TABLE 4
Sex-specific hazard ratios (HRS) and 95% CIs of mortality from coronary heart disease and total cardiovascular disease according to quintiles of potassium intake

	Quintile of potassium intake					*P* for trend[1]
	1 (low)	2	3	4	5 (high)	
Men						
No. of subjects	4623	4624	4624	4624	4624	
Person-years	57 531	57 542	58 030	58 172	57 873	
Coronary heart disease[2]						
n	41	47	42	46	57	
Multivariable HR[3]	1.00	1.08 (0.65, 1.80)	0.84 (0.46, 1.52)	0.75 (0.39, 1.42)	0.67 (0.33, 1.35)	0.159
Total cardiovascular disease[4]						
n	180	194	190	220	282	
Multivariable HR[3]	1.00	0.94 (0.74, 1.20)	0.82 (0.62, 1.09)	0.82 (0.61, 1.10)	0.87 (0.63, 1.21)	0.503
Women						
No. of subjects	7122	7122	7123	7122	7122	
Person-years	88 828	89 948	90 829	92 331	94 075	
Coronary heart disease[2]						
n	59	41	28	33	30	
Multivariable HR[3]	1.00	0.62 (0.39, 0.99)	0.44 (0.25, 0.77)	0.48 (0.26, 0.86)	0.40 (0.20, 0.80)	0.008
Total cardiovascular disease[4]						
n	235	198	183	214	191	
Multivariable HR[3]	1.00	0.80 (0.64, 0.99)	0.77 (0.60, 0.98)	0.83 (0.64, 1.07)	0.67 (0.49, 0.90)	0.027

[1] Based on tests for trend across quintiles of potassium intake by assigning the median value of each quintile.
[2] *P* value for sex interaction for coronary heart disease was 0.04.
[3] Cox proportional hazard models adjusted for the variables listed in footnote 1 of Table 2 and sodium intake (sex-specific quintiles).
[4] *P* value for sex interaction for total cardiovascular disease was 0.03.

and ≥25.0. The multivariable hazard ratios associated with a 100-mmol increment in uncalibrated daily sodium intake among nonoverweight persons were 1.87 (95% CI: 1.44, 2.43) for total stroke, 2.28 (95% CI: 1.59, 3.27) for ischemic stroke, 1.44 (95% CI: 0.95, 2.18) for coronary heart disease, and 1.70 (95% CI: 1.41, 2.03) for total cardiovascular disease, and those among the overweight were 1.77 (95% CI: 1.01, 3.09), 2.89 (95% CI: 1.33, 6.31), 1.06 (95% CI: 0.48, 2.34), and 1.22 (95% CI: 0.83, 1.79), respectively.

DISCUSSION

The main findings of our large prospective study of Japanese men and women were that a high sodium intake was associated with high risks of mortality from total stroke, ischemic stroke, and total cardiovascular disease, whereas a high potassium intake was associated with a reduced risk of mortality from coronary heart disease and total cardiovascular disease after adjustment for cardiovascular disease risk factors. These associations were strengthened slightly when adjusted further for the other cation. The positive associations between sodium intake and mortality from stroke and total cardiovascular disease were independent of potassium intake and were similarly observed for nonoverweight and overweight persons. The inverse associations between potassium intake and mortality from coronary heart disease were more pronounced when sodium intake was high.

Our results were supported by the findings of previous studies. Two prospective studies of Americans (1) and Japanese (6) showed that sodium intake was associated with an increased risk of stroke incidence and mortality. A 100-mmol increment in daily sodium intake was reported to be associated with 32% higher incidence of stroke among overweight Americans (1). Japanese men with the highest tertile of daily sodium intake (306 mmol) had a 2-fold increased risk of stroke mortality compared with the lowest tertile (174 mmol) (6). In the present study, a 100-mmol increment in uncalibrated daily sodium intake was associated with 83% higher mortality from total stroke.

Several studies have shown that potassium intake is associated with a reduced risk of stroke incidence (5) and mortality (3). A 10-mmol increment in daily potassium intake was associated with 40% reduced risk of death from stroke (3). Americans had a 28% higher risk of stroke incidence in the lowest versus the highest quartiles of potassium intake (< versus ≥34.6 mmol/d) (5). On the other hand, the association between dietary potassium intake and risk of coronary heart disease was not significant among Americans (5). In the present study, we found an inverse association between potassium intake and mortality from coronary heart disease and total cardiovascular disease, but not from stroke.

Overweight may enhance salt-sensitivity for blood pressure (14), and a previous prospective study of Americans showed positive association between sodium intake and risk of cardiovascular disease only in overweight individuals (1). However, we found a strong positive association between sodium intake and mortality from stroke for persons with either a BMI < 25.0 or a BMI ≥ 25.0. Our findings suggests that a high sodium intake was a risk factor for cardiovascular disease not only in overweight but also in nonoverweight Japanese.

The limitations of the present study warrant discussion. First, the estimated sodium intake from the present questionnaire study

TABLE 5
Hazard ratios (HRs) and 95% CIs of mortality from stroke, coronary heart disease, and total cardiovascular disease according to the combination of sodium and potassium intakes

	Low sodium intake		High sodium intake	
	Low potassium intake	High potassium intake	Low potassium intake	High potassium intake
No. of subjects	20 760	8605	8605	20 760
Person-years	256 676	106 909	110 817	270 759
Reference = low sodium and high potassium intake				
Total stroke				
n	293	93	198	402
Multivariable HR[1]	1.15 (0.89, 1.48)	1.00	1.46 (1.13, 1.89)	1.44 (1.15, 1.82)
Ischemic stroke				
n	133	44	110	223
Multivariable HR[1]	1.13 (0.78, 1.63)	1.00	1.61 (1.12, 2.33)	1.61 (1.16-2.24)
Coronary heart disease				
n	152	47	88	137
Multivariable HR[1]	1.28 (0.89, 1.84)	1.00	1.36 (0.94, 1.98)	0.93 (0.66, 1.30)
Total cardiovascular disease				
n	641	224	408	814
Multivariable HR[1]	1.08 (0.92, 1.28)	1.00	1.28 (1.08, 1.53)	1.19 (1.03, 1.39)
Reference = high sodium and low potassium intake				
Total stroke				
n	293	93	198	402
Multivariable HR[1]	0.79 (0.66, 0.95)	0.69 (0.53, 0.89)	1.00	0.99 (0.81, 1.21)
Ischemic stroke				
n	133	44	110	223
Multivariable HR[1]	0.70 (0.54, 0.91)	0.62 (0.43, 0.90)	1.00	1.00 (0.76, 1.31)
Coronary heart disease				
n	152	47	88	137
Multivariable HR[1]	0.94 (0.72, 1.24)	0.74 (0.51, 1.07)	1.00	0.68 (0.50, 0.93)
Total cardiovascular disease				
n	641	224	408	814
Multivariable HR[1]	0.85 (0.74, 0.96)	0.78 (0.66, 0.93)	1.00	0.93 (0.81, 1.07)

[1] Cox proportional hazard models adjusted for age (y), sex, BMI (sex-specific quintiles), smoking status (4 categories), ethanol intake (6 categories), history of hypertension (yes or no), history of diabetes (yes or no), menopause (yes or no), hormone replacement therapy (yes or no), time spent on sports activity (4 categories), walking time (4 categories), educational status (4 categories), perceived mental stress (4 categories), and calcium intake (high or low).

was ≈50% lower than that estimated from dietary records (13). However, the Spearman correlation coefficient between the sodium intakes from questionnaire and dietary records was fairly good; thus, the misclassification for the rank of sodium intake was not large. In addition, any errors concerning the misclassification were likely nondifferential and would have attenuated the associations between sodium intake and mortality from cardiovascular disease. Second, we classified stroke subtypes according to the ICD codes, which may have led to misclassification. However, in Japan, computerized tomography has been widely used in local hospitals nationally since the 1980s. This widespread use of computerized tomography made a death certificate diagnosis of stroke subtypes sufficiently accurate (15, 16). Third, we estimated sodium intakes with an FFQ, which is considered to be a weaker tool than is urinary measurement (17). However, in Japan, salty seasonings such as soy sauce, soybean paste, and salty pickles account for 74% of total sodium intake (7), which may allow us to evaluate ranks of sodium intake by FFQ.

Poor nutrition may reflect poor compliance on FFQs. Then, we examined the association between sodium and potassium intakes and the risk of mortality from cardiovascular disease excluding subjects whose energy intake was <840 kcal/d (<5% of subjects). However, the results did not change significantly.

In conclusion, our large prospective study of Japanese men and women showed that a high dietary sodium intake is associated with the risk of mortality from stroke and total cardiovascular disease and that a high dietary potassium intake is inversely associated with the risk of mortality from total cardiovascular disease. The inverse association between a high dietary potassium intake and the risk of mortality from coronary heart disease was nearly significant in the subjects as a whole and was significant in women. Our findings suggest that a reduction in sodium intake may help prevent stroke and an increase in potassium intake may help prevent coronary heart disease.

We sincerely express our appreciation to Kunio Aoki (Professor Emeritus, Nagoya University School of Medicine and former chairman of the JACC Study) and to Haruo Sugano (former Director of the Cancer Institute, Tokyo), who greatly contributed to the initiation of the JACC Study.

The authors' responsibilities were as follows—MU and HI: developed the study hypothesis; MU: conducted the analysis and drafted the manuscript; and HI, CD, AY, HT, YW, SK, AK, TK, YI, NT, and AT: critically revised the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES

1. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA 1999;282:2027–34.
2. Iso H, Stampfer MJ, Manson JE, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke 1999;30:1772–9.
3. Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. N Engl J Med 1987; 316:235–40.
4. Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 1998;98:1198–204.
5. Bazzano LA, He J, Ogden LG, et al. Dietary potassium intake and risk of stroke in US men and women: National Health and Nutrition Examination Survey I epidemiologic follow-up study. Stroke 2001;32:1473–80.
6. Nagata C, Takatsuka N, Shimizu N, Shimizu H. Sodium intake and risk of death from stroke in Japanese men and women. Stroke 2004;35: 1543–7.
7. Ministry of Health, Labour and Welfare. [The National Health and Nutrition Survey in Japan, 2004.] Tokyo, Japan: Daiichi Shuppan, 2006 (in Japanese).
8. Ervin RB, Wang CY, Wright JD, Kennedy-Stephenson J. Dietary intake of selected minerals for the United States population: 1999–2000. Adv Data 2004;341:1–5.
9. Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA project. World Health Organization Monitoring Trends and Determinants in Cardiovascular Disease. Stroke 1995;26:361–7.
10. Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. BMJ 1988;297:319–28.
11. Ohno Y, Tamakoshi A, JACC Study Group. Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). J Epidemiol 2001;11:144–50.
12. Iso H, Date C, Yamamoto A, et al. Perceived mental stress and mortality from cardiovascular disease among Japanese men and women. The Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study). Circulation 2002;106:1229–36.
13. Date C, Fukui M, Yamamoto A, et al. Reproducibility and validity of a self-administered food frequency questionnaire used in JACC Study. J Epidemiol 2005;15(suppl 1):S9–23.
14. Rocchini AP, Key J, Bondie D, et al. The effect of weight loss on the sensitivity of blood pressure to sodium in obese adolescents. N Engl J Med 1989;321:580–5.
15. Iso H, Jacobs DR Jr, Goldman L. Accuracy of death certificate diagnosis of intracranial hemorrhage and nonhemorrhagic stroke. The Minnesota Heart Survey. Am J Epidemiol 1990;132:993–8.
16. Sankai T, Miyagaki T, Iso H, et al. [A population-based study of the proportion by type of stroke determined by computed tomography scan.] Nippon Koshu Eisei Zasshi 1991;38:901–9 (in Japanese).
17. Day N, McKeown N, Wong M, Welch A, Bingham S. Epidemiological assessment of diet: a comparison of a 7-day diary with a food frequency questionnaire using urinary markers of nitrogen, potassium and sodium. Int J Epidemiol. 2001;30:309–17.

