

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

著者	Kikuya Masahiro, Ohkubo Takayoshi, Metoki Hirohito, Asayama Kei, Hara Azusa, Obara Taku, Inoue Ryusuke, Hoshi Haruhisa, Hashimoto Junichiro, Totsune Kazuhito, Satoh Hiroshi, Imai Yutaka
journal or publication title	Hypertension
volume	52
number	6
page range	1045-1050
year	2008
URL	<a href="http://hdl.handle.net/10097/51531">http://hdl.handle.net/10097/51531</a>

doi: 10.1161/?HYPERTENSIONAHA.107.104620

# 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.<sup>1</sup> Home blood pressure measurement offers more prognostic significance than office blood pressure<sup>2</sup> and is more indicative of target organ damage.<sup>3</sup> The clinical significance of home blood pressure measurement is primarily produced by multiple measurements of blood pressure.<sup>2</sup> These multiple measurements also provide information on day-by-day blood pressure variability under relatively controlled conditions.<sup>4</sup> Previous studies of ambulatory blood pressure monitoring have highlighted that circadian variation<sup>5</sup> and short-term blood pressure variability<sup>6</sup> 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 hypothe-

sized 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.<sup>7</sup>

## 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.<sup>2,6</sup> 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

© 2008 American Heart Association, Inc.

*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  $\geq 35$  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  $\geq 10$  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:  $63.5 \pm 10.1$  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:  $9.0 \pm 3.7$  mm Hg; diastolic:  $6.3 \pm 2.7$  mm Hg) did not differ significantly from that obtained over 30 days (systolic:  $9.2 \pm 3.0$  mm Hg; diastolic:  $6.5 \pm 2.4$  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.<sup>4,8</sup> 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.<sup>6</sup> 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,<sup>9</sup> diabetes mellitus was defined as a fasting or random blood glucose level of  $\geq 7.0$  or  $\geq 11.1$  mmol/L, respectively, or as the use of antidiabetic drugs. Hypercholesterolemia was a serum level of total cholesterol of  $\geq 5.68$  mmol/L (220 mg/dL) or use of lipid-lowering drugs. Obesity was defined as a body mass index of  $\geq 25$  kg/m<sup>2</sup>.

### 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.

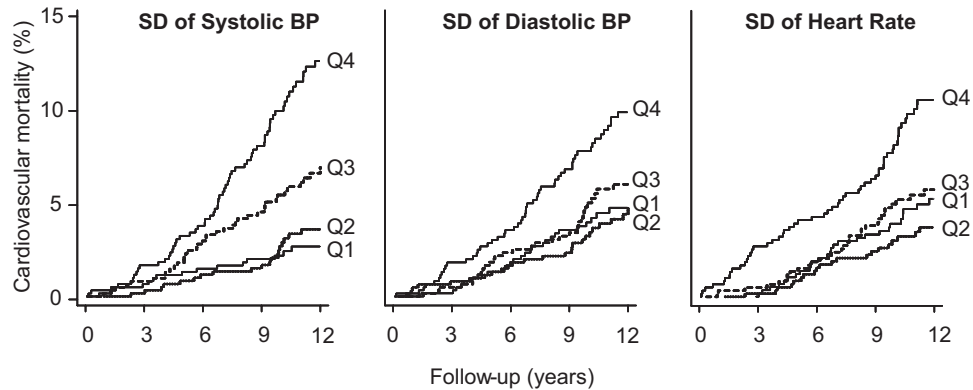
### Statistical Analysis

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  $\chi^2$  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  $59.4 \pm 12.3$  years for age,  $23.5 \pm 3.1$  for body mass index, and  $5.0 \pm 0.9$  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  $24.5 \pm 5.3$ . 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  $124.6 \pm 15.2/74.7 \pm 9.9$  mm Hg, respectively. The SDs and CVs of systolic/diastolic blood pressure were  $8.6 \pm 3.2/6.4 \pm 2.3$  mm Hg and  $6.9 \pm 2.3/5.2 \pm 1.9\%$ , respectively. The level, SD, and CV of heart rate were  $67.4 \pm 7.8$  bpm,  $5.7 \pm 2.3$  bpm, and  $8.4 \pm 3.2\%$ , 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:  $57.8 \pm 10.7$  years) were re-examined with long-term measurement ( $24.2 \pm 4.4$  days) of home blood pressure in the morning after  $7.5 \pm 1.5$  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:  $11.9 \pm 3.9$  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%).<sup>10</sup> 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 ( $P \geq 0.11$ ). With multiple adjustments applied, both levels and variabilities of systolic blood pres-

sure 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 ( $P \geq 0.74$ ), neoplasms ( $P \geq 0.25$ ), diseases of the respiratory system ( $P \geq 0.10$ ), or senility ( $P \geq 0.16$ ), 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.

