

# Silent and Clinically Overt Stroke in Older Japanese Subjects With White-Coat and Sustained Hypertension

Kazuomi Kario, MD, PhD, FACC,\*† Kazuyuki Shimada, MD, PhD,\* Joseph E. Schwartz, PhD,‡ Takefumi Matsuo, MD, PhD,§ Satoshi Hoshida, MD,\* Thomas G. Pickering, MD, DPHIL†

*Tochigi and Hyogo, Japan, and New York and Stony Brook, New York*

<b>OBJECTIVES</b>	We investigated whether white-coat hypertension is a risk factor for stroke in relation to silent cerebral infarct (SCI) in an older Japanese population.
<b>BACKGROUND</b>	It remains uncertain whether white-coat hypertension in older subjects is a benign condition or is associated with an increased risk of stroke.
<b>METHODS</b>	We studied the prognosis for stroke in 958 older Japanese subjects (147 normotensives [NT], 236 white-coat hypertensives [WCHT] and 575 sustained hypertensives [SHT]) in whom ambulatory blood pressure monitoring was performed in the absence of antihypertensive treatment. In 585 subjects (61%), we also assessed SCI using brain magnetic resonance imaging.
<b>RESULTS</b>	Silent cerebral infarcts were found in 36% of NT (n = 70), 42% of WCHT (n = 154), and 53% of SHT (n = 361); multiple SCIs (the presence of $\geq 2$ SCIs) were found in 24% of NT, 25% of WCHT and 39% of SHT. During a mean 42-month follow-up period, clinically overt strokes occurred in 62 subjects (NT: three [2.0%]; WCHT: five [2.1%]; SHT: 54 [9.4%]), with 14 fatal cases (NT: one [0.7%]; WCHT: 0 [0%]; SHT: 13 [2.3%]). A Cox regression analysis showed that age (p = 0.0001) and SHT (relative risk, [RR] [95% confidence interval, CI]: 4.3 [1.3–14.2], p = 0.018) were independent stroke predictors, whereas WCHT was not significant. When we added presence/absence of SCI at baseline into this model, the RR (95% CI) for SCI was 4.6 (2.0–10.5) (p = 0.003) and that of SHT was 5.5 (1.8–18.9) versus WCHT (p = 0.004) and 3.8 (0.88–16.7) versus NT (p = 0.07).
<b>CONCLUSIONS</b>	In older subjects the incidence of stroke in WCHT is similar to that of NT and one-fourth the risk in SHT. Although SCI is a strong predictor of stroke, the difference in stroke prognosis between SHT and WCHT was independent of SCI. It is clinically important to distinguish WCHT from SHT even after assessment of target organ damage in the elderly. (J Am Coll Cardiol 2001;38:238–45) © 2001 by the American College of Cardiology

White-coat hypertension (WCHT), defined by persistently high clinic blood pressure (BP) levels and normal ambulatory BP (ABP), is common in clinical practice (1), particularly in older hypertensive subjects (2), in whom its frequency may be as high as 40% (3). However, it is still controversial whether WCHT is a benign condition. In cross-sectional studies, some authors have found a clustering of cardiovascular risk factors or increased target organ damage in WCHT compared with normotensives (NT) (4–7), whereas others have not (8–13). One way to diagnose WCHT is by using ABP monitoring (ABPM) (14). There are now six published prospective studies using ABPM to define cardiovascular prognosis (15–21). These

prognostic studies differed widely in design, ranging from a population study to a study of refractory hypertension. In most of these studies the subjects were relatively young, and only one (20) dealt with older subjects with isolated systolic hypertension. Although all these reports demonstrate that ABP is a better predictor of cardiovascular prognosis than is clinic BP, only three of these reports (16,19,21) compared the event rates in patients with WCHT and those with sustained hypertension (SHT), whereas the other four reports estimated the predictive value of ABP after controlling for clinic BP in the entire cohort (15,17,18,20).