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Day-by-Day Variability of Blood Pressure and Heart Rate at Home as a Novel Predictor of Prognosis: The Ohasama Study

Masahiro Kikuya, Takayoshi Ohkubo, Hirohito Metoki, Kei Asayama, Azusa Hara, Taku Obara, Ryusuke Inoue, Haruhisa Hoshi, Junichiro Hashimoto, Kazuhito Totsune, Hiroshi Satoh and Yutaka Imai

Hypertension 2008;52;1045-1050; originally published online Nov 3, 2008;
DOI: 10.1161/HYPERTENSIONAHA.107.104620
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Day-by-Day Variability of Blood Pressure and Heart Rate at Home as a Novel Predictor of Prognosis

The Ohasama Study

Masahiro Kikuya, Takayoshi Ohkubo, Hirohito Metoki, Kei Asayama, Azusa Hara, Taku Obara, Ryusuke Inoue, Haruhisa Hoshi, Junichiro Hashimoto, Kazuhito Totsune, Hiroshi Satoh, Yutaka Imai

Abstract—Day-by-day blood pressure and heart rate variability defined as within-subject SDs of home measurements can be calculated from long-term self-measurement. We investigated the prognostic value of day-by-day variability in 2455 Ohasama, Japan, residents (baseline age: 35 to 96 years; 60.4% women). Home blood pressure and heart rate were measured once every morning for 26 days (median). A total of 462 deaths occurred over a median of 11.9 years, composing 168 cardiovascular deaths (stroke: n=83; cardiac: n=85) and 294 noncardiovascular deaths. Using Cox regression, we computed hazard ratios while adjusting for baseline characteristics, including blood pressure and heart rate level, sex, age, obesity, current smoking and drinking habits, history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and treatment with antihypertensive drugs. An increase in systolic blood pressure variability of +1 between-subject SD was associated with increased hazard ratios for cardiovascular (1.27; P=0.002) and stroke mortality (1.41; P=0.0009) but not for cardiac mortality (1.13; P=0.26). Conversely, heart rate variability was associated with cardiovascular (1.24; P=0.002) and cardiac mortality (1.30; P=0.003) but not stroke mortality (1.17; P=0.12). Similar findings were observed for diastolic blood pressure variability. Additional adjustment of heart rate variability for systolic blood pressure variability and vice versa produced confirmatory results. Coefficient of variation, defined as within-subject SD divided by level of blood pressure or heart rate, displayed similar prognostic value. In conclusion, day-by-day blood pressure variability and heart rate variability by self-measurement at home make up a simple method of providing useful clinical information for assessing cardiovascular risk. (***Hypertension*. 2008;52:1045-1050.)**

Key Words: epidemiology ■ cerebrovascular disease/stroke ■ population science ■ risk factors ■ blood pressure measurement/monitoring

Home blood pressure measurement is reportedly more reliable than conventional blood pressure measurement, because this approach avoids both observer and regression dilution biases and eliminates the white coat effect.[1] Home blood pressure measurement offers more prognostic significance than office blood pressure[2] and is more indicative of target organ damage.[3] The clinical significance of home blood pressure measurement is primarily produced by multiple measurements of blood pressure.[2] These multiple measurements also provide information on day-by-day blood pressure variability under relatively controlled conditions.[4] Previous studies of ambulatory blood pressure monitoring have highlighted that circadian variation[5] and short-term blood pressure variability[6] can predict cardiovascular events above and beyond traditional risk factors. However, no studies have investigated associations between home blood pressure variability and cardiovascular events. We hypothesized that day-by-day blood pressure variability derived from self-measurement at home would provide further insights into prognosis. The objective of the present study was to clarify whether day-by-day variability in home blood pressure could have prognostic significance in the general population. We also tested the prognostic significance of variability in home heart rate, because we had observed previously an association between high home heart rate and increased risk of cardiovascular mortality.[7]

Methods

Design

This report was based on longitudinal observations of subjects who have been participating in a blood pressure measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. Socioeconomic and demographic characteristics of this region and details of the study project have been described previously.[2,6] The institutional review

Received November 7, 2007; first decision November 28, 2007; revision accepted September 26, 2008.

From the Departments of Clinical Pharmacology and Therapeutics (M.K., H.M., A.H., T. Obara, K.T., Y.I.), Drug Development and Clinical Evaluation (K.A., T. Ohkubo, J.H.), and Environmental Health Sciences (H.S.), Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Comprehensive Research and Education Center for Planning of Drug Development and Clinical Evaluation (T. Ohkubo, R.I., H.M., K.A., J.H., K.T., H.S., Y.I.), Tohoku University 21st Century COE Program, Sendai, Japan; Ohasama Hospital (H.H.), Iwate, Japan.

Correspondence to Masahiro Kikuya, Department of Clinical Pharmacology and Therapeutics, Graduate School of Medicine and Pharmaceutical Sciences, Tohoku University, 1-1 Seiryomachi, Sendai 980-8574, Japan. E-mail kikuyam@mail.tains.tohoku.ac.jp

Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.107.104620**

boards of Tohoku University School of Medicine and the Ohasama Municipal Government Department of Health approved the study. All of the participants provided written informed consent.

Study Population

From 1988 until 1995, we contacted all 4969 of the subjects ≥35 years old and living in 4 districts of Ohasama town. Subjects who were not at home during the normal working hours of the study nurses (n=1057) and those hospitalized (n=166) or incapacitated (n=94) were ineligible. Of the remaining 3652 residents, 2933 (80%) participated in baseline examinations and underwent follow-up. We excluded 478 subjects because home heart rate had not been measured (n=53) or because home blood pressure (n=415) or home heart rate (n=10) was based on averages of <10 readings (10 days). We consider that ≥10 home blood pressure measurements are necessary to provide a reliable SD of blood pressure. This criterion was based on an observation in 153 inhabitants of Ohasama (mean age: 63.5±10.1 years; 65.4% women) who measured home blood pressure over 30 days that within-subject SD of home measurements for the first 10 days (systolic: 9.0±3.7 mm Hg; diastolic: 6.3±2.7 mm Hg) did not differ significantly from that obtained over 30 days (systolic: 9.2±3.0 mm Hg; diastolic: 6.5±2.4 mm Hg; $P \geq 0.10$). Given that home blood pressure measurement is easily accepted by subjects and has a relatively low cost, using more readings than the statistically reliable minimum number (10 readings) thus appears reasonable to calculate the SD of blood pressure. We, therefore, adopted a varying number of measurements. Finally, the total number of subjects included in the present analyses was 2455.

Data Collection

At public health centers, trained nurses of Ohasama town measured anthropometric characteristics. Physicians and/or public health nurses instructed participants on how to perform home blood pressure measurements. Participants were asked to measure blood pressure and heart rate once every morning over a period of 4 weeks using an oscillometric device (HEM 401C, Omron Healthcare) within 1 hour of waking, with measurements performed in a sitting position after >2 minutes of rest.[4,8] Home hypertension was defined as a morning blood pressure of 135 mm Hg systolic or 85 mm Hg diastolic or as the use of antihypertensive drugs. We computed the level and variability of home blood pressure as average and within-subject SD of measurements, respectively.[6] We also considered coefficient of variation (CV), defined as the within-subject SD divided by blood pressure level. Using the same procedure, we defined the level and variability of home heart rate. In sensitivity analyses, we tested the prognostic significance of the variability of blood pressure and heart rate using only the first 10 days of data in all 2455 of the subjects.

Study nurses administered a standardized questionnaire, inquiring into medical history, intake of medications, and smoking and drinking habits of each patient. Previous cardiovascular disease included stroke, transient ischemic attack, coronary heart disease, and atrial fibrillation. Venous blood samples were analyzed using standard automated enzymatic methods for total cholesterol and blood glucose. According to published criteria,[9] diabetes mellitus was defined as a fasting or random blood glucose level of ≥7.0 or ≥11.1 mmol/L, respectively, or as the use of antidiabetic drugs. Hypercholesterolemia was a serum level of total cholesterol of ≥5.68 mmol/L (220 mg/dL) or use of lipid-lowering drugs. Obesity was defined as a body mass index of ≥25 kg/m^2.

Ascertainment of Events

We ascertained vital status until December 31, 2004, via resident registration cards, which are the basis for pension and social security benefits in Japan. Causes of death were obtained from the National Japanese Mortality Registry. Diagnoses on death certificates were verified against the medical charts of Ohasama hospital, where >90% of Ohasama residents undergo regular health checkups. End points considered in the present analysis were death from all causes, cardiovascular (International Classification of Diseases, 10th Revision [ICD-10] codes "I") and noncardiovascular mortality, mortality from stroke (ICD-10 code I6), intracerebral hemorrhage (ICD-10 code I61), cardiac disorders (ICD-10 codes I05, I11, I20–I25, I34, I35, I38, I46–I50, I71, I74, I77, and I99), cerebral infarction (ICD-10 code I63), myocardial infarction (ICD-10 codes I21 and I22), neoplasms (ICD-10 codes C00-D48), diseases of the respiratory system (ICD-10 codes "J"), and senility (ICD-10 code R54). Thus, cardiovascular mortality includes mortality from all stroke and cardiac events. We only classified cause of death as senility when all other diseases were excluded. Participants who died from other causes or who were lost to follow-up were treated as censored.

Statistical Analysis

SAS 9.1 software (SAS Institute, Inc) was used for statistical analysis. We compared means and proportions using the standard normal z test for large samples or ANOVA and the χ^2 statistic, respectively, and survival curves by Kaplan-Meier survival function estimates for cardiovascular mortality across quartiles of blood pressure and heart rate variability. Pearson's correlation coefficients were computed for blood pressure and heart rate parameters. In Cox regression, the proportional hazards assumption was checked using the Kolmogorov-type supremum test. We calculated hazard ratios of variability (SD or CV of measurements) using multiple Cox regression while adjusting for baseline characteristics, including sex, age, obesity, current smoking and drinking habits, history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and treatment with antihypertensive drugs. In Cox models for SD of parameters (blood pressure and heart rate), we also accounted for levels of the parameters. In a fully adjusted model, we further accounted for heart rate variability when analyzing blood pressure variability and vice versa.

Results

Baseline Characteristics of Participants

The 2455 participants included 1483 women (60.4%) and 1021 patients with home hypertension (41.6%), of whom 741 (72.6%) were taking antihypertensive drugs. Mean values were 59.4±12.3 years for age, 23.5±3.1 for body mass index, and 5.0±0.9 mmol/L for total cholesterol. At enrollment, 474 participants (19.3%) were current smokers and 472 (25.8%) reported intake of alcohol, 653 (26.6%) had hypercholesterolemia, 232 (9.5%) had diabetes mellitus, and 131 (5.3%) had a history of cardiovascular disease. Mean number of blood pressure readings per participant was 24.5±5.3. The 95th, 75th, 50th (median), 25th, and 5th percentile cutoff values for the number of home readings were 30, 28, 26, 22, and 13, respectively. Systolic/diastolic blood pressure levels were 124.6±15.2/74.7±9.9 mm Hg, respectively. The SDs and CVs of systolic/diastolic blood pressure were 8.6±3.2/6.4±2.3 mm Hg and 6.9±2.3/5.2±1.9%, respectively. The level, SD, and CV of heart rate were 67.4±7.8 bpm, 5.7±2.3 bpm, and 8.4±3.2%, respectively. Systolic blood pressure correlated positively with the SD of systolic blood pressure ($r=+0.40$). Heart rate also correlated positively with the SD of heart rate ($r=+0.32$). Diastolic blood pressure, on the other hand, did not correlate with SD of diastolic blood pressure ($r=+0.07$). Blood pressure was not correlated with heart rate ($r=-0.06$ for systolic; $r=+0.03$ for diastolic). In contrast, SD of blood pressure correlated positively with SD of heart rate ($r=+0.28$ for systolic; $r=+0.39$ for diastolic). Age did not correlate with day-by-day variability of heart rate ($r=-0.027$).

