women and Japanese men from the general population. The observational design of our study had the advantage of allowing evaluation of long-term use of tocopherol supplements in relation to mortality. Because the participants in the present nested case-control study were recruited throughout Japan, our study results can be generalized to the entire Japanese population.

The present study has several potential limitations. First, serum samples were collected from only approximately 35% of the total participants. However, because there were no apparent differences in age-adjusted mean values or proportions of major cardiovascular risk factors between the participants who did and did not provide serum samples (data not shown), selection bias in our evaluation of the association between serum tocopherol levels and cardiovascular disease mortality is likely to be limited. Second, we did not examine the long-term stability of tocopherols in deeply frozen serum. However, a previous study found that tocopherol was stable for at least 15 years in serum stored at temperatures of −70°C or lower.[43] Third, we used only mortality data as an endpoint, which may have led to misclassification of diagnoses. However, use of computed tomography scans has been widespread in Japan since the 1980s, even in local hospitals; thus, it is likely that our use of death certificate records to classify stroke and its subtypes was sufficiently accurate.[44] However, approximately one-third of deaths categorized as coronary heart disease on death certificates were misdiagnosed, as demonstrated by validation studies.[45] This discrepancy may have partly contributed to the lack of association between serum tocopherols levels and coronary heart disease mortality observed in the present study.

In conclusion, serum α-tocopherol was associated with lower mortality from total and hemorrhagic strokes in women. γ-Tocopherol tended to be associated with lower mortality from ischemic stroke in men and increased mortality from hemorrhagic stroke in women. No association was found between α- or γ-tocopherol and coronary heart disease mortality in men or women. Further studies are required to evaluate the effectiveness of vitamin E in the prevention of cardiovascular disease.

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Conflicts of interest: None declared.

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Ambulatory Versus Home Versus Clinic Blood Pressure
The Association With Subclinical Cerebrovascular Diseases: The Ohasama Study

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See Editorial Commentary, pp 2–4

Abstract—The usefulness of ambulatory, home, and casual/clinic blood pressure measurements to predict subclinical cerebrovascular diseases (silent cerebrovascular lesions and carotid atherosclerosis) was compared in a general population. Data on ambulatory, home, and casual/clinic blood pressures and brain MRI to detect silent cerebrovascular lesions were obtained in 1007 subjects aged ≥55 years in a general population of Ohasama, Japan. Of the 1007 subjects, 583 underwent evaluation of the extent of carotid atherosclerosis. Twenty-four–hour, daytime, and nighttime ambulatory and home blood pressure levels were closely associated with the risk of silent cerebrovascular lesions and carotid atherosclerosis (all $P<0.05$). When home and one of the ambulatory blood pressure values were simultaneously included in the same regression model, each of the ambulatory blood pressure values remained a significant predictor of silent cerebrovascular lesions, whereas home blood pressure lost its predictive value. Of the ambulatory blood pressure values, nighttime blood pressure was the strongest predictor of silent cerebrovascular lesions. The home blood pressure value was more closely associated with the risk of carotid atherosclerosis than any of the ambulatory blood pressure values when home and one of the ambulatory blood pressure values were simultaneously included in the same regression model. The casual/clinic blood pressure value had no significant association with the risk of subclinical cerebrovascular diseases. Although the clinical indications for ambulatory blood pressure monitoring and home blood pressure measurements may overlap, the clinical significance of each method for predicting target organ damage may differ for different target organs. (*Hypertension*. 2012;59:22-28.) • Online Data Supplement

Key Words: home blood pressure ■ ambulatory blood pressure ■ casual/clinic blood pressure ■ silent cerebrovascular lesions ■ carotid atherosclerosis ■ general population

Elevated blood pressure (BP) is a strong, independent risk factor for incident cardiovascular diseases.[1] The recent international hypertension management guidelines[2–4] confer increasing weight to methods of measuring BP outside the medical environment, 24-hour ambulatory BP (ABP) measurements, self-measurements at home (HBP), or both. Indeed, many studies have demonstrated their relationship with target organ damage[5–10] and their prognostic values for cardiovascular diseases.[11–15]

There have been a few small studies that directly compared the usefulness of these 2 measurement methods. Overall, these data suggested that ABP and HBP are equally reliable for predicting target organ damage,[16–18] that ABP is strongly associated with target organ damage,[19] and that HBP has a closer association with target organ damage.[20] However, there are still insufficient data comparing the predictive values for target organ damage of ABP, HBP, and casual/clinic BP (CBP), especially for subclinical cerebrovascular diseases, such as silent cerebrovascular lesions (SCLs) or carotid atherosclerosis.

SCLs, seen as white matter hyperintensities and lacunar infarcts, which are frequently observed on MRI scans in elderly individuals, constitute an independent predictor of the risk of symptomatic stroke[21] and are associated with cogni-

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tive impairment or dementia.[22] Carotid atherosclerosis (carotid intima-media thickness and plaques) more accurately predicts the risk of future myocardial infarction and stroke than traditional risk factors.[23,24]

The objective of this study was to compare the usefulness of ABP monitoring, HBP measurements, and CBP measurements for the prediction of subclinical cerebrovascular diseases in a general Japanese population.

Methods

Design

This study was a part of the Ohasama Study, a community-based project to measure ABP and HBP. The socioeconomic and demographic characteristics of this region and the full details of the project have been described elsewhere.[25,26] The study protocol was approved by the institutional review board of Tohoku University School of Medicine (Sendai, Japan) and by the Department of Health of the Ohasama Town Government.

Study Population

Of the 2400 eligible individuals aged ≥55 years; 1007 subjects (42.0%; mean age 66.3±5.8 years; 67.4% women) gave informed consent; had ABP, HBP, and CBP measurements; completed MRI; and provided details of their medical histories and cardiovascular risk factors. Of the 1007 subjects, 583 underwent carotid ultrasound examination for further evaluation of the extent of carotid atherosclerosis. The details of the selection and the representativeness of study subjects are described in the online Data Supplement (please see http://hyper.ahajournals.org).

Subclinical Cerebrovascular Diseases

The evaluations of SCLs and carotid atherosclerosis are described in the online Data Supplement.

BP Measurements

ABP monitoring was performed using the ABPM-630 (Nippon Colin, Komaki, Japan),[27] a fully automatic device that uses the cuff-oscillometric method to measure BP, which was preset to measure BP every 30 minutes. According to the diary, "daytime" and "nighttime" were determined as periods of being awake and asleep, respectively. The mean (±SD) number of total ABP measurements was 43.6±4.9 (daytime: 28.3±4.7; nighttime: 15.3±2.8).

HBP was measured with the HEM701C (Omron Healthcare Co Ltd, Kyoto, Japan), a semiautomatic device based on the cuff-oscillometric method.[28] The subjects were asked to measure their BP every morning and evening[29] and to record the results over a 4-week period. The mean (±SD) number of HBP measurements was 49.0±11.3 (morning: 24.7±5.7; evening: 24.2±6.2).

At the time of MRI and carotid ultrasound examination, a physician measured the CBP twice consecutively with the participant sitting after an interval of rest of >2 minutes using a mercury sphygmomanometer or an automatic device (HEM907, Omron Healthcare Co. Ltd.). The average of the 2 readings was defined as the CBP.

Each subject had ABP, HBP, and CBP measurements within a year. Details of BP measurements are described in the online Data Supplement.

Biochemical Examination

The biochemical examinations and the definitions of cardiovascular diseases, hypercholesterolemia, and diabetes mellitus in the Ohasama Study have been reported previously.[5–7,30]

Data Analysis

The analyses of the data in the present study are described in the online Data Supplement.

Table. Population Characteristics and the Association Between SCLs and Cardiovascular Risk Factors

Variables	SCLs (−)	SCLs (+)	*P*
No. of subjects	501	506	
Men, %	29	36	0.03
Age, y	64±5	68±6	<0.0001
BMI, kg/m^2	24±3	23±3	0.03
Blood pressure, mm Hg			
Ambulatory			
24-h			
Systolic	123±12	128±12	<0.0001
Diastolic	72±7	74±7	<0.0001
Daytime			
Systolic	129±13	134±13	<0.0001
Diastolic	76±8	78±8	<0.0001
Nighttime			
Systolic	111±13	117±14	<0.0001
Diastolic	63±7	66±8	<0.0001
Home			
Systolic	122±14	128±14	<0.0001
Diastolic	73±9	76±9	<0.0001
Casual/Clinic			
Systolic	139±20	142±20	0.06
Diastolic	78±11	78±10	0.5
Smoker, %	17	21	0.1
Drinker, %	28	28	0.97
Antihypertensive medication, %	27	52	<0.0001
Hypercholesterolemia, %	36	36	0.9
Diabetes mellitus, %	13	17	0.1
Atrial fibrillation, %	2	4	0.1
Cardiovascular diseases, %	9	16	0.001

Values are shown as mean±SD or percentage. SCL indicates silent cerebrovascular disease; BMI, body mass index.

