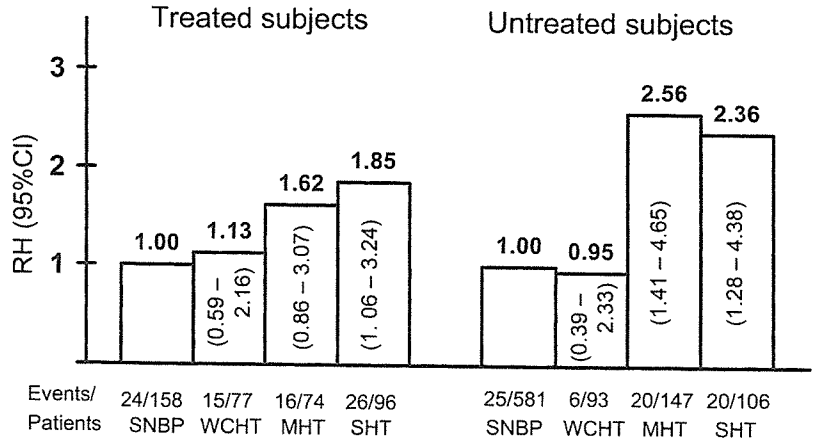


**Figure 3.** Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for risk of the composite of cardiovascular disease (CVD) mortality/stroke morbidity by use of antihypertensive treatment. Treated subjects, subjects treated using antihypertensive medication; Untreated subjects, subjects not treated using antihypertensive medication. **Numbers inside bars** indicate 95% CI. The SNBP group was treated as the reference category.

best of our knowledge, this is the first prospective study to reveal the risks associated with WCHT and MHT in a representative sample of the general population.

**Prognostic significance of MHT.** One smaller cohort study has reported poor prognosis in MHT detected by ambulatory BP monitoring compared with normotensive subjects (7). However, study subjects were limited to untreated men who were exactly 70 years of age with no history of cardiovascular disease, and WCHT was excluded from analysis. The present study is the first to report that MHT is related to increased cardiovascular risk among women and treated subjects, irrespective of the number of risk factors or cardiovascular complications. Importantly, even among subjects with a low cardiovascular risk profile, MHT is associated with a significantly greater risk of stroke and cardiovascular mortality. These results are consistent with a recent prospective study of hypertensive patients receiving antihypertensive medication, which showed that masked uncontrolled hypertension as detected by self-measured BP at home is associated with increased risk of cardiovascular events compared with sustained controlled hypertension (25). These results support the concept that BP measurements outside the clinical setting offer stronger predictive power for cardiovascular disease than casual BP (29) because this method allows multiple BP measurements outside the hospital, subtly reflects duration of action of antihypertensive drugs (26), is free of observer bias and the white-coat effect, and provides more reproducible information than casual BP measurements (1,2), although reproducibility of the condition of MHT remains to be investigated.

**Prognostic significance of WCHT.** The present results are consistent with some previous studies in that WCHT was associated with a more benign outcome than SHT (8–12). This is the first report to compare risk in WCHT with representative subjects displaying SNBP, and we showed that risk in WCHT does not differ significantly from that in SNBP after follow-up for 10 years. These results are again consistent with some previous smaller and shorter studies (8,11). However, given the 95% CI (0.76 to 2.14), small- to moderate-sized increases in risk remain

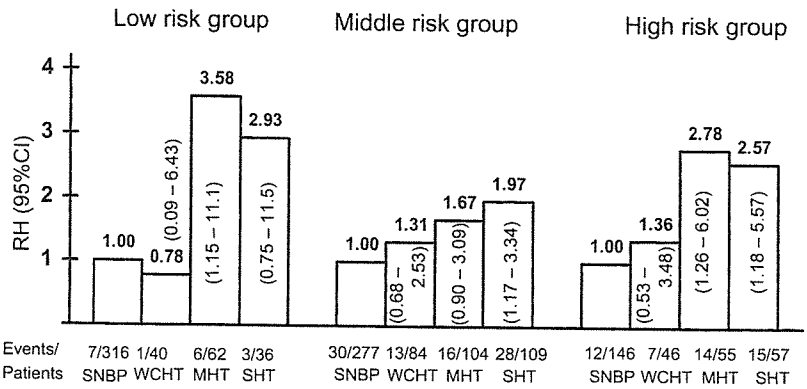


**Figure 4.** Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for risk of the composite of cardiovascular disease (CVD) mortality/stroke morbidity by CVD risk profile. Low-risk group, patients without history of CVD or diabetes and with no risk factors; Middle-risk group, patients without history of CVD or diabetes but with one to two risk factors; High-risk group, patients with history of CVD or diabetes or with three risk factors. **Numbers inside bars** indicate 95% CI. The SNBP group was treated as the reference category.

possible with WCHT as compared with SNBP. Actually, a prospective study (13) and some cross-sectional studies (6,30–32) have reported that WCHT could be associated with more advanced cardiovascular target organ damage compared with normotensive subjects. Thus, WCHT remains a condition warranting careful follow-up.

**Study limitations.** In this study, BPs measured at the beginning of the follow-up period were used because the objective of the study was to examine the risk of MHT and WCHT as defined according to initial baseline BP. Whether the results might differ for patients classified into subgroups according to levels obtained during follow-up remains yet to be investigated, particularly with regard to treated patients, because BP levels achieved by treatment offer the most relevant prognostic information (33).

In our study, two BP readings from a single visit were averaged for use as a measure of casual BP. In contrast, casual BP calculated on the basis of six readings (two readings from each of three visits) demonstrated that correlations between left ventricular mass and either casual or ambulatory BP became much stronger when readings were averaged over more than one visit (34). Future studies need to test whether the present findings will remain applicable when MHT and WCHT are defined according to repeated casual readings.

Casual and ambulatory BPs were measured using two different technical approaches in our study. However, mean differences in BP measurements between the auscultatory method and those using other devices were small (35), and all BP measuring devices have been validated formally according to the AAMI (20). These methods are thus unlikely to have resulted in misclassification of BP. In addition, marked differences exist in the epidemiologies of cardiovascular disease between Japan and the U.S. or European countries. Among Japanese, coronary artery disease is much less common, whereas stroke is more common than among white or black populations. Further research in other ethnic and cultural populations is needed to confirm the generalizability of our findings.

**Clinical implications and conclusions.** Masked hypertension represents a strong predictor of cardiovascular risk and was present in 16% of subjects without antihypertensive medication and 18% of those with antihypertensive medication. Our results thus suggest that 16 truly high-risk subjects of every 100 persons without antihypertensive medication may not be identified under conventional casual BP measurements but could be detected using ambulatory BP measurements, whereas 18 truly uncontrolled patients out of every 100 patients under antihypertensive medication may not be identified under casual BP measurements but could be detected using ambulatory BP measurements. Unless individuals with MHT are identified, they will remain untreated or inadequately controlled and might experience cardiovascular complications and target organ damage, with poor quality of life the eventual result. Unnecessary medical costs also will be incurred. This in turn suggests the possibility that detection and management of hypertension based on ambulatory BP could improve prognosis for at-risk populations. However, direct evidence from randomized controlled trials comparing ambulatory and casual BP-based management of hypertension on risk of cardiovascular outcomes is necessary to truly elucidate the clinical significance of ambulatory BP monitoring.

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# Ambulatory Blood Pressure and 10-Year Risk of Cardiovascular and Noncardiovascular Mortality

## The Ohasama Study

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*Abstract*—The objective of this study was to elucidate the long-term prognostic significance of ambulatory blood pressure. Ambulatory and casual blood pressure values were obtained from 1332 subjects (872 women and 460 men) aged ≥40 years from the general population of a rural Japanese community. Survival was then followed for 14 370 patient years and analyzed by a Cox hazard model adjusted for possible confounding factors. There were 72 cardiovascular deaths during the 10.8-year follow-up. The relationship between 24-hour systolic blood pressure and the cardiovascular mortality risk was U-shaped in the first 5 years, then changed to J-shaped over the rest of the 10.8-year follow-up. After censoring the first 2 years of data, the risk flattened until it again increased for the fifth quintile of 24-hour systolic blood pressure for the 10.8-year follow-up period. For 24-hour diastolic blood pressure, the J-shaped relationship remained unchanged, regardless of follow-up duration and censoring. Ambulatory systolic blood pressure values consistently showed stronger predictive power for cardiovascular mortality risk than did casual systolic blood pressure in the 10.8-year follow-up data, whereas such relationships became more marked after censoring the first 2 years. When nighttime and daytime systolic blood pressure values were simultaneously included in the same Cox model, only nighttime blood pressure significantly predicted the cardiovascular mortality risk for the 10.8-year follow-up data. We conclude that the relationship between ambulatory systolic blood pressure and cardiovascular mortality is not U-shaped or J-shaped, and that nighttime blood pressure has better prognostic value than daytime blood pressure. (***Hypertension.* 2005;45:240-245.**)

**Key Words:** blood pressure monitoring, ambulatory ■ cardiovascular diseases ■ prospective studies

Ambulatory blood pressure (BP) has been used widely to diagnose and evaluate hypertension and to monitor treatment in the clinical setting.[1,2] Moreover, ambulatory BP is known to provide more reproducible information than does casual BP for individual patients with hypertension,[3,4] and is more strongly correlated with target-organ damage than casual BP in hypertensive subjects. Furthermore, the international guidelines for hypertension have emphasized the usefulness of ambulatory BP.[5,6] However, in contrast to the plethora of evidence about casual BP, there is still a lack of data that address the long-term prognostic significance of ambulatory BP. Few longitudinal studies, after ≥10 years, have so far examined the relationship between 24-hour BP and prognosis. Since 1987, we have been conducting a prospective cohort study to investigate the relationship between ambulatory BP and survival in the general population of Ohasama, Japan (the Ohasama Study).[7–9] In a previous report, we presented the results from a 5.1-year follow-up period.[8] The objective of the present study was to determine the prognostic significance of ambulatory BP for cardiovascular mortality risk based on a longer follow-up period, of the same subjects, of >10 years.