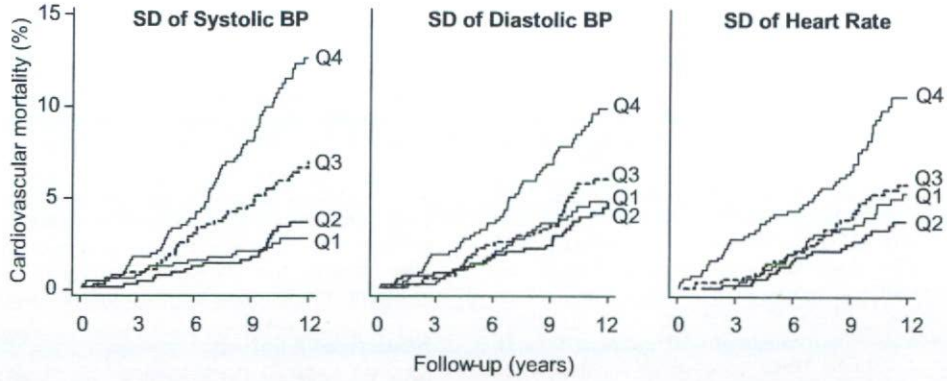

Figure 1. Kaplan-Meier survival estimates for cardiovascular mortality across quartiles of day-by-day variability, ie, SD of systolic blood pressure (left), diastolic blood pressure (middle), and heart rate (right). Q1 to Q4 indicate ascending quartiles; cutoff points were 6.5, 8.2, and 10.3 mm Hg for systolic; 4.9, 6.1, and 7.6 mm Hg for diastolic; and 4.2, 5.4, and 6.9 bpm for heart rate.

Among 2455 study subjects, 1194 subjects (64.1% women; mean age: 57.8±10.7 years) were re-examined with long-term measurement (24.2±4.4 days) of home blood pressure in the morning after 7.5±1.5 years (second examination). Differences between baseline and second examination were <2 mm Hg for level, <1 mm Hg for SD, and <1% for the CV of home blood pressure. In relation to home heart rate, differences were also small (<1 bpm and <1%). Variabilities (SD and CV) of both blood pressure and heart rate correlated moderately with first and second examinations (>0.30).

Analysis of Mortality

During follow-up (mean: 11.9±3.9 years; median: 11.9 years; 5th to 95th percentile interval: 3.8 to 16.9 years), 29 224 person-years were accrued. A total of 81 participants (3.3%) were lost to follow-up. The total of 462 deaths included 168 cardiovascular deaths (36.4%), with 83 strokes (18.0%) and 85 cardiac deaths (18.4%). These results were similar to mortality throughout Japan according to the National Vital Statistics; total number of deaths in Japan in 2000 was 961 653, including 285 333 cardiovascular deaths (29.7%), with 132 529 strokes (13.8%) and 152 804 cardiac deaths (15.9%).[10] Stroke deaths were because of cerebral infarction in 51 subjects, intracerebral hemorrhage in 21 subjects, subarachnoid hemorrhage in 8 subjects, or other cerebrovascular or ill-defined causes in 3 subjects. Cardiac mortality included myocardial infarction (n=33), heart failure (n=18), sudden death (n=7), chronic coronary heart disease (n=6), arrhythmia (n=5), and various other cardiac disorders (n=16). Noncardiovascular deaths (n=294) resulted from neoplasms (n=112), diseases of the respiratory system (n=69), senility (n=21), suicide (n=19), diseases of the genitourinary system (n=15), injuries (n=14), diseases of the digestive system (n=13), and various other diseases (n=31).

Cumulative incidence for cardiovascular mortality differed across quartiles of the distributions of SDs for blood pressure and heart rate (Figure 1; log-rank test; all $P<0.0001$). In Cox regression, the Kolmogorov-type supremum test showed that, for all of the outcomes in relation to variability and level of blood pressure and heart rate, the proportional hazards assumption was satisfied ($P\geq0.11$). With multiple adjustments applied, both levels and variabilities of systolic blood pressure and heart rate were independent and consistent predictors of total and cardiovascular mortality (Table 1), with the exception of SD of heart rate as a predictor of total mortality ($P=0.31$; fully adjusted model). In stepwise regression analysis for cardiovascular mortality in the fully adjusted model with P values to enter and stay in the model at 0.10, we identified sex ($P<0.0001$), age ($P<0.0001$), history of cardiovascular disease ($P<0.0001$), SD of systolic blood pressure ($P=0.027$), systolic blood pressure ($P=0.009$), SD of heart rate ($P=0.036$), and heart rate ($P=0.029$). When office blood pressure level was included in the model instead of home blood pressure level (n=2243), both office blood pressure ($P=0.004$) and SD of home blood pressure ($P=0.006$) remained as significant predictors for cardiovascular mortality. The predictive capacity for noncardiovascular mortality was no longer significant when deaths within 2 years of enrollment were censored ($P>0.06$).

Table 2 shows hazard ratios for cause-specific mortality in cardiovascular death. The SD of systolic blood pressure was predictive of stroke and cerebral infarction but not cardiac disease. Conversely, SD of heart rate was predictive of cardiac mortality and death from myocardial infarction but not from stroke. The SD of heart rate was also significantly associated with risk of neoplasms (hazard ratio: 1.24; 95% CI: 1.04 to 1.49; $P=0.02$), whereas this association was weakened to a nonsignificant level when we censored deaths within 2 years of enrollment (hazard ratio: 1.20; 95% CI: 0.99 to 1.46; $P=0.06$). We did not find any association of intracerebral hemorrhage ($P\geq0.74$), neoplasms ($P\geq0.25$), diseases of the respiratory system ($P\geq0.10$), or senility ($P\geq0.16$), with SD of either systolic blood pressure or heart rate. We repeated all of the analyses using SD of diastolic blood pressure instead of the SD of systolic blood pressure, yielding results that were largely consistent. As sensitivity analyses, we investigated the hazard ratio for SDs of blood pressure and heart rate using only the first 10 days of data, variabilities defined by CV, variabilities of evening measurement, and variabilities of average of morning and evening readings (the average of 2 measurement per day). The results were largely confirmatory (for further clarification, please see the online supplemental data, available at http://hyper.ahajournals.org).

Table 1. Hazard Ratios for Mortality According to Blood Pressure and Heart Rate Parameters at Entry

Mortality	Total*	Cardiovascular*	Noncardiovascular*
Deaths, n	462	168	294
Base model			
Systolic BP, mm Hg	1.18 (1.07 to 1.31)‖	1.33 (1.13 to 1.57)‖	1.11 (0.98 to 1.26)
Heart rate, bpm	1.21 (1.11 to 1.31)‖	1.24 (1.08 to 1.42)§	1.19 (1.07 to 1.32)‖
Adjusted			
SD of systolic BP, mm Hg	1.21 (1.10 to 1.32)‖	1.27 (1.09 to 1.47)§	1.17 (1.04 to 1.32)§
SD of heart rate, bpm	1.11 (1.02 to 1.21)‡	1.24 (1.09 to 1.41)§	1.03 (0.92 to 1.16)
Fully adjusted			
Systolic BP, mm Hg	1.13 (1.01 to 1.25)‡	1.26 (1.06 to 1.49)§	1.06 (0.93 to 1.21)
Heart rate, bpm	1.19 (1.09 to 1.30)‖	1.16 (1.01 to 1.34)‡	1.21 (1.07 to 1.35)‖
SD of systolic BP, mm Hg	1.18 (1.07 to 1.31)‖	1.20 (1.02 to 1.40)‡	1.18 (1.04 to 1.34)§
SD of heart rate, bpm	1.05 (0.96 to 1.16)	1.18 (1.02 to 1.36)‡	0.97 (0.86 to 1.10)

*Hazard ratios (95% CIs) reflect risk associated with an increase in parameters of 1 between-subject SD. Base model was adjusted for sex, age, obesity, smoking and drinking, history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and treatment with antihypertensive drugs. The adjusted model was additionally adjusted for systolic BP and heart rate. The fully adjusted model was additionally adjusted for systolic BP, heart rate, SD of systolic BP, and SD of heart rate (forced in the same model).

Significance of hazard ratios: †$P \leq 0.06$; ‡$P \leq 0.05$; §$P \leq 0.01$; ‖$P \leq 0.00143$ (0.05/35, Bonferroni correction).

The 10-year absolute risk was steeper with stroke mortality than with cardiac mortality (Figure 2, left). In contrast, in relation to SD of heart rate, the risk was steeper with cardiac mortality than with stroke mortality (Figure 2, right). SDs of systolic blood pressure and heart rate were significantly and independently correlated with cardiovascular mortality (Figure 3).

Discussion

The key finding of the present study was that, in middle-aged and older subjects recruited from a Japanese population, day-by-day blood pressure and heart rate variability, defined as within-subject SDs of home measurements, were predictive of cardiovascular mortality, while adjusting for blood pressure, heart rate, and other risk factors, including sex, age, obesity, current smoking and drinking habits, history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and treatment with antihypertensive drugs. CV of measurements offered similar prognostic value. This study addressed for the first time the prognostic implications of day-by-day blood pressure and heart rate variability based on self-measurement at home in a general population.

The link between variability and outcome may not necessarily imply a cause-effect relationship. Errors in self-measurements could have been responsible for failure to constantly identify a hypertensive condition at the time of different home measurement sessions. Underlying irregular-

Table 2. Hazard Ratios for Cause-Specific Cardiovascular Mortality According to Blood Pressure and Heart Rate Parameters at Entry

Mortality	Stroke*	Cerebral Infarction*	Cardiac*	Myocardial Infarction*
Deaths, n	83	51	85	33
Base model				
Systolic BP, mm Hg	1.43 (1.13 to 1.80)§	1.55 (1.15 to 2.08)§	1.24 (0.98 to 1.57)	1.17 (0.80 to 1.72)
Heart rate, bpm	1.27 (1.06 to 1.53)§	1.14 (0.90 to 1.45)	1.20 (0.99 to 1.46)†	0.98 (0.69 to 1.38)
Adjusted				
SD of systolic BP, mm Hg	1.41 (1.15 to 1.73)‖	1.46 (1.14 to 1.89)§	1.13 (0.91 to 1.40)	1.01 (0.71 to 1.44)
SD of heart rate, bpm	1.17 (0.96 to 1.43)	1.16 (0.89 to 1.51)	1.30 (1.09 to 1.55)§	1.43 (1.10 to 1.86)§
Fully adjusted				
Systolic BP, mm Hg	1.29 (1.01 to 1.64)‡	1.38 (1.02 to 1.88)‡	1.22 (0.96 to 1.56)	1.20 (0.80 to 1.79)
Heart rate, bpm	1.25 (1.02 to 1.52)‡	1.15 (0.88 to 1.50)	1.09 (0.89 to 1.33)	0.85 (0.60 to 1.21)
SD of systolic BP, mm Hg	1.38 (1.12 to 1.72)§	1.46 (1.11 to 1.91)§	1.02 (0.81 to 1.29)	0.87 (0.59 to 1.27)
SD of heart rate, bpm	1.06 (0.84 to 1.33)	1.01 (0.74 to 1.38)	1.30 (1.08 to 1.56)§	1.47 (1.13 to 1.92)§

*Hazard ratios (95% CIs) reflect risk associated with an increase in parameters of 1 between-subject SD. Base model was adjusted for sex, age, obesity, smoking and drinking, history of cardiovascular disease, diabetes mellitus, hyperlipidemia, and treatment with antihypertensive drugs. The adjusted model was additionally adjusted for systolic BP and heart rate. The fully adjusted model was additionally adjusted for systolic BP, heart rate, SD of systolic BP, and SD of heart rate (forced in the same model).

Significance of hazard ratios: †$P \leq 0.06$; ‡$P \leq 0.05$; §$P \leq 0.01$; ‖$P \leq 0.00143$ (0.05/35, Bonferroni correction).

