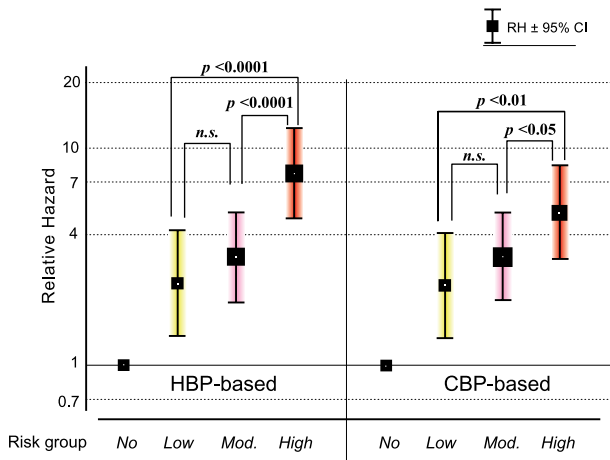


Fig. 2. Risk of first stroke or TIA among 4 groups defined on the basis of risk stratification. Relative hazard (RH) and 95% confidence intervals (CI) for classifications based on stratification of risk are displayed. Group definitions of A, B, and C are shown in each upper panel and are fully described in the text. Risk factors were age ≥60 for men, age ≥65 for women, body mass index (BMI) ≥25 kg/m², habitual smoking, and hypercholesterolemia. The No risk group was treated as the reference category. Solid squares indicate the RH point and are sized in proportion to the number of events observed. HBP, home blood pressure; CBP, casual-screening blood pressure; HT, hypertension; DM, diabetes mellitus; PHCVD, past history of cardiovascular disease; Mod., moderate.

BP when the assessment was based on HBP. Furthermore, on the basis of risk stratification, significant risk increases were observed regardless of BP information. In addition, normal BP and high-normal BP individuals with high cardiovascular risks (third class) had significantly different risk levels for stroke or TIA when the assessment was based on HBP. Several previous studies conducted in the Japanese population also support the current results, even based on CBP (18, 19). It seems reasonable to suppose that we should assess both hypertensives and non-hypertensives in the next version of the Japanese BP guidelines, and that the importance of HBP should be more heavily emphasized in the revised guidelines for accurate evaluation of BP risks in individuals.

Individuals with optimal BP should not be overlooked if they have high cardiovascular risks. In the current analysis, we could not determine the statistical differences among cardiovascular risk classes in subjects with optimal BP, since there were insufficient numbers of subjects in these categories, which could have reduced the data's predictive power. However, in accordance with the absolute risk table, there would be residual stroke or TIA risk for subjects with optimal BP if they have high cardiovascular risk factors. Although they might not be treated with antihypertensive medications, they should be managed in relation to other risk factors, such as diabetes mellitus. Nonpharmacologic interventions, such as dietary approaches including a low-salt diet (20, 21), exercise therapy (22), or smoking cessation, would also be useful (23). We have shown only the most relevant stratification tables among several possibilities, since space is limited. However, in the European guidelines, a curved line on the risk stratification table expresses a risk threshold for the recommendation of antihypertensive medication (4). Our results are in complete agreement with that recommendation. Accordingly, the point we wish to emphasize is that a robust risk-stratification system should include these non-hypertensive individuals.

In the present study, HBP was classified on the basis of the percentage distribution of subjects according to the corresponding ratio of CBP (e.g., 140/90 mmHg by CBP is approximately equivalent to 135/85 by HBP). This classification was reasonable, since stroke risk increased stepwise from optimal to Stage 3 HT. We previously reported the superiority of HBP in relation to recent American and European guidelines (1, 2). Information on BP in relation to the time of day improves data quality, as does an increased number of measurements. Furthermore, HBP is usually measured under more controlled conditions than CBP. The average of multiple values of HBP obtained under controlled conditions provides individual BP information without biases such as the white-coat effect, regression dilution biases, and the time effect (24). HBP should be emphasized in the revised guidelines for treatment of high-normal and normotensive individuals as well as hypertensive individuals. Accordingly, the widespread use of HBP measurements would improve the health of the overall population.

In conclusion, we have demonstrated that HBP measurements provide more useful prognostic information on stroke and TIA than CBP measurement. HBP measurements are recommended to improve clinical decision-making, since their prognostic significance was demonstrated in the present study. Furthermore, CBP values also provide useful parameters for a risk-stratification system. It is important to note that the non-hypertensive population is heterogeneous and that a risk-stratification system would be applicable to these individuals.

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