## Methods

### Design

The background rationale, study population, and BP measurement of the Ohasama Study have been presented in detail previously.[7–9] 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, and all participants gave written informed consent.

### Study Population

Ambulatory BP data were obtained from 1542 subjects aged ≥40 years from the general population of a rural Japanese community.[8] The 1542 subjects were confirmed previously to be representative of the general Japanese population.[8] Of the 1542 subjects, the 1332

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(86%) who underwent casual BP measurement were the final study population.[8]

### Ambulatory BP Monitoring and Casual BP Measurement

Ambulatory BP was monitored every 30 minutes oscillometrically using an automatic device (ABPM-630; Nippon Colin) and was edited according to criteria described previously.[10] Next, 24-hour daytime (waking periods) and nighttime (sleeping periods) BP was calculated for each subject.[8] Casual BP was the mean of 2 consecutive readings measured by nurses or technicians with subjects in a seated position after resting for ≥2 minutes, using a fully automatic device (USM-700F; UEDA Electronic Works Co.), based on the Korotkoff sound technique. Both devices for ambulatory and casual BP have been validated previously[11,12] and meet the criteria of the Association for the Advancement of Medical Instrumentation.[13]

### Follow-Up and Outcomes

Primary and secondary outcomes were determined as mortality from cardiovascular disease and noncardiovascular disease, respectively (censor date September 30, 2002). We reviewed death certificates from the national mortality registry and confirmed the results by checking the medical records of Ohasama Hospital, which is the only hospital in the town, and where >90% of subjects undergo regular check-ups. Most cases were admitted to Ohasama Hospital, where stroke was diagnosed by computed tomography or MRI of the brain. According to recommendations of the 10th Revision of the International Classification of Diseases (ICD-10) of the World Health Organization, cardiovascular death was defined as mortality related to disease of the circulatory system (ICD-10 code I). Stroke, heart disease, cancer, and respiratory diseases were ICD code I6, I other than I6, C00-D48, and J, respectively.

### Data Analysis

Association between the BP values and mortality was examined using the Cox proportional hazards regression model adjusted for age, gender, smoking status, use of antihypertensive medication at baseline, and history of cardiovascular disease, diabetes, and hypercholesterolemia.[9]

We used 4 durations of follow-up: the first analyses involved the first 5 years of follow-up from the baseline; the second involved 10.8 years of follow-up; the third involved 10.8 years of follow-up but excluded death within the first 2 years; and the fourth involved 10.8 years of follow-up but excluded death within the first 4 years. The rationale for exclusion of the first 2 years of follow-up was based on a previous study on casual BP,[14] which determined that removal of such data adjusted the reverse-causality bias supposedly derived from the poor health conditions of subjects with lower BP.[14-17]

Data represent mean±SD. Differences at $P<0.05$ were considered statistically significant. All statistical analyses were conducted using SAS version 8.2 software (SAS Institute).

## Results

### Clinical Characteristics at Baseline

The mean age of the 1332 participants was 61.8±9.9 years. Of those, 460 (34.5%) were male, 416 (31.2%) were overweight (body mass index ≥25 kg/m$^2$), 405 (30.4%) were taking antihypertensive medication, 272 (20.4%) were current or past smokers, 217 (16.3%) had hypercholesterolemia, 232 (17.4%) had diabetes mellitus, and 75 (5.6%) experienced previous cardiovascular disease. The mean duration of ambulatory BP monitoring was 22.3±2.3 hours. The 24-hour daytime and nighttime BP values were 123.3±13.0/72.0±7.7, 128.9±13.9/76.1±8.4, and 112.3±14.4/64.1±8.1 mm Hg, respectively, and were significantly lower than the casual systolic and diastolic BP values (131.2±18.5 and74.1±11.3 mm Hg, respectively; both $P<0.001$).

### Follow-Up and Outcomes

The mean duration of follow-up was 10.8±2.9 (maximum 14.3) years. Of the 1332 study subjects, 26 (2.0%) moved away or were lost to follow-up. The total number of patient years was 14 370. Cardiovascular and noncardiovascular death occurred in 72 and 142 subjects (5.0 and 9.9 deaths per 1000 person years), respectively. Among the 72 cardiovascular deaths, 37 were from stroke, and 35 were from heart disease. Among the 142 noncardiovascular deaths, the most common cause was cancer (61 deaths), followed by diseases of the respiratory system (26 deaths).

Of the 72 cardiovascular deaths, the 10 who died in the first 2 years of follow-up tended to have lower baseline 24-hour and casual systolic BP values than the remaining cardiovascular victims; the differences and 95% confidence interval (CI) were on average 9.3 mm Hg (−0.18≈18.8; $P=0.05$) for 24-hour systolic BP and 10.3 mm Hg (−2.28≈22.9; $P=0.10$) for casual systolic BP. The differences and 95% CI between cardiovascular disease victims in the first 4 years (n=18) and the remaining cardiovascular disease victims were 4.7 mm Hg (−2.98≈12.4; $P=0.23$) for 24-hour systolic BP and 6.7 mm Hg (−3.42≈16.8; $P=0.23$) for casual systolic BP. Among the 142 noncardiovascular disease victims, there were rather small differences in mean ambulatory and casual systolic BP between those who died in the first 2 years (n=10) and the remaining noncardiovascular disease victims. The differences were on average −2.2 mm Hg (−11.3≈6.92; $P=0.60$) for 24-hour systolic BP and 0.6 mm Hg (−13.1≈14.3; $P=0.93$) for casual systolic BP. For diastolic 24-hour and casual BP, the differences in BP values between subjects who died in the first 2 years of follow-up and the remaining victims were not statistically significant, regardless of cardiovascular or noncardiovascular death (all $P>0.2$).

### Cardiovascular Mortality (Nonparametric Analyses)

In the first 5 years of follow-up, a so-called U-shaped relationship was observed between 24-hour ambulatory systolic BP and the risk of the cardiovascular mortality (Figure 1a). When the follow-up period was extended to 10.8 years (up to 14.3 years), the relationship between 24-hour systolic BP and risk changed from a U-shaped to a J-shaped relationship (Figure 1b). The highest quintiles of 24-hour ambulatory systolic and diastolic BP and casual systolic BP were associated with a significantly increased risk of cardiovascular mortality. After censoring deaths in the first 2 years, the risks for the highest quintiles became more prominent, and the risks for lower quintiles of systolic 24-hour BP were reduced (Figure 1c). Censoring of death in the first 4 years did not change the results (data not shown). The other BP values, except for casual diastolic BP, showed similar results (Figure 1b and 1c).

### Cardiovascular Mortality (Parametric Analyses)

In the first 5 years of follow-up, only nighttime BP values were associated with cardiovascular mortality risk (Table). In

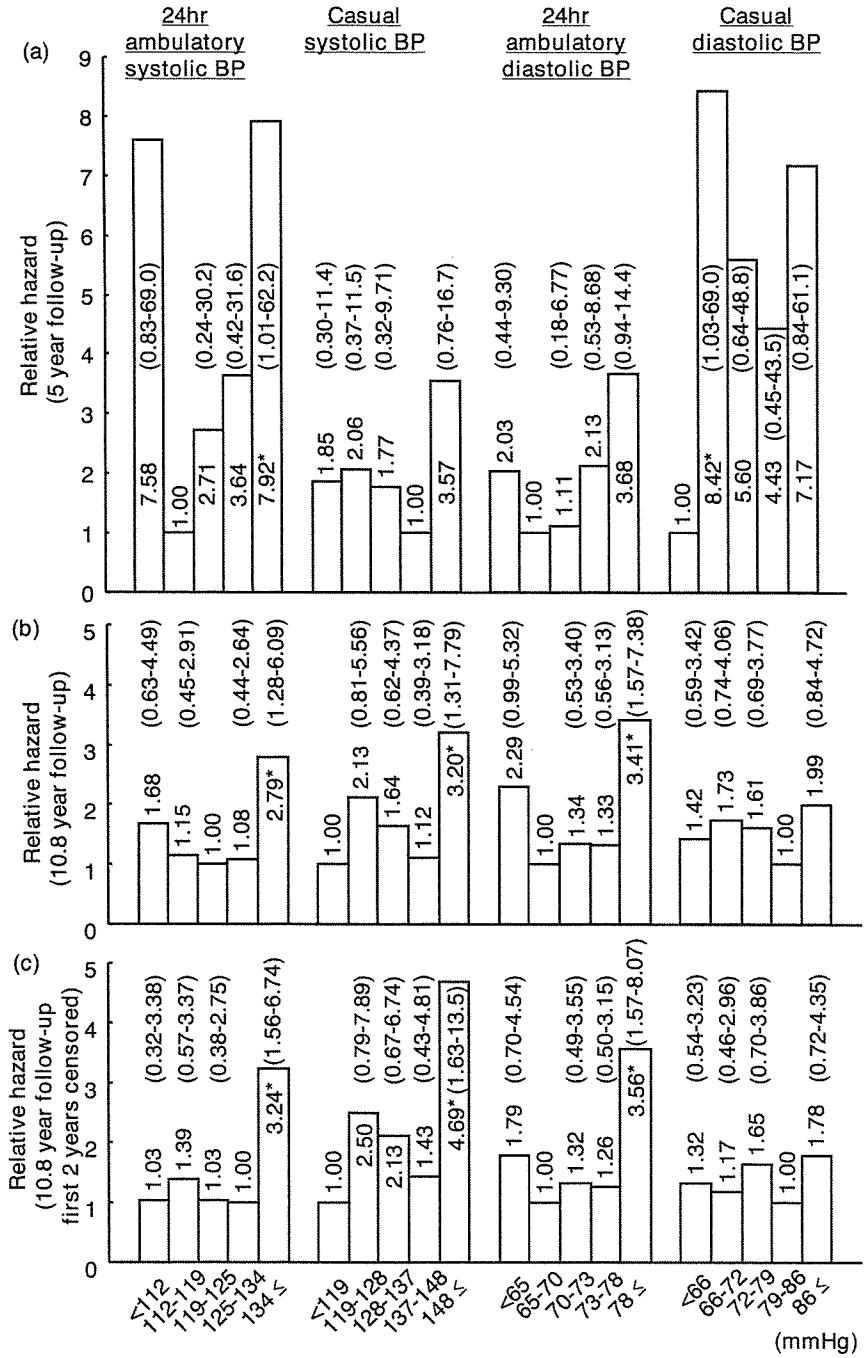


**Figure 1.** RHs and 95% CIs (in parentheses) for cardiovascular mortality adjusted for gender, age, antihypertensive medication, smoking habit, hypercholesterolemia, diabetes mellitus, and past history of cardiovascular disease during 5-year follow-up (a), 10.8-year follow-up (b), and 10.8-year follow-up (c) after censoring of death in the first 2 years. *$P<0.05$.

