for sustained hypertension than WCH [7,30,33]. As, in most medical settings, diagnosis and treatment of hypertension are currently based mainly on office BP, it would be practically more important, at least at present, to clarify the cost-effectiveness of the introduction of HBP measurement in office hypertensive patients than in office normotensive subjects, including those with MHT. We are conducting analyses to evaluate the cost-effectiveness of the introduction of HBP measurement in office normotensive patients. Second, we assumed that the decision to treat is simply based on the categorization of patients according to BP patterns. Essentially, the decision to treat should not be based simply on BP patterns but on total cardiovascular risk, as indicated in the latest European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines [3]; however, a simulation including parameters regarding the degree of total cardiovascular risk in each individual would be too complex for use of the Markov model. Therefore, in the present study, we attempted to calculate the cost-effectiveness of introduction of HBP measurement from changes in patients' status of BP patterns only, using the Markov model. A previous study has examined the cost-effectiveness of ambulatory BP introduction using a similar method [11]. Third, the present study is based on the assumption that WCH has a similarly lower risk as that of true normotensive subjects over a 5-year period. Since no agreement exists as to whether WCH is clinically innocent for more than 5 years, it is uncertain whether the present findings could be applicable to those assuming follow-up periods of more than 5 years. Finally, in this analysis, the calculations used are based on currently available estimates for the prevalence of WCH in recently detected hypertensive groups, and costs for treatment of hypertension, in Japan only. Therefore, it is unclear whether the results of this analysis are applicable to other countries. As we assume that the utility of HBP measurement is evident, this analysis is intended to demonstrate the usefulness of HBP from an economic viewpoint.

Recently published guidelines for the management of hypertension recognize the role of HBP for the detection of WCH in the initial assessment of selected patients [3,4,34]. For those found to have WCH, long-term surveillance using HBP has been recommended [4]. As the results of this study, the introduction of HBP for hypertension treatment would be a very effective method of reducing costs of hypertension treatment and treatment years for hypertension. Given its cost-effectiveness, extensive application of HBP measurement in clinical practice is expected.

Acknowledgements

This work was supported by Grants for Scientific Research (15790293, 17790382, 18390192 and 18590587) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; Grant-in-Aid for Japan Society for the Promotion of Science (JSPS) fellows (16.54041, 18.54042); Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; Japan Atherosclerosis Prevention Fund; Uehara Memorial Foundation; and Takeda Medical Research Foundation.

There are no conflicts of interest.

References

1 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. *Estimates of national medical care expenditure 2002*. Tokyo: Health and Welfare Statistics Association; 2003.
2 Hansson L, Lloyd A, Anderson P, Kopp Z. Excess morbidity and cost of failure to achieve targets for blood pressure control in Europe. *Blood Press* 2002; **11**:35–45.
3 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, *et al.*, Task Force for the Management of Arterial Hypertension of the European Society of Hypertension, European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension and of the European Society of Cardiology. *J Hypertens* 2007; **25**:1105–1087.
4 Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, *et al.* Japanese Society of Hypertension (JSH) guidelines for self-monitoring of blood pressure at home. *Hypertens Res* 2003; **26**:771–782.
5 Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, *et al.* Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998; **16**:971–975.
6 Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, *et al.* How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004; **22**:1099–1104.
7 Bobrie G, Chatellier G, Genes N, Clerson P, Vaur L, Vaisse B, *et al.* Cardiovascular prognosis of 'masked hypertension' detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004; **291**:1342–1349.
8 Pickering TG. White coat hypertension. *Curr Opin Nephrol Hypertens* 2002; **5**:192–198.
9 Verdecchia P, Roboldi GP, Angeli F, Schillaci G, Schwartz JE, Pickering TG, *et al.* Short- and long-term incidence of stroke in white-coat hypertension. *Hypertension* 2005; **45**:203–208.
10 Bjorklund K, Lind L, Vessby B, Andren B, Lithell H. Different metabolic predictors of white-coat and sustained hypertension over a 20-year follow-up period: a population-based study of elderly men. *Circulation* 2002; **106**:63–68.
11 Krakoff LR. Cost-effectiveness of ambulatory blood pressure: a reanalysis. *Hypertension* 2006; **47**:29–34.
12 Eward B, Pekarsky B. Cost analysis of ambulatory blood pressure monitoring in initiating antihypertensive drug treatment in Australian general practice. *Med J Aust* 2002; **176**:580–583.
13 Imai Y, Satoh H, Nagai K, Sakuma M, Minami N, Munakata M, *et al.* Characteristics of a community-based distribution of home blood pressure in Ohasama in northern Japan. *J Hypertens* 1993; **11**:1441–1449.
14 Imai Y, Ohkubo T, Tsuji I, Hozawa A, Nagai K, Kikuya M. Relationships among blood pressure obtained using different measurement methods in the general population of Ohasama, Japan. *Hypertens Res* 1999; **22**:261–272.
15 Hozawa A, Ohkubo T, Nagai K, Kikuya M, Matsubara M, Tsuji I, *et al.* Factors affecting the difference between screening and home blood pressure measurements: the Ohasama Study. *J Hypertens* 2001; **19**:13–19.
16 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. *The fifth national survey of cardiovascular diseases*. Tokyo: Health and Welfare Statistics Association; 2002.
17 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. *Patient survey 2002*. Tokyo: Health and Welfare Statistics Association; 2004.
18 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. *Report of survey of medical care activities in public health insurance 2002*. Tokyo: Health and Welfare Statistics Association; 2004.

19 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. *Comprehensive survey of living conditions of the people on health and welfare 2001*. Tokyo: Health and Welfare Statistics Association; 2003.

20 Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. *Survey on long-term care service fees 2002*. Tokyo: Health and Welfare Statistics Association; 2004.

21 Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, *et al.* White-coat hypertension as a risk factor for development of home hypertension: the Ohasama study. *Arch Intern Med* 2005; **165**:1541–1546.

22 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**:2981–2997.

23 Wing LMH, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GLR, *et al.*, for the Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; **348**:583–592.

24 Shirasaki O, Terada H, Niwano K, Nakanishi T, Kanai M, Miyawaki Y, *et al.* The Japan Home-health Apparatus Industrial Association: investigation of home-use electronic sphygmomanometers. *Blood Press Monit* 2001; **6**:303–307.

25 Imai Y, Obara T, Ohkubo T. How many times should we ask subjects to measure blood pressure at home on each occasion? *J Hypertens* 2007; **25**:1987–1991.

26 Staessen JA, Den Hond E, Celis H, Fagard R, Keary L, Vandenhoven G, *et al.* Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. *JAMA* 2004; **291**:955–964.

27 Mena-Martin FJ, Martin-Escudero JC, Simal-Blanco F, Carretero-Ares JL, Arzua-Mouronte D, Herreros-Fernandez V. Health-related quality of life of subjects with known and unknown hypertension: results from the population-based Hortega study. *J Hypertens* 2003; **21**:1283–1289.

28 Bidlingmeyer I, Burnier M, Bidlingmeyer M, Waeber B, Brunner HR. Isolated office hypertension: a prehypertensive state? *J Hypertens* 1996; **3**:327–332.

29 Polonia JJ, Gama GM, Silva JA, Amaral C, Martins LR, Bertoquini SE. Sequential follow-up clinic and ambulatory blood pressure evaluation in a low risk population of white-coat hypertensives and normotensives. *Blood Press Monit* 2005; **10**:57–64.

30 Hansen TW, Kikuya M, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, *et al.* Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. *J Hypertens* 2007; **25**:1554–1564.

31 Sega R, Facchetti R, Bombelli M, Cesana G, Corrao G, Grassi G, Mancia G. Prognostic value of ambulatory and home blood pressures compared with office blood pressure in the general population: follow-up results from the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study. *Circulation* 2005; **111**:1777–1783.

32 Thijs L, Staessen JA, Celis H, Fagard R, De Cort P, de Gaudemaris R, *et al.* The international database of self-recorded blood pressures in normotensive and untreated hypertensive subjects. *Blood Press Monit* 1999; **4**:77–86.