There are significant racial differences between Japanese and Caucasians in the demographics of cardiovascular disease. In Japan, stroke is more common than in Western countries, whereas coronary artery disease (CAD) is less common (22). Recently, silent cerebral infarct (SCI) has often been detected by brain computed tomography or magnetic resonance imaging (MRI) in older subjects, particularly in those with hypertension (23–25). Silent cerebral infarct is the strongest predictor of subsequent clinically overt stroke (26). The prognosis of WCHT may depend on the presence or absence of subclinical target organ damage, and the risk of stroke could be augmented when accompanied by SCI. Furthermore, in older patients with WCHT,

From the \*Department of Cardiology, Jichi Medical School, Tochigi, Japan; †The Zena and Michael A. Weiner Cardiovascular Center, Mount Sinai School of Medicine, New York, New York; ‡Department of Psychiatry and Behavioral Science, State University of New York at Stony Brook, Stony Brook, New York; and §Department of Internal Medicine, Hyogo Prefectural Awaji Hospital, Hyogo, Japan. This study was supported by grants-in-aid (1992 to 1999) from the Foundation for the Development of the Community (K.K.), Tochigi, Japan; by a grant-in-aid from the Japan Foundation for Aging and Health General Sciences Center (K.K.); by a Scientific Research Grant-in-Aid (09670746) from the Ministry of Education of the Government of Japan (K.K.) and by a grant (HL57450) from the United States National Heart, Lung, and Blood Institute (TGP).

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#### Abbreviations and Acronyms

ABPM	=	ambulatory blood pressure monitoring
BMI	=	body mass index
BP	=	blood pressure
MRI	=	magnetic resonance imaging
NT	=	normotension
RR	=	relative risk
SCI	=	silent cerebral infarct
SHT	=	sustained hypertension
WCHT	=	white-coat hypertension

transient rises of BP might be more likely to trigger cardiovascular events than in younger patients.

In this study, we investigate whether WCHT is a risk factor for stroke in relation to SCI in an older Japanese population.

## METHODS

**Subjects.** This study is based on 958 Japanese subjects, composed of 811 subjects diagnosed with essential hypertension and 147 NT subjects. This represents 98% of the 973 subjects who were initially enrolled into the study from six participating institutes (three clinics, two hospitals and one outpatient clinic of the university hospital) between January 1, 1992, and January 1, 1998. Hypertensive patients were selected by the following criteria: 1) essential hypertension with average clinic systolic BP (SBP)  $\geq 140$  mm Hg and/or average clinic diastolic BP (DBP) of  $\geq 90$  mm Hg (average for each patient on two or more occasions); 2) age  $\geq 50$  years. Clinic BP was measured after resting for at least 5 min in the sitting position. No patient had taken any antihypertensive medication for at least 14 days before the ABPM study, but 51% had a prior history of antihypertensive medication use (1.4% for the NT group, 34% for the WCHT group and 58% for the SHT group). Normotensive subjects (age  $\geq 50$  years) with clinic BPs  $< 140/90$  mm Hg were volunteers recruited from those enrolled in the annual health examination and outpatients without symptomatic medical problems. All of the subjects studied were ambulatory and all gave informed consent for the study. We excluded patients with renal failure (serum creatinine level  $\geq 176$  mmol/l) or hepatic damage, with obvious present or past CAD, stroke (including transient ischemic attacks [TIA]), congestive heart failure or arrhythmia. All the results of the ABPM and brain MRI were returned to the physicians who followed up the subjects. All 131 patients with hypertension reported in our previous cross-sectional study were included in this study (24). Of the 958 patients, 585 (61%) agreed to and had a brain MRI. There were no significant differences in the age, gender, body mass index (BMI) and incidence of cardiovascular disease between these 585 subjects and the other 373 subjects without brain MRI examination, whereas the clinic BPs were slightly higher in the former group than in the latter group (160 vs.