the 10.8 years of follow-up, the risk of cardiovascular mortality significantly increased, with an increase in BP values other than casual systolic, casual diastolic, 24-hour diastolic, and daytime diastolic BP (Table). After censoring of death in the first 2 years, the relative hazards (RHs) of cardiovascular mortality with all BP values tended to be higher; however, casual, 24-hour, and daytime diastolic BP were not significantly associated with cardiovascular mortality (Table). The effect of censoring the first 4 years of data on the elevation of RH was similar to that of the 2 years of censoring (Table). No significant interaction was observed between antihypertensive treatment and BP values on the risk of cardiovascular mortality in the first 10.8 years of follow-up (all $P>0.05$).

When 24-hour and casual systolic values were simultaneously included into a Cox model of the 10.8 years of follow-up, only 24-hour systolic BP was significantly related to the cardiovascular mortality risk: the RHs (95% CI) with 10-mm Hg increments in BP values were 1.28 (1.05≈1.55) for 24-hour systolic and 1.06 (0.93≈1.21) for casual systolic. Furthermore, after removal of 24-hour systolic BP from the model, −2log likelihood (ie, "goodness of model fit") was significantly impaired ($P=0.02$), whereas removal of casual systolic BP from the model did not change the goodness of

**RHs (95% CIs) for BP Values as a Continuous Variable**

| Duration of Follow-Up | 5-Year Follow-Up | 10.8-Year Follow-Up | 10.8-Year Follow-Up (First 2 Years Censored) | 10.8-Year Follow-Up (First 4 Years Censored) |
|---|---|---|---|---|
| Cardiovascular death | | | | |
| Death, No. | 23 | 72 | 62 | 54 |
| Systolic BP | | | | |
| 24-hour | 1.31 (0.96–1.77) | 1.32 (1.10–1.58)† | 1.45 (1.19–1.75)‡ | 1.46 (1.18–1.80)‡ |
| Daytime | 1.20 (0.91–1.59) | 1.23 (1.05–1.46)* | 1.33 (1.12–1.59)† | 1.34 (1.10–1.62)† |
| Nighttime | 1.39 (1.05–1.85)* | 1.34 (1.14–1.59)‡ | 1.45 (1.21–1.73)‡ | 1.48 (1.22–1.80)‡ |
| Casual | 1.08 (0.87–1.34) | 1.12 (0.99–1.27) | 1.18 (1.04–1.34)* | 1.19 (1.04–1.36)* |
| Diastolic BP | | | | |
| 24-hour | 1.22 (0.94–1.60) | 1.13 (0.97–1.33) | 1.20 (1.01–1.41)* | 1.18 (0.98–1.42) |
| Daytime | 1.14 (0.89–1.45) | 1.10 (0.95–1.26) | 1.15 (0.99–1.34) | 1.13 (0.96–1.34) |
| Nighttime | 1.31 (1.02–1.68)* | 1.19 (1.02–1.38)* | 1.24 (1.05–1.46)* | 1.24 (1.04–1.48)* |
| Casual | 1.16 (0.97–1.39) | 1.02 (0.92–1.13) | 1.02 (0.92–1.14) | 1.00 (0.89–1.12) |
| Noncardiovascular death | | | | |
| Death, No. | 35 | 142 | 132 | 113 |
| Systolic BP | | | | |
| 24-hour | 0.94 (0.72–1.22) | 0.95 (0.83–1.09) | 0.94 (0.82–1.08) | 0.91 (0.78–1.07) |
| Daytime | 0.89 (0.70–1.15) | 0.95 (0.84–1.08) | 0.95 (0.84–1.08) | 0.94 (0.81–1.08) |
| Nighttime | 1.08 (0.86–1.37) | 1.00 (0.88–1.13) | 0.98 (0.86–1.11) | 0.94 (0.82–1.09) |
| Casual | 1.02 (0.85–1.23) | 0.98 (0.90–1.08) | 0.98 (0.89–1.08) | 0.97 (0.87–1.07) |
| Diastolic BP | | | | |
| 24-hour | 0.83 (0.65–1.06) | 0.90 (0.80–1.01) | 0.90 (0.79–1.01) | 0.88 (0.77–1.01) |
| Daytime | 0.84 (0.67–1.04) | 0.92 (0.83–1.02) | 0.93 (0.83–1.03) | 0.91 (0.81–1.03) |
| Nighttime | 0.94 (0.75–1.17) | 0.93 (0.83–1.04) | 0.92 (0.82–1.03) | 0.90 (0.79–1.03) |
| Casual | 0.98 (0.84–1.14) | 0.97 (0.91–1.05) | 0.98 (0.91–1.06) | 0.97 (0.90–1.06) |

RH (95% CIs) indicated the risk associated with a 10-mm Hg and 5-mm Hg increase in systolic and diastolic BP, respectively. RHs were adjusted for sex, age, antihypertensive medication, smoking status, hypercholesterolemia, diabetes mellitus, and past history of cardiovascular disease.

*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

model fit ($P=0.4$). These results were more obvious after censoring of the first 2 or 4 years: all $P<0.005$ when ambulatory BP was removed; all $P>0.2$ when casual BP was removed. In addition, these results were almost identical for the other ambulatory BP values other than 24-hour or daytime diastolic BP values, which were not associated with cardiovascular mortality after adjusting casual BP.

When daytime and nighttime systolic ambulatory BP values were simultaneously included into a Cox model of 10.8 years follow-up, only nighttime systolic BP was significantly related to the cardiovascular mortality risk: the RHs (95% CI) with 10-mm Hg increments in BP values were 1.32 (1.06≈1.64) for nighttime systolic and 1.03 (0.83≈1.29) for daytime systolic BP. Furthermore, removal of nighttime systolic BP from the model of 10.8 years of follow-up significantly impaired the goodness of model fit ($P=0.02$), whereas removal of daytime systolic BP from the model did not change the goodness of model fit ($P=0.8$). After censoring of the first 2 or 4 years, these results were more obvious: all $P<0.01$ when nighttime systolic BP was removed; all $P>0.5$ when daytime systolic BP was removed. For diastolic BP values, these results were similar but not significant.

### Noncardiovascular Mortality

In the nonparametric analyses, the lowest quintile of 24-hour and daytime diastolic BP values was associated with a significantly increased risk of noncardiovascular mortality, regardless of follow-up period or censoring of death (Figure 2). This tendency did not change after censoring of the first 4 or 6 years (data not shown). The other BP values showed inconsistent or no association with noncardiovascular mortality. In the parametric analyses, decreases in BP values tended to be related to noncardiovascular death risks but not statistically significantly (Table). Death by cancer, which was the leading cause of noncardiovascular death, was also significantly related to lower levels of 24-hour ambulatory BP (RH, 0.76; 95% CI, 0.63≈0.92; $P=0.005$ for each 5 mm Hg) and casual diastolic BP (RH, 0.86; 95% CI, 0.76≈0.96; $P=0.008$ for each 5 mm Hg) in the 10.8-year follow-up. After censoring of the first 2 or 4 years, the significant relationship was maintained (all $P<0.02$). The other BP values, except for ambulatory and casual systolic BP, produced almost identical results (data not shown).

## Discussion

Several meta-analyses of prospective observational cohort studies[18–19] and randomized clinical trials[20] based on casual

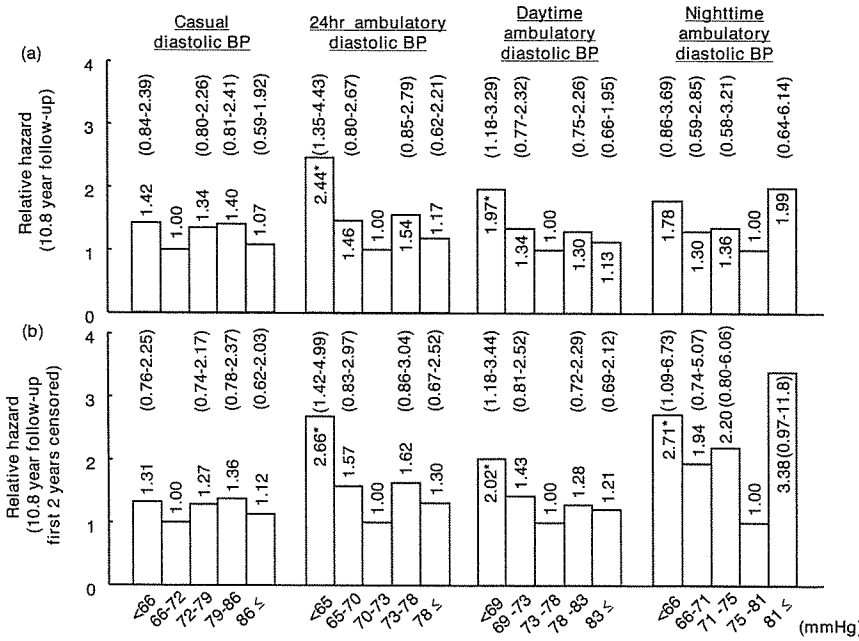


**Figure 2.** RHs and 95% CIs (in parentheses) for noncardiovascular mortality adjusted for gender, age, antihypertensive medication, smoking, hypercholesterolemia, diabetes mellitus, and past history of cardiovascular disease during 10.8-year follow-up (a), and 10.8-year follow-up (b) after censoring of death in the first 2 years. *$P<0.05$.