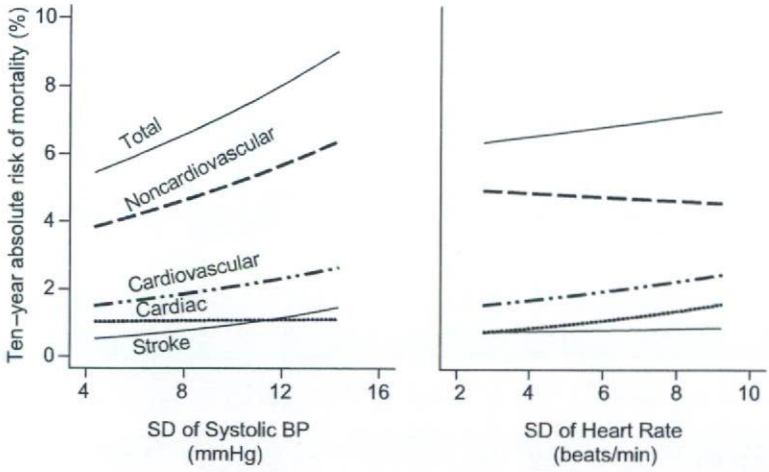

Figure 2. Absolute 10-year risk of total, noncardiovascular, cardiovascular, cardiac, and stroke mortality in relation to SD of systolic blood pressure (left) and SD of heart rate (right). Using Cox regression, risks were standardized to central tendencies in the other cardiovascular risk factors used in Table 1. The SD of blood pressure and heart rate spans the 5th to 95th percentile interval.

ity of measurement might, thus, have been responsible for higher variability of home blood pressure values and might account for the relationship between such variability and prognosis. Variations in patient activities before measurement may still represent a source of hemodynamic variability. Increased variability may also reflect underlying disease states. Arterial stiffness caused by aging and hypertension can magnify random blood pressure changes and increase variability. Autonomic dysfunction can also cause swings in hemodynamic variables. Elevated variability may, thus, only offer a marker of the above-mentioned conditions rather than an independent risk factor. Elevated variability of blood pressure could also be derived from an elevated level of blood pressure. Level of blood pressure remained a major confounder, although we adjusted the level of home blood pressure in Cox regression analyses.

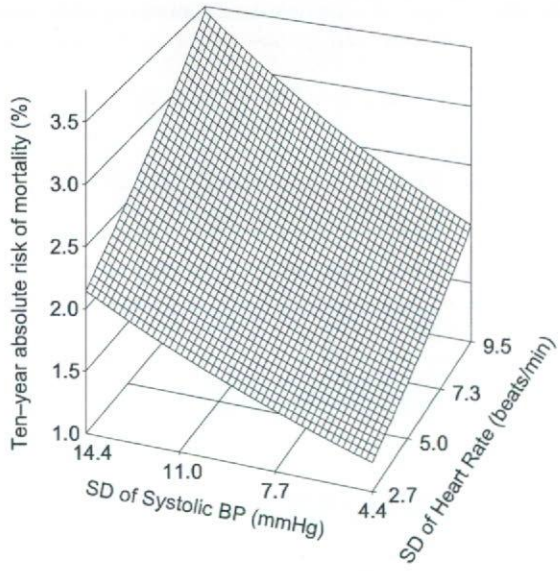

Figure 3. Absolute 10-year risk of cardiovascular mortality in relation to SD of systolic blood pressure and SD of heart rate. Using Cox regression, risk was standardized to central tendencies in the other cardiovascular risk factors used in Table 1. Both SD of systolic blood pressure and SD of heart rate are shown in the interval corresponding with the 5th to 95th percentiles.

Poor drug compliance by patients on treatment with antihypertensive therapy might have played a role in increasing blood pressure variability and could result in poor prognosis via inadequate blood pressure control in medical practice. Irregular antihypertensive drug administration may possibly have affected not only blood pressure variability but also heart rate variability. The attenuation of antihypertensive therapy could increase events. However, after excluding patients taking antihypertensive medications, similar results were observed in terms of the prediction of blood pressure and heart rate variabilities for cardiovascular mortality (Table S5). Poorer adherence to therapy alone, therefore, may not explain the relationship between larger variability and cardiovascular mortality.

We found adverse effects of increased day-by-day variability for both blood pressure and heart rate at home. Conversely, short-term variability of both blood pressure[6,11] and heart rate[6,12–14] reportedly displays an opposite prognostic significance. This discrepancy between existing evidence and the present study is probably attributable to the noncontribution of baroreflex function to day-by-day variability. An inverse relation between short-term blood pressure and heart rate variabilities reflects baroreflex function.[15] However, day-by-day variability of blood pressure positively correlates with that of heart rate ($r \geq +0.28$). Age did not correlate with day-by-day variability of heart rate ($r = -0.027$), although beat-by-beat heart rate variability is known to be negatively associated with age.[16] The link found in the present study could possibly depend on other confounding factors, such as the effects of environmental conditions (eg, mental and physical stress causing simultaneous elevations in blood pressure and heart rate in response to activation of the sympathetic nervous system).

In the present study, both variability and level of home blood pressure were predictive of stroke but not cardiac disease (Table 2). For the level of home blood pressure, this observation is not completely surprising. In Asia, the association between blood pressure level and stroke is stronger than the association between blood pressure level and ischemic heart disease.[17] Moreover, the incidence of and mortality rate because of stroke are higher than the incidence of and mortality rate because of myocardial infarction in Japan.[10] In

fact, in the present study, the number of deaths from stroke was more than double that from myocardial infarction. Such characteristics of the study population may explain why we observed the predictive power of home blood pressure level only for stroke and not for cardiac disease. In relation to the prognostic significance of home blood pressure variability, no data are available in the literature. Thus, whether these findings are because of specific characteristics of the Japanese population remains to be determined. The present findings await testing in different ethnic groups.

Study Limitations

The present study must be interpreted within the context of the potential limitations. First, the analysis rested exclusively on Japanese patients and might, therefore, not be representative of non-Asian or non-Japanese subjects. Second, the study population predominantly included middle-aged and elderly individuals. This imbalance in age distribution might, to some extent, limit the external validity of the findings. Third, the quality of the measurement procedure could have affected blood pressure variability, although we asked participants to measure blood pressure under relatively controlled conditions. Fourth, although information on smoking habits (current=1) was obtained using a standardized questionnaire, we did not collect data on the number of cigarettes smoked per day or smoking years. This is probably why we failed to identify any significant association between smoking and cardiovascular mortality (hazard ratio: 1.24; $P=0.30$). Fifth, the present results could not be confirmed by an analysis of variability in office blood pressure, as we did not have data on both daily and monthly measurements of office blood pressure.

Perspectives

To the best of our knowledge, the present study provides the first prospective evidence that, in Japanese populations, day-by-day variability might predict cardiovascular mortality. This index adds to the stratification of risk based on self-measurements of blood pressure and heart rate at home. Our observational study was unable to resolve the issue of how to treat patients with high variability of blood pressure and heart rate. No detailed information on the factors that affect day-by-day variability has been published. Urgent clarification of modifiable factors that affect blood pressure and heart rate variability appears warranted to reduce the risk of cardiovascular death. Until this knowledge becomes available, our current opinion is that careful management of global cardiovascular risk is important for high-risk patients with high day-by-day blood pressure and heart rate variability.

Sources of Funding

This study was supported in part by Grants for Scientific Research (15790293, 16590433, 17790381, 18390192, 18590587, 19590929, and 19790423) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan; Grant-in-Aid (H17-Kenkou-007, H18-Junkankitou[Seishuu]-Ippan-012, and H20-Junkankitou[Seishuu]-Ippan-009, 013) from the Ministry of Health, Labor and Welfare, Health and Labor Sciences Research Grants, Japan; Grant-in-Aid for Japan Society for the Promotion of Science fellows (16.54041, 18.54042, 19.7152, 20.7198, 20.7477, and 20.54043); 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; Takeda Medical Research Foundation; National Cardiovascular Research Grants: and Biomedical Innovation Grants.

Disclosures

None

References

1. O'Brien E, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens.* 2003;21:821–848.
2. Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. 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.
3. Hara A, Ohkubo T, Kikuya M, Shintani Y, Obara T, Metoki H, Inoue R, Asayama K, Hashimoto T, Harasawa T, Aono Y, Otani H, Tanaka K, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Detection of carotid atherosclerosis in individuals with masked hypertension and white-coat hypertension by self-measured blood pressure at home: The Ohasama Study. *J Hypertens.* 2007;25:321–327.
4. 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.
5. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension.* 1994;24:793–801.
6. Kikuya M, Hozawa A, Ohkubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, Ito S, Hisamichi S, Imai Y. Prognostic significance of blood pressure and heart rate variabilities. The Ohasama Study. *Hypertension.* 2000;36:901–906.
7. Hozawa A, Ohkubo T, Kikuya M, Ugajin T, Yamaguchi J, Asayama K, Metoki H, Ohmori K, Hoshi H, Hashimoto J, Satoh H, Tsuji I, Imai Y. Prognostic value of home heart rate for cardiovascular mortality in the general population: the Ohasama Study. *Am J Hypertens.* 2004;17:1005–1010.
8. Imai Y, Satoh H, Nagai K, Sakuma M, Sakuma H, Minami N, Munakata M, Hashimoto J, Yamagishi T, Watanabe N, Yabe T, Nishiyama A, Nakatsuka H, Koyama H, Abe K. Characteristics of a community-based distribution of home blood pressure in Ohasama in Northern Japan. *J Hypertens.* 1993;11:1441–1449.
9. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2003;26(suppl 1):S5–S20.
10. Statistical Research and Training Institute. *M Japan Statistical Yearbook 2007.* Tokyo, Japan: Japan Statistical Association; 2007.
11. Verdecchia P, Angeli F, Gattobigio R, Rapicetta C, Reboldi G. Impact of blood pressure variability on cardiac and cerebrovascular complications in hypertension. *Am J Hypertens.* 2007;20:154–161.
12. Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation.* 1996;94:2850–2855.
13. Casolo GC, Stroder P, Sulla A, Chelucci A, Freni A, Zerauschek M. Heart rate variability and functional severity of congestive heart failure secondary to coronary artery disease. *Eur Heart J.* 1995;16:360–367.
14. Zuanetti G, Neilson JM, Latini R, Santoro E, Maggioni AP, Ewing DJ. Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico. *Circulation.* 1996;94:432–436.
15. Coats AJ, Conway J, Sleight P, Meyer TE, Somers VK, Floras JS, Vann JJ. Interdependence of blood pressure and heart period regulation in mild hypertension. *Am J Hypertens.* 1991;4:234–238.
16. Stolarz K, Staessen JA, Kuznetsova T, Tikhonoff V, State D, Babeanu S, Casiglia E, Fagard RH, Kawecka-Jaszcz K, Nikitin Y. Host and environmental determinants of heart rate and heart rate variability in four European populations. *J Hypertens.* 2003;21:525–535.
17. Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens.* 2003;21:707–716.