Results

Risk of SCLs

The characteristics of the study subjects and the associations between the risk factors and SCLs are presented in the Table. A total of 506 subjects (50%) had SCLs. The presence of SCLs was associated with older age, lower body mass index, a higher percentage of men, antihypertensive medication, and cardiovascular diseases (all $P<0.05$). The subjects with SCLs had higher ABP and HBP levels (all $P\leq0.0001$).

On multiple logistic regression analyses adjusted for the possible confounding factors, 24-hour, daytime, nighttime ambulatory systolic BP (SBP), and home SBP values were significantly associated with the risk of SCLs, whereas casual/clinic SBP values had no association with the risk of SCLs (Figure 1). However, when home SBP and one of the ambulatory SBP values were simultaneously included in the same regression model, the home SBP value was not significantly associated with the risk of SCLs, whereas ambulatory SBP values remained a significant predictor (Figure 2). Of the

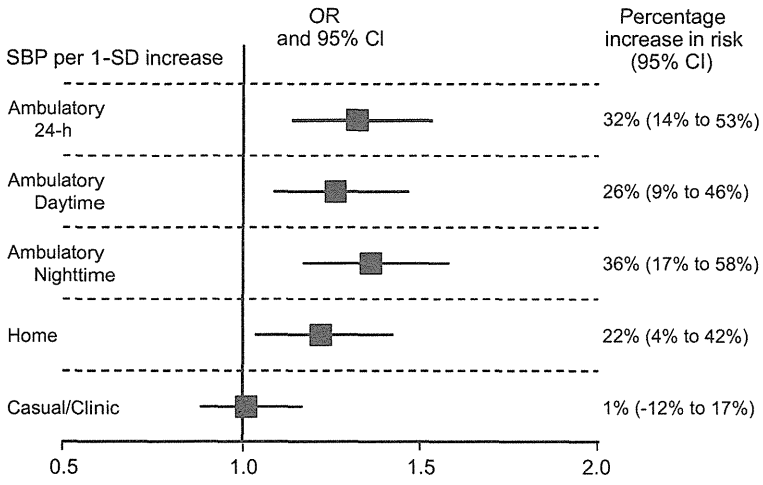

Figure 1. Odds ratios (ORs) and 95% CIs for the risk of silent cerebrovascular lesions per 1-SD increase in systolic blood pressure (SBP). Adjusted for age, sex, body mass index, smoking status, drinking status, antihypertensive medication, and history of cardiovascular diseases, atrial fibrillation, hypercholesterolemia, or diabetes mellitus. The pressures were included in the regressions one at a time. The solid squares are centered on the point estimate, and the horizontal lines extending from squares represent 95% CIs.

ambulatory SBP values, the nighttime SBP value was more strongly associated with the risk of SCLs than the daytime SBP value (Figure 2).

Casual/clinic SBP values had no significant association with the risk of SCLs when one of the ambulatory or home SBP values was simultaneously included in the same logistic regression model (Figure S1 in the online Data Supplement). Similar trends were observed when the risk for either white matter hyperintensities or lacunar infarcts was evaluated (Figures S2 and S3, respectively). The results for the risk of SCLs among the 583 subjects with carotid ultrasonography data were similar to those obtained for all 1007 subjects (Figure S4).

Risk of Carotid Atherosclerosis

Then, the associations among several ABP, HBP, and CBP values and carotid atherosclerosis were compared. The associations between cardiovascular risk factors and the presence of carotid atherosclerosis are presented in Table S2. Similar to SCLs, the subjects with carotid atherosclerosis had higher ambulatory and home BP levels than those without (all $P<0.05$), except for daytime diastolic BP ($P=0.07$).

In the logistic regression analysis, several ambulatory and home SBP values were significantly associated with the risk of carotid atherosclerosis, whereas the casual/clinic SBP value was not (Figure 3). When home SBP and one of the ambulatory SBP values were simultaneously included in the same regression model, the home SBP value was more strongly associated with carotid atherosclerosis than any of the ambulatory SBP values (Figure 4). Of the ambulatory SBP values, daytime and nighttime SBP values were similarly associated with the risk of carotid atherosclerosis (Figure 4).

Casual/clinic SBP values had no significant associations with the risk of carotid atherosclerosis when one of the ambulatory or home SBP values was simultaneously included in the same logistic regression model (Figure S5).

When ambulatory and home diastolic BP values were entered into this model instead of SBP values, all of the ambulatory and home diastolic BP values were similarly associated with the risk of subclinical cerebrovascular diseases (Figure S6 for SCLs and Figure S7 for carotid atherosclerosis).

In stratified analyses by antihypertensive treatment, similar results were more clearly observed among treated subjects,

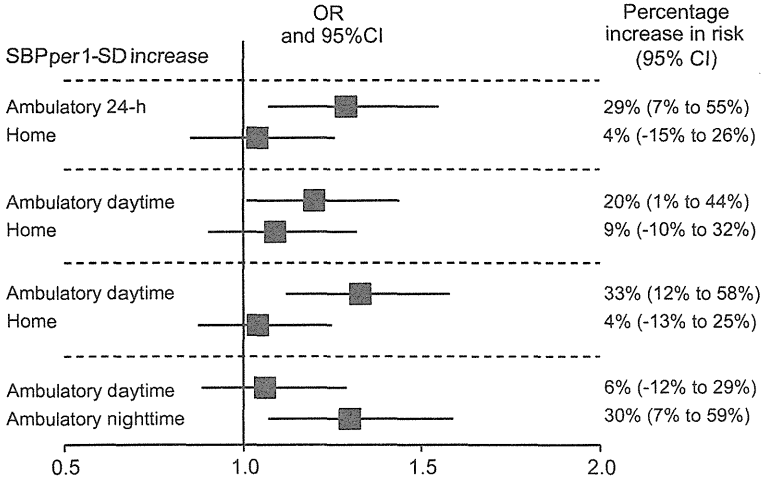

Figure 2. Odds ratios (ORs) and 95% CIs for the risk of silent cerebrovascular lesions per 1-SD increase in systolic blood pressure (SBP) when one of the ambulatory blood pressure and home blood pressure values is included in the same multiple logistic regression model. Data were adjusted for age, sex, body mass index, smoking status, drinking status, antihypertensive medication, and history of cardiovascular diseases, atrial fibrillation, hypercholesterolemia, or diabetes mellitus. The solid squares are centered on the point estimate, and the horizontal lines extending from squares represent 95% CIs.

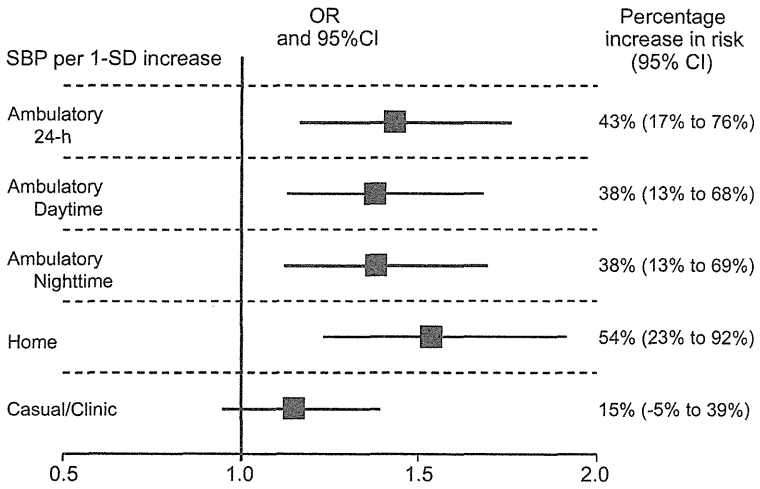

Figure 3. Odds ratios (ORs) and 95% CIs for the risk of carotid atherosclerosis per 1-SD increase in systolic blood pressure (SBP). Adjusted for age, sex, body mass index, smoking status, drinking status, antihypertensive medication, and history of cardiovascular diseases, hypercholesterolemia, or diabetes mellitus. The pressures were included in the regressions one at a time. The solid squares are centered on the point estimate, and the horizontal lines extending from squares represent 95% CIs.

although there were no significant interactions (all P values for interaction: >0.1; Figure S8 and S9 for SCLs among untreated subjects; Figure S10 and S11 for SCLs among treated subjects; Figure S12 and S13 for carotid atherosclerosis among untreated subjects; and Figure S14 and S15 for carotid atherosclerosis among treated subjects).

When one of morning pressor surges in BP, nocturnal decline, or BP variability was included in the regression model one at a time, there was a significant association only between nighttime SBP variability and the risk of carotid atherosclerosis (Figure S16 for SCLs and Figure S17 for carotid atherosclerosis). However, when the nighttime SBP value was simultaneously included in the same regression model, nighttime SBP variability did not remain significantly associated (Figure S18).

