Hypertension

Prognosis of "Masked" Hypertension and "White-Coat" Hypertension Detected by 24-h Ambulatory Blood Pressure Monitoring

10-Year Follow-Up From the Ohasama Study

Takayoshi Ohkubo, MD, PHD,*§‖ Masahiro Kikuya, MD, PHD,*§ Hirohito Metoki, MD,†§‖
Kei Asayama, MD,†§ Taku Obara, MS,†§ Junichiro Hashimoto, MD, PHD,*§‖
Kazuhito Totsune, MD, PHD,†§‖ Haruhisa Hoshi, MD, PHD,¶ Hiroshi Satoh, MD, PHD,‡§‖
Yutaka Imai, MD, PHD†§‖

Sendai and Iwate, Japan

OBJECTIVES	We sought to investigate the prognosis in subjects with "white-coat" hypertension (WCHT) and "masked" hypertension (MHT), in which blood pressure (BP) is lower in clinical measurements than during ambulatory monitoring.
BACKGROUND	The prognostic significance of WCHT remains controversial, and little is known about MHT.
METHODS	We obtained 24-h ambulatory BP and "casual" BP (i.e., obtained in clinical scenarios) values from 1,332 subjects (872 women, 460 men) ≥40 years old in a representative sample of the general population of a Japanese community. Survival and stroke morbidity were then followed up for a mean duration of 10 years.
RESULTS	Composite risk of cardiovascular mortality and stroke morbidity examined using a Cox proportional hazards regression model for subjects with WCHT (casual BP ≥140/90 mm Hg, daytime BP <135/85 mm Hg; relative hazards [RH])1.28; 95% confidence interval [CI] 0.76 to 2.14) was no different from risk for subjects with sustained normal BP (casual BP <140/90 mm Hg, daytime BP <135/85 mm Hg). However, risk was significantly higher for subjects with MHT (casual BP <140/90 mm Hg, daytime BP ≥135/85 mm Hg; RH 2.13; 95% CI 1.38 to 3.29) or sustained hypertension (casual BP ≥140/90 mm Hg, daytime BP ≥135/85 mm Hg; RH 2.26; 95% CI 1.49 to 3.41) than for subjects with sustained normal BP. Similar findings were observed for cardiovascular mortality and stroke morbidity among subgroups by gender, use of antihypertensive medication, and risk factor level (all p for heterogeneity >0.2).
CONCLUSIONS	Conventional BP measurements may not identify some individuals at high or low risk, but these people may be identifiable by the use of ambulatory BP. (J Am Coll Cardiol 2005;46: 508–15) © 2005 by the American College of Cardiology Foundation

The utility of ambulatory blood pressure (BP) monitoring has been recognized, and the practice has been adopted

widely (1,2). This method of measuring BP evaluates BP during the daily life of the patient and has revealed a

subgroup of individuals who display elevated BP in clinical scenarios (i.e., "casual" BP) but normal ambulatory BP. The term "white-coat" hypertension (WCHT) has been used to describe this phenomenon (3). Another subgroup has recently gained attention that comprises individuals with elevated ambulatory BP but normal casual BP. Pickering et al. (4) named this trait "masked" hypertension (MHT). Two cross-sectional studies have shown a higher prevalence of target organ damage in MHT groups (5,6). A cohort of an unusual population (all exactly 70-year-old men, without major cardiovascular complications and without antihypertensive medication) has suggested a poor prognosis for MHT detected by ambulatory BP monitoring compared with normotensive subjects (7). However, the applicability of this finding to the general population remains unclear.

Several longitudinal studies have investigated the prognostic significance of WCHT as detected by ambulatory BP monitoring (8–13). Although three of the studies used control subjects with normal BP (8,11,13), these were volunteer subjects and thus did not comprise a representative sample. Results were ambiguous: two studies with mean

```
Abbreviations and Acronyms
BP    = blood pressure
CI    = confidence interval
MHT   = masked hypertension
RH    = relative hazard
SHT   = sustained hypertension
SNBP  = sustained normal blood pressure
TIA   = transient ischemic attack
WCHT  = white-coat hypertension
```

follow-up periods of less than five years showed similarly low cardiovascular risks in WCHT and normotensive control patients (8,11), but one study with a longer follow-up of 10 years demonstrated a higher risk compared with normotensive control patients (13). Thus, the question of the long-term prognosis of WCHT remains unanswered.