BP have concluded that the relationship between casual BP and cardiovascular mortality is essentially linear. Ambulatory BP has also been suggested to have a positively linear or curvilinear relationship with cardiovascular mortality and morbidity.[21–24] This may be partially supported by the observation noted in the present study that the increased risk for cardiovascular mortality at lower BP was reduced after censoring of death in the first several years to adjust the reverse-causality bias supposedly derived from the poor health conditions of subjects with lower BP.[14–17]

In the present study, cardiovascular victims in the first 2 years of follow-up tended to have lower baseline systolic BP values than the remaining cardiovascular victims. However, the magnitude of the BP difference between the cardiovascular victims in the first 4 years of follow-up and those after the 4 years was lower. Furthermore, the effect of the 2-year censoring on the RH of cardiovascular mortality was similar to that of the 4-year censoring (Table). These results suggest that 2-year censoring is an appropriate period with which to exclude reverse-causality bias effectively without losing statistical power.

After adjustment of the reverse-causality by censoring of the first several years of follow-up, we found a stronger RH of cardiovascular mortality with ambulatory BP compared with those of previous studies in which censoring was not conducted.[21–23] For example, the RH (95% CI) of cardiovascular mortality with a 10 mm Hg increase in the 24-hour systolic BP before censoring of the first several years was only 1.32 (1.10≈1.58), which is very similar to that observed in the Syst-Eur Trial,[21] in which censoring of the first several years was not conducted (RH, 1.34 [1.03≈1.75]). In the present study, censoring of death in the first 2 years produced an enhanced RH of 1.45 (1.19≈1.75).

There is a growing body of evidence,[21–24] including our previous reports,[8,9,25] that ambulatory BP provides better prognostic value than casual BP, although the median follow-up of all these reports was <10 years. In the present study, we validated the previous findings using data from long-term follow-up (ie, >10 years). We also found that censoring of the first several years made the superiority of ambulatory BP to casual BP more marked.

Although daytime BP has been reported to be a good predictor of outcomes,[8,21–25] some studies have shown nighttime BP to be a stronger predictor of cardiovascular mortality.[21,26] The Syst-Eur Trial[21] found that only nighttime BP was a significant predictor of cardiovascular mortality the among placebo and total groups when daytime and nighttime BP were included in the same Cox model. This previous finding was confirmed with the longer follow-up period and censoring of the first several years in the present study.

For noncardiovascular mortality, we observed an increased risk in lower BP values regardless of follow-up period and censoring. A deterioration in general health is a possible mechanism.[17] Another possibility is that low BP is mediated by less activity. In fact, in the present study, the association between low BP and noncardiovascular mortality was observed only for 24-hour and daytime ambulatory diastolic BP values, which were measured under unrestricted physical activity, and was not observed for casual and nighttime ambulatory BP values, which were measured under fixed conditions and during sleep, respectively. In the present study, we also observed an inverse association between cancer death risk and diastolic BP values, regardless of censoring of the first several years, supporting a previous study[27] but not all.[28,29] Further studies are required to clarify this controversy.

## Perspectives

We conclude that in the general Japanese population, ambulatory systolic BP predicts cardiovascular mortality risk after correcting for reverse-causality bias. In addition, nighttime BP is a stronger predictor of cardiovascular mortality than

daytime BP. The present study further demonstrated the better prognostic value of ambulatory BP than casual BP, using long-term follow-up data from >10 years and censoring of the first several years.

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# Determinants of the Second Derivative of the Finger Photoplethysmogram and Brachial–Ankle Pulse-Wave Velocity: The Ohasama Study

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**Background:** We examined different characteristics of the second derivative of the finger photoplethysmogram (SDPTG) and brachial–ankle pulse wave velocity (BAPWV) for assessing arterial function in a large general population, along with the alteration of SDPTG in hypertension.

**Methods:** Finger SDPTG and BAPWV were measured in 848 (544 normotensive and 304 untreated hypertensive) subjects 34 to 88 years of age. For assessing SDPTG, we calculated the B:A and D:A ratios and the aging index (AGI), based on the height of the wave components. Using univariate and multivariate analyses, determinants of SDPTG indices and BAPWV as well as differences between normotensive and hypertensive subjects were evaluated.

**Results:** We found that BAPWV was independently and positively correlated with age, blood pressure (BP), heart rate (HR), and hemoglobin $A_{1c}$. The D:A ratio and AGI showed a positive and the B:A ratio a negative independent correlation with age and BP. In contrast, the D:A ratio and AGI showed a negative and the B:A ratio a positive correlation with HR. The SDPTG indices, but not BAPWV, were independently associated with gender. The multivariate-adjusted D:A ratio, AGI, and BAPWV were significantly higher and the adjusted B:A ratio was lower in hypertensive than in normotensive subjects, and hypertensive subjects showed two-fold greater adjusted risks of having high D:A and low B:A ratios. The SDPTG indices and BAPWV were mildly correlated with each other in normotensive but not in untreated hypertensive subjects.

**Conclusion:** Although the SDPTG depends on various factors in a manner different from BAPWV, it may be useful for detecting vascular aging accelerated by hypertension. Am J Hypertens 2005;18:477–485 © 2005 American Journal of Hypertension, Ltd.

**Key Words:** Pulse wave, arteriosclerosis, aging, photoplethysmogram, hypertension.

The development of cardiovascular diseases is attributed to pathologic changes in the structure and function of arteries. The progression of arterial wall changes is accelerated by the presence of cardiovascular risk factors, including hypertension.[1–3] Recent technologic advances in assessing the properties of arterial walls may make it possible to identify individuals with cardiovascular risk earlier and apply therapeutic interventions for preventing complications.

So far, several noninvasive methods have been developed for quantitatively evaluating arterial wall distensibility using the pulse wave.[1] The measurement of pulse wave velocity (PWV) is one of the most representative methods for assessing arterial stiffness.[4–10] Another method for evaluating arterial properties uses the finger photoplethysmogram (PTG).[7,11–13] The second derivative of the finger photoplethysmogram (SDPTG) is a simple and convenient technique for pulse wave analysis and serves as a marker

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of vascular aging.[11] Previous studies have shown some associations of SDPTG with the existence of cardiovascular complications in hypertensive patients.[14,15] We recently demonstrated that SDPTG indices and carotid-femoral PWV (CFPWV) provide different information about arterial characteristics.[7] However, the clinical significance of SDPTG in the evaluation of arteriosclerosis for the general population still remains uncertain, because the determinants of SDPTG indices have not yet been fully evaluated. Moreover, it has not been clarified whether hypertension itself induces any alterations in SDPTG waveform independently of other cardiovascular risk.

In the present study, we conducted a cross-sectional population survey to establish the determinants of brachial–ankle PWV (BAPWV) and SDPTG indices in the general population and to clarify the differences in these arterial markers between normotensive and hypertensive subjects.

# Methods

## Subjects

The present study was based on a health examination survey performed on members of the population age 34 years or older and resident in the town of Ohasama, Japan. The geographic and demographic characteristics of Ohasama have been reported elsewhere.[16,17] Of 1739 individuals who underwent the health examination, 1190 completed both BAPWV and SDPTG measurements and both anthropometric and biochemical examinations. Subjects were excluded from the present analysis if they were taking antihypertensive medication ($n$ = 242). The study included 848 individuals (544 normotensive and 304 untreated hypertensive subjects). Of the 848 subjects, 30 (3.4%) had a past history of cardiovascular disease. The study protocol was approved by the Department of Health of the Ohasama Town Government. Informed consent was obtained from all subjects.

## Basic Examinations

Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with the subject sitting after at least 2 min of rest, using an automatic device based on the cuff-oscillometric method (HEM-907, Omron Healthcare, Kyoto, Japan). Pulse pressure (PP) and mean arterial pressure (MAP) were calculated according to the formulae: PP = SBP − DBP, and MAP = [SBP + (DBP × 2)]/3, respectively. Individual BP and heart rate (HR) were defined as the average of the two readings. Hypertension was defined as a SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg.[18] Body height and weight were measured in each subject. Blood samples were drawn to determine plasma total cholesterol, high-density lipoprotein (HDL) cholesterol, and hemoglobin $A_{1c}$ ($HbA_{1c}$).

Information concerning current smoking status, treatment of hypertension, hypercholesterolemia, and diabetes was obtained from questionnaires sent to the subjects before the examinations, and this information was confirmed by specifically trained medical staff on the day of the examinations.