There were no significant associations between casual/clinic, home, and any ambulatory heart rate values and the risk of subclinical cerebrovascular diseases for the subjects without a history of cardiovascular diseases (Figure S19 for SCLs and Figure S20 for carotid atherosclerosis).

Similar results were obtained when HBP values averaged over 7 days of measurements (with the exception of the first day) in accordance with a guideline of the European Society of Hypertension[31] and one of the ABP or CBP values was included in the same multiple logistic regression model (Figure S21 for SCLs and Figure S22 for carotid atherosclerosis).

Discussion

To the best of our knowledge, this is the first study to compare ABP, HBP, and CBP values for their associations with the risk of subclinical cerebrovascular diseases in a large general population. ABP monitoring and HBP measurements have several advantages over CBP measurements, the absence of the white-coat effect,[29,31] the lack of digit preference and observer bias when automated devices are used, and better correlation to target organ damage[5–10] and prognosis.[11–15] Notwithstanding the above similarities, there are major differences in the characteristics between ABP monitoring and HBP measurements.

One of the advantages of ABP monitoring is its ability to provide a series of frequent and automated BP measurements throughout a 24-hour period. This might have clinical implications in light of the evidence supporting the adverse

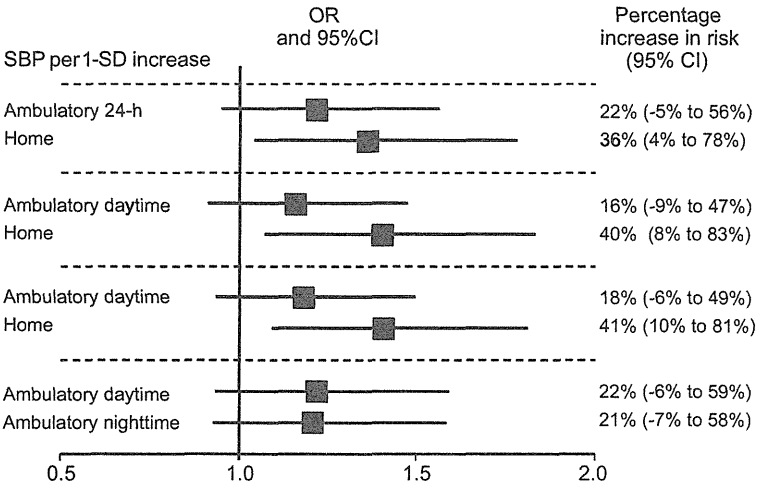

Figure 4. Odds ratios (ORs) and 95% CIs for the risk of carotid atherosclerosis per 1-SD increase in systolic blood pressure (SBP) when one of the ambulatory blood pressure and home blood pressure values are included in the same multiple logistic regression model. Adjusted for age, sex, body mass index, smoking status, drinking status, antihypertensive medication, and history of cardiovascular diseases, hypercholesterolemia, or diabetes mellitus. The solid squares are centered on the point estimate, and the horizontal lines extending from squares represent 95% CIs.

prognostic relevance of specific patterns of BP variability over 24 hours.[32,33] On the other hand, HBP measurements have been reported to provide more reliable and reproducible BP information, because they allow multiple measurements under controlled conditions and avoid the placebo effect.[13]

There have been a few direct comparisons between ABP monitoring and HBP measurements with respect to the association with target organ damage, but the results were controversial. The degree of association between left ventricular hypertrophy assessed by echocardiography and ABP or HBP is comparable.[16–18] In one study, ABP was more closely associated with left ventricular mass index and left ventricular wall thickness.[19] Another study showed that left ventricular mass was associated more strongly with HBP than with ABP.[20] For different markers of target organ damage, including urinary albumin excretion[16–18] and carotid intima-media thickening,[16,17] it showed a comparable degree of association for ABP and HBP. However, these results are based on a small series, and a large population sample has not yet been studied. With respect to the association of ABP and HBP values with the risk of SCLs, no data are available. In this relatively large population study, the nighttime ABP value was the strongest predictor of SCLs, whereas the HBP value was more strongly associated with the risk of carotid atherosclerosis than any of the ABP values.

In the present study, the nighttime BP value had the strongest association with SCLs. Normally, BP falls during sleep and rises in the waking hours. It is possible that a high BP at nighttime promoted the development of SCLs. Several reports have demonstrated the association between SCLs and clinical conditions that cause nighttime hypertension, such as activation of the renin-angiotensin system, salt-sensitive hypertension, and the sleep apnea syndrome.[34,35] These conditions might mediate the association between the nighttime BP value and the risk of SCLs in the present study. However, the cross-sectional design of the present study did not allow us to clarify cause-and-effect relationships.

It was demonstrated that the HBP value had the strongest association with the risk of carotid atherosclerosis. It has been shown previously that ABP has poorer reproducibility than HBP.[36,37] The present result, that the HBP value had the strongest association with the risk of carotid atherosclerosis, suggests that carotid atherosclerosis may be affected by the continuous and stable stress of BP.[5,7] However, we have also reported previously that carotid plaque was associated with not only BP itself but also with BP variability.[7] Further studies are required to clarify the associations of BP levels, day-by-day variability, and circadian BP variation with the risk of carotid atherosclerosis.

In the present study, means of 44 (daytime: 28; nighttime: 15) ABP measurements, 49 HBP measurements, and 2 CBP measurements were obtained. It is possible that such a number of measurements may be responsible for the strong association with subclinical cerebrovascular diseases that was found. However, the nighttime BP value taken as an average of 15 measurements was the strongest predictor for SCLs, and the HBP value of 49 measurements was the strongest one for carotid atherosclerosis in the present study. Furthermore, when HBP values averaged over 7 days of measurements (with the exception of the first day) in accordance with the European Society of Hypertension guideline[31] and one of the ABP or CBP values was included in the same multiple logistic regression model, BP values were similarly associated with the risk of subclinical cerebrovascular diseases. As for the number of CBP measurements, we compared previously the predictive value of CBP and HBP values using the same or fewer measurements (1 or 2 measurements) and showed that HBP had a stronger predictive power than CBP, even when fewer measurements were used.[12] We also reported that HBP was more closely associated with the risk of SCLs or carotid atherosclerosis than CBP using the same number of HBP measurements (2 measurements) as for the CBP.[5,6] These results suggest that not only the number, duration, or intensiveness of measurements, but other factors that have already been described above, may be associated with the superior predictive power of nighttime BP and HBP.

The possibility of selection bias needs to be considered when generalizing the present findings, because the participation rate of the study population was only 42.0%. Furthermore, it is possible that 424 high-risk subjects might have been excluded in the analysis examining the associations with carotid atherosclerosis, because the 424 subjects without carotid ultrasonography data had a higher risk than those with the data. Meanwhile, the casual/clinic SBP level was significantly higher in the 583 subjects with carotid ultrasonography data. There might be selection bias in the excluded 424 subjects without carotid ultrasonography data, although the results for the risk of SCLs among the 583 subjects with carotid ultrasonography data were similar to those of all 1007 subjects. In addition, our conclusions about HBP are applicable only when HBP is measured using a similar scheme. Furthermore, marked differences exist in the epidemiology of cardiovascular diseases between Japan and the United States or European countries. Thus, further research involving other ethnic and cultural populations is needed to confirm the generalizability of the findings in the present study.

Perspectives

The findings of the present study suggest that the nighttime ABP value is the strongest predictor for SCLs, whereas the HBP value is the strongest predictor for carotid atherosclerosis among several ABP, HBP, and CBP values. Further prospective studies that directly compare the use of ABP, HBP, and CBP values for predicting associated target organ damage and prognosis are necessary. Both ABP monitoring and HBP measurements are extremely useful for determining hypertensive cardiovascular diseases. Although the clinical indications for ABP monitoring and HBP measurements may overlap, the clinical significance of each method for predicting target organ damage may differ among different target organs.

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Disclosures

None.

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ORIGINAL CONTRIBUTIONS

Prognostic Significance of Home Arterial Stiffness Index Derived From Self-Measurement of Blood Pressure: The Ohasama Study

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BACKGROUND
Arterial stiffness is a stroke risk factor. The home arterial stiffness index (HASI) can be calculated from self-measured blood pressure using the same formula as the calculation of ambulatory arterial stiffness index (AASI).

METHODS
In 2,377 inhabitants (baseline age, 35–96 years) without a history of stroke, home blood pressure was measured once every morning for 26 days (median). HASI was defined as 1 minus the regression slope of diastolic over systolic on home blood pressure in individual subjects. The standardized hazard ratio (HR) of HASI was computed for cerebral infarction, while adjusting for sex, age, body mass index, pulse pressure, mean arterial pressure, heart rate, day-by-day variability of systolic blood pressure, smoking and drinking habits, serum total cholesterol, diabetes mellitus, and antihypertensive treatment.