We initiated ambulatory BP monitoring in a representative sample of men and women in a Japanese community (14) and have since been monitoring survival status and stroke occurrence (15,16). The present longitudinal study compared risks in subjects with WCHT, MHT, sustained hypertension (SHT), and sustained normal blood pressure (SNBP) in this representative cohort of a general population, including a broad range of subgroups, using data from a 10-year follow-up.

METHODS

Design. This report was based on longitudinal observations of subjects who have been participating in an ambulatory BP measurement project in Ohasama, Iwate Prefecture, Japan, since 1987. Socioeconomic and demographic characteristics of this region and details of the study project have been described previously (14–16). All study protocols were approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama town government.

Study cohort. Selection of study subjects has been described previously (15). Of the 2,716 residents of Ohasama who were ≥40 years of age, 575 were excluded because they worked outside of town. This exclusion criterion was necessary because public health nurses visited subjects to attach ambulatory BP monitoring devices during workdays. Individuals who were in hospital (n = 121) or who were suffering dementia or bedridden (n = 31) also were excluded. Of the remaining 1,989 eligible residents, 1,542 provided informed consent and participated in the study. Casual BP measurements were not obtained from 210 individuals who did not participate in annual health checkups; therefore, the study cohort comprised 1,332 people, representing 67% of the total eligible population. Mean age was 61.0 years, and the male:female ratio was 40:60. The representative nature of the study cohort has been fully reported elsewhere (15).

Ambulatory BP monitoring. Well-trained public health nurses visited participants on a weekday morning to attach

the ambulatory BP monitoring device and returned to detach it the next morning. Participants were asked to keep a diary in which they recorded daily activities, including times at which they went to bed and got up. Ambulatory BP data were included in the analysis if the monitoring period included more than 8 h of time spent during the waking period (daytime) and more than 4 h during which the subject was in bed (nighttime). These periods were estimated from subject diaries. Artifactual readings during ambulatory BP monitoring were defined according to previously described criteria (17) and were omitted from analysis. Mean 24-h, daytime, and nighttime values for ambulatory BP were calculated for each subject.

Casual BP measurements. BP was measured twice by nurses or technicians at local medical centers using an automatic device with subjects in a seated position after resting for at least 2 min. Casual BP was defined as the mean of the two readings.

BP monitoring device. Ambulatory BP was monitored using a fully automatic ABPM-630 device (Nippon Colin, Komaki, Japan) (18) preset to measure BP every 30 min. Although systolic and diastolic BP were measured using both cuff-oscillometric and microphone methods, only data obtained by the cuff-oscillometric method was used for analysis. Casual BP was measured using an automatic USM-700F device (UEDA Electronic Works, Tokyo, Japan) based on the Korotkoff sound technique (microphone method). Devices used to measure ambulatory and casual BP have been previously validated (18,19) and meet all criteria of the Association for the Advancement of Medical Instrumentation (AAMI) (20). The device used to measure casual BP also was calibrated annually by the Department of Health in Ohasama.

Classification of subjects. Subjects were classified into four groups on the basis of daytime ambulatory BP and casual BP levels: 1) SNBP (n = 739, 55%), displaying casual BP <140/90 mm Hg and daytime ambulatory BP <135/85 mm Hg; 2) WCHT (n = 170, 13%), displaying casual BP ≥140/90 mm Hg and ambulatory BP <135/85 mm Hg; 3) MHT (n = 221, 17%), displaying casual BP <140/90 mm Hg and ambulatory BP ≥135/85 mm Hg; and 4) SHT (n = 202, 15%), displaying casual BP ≥140/90 mm Hg and ambulatory BP ≥135/85 mm Hg. Cut-off values were derived from several guidelines (21–24). In the present analysis, subjects with SNBP included untreated subjects with "SNBP" and treated subjects with "controlled SNBP." The WCHT group included treated subjects with uncontrolled BP status only under medical settings. Similarly, the MHT group included those with "masked uncontrolled hypertension" that would represent uncontrolled BP status "masked" by the use of casual BP measurement alone. These concepts are consistent with those used in a previous study (25) and are based on previous reports showing that an insufficient duration of action for antihypertensive drugs represents an important factor in causing higher ambulatory or home BP values compared with casual BP (26).