## Measurement of SDPTG

After basic examinations, the finger PTG and SDPTG were recorded using a transducer placed on the cuticle on the second finger of the left hand. The signal was fed to an automatic analytical device FCP-4731 with the aid of a pulse-wave input box IB-70 (Fukuda Denshi, Tokyo, Japan). Details of the methodology for PTG and SDPTG measurements have been reported elsewhere.[7,11,19] Briefly, the PTG expresses changes in the absorbance of hemoglobin using a waveform and thus reflects regional blood flow changes (Fig. 1). The SDPTG is obtained to specify inflection points on PTG waves, and consists of five waves, $a$ to $e$. The $a$, $b$, $c$, $d$, and $e$ waves represent the initial positive, early negative, re-increasing, late re-decreasing, and diastolic positive waves, respectively. To describe these SDPTG components quantitatively, the height of each wave was measured from the baseline, the values above the baseline being positive and those under it negative, and was termed $a$ to $e$. As in our previous study,[7] absolute values for the height of the waves $a$, $b$, and $d$ were referred to as A, B, and D, respectively. The B:A ratio was calculated as the ratio of B to A, and the D:A ratio as the ratio of D to A. The aging index (AGI) was defined as $(b - c - d - e)/a$, according to a previous study by Takazawa et al.[11] In general, the B:A ratio, the D:A ratio, and the AGI have been considered as markers of the distensibility of large arteries, the intensity of the reflected wave from the periphery, and vascular aging, respectively.[7,11] The validation of this automatic device and the reproducibility of SDPTG indices have been previously reported.[11,14,19]

## Measurement of BAPWV

Subsequently to the SDPTG recording, BAPWV was measured, using an automatic device, Form PWV/ABI (Colin AT, Komaki, Japan). The methodology for measurement of BAPWV using this device has been described.[20,21] The device is equipped with four pneumatic pressure cuffs that are used for pulse volume wave recordings at both the arms and ankles. Instantaneous pressure changes in the cuffs were detected by transducers while the cuffs were inflated at 60 mm Hg (if DBP > 60 mm Hg) or 5 mm Hg lower than DBP (if DBP ≤ 60 mm Hg) for 9 sec. The oscillations of pressure signals, which express volume changes in the limb segment caused by BP changes, were recorded as pulse volume waves. Thus, the BAPWV was determined as the length of an arterial segment divided by the transit time of the pulse wave: PWV = $(D_1 - D_2)/t$, where $t$ is the time difference in the foot between the right brachial pulse wave and the right ankle pulse wave, $D_1$ is the distance between the suprasternal notch and the ankle, and $D_2$ is the distance between the suprasternal notch and the brachial site. $D_1 - D_2$ was estimated according to the

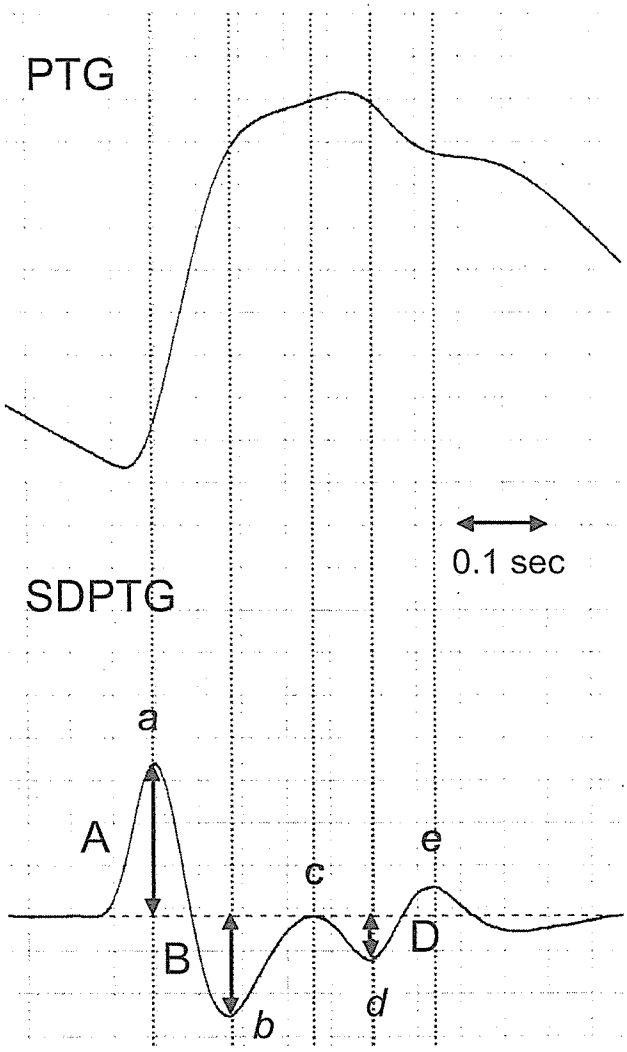


**FIG. 1.** Representative traces of finger photoplethysmogram (PTG) and second derivative of finger photoplethysmogram (SDPTG) waves. The SDPTG wave is comprised of five wave components *a* to *e:* the initial positive (*a*), early negative (*b*), re-increasing (*c*), late re-decreasing (*d*), and diastolic positive (*e*) waves. The B:A ratio was calculated as the ratio of the absolute value for the height of the *b* wave (B) to that of the *a* wave (A), and the D:A ratio was calculated as the ratio of the absolute value for the height of the *d* wave (D) to A. The aging index (AGI) was defined as $(b - c - d - e)/a$.

following regression equation: $D_1 - D_2$ (in cm) = 0.5934 × body height (in cm) + 14. The validity of the device has been confirmed and the reproducibility of BAPWV has been reported.[20–22]

### Statistical Analysis

Using univariate analysis, we first assessed the relationships between BAPWV and their potentially related variables. Univariate linear regression analysis and the Student *t* test were used for continuous variables and for categorical variables, respectively. Thereafter, multivariate stepwise linear regression analysis was performed using the following variables: age, gender, body height, body weight, SBP, HR, total cholesterol, HDL cholesterol, $HbA_{1c}$, current smoking status, treatment of hypercholesterolemia, and treatment of diabetes. Furthermore, using multiple stepwise logistic regression analysis, we examined factors related to an elevated BAPWV. Based on the BAPWV data in 848 subjects, those individuals whose BAPWV exceeded the mean + SD were defined as having a high BAPWV. The adjusted-odds ratios (OR) and 95% confidence intervals (CI) of cases with a high BAPWV were determined using potentially relating categorical variables, namely, age: younger (<60 years), older (≥60 years); gender: male, female; obesity (defined as BMI ≥ 25 kg/m$^2$, according to the criterion by Japan society for study of obesity): yes, no; current smoking: yes, no; hypertension: yes, no; HR, lower (<68/min), higher (≥68/min); hypercholesterolemia (plasma total cholesterol ≥ 240 mg/dL): yes, no; an elevated $HbA_{1c}$ (≥5.8%): yes, no; treatment of hypercholesterolemia: yes, no; treatment of diabetes: yes, no.

Similar univariate and multivariate analyses were performed on SDPTG indices, namely, B:A and D:A ratios and AGI. In multiple stepwise logistic regression analysis, we examined factors related to low B:A ratio, high D:A ratio, and high AGI because the results of a previous study indicate that, as arteriosclerosis progresses, the D:A ratio and AGI become higher and the B:A ratio lower.[11] Based on the data on SDPTG indices in all subjects, those subjects with a B:A ratio below the mean − SD, those with a D:A ratio above the mean + SD, and those with an AGI above the mean + SD were considered to have a low B:A ratio, a high D:A ratio, and a high AGI, respectively.

Comparisons between two groups were made using the Student *t* test or $\chi^2$ test when appropriate. Multivariate comparisons of BAPWV and SDPTG indices between normotensive and hypertensive subjects were performed by analysis of covariance (ANCOVA) using the same covariates as multiple linear regression analysis (except for SBP). Relationship between SDPTG indices and BAPWV was assessed by univariate and multivariate correlation analyses.

The data are expressed as the mean ± SD. Differences at $P < .05$ were accepted as being statistically significant. All statistical analyses were performed with SPSS software version 11.0 (SPSS Inc., Chicago, IL).

## Results

### Characteristics of Study Population

The study population consisted of 294 male and 554 female subjects and the mean age of the population was 60.8 ± 11.2 years (range, 34 to 88 years). Characteristics of normotensive and hypertensive subjects are given in Table 1. The hypertensive subjects were older and had higher BMI, HR, and total cholesterol level than the normotensive subjects. There were no differences in the gender ratio, $HbA_{1c}$, current smoking status, or treatment of hypercholesterolemia or diabetes between normotensive and hypertensive subjects. Table 2 shows the mean values

**Table 1.** Characteristics of the study population

| | All Subjects ($n$ = 848) | Normotensive Subjects ($n$ = 544) | Hypertensive Subjects ($n$ = 304) | $P$* |
|---|---|---|---|---|
| Age (y) | 60.8 ± 11.2 | 59.0 ± 11.8 | 63.9 ± 9.3 | <.001 |
| Gender (male/female) | 294/554 | 179/365 | 115/189 | .148 |
| Body height (cm) | 154.2 ± 8.8 | 154.7 ± 8.7 | 153.4 ± 8.9 | .030 |
| Body weight (kg) | 56.6 ± 9.9 | 56.0 ± 10.0 | 57.7 ± 9.6 | .016 |
| BMI (kg/m$^2$) | 23.7 ± 3.1 | 23.3 ± 3.1 | 24.5 ± 3.0 | <.001 |
| SBP (mm Hg) | 133.8 ± 19.4 | 122.5 ± 11.1 | 154.1 ± 13.8 | <.001 |
| DBP (mm Hg) | 74.5 ± 11.3 | 69.5 ± 8.5 | 83.3 ± 10.5 | <.001 |
| MAP (mm Hg) | 106.3 ± 15.7 | 99.1 ± 11.7 | 119.2 ± 13.7 | <.001 |
| PP (mm Hg) | 59.3 ± 14.2 | 52.9 ± 8.8 | 70.8 ± 14.8 | <.001 |
| HR (beats/min) | 73.9 ± 12.0 | 73.1 ± 11.0 | 75.4 ± 13.6 | .012 |
| Total cholesterol (mg/dL) | 204.1 ± 33.6 | 201.0 ± 34.2 | 209.6 ± 31.7 | <.001 |
| HDL cholesterol (mg/dL) | 61.0 ± 15.8 | 61.5 ± 16.1 | 59.9 ± 15.1 | .159 |
| $HbA_{1c}$ (%) | 5.02 ± 0.70 | 5.00 ± 0.72 | 5.04 ± 0.66 | .442 |
| Current smoker (%) | 14.4 | 14.2 | 14.8 | .796 |
| Treatment of hypercholesterolemia (%) | 4.2 | 4.6 | 3.6 | .499 |
| Treatment of diabetes (%) | 2.7 | 2.9 | 2.3 | .583 |

DBP = diastolic blood pressure; $HbA_{1c}$ = hemoglobin $A_{1c}$; HDL = high-density lipoprotein; HR = heart rate; MAP = mean arterial pressure; PP = pulse pressure; SBP = systolic blood pressure.
* $P$ values for comparison between normotensive subjects and hypertensive subjects.

of cardiovascular parameters, BAPWV, and SDPTG indices in the subjects.