RESULTS
A total of 191 (8.0%) cerebral infarctions and 75 (3.2%) hemorrhagic strokes occurred over a median of 13.8 years. Mean ± s.d. of HASI was 0.60 ± 0.23 units. An increase in HASI of 1 s.d. was associated with an increased HR for cerebral infarction in all subjects (1.19, $P = 0.034$), men (1.37, $P = 0.002$), and normotensive subjects (1.46, $P = 0.006$), but not in women or hypertensive patients ($P > 0.56$). For hemorrhagic stroke, HASI was not prognostic.

CONCLUSIONS
HASI predicted cerebral infarction independent of pulse pressure and other risk factors in men and normotensive subjects. One important role of home blood pressure measurement is early recognition of onset of hypertension in normotensive subjects who are at risk of developing hypertension. HASI provides additional benefits for such subjects.

Keywords: AASI; blood pressure; epidemiology; HASI; hypertension; home blood pressure; prognosis; stroke

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Arterial stiffness has been established as a predictor of adverse cardiovascular outcome including stroke.[1] The ambulatory arterial stiffness index (AASI) has been proposed as a measure that reflects arterial stiffness.[2,3] Several studies have demonstrated significant association of AASI with signs of target organ damage[4,5] or with incidence of cardiovascular events.[2,6,7] AASI reflects the dynamic relationship between systolic and diastolic blood pressure during the day. AASI has been defined as unity minus the regression slope of diastolic divided by systolic blood pressure, as measured by ambulatory blood pressure monitoring.[2,3] The stiffer the arterial tree, the closer the regression slope[8] is to zero and the AASI is to unity. Until now, most previous studies relied on ambulatory blood pressure monitoring to derive AASI. However, it is conceptually possible to calculate AASI by other techniques of blood pressure measurement, which provide multiple measurements over a given period,[9,10] such as the self-measured blood pressure at home.[9,10] Home blood pressure is currently widely used as an adjunct to office blood pressure for diagnosis and treatment of hypertension,[11] and has a better prognostic value.[11] Automated techniques of self-measurement reduce observer bias and the white-coat effect.[11] However, to our knowledge, no previous study has addressed the prognostic significance of the home arterial stiffness index (HASI). To address this question, to what extent HASI predicted stroke was investigated in Japanese subjects recruited from the population of Ohasama, Iwate Prefecture, Japan.

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METHODS

Study population. From 1988 until 1995, all 4,969 inhabitants of Ohasama who were 35 years or older were contacted. Subjects who worked outside the town during the normal working hours of the study nurses (n = 1057), and those who were hospitalized (n = 166) or incapacitated (n = 94) were not eligible. Of the remaining 3,652 residents, 2,920 (80%) participated in the baseline examinations and agreed to follow-up. Subjects who had a previous history of stroke (n = 136) were excluded from the present analysis. An additional 407 subjects were excluded from analyses because their home blood pressure measurements included less than ten readings (10 days).[12] Thus, the number of participants statistically analyzed totaled 2,377.

All participants gave written informed consent. The Institutional Review Boards of Tohoku University School of Medicine and the Department of Health of the Ohasama Municipal Government approved the study. Information on demographic and socioeconomic characteristics of this region and the details of the protocol have been described previously.[12]

Collection of baseline data. Trained nurses collected anthropometric data at public health centers. Body mass index was weight in kilograms divided by height in meters squared. Physicians and/or public health nurses instructed participants on how to perform home blood pressure measurements. Subjects were asked to measure blood pressure once every morning over a period of 4 weeks using an oscillometric device (HEM 401C; Omron Healthcare, Kyoto, Japan)[13] within 1 h of waking up, with measurements performed in a sitting position after at least 2 min of rest.[12] The average of all readings was defined as the home blood pressure and was used for analysis and diagnosis of hypertension. Hypertension was home blood pressure of at least 135 mm Hg systolic or 85 mm Hg diastolic,[11] or the use of antihypertensive drugs. HASI was computed for each individual using a modification of the procedure for derivation of AASI.[2,3] From the home blood pressure readings for each participant the regression slope of home diastolic divided by systolic blood pressure was computed using simple regression analysis.[2,3] HASI[9] was 1 minus the regression slope.[2,3] The regression line was not forced through the origin (intercept = 0). The stiffer the arterial tree, the closer the regression slope and HASI are to 0 and 1, respectively.[8] The square of the correlation coefficient between systolic and diastolic blood pressure was recognized as a measure of the "goodness of fit" of the AASI regression line.[14] Using the same procedure, the "goodness of fit" of the HASI was calculated as the correlation coefficient of home systolic and diastolic blood pressure in each individual. In addition, from individual recordings and readings used for HASI, pulse pressure was computed as the difference between the home systolic and diastolic blood pressures and mean arterial pressure as home diastolic blood pressure plus one third of the pulse pressure. Day-by-day variability of blood pressure was defined as the within-subject standard deviation of the home blood pressure readings.[12]

Study nurses administered a standardized questionnaire which included questions concerning each subject's medical history, intake of medications, and smoking and drinking habits. Smoking was defined as the present use of tobacco,[12] and likewise drinking was defined as the current consumption of alcoholic beverages.[12] Previous cardiovascular disease included stroke, transient ischemic attack, coronary heart disease, and atrial fibrillation. Venous blood samples were analyzed by automated enzymatic methods for serum total cholesterol and blood glucose. Hypercholesterolemia was a serum cholesterol level of at least 5.68 mmol/l (220 mg/dl) or use of lipid-lowering drugs. Diabetes mellitus was defined as a fasting glucose level of ≥7.0 mmol/l (≥126 mg/dl), a random glucose level of ≥11.1 mmol/l (≥200 mg/dl), or the use of insulin or oral antidiabetic drugs.[15]

Follow-up and outcomes. The ascertainment of outcomes and events has been described in detail previously.[12] Vital status was ascertained until 31 May 2007 via the residents' registration cards, which are required for payment of pension and social security benefits. The incidence of stroke was ascertained from the Stroke Registration System of Iwate Prefecture, death certificates, receipts of National Health Insurance, and questionnaires sent to each household. This was then confirmed by checking the medical records of Ohasama Hospital, which is the only hospital in the town and was where more than 90% of the subjects had their regular check-ups. The endpoints considered in the present analysis were stroke (ICD-10 codes I60–I69), cerebral infarction (ICD-10 code I63), and hemorrhagic stroke (ICD-10 codes, I60 and I61). Among participants who had multiple events, only the first event was considered for analysis.

Statistical analysis. For database management and statistical analysis, SAS software, version 9.1 (SAS Institute, Cary, NC) was used. Means and proportions were compared by the large-sample z test or ANOVA and the χ^2-statistic, respectively. Statistical methods also included single correlation analysis. To explore the plausibility of the Cox model, first, incidence rates were plotted by tertiles of the HASI distributions. Standardized hazard ratios (HRs) of HASI were then calculated using multiple Cox regression while adjusting for baseline characteristics including sex, age, body mass index, pulse pressure, mean arterial pressure, heart rate, day-by-day variability of systolic blood pressure,[12] smoking and drinking habits, serum total cholesterol, diabetes mellitus, and antihypertensive treatment. HASI was further accounted for (instead of pulse pressure) when analyzing HR of pulse pressure. Standardized HRs were used to express the risk per standard deviation increase in the explanatory variable. Differences in the predictive value of HASI across subgroups were tested by introducing the appropriate interaction terms in the Cox models.

RESULTS

Baseline characteristics

The 2,377 participants consisted of 1,454 (61.2%) women, and 944 (39.7%) patients with hypertension, of whom 669 (70.9%)

were taking antihypertensive drugs. Mean ± s.d. were 58.9 ± 12.2 years for age, 0.60 ± 0.23 units for HASI, and 0.53 ± 0.25 for the within-subject correlation coefficients between home systolic and diastolic blood pressures. Compared to women, men had higher rates of smoking (18.0 vs. 1.4%, $P < 0.0001$), drinking (21.6 vs. 4.1%, $P < 0.0001$), and higher mean arterial pressure (95.1 ± 10.5 vs. 88.6 ± 10.3, $P < 0.0001$). The differences between women and men were not significant for mean age (59.1 ± 12.1 vs. 58.7 ± 12.3 years, $P = 0.36$), use of antihypertensive drug treatment (17.9 vs. 10.2%, $P = 0.12$), prevalence of diabetes mellitus (5.3 vs. 4.0%, $P = 0.19$), and history of heart disease (0.4 vs. 0.3%, $P = 0.93$). HASI was similar among women and men (0.59 ± 0.26 vs. 0.60 ± 0.22, $P = 0.10$). On the contrary, HASI was higher in hypertensive patients than in normotensive subjects (0.64 ± 0.23 vs. 0.57 ± 0.24, $P < 0.0001$). The within-subject correlation coefficients between home systolic and diastolic blood pressure did not differ between women and men (0.52 ± 0.24 vs. 0.53 ± 0.27, $P = 0.32$), and between hypertensive patients and normotensive subjects (0.52 ± 0.26 vs. 0.53 ± 0.25, $P = 0.58$).