Follow-up and outcomes. The residence of patients in Ohasama as of December 31, 2001, was confirmed using residents' registration cards, which are considered accurate and reliable, as they are the basis for pension and social security benefits in Japan. Causes of death by December 31, 2001, were investigated with reference to the national mortality registry, in which underlying cause of death was classified by death certificate according to the recommendations of the International Classification of Diseases-Tenth Revision (ICD-10). Primary outcome was determined as the composite of cardiovascular mortality and stroke morbidity. Secondary outcomes comprised: 1) cardiovascular mortality and 2) stroke morbidity. Cardiovascular mortality was defined as death from diseases of the circulatory system (ICD-10 code "I"). Incidence of stroke and transient ischemic attack (TIA) by December 31, 2001, was investigated with reference to the Stroke Registration System of Iwate Prefecture, national mortality registry, National Health Insurance receipts, and questionnaires sent to each household at the time of ambulatory BP monitoring. Results were then confirmed by checking the medical records of Ohasama Hospital, which is the only hospital in the town and is where >90% of patients undergo regular check-ups. Death certificates comprised the sole source of information for only 2% of stroke cases. Most cases were admitted to Ohasama Hospital, where diagnosis was confirmed by computed tomography or magnetic resonance imaging of the brain. Diagnostic criteria for stroke and stroke subtypes were based on the Classification of Cerebrovascular Disease 3 by the National Institute of Neurological Disorders and Stroke (27).

Data analysis. Associations between each BP category and outcome risks were examined using the Cox proportional hazard regression model (28). In all Cox analyses, the SNBP group was treated as the reference category. Among participants who experienced more than one outcome event during follow-up, survival time to the first relevant event was used in each analysis. If a participant experienced more than one type of outcome event during follow-up, each event contributed to the relevant outcome analysis, but only the first event for any individual contributed to the combined outcome analysis (stroke morbidity or cardiovascular mortality). For example, if a participant experienced a nonfatal stroke on December 12, 1998, and then died from coronary heart disease on February 7, 2001, the time from baseline to December 12, 1998, was used as the survival time for stroke morbidity analysis and for combined outcome, whereas time from baseline to February 7, 2001, was used as the survival time for analysis of cardiovascular mortality. Participants who died from other causes or who were lost to follow-up were treated as censored. In Cox analyses, age; gender; smoking status; use of antihypertensive medications; and history of cardiovascular disease, hypercholesterolemia, or diabetes mellitus were included as possible confounding variables in multivariate models.

Three subgroup analyses were conducted for the composite outcome of cardiovascular mortality and stroke morbidity: 1) comparison of risks in BP category between men and women; 2) comparison of risks in BP category between subjects with and without antihypertensive medications; and 3) comparison of risks in BP category among subjects classified as low risk (no history of cardiovascular disease or diabetes, and no risk factors), middle risk (no history of cardiovascular disease or diabetes, but one to two risk factors), or high risk (history of cardiovascular disease or diabetes or three risk factors). Risk factors comprised: age >55 years for men; age >65 years for women; ever smoker; and hypercholesterolemia. Information on smoking status; use of antihypertensive medications at baseline; and history of heart disease, diabetes mellitus, or hypercholesterolemia was obtained from questionnaires sent to each household at the time of ambulatory BP measurements and from medical records at Ohasama Hospital. Subjects who were administered lipid-lowering drugs or who had serum cholesterol levels of ≥5.68 mmol/l (220 mg/dl) were considered to have hypercholesterolemia. Subjects with a fasting glucose level of ≥77 mmol/l (140 mg/dl) or nonfasting glucose level of ≥11.11 mmol/l (200 mg/dl) or who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Estimated relative hazards (RHs) and 95% confidence intervals (CIs) for variables were derived from the coefficient and standard error of the mean as determined using the Cox proportional hazards regression model (28). Homogeneity between subgroups was tested by adding interaction terms to the relevant Cox models. Data are shown as (mean [SD]). Values of $p < 0.05$ were accepted as statistically significant. All statistical analyses were conducted using SAS version 8.2 software (SAS Institute, Cary, North Carolina).