33 Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, *et al.* Prognosis of 'masked' hypertension and 'white-coat' hypertension detected by 24-h ambulatory blood pressure monitoring: 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005; **46**:508–515.

34 Chobanian AV, Bakris GL, Black HR, Green L, Izzo JL Jr, Jones DW, *et al.* The seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 Report. *JAMA* 2003; **289**:2560–2572.

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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This work was supported by Grants-in-Aid for Scientific Research (15790293, 17790381, 18390192, 18590587, and 19790423) from the Ministry of Education, Culture, Sports, Science and Technology, Japan; by Grants-in-Aid for Japan Society for the Promotion of Science (JSPS) Fellows (16.54041, 18.54042); by Health Science Research Grants, Medical Technology Evaluation Research Grants and Grants-in-Aid (H17-Kenkou-007, H18-Junkankitou [Seishuu]-Ippan-012, and H20-Junkankitou [Seishuu]-Ippan-013) from the Ministry of Health, Labour and Welfare, Health and Labour Sciences Research Grants, Japan; and by the Japan Atherosclerosis Prevention Fund, the Uehara Memorial Foundation, the Takeda Medical Research Foundation, and the Mitsubishi Pharma Research Foundation.

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Received February 5, 2008; Accepted in revised form March 2, 2008.

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≥165/105, CBP≥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 factors were defined as follows: age ≥60 for men, age ≥65 for women, body mass index (BMI) ≥25 kg/m^2, 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

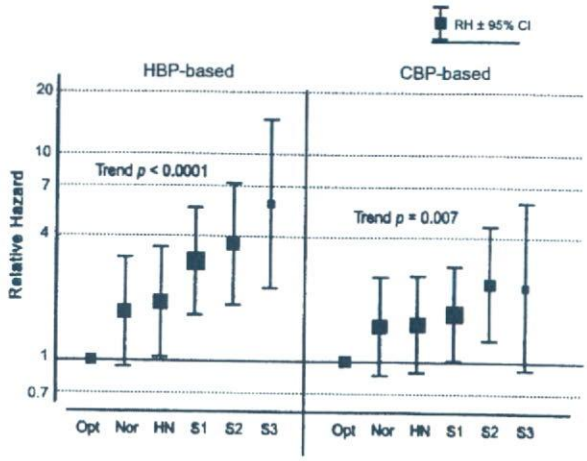

Fig. 1. *Risk of first stroke or TIA among 6 categories defined on the basis of BP levels. Relative hazard (RH) and 95% confidence intervals (CI) for classifications based on BP levels are displayed. Criteria are shown in Table 1. The optimal BP category was treated as the reference category. Solid squares 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 measurements, 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±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

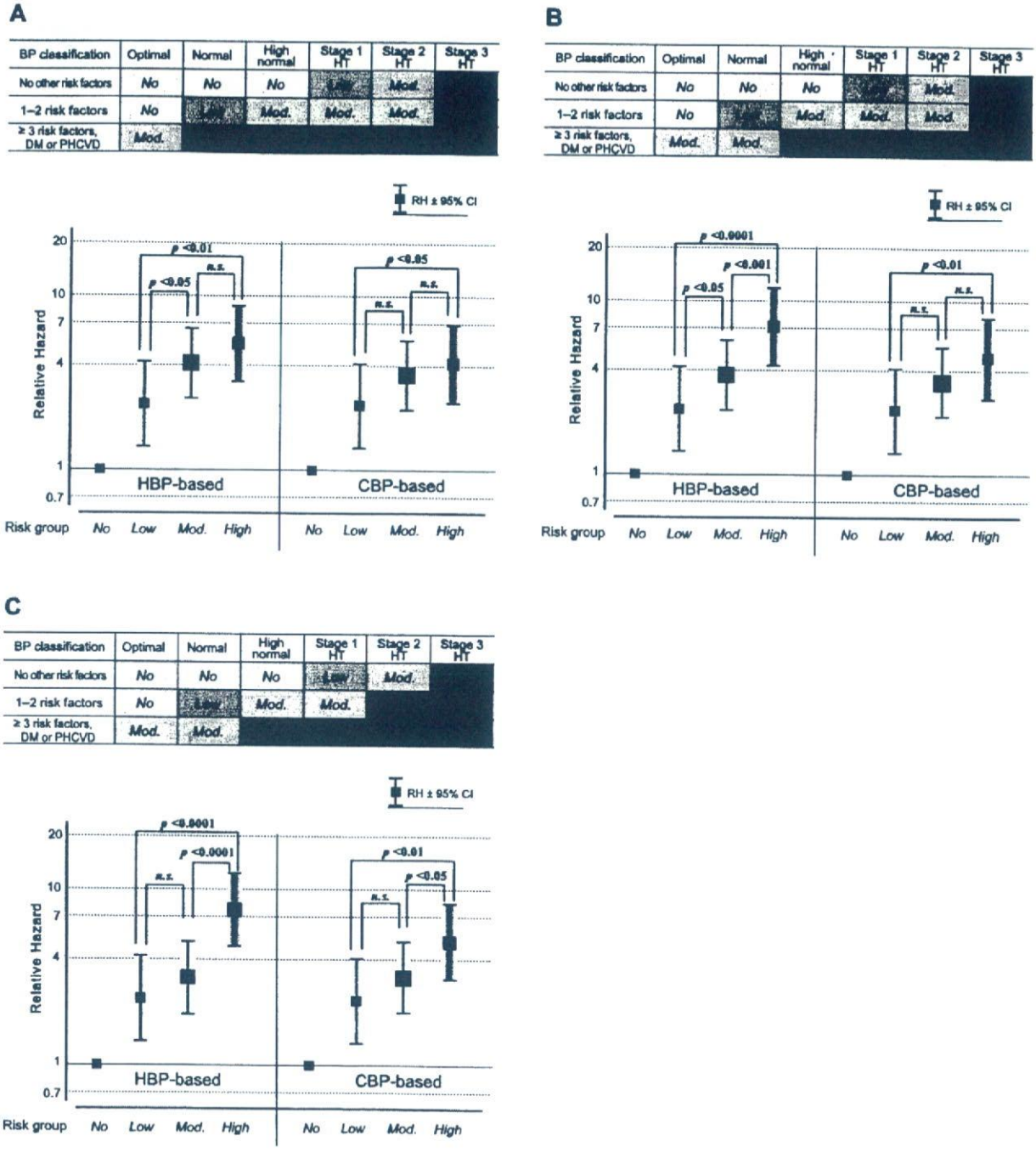

Fig. 2. *Risk of first stroke or TIA among 4 groups defined on the basis of risk stratification. Relative hazard (RH) and 95% confidence intervals (CI) for classifications based on stratification of risk are displayed. Group definitions of A, B, and C are shown in each upper panel and are fully described 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.

Acknowledgements

The authors are grateful to the staff members of the Iwate Prefectural Stroke Registry for their valuable support with the follow-up survey. We are also grateful to the public health nurses in Ohasama for their valuable support of this project.