## Factors Influencing BAPWV

In univariate linear regression analysis, the BAPWV was significantly and positively correlated with age and BP (Table 3). Among the BP components, SBP had the strongest correlation with BAPWV, with a correlation coefficient of 0.70. The HR was also positively correlated with BAPWV. There was no difference in BAPWV between male (1640 ± 366 cm/sec) and female (1633 ± 438 cm/sec) subjects ($P$ = .82). Although the BAPWV in the subjects treated for hypercholesterolemia ($n$ = 36) or diabetes ($n$ = 23) was not different from that in the remainder (1661 ± 375 $v$ 1635 ± 416 cm/sec, $P$ = .71; 1697 ± 388 $v$ 1634 ± 415 cm/sec, $P$ = .47), total cholesterol and $HbA_{1c}$ values were significantly and positively correlated with BAPWV.

**Table 2.** Cardiovascular parameters during pulse wave measurements in subjects resting in the supine position ($n$ = 848)

| | |
|---|---|
| SBP (mm Hg) | 141.7 ± 20.8 |
| DBP (mm Hg) | 84.4 ± 10.7 |
| MAP (mm Hg) | 106.3 ± 15.7 |
| PP (mm Hg) | 57.3 ± 13.6 |
| HR (beats/min) | 67.7 ± 11.2 |
| BAPWV (cm/sec) | 1636 ± 414 |
| B:A ratio | 0.467 ± 0.143 |
| D:A ratio | 0.371 ± 0.127 |
| AGI | −0.091 ± 0.302 |

BAPWV = brachial–ankle pulse wave velocity; other abbreviations as in Fig. 1 and Table 1.

As expected, the BAPWV in untreated hypertensive subjects was higher than that in normotensive subjects (Fig. 2). A significant BAPWV difference between hypertensive and normotensive subjects was also observed when adjusted for possibly relevant factors.

Multiple stepwise linear regression analysis revealed that SBP, age, HR, and $HbA_{1c}$ were independently and positively correlated with BAPWV, accounting for 66% of the variance (Table 4). There was no independent association between BAPWV and gender, body height, body weight, total cholesterol, HDL cholesterol, smoking status, or treatment of hypercholesterolemia or diabetes.

According to the multiple stepwise logistic regression analysis in which adjustment was performed using various confounding factors, older subjects showed an approximately 15 times greater risk of having a high BAPWV (≥2050 cm/sec) than younger subjects (Table 5). The presence of hypertension was significantly and independently associated with a greater risk of high BAPWV. There was also significantly greater likelihood of having high BAPWV for subjects with an elevated $HbA_{1c}$ compared with those with a normal $HbA_{1c}$.

## Factors Influencing SDPTG Indices

Univariate analysis showed that age, BP, and total cholesterol were correlated positively with the D:A ratio and AGI and negatively with the B:A ratio (Table 3). Body height and weight were significantly correlated with the SDPTG indices. Male subjects had a significantly lower AGI (−0.178 ± 0.325) and a higher B:A ratio (0.508 ± 0.153) than female subjects (−0.044 ± 0.278, $P$ < .001; and 0.446 ± 0.133, $P$ < .001, respectively). Heart rate was correlated positively with the B:A ratio and negatively

**Table 3.** Correlation of BAPWV or SDPTG indices with various factors in the studied subjects ($n$ = 848)

| Variable | BAPWV (cm/s) | | B:A ratio | | D:A ratio | | AGI | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *P* | *r* | *P* | *r* | *P* | *r* | *P* |
| Age (y) | 0.55 | <0.001 | −0.35 | <0.001 | 0.37 | <0.001 | 0.42 | <0.001 |
| Body height (cm) | −0.23 | <0.001 | 0.35 | <0.001 | −0.22 | <0.001 | −0.35 | <0.001 |
| Body weight (kg) | −0.13 | <0.001 | 0.22 | <0.001 | −0.13 | <0.001 | −0.21 | <0.001 |
| BMI (kg/m$^2$) | 0.03 | 0.436 | −0.02 | 0.479 | 0.03 | 0.461 | 0.04 | 0.290 |
| SBP (mm Hg) | 0.70 | <0.001 | −0.29 | <0.001 | 0.41 | <0.001 | 0.27 | <0.001 |
| DBP (mm Hg) | 0.59 | <0.001 | −0.16 | <0.001 | 0.39 | <0.001 | 0.19 | <0.001 |
| MAP (mm Hg) | 0.69 | <0.001 | −0.26 | <0.001 | 0.41 | <0.001 | 0.25 | <0.001 |
| PP (mm Hg) | 0.61 | <0.001 | −0.32 | <0.001 | 0.32 | <0.001 | 0.26 | <0.001 |
| HR (beats/min) | 0.28 | <0.001 | 0.13 | <0.001 | −0.12 | 0.001 | −0.03 | 0.454 |
| Total cholesterol (mg/dL) | 0.15 | <0.001 | −0.07 | 0.047 | 0.10 | 0.005 | 0.11 | 0.002 |
| HDL cholesterol (mg/dL) | −0.05 | 0.188 | 0.02 | 0.565 | −0.02 | 0.532 | −0.02 | 0.639 |
| $HbA_{1c}$ (%) | 0.19 | <0.001 | −0.02 | 0.643 | 0.07 | 0.060 | 0.05 | 0.166 |

$r$ = Pearson correlation coefficient; other abbreviations as in Tables 1 and 2.

with the D:A ratio. Subjects treated for hypercholesterolemia had a lower B:A ratio than the remainder (0.412 ± 0.136 *v* 0.470 ± 0.143, $P$ = .02). Although the relationship was not significant, $HbA_{1c}$ tended to be positively correlated with the D:A ratio.

Age, SBP, HR, and gender were common independent factors of the SDPTG indices (Table 4). Age and SBP were correlated positively with the D:A ratio and AGI and negatively with the B:A ratio. Conversely, HR was correlated negatively with the D:A ratio and AGI and positively with the B:A ratio. Body height was an additional independent factor relating to the B:A ratio. The SDPTG indices did not have any independent relationships with total cholesterol or $HbA_{1c}$ level, or treatment of hypercholesterolemia or diabetes. Compared with normotensive subjects, hypertensive subjects had a significantly higher D:A ratio and AGI, and a lower B:A ratio (Fig. 2). Even after adjustment for multiple confounding factors, these differences between both sets of subjects were also found to be statistically significant.

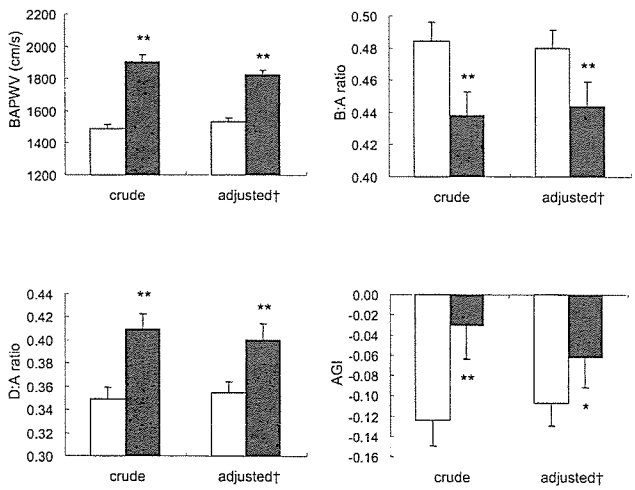


**FIG. 2.** Univariate and multivariate comparisons in BAPWV and SDPTG indices between normotensive subjects (□, n = 544) and hypertensive subjects (■, $n$ = 304). Data are mean ± SE. AGI = aging index of SDPTG. *$P$ < .05, **$P$ < .001 *v* values in normotensive subjects, based on Student $t$ test (for crude values) or analysis of covariance (for adjusted values). †Adjusted by age, gender, body height, body weight, heart rate, total cholesterol, HDL cholesterol, $HbA_{1c}$, cigarette smoking, treatment of hypercholesterolemia, and treatment of diabetes.

Multivariate logistic regression analysis revealed that older age was independently associated with greater risks of high AGI (≥0.22), high D:A ratio (≥0.50), and low B:A ratio (≤0.32) (Table 5). In addition, hypertensive subjects showed approximately twofold greater adjusted odds of having high D:A ratio or low B:A ratio compared with normotensive subjects. Neither hypercholesterolemia nor elevated $HbA_{1c}$ level was significantly associated with those risks. Male gender and higher HR were independent factors that were associated with a lesser risk of a low B:A ratio.

### Correlation Between SDPTG Indices and BAPWV

In normotensive subjects, the B:A ratio, D:A ratio and AGI were mildly correlated with BAPWV ($r$ = −0.26, 0.34, and 0.30, respectively; $P$ < .001 for all). When adjusted by age, a significant correlation was still observed only for the D:A ratio (partial $r$ = 0.12, $P$ = .006) but not for the B:A ratio or AGI. The correlation between the D:A ratio and BAPWV was no longer found after further adjustment by age and SBP. In hypertensive subjects, univariate analysis showed no significant correlations between SDPTG indices and BAPWV.