Table 1 lists the baseline characteristics of participants across thirds of the HASI distribution. In single correlation, HASI correlated positively with age ($r = + 0.18$; $P < 0.0001$), pulse pressure ($r = + 0.30$; $P < 0.0001$), mean arterial pressure ($r = + 0.12$; $P < 0.0001$), and day-by-day variability of systolic blood pressure ($r = + 0.04$; $P = 0.08$). The number of readings available per recording for the calculation of HASI, blood pressure level and blood pressure variability averaged 24.4. The 50th, 25th, 10th, 5th, and 1st percentile values were 26, 22, 16, 13, and 10, respectively.

Follow-up and outcome

The mean duration of follow-up was 13.2 ± 4.8 years (maximum 19.3). Of 2,377 study subjects, 78 were lost to follow-up. A first stroke occurred in 268 participants, which was due to cerebral infarction in 191, intracerebral hemorrhage in 57, subarachnoid hemorrhage in 18, and unknown causes in 2. In the entire study population, the incidence of cerebral infarction tended to increase across thirds of HASI (4.1, 6.5, and 7.7 infarctions per 1,000 subjects-years; trend $P = 0.13$). A log-linear relationship was observed in men and in normotensive subjects (**Figure 1**).

Unadjusted HRs were computed for HASI and other blood pressure parameters (**Table 2**). In an adjusted model, these parameters, except for pulse pressure, also significantly predicted cerebral infarction in the overall study population. When systolic blood pressure and diastolic blood pressure were adjusted for instead of mean blood pressure and pulse pressure (alternative adjusted model), the results were confirmatory with the exception of diastolic blood pressure (**Table 2**). **Figure 2** also demonstrates the HR of HASI. The HR of HASI was significant in men (1.37, $P = 0.002$), and normotensive subjects (1.46, $P = 0.006$), but not in women, treated hypertensive patients, or untreated hypertensive patients ($P > 0.71$). When hypercholesterolemia was adjusted for instead of serum total cholesterol, and for body height or weight instead of body

Table 1 | Clinical characteristics across tertiles of the home arterial stiffness index (HASI)

HASI tertiles limits	<0.50	0.50–0.68	≥0.68	*P* value
Number of subjects	792	793	792	
Women, n (%)	460 (58.1)	495 (62.4)	499 (63.0)	0.090
Age, years	55.6 ± 11.3	60.3 ± 12.0	61.0 ± 12.4	<0.0001
Body mass index, kg/m^2	23.3 ± 2.9	23.5 ± 2.9	23.6 ± 2.9	0.071
Home BP, mm Hg				
Systolic	119.6 ± 13.5	124.5 ± 15.4	128.3 ± 14.9	<0.0001
Diastolic	74.1 ± 10.0	74.6 ± 9.7	75.2 ± 9.9	0.107
Pulse pressure	45.4 ± 7.6	49.9 ± 10.3	53.1 ± 10.5	<0.0001
Mean arterial pressure	89.3 ± 10.7	91.3 ± 10.8	92.9 ± 10.8	<0.0001
Home heart rate, beats/min	67.2 ± 7.9	67.4 ± 7.7	67.7 ± 7.7	0.454
Day-by-day systolic BP variability, mm Hg	8.2 ± 2.9	8.8 ± 3.2	8.7 ± 3.4	<0.0001
Current smokers, n (%)	176 (22.2)	146 (18.4)	137 (17.3)	0.034
Current drinkers, n (%)	162 (27.5)	160 (26.4)	140 (23.2)	0.215
Serum total cholesterol, mmol/l	5.0 ± 0.9	5.0 ± 0.9	5.0 ± 1.0	0.381
Hypercholesterolemia, n (%)	207 (26.1)	207 (26.1)	222 (28.3)	0.612
Diabetes mellitus, n (%)	72 (9.1)	83 (10.5)	64 (8.1)	0.257
Previous heart disease, n (%)	3 (0.4)	6 (0.8)	6 (0.8)	0.547
Antihypertensive drug treatment, n (%)	169 (21.3)	239 (30.1)	261 (33.0)	<0.0001

Means and proportions were compared by ANOVA and the χ^2-statistic, respectively. Values are mean ± s.d.. Day-by-day systolic BP variability was defined as the within-subject s.d. of home systolic blood pressure in the morning. Hypercholesterolemia was a serum cholesterol level of at least 5.68 mmol/l (220 mg/dl) or use of lipid-lowering drugs. Diabetes mellitus was a fasting glucose level of ≥7.0 mmol/l (≥126 mg/dl), a random glucose level of ≥11.1 mmol/l (≥200 mg/dl) or the use of insulin or oral antidiabetic drugs.
BP, blood pressure.

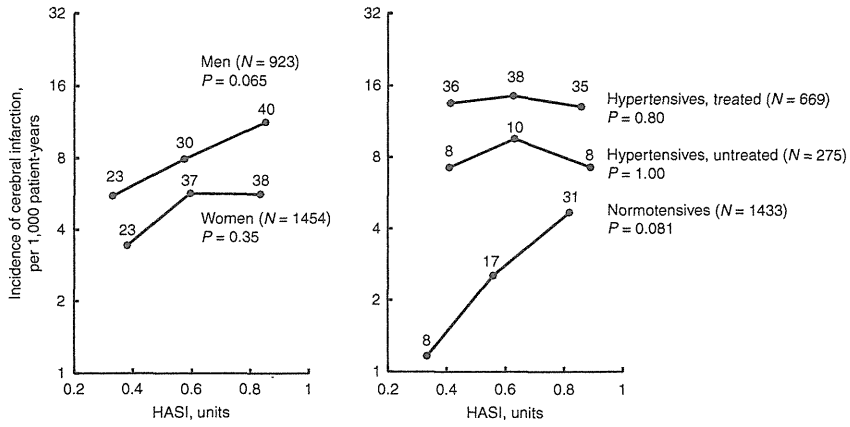

Figure 1 | Crude incidence of cerebral infarction in thirds of the distribution of the home arterial stiffness index (HASI) at entry in subgroups stratified by sex (left) and hypertension status (right). The ordinate has a logarithmic scale. Numbers represents the number of stroke occurred in each third. Hypertension was defined as a home blood pressure in the morning of at least 135 mm Hg systolic or 85 mm Hg diastolic, or as the use of antihypertensive drugs.

Table 2 | Hazard ratios for cerebral infarction according to the home arterial stiffness index (HASI) and related parameters at entry

	Total	Men	Normotensives
Subjects, no.	2,377	923	1,433
End points, no.	191	93	56
Unadjusted			
HASI, units	1.38 (1.21–1.57)***	1.48 (1.27–1.72)***	1.59 (1.31–1.94)***
Pulse pressure, mm Hg	1.89 (1.70–2.11)***	1.97 (1.68–2.30)***	3.21 (2.28–4.52)***
Mean BP, mm Hg	1.89 (1.65–2.16)***	1.86 (1.53–2.27)***	1.94 (1.28–2.93)***
Systolic BP, mm Hg	2.19 (1.92–2.50)***	2.22 (1.83–2.69)***	3.67 (2.27–5.94)***
Diastolic BP, mm Hg	1.56 (1.36–1.78)***	1.51 (1.23–1.85)***	1.28 (0.89–1.84)
Day-by-day systolic BP variability, mm Hg	1.67 (1.50–1.86)***	1.68 (1.45–1.95)***	1.65 (1.28–2.14)***
Adjusted			
HASI, units	1.19 (1.01–1.41)*	1.37 (1.12–1.67)***	1.46 (1.12–1.90)**
Pulse pressure, mm Hg	1.10 (0.93–1.30)	1.11 (0.86–1.40)	1.61 (1.02–2.56)*
Mean BP, mm Hg	1.31 (1.10–1.56)***	1.43 (1.12–1.81)***	1.38 (0.83–2.29)
Day-by-day systolic BP variability, mm Hg	1.23 (1.07–1.42)***	1.26 (1.03–1.54)*	1.29 (0.95–1.76)
Alternative adjusted			
HASI, units	1.19 (1.01–1.41)*	1.37 (1.12–1.67)***	1.46 (1.12–1.90)**
Systolic BP, mm Hg	1.30 (1.02–1.65)*	1.36 (0.96–1.92)	2.38 (1.20–4.69)*
Diastolic BP, mm Hg	1.08 (0.86–1.35)	1.13 (0.83–1.54)	0.76 (0.42–1.38)
Day-by-day systolic BP variability, mm Hg	1.23 (1.07–1.42)***	1.26 (1.03–1.54)*	1.29 (0.95–1.76)