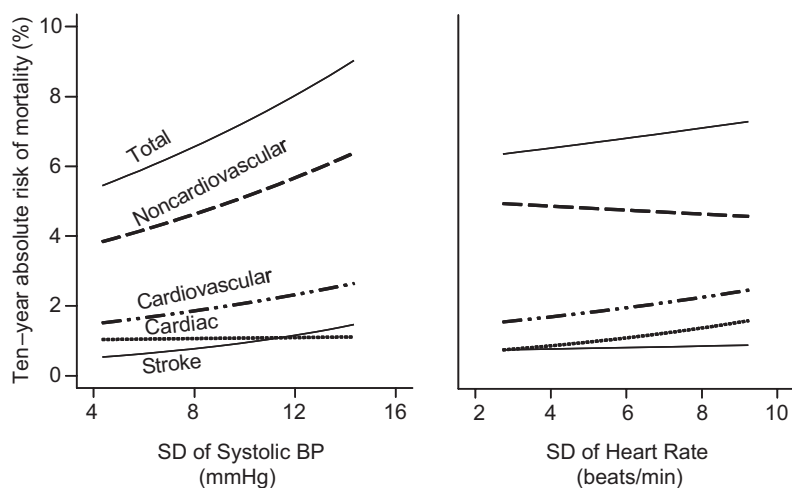
The link between variability and outcome may not necessarily imply a cause-effect relationship. Errors in self-measurements could have been responsible for failure to constantly identify a hypertensive condition at the time of different home measurement sessions. Underlying irregular-

**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).



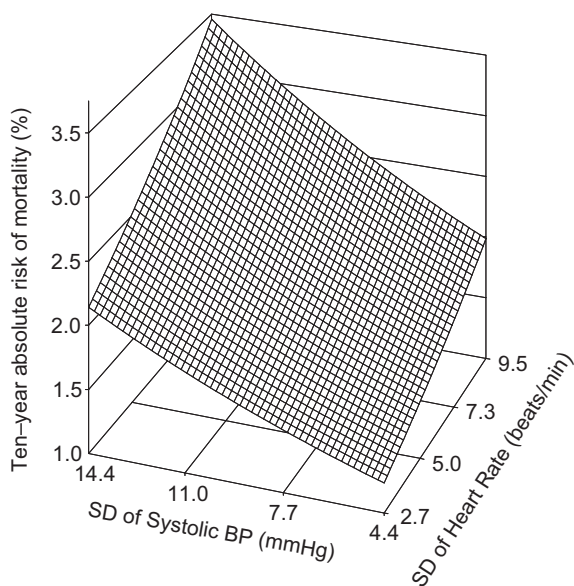
**Figure 2.** Absolute 10-year risk of total, noncardiovascular, cardiovascular, cardiac, and stroke mortality in relation to SD of systolic blood pressure (left) and SD of heart rate (right). Using Cox regression, risks were standardized to central tendencies in the other cardiovascular risk factors 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.

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<sup>6,11</sup> and heart rate<sup>6,12-14</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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.<sup>17</sup> 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.<sup>10</sup> In



**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.

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

- 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.
- 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.
- 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.
- Imai Y, Otsuka K, Kawano Y, Shimada K, Hayashi H, Tochikubo O, Miyakawa M, Fukuyama 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.
- 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.
- 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.
- Hozawa A, Ohkubo T, Kikuya M, Uga J, 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.
- 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.
- 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.
- Statistical Research and Training Institute. *M Japan Statistical Yearbook 2007*. Tokyo, Japan: Japan Statistical Association; 2007.
- 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.
- 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.
- Casolo GC, Stroder P, Sulla A, Chelucci A, Freni A, Zeraushek M. Heart rate variability and functional severity of congestive heart failure secondary to coronary artery disease. *Eur Heart J*. 1995;16:360-367.
- 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.
- 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.
- Stolarz K, Staessen JA, Kuznetsova T, Tikhonoff V, State D, Babeau 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.
- Asia Pacific Cohort Studies Collaboration. Blood pressure and cardiovascular disease in the Asia Pacific region. *J Hypertens*. 2003;21:707-716.