References

1. Asayama K, Ohkubo T, Kikuya M, *et al*: Prediction of stroke by self-measurement of blood pressure at home *versus* casual screening blood pressure measurement in relation to the JNC-7 classification: the Ohasama study. *Stroke* 2004; **35**: 2356–2361.
2. Asayama K, Ohkubo T, Kikuya M, *et al*: Use of 2003 European Society of Hypertension–European Society of Cardiology guidelines for predicting stroke using self-measured blood pressure at home: the Ohasama study. *Eur Heart J* 2005; **26**: 2026–2031.
3. Japanese Society of Hypertension: Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Hypertens Res* 2006; **29** (Suppl): S1–S105.
4. Mancia G, De Backer G, Dominiczak A, *et al*: 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; **28**: 1462–1536.
5. Chobanian AV, Bakris GL, Black HR, *et al*: Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.
6. Ohkubo T, Imai Y, Tsuji I, *et al*: Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998; **16**: 971–975.
7. Tsuji I, Imai Y, Nagai K, *et al*: Proposal of reference values for home blood pressure measurement: prognostic criteria based on a prospective observation of the general population in Ohasama, Japan. *Am J Hypertens* 1997; **10**: 409–418.
8. Nagai K, Imai Y, Tsuji I, *et al*: Prevalence of hypertension and rate of blood pressure control as assessed by home blood pressure measurements in a rural Japanese community, Ohasama. *Clin Exp Hypertens* 1996; **18**: 713–728.
9. Imai Y, Satoh H, Nagai K, *et al*: Characteristics of a com-

munity-based distribution of home blood pressure in Ohasama in northern Japan. *J Hypertens* 1993; **11**: 1441–1449.
10. Ohkubo T: Prognostic significance of variability in ambulatory and home blood pressure from the Ohasama study. *J Epidemiol* 2007; **17**: 109–113.
11. Imai Y, Otsuka K, Kawano Y, *et al*: Japanese society of hypertension (JSH) guidelines for self-monitoring of blood pressure at home. *Hypertens Res* 2003; **26**: 771–782.
12. Imai Y, Abe K, Sasaki S, *et al*: Clinical evaluation of semi-automatic and automatic devices for home blood pressure measurement: comparison between cuff-oscillometric and microphone methods. *J Hypertens* 1989; **7**: 983–990.
13. Association for the Advancement of Medical Instrumentation: American National Standards for Electronic or Automated Sphygmomanometers. Washington DC, AAMI, 1987.
14. National Institute of Neurological Disorders and Stroke Ad Hoc Committee: Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. *Stroke* 1990; **21**: 637–676.
15. Perry HM, Roccella EJ: Conference report on stroke mortality in the southeastern United States. *Hypertension* 1998; **31**: 1206–1215.
16. Menotti A, Jacobs Jr DR, Blackburn H, *et al*: Twenty-five–year prediction of stroke deaths in the seven countries study: the role of blood pressure and its changes. *Stroke* 1996; **27**: 381–387.
17. Arima H, Tanizaki Y, Kiyohara Y, *et al*: Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. *Arch Intern Med* 2003; **163**: 361–366.
18. Nakamura Y, Yamamoto T, Okamura T, *et al*: Combined cardiovascular risk factors and outcome: NIPPON DATA80, 1980–1994. *Circ J* 2006; **70**: 960–964.
19. Shimamoto K, Kita T, Mabuchi H, *et al*: The risk of cardiovascular events in Japanese hypertensive patients with hypercholesterolemia: sub-analysis of the Japan Lipid Intervention Trial (J-LIT) Study, a large-scale observational cohort study. *Hypertens Res* 2005; **28**: 879–887.
20. Jones DW: Dietary sodium and blood pressure. *Hypertension* 2004; **43**: 932–935.
21. Sacks FM, Svetkey LP, Vollmer WM, *et al*: Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; **344**: 3–10.
22. Fagard RH: The role of exercise in blood pressure control: supportive evidence. *J Hypertens* 1995; **13**: 1223–1227.
23. Khan NA, Hemmelgarn B, Padwal R, *et al*: The 2007 Canadian Hypertension Education Program recommendations for the management of hypertension: part 2—therapy. *Can J Cardiol* 2007; **23**: 539–550.
24. Imai Y, Ohkubo T, Kikuya M, Hashimoto J: Practical aspect of monitoring hypertension based on self-measured blood pressure at home. *Intern Med* 2004; **43**: 771–778.

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See COMMENTARY page 486

Optimal Cutoff Point of Waist Circumference and Use of Home Blood Pressure as a Definition of Metabolic Syndrome: The Ohasama Study

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BACKGROUND
Self-measured blood pressure (BP) at home (HBP) has a stronger predictive power for cardiovascular mortality and morbidity than casual-screening BP (CBP). No studies have evaluated the clinical significance of self-measured HBP for diagnosing metabolic syndrome (MS). Eight scientific associations recently defined MS for the Japanese population. However, this definition remains controversial, especially with respect to the cutoff value of waist circumference (WC) being higher in women than in men.

METHODS
The participants of this population-based survey were the 395 residents (≥35 years of age) of Ohasama, a rural Japanese community. They measured HBP and underwent the oral glucose tolerance test between the years 2000 and 2006. We calculated the optimal cutoff values of WC required to diagnose MS, and examined the association of HBP with metabolic risk-factor clustering using multivariate analyses.

RESULTS
Receiver operation characteristic analysis indicated that the optimal WC cutoff values for identifying clusters of metabolic risk factors were 87 and 80 cm in men and women, respectively. Elevated HBP was significantly associated with the clustering of metabolic risk factors but CBP was not.

CONCLUSION
The appropriate WC cutoff value in the current MS criteria for Japanese women would be 80 cm. We suggest that HBP would be useful when considering a diagnosis of MS. The association between MS determined using HBP and the prognosis of cardiovascular diseases (CVDs) requires further investigation.

Am J Hypertens 2008; **21**:514-520 © 2008 American Journal of Hypertension, Ltd.

Metabolic syndrome (MS) is a cluster of metabolic risk factors that increases morbidity and mortality due to cardiovascular diseases (CVDs).[1,2] The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III; 2001) defined and emphasized the importance of treatment for MS.[3] In Asia, as well as in other countries, MS is becoming a considerable threat due to rapid dietary and lifestyle changes. Therefore, the ATP III criteria have been commonly applied in Asia while an obesity-related anthropometric index in the criteria has been specifically designed for the U.S. population. Eight scientific associations recently collaborated to find a suitable definition of MS for the Japanese population.[4] However, such a definition remains controversial. The main issue is the higher cutoff value for female, than male waist circumference (WC). Some Japanese cohort studies have found that a lower female WC cutoff value in the Japanese MS criteria is needed to discriminate individuals with metabolic risk-factor clustering.[5–10] In addition, health check-ups for MS among those aged ≥40 years of age will begin in April 2008 as a national policy with the objective of preventing lifestyle-related diseases. Conclusions gathered from additional evidence generated by population-based cohort studies should end the controversy.

Self-measured blood pressure (BP) at home (HBP) has a stronger predictive power for cardiovascular mortality and morbidity than casual-screening BP (CBP).[11–14] Values of HBP improve the accuracy of screening for hypertension and for assessing BP control during treatment and encourage drug compliance.[15] Moreover, HBP measurements would provide

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Received 11 October 2007; first decision 11 October 2007; accepted 22 December 2007; advance online publication 6 March 2008. doi:10.1038/ajh.2007.88

a cost benefit to diagnosing and treating hypertension.[15] However, no studies have yet attempted to improve the clinical significance of MS using HBP information.

This study proposes appropriate WC cutoff values as Japanese criteria for MS and evaluates the clinical significance of HBP for diagnosing MS.

METHODS

Study population. This investigation is a part of a longitudinal observational study of HBP measurements among Ohasama residents that started in 1987. The socioeconomic and demographic characteristics of this region and full details of the project have been described elsewhere.[16] The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine, Sendai, Japan, and by the Department of Health of the Ohasama Town Government. Between 2000 and 2006, we attempted to contact all 4,809 individuals aged 35 years or over in four districts of Ohasama town. Those who were absent during the normal working hours of the study nurses (n = 1,298) and those hospitalized (n = 192) or incapacitated (n = 120) were not eligible. Of the remaining 3,199 residents, 2,181 (68%) provided written, informed consent to participate in the HBP measurement program. We excluded 68 individuals from the present analysis, as their morning HBP values were the averages of less than three readings (3 days). Of those, 397 volunteers (19%) participated in the diabetes screening program including the oral glucose tolerance test and measurement of WC. We excluded those treated with antidiabetic agents (n = 2) from the present analysis. The total number of participants statistically analyzed was thus 395. The 395 individuals who participated in the diabetes screening program were significantly older, had lower systolic HBP levels, and comprised a lower proportion of men than those who did not participate (n = 1786).