157 mm Hg for systolic,  $p = 0.04$ ; 89 vs. 87 mm Hg for diastolic,  $p = 0.03$ ). This study was approved by the Research Ethics Committee, Department of Cardiology, Jichi Medical School, Japan.

Diabetes mellitus was defined by a fasting glucose level  $\geq 7.8$  mmol/l, a random nonfasting glucose level  $\geq 11.1$  mmol/l, hemoglobin A1c  $\geq 6.2\%$ , or the use of an oral hypoglycemic agent or insulin. Hyperlipidemia was defined by a total cholesterol level  $\geq 6.2$  mmol/l or the use of an oral lipid-lowering agent. Smokers were defined as current smokers. Body mass index was calculated as weight (kg)/height (m)<sup>2</sup>. Electrocardiographically verified left ventricular hypertrophy (ECG-LVH) was defined as abnormally high voltages of QRS-complexes (R in V<sub>5</sub> plus S in V<sub>1</sub>  $\geq 3.5$  mV) associated either with flat T waves ( $< 10\%$  of R) or with ST-segment depression and biphasic T waves.

**24-h ABPM.** Noninvasive ABPM was carried out on a weekday with one of three automatic ABPM devices (ABPM-630, Nippon Colin Co.; TM-2421 or TM-2425, A and D Co., Japan), which recorded BP and heart rate every 30 min for 24 h. The accuracy of these devices was previously validated. The ambulatory data used in the present study were those obtained by the oscillometric method. We excluded those who obtained valid BP readings  $< 80\%$  of either awake attempts or asleep attempts ( $n = 66$ ). Patients who reported in our post-ABPM questionnaire that their sleep was severely disturbed by wearing the ABPM were excluded from this study ( $n = 53$ ). We used a cutoff value of 130/80 mm Hg for normal ABP to define WCHT according to the recommendation of the American Society of Hypertension (ASH) (27) as follows: clinic BPs  $\geq 140/90$  mm Hg (either) and 24-h ABPs  $< 130/80$  mm Hg (both) for WCHT; clinic BPs  $\geq 140/90$  (either) mm Hg and 24-h ABPs  $\geq 130/80$  mm Hg (either) for SHT.

**Brain MRI.** Brain MRI was carried out using a superconducting magnet with a main strength of 1.5 T (MRT200FXII, Toshiba; SIGNA-Horizon Ver.5.8, General Electric Co. or Vision, Siemens, Tokyo) within three months of the ABPM. T1-weighted images and T2-weighted images were obtained in the transverse plane with 7.8 to 8.0-mm-thick sections. A SCI was defined as a low signal intensity area (3 to 15 mm) on T1-weighted images that was also visible as a hyperintense lesion on T2-weighted images as described previously (24,25). Multiple SCI was defined as  $\geq 2$  SCIs in a person. The MRI images of the subjects were randomly stored and interpreted by reviewers blind to the subjects' names and characteristics. The interclass (non-SCI = 0, one SCI = 1, multiple SCIs = 2) kappa statistics were 0.70 and 0.80 for interreader and intrareader, respectively, in our laboratory.

**Follow-up and events.** The patients' medical records were intermittently reviewed since entering the study for drug therapy and the occurrence of cardiovascular events. The follow-up evaluation was performed during a 20-month period from 1996 to 1998; the mean follow-up was 42