Predictive value of ambulatory heart rate in the Japanese general population: the Ohasama study

Atsushi Hozawa[a], Ryusuke Inoue[b], Takayoshi Ohkubo[b,c], Masahiro Kikuya[d], Hirohito Metoki[d,e], Kei Asayama[b], Azusa Hara[b,d], Takuo Hirose[b,d], Atsuhiro Kanno[d], Taku Obara[b,d], Haruhisa Hoshi[g], Junichiro Hashimoto[b,c], Kazuhito Totsune[b,d], Hiroshi Satoh[b,f] and Yutaka Imai[b,d]

Background **Resting heart rate can predict cardiovascular disease mortality or all-cause mortality. Because of the effect of the alert reaction, heart rates measured out-of-office should have better predictive power than those obtained at clinics. However, only a few studies have described the relationship between heart rate measured by ambulatory blood pressure monitoring devices and cardiovascular disease prediction.**

Methods **We studied 1444 individuals from the Japanese general population who did not have a history of cardiovascular diseases including arrhythmia. We used multiple adjusted Cox proportional hazards to calculate the mortality risk of daytime heart rate, night-time heart rate, and the day–night heart rate dip ratio [day–night heart rate dip ratio = (daytime heart rate − night-time heart rate)/daytime heart rate × 100].**

Results **After 12 years of follow-up, 101, 195, and 296 participants died due to cardiovascular diseases, noncardiovascular diseases, and all causes, respectively. As shown by others, neither daytime nor night-time heart rate predicted cardiovascular disease mortality, whereas both predicted noncardiovascular disease mortality. The day–night heart rate dip ratio was significantly related to all-cause mortality. When night-time heart rate and day–night heart rate dip ratio were simultaneously included into the same Cox model, only night-time heart rate significantly and independently predicted all-cause mortality (relative hazard per 10 bpm increase = 1.29, 95% confidence interval, 1.07–1.54).**

Conclusion **Night-time heart rate value seems to have the most important predictor of all-cause mortality among ambulatory heart rate parameters in this population.**
J Hypertens **26:1571–1576 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2008, 26:1571–1576

Keywords: ambulatory, daytime, general population, heart rate, mortality, night-time

Abbreviations: CVD, cardiovascular diseases; ICD, International Classification of Diseases; PAMELA study, Pressioni Arteriose Monitorate E Loro Associazioni study; PIUMA study, Progetto Ipertensione Umbria Monitoraggio Ambulatoriale study; Syst-Eur study, Systolic Hypertension in Europe study

[a]Department of Health Science, Shiga University of Medical Science, Otsu, [b]Tohoku University 21st Century COE Program 'Comprehensive Research and Education Center for Planning of Drug Development and Clinical Evaluation', [c]Department of Planning for Drug Development and Clinical Evaluation, [d]Department of Clinical Pharmacology and Therapeutics, [e]Department of Medical Genetics, [f]Department of Environmental Health Sciences, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Sendai and [g]Ohasama Hospital, Iwate, Japan

Correspondence to Takayoshi Ohkubo, MD, PhD, Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Tohoku University Hospital, Sendai 980-8574, Japan
Tel: +81 22 717 8590; fax: +81 22 717 8591;
e-mail: tohkubo@mail.tains.tohoku.ac.jp

Received 30 January 2008 **Revised** 27 March 2008
Accepted 8 April 2008

See editorial commentary on page 1540

Introduction

Resting heart rate (HR) can predict mortality due to cardiovascular diseases (CVD) and all causes [1,2]. These findings have mainly been obtained in clinical settings [2]. Heart rate and blood pressure (BP) measured in a clinical environment are affected by the alert reaction, also known as the white-coat phenomenon [3]. Thus, out-of-office values should be more relevant predictors of mortality. Ambulatory BP values or self-measured BPs at home (home BP) do in fact have better predictive power than office BP [4–7]. However, only a few investigators have reported the predictive value of HR measured by ambulatory BP monitoring [8–11]. Most of these studies found that daytime HR did not predict CVD mortality [8–10]. Conversely, night-time HR predicted all-cause mortality in some of these studies [9,11]. These results suggest that HR at night, that is, at rest, might have better predictive power than daytime HR and that the day–night HR dip can also predict all-cause mortality. The prognostic value of ambulatory HR has mostly been investigated among participants with hypertension [8,9,11].

Therefore, the present study investigated (1) which component of ambulatory HR predicts mortality, (2) whether the day–night HR dip predicts mortality, or (3) the night–day difference in HR predicts mortality, independently of night HR in the general Japanese population.

Methods

Study population

The general population of Ohasama, a rural community of Japan, participated in a longitudinal, observational study of ambulatory BP monitoring called the Ohasama study, details of which have been reported elsewhere [12,13]. From 1988 until 1994, we contacted all 2716 individuals aged 40 years or more who resided in three of four Ohasama districts. We excluded individuals who worked outside the town ($n=575$), who were hospitalized ($n=121$), or who had dementia or who were bedridden ($n=31$). We obtained ambulatory BP data on 1542 residents (mean age, 61.7 years; men, 37%). We then excluded 98 residents with a history of CVD including those with arrhythmia because the HR value might be affected. Consequently, we analyzed 1444 residents who provided written, informed consent to participate in the study, which was approved by the Institutional Review Board of Tohoku University School of Medicine.

Ambulatory blood pressure monitoring

The ambulatory BP and HR were monitored every 30 min with a fully automatic device (ABPM630, Nippon Colin, Komaki, Japan) that met the criteria of the Association for the Advancement of Medical Instrumentation [14]. We used the cuff-oscillometric method for the analysis. Participants were instructed to proceed with their normal activities during measurements. We determined 'daytime' and 'night-time' as the waking and sleeping periods, respectively, of each participant recorded in diaries. The mean duration of monitoring was 23.3 ± 1.6 h, and the mean number of measurements was 45.5 ± 4.8. Artifacts of BP measurements during monitoring were defined as described [15] and were omitted from the analysis. We only analyzed ambulatory BP and HR data that were obtained for 8 and 4 h or more during the daytime and night-time, respectively. The day–night BP dip ratio was estimated as (daytime BP − night-time BP)/daytime BP × 100 [16]. The day–night HR dip ratio was estimated as (daytime HR − night-time HR)/daytime HR × 100.

Follow-up

Residence in Ohasama as of December 31, 2004, was confirmed by examining the registration cards of the residents. We reviewed death certificates from the national mortality registry and confirmed the results by comparison with the medical records of Ohasama Hospital, which is the only hospital in the town, and where more than 90% of residents undergo regular check-ups. Most patients were admitted to Ohasama Hospital, where stroke was diagnosed by computed tomography or MRI of the brain. According to recommendations of the 10th Revision of the International Classification of Diseases (ICD-10) of the World Health Organization, we defined CVD death as mortality related to diseases of the circulatory system (ICD-10 code I). Stroke, heart disease, cancer, and respiratory diseases were ICD code I6, I other than I6, C00-D48, and J, respectively. The characteristics of the causes of death in the Ohasama study are described elsewhere [13].

Data analysis

We investigated the association between ambulatory HR or the day–night HR dip ratio and mortality in this population. We compared the baseline characteristics according to daytime HR, night-time HR, and the day–night HR dip ratio using analysis of variance or the χ^2 test. The relative hazards of daytime, night-time HR, or the day–night HR dip ratio were calculated using the Cox proportional hazards regression model. We tested the age–sex adjustment model and the multiple adjustment model adjusted for age, sex, antihypertensive medication, smoking habit (current vs. nonsmoking), history of diabetes mellitus, hyperlipidemia, and systolic BP at corresponding measurement. In the quartile analysis, the lowest HR quartile or the largest day–night HR dip ratio quartile comprised the reference group. To exclude the effect of antihypertensive medication on HR, we further analyzed an untreated subgroup. To test whether the prognostic significance of the day–night HR dip ratio on mortality was independent of night-time HR, we included both night-time HR and day–night HR dip ratio into the same Cox model. A value of P less than 0.05 was considered to indicate statistical significance.

Results

Table 1 shows the baseline characteristics of participants according to the ambulatory HR value quartile. Younger residents tended to have a higher daytime HR. As a consequence, the prevalence of residents who were taking antihypertensive medication was higher in the group in the lowest daytime HR quartile. We also found an inverse relationship between night-time HR and age. The proportion of men was higher in the lower daytime and night-time HR quartiles. Although the individuals were relatively young, both daytime and night-time systolic BP were the highest in the highest night-time HR quartile. A smaller day–night HR dip ratio was associated with more advanced age, higher smoking rate, and more frequent use of antihypertensive medication. The BP and HR dip ratios were not closely associated.

After an average 12.5 ± 3.4 years (up to 16.6 years) of follow-up, 101 residents died of CVD (stroke, 46; heart disease, 55) and 195 of non-CVD (cancer, 83; noncancer non-CVD, 112; comprising respiratory diseases, 41; other, 71). Of the 1444 original participants, 32 (2.2%) moved or were lost to follow-up.

Table 2 shows the relationships between daytime HR and night-time HR and CVD, non-CVD, and all-cause mortality. Neither daytime nor night-time HR was significantly associated with CVD mortality, but both predicted non-CVD mortality. The relative hazard [95% confidence

Table 1 Baseline characteristics according to ambulatory heart rate: the Ohasama study

	Whole	Daytime heart rate (bpm)				Night-time heart rate (bpm)				Heart rate dip ratio (%)			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
HR or HR dip ratio value		<68.2	68.3–73.5	73.6–78.7	78.8<	<54.2	54.3–58.4	58.5–63.1	63.2<	<14.7	14.8–19.4	19.5–24.4	24.5<
Numbers of participants	1444	361	361	361	361	359	362	362	361	361	360	362	361
Age (years)	61.2 ± 10.6	64.0 ± 10.4	61.4 ± 10.6	60.2 ± 10.4	59.0 ± 10.3	63.0 ± 10.2	61.3 ± 10.4	60.1 ± 10.8	60.2 ± 10.7	63.2 ± 10.6	60.7 ± 10.6	61.2 ± 10.7	59.6 ± 10.0
Sex (male) (%)	35.4	43.8	36.6	25.5	35.7	41.2	28.5	37.0	34.9	46.8	30.8	28.7	35.2
Obesity (%)	29.3	28.8	29.1	33.0	26.3	28.7	26.0	31.5	31.0	31.0	31.7	28.2	26.3
Smoking (current %)	20.5	21.9	21.6	14.7	23.8	17.0	16.6	24.6	23.8	27.2	19.7	16.3	18.8
History of DM (%)	17.3	16.3	19.7	13.9	19.4	15.3	16.9	18.2	18.8	17.2	21.4	16.6	14.1
History of HL (%)	15.6	18.0	18.6	13.0	12.7	18.7	14.4	13.3	16.1	16.9	17.2	14.6	13.6
Treatment of HT (%)	27.4	40.2	23.0	23.3	23.0	32.3	25.7	24.0	27.4	36.6	27.2	24.6	21.1
24-h													
Systolic BP (mmHg)	123.1 ± 13.0	124.9 ± 13.2	123.3 ± 13.3	121.4 ± 12.6	122.7 ± 12.8	122.7 ± 12.6	122.7 ± 13.6	122.5 ± 13.0	124.3 ± 13.0	125.6 ± 13.1	123.8 ± 13.7	122.0 ± 12.4	120.8 ± 12.5
Diastolic BP (mmHg)	71.9 ± 7.8	71.9 ± 7.6	71.8 ± 7.8	71.3 ± 7.6	72.7 ± 8.0	70.5 ± 7.1	71.6 ± 7.7	72.0 ± 7.9	73.7 ± 7.9	73.4 ± 7.9	72.6 ± 8.0	71.2 ± 7.2	70.6 ± 7.7
HR (bpm)	68.7 ± 7.1	60.3 ± 3.5	66.4 ± 2.2	70.8 ± 2.4	77.5 ± 4.7	61.4 ± 4.7	66.8 ± 4.1	70.4 ± 4.2	76.3 ± 5.5	67.8 ± 8.3	68.8 ± 6.6	68.5 ± 6.7	69.9 ± 6.6
Daytime													
Systolic BP (mmHg)	128.7 ± 13.9	130.0 ± 13.8	128.8 ± 14.1	127.4 ± 13.9	128.5 ± 13.7	128.0 ± 13.1	128.4 ± 14.3	128.3 ± 14.1	130.0 ± 14.0	131.2 ± 14.1	129.1 ± 14.3	127.7 ± 13.2	126.7 ± 13.6
Diastolic BP (mmHg)	76.0 ± 8.4	75.9 ± 8.2	75.9 ± 8.4	75.6 ± 8.4	76.7 ± 8.6	74.5 ± 7.7	75.7 ± 8.4	76.1 ± 8.6	77.7 ± 8.6	77.5 ± 8.5	76.6 ± 8.6	76.2 ± 7.8	74.8 ± 8.5
HR (bpm)	73.7 ± 8.0	63.8 ± 3.7	71.0 ± 1.6	76.0 ± 1.5	84.0 ± 4.5	66.8 ± 6.4	72.1 ± 5.8	75.3 ± 6.1	80.6 ± 6.8	70.3 ± 8.7	73.0 ± 6.9	74.1 ± 7.3	77.5 ± 7.4
Night-time													
Systolic BP (mmHg)	112.0 ± 14.5	114.8 ± 15.5	112.1 ± 14.4	109.7 ± 13.5	111.4 ± 14.0	112.1 ± 15.1	111.6 ± 14.8	111.2 ± 13.5	113.1 ± 14.4	114.7 ± 14.8	113.0 ± 15.0	111.1 ± 14.0	109.2 ± 13.5
Diastolic BP (mmHg)	63.9 ± 8.1	64.0 ± 8.1	63.7 ± 8.1	63.0 ± 7.8	64.9 ± 8.3	62.5 ± 7.8	63.3 ± 7.9	63.9 ± 8.0	65.8 ± 8.4	65.5 ± 8.5	64.5 ± 8.1	63.4 ± 7.8	62.3 ± 7.7
HR (bpm)	59.2 ± 6.9	53.5 ± 4.8	57.4 ± 4.6	60.7 ± 5.1	65.0 ± 7.1	51.0 ± 2.5	56.5 ± 1.2	60.8 ± 1.3	68.3 ± 4.9	63.1 ± 8.0	60.4 ± 5.8	57.9 ± 5.8	55.3 ± 5.3
BP dip ratio (%)	12.8 ± 7.9	11.6 ± 8.7	12.8 ± 7.6	13.7 ± 7.4	13.2 ± 7.6	12.3 ± 8.6	13.0 ± 7.8	13.2 ± 7.1	12.8 ± 8.0	12.4 ± 8.5	12.4 ± 7.5	12.9 ± 7.7	13.6 ± 7.8
HR dip ratio (%)	19.5 ± 7.2	16.0 ± 7.0	19.1 ± 6.4	20.2 ± 6.5	22.6 ± 7.4	23.1 ± 7.0	21.2 ± 6.3	18.7 ± 6.4	14.9 ± 6.6	10.2 ± 4.1	17.3 ± 1.3	21.9 ± 1.4	28.5 ± 3.3