RESULTS

Baseline characteristics. Mean ambulatory systolic BP (123.3 [13.0] mm Hg) and diastolic BP (72.0 [7.7] mm Hg) were significantly lower than casual systolic BP (131.2 [18.5] mm Hg) and diastolic BP (74.1 [11.3] mm Hg). Of the 1,332 study subjects, 272 (20%) were classified as current or ex-smokers, and 405 (30%) were using antihypertensive medications at baseline. A history of cardiovascular disease, diabetes mellitus, or hypercholesterolemia was present in 75 (6%), 232 (17%), and 217 subjects (16%), respectively.

Table 1 shows subject characteristics in each group. The WCHT and MHT groups displayed similar ages, gender ratios, and proportions of other risk factors. The SHT group was older and included a higher proportion of men, smokers, and hypercholesterolemic subjects compared with the WCHT and MHT groups. The SNBP group displayed lower proportions of risk factors compared with the other groups. Casual systolic/diastolic BP was significantly higher in the WCHT group (152/82 mm Hg) than in the MHT group (127/73 mm Hg), whereas 24-h ambulatory systolic/

Table 1. Baseline Characteristics

	Sustained Normal BP (n = 739)	White-Coat Hypertension (n = 170)	Masked Hypertension (n = 221)	Sustained Hypertension (n = 202)	p Value
Age (yrs)	60 (10)	64 (9)	63 (9)	66 (10)	<0.001
Male (%)	30	38	36	47	<0.001
Casual BP (mm Hg)					
Systolic	121 (12)	152 (12)	127 (9)	155 (15)	<0.001
Diastolic	70 (9)	82 (12)	73 (9)	86 (11)	<0.001
Ambulatory BP (mm Hg)					
24-h					
Systolic	116 (8)	120 (7)	136 (8)	140 (10)	<0.001
Diastolic	68 (5)	70 (5)	79 (6)	81 (7)	<0.001
Daytime					
Systolic	121 (8)	125 (7)	143 (8)	147 (9)	<0.001
Diastolic	72 (6)	74 (6)	84 (6)	86 (7)	<0.001
Nighttime					
Systolic	106 (10)	111 (11)	122 (13)	127 (14)	<0.001
Diastolic	61 (6)	63 (7)	70 (8)	71 (8)	<0.001
Antihypertensive treatment (%)	21	45	34	48	<0.001
Current or ex-smoker (%)	19	19	22	26	0.2
History of cardiovascular disease (%)	4	9	6	7	0.06
History of hypercholesterolemia (%)	14	21	20	18	0.02
History of diabetes (%)	15	19	19	22	0.01

Continuous values are shown as mean (SD).
BP = blood pressure.

diastolic BP was significantly lower in the WCHT group (120/70 mm Hg) than in the MHT group (136/79 mm Hg). Similar tendencies were observed for daytime and nighttime ambulatory BP.

Follow-up and outcomes. Mean duration of follow-up was 10.2 (2.7) years. A total of 26 subjects (2%) moved away and were lost to follow-up, whereas 67 cardiovascular deaths (5%) and 124 noncardiovascular deaths (9%) were recorded. The number of deaths was somewhat increased compared with the number during the pilot phase based on a five-year follow-up (37 cardiovascular deaths, 56 noncardiovascular deaths) (15). Of the cardiovascular deaths, 35 (52%) were due to stroke and 32 (48%) were due to heart disease. Of the 32 deaths due to heart disease, 12 were due to coronary heart disease (myocardial infarction, n = 9; angina pectoris, n = 3), whereas the remaining were due to congestive heart failure (n = 7), arrhythmia (n = 3), and other heart diseases

(n = 10), respectively. Stroke or TIA occurred in 112 subjects (8%), because of cerebral infarction in 75 (67%), intracerebral hemorrhage in 23 (21%), subarachnoid hemorrhage in 10 (9%), TIA in 3 (3%), and unknown causes in 1 (1%). Of the 112 subjects who experienced stroke or TIA, 27 (24%: 23 due to stroke, 4 due to heart disease) died during the follow-up period. Composite cardiovascular mortality and stroke morbidity thus comprised 152 events.