**Table 1.** Baseline Characteristics

Measures	Normotensive Control Group (n = 147)	White-Coat Hypertension Group (n = 236)	Sustained Hypertension Group (n = 575)	p Value*
Age, years	68 (9.7)	72 (9.9)†	73 (9.8)†	0.000
Male, %	38	34	40	0.248
Body mass index, kg/m <sup>2</sup>	23.0 (3.7)	23.8 (3.5)	24.0 (3.5)§	0.791
Clinic systolic BP, mm Hg	126 (12)	156 (11)†	168 (19)†	0.000
Clinic diastolic BP, mm Hg	77 (11)	83 (12)†	93 (14)†	0.000
24-h systolic BP, mm Hg	123 (13)	120 (7.7)§	146 (13)†	0.000
24-h diastolic BP, mm Hg	70 (7.4)	69 (5.7)	82 (8.4)†	0.000
Current smoker, %	21	17	22	0.279
Family history (either parent)				
Hypertension, %	16	25§	27‡	0.016
Cardiovascular disease, %	14	14¶	22§	0.008
Diabetes mellitus (treated), %	8.8 (6.8)	9.7 (8.1)	13 (11)	0.190
Hyperlipidemia (treated), %	23 (20)	21 (16)	18 (13)	0.272
Hematocrit	0.39 (0.06)	0.40 (0.07)	0.40 (0.04)	0.759
Creatinine, μmol/l	79 (22)	79 (21)	80 (19)	0.823
ECG-LVH, %	2.7	6.4#	19‡	0.000
Duration of follow-up, months	43 (12)	43 (14)	41 (14)	0.065

Data are shown as means (SD) or percentages. \*Overall p-values for three-group comparisons of means (ANOVA F-test) or percentages ( $\chi^2$ -test); †p < 0.001, ‡p < 0.01, §p < 0.05 vs. normotensive control group; ||p < 0.001, ¶p < 0.01, #p < 0.05 vs. sustained hypertensive group.

BP = blood pressure; ECG-LVH = left ventricular hypertrophy diagnosed by echocardiography.

months, with a range from one to 68 months. When subjects stopped coming to the clinic, we conducted telephone interviews with them. Events were classified as cardiac events, stroke events and noncardiovascular deaths. Stroke events include ischemic stroke (cerebral infarction and cerebral embolism), hemorrhagic stroke (cerebral hemorrhage and subarachnoid hemorrhage) and undefined type of stroke, but exclude TIA (transient neurological deficits that disappear within 24 h after the onset). Cardiac events include fatal and nonfatal acute myocardial infarction (AMI), unexplained sudden death within 6 h of the abrupt onset of symptoms, and coronary revascularization. These events were accepted if documented in the medical records or if confirmed by the general practitioner. We excluded 17 TIA from the stroke events. Of the total 973 eligible subjects at baseline, follow-up was obtained in 958 subjects (98%), and the data analysis was restricted to these subjects. There was no significant difference among groups in duration of follow-up.

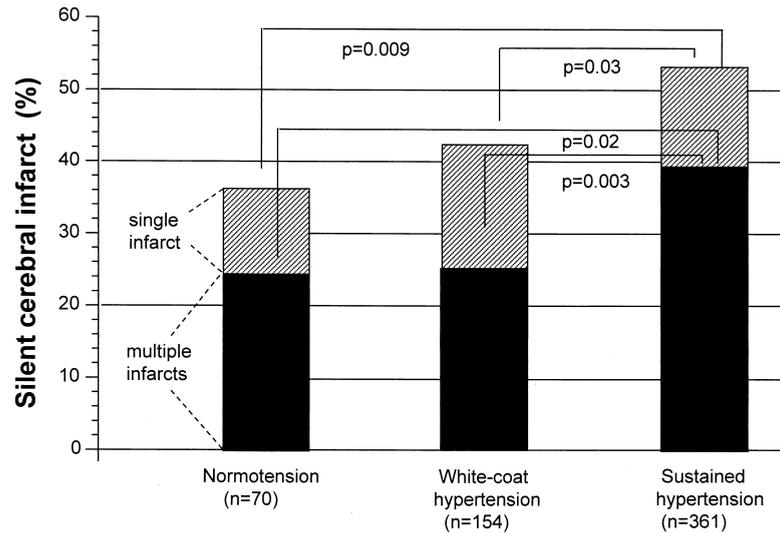
**Statistical analysis.** Data are expressed as the mean (standard deviation, SD). One-way analysis of variance was performed to detect differences among groups in mean values, and the  $\chi^2$  test was used to detect differences among groups in prevalence rates. Survival curves were estimated using the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. Adjusted relative risks (RR) and 95% confidence intervals were calculated using Cox regression analysis. For the subjects who experienced multiple nonfatal cardiovascular events, the analysis included only the first stroke event. The above statistics were performed using SPSS version 8.0J (SPSS Inc., Chicago, Illinois). Differences with p < 0.05, two-tailed, were considered statistically significant.