## Discussion

It has been suggested that the finger PTG provides useful information about arterial properties.[7,11–13] The SDPTG has been used primarily for assessing age-dependent

**Table 4.** Multivariate stepwise linear regression analysis of factors influencing BAPWV and SDPTG indices ($n$ = 848)

| Index | $\beta$ | $t$ | $P$ |
|---|---|---|---|
| BAPWV (cm/sec) | | | |
| SBP (mm Hg) | 0.54 | 25.14 | <.001 |
| Age (years) | 0.36 | 16.87 | <.001 |
| HR (bpm) | 0.22 | 10.68 | <.001 |
| $HbA_{1c}$ (%) | 0.08 | 3.87 | <.001 |
| B:A ratio | | | |
| Age (y) | −0.23 | −6.35 | <.001 |
| SBP (mm Hg) | −0.22 | −6.90 | <.001 |
| HR (beats/min) | 0.21 | 6.66 | <.001 |
| Gender (F = 0, M = 1) | 0.18 | 4.03 | <.001 |
| Body height (cm) | 0.12 | 2.59 | .010 |
| D:A ratio | | | |
| SBP (mm Hg) | 0.35 | 11.00 | <.001 |
| Age (y) | 0.24 | 7.68 | <.001 |
| HR (beats/min) | −0.18 | −5.87 | <.001 |
| Gender (F = 0, M = 1) | −0.12 | −3.88 | <.001 |
| AGI | | | |
| Age (y) | 0.37 | 11.66 | <.001 |
| Gender (F = 0, M = 1) | −0.25 | −8.09 | <.001 |
| SBP (mm Hg) | 0.16 | 5.04 | <.001 |
| HR (beats/min) | −0.09 | −2.94 | .003 |

$\beta$ = standardized partial regression coefficient; F = female; M = male; other abbreviations as in Tables 1 and 2.

BAPWV: model $R^2$ = 0.66, $F$ = 408.36, model probability $P < .001$; B:A ratio: model $R^2$ = 0.26, $F$ = 57.54, $P < .001$; D:A ratio: model $R^2$ = 0.26, $F$ = 74.10, $P < .001$; AGI: model $R^2$ = 0.25, $F$ = 71.73, $P < .001$.

changes in the vasculature.[11] The results of our previous study in treated hypertensive patients suggested associations of various cardiovascular risk factors other than age with SDPTG indices.[7] To our knowledge, the present study is the first to demonstrate, in a large population including normotensive and untreated hypertensive subjects, that the SDPTG is capable of detecting vascular changes induced by hypertension. Considering the results of a previous study showing a relationship between SDPTG and the existence of cardiovascular atherosclerotic complications in hypertensive patients,[14] the hypertension-induced SDPTG changes observed in the current study are likely to reflect some structural alterations in the arterial wall properties as well as the functional alterations.

Previous studies have postulated that a lower B:A ratio, a higher D:A ratio, and a higher AGI could be signs of arteriosclerosis.[11] The present analysis revealed that, even after adjustment for multiple factors, the B:A ratio was significantly lower and the D:A ratio and AGI were significantly higher in hypertensive subjects than in normotensive subjects. Moreover, multivariate logistic regression analysis showed that hypertensive subjects had greater risks of having low B:A and high D:A ratios than did normotensive subjects. These results accurately reflect the phenomenon that hypertension accelerates the progression of arteriosclerosis with age, and indicate clinical usefulness of the SDPTG.

The $a$ and $b$ waves in the SDPTG correspond to the early systolic component of the PTG, and the B:A ratio has been considered as a marker of the distensibility of large arteries, which is little affected by the reflection wave.[11,23] Therefore, the present study showing an independent correlation of BP with the B:A ratio indicates a decrease of arterial distensibility with increasing BP. In contrast, the $d$ wave corresponds to the late systolic component of the PTG, which is related to the reflected pulse wave traveling backward from peripheral sites. The D:A ratio is closely related to the late systolic pressure augmentation in the ascending aorta,[11] and therefore it is regarded as a marker of the intensity of wave reflection. The observed significant relationship between the D:A ratio and BP may be explained by the fact that BP influences the amplitude and timing of the reflected wave.[1] The AGI has been proposed specifically as a marker of vascular aging,[11] and actually in this study showed the strongest correlation with age among SDPTG indices. The observed positive correlation between BP and AGI, which is independent of age, also indicates an acceleration of vascular aging with increasing BP. Importantly, HR had significant and independent influences on SDPTG indices. Because the SDPTG depends not only on arterial properties but also on left ventricular function including stroke volume and ejection duration,[1] these cardiac factors may be responsible for the influence of HR on SDPTG. Gender was also an additional factor for the SDPTG indices, and a similar result has previously been reported.[11] Although the reason for the association of gender with SDPTG indices could not be determined by the present study, it should be noted that body height was significantly correlated with the SDPTG indices, and therefore the gender differences might be due in part to the correlation between body height and SDPTG indices. In fact, the significant effect of body height as a determinant of the travel time of the reflected wave and of the arterial wave reflections has already been demonstrated.[24] However, it is also possible that the gender differences in cardiac performance, arterial properties, and arterial wave reflection exist beyond the effect of body height alone,[25] because body height was not necessarily sufficient to fully explain the gender differences in SDPTG indices on the multivariate analyses.

The BAPWV was independently correlated with age, BP, and HR. The dependence of CFPWV on age and BP has been well established.[5–7,26] In contrast, the influence of HR on CFPWV has been controversial.[7–10] In the present study, $HbA_{1c}$ was also independently correlated with BAPWV and, for subjects with a high $HbA_{1c}$ ($\geq$5.8%), the adjusted risk of having high BAPWV was 4.6 times as high as that for those with a normal $HbA_{1c}$. Previous studies have shown a significant correlation between CFPWV and fasting serum glucose concentration[27,28] and a high CFPWV in diabetic patients.[28] Taken together with these results, the present findings may indicate an important effect of glucose metabolism on the wall properties of large arteries.[29]

It is of note that some physiologic factors showed

**Table 5.** Multivariate stepwise logistic regression analysis of factors associating with BAPWV and SDPTG levels above mean + 1 SD or below mean − 1 SD

| | Adjusted OR | 95% CI | *P* |
|---|---|---|---|
| BAPWV ≥ 2050 cm/sec | | | |
| Age | | | |
| Younger (<60 y) | 1.00 (Ref.) | | |
| Older (≥60 y) | 14.58 | 6.03–35.24 | <.001 |
| BP | | | |
| Normotension | 1.00 (Ref.) | | |
| Hypertension | 8.97 | 5.19–15.52 | <.001 |
| $HbA_{1c}$ | | | |
| Normal (<5.8%) | 1.00 (Ref.) | | |
| Elevated (≥5.8%) | 4.58 | 2.12–9.90 | <.001 |
| HR | | | |
| Lower (<68 beats/min) | 1.00 (Ref.) | | |
| Higher (≥68 beats/min) | 4.41 | 2.66–7.31 | <.001 |
| B:A ratio ≤ 0.32 | | | |
| Age | | | |
| Younger (<60 y) | 1.00 (Ref.) | | |
| Older (≥60 y) | 2.06 | 1.37–3.10 | .001 |
| BP | | | |
| Normotension | 1.00 (Ref.) | | |
| Hypertension | 1.91 | 1.35–2.69 | <.001 |
| Gender | | | |
| Female | 1.00 (Ref.) | | |
| Male | 0.51 | 0.35–0.74 | <.001 |
| HR | | | |
| Lower (<68 beats/min) | 1.00 (Ref.) | | |
| Higher (≥68 beats/min) | 0.35 | 0.24–0.52 | <.001 |
| D:A ratio ≥ 0.50 | | | |
| BP | | | |
| Normotension | 1.00 (Ref.) | | |
| Hypertension | 2.20 | 1.50–3.23 | <.001 |
| Age | | | |
| Younger (<60 y) | 1.00 (Ref.) | | |
| Older (≥60 y) | 1.68 | 1.10–2.56 | .016 |
| AGI ≥ 0.22 | | | |
| Age | | | |
| Younger (<60 y) | 1.00 (Ref.) | | |
| Older (≥60 y) | 2.85 | 1.79–4.53 | <.001 |

BP = blood pressure; CI = confidence interval; OR = odds ratio; Ref. = reference value; other abbreviations as in Tables 1 and 2.

different influences on SDPTG and BAPWV. For instance, HR was correlated positively with BAPWV, whereas it was correlated negatively with the D:A ratio and AGI. It is possible that such opposite effects of HR on SDPTG indices and BAPWV would affect the interpretation of results. Therefore, when various markers are used to assess arterial properties, some different interaction with their determinants should be considered.

There seem to be specific differences between PWV and SDPTG,[7,14] and the two methods may provide different information about arterial properties at central and peripheral sites. The present univariate analysis showed that SDPTG indices and BAPWV were correlated each other in normotensive subjects but not in untreated hypertensive subjects. In normotensive subjects, when age and BP were taken into account, SDPTG indices were not independently correlated with BAPWV. Some of these results agree with those of a previous study evaluating the correlation between CFPWV and the augmentation index as a measure of wave reflection.[30] The present findings suggest that SDPTG and BAPWV are regulated by different mechanisms, and they cannot be regarded as interchangeable markers of arterial stiffness. The lack of correlation between these two markers in hypertensive subjects may be explained by an expected independent relationship between SDPTG and hypertension-induced change in the wall properties of peripheral small arteries and arterioles. In addition, taken together with the results of our previous study in treated hypertensive subjects,[7] such wall change may be restored partly by medical therapy of hypertension.