Hazard ratios (95% confidence intervals) reflect the risk associated with a one standard deviation increase in the explanatory variables. Adjusted model accounted for sex, age, body mass index, heart rate, smoking and drinking habits, serum total cholesterol, diabetes mellitus, and antihypertensive treatment and included HASI, pulse pressure, mean arterial pressure, and day-by-day variability of systolic blood pressure. Alternative adjusted model further included systolic BP and diastolic BP instead of mean BP and pulse pressure.
*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.005$.
BP, blood pressure.

mass index, the results were confirmatory. A significant or marginally significant interaction of the HR for cerebral infarction was observed between men and women ($P = 0.014$), and between normotensive subjects and hypertensive patients ($P = 0.056$). However, the interaction between women and men dropped to a nonsignificant level after exclusion of patients on antihypertensive medication ($P = 0.16$). Then, we stratified the subject at age of 65, which was considered the beginning of elderly citizen, and pensionable age in Japan. Stratification by age group (<65 years, $N = 1,604$ vs. ≥65 years, $N = 773$) did not significantly affect the associations of HASI and cerebral infarction ($P = 0.22$ for interactions). For hemorrhagic stroke, the adjusted HRs for HASI were not significant ($0.76 \leq HR \leq 1.34$, $P \geq 0.12$).

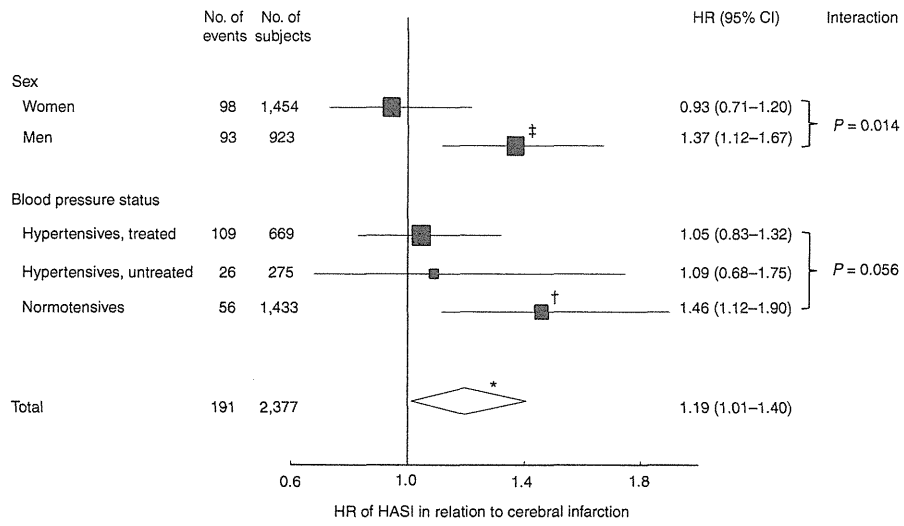

Figure 2 | Adjusted hazard ratios (HR) and 95% confidence intervals (CI) for cerebral infarction associated with 1 s.d. increments in the home arterial stiffness index (HASI), adjusted for sex, age, body mass index, pulse pressure, mean arterial pressure, heart rate, day-by-day variability of systolic blood pressure, smoking and drinking habits, serum total cholesterol, diabetes mellitus, and antihypertensive treatment. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.005$.

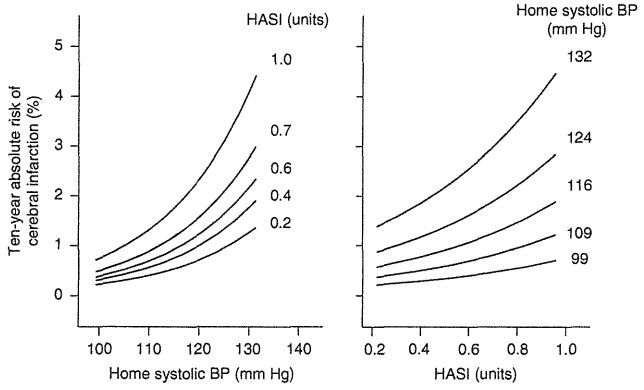

Figure 3 | Ten-year absolute risk of cerebral infarction (no. of events 56) in normotensives ($N = 1433$) in relation to home systolic blood pressure (left) at different levels of HASI, and in relation to HASI (right) at different levels of home systolic blood pressure. The analyses were standardized to the distributions (mean or ratio) of sex, age, body mass index, diastolic blood pressure, heart rate, day-by-day variability of systolic blood pressure, smoking and drinking habits, serum total cholesterol, diabetes mellitus, and antihypertensive treatment (Alternative adjusted model in Table2). In left panel, the risk functions span the 5th–95th percentile interval of the home systolic blood pressure and correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of HASI. In right panel, the risk functions span the 5th to 95th percentile interval of HASI and correspond to the 5th, 25th, 50th, 75th, and 95th percentiles of the home systolic blood pressure. The *P* values for the independent effect were $P = 0.006$ for HASI and $P = 0.013$ for home systolic blood pressure. BP, blood pressure; HASI, home arterial stiffness index.

Figure 3 shows 10-year absolute risk of cerebral infarction in normotensives in relation to home systolic blood pressure (left panel) at different levels of HASI and in relation to HASI (right panel) at different levels of home systolic blood pressure. Home systolic blood pressure and HASI were independent predictors of cerebral infarction in normotensives.

DISCUSSION

In the present study, HASI had a predictive value for cerebral infarction independent of pulse pressure. This finding was consistent with previous studies of AASI.[2,6,7] In the Dublin Outcome Study, the AASI was a stronger predictor of stroke mortality than pulse pressure, with an opposite trend for cardiac mortality.[2] In the general population of Denmark, the standardized HR of AASI for stroke was 1.62 ($P = 0.007$), while that of pulse pressure did not reach statistical significance ($P > 0.47$) when the AASI and pulse pressure were forced into the model.[7] Previous studies which investigated associations between stroke and blood pressure levels using conventional blood pressure[16,17] and ambulatory blood pressure[18] showed that pulse pressure was not very strongly associated with stroke. In relation to cerebral infarction, it has recently been observed that mean arterial pressure was more strongly associated with cerebral infarction than pulse pressure in 2,369 Ohasama residents aged ≥35 years (mean, 59 years).[19] Compared to mean arterial pressure, pulse pressure may not be important for prediction of cerebral infarction. The present result that HASI had no predictive value for hemorrhagic stroke was not surprising. HASI is an index of arterial stiffness. However, hemorrhagic stroke is due to high blood pressure load rather than atherosclerosis.[20]

In line with recent cross-sectional studies,[9,10] HASI was associated with age ($r = + 0.18$; $P < 0.0001$) and pulse pressure ($r = + 0.30$; $P < 0.0001$). These associations were comparable to those observed in studies of AASI.[2,3,6,7,9,14] It has previously been observed that the correlation coefficient of AASI with age and with 24h pulse pressure was 0.26 and 0.24, respectively, in the Ohasama population.[6] In 7,604 subjects from six general populations,[14] AASI was correlated with age ($r = + 0.37$; $P < 0.001$) and 24h pulse pressure ($r = + 0.49$; $P < 0.0001$).

Stergiou *et al.*[9] directly compared HASI vs. AASI in 483 hypertensive patients, and reported that the correlation coefficients of HASI with age and pulse pressure were less close than those of 24h AASI ($P < 0.001$). Based on these findings, they concluded that HASI appears to be similar but also has important differences from AASI. It is still uncertain whether HASI is a surrogate measure of AASI. However, given the link between HASI and cerebral infarction demonstrated in this study, HASI in itself is realistically important.

At this point, devices for home blood pressure measurement are produced worldwide at a rate of more than 10 million per year, and 30 million such devices have already been distributed in Japan, with most being purchased by the general public or patients themselves.[21] One important role of home blood pressure measurement is early recognition of the onset of hypertension. For this aim, the main target of the measurement is normotensive subjects who are at risk of developing hypertension. HASI provides additional benefits for these subjects. Conversely, ambulatory blood pressure monitoring is expensive, and constitutes an excessive physical and mental load on patients. Therefore, for normotensive subjects, it would not be realistic to measure AASI. With similar reasons, measurement of other stiffness parameters, such as pulse wave velocity and augmentation index, is also not suitable for normotensive subjects. Among currently available stiffness parameters, only HASI has the potential to provide additional benefits for normotensive subjects in terms of feasibility. Presently, most home blood pressure devices at mainstream price points have a memory function for blood pressure readings. It would not be difficult for manufacturers to add a function of automated computation of HASI to home blood pressure device.