## RESULTS

**Baseline characteristics.** The mean age was significantly higher in the WCHT and SHT groups than in the NT group (Table 1). Clinic BP was significantly higher in the WCHT and SHT groups than in the NT group. The 24-h SBP of the WCHT group was slightly (3 mm Hg) lower than that of the NT group, whereas 24-h DBP was not different between the WCHT and NT groups. ECG-LVH was more common in the SHT group (19%) than in the NT or WCHT groups, and tended to be more common in WCHT than in NT (6.4 vs. 2.7%, p = 0.15). The prevalence of SCI was comparable in the WCHT and the NT groups, whereas it was significantly higher in the SHT group (Fig. 1). Frequencies of SCI were 39% in previously untreated WCHT (n = 91) and 48% (p = 0.32 vs. untreated WCHT) in previously treated WCHT (n = 63); frequencies were 47% in previously untreated SHT (n = 138) and 57% (p = 0.08 vs. untreated SHT) in previously treated SHT (n = 223).

**Stroke incidence.** During the 42-month follow-up period, 62 clinically overt stroke events (40 ischemic strokes, 10 hemorrhagic strokes, 12 unknown subtype) occurred, including 14 fatal cases. The incidences of fatal and nonfatal stroke events were more common than those of fatal and nonfatal cardiac events (Fig. 2, Table 2). The incidence of total stroke events and fatal events with WCHT was comparable to the incidence with NT, but significantly lower than that with SHT. Marked differences were observed between the SHT and NT groups (p = 0.003) and between the SHT and WCHT groups (p = 0.0003), whereas there was no difference between WCHT and NT groups (Fig. 3). Recurrent strokes occurred in two patients, but for this analysis we ignored recurrent events. In the

White-Coat vs. Sustained Hypertension and Stroke



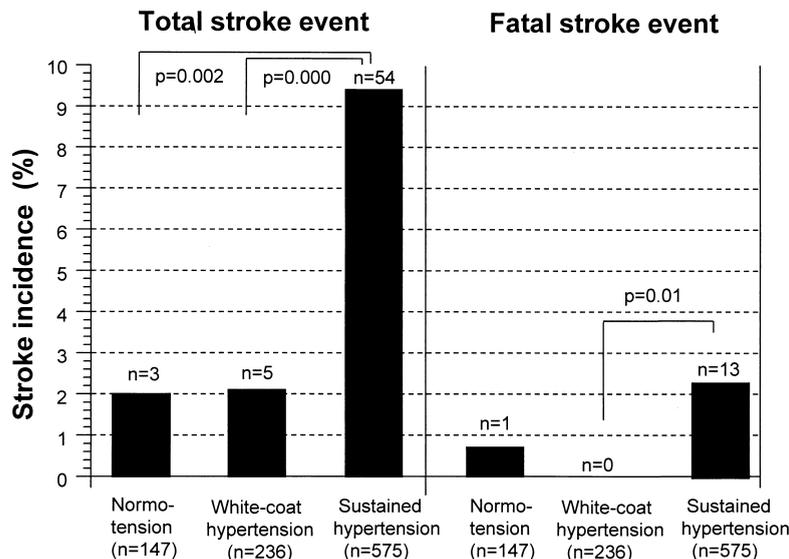
**Figure 1.** Prevalence of silent cerebral infarcts (SCI) detected by brain MRI. Multiple infarcts are defined as  $\geq 2$  infarcts per person. Overall p values for three groups comparisons are 0.006 for SCIs and 0.002 for multiple SCIs.