A substantial number of studies have shown that CFPWV correlates with cardiovascular risk and outcome, whereas corresponding data on SDPTG are limited. Only a few cross-sectional studies have shown the association of SDPTG with cardiovascular complications, such as

atherosclerotic alterations[14] and left ventricular hypertrophy[15] in hypertensive patients. To clarify the different clinical significance of SDPTG and PWV, prospective and comparative evaluation of their prognostic value will be necessary.

There are some limitations to the present study. First, PWV was measured by the air-plethysmographic method between the brachial and ankle regions (BAPWV), instead of by the standard method between the carotid and femoral regions (CFPWV). The BAPWV depends on the wall properties of both central elastic arteries and peripheral muscular arteries, and therefore we cannot completely rule out the possibility that the presence of peripheral vascular disease might have affected the results of the current study. However, it seems unlikely because overall results were similar even if 10 subjects (1.2% of the total subjects) having a low ankle/brachial pressure index (<0.9) were excluded from the analysis. The PWV values for brachial–ankle regions observed in our study were higher than those for central regions reported previously in other studies; this is probably due in part to the dependence of BAPWV on the properties of peripheral muscular arteries and to methodologic differences in PWV measurements. Although BAPWV has been shown to provide some useful information on arterial stiffness,[4,20,21,31] it does not agree with CFPWV[21] and its prognostic value remains to be established. Second, for the classification of subjects in logistic analysis, arbitrary thresholds of BAPWV and SDPTG parameters were determined by a distribution criterion using the SD of the mean. More precise classification would require the future establishment of normal reference values for these parameters.

In conclusion, the multivariate analysis–based results of the present study in a large population including normotensive and untreated hypertensive subjects indicate that the SDPTG depends on various factors in a manner different from BAPWV. The SDPTG indices may be useful noninvasive measures of vascular aging accelerated by hypertension, even in untreated hypertensive patients.

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# White-Coat Hypertension as a Risk Factor for the Development of Home Hypertension

## *The Ohasama Study*

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**Background:** White-coat hypertension is a condition characterized by elevated blood pressure (BP) in medical settings combined with normal ambulatory-recorded BP or self-measured BP at home (home BP). However, it is unknown whether this condition represents a transient state in the development of hypertension outside medical settings.

**Methods:** We followed up 128 subjects with white-coat hypertension (home BP <135/85 mm Hg and office BP ≥140/90 mm Hg) for 8 years and compared the risk of progression with home hypertension (home BP ≥135/85 mm Hg or start of treatment with antihypertensive medication) with 649 sustained normotensive subjects (home BP <135/85 mm Hg and office BP <140/90 mm Hg) using data from population-based home BP measurement projects in Japan.

**Results:** During the 8-year follow-up period, 60 subjects (46.9%) with white-coat hypertension and 144 (22.2%) with sustained normotension progressed to home hypertension. The odds ratio of subjects with white-coat hypertension for progression to home hypertension (adjusted for possible confounding factors) was significantly higher than for subjects with sustained normotension (odds ratio, 2.86; $P<.001$). This association was observed independent of baseline home BP levels.

**Conclusion:** The results from the present 8-year follow-up study demonstrate that white-coat hypertension is a transitional condition to hypertension outside medical settings, suggesting that white-coat hypertension may carry a poor cardiovascular prognosis.

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WHITE-COAT HYPERtension (WCHT) is a condition characterized by an elevated blood pressure (BP) in a medical setting, combined with normal self-measured or ambulatory-recorded BP. In contrast, sustained hypertension is the presence of an elevated BP regardless of setting or circumstance.[1] However, the clinical relevance of WCHT has not been established, and it is controversial whether this condition involves an increased cardiovascular risk. Results from cross-sectional and prospective studies have been contradictory; some had found increased cardiovascular risk in patients with WCHT,[2-6] whereas others did not.[7-11]

It is also unknown whether this condition represents a transient state in the development of hypertension outside medical settings. One small and short-term study [12] reported a similar rate of transition to ambulatory hypertension (high BP during ambulatory readings) in subjects with sustained normotension (SNT) (normal BP during office and ambulatory readings) and in subjects with WCHT. Although 2 other studies[13,14] reported a high rate for the development of ambulatory hypertension in subjects with WCHT, these studies did not have normotensive control subjects for comparison. Thus, these studies[13,14] failed to demonstrate that WCHT was truly a transient state compared with SNT or that it posed a greater risk for progression to hypertension outside medical settings.

Self-measurements of BP at home (home BP measurements) make it possible to obtain multiple measurements over a long observation period under relatively controlled conditions.[15-17] It has been reported that multiple measurements eliminate observer bias and regression dilution bias; therefore, home BP measurements are more reliable than conventional BP measurements taken in medical settings (office BP).[15-17] A few studies have also reported that home BP measurements are better predictors of cerebrovascular and cardiovascular events compared with office BP.[18-20]

We have followed home BP measurements in a general population sample in Japan since 1987.[18,20-22] The present 8-year follow-up study, conducted with 777 normotensive subjects 40 years or older, aims to quantitatively determine the risk of transition to hypertension outside medical settings (at home) in subjects with WCHT and to compare the risk with that in subjects with SNT.

## METHODS

### DESIGN

This study was a part of a longitudinal observational study of subjects who have been participating in a BP measurement project in Ohasama, Japan. The socioeconomic and demographic characteristics of this region and full details of the project have been described elsewhere.[18,20-22] 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.

### DEFINITION OF HYPERTENSION

Based on several guidelines,[15-17] subjects with a home systolic BP of 135 mm Hg or higher and/or a home diastolic BP of 85 mm Hg or higher were classified as having high home BP, while others were classified as having normal home BP. Similarly, those who had office systolic/diastolic BP of 140/90 mm Hg or higher were classified as having high office BP. White-coat hypertension was defined as the occurrence of high office BP and normal home BP. Sustained normotension was defined as the occurrence of normal office BP and normal home BP. Development of home hypertension (hypertension based on home BP measurements) was defined as either progression to high home BP or start of treatment with antihypertensive medication.

### STUDY POPULATION

The selection of subjects for this study has been reported previously.[18] Briefly, the subjects were 40 years or older and were residents from 3 of 4 subdivisions of Ohasama (n=2716). Hospitalized persons (n=121) and persons with dementia or those who were bedridden (n=31) were excluded from the study. Individuals who worked out of town (n=575) were also excluded because the project involved consistent and routine ambulatory BP monitoring. Informed consent to participate in the study was given by 1957 of 1989 eligible individuals. Home BP measurements at baseline were conducted among 1913 subjects who collected their own BP data at least 3 days during the 4-week study period. This criterion was based on our previous observation that the average BP value obtained for the first 3 days was not significantly different from the values obtained for the entire study period.[21] We had previously confirmed that these 1913 subjects were a representative sample of the general population.[18] In the present analysis, to compare the risk for development of hypertension between WCHT and SNT, we excluded subjects who did not have office BP measured (n=124) or those who regularly used antihypertensive medication (n=582). We further excluded 235 subjects who had home hypertension at baseline. Thus, we followed up the remaining 972 participants.

### HOME BP MEASUREMENTS

Physicians and public health nurses instructed subjects on how to perform home BP measurements.[21] Subjects were asked to measure their BP every morning within 1 hour of waking, while seated and rested for more than 2 minutes, for 4 weeks. The home BP of an individual was defined as the mean of all measurements obtained for that person. The mean (SD [range]) number of baseline home BP measurements was 23.2 (6.8 [3-60]). The clinical utility of those methods of home BP measurements in this project has been previously reported.[18,20-22] The same procedure was used for the follow-up home BP measurements.

### OFFICE BP MEASUREMENTS

Annual health check-ups including BP measurements are available to all Japanese citizens 40 years or older once per year. Two consecutive measurements of BP are taken by a nurse or technician, using a semiautomatic device, after the subject has been seated at rest for at least 2 minutes.[21] The office (screening) BP was defined as the average of the 2 readings and was obtained in the same year as the initiation of home BP measurement.

### BP MEASURING DEVICE

Home BP was measured with the HEM401C (Omron Healthcare Co Ltd, Kyoto, Japan), a semiautomatic device, based on the cuff-oscillometric method that generates a digital display of systolic and diastolic BP at baseline. We also used the HEM401C and HEM747ICN devices for measurement at follow-up measurement. The screening BP was measured with an USM-700F (UEDA Electronic Works Co Ltd, Tokyo, Japan), a fully automatic device, based on the Korotkoff sound technique (a microphone method). The circumference of the arm was less than 34 cm in most cases, so we used a standard armcuff for both BP measurements. All devices used in this study were validated[23,24] and satisfied the criteria of the Association for the Advancement of Medical Instrumentation.[25]

### DATA COLLECTION AND ANALYSIS

Residential status in the town of Ohasama on October 31, 1999, was confirmed using the residents' registration cards, which were considered accurate and reliable because they are required for pension and social security benefits in Japan. Information on smoking status, obesity, family history of hypertension, and a history of hypercholesterolemia or diabetes mellitus was obtained from questionnaires sent to each household during the time of home BP measurements and from the medical records at Ohasama Hospital. Ohasama Hospital is the only hospital in the town, and more than 90% of the participants go there for regular checkups.

All data are given as mean (SD). The association between the baseline BP and the likelihood of progression to home hypertension was investigated using multiple logistic regression models, adjusted for age, sex, smoking status, obesity (body mass index [BMI; calculated as weight in kilograms divided by the square of height in meters] $\geq$25), family history of hypertension, and a history of hypercholesterolemia or diabetes mellitus. In all analyses, we treated the subjects with SNT as the reference group. Variables were compared using the unpaired, 2-tailed $t$ test, $\chi^2$ test, or analysis of variance, as appropriate. Differences of $P<.05$ were considered statistically significant. All analyses were conducted using the SAS package (version 8.2; SAS Institute Inc, Cary, NC).

## RESULTS

### FOLLOW-UP

Among the 972 subjects with WCHT or SNT, who did not take antihypertensive medication at the time of baseline sur-