BP measurements. The participants measured HBP using a semi-automatic device (HEM-747IC-N; Omron Healthcare, Kyoto, Japan), which is based on the cuff-oscillometric method[17] that generates a digital display of both systolic and diastolic BP values. Physicians and public health nurses instructed the participants on how to use the device and record HBP. The participants measured their own BP once in the morning while seated within 1 h after waking, and after ≥2 min of rest and recorded the measurements for 4 weeks. Those on antihypertensive drugs measured BP before the morning dose. Although many participants measured BP at least twice per occasion, we used the first value from each measurement to exclude individual selection bias.[18] We defined HBP as the mean of all measurements.

During health check-ups held in Ohasama, nurses or technicians consecutively measured the CBP of seated participants twice using an automatic device (HEM-907, Omron Healthcare, Kyoto, Japan) after at least 2 min of rest. The CBP measurements were taken in the morning before the oral glucose tolerance test. The CBP was the average of two consecutive readings from each individual.

Both the HBP and CBP measuring devices used in this study have been validated[17,19] and meet the criteria established by the Association for the Advancement of Medical Instrumentation.[20]

Definition of metabolic risk-factor clustering. We first investigated the association between obesity-related anthropometric indices (WC or body mass index: BMI) and metabolic risk-factor clustering. Metabolic risk-factor clustering was defined based on the MS criteria for Japanese and of the ATP III, respectively.[3,4] The Japanese-based criteria defined those with two or more of the following as having multiple risk factors: (i) triglycerides ≥150 mg/dl (1.7 mmol/l) and/or HDL cholesterol <40 mg/dl (1.03 mmol/l) and/or taking antihyperlipidemic drugs, (ii) fasting plasma glucose ≥ 110 mg/dl (6.1 mmol/l), and/or previously diagnosed with diabetes mellitus, (iii) CBP systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg (in the CBP-based definition), or HBP systolic ≥125 mm Hg and/or diastolic ≥80 mm Hg (in the HBP-based definition) and/or taking antihypertensive drugs.

The ATP III-based criteria defined those with two or more of the following as having multiple risk factors: (i) triglycerides ≥150 mg/dl, (ii) HDL cholesterol <40 mg/dl in men, <50 mg/dl (1.29 mmol/l) in women, (iii) fasting plasma glucose ≥110 mg/dl, (iv) CBP systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg (in the CBP-based definition), HBP systolic ≥125 mm Hg and/or diastolic ≥80 mm Hg (in the HBP-based definition). The HBP criteria were established in accordance with 1999 WHO/ISH guidelines[21] and 2003 ESH/ESC guidelines[22] based on the Ohasama,[16] PAMELA[23] and other cohort studies. In both the Ohasama and PAMELA studies, the regression line analyzed by correlation between CBP and HBP indicated that the HBP value corresponding to CBP 140/90 mm Hg was ~125/80 mm Hg. The guidelines thus defined the normal range of HBP as <125/80 mm Hg.

We also investigated whether HBP is more useful in diagnosing MS than CBP. Metabolic risk-factor clustering was also defined based on the MS criteria for Japanese or the ATP III, respectively.[3,4] The Japanese-based criteria defined those with high WC (defined according to the first analysis) and any one of the following values as having multiple risk factors: (i) triglycerides ≥150 mg/dl and/or HDL cholesterol <40 mg/dl, and/or taking antihyperlipidemic drugs, (ii) fasting plasma glucose ≥110 mg/dl and/or previously diagnosed with diabetes mellitus. The ATP III-based criteria defined two or more of the following as having multiple risk factors: (i) high WC (defined according to the first analysis), (ii) triglycerides ≥150 mg/dl, (iii) HDL cholesterol <40 mg/dl in men, <50 mg/dl in women, (iv) fasting plasma glucose ≥110 mg/dl.

Statistical analysis. Data were analyzed using the Wilcoxon rank-sum test and the χ^2-test. We extracted samples in the first analysis using the Bootstrap method[24] and calculated the areas under receiver-operating characteristic curves (AUCs) by logistic regression analysis. The odds ratios for risk-factor clusters per 1 s.d. increase in CBP or HBP were examined using the logistic regression model adjusted for age and gender.

All data are shown as means (s.d.) unless otherwise stated. Statistical significance was established at $P < 0.05$ (two-tailed). All statistical calculations were performed using the SAS system (version 9.1, SAS Institute).

RESULTS

The mean number of HBP measurements was 25 (5). **Table 1** shows the characteristics of the participants classified by gender. The WC in men was significantly higher than that in women.

Table 2 shows the prevalence of each metabolic risk factor. According to the Japanese criteria, ~5% of the women had a WC of >90 cm, and the prevalence of MS among women was only 1.4%. The frequency of men taking diuretics among those prescribed with antihypertensive drugs tended to be higher than that of women.

Table 3 shows the AUCs for identification of risk-factor clustering when defined based on WC or BMI. Among men, BMI tended to be associated with higher AUCs for the identification of any two or more risk factors other than WC regardless of BP information, whereas WC tended to have higher AUCs than BMI among women regardless of BP information. However, AUCs did not significantly differ between WC and BMI. When based on Japanese criteria, the AUCs for identifying three risk factors were distributed with wide 95% confidence intervals, since only a few individuals ($n = 4$ in both genders) had all three risk factors (data not shown).

Table 1 | Characteristics of the study subjects

	Men ($n = 118$)	Women ($n = 277$)	P
Age (years)	63.6 ± 8.5	63.4 ± 9.1	0.8
Height (cm)	163.1 ± 6.3	150.0 ± 6.1	<0.001
Weight (kg)	64.1 ± 10.7	52.7 ± 8.2	<0.001
BMI (kg/m^2)	24.0 ± 3.1	23.4 ± 3.1	0.07
WC (cm)	83.4 ± 8.9	76.6 ± 8.9	<0.001
Hip circumference (cm)	93.4 ± 5.6	92.5 ± 6.4	0.2
CBP systolic (mm Hg)	136 ± 18	132 ± 19	0.09
CBP diastolic (mm Hg)	79 ± 11	77 ± 13	0.2
HBP systolic (mm Hg)	135 ± 16	125 ± 16	<0.001
HBP diastolic (mm Hg)	80 ± 9	74 ± 9	<0.001
Triglyceride (mg/dl)	109.9 ± 59.8	94.3 ± 60.1	<0.001
HDL-C (mg/dl)	55.7 ± 15.5	63.0 ± 13.9	<0.001
FPG (mg/dl)	96.4 ± 11.8	93.6 ± 10.3	0.007
HbA_{1c} (%)	5.20 ± 0.45	5.22 ± 0.35	0.3
HOMA-IR	1.62 ± 2.31	1.32 ± 0.85	0.7
Antihypertensive drugs (%)	30.5	24.9	0.2
Antihyperlipidemic drugs (%)	0.9	6.1	0.02

BMI, body mass index; CBP, casual-screening blood pressure; FPG, fasting plasma glucose; HBP, self-measured blood pressure at home; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment–insulin resistance; WC, waist circumference.

Table 2 | Prevalence of each metabolic risk factor

Risk factors	Men	Women
Japanese criteria		
WC ≥85 cm in men, ≥90 cm in women	45.8	5.4
CBP systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg and/or taking antihypertensive drugs	72.9	61.4
Triglyceride ≥150 mg/dl and/or HDL-C <40 mg/dl and/or taking antihyperlipidemic drugs	22.0	18.1
FPG ≥110 mg/dl and/or diagnosed as DM	11.0	8.3
MS (Japanese criteria)	17.8	1.4
HBP systolic ≥125 mm Hg and/or diastolic ≥80 mm Hg and/or taking antihypertensive drugs	75.4	58.1
ATP III criteria		
WC ≥102 cm in men, ≥88 cm in women	2.5	9.8
CBP systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg	70.3	57.4
Triglyceride ≥150 mg/dl	16.1	10.8
HDL-C <40 mg/dl in men, <50 mg/dl in women	6.8	15.2
FPG ≥110 mg/dl	11.0	6.9
MS (ATP III criteria)	5.9	7.9
HBP systolic ≥125 mm Hg and/or diastolic ≥80 mm Hg	71.2	53.1
Taking diuretics among recipients of antihypertensive drugs	12.9	1.75

CBP, casual-screening blood pressure; FPG, fasting plasma glucose; HBP, self-measured blood pressure at home; HDL-C, high-density lipoprotein cholesterol; MS, metabolic syndrome; WC, waist circumference.