SHT group, one subject had a fatal stroke after an AMI, two suffered sudden death, and one had an AMI after an initial stroke during the follow-up period. In the Cox regression analysis (Table 3), age (RR of 1.8 for a 10-year-increase,  $p < 0.0001$ ) and SHT (RR vs. NT 4.3,  $p = 0.018$ , vs. WCHT 5.6,  $p = 0.001$ ) were independent predictors for stroke, whereas the predictive value of WCHT was not significantly different from that of NT.

**Impact of silent cerebral infarct.** When we divided the 585 subjects who had both ABPM and brain MRI into 303 without SCI and 282 with SCI (Fig. 4), strokes occurred in seven (2.3%) of the former and in 38 (13.5%) of the latter, indicating that SCI is a strong predictor of clinical stroke (RR = 5.9). Strokes occurred in 6.2% of WCHT with SCI, but in no patients with WCHT but without SCI. To study

the potential mediating role of SCI in explaining the different stroke prognosis between WCHT and SHT, we added SCI (0 = absent, 1 = present) into the model shown in Table 3 in the 585 subjects who had a brain MRI (Table 4). The RR of present SCI was 4.6 ( $p = 0.003$ ). The RR of SHT was 5.5 versus WCHT ( $p = 0.004$ ) and 3.8 versus NT ( $p = 0.07$ ), whereas that of WHT was comparable to that of NT.

**Impact of antihypertensive treatment.** At the time of follow-up, three (2%) of 147 NT, 76 (32%) of 236 WCHT and 350 (61%) of 575 SHT were receiving antihypertensive medications (diuretics, alpha- or beta-blockers, calcium antagonists or angiotensin-converting enzyme inhibitors). Strokes occurred in 28 (12.4%) of 225 untreated patients with SHT and in 26 (7.4%) of 350 treated patients with



**Figure 2.** Stroke and fatal stroke incidence. Overall p values for three groups comparisons are  $< 0.0001$  for stroke incidence and 0.036 for fatal stroke incidence.

**Table 2.** Cardiovascular Prognosis

Measures	Normotensive Control Group (n = 147)	White-coat Hypertension Group (n = 236)	Sustained Hypertension Group (n = 575)	p Value*
Nonfatal cardiovascular events				
Stroke event, n (%)	3 (2.0)	5 (2.1)§	54 (9.4)†	0.000
Stroke subtype				
Ischemic stroke, n	23	35		
Hemorrhagic stroke, n	12	7		
Unknown, n	0	12		
Cardiac event, n (%)	1 (0.7)	1 (0.4)	10 (1.7)	0.247
Total cardiovascular event, n (%)	4 (2.7)	6 (2.5)§	60 (10)†	0.000
Fatal events				
Stroke death, n (%)	1 (0.7)	0 (0)‡	13 (2.3)	0.036
Cardiac death, n (%)	1 (0.7)	1 (0.4)	6 (1.0)	0.662
Total cardiovascular death, n (%)	2 (1.4)	1 (0.4)‡	19 (3.3)	0.032
Noncardiac death, n (%)	4 (2.7)	10 (4.2)	19 (3.3)	0.701
Total death, n (%)	6 (4.1)	11 (4.7)	38 (6.6)	0.358

Data are shown as the number (percentages). \*Overall p-values for three-group comparisons by  $\chi^2$ -test. †p < 0.01 vs. normotension control group; ‡p < 0.05, §p < 0.001 vs. sustained hypertension group.

SHT; thus the stroke incidence was 40% lower in the treated group ( $\chi^2 = 4.0$ ,  $p = 0.056$ ). Strokes occurred in four (2.5%) of 160 untreated patients with WCHT and in one (1.3%) of 76 treated patients with WCHT; thus the stroke incidence was 47% lower in the treated group ( $\chi^2 = 0.35$ ,  $p = 0.56$ ).

## DISCUSSION

This study has demonstrated that the prevalence of SCI and the incidence of clinically overt stroke in patients with strictly defined WCHT are similar to those of NT, and stroke incidence in both groups was approximately one quarter of the incidence seen in SHT. It also confirms that the risk of stroke is strongly predicted by SCI in older Japanese subjects. When we used daytime BP to distinguish WCHT from SHT, the results were essentially the same.