Figure 1 shows risk of primary and secondary outcomes in each group. RH for the composite events was significantly higher in the SHT (RH = 2.26, p < 0.0001) and MHT groups (RH = 2.13, p = 0.0006) compared with the SNBP group, whereas no difference was identified with the WCHT group (RH = 1.28, p = 0.4). Similar relationships were observed for risk of cardiovascular mortality and stroke morbidity (Fig. 1). Further adjustment for casual systolic and diastolic BP levels did not change the increased risk in

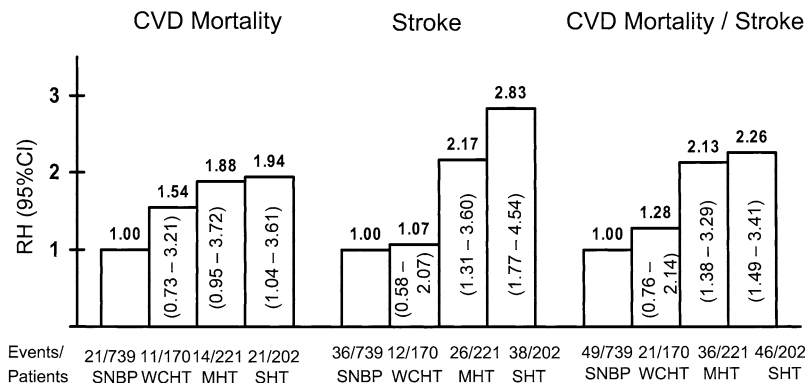**Figure 1.** Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for cardiovascular disease (CVD) mortality, stroke morbidity, and the composite of CVD mortality/stroke morbidity. **Numbers inside bars** indicate 95% CI. The SNBP group was treated as the preference category.

Table 2. RH and 95% CIs With a BP Increase of 10 mm Hg for CVD Mortality, Stroke Morbidity, and the Composite of CVD Mortality/Stroke Morbidity

Models*	CVD Mortality		Stroke		CVD Mortality/Stroke	
BP Variables	RH (95% CI)	p Value	RH (95% CI)	p Value	RH (95% CI)	p Value
Systolic BP						
Casual + 24 h						
Casual	1.04 (0.91–1.19)	0.5	1.04 (0.94–1.15)	0.3	1.05 (0.96–1.15)	0.3
24-h	1.27 (1.04–1.55)	0.02	1.40 (1.21–1.62)	<0.0001	1.33 (1.17–1.51)	<0.0001
Casual + daytime						
Casual	1.06 (0.93–1.21)	0.4	1.03 (0.93–1.15)	0.4	1.05 (0.96–1.15)	0.3
Daytime	1.17 (0.97–1.41)	0.1	1.37 (1.19–1.57)	<0.0001	1.27 (1.12–1.43)	0.0001
Casual + nighttime						
Casual	1.05 (0.92–1.20)	0.5	1.08 (0.98–1.19)	0.09	1.07 (0.99–1.17)	0.1
Nighttime	1.33 (1.11–1.58)	0.002	1.26 (1.10–1.43)	<0.0001	1.26 (1.13–1.41)	<0.0001
Diastolic BP						
Casual + 24 h						
Casual	1.00 (0.80–1.25)	0.9	1.07 (0.90–1.27)	0.4	1.05 (0.91–1.22)	0.5
24-h	1.27 (0.89–1.80)	0.2	1.73 (1.35–2.21)	<0.0001	1.54 (1.24–1.92)	<0.0001
Casual + daytime						
Casual	1.02 (0.81–1.27)	0.9	1.06 (0.90–1.26)	0.4	1.06 (0.91–1.23)	0.4
Daytime	1.14 (0.83–1.58)	0.4	1.67 (1.33–2.10)	<0.0001	1.43 (1.17–1.75)	0.0005
Casual + nighttime						
Casual	0.99 (0.80–1.23)	0.9	1.14 (0.96–1.34)	0.1	1.08 (0.94–1.25)	0.3
Nighttime	1.45 (1.05–1.99)	0.02	1.46 (1.16–1.85)	<0.0001	1.47 (1.20–1.80)	0.0002

*All models were adjusted for age, gender, smoking status, use of antihypertensive medications, and history of cardiovascular disease, hypercholesterolemia, or diabetes mellitus, and simultaneously adjusted for each BP value.