Table 3 | AUCs for identification of the risk-factor clustering by WC or BMI

	AUC (95% confidence interval)	
	WC	BMI
Japanese criteria (men)		
CBP based	0.743 (0.636–0.850)	0.798 (0.699–0.886)
HBP based	0.749 (0.649–0.842)	0.798 (0.702–0.886)
ATP III criteria (men)		
CBP based	0.736 (0.627–0.839)	0.798 (0.706–0.878)
HBP based	0.768 (0.657–0.860)	0.829 (0.740–0.905)
Japanese criteria (women)		
CBP based	0.674 (0.603–0.748)	0.612 (0.523–0.699)
HBP based	0.672 (0.597–0.750)	0.594 (0.511–0.683)
ATP III criteria (women)		
CBP based	0.685 (0.611–0.763)	0.682 (0.602–0.755)
HBP based	0.707 (0.631–0.779)	0.656 (0.573–0.732)

All values were adjusted by age.
ATP III, The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; AUC, areas under the receiver operating characteristic curves; BMI, body mass index; CBP based, BP information of the risk factors based on casual-screening blood pressure; HBP based, BP information of the risk factors based on self-measured blood pressure at home; WC, waist circumference.

Table 4 | The optimal cutoff values of WC and BMI for identification of the risk-factor clustering

	Cutoff value	Sensitivity	Specificity
WC (men)			
Japanese criteria based	87.0	0.625	0.750
ATP III criteria based	86.5	0.690	0.742
WC (women)			
Japanese criteria based	80.0	0.490	0.668
ATP III criteria based	80.0	0.611	0.700
BMI (men)			
Japanese criteria based	24.0	0.844	0.614
ATP III criteria based	24.0	0.897	0.618
BMI (women)			
Japanese criteria based	24.0	0.529	0.633
ATP III criteria based	25.0	0.519	0.731

We considered cutoff values yielding the maximal sensitivity plus specificity for predicting the presence of multiple risk factors.
ATP III, The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; BMI, body mass index; WC, waist circumference.

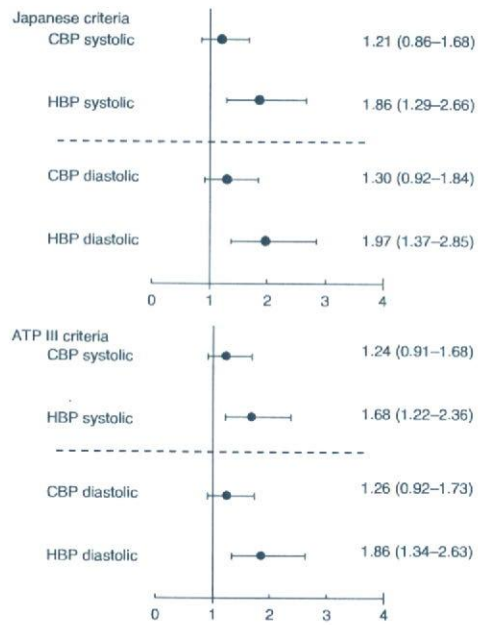

Figure 1 | Odds ratios (95% confidence interval) for presence of risk-factor clustering per single standard deviation increase in CBP or HBP. CBP systolic and HBP systolic were simultaneously included into the logistic regression model. CBP diastolic and HBP diastolic were also simultaneously analyzed. The horizontal axis shows odds ratios and dots show point estimates of odds ratios. Bars across dots show 95% confidence intervals. Adjusted factors were age and gender. CBP, casual-screening blood pressure; HBP, self-measured blood pressure at home.

Table 4 shows the optimal cutoff values of WC and BMI for identifying HBP-based risk-factor clustering. The boundary values between the Japanese and ATP III criteria did not significantly differ. The appropriate cutoffs were WC ≥ 87 cm for men, ≥80 cm for women, and BMI ≥24 kg/m^2 for both genders.

Table 5 | Gender specific odds ratios (95% confidence interval) for the presence of the risk-factor clustering per one standard deviation increase in CBP or HBP

	Odds ratio (95% confidence interval)	
	Men	Women
Japanese criteria		
CBP systolic	0.918 (0.478–1.698)	1.461 (0.967–2.222)
HBP systolic	2.450 (1.330–4.884)	1.417 (0.924–2.202)
CBP diastolic	0.921 (0.489–1.685)	1.591 (1.033–2.499)
HBP diastolic	2.713 (1.453–5.584)	1.492 (0.973–2.316)
ATP III criteria		
CBP systolic	0.976 (0.517–1.783)	1.431 (0.995–2.071)
HBP systolic	2.171 (1.199–4.203)	1.374 (0.943–2.025)
CBP diastolic	1.041 (0.569–1.863)	1.402 (0.960–2.072)
HBP diastolic	2.221 (1.233–4.337)	1.566 (1.073–2.314)

All values were adjusted by age.
ATP III, The Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; CBP, casual-screening blood pressure; HBP, self-measured blood pressure at home.

The odds ratios for the presence of risk-factor clustering based on HBP were statistically significant (**Figure 1**), whereas risk did not significantly increase when CBP was included in risk-factor clustering. We identified significant interactions between systolic CBP and systolic HBP (Japanese criteria, $P = 0.04$; ATP III criteria, $P = 0.02$). An analysis of these findings by gender indicated that the association was stronger in men than in women (**Table 5**).

We compared HBP readings over the first 3 days (3-day HBP) with the total 25 (5) day HBP (total HBP). The mean 3-day HBP values were 138 ± 18/82 ± 10 and 129 ± 18/76 ± 10 mm Hg for men and women, respectively. The results of the AUCs for identification of the risk-factor clustering by WC or BMI and the optimal cutoff values of WC and BMI for such identification were almost identical (data not shown). The odds ratios for the presence of risk-factor clustering per one standard deviation increase in the 3-day HBP were lower than in total HBP (data not shown).

DISCUSSION

We found that the differences between WC and BMI as a component for a definition of MS were not statistically significant. If BMI was used as an obesity-related anthropometric index instead of WC, 24 kg/m^2 would be the optimal cutoff value. The present findings suggest a lower WC cutoff value (80 cm) for Japanese women than the current value based on the Japanese criteria for MS (90 cm). We also found that elevated HBP was associated with the clustering of metabolic risk factors.

The optimal cutoff values of WC based on the first analysis were 87 cm for men and 80 cm for women, and the latter value considerably differs from the current Japanese criterion of 90 cm. Ohkubo *et al.*[5] and Hara *et al.*[6] proposed cutoff

values of 75 cm and 78 cm, respectively, for Japanese women in relation to insulin resistance, and to metabolic risk-factor clustering except WC. Miyawaki *et al.*[7] and Eguchi *et al.*[8] also proposed cutoff values of 77 and 78 cm, respectively, in relation to visceral fat area. They both estimated visceral fat area cutoff points by gender to identify clustering of other risk factors or atherosclerotic CVD, and then calculated WC cutoff values corresponding to the visceral fat area cutoff points. Thus, lowering the standard value of WC for women compared to the current Japanese criteria for MS seems more reliable.

We could not identify a significant difference between the usefulness of WC and of BMI. Some studies have indicated that WC is more appropriate than BMI for a diagnosis of MS.[25,26] Wildman *et al.* reported that WC in a Chinese population added further CVD risk information to that of BMI and vice versa.[27] However, reports addressing the predictive power of WC for CVD are sparse, whereas BMI has a proven predictive power for CVD and for coronary heart disease.[28] The prognostic value of WC remains to be investigated.

The optimal boundary value of BMI for diagnosing MS was 24 kg/m^2 for both genders. This result would be reasonable since the current standard of obesity in Japan is ≥25 kg/m^2.[29] The cutoff WC value from the current study should also be reasonable since WC and BMI were calculated using the same analytical method.