HR dip ratio = (daytime HR – night-time HR)/daytime HR × 100; BP dip ratio = (daytime BP – night-time BP)/daytime BP × 100. BP, blood pressure; CVD, cardiovascular diseases; DM, diabetes mellitus; HL, hyperlipidemia; HR, heart rate; HT, hypertension.

interval (CI)] values of daytime or night-time HR per 10 bpm increase for non-CVD mortality were 1.28 (1.08–1.52) and 1.48 (1.22–1.79), respectively. Due to the close association between ambulatory HR components and non-CVD mortality, both daytime and night-time HR also tended to be associated with all-cause mortality. The magnitude of relative hazard was higher in night-time than in daytime HR. These associations between daytime or night-time HR and mortality persisted in participants who were not taking antihypertensive medication. For cause-specific mortality, night-time HR was significantly associated with cancer mortality (relative hazard per 10 bpm increase = 1.69, 95% CI, 1.27–2.24) and noncancer non-CVD mortality (relative hazard per 10 bpm increase = 1.34, 95% CI, 1.30–1.73). Daytime HR was also significantly associated with noncancer non-CVD mortality (relative hazard per 10 bpm increase = 1.34, 95% CI, 1.07–1.69). However, daytime HR did not significantly relate to cancer mortality (relative hazard per 10 bpm increase = 1.21, 95% CI, 0.92–1.57).

Table 3 shows that the relationship between the day–night HR dip ratio and all-cause mortality was weaker, but significant. The relative hazard (95% CI) of a 10% increase in the day–night HR dip was 0.85 (0.72–0.99). The magnitude of relative hazard values was similar between CVD mortality and non-CVD mortality, although statistical significance was not achieved. These associations became closer when participants on antihypertensive medication were excluded from the analysis.

When we included both night-time HR and day–night HR dip ratio into the same model, only night-time HR significantly and independently predicted non-CVD mortality (relative hazard per 10 bpm increase = 1.48, 95% CI, 1.19–1.84) and all-cause mortality (relative hazard per 10 bpm increase = 1.29, 95% CI, 1.07–1.54). Day–night HR dip ratio predicted neither mortality: relative hazards (95% CI) of a 10% increase in the day–night HR dip for non-CVD mortality and all-cause mortality were 1.01 (0.81–1.25) and 0.94 (0.79–1.13), respectively. Neither night-time HR nor day–night HR dip ratio significantly predicted CVD mortality (data not shown).

Discussion

Ambulatory HR and CVD mortality were not significantly associated, whereas ambulatory HR predicted non-CVD mortality in this general Japanese population. Although the day–night HR dip ratio was significantly related to all-cause mortality, the relation disappeared when night-time HR was simultaneously adjusted in the multivariate analysis. Thus, the night-time HR is the most important parameter among ambulatory HR components to predict all-cause mortality.

Resting HR is considered an integrated index of the influence on the heart of the autonomic nervous system,

Table 2 Relationship between ambulatory heart rate and mortality: the Ohasama study, 1988–2004

	Q1	Q2	Q3	Q4	Relative hazard per 10 bpm increase (continuous)	Relative hazard per 10 bpm increase (continuous)[a]
CVD mortality						
Daytime HR	<68.2	68.3–73.5	73.6–78.7	78.8<		
N	361	361	361	361	1444	1049
CVD deaths	38	33	14	16	101	53
Age–sex adjusted RH (95% CI)	Reference	1.16 (0.73–1.86)	0.76 (0.40–1.46)	0.79 (0.43–1.46)	0.90 (0.70–1.16)	1.003 (0.70–1.44)
Multiple adjusted RH (95% CI)	Reference	1.25 (0.76–2.04)	0.77 (0.41–1.48)	0.81 (0.43–1.52)	0.90 (0.70–1.16)	0.95 (0.65–1.40)
Night-time HR	<54.2	54.3–58.4	58.5–63.1	63.2<		
N	359	362	362	361	1444	1049
CVD deaths	27	30	23	21	101	53
Age–sex adjusted RH (95% CI)	Reference	1.46 (0.86–2.46)	1.26 (0.72–2.22)	1.14 (0.64–2.04)	1.09 (0.82–1.44)	1.24 (0.85–1.81)
Multiple adjusted RH (95% CI)	Reference	1.54 (0.89–2.67)	1.41 (0.79–2.53)	1.09 (0.59–2.01)	1.07 (0.80–1.43)	1.18 (0.80–1.75)
Non-CVD mortality						
Daytime HR	<68.2	68.3–73.5	73.6–78.7	78.8<		
N	361	361	361	361	1444	1049
Non-CVD deaths	56	46	47	46	195	117
Age–sex adjusted RH (95% CI)	Reference	1.06 (0.72–1.57)	1.38 (0.91–2.08)	1.32 (0.88–1.98)	1.30 (1.10–1.54)	1.29 (1.02–1.62)
Multiple adjusted RH (95% CI)	Reference	1.03 (0.68–1.55)	1.33 (0.88–2.01)	1.26 (0.83–1.91)	1.28 (1.08–1.52)	1.27 (1.002–1.60)
Night-time HR	<54.2	54.3–58.4	58.5–63.1	63.2<		
N	359	362	362	361	1444	1049
Non-CVD deaths	47	42	44	62	195	117
Age–sex adjusted RH (95% CI)	Reference	1.06 (0.70–1.61)	1.29 (0.85–1.95)	1.76 (1.20–2.58)	1.51 (1.25–1.82)	1.58 (1.25–2.00)
Multiple adjusted RH (95% CI)	Reference	1.05 (0.69–1.61)	1.18 (0.77–1.80)	1.74 (1.17–2.58)	1.48 (1.22–1.79)	1.56 (1.23–1.98)
All-cause mortality						
Daytime HR	<68.2	68.3–73.5	73.6–78.7	78.8<		
N	361	361	361	361	1444	1049
All cause deaths	94	79	61	62	296	170
Age–sex adjusted RH (95% CI)	Reference	1.10 (0.81–1.49)	1.15 (0.82–1.62)	1.12 (0.80–1.56)	1.15 (1.001–1.33)	1.20 (0.98–1.45)
Multiple adjusted RH (95% CI)	Reference	1.11 (0.81–1.52)	1.13 (0.80–1.60)	1.09 (0.78–1.54)	1.14 (0.99–1.32)	1.17 (0.96–1.43)
Night-time HR	<54.2	54.3–58.4	58.5–63.1	63.2<		
N	359	362	362	361	1444	1049
All cause deaths	74	72	67	83	296	170
Age–sex adjusted RH (95% CI)	Reference	1.20 (0.86–1.66)	1.28 (0.92–1.79)	1.54 (1.12–2.11)	1.36 (1.16–1.59)	1.47 (1.21–1.80)
Multiple adjusted RH (95% CI)	Reference	1.21 (0.86–1.69)	1.25 (0.89–1.76)	1.51 (1.08–2.09)	1.33 (1.13–1.56)	1.44 (1.18–1.77)

Multiple adjusted RH: adjusted for age, sex antihypertensive medication, smoking, history of DM, hyperlipidemia, and systolic BP at corresponding measurement. CI, confidence interval; CVD, cardiovascular diseases; DM, diabetes mellitus; HR, heart rate; RH, relative hazard. [a]No antihypertensive medication.

which is associated with atherosclerosis [2]. Resting HR is also a marker of several CVD risk factors, such as impaired physical activity, pulmonary function, or subclinical heart failure [2]. Through these mechanisms, resting HR, including HR measured at home [17], is related to CVD mortality and morbidity in large epidemiological studies [1,2]. As night-time HR should be better marker of resting HR, we primarily postulated that night-time HR could predict CVD mortality. However, the present findings contradicted this notion and were consistent with those of prior studies of the relationship between ambulatory HR and CVD mortality and morbidity. Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study [8], Systolic Hypertension in Europe (Syst-Eur) study [9], and Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study [10]

Table 3 Relationship between day–night heart rate dip ratio and mortality: the Ohasama study, 1988–2004

	Q1	Q2	Q3	Q4	Relative hazard per 10% increase (continuous)	Relative hazard per 10% increase (continuous)[a]
HR dip ratio	>24.5	19.5–24.4	14.8–19.4	14.8>		
N	361	362	360	361	1444	1049
CVD mortality						
Event	15	17	39	30	101	53
Age–sex adjusted RH (95% CI)	Reference	0.98 (0.48–1.99)	2.48 (1.36–4.52)	1.31 (0.69–2.47)	0.78 (0.60–1.02)	0.78 (0.54–1.12)
Multiple adjusted RH (95% CI)	Reference	0.89 (0.43–1.83)	2.19 (1.19–4.03)	1.20 (0.63–2.27)	0.85 (0.65–1.12)	0.77 (0.53–1.13)
Non-CVD mortality						
Event	39	42	45	69	195	117
Age–sex adjusted RH (95% CI)	Reference	0.95 (0.61–1.49)	1.08 (0.70–1.66)	1.25 (0.84–1.87)	0.83 (0.69–1.01)	0.75 (0.59–0.96)
Multiple adjusted RH (95% CI)	Reference	0.99 (0.64–1.55)	1.05 (0.68–1.63)	1.25 (0.83–1.87)	0.84 (0.70–1.02)	0.76 (0.60–0.97)
All-cause mortality						
Event	54	59	84	99	296	170
Age–sex adjusted RH (95% CI)	Reference	0.96 (0.66–1.40)	1.46 (1.04–2.06)	1.27 (0.90–1.78)	0.82 (0.70–0.95)	0.76 (0.62–0.93)
Multiple adjusted RH (95% CI)	Reference	0.98 (0.67–1.43)	1.37 (0.97–1.94)	1.23 (0.88–1.74)	0.85 (0.72–0.99)	0.76 (0.62–0.94)

Multiple adjusted RH: adjusted for age, sex antihypertensive medication, smoking, history of DM, hyperlipidemia, and 24-h systolic BP. HR dip ratio = (daytime HR – night-time HR)/daytime HR × 100. CI, confidence interval; CVD, cardiovascular diseases; HR, heart rate; RH, relative hazard. [a]No antihypertensive medication.

reported the relation of night-time HR with CVD mortality or morbidity, whereas none of them found statistically significant associations. Although the reason for discrepancy between relation of clinic HR with CVD mortality and relation of ambulatory HR with CVD mortality was unknown, sympathetic activation due to alarm reaction on HR might have some prognostic significance. Further studies, which investigated the relation between alarm reaction on HR and CVD mortality, might be able to answer the reason for the discrepancy. In any case, as resting HR measured at the office is known to be a risk factor for CVD mortality, risk of office tachycardia should not be overlooked.