BP = blood pressure; CI = confidence interval; CVD = cardiovascular disease; RH = relative hazard.

the MHT group: RHs (95% CI) in the MHT group compared with the SNBP group for cardiovascular mortality, stroke morbidity, and composite events were 1.88 (0.94 to 3.74), 2.13 (1.28 to 3.56), and 2.01 (1.30 to 3.11), respectively. In a multivariate Cox model with continuous BP variables, ambulatory BP parameters represented a significant predictor of cardiovascular outcomes, whereas casual BP did not represent a significant predictor after simultaneous adjustment for ambulatory BP parameters (Table 2).

Subgroup analyses. Similar relationships were observed among men and women (Fig. 2); among subjects with and without antihypertensive medications (Fig. 3); and among subjects classified as low, middle, or high risk (Fig. 4) for

risk of composite outcomes. No significant interactions were observed for risk among the aforementioned subgroups (p for interaction >0.2 for all).

DISCUSSION

This study was based on a 10-year observation of a representative sample of the general population in Japan. We demonstrated that risk of cardiovascular mortality and stroke morbidity in subjects with MHT or SHT was significantly higher than risk in subjects with SNBP, whereas the risk in subjects with WCHT did not differ from that for subjects with SNBP. Importantly, these relationships were observed among a broad range of subgroups without significant heterogeneity. To the
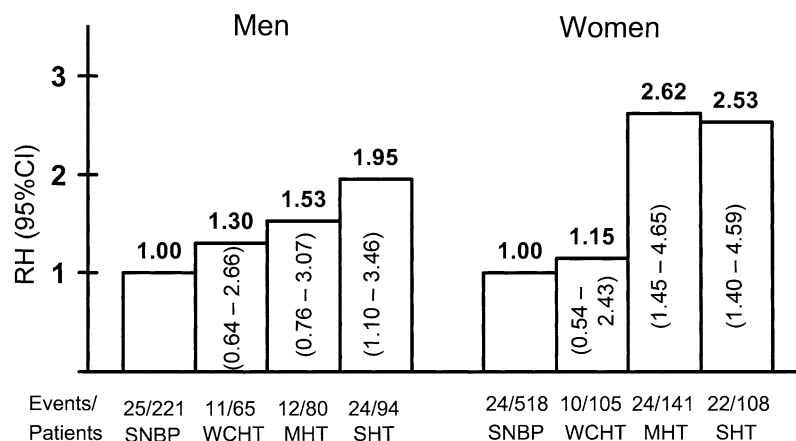

Figure 2. Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for risk of the composite of cardiovascular disease (CVD) mortality/stroke morbidity by gender. **Numbers inside bars** indicate 95% CI. The SNBP group was treated as the reference category.

Treated subjects   **Untreated subjects**

RH (95%CI)

1.00	1.13 (0.59 – 2.16)	1.62 (0.86 – 3.07)	1.85 (1.06 – 3.24)	1.00	0.95 (0.39 – 2.33)	2.56 (1.41 – 4.65)	2.36 (1.28 – 4.38)