Information about BP is necessary for a diagnosis of MS since the clinical state of MS includes having high BP. Whether CBP or HBP should be used to diagnose MS remains uncertain. The incidence of CVD is higher among individuals with MS than without MS.[30,31] Since the BP information used in these reports was based on CBP, MS based on CBP would be a useful predictor of CVD. However, other investigators have reported that HBP has stronger predictive power for CVD morbidity and mortality than CBP.[11–14] The present study revealed that HBP was more closely associated with clustering of metabolic risk factors than CBP. This association was closer in men than in women. The prevalence of masked hypertension (normal CBP and high HBP) was significantly higher among men than in women (25 and 12% in men and women, respectively; $P < 0.01$). We previously reported that masked hypertension has a powerful prognostic value for CVDs.[32] Measuring HBP would be effective for detecting masked hypertension among men. On the contrary, the prevalence of white-coat hypertension (high CBP and normal HBP) was significantly higher in women than in men (11 and 19% in men and women, respectively; $P = 0.04$). Ugajin *et al.* reported that white-coat hypertension is a transitional cause of sustained hypertension among Ohasama residents and suggested that white-coat hypertension would carry a poor cardiovascular prognosis.[33] Therefore, HBP measurement would be also important in women, as well as in men, for detecting the development of sustained hypertension. However, these unstable results with an extension of 95% confidence intervals indicate that further analyses are needed to define gender specificities. In general, a diagnosis of MS based on HBP would be a more powerful predictor of CVD than that of MS based on CBP. Although mass screening would be easier by measuring CBP than HBP, an accurate evaluation of metabolic risks using HBP would be necessary for therapeutic intervention. Approximately 30 million devices for measuring HBP are used in Japan,[34] and two thirds of treated hypertensive individuals in Italy and Greece are practicing HBP measurement.[35,36] Therefore, mass screening by HBP measurement might be reasonably straightforward at present. Although the association between MS determined based on HBP and the prognosis of CVDs requires further study, we nevertheless suggest using HBP instead of CBP for diagnosing MS.

This study found that the Japanese and ATP III criteria were similarly associated with HBP values when we used cutoff values of WC calculated in first analysis that were applicable to the detection of MS risk-factor clustering. The ATP III criteria would be globally useful in comparisons of the prevalence of MS with that in other countries since they have been widely applied in investigations of prevalence and risk factors for MS. Further studies are required to clarify the appropriate cutoff values of WC and the applicability of the ATP III criteria to the Japanese population.

Among antihypertensive drugs, diuretics are associated with an increase in blood glucose and incidence of diabetes mellitus.[37] In this study, the prevalence of diuretic use was higher among men than women. This might influence the prevalence of fasting plasma glucose ≥110 mg/dl and MS (Japanese criteria). On the contrary, women were more frequently prescribed with antihyperlipidemic drugs than men in the present study. Generally, the serum lipid levels of Japanese women increase after menopause and exceed those of men. Thus, women >60 years of age are more often on antihyperlipidemic drugs than men.[38] Our results corresponded with this fact, since many women in this study were postmenopausal (63.4 ± 9.1 years old).

The odds ratios for the presence of risk-factor clustering per single standard deviation increase in 3-day HBP were lower than those in total HBP. We previously reported that the predictive value of HBP progressively increases with the number of measurements.[39] Therefore, the utility of HBP as MS criteria would likewise increase.

This study has some limitations. First, the participants are residents of a rural community and whether these results can be extrapolated to urban populations is debatable. The study cohort was significantly older, had lower systolic HBP levels, and comprised a lower proportion of men than nonparticipants. Those with sufficient time and health concerns might have been more likely to voluntarily participate. Moreover, diabetes is screened on weekdays, which might lead to a lower proportion of men. We included age and gender in the logistic regression models as major confounding factors. However, the possibility of selection bias needs to be considered when generalizing the present findings. Second, the number of participants was relatively small, so the frequency of having all risk factors was very low. Finally, this study was cross-sectional, so the cause-and-effect relationship was undetermined. A further

prospective study is required to assess whether HBP predicts the progression of MS and CVDs.

We concluded that the cutoff for WC among Japanese women should be lower than the current value of 90 cm. When BMI is used as an obesity-related anthropometric index instead of WC, the appropriate BMI cutoff for diagnosing MS would be 24 kg/m^2. Furthermore, HBP (systolic ≥125 mm Hg and/or diastolic ≥80 mm Hg) would be more valuable than CBP for diagnosing MS.

Acknowledgments: We are grateful to the Ohasama public health nurses and technicians, as well as the secretarial staff of our laboratory. The study was supported by the following grants: (i) Grants for scientific research (15790293, 17790381, 18390192, 18590587 and 19790423) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; (ii) Grant-in-aid for Japan Society for the Promotion of Science (JSPS) fellows (16.54041, 18.54042); (iii) Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labor and Welfare, Japan; Japan Atherosclerosis Prevention Fund; (iv) Uehara Memorial Foundation; (v) Takeda Medical Research Foundation; and (vi) Mitsubishi Pharma Research Foundation.

Disclosure: The authors declared no conflict of interest.

1. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen MR, Groop L. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24:683–689.
2. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109:433–438.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486–2497.
4. Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Definition and the diagnostic standard for metabolic syndrome. *Nippon Naika Gakkai Zasshi* 2005; 94:794–809 (in Japanese).
5. Ohkubo T, Kikuya M, Asayama K, Imai Y. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006; 29:1986–1987.
6. Hara K, Matsushita Y, Horikoshi M, Yoshiike N, Yokoyama T, Tanaka H, Kadowaki T. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care* 2006; 29:1123–1124.
7. Miyawaki T, Hirata M, Moriyama K, Sasaki Y, Aono H, Saito N, Nakao K. Metabolic syndrome in Japanese diagnosed with visceral fat measurement by computed tomography. *Proc Jpn Acad Ser B Phys Biol Sci* 2005; 81:471–479.
8. Eguchi M, Tsuchihashi K, Saitoh S, Odawara Y, Hirano T, Nakata T, Miura T, Ura N, Hareyama M, Shimamoto K. Visceral obesity in Japanese patients with metabolic syndrome: reappraisal of diagnostic criteria by CT scan. *Hypertens Res* 2007; 30:315–323.
9. Shiwaku K, Anuurad E, Enkhmaa B, Nogi A, Kitajima K, Yamasaki M, Yoneyama T, Oyunsuren T, Yamane Y. Predictive values of anthropometric measurements for multiple metabolic disorders in Asian populations. *Diabetes Res Clin Pract* 2005; 69:52–62.
10. Oizumi T, Daimon M, Wada K, Jimbu Y, Kameda W, Susa S, Yamaguchi H, Ohnuma H, Kato T. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Circ J* 2006; 70:1663.
11. Asayama K, Ohkubo T, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Prediction of stroke by self-measurement of blood pressure at home versus casual screening blood pressure measurement in relation to the JNC-7 classification: the Ohasama study. *Stroke* 2004; 35:2356–2361.
12. Ohkubo T, Imai Y, Tsuji I, Nagai K, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Kikuya M, Ito S, Satoh H, Hisamichi S. Home blood pressure measurement has a stronger predictive power for mortality than does screening blood pressure measurement: a population-based observation in Ohasama, Japan. *J Hypertens* 1998; 16:971–975.
13. Asayama K, Ohkubo T, Kikuya M, Obara T, Metoki H, Inoue R, Hara A, Hirose T, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. Prediction of stroke by home "morning" versus "evening" blood pressure values: the Ohasama study. *Hypertension* 2006; 48:737–743.
14. Ohkubo T, Asayama K, Imai Y. The value of self-measured home blood pressure in predicting stroke. *Expert Rev Neurother* 2006; 6:163–173.
15. Imai Y, Ohkubo T, Kikuya M, Hashimoto J. Practical aspect of monitoring hypertension based on self-measured blood pressure at home. *Intern Med* 2004; 43:771–778.
16. Imai Y, Satoh H, Nagai K, Sakuma M, Sakuma H, Minami N, Munakata M, Hashimoto J, Yamagishi T, Watanabe N. Characteristics of a community-based distribution of home blood pressure in Ohasama in northern Japan. *J Hypertens* 1993; 11:1441–1449.
17. Imai Y, Abe K, Sasaki S, Minami N, Munakata M, Sakuma H, Hashimoto J, Sekino H, Imai K, Yoshinaga K. Clinical evaluation of semiautomatic and automatic devices for home blood pressure measurement: comparison between cuff-oscillometric and microphone methods. *J Hypertens* 1989; 7:983–990.
18. Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, Fukiyama K; Japanese Society of Hypertension. Japanese society of hypertension (JSH) guidelines for self-monitoring of blood pressure at home. *Hypertens Res* 2003; 26:771–782.
19. Imai Y, Nishiyama A, Sekino M, Aihara A, Kikuya M, Ohkubo T, Matsubara M, Hozawa A, Tsuji I, Ito S, Satoh H, Nagai K, Hisamichi S. Characteristics of blood pressure measured at home in the morning and in the evening: the Ohasama study. *J Hypertens* 1999; 17:889–898.
20. Association for the Advancement of Medical Instrumentation. American national standards for electronic or automated sphygmomanometers. AAMI Analysis and Review: Washington DC, 1987.
21. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens* 1999; 17:151–183.
22. European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21:1011–1053.
23. Mancia G, Sega R, Bravi C, De Vito G, Valagussa F, Cesana G, Zanchetti A. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens* 1995; 13:1377–1390.
24. Hesterberg T, Moore DS, Monaghan S, Clipson A, Epstein R. Bootstrap methods and permutation tests. In Hesterberg T, Moore DS (eds), *Introduction to the Practice of Statistics*, 5th edn. Freeman: New York, 2005, pp. 14-1–14-70.
25. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004; 79:379–384.
26. Lofgren I, Herron K, Zern T, West K, Patalay M, Shachter NS, Koo SI, Fernandez ML. Waist circumference is a better predictor than body mass index of coronary heart disease risk in overweight premenopausal women. *J Nutr* 2004; 134:1071–1076.
27. Wildman RP, Gu D, Reynolds K, Duan X, Wu X, He J. Are waist circumference and body mass index independently associated with cardiovascular disease risk in Chinese adults? *Am J Clin Nutr* 2005; 82:1195–1202.
28. Jee SH, Sull JW, Park J, Lee SY, Ohrr H, Guallar E, Samet JM. Body-mass index and mortality in Korean men and women. *N Engl J Med* 2006; 355:779–787.
29. Examination Committee of Criteria for "Obesity Disease" in Japan; Japan Society for the Study of Obesity. New criteria for "obesity disease" in Japan. *Circ J* 2002; 66:987–992.
30. Sundstrom J, Riserus U, Byberg L, Zethelius B, Lithell H, Lind L. Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. *BMJ* 2006; 332:878–882.
31. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* 2006; 119:812–819.
32. Ohkubo T, Kikuya M, Metoki H, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognosis of "masked" hypertension and "white-coat" hypertension detected by 24-h ambulatory blood pressure monitoring 10-year follow-up from the Ohasama study. *J Am Coll Cardiol* 2005; 46:508–515.
33. Ugajin T, Hozawa A, Ohkubo T, Asayama K, Kikuya M, Obara T, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Tsuji I, Imai Y. White-coat hypertension as a risk factor for the development of home hypertension: the Ohasama study. *Arch Intern Med* 2005; 165:1541–1546.
34. Imai Y, Obara T, Ohkubo T. How many times should we ask subjects to measure blood pressure at home on each occasion? *J Hypertens* 2007; 25:1987–1991.
35. Cuspidi C, Meani S, Fusi V, Salerno M, Valerio C, Severgnini B, Catini E, Leonetti G, Magrini F, Zanchetti A. Home blood pressure measurement and its relationship with blood pressure control in a large selected hypertensive population. *J Hum Hypertens* 2004; 18:725–731.

36. Lydakis HC, Tzinas J, Athousakis E, Mihou E. Use of home blood pressure measurement by hypertensive patients in Southern Greece. *J Hum Hypertens* 2006; 20:291–293.
37. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HA, Viigimaa M, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Viigimaa M, Waeber B, Williams B, Zamorano JL. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007; 28:1462–1536.
38. The National Nutrition Survey in Japan 2002. Ministry of Health, Labor and Welfare, Japan.
39. Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y; Ohasama study. How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004; 22:1099–1104.

Original Article

Masked Hypertension Determined by Self-Measured Blood Pressure at Home and Chronic Kidney Disease in the Japanese General Population: The Ohasama Study

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Both chronic kidney disease (CKD) and masked hypertension (MHT) are known to be linked with an increased risk of cardiovascular disease (CVD), but their relationship has remained unclear. The present study aimed to evaluate the CKD incidence in individuals with MHT in the general Japanese population. We recorded self-measured blood pressure at home (HBP) and casual blood pressure (CBP) in 1,365 individuals (mean 63.0 years old; males, 32.5%; mean creatinine clearance [CCr], 60.9 mL/min; positive proteinuria, 6.7%) and classified the subjects into four groups: sustained normal blood pressure (SNBP, 60.3%), white-coat hypertension (WCHT, 14.9%), MHT (12.8%), and sustained hypertension (SHT, 12.0%). Kidney parameter results for the respective groups (SNBP, WCHT, MHT, and SHT) were as follows: 61.7 mL/min, 61.8 mL/min, 59.6 mL/min, and 57.3 mL/min for CCr, 4.2%, 8.9%, 10.3%, and 12.8% for the prevalence of positive proteinuria, and 2.3%, 3.0%, 6.3%, and 9.8% for the proportion with CCr<60 mL/min with proteinuria. Compared with the SNBP group, the MHT and SHT groups exhibited significant differences in these parameters ($p<0.05$, for each). The adjusted odds ratios for CCr<60 mL/min with proteinuria were significantly higher in the MHT (2.56) and SHT (3.60) groups compared with the SNBP group (reference). MHT, like SHT, is closely related to CKD, and HBP measurement could be a useful screening strategy to detect CKD in the general population. (*Hypertens Res* 2008; 31: 2129–2135)

***Key Words*: masked hypertension, white-coat hypertension, chronic kidney disease, general population, home blood pressure**

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This work was supported by Grants-in-Aid for Scientific Research (15790293, 17790382, 18390192, and 18590587) from the Ministry of Education, Culture, Sports, Science and Technology, Japan; by Grants-in-Aid for the Japan Society for the Promotion of Science (JSPS) Fellows (16.54041, 18.54042); by Health Science Research Grants and Medical Technology Evaluation Research Grants from the Ministry of Health, Labour and Welfare, Japan; by the Japan Atherosclerosis Prevention Fund; by the Uehara Memorial Foundation; and by the Takeda Medical Research Foundation.

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Received March 28, 2008; Accepted in revised form October 21, 2008.

Introduction

Accumulative evidence has revealed that a decreased glomerular filtration rate (GFR) and the presence of proteinuria are independent risk factors for death and/or cardiovascular disease (CVD) events among general populations (*1–3*). Thus, it is now recognized that chronic kidney disease (CKD) (*4*) is an emerging new target for investigation from the viewpoint of public health.

Hypertension, a classic risk factor for CVD events, can be clinically classified into subgroups: sustained hypertension (SHT), white-coat hypertension (WCHT), and masked hypertension (MHT) (*5*), which is characterized by normal casual blood pressure (CBP) and elevated home blood pressure (HBP) or ambulatory blood pressure (BP) levels. Among the subtypes, it has been revealed that patients with MHT are at a high risk for CVD morbidity and mortality similar to that of patients with SHT (*6, 7*). Accordingly, it is clinically important to clarify the relationship between CKD and MHT in terms of screening high-risk populations and targeting therapeutic levels of BP in CKD patients; however, little is known regarding this issue.