Resting HR is also related to non-CVD mortality [2] and has been explained as being due to flailed condition, poor respiratory function, or hypoxia [9]. Because we did not have baseline information about the above confounding factors, we could not clarify whether HR itself can predict non-CVD mortality. However, we found a statistically significant relationship between ambulatory HR and non-CVD mortality, as did the Syst-Eur study [9]. Palatini *et al.* [9] reported that the highest quartile of daytime or night-time HR had significantly higher non-CVD mortality than any other HR quartile. Thus, ambulatory HR has the potential to predict non-CVD mortality. Furthermore, as a consequence of this positive relationship with non-CVD mortality, daytime or night-time HR can also predict all-cause mortality. This finding is also consistent with those of the Syst-Eur study [9] and the recent findings of Ben-Dov *et al.* [11], indicating a positive relationship between sleep HR and all-cause mortality.

Because of the closer relationship between night-time HR, than daytime HR and non-CVD mortality, the absence of a dip in day–night HR should be related to non-CVD mortality or all-cause mortality. We uncovered a significant relationship in the present study, as did the PIUMA study [8] and that of Ben-Dov *et al.* [11]. The magnitude of relative hazard per 10% increase in the day–night HR dip ratio was mostly consistent for CVD, non-CVD, and all-cause mortality. Thus, this indicator might predict not only non-CVD mortality but also CVD mortality. Further, larger studies are required to confirm this supposition.

However, whether night-time HR itself or the absence of a day–night dip is important for predicting non-CVD mortality remained obscure. We, therefore, included both night-time HR and day–night HR dip ratio into the same model for predicting mortality. In the analyses, we found that night-time HR alone significantly predicted non-CVD mortality and all-cause mortality. Thus, night-time HR rather than the dip ratio seemed important for predicting all-cause mortality. That is, night-time HR is important for predicting all-cause mortality. Further studies are also required to confirm these findings.

We identified a linear association between night-time HR and non-CVD mortality. Because risk was statistically and significantly increased in the highest quartile of night-time HR for risk of both non-CVD mortality and all-cause mortality, participants in this population with night-time HR greater than 63 bpm could be considered as being at high risk for non-CVD mortality.

The present study has several limitations. Firstly, because the Ohasama study did not obtain HR values in the clinical setting, we did not examine whether the predictive power of night-time HR was superior to that of clinic HR. Thus, we could not test whether ambulatory HR monitoring can generate additional predictive information to clinic HR. Secondly, as this study is observational, we could not conclude that reducing HR could reduce mortality rates. Interpretation of an intervention study that targets a reduction in heart rate is required to address this issue. Thirdly, because we did not have data about possible confounding factors such as level of physical activity, presence of anemia, or respiratory function, we could not conclude whether or not HR itself predicts mortality. However, we could at least conclude that ambulatory HR can be a marker of prognosis.

In conclusion, we found that ambulatory HR has the potential to predict non-CVD mortality and that the absence of a dip in the day–night HR ratio could predict all-cause mortality. Finally, night-time HR seemed to be the most important predictor of all-cause mortality among ambulatory HR parameters in this Japanese population.

Acknowledgements

This work was supported by Grants for Scientific Research (15790293, 17790381, 18390192, 18590587, and 19790425) 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 Palatini P. Elevated heart rate as a predictor of increased cardiovascular morbidity. *J Hypertens Suppl* 1999; **17**:S3–S10.

2 Palatini P, Benetos A, Grassi G, Julius S, Kjeldsen SE, Mancia G, *et al.*, European Society of Hypertension. Identification and management of the hypertensive patient with elevated heart rate: statement of a European Society of Hypertension Consensus Meeting. *J Hypertens* 2006; **24**:603–610.

3 Parati G, Mancia G. Assessing the white-coat effect: which blood pressure measurement should be considered? *J Hypertens* 2006; **24**:29–31.

4 Ohkubo T. Prognostic significance of variability in ambulatory and home blood pressure from the Ohasama study. *J Epidemiol* 2007; **17**:109–113.
5 Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, *et al.* Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens* 2000; **18**:847–854.
6 Hansen TW, Kikuya M, Thijs L, Björklund-Bodegård K, Kuznetsova T, Ohkubo T, *et al.* IDACO Investigators. 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.
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 Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Telera MP, Pede S, *et al.* Adverse prognostic value of a blunted circadian rhythm of heart rate in essential hypertension. *J Hypertens* 1998; **16**:1335–1343.
9 Palatini P, Thijs L, Staessen JA, Fagard RH, Bulpitt CJ, Clement DL, *et al.* Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Predictive value of clinic and ambulatory heart rate for mortality in elderly subjects with systolic hypertension. *Arch Intern Med* 2002; **162**:2313–2321.
10 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.
11 Ben-Dov IZ, Kark JD, Ben-Ishay D, Mekler J, Ben-Arie L, Bursztyn M. Blunted heart rate dip during sleep and all-cause mortality. *Arch Intern Med* 2007; **167**:2116–2121.
12 Imai Y, Nagai K, Sakuma M, Sakuma H, Nakatsuka H, Satoh H, *et al.* Ambulatory blood pressure of adults in Ohasama, Japan. *Hypertension* 1993; **22**:900–912.
13 Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, *et al.* Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens* 1997; **15**:357–364.
14 Association for the Advancement of Medical Instrumentation. *American national standards for electronic or automated sphygmomanometers.* Washington, DC: AAMI; 1987.
15 Imai Y, Nihei M, Abe K, Sasaki S, Minami N, Munakata M, *et al.* A finger volume-oscillometric device for monitoring ambulatory blood pressure: laboratory and clinical evaluations. *Clin Exp Hypertens* 1987; **9**:2001–2025.
16 Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, *et al.* Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. *Hypertension* 2006; **47**:149–154.
17 Hozawa A, Ohkubo T, Kikuya M, Ugajin T, Yamaguchi J, Asayama K, *et al.* Prognostic value of home heart rate for cardiovascular mortality in the general population: the Ohasama study. *Am J Hypertens* 2004; **17**:1005–1010.

Cost-effectiveness of the introduction of home blood pressure measurement in patients with office hypertension

Hidefumi Fukunaga[a], Takayoshi Ohkubo[a,c], Makoto Kobayashi[d], Yuichiro Tamaki[b], Masahiro Kikuya[a], Taku Obara[b,c], Miwa Nakagawa[b], Azusa Hara[a,c], Kei Asayama[c], Hirohito Metoki[b,c], Ryusuke Inoue[c], Junichiro Hashimoto[a,c], Kazuhito Totsune[b,c] and Yutaka Imai[b,c]

Objective **Cost-effectiveness of hypertension treatment is an important social and medical issue in Western as well as in Eastern countries, including Japan. Home blood pressure (HBP) measurements have a stronger predictive power for cardiovascular events than casual clinic blood pressure (CBP) measurements. Therefore, the introduction of HBP measurement for the diagnosis and treatment of hypertension should lead to a decrease in medical expenditure. This study presents calculations of the cost savings likely to take place when HBP is implemented for newly detected hypertensive subjects in Japan.**

Design and methods **We estimate the cost savings from the perspective of a Japanese healthcare system. To estimate the costs associated with changing from CBP to HBP measurement as the diagnostic tool, we constructed a simulation model using data from the Ohasama study. These calculations are based on current estimates for cost of treatment, prevalence of white-coat hypertension at baseline, and varying the incidence of new hypertension after the initial screening.**

Results **When HBP measurement is not incorporated into the diagnostic process, the medical cost is estimated at US$10.89 million per 1000 subjects per 5 years. When HBP measurement is incorporated, the medical cost is estimated at US$9.33 million per 1000 subjects per 5 years. The reductions in medical costs vary from US$674 000 to US$2.51 million per 1000 subjects per 5 years for treatment of hypertension, when sensitivity analysis is performed.**

Conclusions **The introduction of HBP measurement for the treatment of hypertension is very useful for reducing medical costs.** *J Hypertens* **26:685–690 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Journal of Hypertension 2008, 26:685–690

Keywords: cost-effectiveness, home blood pressure, Ohasama study, white-coat hypertension

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CBP, casual clinic blood pressure; CI, confidence interval; HB, home blood pressure; MHT, masked hypertension; WCH, white-coat hypertension

[a]Department of Planning for Drug Development and Clinical Evaluation, [b]Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Sendai, [c]Tohoku University 21st Century COE Program 'Comprehensive Research and Education Center for Planning of Drug Development and Clinical Evaluation', Sendai and [d]The Healthcare Assessment Research Department, Crecon Research and Consulting Inc., Tokyo, Japan

Correspondence to Takayoshi Ohkubo, MD, PhD, Department of Planning for Drug Development and Clinical Evaluation, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Tohoku University Hospital, Sendai 980-8574, Japan
Tel: +81 22 717 8590; fax: +81 22 717 8591;
e-mail: tohkubo@mail.tains.tohoku.ac.jp

Received 31 May 2007 **Revised** 17 October 2007
Accepted 4 November 2007

Introduction

Soaring medical costs have become a major social problem in developed countries in recent years, and there is an increasing need to examine healthcare from an economic perspective in order to make truly effective and efficient use of limited healthcare resources. For example, in 2002, medical costs for hypertensive disease in Japan totaled approximately US$16.2 billion (1.95 trillion yen) and accounted for one-third of the medical costs associated with all cardiovascular disease [1]. Moreover, because hypertension is a major risk factor for diseases such as ischemic heart disease, congestive heart failure, and stroke, it is predicted that the medical costs associated with these and other hypertension-related diseases will eventually escalate to enormous levels [2].

The diagnosis, prevention and treatment of hypertension has generally been based on the measurement of casual clinic blood pressure (CBP), which is the blood pressure (BP) determined in a healthcare setting. However, CBP may be affected by biases such as the so-called white-coat effect, which results from a defense reaction, and may not reflect the individual's true blood pressure [3,4].

Self-measurement of BP at home (HBP) more closely reflects the individual's BP and is useful in treating hypertension. HBP measurements have been reported to provide more reliable and reproducible blood pressure information, since they allow multiple measurements and avoid observer bias as well as regression dilution biases [5]. Moreover, the use of HBP measurement helps

patients feel involved in their own treatment and can therefore improve medication compliance [3,4]. HBP is also a better predictor of cardiovascular complications than CBP [5–7].

The use of HBP for untreated hypertensive patients, initially detected by CBP, to define those with lower home blood pressures, has led to concept of white-coat hypertension (WCH) [8]. Pooled results from several prospective observational studies have shown that the likelihood for future stroke in WCH is nearly that of normal subjects at 5-year follow-up intervals [9]. WCH may also be related to a more favorable overall cardiovascular risk profile, reflected by lower body mass index and favorable serum lipid patterns [10].

Otherwise, introduction of ambulatory blood pressure monitoring (ABPM), which can detect WCH, has also been reported to lower medical costs [11,12]. In a recent cost analysis from the USA, the reduction in costs due to use of ABPM varied from 3 to 14% [11]. Likewise, in another cost analysis from Australia, the reduction in costs due to ABPM varied from 7 to 14% [12]. A similar analysis for HBP has not yet been conducted.

In the present analysis, we used data from the Ohasama study [5,6,13–15], a cohort study of hypertension in which both HBP and CBP were measured, and statistical data published by the Ministry of Health, Labor and Welfare of Japan [16–20]. The present study presents calculations of the cost reductions likely to take place when HBP monitoring is implemented for newly detected hypertensive subjects.