In regards to prediction of cerebral infarction, a distinct sex difference was found in HASI; however the predictive power was evident only in men but not women. Conversely, in relation to AASI, the standardized HRs of AASI for stroke tended to be higher in women than men.[2,7] No previous prospective studies of AASI have reported that the predictive power of AASI was more pronounced in men than in women. The 'goodness of fit' of the HASI regression line did not differ between women and men (0.52 ± 0.24 vs. 0.53 ± 0.27, $P = 0.32$) in the present study. Thus, the quality of measurement of HASI was comparable in women and men, at least in terms of the goodness of fit. In the present study, compared to women, men tended to have a lower rate of antihypertensive treatment (10.2 vs. 17.9%, $P = 0.12$). Furthermore, the interaction of the HR for cerebral infarction between women and men dropped to a nonsignificant level after exclusion of patients on antihypertensive medication ($P = 0.16$). Thus, difference in treatment rates between women and men might partly explain the sex difference seen in the predictive value of HASI. Other possible reasons why the predictive power of HASI was evident only in men but not women could have been that, compared to women, men showed a higher cardiovascular risk level in terms of smoking and drinking habits and their blood pressure level in the present study. However, even after adjustment of cardiovascular risk factors, the interaction term between men and women on the risk of cerebral infarction was still significant (**Figure 2**). It was difficult to answer whether the sex difference seen in prognostic accuracy was specific for HASI or for the study population. Further studies are needed to assess the prognostic significance for stroke.

Several studies have reported the prognostic significance of AASI for nonfatal[7] and fatal strokes,[2,6,7] but not for cardiac events. These studies[2,6,7] consistently demonstrated that AASI predicted stroke. In the Dublin Outcome Study[2] and in a population study in Copenhagen,[7] AASI was a stronger predictor of stroke in normotensive subjects than in hypertensive patients. The present study supports these previous observations.[2,7] Indeed, the prognostic value of HASI was significant in normotensive subjects (1.52, $P = 0.0006$), but not in hypertensive patients ($P > 0.61$). One possible explanation is that treatment to lower blood pressure might be a major confounder that weakens the association between the risk of stroke and HASI. In the present study, 70.9% of hypertensive patients were under antihypertensive medication. However, in untreated hypertensive patients, HASI was not predictive of cerebral infarction. Hypertension is one of the major causes of stroke. Among patients with such a major risk factor, the impact of HASI on cerebral infarction may be relatively reduced. As seen in **Figure 1**, hypertensive patients (irrespective of receiving antihypertensive medication) showed a much higher incidence of cerebral infarction compared to normotensive subjects, and were not affected by HASI. Thus, the prognostic significance of HASI may be limited to relatively healthy subjects. HASI may reflect mild or early atherosclerosis rather than advanced atherosclerosis.

The present study has several limitations. First, the present analysis was exclusively based on stroke, not on cardiac events. Second, middle-aged or older women made up the majority of the Ohasama participants. To some extent this imbalance in the age distribution might limit the generalizability of the current findings. Third, data on use of antiplatelet agents were not included. However, because of the low prevalence of history of heart disease (0.4%), the prevalence of patients taking antiplatelet agents is probably very small.

In conclusion, HASI derived from self-measurement of home blood pressure according to the same formula as the AASI was predictive of cerebral infarction independent of pulse pressure, mean arterial pressure, and day-by-day blood pressure variability in men and normotensive subjects recruited from a Japanese population. However, the predictive power of HASI was restricted to men and to normotensive subjects. Therefore, further population studies should be carried out in order to establish the predictive significance of HASI.

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Predictive Value for Mortality of the Double Product at Rest Obtained by Home Blood Pressure Measurement: The Ohasama Study

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BACKGROUND
To clarify whether the double product (DP) (product of systolic blood pressure (SBP) and pulse rate (PR)) at rest based on home blood pressure (HBP) measurement has prognostic value for mortality.

METHODS
HBP data of 2,583 participants from a Japanese general population (40% men) ≥35 years of age (mean, 59 years) without a history of cardiovascular disease (CVD) were obtained. The prognostic significance for a 1,000 mm Hg × beats/min elevation in the DP was determined by Cox proportional hazard regression analysis. The association between mortality and the DP was compared to that between mortality and the SBP or the PR using the likelihood ratio (LR) test.

RESULTS
During a mean follow-up of 12.0 years, 454 total deaths, 153 CVD deaths (85 cardiac diseases, 68 strokes), and 301 non-CVD deaths occurred. The DP was positively and significantly associated with total, CVD, cardiac, stroke, and non-CVD mortality. The LR test showed that the DP was more strongly associated with total mortality, mortality from cardiac disease, and non-CVD than SBP. Similarly, the DP was more strongly associated with total death, CVD death, and death from stroke than PR.

CONCLUSIONS
The home DP was significantly associated with mortality, and the LR test indicated that the association between the DP and mortality would be stronger than that between mortality and SBP or PR. These findings are preliminary, and further study is needed to confirm the usefulness of the DP in risk stratification.

Keywords: blood pressure; double product / rate pressure product; general population; home blood pressure measurement; hypertension; mortality

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It is widely recognized that high blood pressure (BP), especially high systolic BP (SBP), is a risk factor for cardiovascular disease (CVD).[1,2] Furthermore, several reports showed that a high pulse rate (PR) is a risk for CVD and non-CVD death.[3–7] The double product (DP) (or the rate pressure product), the product of SBP and PR, is known to be a marker of myocardial oxygen consumption[8] and is mainly used as an index of tolerance for exercise during rehabilitation or for evaluation of efficacy of drugs, such as diltiazem, that affect BP and PR simultaneously.[9] A previous study showed that the DP measured during exercise has prognostic value among patients with a history of angina pectoris, myocardial infarction, or congestive heart failure.[10] It was also shown that the DP obtained by 24-h ambulatory BP monitoring reflects silent myocardial ischemia.[11] In addition, recent studies reported that a high DP in the acute phase of stroke predicts poor outcome.[12,13] However, no previous studies have investigated whether the DP at rest based on home BP (HBP) measurement predicts long-term prognosis in the general population. The aim of the present study was to investigate whether the DP at rest is associated with mortality.

METHODS

Study population. The present study was a part of the longitudinal observational study of subjects who have been participating in our HBP measurement project in Ohasama, a rural

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community in the northern part of Japan, since 1987.[6,7,14–22] The study protocol was approved by the institutional review board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. Informed consent was obtained from each subject.

The socioeconomic and demographic characteristics of this region[14–20] and the details of the selection procedure of study populations have been described previously[21,22]. In brief, from 1988 until 1995, all 4,969 subjects ≥35 years old and living in four districts of Ohasama town were contacted. Subjects who were not at home during the normal working hours of the study nurses (n = 1,057) and those hospitalized (n = 166) or incapacitated (n = 94) were ineligible. Of the remaining 3,652 residents, 2,933 (80%) participated in baseline examinations and underwent follow-up. We excluded 205 participants because their HBP and PR values in the morning were the averages of <3 readings (3 days). This criterion was based on our previous observation that the HBP level obtained for the first 3 days was not significantly different from that obtained for the entire study period.[17] Of the remaining 2,728, 145 participants who had a previous history of CVD, including those with arrhythmia (sick sinus syndrome, second-degree or complete atrioventricular block, pacemaker implantation, atrial fibrillation, and atrial flutter) were excluded because the PR value might be affected by arrhythmia. Therefore, the study population consisted of 2,583 individuals.

Measurements of HBP and PR. Physicians and well-trained public health nurses conducted health education classes to teach subjects how to measure and record HBP and PR. After their ability to measure HBP was verified, subjects were asked to measure their own BPs and PRs once in the morning, in the sitting position, within 1 h after awakening and after ≥2 min of rest and to record the measurements for 4 weeks. When individuals were taking antihypertensive medications, morning BP and PR were measured before taking medications. Subjects were allowed to measure their own BP and PR ≥2 times on each occasion; however, the first measurement value, which was inevitably recorded in the log book, from each occasion was used for analysis to exclude subjects' selection biases. All subjects were instructed to hold their cuff-covered arms at heart level during HBP and PR measurements. These procedures were described in detail in our previous report[17] and followed the Japanese guidelines for HBP self-monitoring.[23]

BP measurement devices. HBP and PR were measured using the HEM401C (Omron Healthcare, Kyoto, Japan), a semiautomatic device based on the cuff-oscillometric principle, which generates a digital display of both SBP and diastolic BP.[24] The device met the criteria set by the Association for the Advancement of Medical Instrumentation.[25] A standard arm cuff was used for HBP measurements, because the subjects' arm circumferences were ≤34 cm.