The present cross-sectional study examined the CKD incidence in subjects with MHT in the Japanese general population.

Methods

Design

This study was a part of the Ohasama study, a longitudinal BP measurement project initiated in 1986. The socio-economic and demographic characteristics of this region and full details of the project have been described previously (*8*). The study was approved by the Institutional Review Board of Tohoku University School of Medicine and the Department of Health of the Ohasama Town Government.

Study Population

In Japan, annual health checkups are available for farmers, the self-employed, retirees, and dependents aged ≥35 years. Among the 7,496 residents of Ohasama, 3,076 were eligible for annual health checkups in 1992. A total of 2,192 residents participated in checkups from 1992 to 1997. Of the 2,192 participants, 215 were excluded due to missing serum creatinine levels, missing dipstick tests for spot-urine, and other confounding factors (age, gender, body mass index [BMI], current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of CVD). Participants who were hospitalized, mentally ill, or bedridden were also excluded (n=185). In addition, participants with less than 14 d of HBP measurements and participants with apparent hematuria were excluded from statistical evaluation (n=427). Thus, 1,365 subjects comprised the study population, representing 62% of the residents participating in checkups.

BP Measurements

HBP was measured with the HEM701C (Omron Healthcare Co. Ltd., Kyoto, Japan), a semi-automatic device based on the cuff-oscillometric method (*9*), which generates a digital display of both systolic and diastolic BP.

Physicians and public health nurses instructed individuals on how to measure their own BP at home. Subjects were asked to measure their BP every morning within 1 h of waking and again after having been in the sitting position for more than 2 min. The results were recorded over a 4-week period. Subjects receiving antihypertensive drugs measured their BP before taking their medication. We allowed the individuals to measure their own BP more than twice on each occasion, although only the first measurement value on each occasion was recorded on the worksheet, to exclude selection bias by the participants (*10*). The measurements taken each morning were averaged, and the averaged values were referred to as the HBP. These measurement procedures were in accordance with Japanese Society of Hypertension (JSH) Guidelines for Self-Monitoring of Blood Pressure at Home published by the Japanese Society of Hypertension (*10*).

At the time of annual health checkup, a technician or a public health nurse measured the CBP two consecutively times, after the subject had been sitting for a minimum of 2 min, using a semiautomatic device (USM-700F; UEDA Electronic Works, Tokyo, Japan). CBP was measured during the day from 10:00 to 13:00 h or 14:00 to 16:00 h. An average of the 2 CBP measurements was calculated, and the averaged values were referred to as the CBP.

The algorisms of both the HBP measuring device and the CBP measuring device have been validated previously (*11*) and meet the criteria of the Association for the Advancement of Medical Instrumentation (*12*).

Categorization of Participants According to BP

Subjects were classified into four groups as follows: sustained normal blood pressure (SNBP): HBP<135/85 mmHg, CBP<140/90 mmHg; WCHT: HBP<135/85 mmHg, CBP≥140/90 mmHg; MHT: HBP≥135/85 mmHg, CBP<140/90 mmHg; and SHT: HBP≥135/85 mmHg, CBP≥140/90 mmHg. The cut-off values were derived from several guidelines (*13–16*). In this study, the SNBP group was composed of all subjects with normal BP, including those with SNBP controlled by medication. The WCHT group included subjects with uncontrolled BP when measured in the medical setting and normal HBP. Conversely, the MHT group included subjects with normal CBP but uncontrolled BP when self-measured at home. The SHT group included subjects with uncontrolled BP measured in the medical setting and at home. These classifications are consistent with those used in

Table 1. Characteristics of the Subjects Divided According to Their Home and Casual Blood Pressure Values

Variable	Total (n=1,365)	SNBP (n=823)	WCHT (n=203)	MHT (n=175)	SHT (n=164)
CCr (mL/min)	60.9	61.7	61.8	59.6*,†	57.3*,†
Prevalence of proteinuria (%)	6.7	4.2	8.9	10.3*	12.8*
CCr<60 mL/min (%)	51.9	51.1	47.8	57.7*,†	56.8*,†
With proteinuria (%)	7.3	2.3	3.0	6.3*	9.8*,†
Without proteinuria (%)	44.6	48.8	44.8	51.4	47.0
CCr≥60 mL/min (%)	48.1	48.9	52.2	42.3*,†	43.2*,†
With proteinuria (%)	5.6	1.9	5.9*	4.0	3.0
Without proteinuria (%)	42.5	46.9	46.3	38.3	40.2
Gender (% male)	32.5	25.5	31.0	48.6*	51.8*,†
Age (years)	63.0	61.4	63.7*	65.5*	67.7*,†
BMI (kg/m^2)	23.4	23.0	24.1*	24.0*	24.1*
CBP systolic (mmHg)	130	121	148*	127*,†	153*
Diastolic (mmHg)	72	68	82*	71*,†	83*
Pulse (mmHg)	58	53	66*	56*,†	70*
HBP systolic (mmHg)	124	117	123*	141*,†	145*,†
Diastolic (mmHg)	75	71	73*	86*,†	85*,†
Pulse (mmHg)	49	46	50*	55*	60*,†
Current smoker (%)	12.5	10.7	12.8	14.3	18.9*
Diabetes mellitus (%)	10.4	10.3	9.4	10.3	12.2
Hypercholestrolemia (%)	31.6	28.3	37.4	34.3	37.8
Hypertension on treatment (%)	31.0	16.9	41.9*	60.6*	56.7*
History of cardiovascular disease (%)	5.3	3.8	4.9	8.0	11.0*

*p<0.05 *vs.* SNBP group, †p<0.05 *vs.* WCHT group (Tukey test). SNBP, sustained normal blood pressure; WCHT, white-coat hypertension; MHT, masked hypertension; SHT, sustained hypertension; CCr, creatinine clearance; BMI, body mass index; CBP, casual blood pressure; HBP, home blood pressure.

previous studies (*6*, *7*).

Background and Laboratory Data Collection

At the time of the annual health checkup, blood and urine samples were collected. The following biochemical tests were performed: creatinine, total cholesterol, glucose, and HbA1c. Serum creatinine was measured using the Jaffe assay. Other biochemical tests were measured with standard laboratory techniques. GFR was calculated using the Cockcroft-Gault formula as endogenous creatinine clearance (CCr) (*17*). The presence of proteinuria was diagnosed by a positive protein screen as measured by a semi-quantitative dipstick test for spot-urine (Urohemobonbix 5G08C; Bayer Medical, Sendai, Japan) for which a urinary protein level ≥30 mg/dL indicated a positive result (*18*).

Participants were questioned about their smoking habits, medications for hypertension, and their history of CVD, hypercholesterolemia, or diabetes mellitus. Subjects with a history of hypercholesterolemia, defined as the presence of a total cholesterol measurement ≥5.68 mmol/L (220 mg/dL) or the use of medication for the treatment of hypercholesterolemia were considered to have hypercholesterolemia. Subjects with a history of diabetes mellitus, defined as a fasting glucose concentration ≥7.0 mmol/L (126 mg/dL), a non-fasting glucose concentration ≥11.1 mmol/L (200 mg/dL), and an HbA1c concentration ≥6.5% or the use of medication for the treatment of diabetes were defined as having diabetes mellitus. BMI was calculated as weight (kg) divided by height squared (m^2).

Data Analysis

SAS software, version 9.1 (SAS Institute, Cary, USA), was used for all statistical analyses. Data are presented as means±SD, unless otherwise specified. Values among the four groups, including CKD markers, were compared by analysis of variance or χ^2-test. Analysis of covariance or a logistic regression model was used to adjust for between-group differences in the following confounding factors: gender, age, BMI, current smoking, diabetes mellitus, hypercholesterolemia, antihypertensive treatment, and history of cardiovascular disease. To quantify the magnitude of the correlation, we used Pearson's correlation coefficient (r). For all analyses, a two-tailed p<0.05 was considered statistically significant. The authors had full access to the data and take responsibility for its integrity.