Methods

The analysis was carried out using a Markov model constructed in the decision-analytic program package DATA (TreeAge Software, Inc., Williamstown, Massachusetts, USA). This model takes into account the following elements: the cost for introduction of HBP and of treatment for hypertension; the prevalence of WCH during initial screening; estimates of the annual incidence of new hypertension during follow-up; and an estimate of annual loss to follow-up and treatment.

We estimated two kinds of cost, the cost for introduction of HBP and the cost of treatment for hypertension, from the Japanese insurance perspective. First, the cost for introduction of HBP is 0 dollars per 5 years. That is, we assumed that patients bought their own HBP devices. We calculated the break-even cost for the introduction of HBP. Second, based on the Annual Statistics Report from the Ministry of Health, Labor and Welfare, in 2002, the total medical cost associated with hypertension was US$16.7 billion (1.94 trillion yen), while the number of hypertensive patients was 6.98 million. From these data, the annual cost of treatment for hypertension per person was calculated to be US$2407 (280 000 yen) (1 dollar = 116.35 yen in February 2006).

For this analysis, a 16.5% prevalence of WCH was chosen for the Ohasama study [21]. Moreover, the effect of varying prevalence of WCH from 8.2 to 24.7% was also evaluated. This is consistent with current recommendations that the diagnosis of WCH be based on $< 135/85$ mmHg for HBP.

We estimated the annual incidence of new hypertension in subjects with WCH as 7.4%, based on the Ohasama study [21]. This rate was varied from 3.7 to 14.9% in a sensitivity analysis.

The estimate of annual dropout or loss to follow-up used in this analysis was 5% for all of the groups and is a conservative one. Although very high rates of retention in treatment have been observed in some clinical trials, such as the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [22], lower retention rates have also been observed in practice-based studies [23]. It is likely that dropout rates in nonresearch settings, that is, usual clinical practice, are far higher than 5%, but additional surveys are needed to establish this estimate.

In summary, the model began with 1000 subjects, initially labeled as hypertensive, based on screening using CBP. The baseline prevalence of WCH was 16.5% and the incidence of newly confirmed hypertension, after initial assessment, was 7.4%. We performed a sensitivity analysis to test the robustness of the results to key assumptions. In a sensitivity analysis, the prevalence of WCH varied from 8.2 to 24.7%, and the incidence of newly confirmed hypertension was varied from 3.7 to 14.9% (Table 1). Calculations for these groups were made over a 5-year period for the following: total treatment years; costs for hypertension treatment; and break-even costs for introduction of HBP.

Results

Baseline case

We separated patients into a group without HBP use and a group with a baseline prevalence of WCH of 16.5% and

Table 1 Estimates of cost and transition probability

	Cost or transition probability (sensitivity analysis)
The cost for introduction of HBP (/5 years)	US$0
The annual cost per patient of treatment for hypertension	US$2407
The prevalence of WCH during initial screening	16.5% (8.2–24.7%)
The annual incidence of new hypertension[a]	7.4% (3.7–14.9%)

HBP, home blood pressure monitoring; WCH, white-coat hypertension. US$1 = 116.35 yen in February 2006. [a]The annual incidence of new hypertension applies only to white-coat hypertensives since patients were limited to subjects with WCH or sustained hypertension.

Table 2 Baseline case

	Total treatment years (person years)	Total medical cost (million US$)
No use of HBP	4524	10.89
Introduction of HBP	3875	9.33
Reduction for HBP	649	1.56

HBP, home blood pressure monitoring. US$1 = 116.35 yen in February 2006.

annual incidence of new hypertension of 7.4%. The results of this model over a 5-year period estimated that the medical cost was US$10.89 million (1.27 billion yen) per 1000 subjects per 5 years when HBP measurement was not incorporated, and US$9.33 million (1.09 billion yen) per 1000 subjects per 5 years when HBP measurement was incorporated. Thus, when HBP measurement was incorporated, the reduction in medical cost was estimated to be US$1.56 million (181.7 million yen) per 1000 subjects per 5 years (Table 2).

Sensitivity analysis

Table 3 compares the effect of varying the initial prevalence of WCH from 8.2 to 24.7% and the annual incidence of new hypertension from 3.7 to 14.9% on the total cost of treatment over 5 years, using the minimum for treatment costs. Compared with the treatment years without using HBP, 4524 person years, the reductions in treatment years vary from minimum of 280 person years to a maximum of 1041 person years. Compared with the cost for treatment without using HBP, US$10.89 million (1.27 billion yen), the reductions in costs vary from a minimum of US$674 000 (78.47 million yen) to a maximum of US$2.51 million (291.7 million yen), resulting in savings of 6.2 to 23.0% (Table 3). When we conducted sensitivity analysis for the estimate of annual dropout or loss to follow-up, varying from 0 to 20%, the results were essentially similar (data not shown).

The break-even cost for introduction of HBP is shown in Table 4. When the prevalence of WCH is 16.5% and the annual incidence of new hypertension is 7.4% (baseline case), the break-even cost is US$1561.8 (181 700 yen) per 5 years per patient. The range of break-even costs of introduction of HBP varies from a minimum of US$674.4 (78 470 yen) when the prevalence of WCH is 8.2% and annual incidence of new hypertension is 14.9%, to a maximum of US$2510 (291 700 yen) when the prevalence of WCH is 24.7% and annual incidence of new hypertension is 3.7%.

Table 4 Break-even cost for introduction of HBP

Prevalence of WCH (%)	Annual incidence of new HT (%)	Break-even cost for introduction of HBP (US$/5 years)
8.2	3.7	832.3
8.2	7.4	776.2
8.2	14.9	674.4
16.5	3.7	1674.9
16.5	7.4	1561.8
16.5	14.9	1357.0
24.7	3.7	2507.2
24.7	7.4	2337.9
24.7	14.9	2031.5

HBP, home blood pressure monitoring; HT, hypertension; WCH, white-coat hypertension. US$1 = 116.35 yen in February 2006.

Discussion

HBP is considered more useful than CBP for many reasons [3–7]. The results presented here indicate that use of HBP to detect definite hypertension, initially and during follow-up of those initially identified as having WCH, may substantially reduce the cost of management for hypertension. It is predicted that the introduction of HBP for hypertension treatment would result in a reduction of US$1.56 million (181.7 million yen) per 1000 persons per 5 years. The reduction in cost will be most evident when the prevalence of WCH is high but the incidence of newly confirmed hypertension is low.

In this analysis, the assumption that patients pay for the devices used for self-measurement of blood pressure at home may favor home blood pressure measurement. However, in Japan, national statistics on industrial products shows that 30 million home blood pressure devices have already been distributed and that 2.5 million devices are being sold annually [24]. Our questionnaire survey conducted in 2005 supports these numbers. The prevalence of home blood pressure users was 77% in hypertensive patients and even 39% in normotensive subjects [25]. Given these data, the proportion of individuals who need to buy HBP devices should be minimal. Furthermore, the break-even costs for the introduction of HBP calculated in the present study (US$674–1560 according to the sensitivity analysis) were apparently

Table 3 Sensitivity analysis

Prevalence of WCH (%)	Annual incidence of new HT (%)	Treatment years	Cost reduction for HBP (thousand US$)	Percentage of no HBP
8.2	3.7	4179	832.3	92.4
8.2	7.4	4202	776.2	92.9
8.2	14.9	4244	674.4	93.8
16.5	3.7	3828	1674.9	84.6
16.5	7.4	3875	1561.8	85.7
16.5	14.9	3960	1357.0	87.5
24.7	3.7	3483	2507.2	77.0
24.7	7.4	3553	2337.9	78.5
24.7	14.9	3680	2031.5	81.3

HBP, home blood pressure monitoring; HT, hypertension; WCH, white-coat hypertension. US$1 = 116.35 yen in February 2006.

over the general purchase cost of HBP devices (around US$50–100 dollars). These data indicate that even if the cost of HBP devices was met by health insurance, the cost to health insurance for the management of hypertension would be reduced. We consider that our present study provides basic information for decision-making on the introduction of HBP measurement in the health insurance system.

The present analysis suggests that introduction of HBP measurement would reduce the cost of hypertension treatment, and that this reduction would be attributed to avoiding unnecessary antihypertensive treatment for subjects with WCH. A previous study also reported a reduction in medical costs in patients diagnosed according to HBP when compared to those diagnosed according to CBP [26]. The latter study also attributed these reductions to avoiding unnecessary antihypertensive treatment in white-coat hypertensive subjects. Moreover, to detect WCH and delay treatment for hypertension will reduce treatment years and may result in sustained quality of life for those not receiving antihypertensive medication who do not need it [27].

The calculations used were based on currently available estimates in Japan for the prevalence of WCH in recently detected hypertensive groups and costs for hypertension treatment. The estimates for incidence of new hypertension in WCH were based on patterns for new clinic hypertension derived from the Ohasama study [21]. These estimates are consistent with small-scale studies using ABPM, with rates for new hypertension varying from $<5\%$ to nearly 20% [28,29]. By using a range of estimates for new hypertension during follow-up of the WCH subjects, the calculated results may apply to different groups where the expected prevalence of WCH and the incidence of newly confirmed hypertension vary in relation to age, level of pressure, and pattern of cardiovascular risk factors. In the present analysis, however, various estimates were adopted from the Ohasama study, while in the sensitivity analysis the cost was reduced in all cases, indicating that these results would be reliable.

The study was based on the assumption that WCH is an innocent condition, although no agreement exists on whether WCH is clinically innocent or has an adverse prognostic significance. A meta-analysis of clinically hypertensive patients has demonstrated that the risk of stroke morbidity in subjects with WCH was similar to that of true normotensive subjects by an average of 5 years of follow-up [9]. Furthermore, in the latest and largest meta-analysis of four prospective studies in the general population, the International Database of Ambulatory blood pressure in relation to Cardiovascular Outcome (IDACO), demonstrated that the risk of total fatal/nonfatal cardiovascular events in subjects with WCH during a median follow-up period of 10 years was similar to the risk in true normotensive subjects [1.22; 95% confidence interval (CI) = 0.96–1.53] without substantial heterogeneity by the duration of follow-up in each study (9.3–13.1 years) [30]. Therefore, for at least for 5 and possibly 10 years, the risk of WCH is considered to be similar to that of true normotensive subjects. In the present analysis we calculated the cost-effectiveness of HBP introduction over 5 years. Thus, our assumption that WCH is an innocent condition would be valid in the current analysis.

The definition of WCH in the present analysis was based on that of the Ohasama study. Therefore, the diagnosis of office hypertension was based on two blood pressure measurements taken at a single office visit by nurses using a semi-automatic device, and that of home hypertension was based on 20 self-measurements obtained during a 4-week period using a semi-automatic device. The thresholds for the definition of WCH were 140/90 and 135/85 mmHg for office and home BP, respectively. This comparison may not be ideal for office blood pressure measurements and may favor self-home blood pressure measurements. However, in the Ohasama study, even when the number of measurements (two) was the same as office measurements, home BP had a stronger predictive power for cardiovascular mortality and stroke morbidity [5,6]. These findings were confirmed in an Italian population study (the PAMELA study) that showed a superior predictive value of home BP over office BP, even though office blood pressure was the average of six readings measured three times at two office visits, while the home BP was the average of only two measurements [31]; no data are currently available regarding the comparison of predictive power of home BP and office BP measured more than six times at three or more office visits. Therefore, the present data may not be applicable to conditions where multiple office measurements are usually available during repeated office visits. Home BP is unique in that it is possible to conduct multiple BP measurements over a long period. Regarding the prevalence of WCH, an increasing number of office BP measurements was reported to be associated with a lower prevalence of WCH [32]. Since the diagnosis of office hypertension was based on two blood pressure measurements in the present study, it is possible that the prevalence of WCH might be overestimated; however, we conducted a sensitivity analysis, varying the initial prevalence of WCH from 8.2 to 24.7%, and found that the introduction of HBP was associated with at least a cost reduction of US$674 000.

The present study has several limitations. First, we did not target masked hypertension (MHT) in this analysis, although increasing evidence has shown that its prognosis is poor. These patients may have greater target organ damage than those with normal home BPs and appear to have morbidity and mortality rates that are closer to those