Events/ Patients:
24/158 SNBP   15/77 WCHT   16/74 MHT   26/96 SHT   25/581 SNBP   6/93 WCHT   20/147 MHT   20/106 SHT
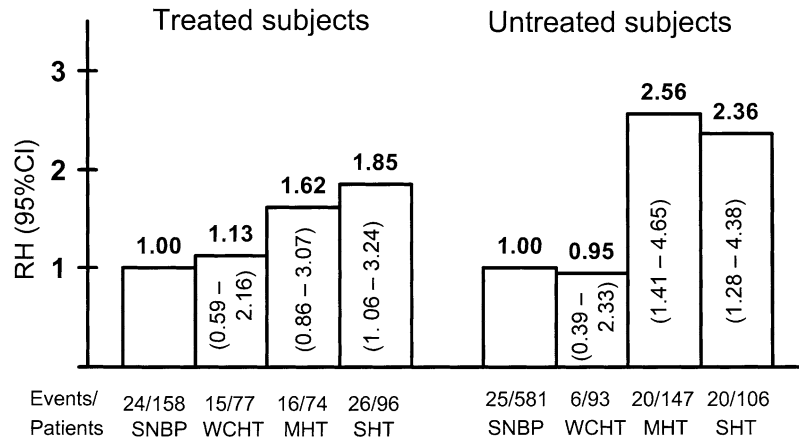
Figure 3. Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for risk of the composite of cardiovascular disease (CVD) mortality/stroke morbidity by use of antihypertensive 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
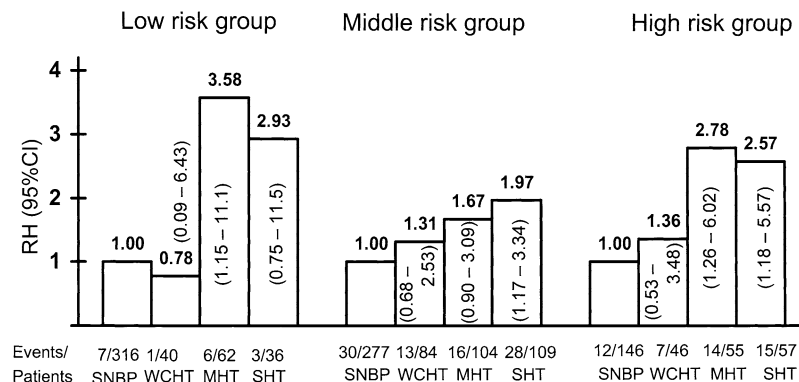
Low risk group   **Middle risk group**   **High risk group**

RH (95%CI)

1.00	0.78 (0.09 – 6.43)	3.58 (1.15 – 11.1)	2.93 (0.75 – 11.5)	1.00	1.31 (0.68 – 2.53)	1.67 (0.90 – 3.09)	1.97 (1.17 – 3.34)	1.00	1.36 (0.53 – 3.48)	2.78 (1.26 – 6.02)	2.57 (1.18 – 5.57)

Events/ Patients:
7/316 SNBP   1/40 WCHT   6/62 MHT   3/36 SHT   30/277 SNBP   13/84 WCHT   16/104 MHT   28/109 SHT   12/146 SNBP   7/46 WCHT   14/55 MHT   15/57 SHT

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.

REFERENCES

1. Pickering T. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. American Society of Hypertension Ad Hoc Panel. Am J Hypertens 1996;9:1–11.
2. O'Brien E, Asmar R, Beilin L, et al. European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. J Hypertens 2003;21: 821–48.
3. Pickering TG, James GD, Boddie C, et al. How common is white-coat hypertension. JAMA 1988;259:225–8.
4. Pickering TG, Davidson K, Gerin W, et al. Masked hypertension. Hypertension 2002;40:795–6.
5. Liu JE, Roman MJ, Pini R, et al. Cardiac and arterial target organ damage in adults with elevated ambulatory and normal office blood pressure. Ann Intern Med 1999;131:564–72.
6. Sega R, Trocino G, Lanzarotti A, et al. Alterations of cardiac structure in patients with isolated office, ambulatory, or home hypertension: data from the general population (Pressione Arteriose Monitorate E Loro Associazioni [PAMELA] Study). Circulation 2001;104:1385–92.
7. Bjorklund K, Lind L, Zethelius B, et al. Isolated ambulatory hypertension predicts cardiovascular morbidity in elderly men. Circulation 2003;107:1297–302.
8. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. Hypertension 1994;24:793–801.
9. Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension. Circulation 1998;24:1892–97.
10. Fagard RH, Staessen JA, Thijs L, et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. Circulation 2000;102:1139–44.
11. Kario K, Shimada K, Schwartz JE, et al. Silent and clinically overt stroke in older Japanese subjects with white-coat and sustained hypertension. J Am Coll Cardiol 2001;38:238–45.
12. Celis H, Staessen JA, Thijs L, et al. Ambulatory Blood Pressure and Treatment of Hypertension Trial Investigators. Cardiovascular risk in white-coat and sustained hypertensive patients. Blood Press 2002;11: 352–6.
13. Gustavsen PH, Hoegholm A, Bang LE, et al. White coat hypertension is a cardiovascular risk factor: a 10-year follow-up study. J Hum Hypertens 2003;17:811–7.
14. Imai Y, Nagai K, Sakuma M, et al. Ambulatory blood pressure of adults in Ohasama, Japan. Hypertension 1993;22:900–12.
15. Ohkubo T, Imai Y, Tsuji I, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening BP measurements: a pilot study in Ohasama. J Hypertens 1997;15:357–64.