Follow-up and outcome. Residency in Ohasama (as of 31 December 2004) was confirmed by the residents' registration cards. In Japan, these cards are considered accurate and reliable because they are used for pensions and social security benefits. Death certificates from the national mortality registry were reviewed and confirmed by comparison with medical records of Ohasama Hospital, which is the only hospital in the town and where >90% of residents undergo regular check-ups. End points considered in the present analysis were death from all causes, CVD (International Classification of Disease 10th Revision (ICD-10) codes "I") and non-CVD mortality, and mortality from stroke (ICD-10 code I6) and cardiac disorders (ICD-10 codes I05, I11, I21–I25, I34, I35, I38, I46–I50, I71, I74, I77, and I99). Thus, CVD mortality included mortality from all stroke and cardiac events. The characteristics of the causes of death in the Ohasama study are described elsewhere.[18]

Data collection. Information on smoking status, use of antihypertensive medication at baseline, and history of diabetes mellitus, hypercholesterolemia, and CVD including arrhythmia was obtained from questionnaires sent to each household at the time of the home BP and PR measurements and from the Ohasama Hospital's medical records, which included results of laboratory investigations performed at the time of annual health check-ups. Subjects using lipid-lowering drugs or those with serum cholesterol levels ≥5.68 mmol/l were considered to have hypercholesterolemia. Subjects with a fasting glucose level ≥7.0 mmol/l or a non-fasting glucose level ≥11.1 mmol/l, or those using insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus. The DP was calculated as SBP × PR.

Statistical analysis. The association between the DP, SBP, or PR and death was examined using Cox proportional hazards regression,[26] adjusted for age, sex, smoking status, the use of antihypertensive medication, and history of diabetes mellitus or hypercholesterolemia. The dependent variable in these analyses was the number of days from the date of the HBP and PR measurement to the date of death or censoring. Survivors were censored as of 31 December 2004. For nonparametric analyses, hazard ratios (HR) and 95% confidence intervals (CI) were estimated among categories of DP equally divided into five categories. For parametric analyses, HR and CI were estimated per 1,000 mm Hg × beats/min elevation in the DP. HRs and 95% CIs for SBP and PR were estimated per 10 mm Hg elevation and 10 beats/min elevation, respectively.

In a subgroup analysis, we included serum creatinine levels, a strong risk factor for CVD, as a confounding factor.

Secondary analyses were conducted using Cox models including the DP and SBP or PR to assess the relationship with mortality with simultaneous adjustment for each other. The likelihood ratio (LR) χ^2 test between the model containing a single parameter (DP, SBP, or PR) and the model containing two parameters (DP and SBP, DP and PR, or SBP and PR) was used to assess whether the additional index significantly improved the adequacy of the model. A significant LR χ^2 indicates that the parameter provides significantly more information.[27]

In addition, the subgroup of subjects that did not take antihypertensive medication was analyzed separately, because antihypertensive medication may influence BP, PR, or DP; thus, the influence of antihypertensive medication was eliminated.

RESULTS

The overall mean age of the study participants was 58.5 years, and the male:female ratio was 40:60. At baseline, of the 2,583 study subjects, 541 (21%) were classified as current or ex-smokers, 699 (27%) were treated with antihypertensive medication, 230 (9%) had a history of diabetes mellitus, and 666 (26%) had a history of hypercholesterolemia.

The mean duration of follow-up was 12.0 years. During follow-up, 454 died and 89 moved out of the region. Of the 454 deaths, 153 were CVD deaths; of these, 85 were deaths from cardiac diseases, and 68 were deaths from stroke. Stroke mortality included cerebral infarction (n = 38), intracerebral hemorrhage (n = 20), subarachnoid hemorrhage (n = 9), and other cerebrovascular cause (n = 1). Cardiac mortality included myocardial infarction (n = 34), heart failure (n = 20), sudden death (n = 6), chronic coronary heart disease (n = 5), arrhythmia (n = 5), and other cardiac disorders (n = 15). Non-CVD deaths (n = 301) resulted from neoplasms (n = 119), diseases of the respiratory system (n = 63), senility (n = 24), suicide (n = 21), diseases of the genitourinary system (n = 13), injuries (n = 26), diseases of the digestive system (n = 11), and other causes (n = 24).

Baseline SBP, diastolic BP, and DP were significantly higher in those who died than in those who did not (**Table 1**). Although there were no differences in PR levels between those who died and those who did not, age-adjusted PR of those who died was significantly higher than that of those who did not. SBP was significantly higher in those who died from CVD than in those who died from non-CVD causes. The analysis excluding subjects treated with antihypertensive medication showed a similar tendency (**Table 1**).

Table 1 | Baseline blood pressure values, pulse rate, the double product, and age

		Death		Death cause		CVD death	
	Overall	Dead	Survivor	CVD	Non-CVD	Stroke	Cardiac disease
All subjects							
N	2,583	454	2,129	153	301	68	85
Age	58.5 ± 12.5	69.6 ± 11.1**	56.1 ± 11.4	70.9 ± 11.6	69.0 ± 10.7	70.0 ± 10.9	71.6 ± 12.2
SBP (mm Hg)	124.0 ± 15.1	132.6 ± 16.7**	122.2 ± 14.1	135.2 ± 17.3*	131.2 ± 16.2	136.9 ± 17.7	133.9 ± 16.9
DBP (mm Hg)	74.7 ± 10.0	76.3 ± 10.5**	74.4 ± 9.8	76.8 ± 11.0	76.1 ± 10.2	78.5 ± 11.1	75.4 ± 10.8
PR (beats/min)	67.6 ± 7.8	67.4 ± 8.4	67.6 ± 7.6	66.8 ± 9.0	67.6 ± 8.1	66.2 ± 8.3	67.3 ± 9.5
DP (mm Hg × beats/min)	8,373.3 ± 1,369.1	8,922.4 ± 1,535.7**	8,256.2 ± 1,301.6	9,024.2 ± 1,603.8	8,870.7 ± 1,500.0	9,041.3 ± 1,458.2	9,010.5 ± 1,719.9
Age adjusted							
SBP (mm Hg)		127.0 ± 0.68**	123.4 ± 0.30	134.7 ± 1.3*	131.5 ± 0.91	137.2 ± 2.0	133.6 ± 1.8
DBP (mm Hg)		75.3 ± 0.50	74.6 ± 0.22	76.9 ± 0.85	76.1 ± 0.60	78.4 ± 1.3	75.5 ± 1.2
PR (beats/min)		68.7 ± 0.39**	67.3 ± 0.17	66.9 ± 0.68	67.6 ± 0.48	66.1 ± 1.1	67.4 ± 0.96
DP (mm Hg × beats/min)		8,710.1 ± 67.4**	8,301.4 ± 29.3	8,993.8 ± 122.7	8,886.1 ± 87.4	9,048.9 ± 195.6	9,004.4 ± 174.9
Subjects who did not take antihypertensive medication							
N	1,884	249	1,635	76	173	36	40
Age	55.6 ± 12.2	67.6 ± 12.3**	53.8 ± 11.1	68.9 ± 13.7	67.1 ± 11.7	68.4 ± 12.9	69.3 ± 14.6
SBP (mm Hg)	120.0 ± 13.4	128.2 ± 15.6**	118.8 ± 12.6	130.7 ± 16.6	127.0 ± 15.0	129.9 ± 15.5	131.4 ± 17.7
DBP (mm Hg)	73.0 ± 9.3	74.7 ± 10.0*	72.7 ± 9.2	75.4 ± 10.1	74.5 ± 10.0	75.6 ± 9.4	75.2 ± 10.9
PR (beats/min)	68.0 ± 7.4	67.7 ± 7.8	68.1 ± 7.3	68.0 ± 8.1	67.5 ± 7.6	67.3 ± 7.3	68.6 ± 8.8
DP (mm Hg × beats/min)	8,163.0 ± 1,258.1	8,667.6 ± 1,426.0**	8,086.2 ± 1,212.7	8,861.0 ± 1,420.9	8,582.7 ± 1,424.0	8,724.4 ± 1,318.6	8,984.0 ± 1,513.1
Age adjusted							
SBP (mm Hg)		123.5 ± 0.83**	119.5 ± 0.30	130.2 ± 1.7	127.3 ± 1.1	1,301 ± 2.7	131.2 ± 2.5
DBP (mm Hg)		73.9 ± 0.63	72.8 ± 0.23	75.4 ± 1.2	74.4 ± 0.76	75.5 ± 1.7	75.5 ± 1.6
PR (beats/min)		69.1 ± 0.49*	67.9 ± 0.18	68.0 ± 0.89	67.5 ± 0.59	67.2 ± 1.4	68.6 ± 1.3
DP (mm Hg × beats/min)		8,530.7 ± 84.0**	8,107.1 ± 30.9	8,831.6 ± 160.4	8,595.6 ± 106.2	8,732.5 ± 236.1	8,976.7 ± 224.0

Data are presented as mean ± s.d. Age adjusted data are presented as mean ± s.e.
CVD, cardiovascular disease; DBP, diastolic blood pressure; DP, double product; PR, pulse rate; SBP, systolic blood pressure.
*P < 0.05; **P < 0.01.