16. Ohkubo T, Hozawa A, Nagai K, et al. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. J Hypertens 2000;18:847–54.
17. Imai Y, Nihei M, Abe K, et al. A finger volume-oscillometric device for monitoring ambulatory blood pressure: laboratory and clinical evaluation. Clin Exp Hypertens [A] 1987;9:2001–25.
18. Imai Y, Abe K, Sasaki S, et al. Determination of clinical accuracy and nocturnal blood pressure pattern by new portable device for monitoring indirect ambulatory blood pressure. Am J Hypertens 1990;293–301.
19. Imai Y, Abe K, Sasaki S, et al. Clinical evaluation of semiautomatic and automatic devices for home blood pressure measurement: comparison between cuff-oscillometric and microphone methods. J Hypertens 1989;7:983–90.
20. Association for the Advancement of Medical Instrumentation. American National Standards for Electronic or Automated Sphygmomanometers. Washington, DC: AAMI, 1987.
21. Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;21;289:2560–72.
22. Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011–53.
23. Japanese Society of Hypertension Guidelines Subcommittee for the Management of Hypertension. Guidelines for the management of hypertension for general practitioners. Hypertens Res 2001;24:613–34.
24. Verdecchia P, Staessen JA, White WB, et al. Properly defining white coat hypertension. Eur Heart J 2002;23:106–9.
25. Bobrie G, Chatellier G, Genes N, et al. Cardiovascular prognosis of "masked hypertension" detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA 2004;291:1342–9.
26. Chonan K, Hashimoto J, Ohkubo T, et al. Insufficient duration of action of antihypertensive drugs mediates high blood pressure in the morning in hypertensive population: the Ohasama study. Clin Exp Hypertens 2002;24:261–75.
27. National Institute of Neurological Disorders and Stroke Ad Hoc Committee. Classification of cerebrovascular disease III. Stroke 1990; 21:637–76.
28. Cox DR. Regression models and life tables. J Roy Stat Soc (B) 1972;34:187–202.
29. Staessen JA, Asmar R, De Buyzere M, et al. Participants of the 2001 Consensus Conference on Ambulatory Blood Pressure Monitoring. Task Force II: blood pressure measurement and cardiovascular outcome. Blood Press Monit 2001;6:355–70.
30. Weber MA, Neutel JM, Smith DH, et al. Diagnosis of mild hypertension by ambulatory blood pressure monitoring. Circulation 1994;90:2291–8.
31. Glen SK, Elliott HL, Curzio JL, et al. White-coat hypertension as a cause of cardiovascular dysfunction. Lancet 1996;348:654–7.
32. Bjorklund K, Lind L, Vessby B, et al. Different metabolic predictors of white-coat and sustained hypertension over a 20-year follow-up period: a population-based study of elderly men. Circulation 2002;106:63–8.
33. Isles CG, Walker LM, Beevers GD, et al. Mortality in patients of the Glasgow Blood Pressure Clinic. J Hypertens 1986;4:141–56.
34. Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. Hypertension 1997;29:22–9.
35. Imai Y, Tsuji I, Nagai K, et al. Ambulatory blood pressure monitoring in evaluating the prevalence of hypertension in adults in Ohasama, a rural Japanese community. Hypertens Res 1996;19:207–12.