In some previous studies that found that WCHT is associated with increased cardiovascular risk factors or with advanced target organ damage, the criteria used to define WCHT have been somewhat loose (4,5). In these studies,

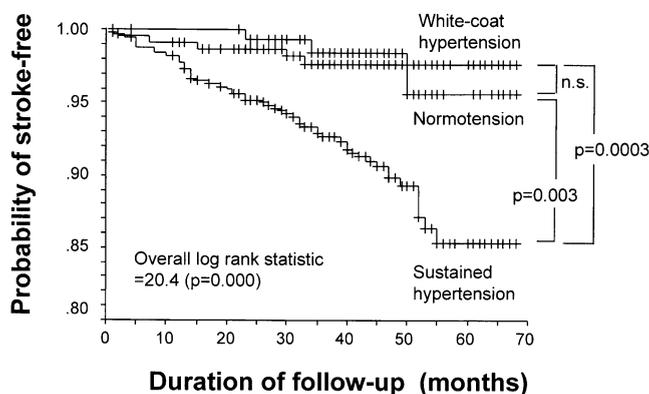
the 24-h or the awake ABP levels of the WCHT patients were often higher than the corresponding levels in the NT controls, although still in the “normal” range for that study. Thus, these studies could not exclude the possibility that higher ABP levels per se lead to progression of target organ damage. Furthermore, in the reports without any differences between 24-h or awake ABP levels between the WCHT and NT groups, WCHT has not usually been found to be associated more often with more advanced target organ damage (ECG-LVH, LV mass index and endothelial cell dysfunction assessed by plasma von Willebrand factor) than with the NT group (8–12), although some authors have still found significant differences (6,7). Accordingly, in this study we used the relatively strict ABP criteria for defining WCHT of the ASH (27), which recommended using 24-h ABP <130/80 mm Hg. However, the prevalence of WCHT in our population (29%) was higher than in other populations (2). This may be due partly to the elderly nature

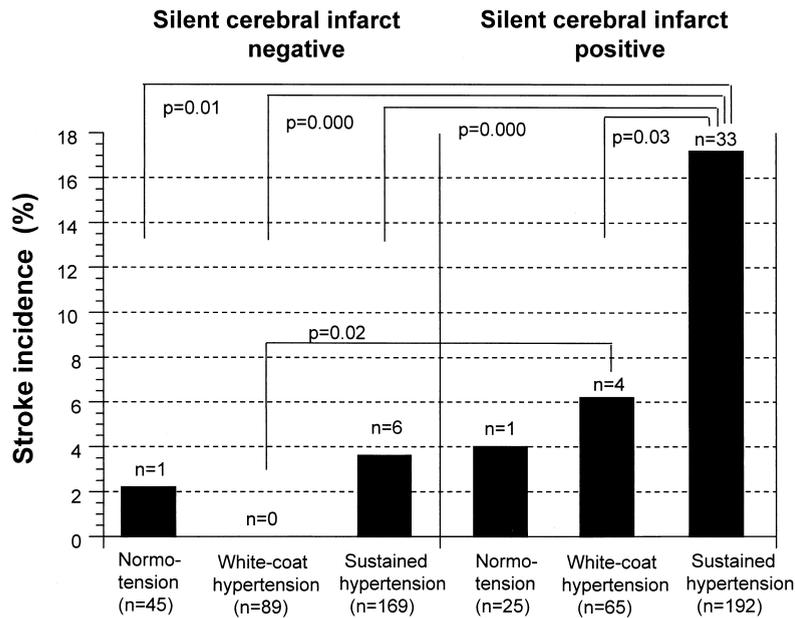
**Table 3.** Cox Regression Analysis for Stroke (n = 958)

Covariates	Relative Risk (95% CI)	p Value
Age (10 years)	1.81 (1.36–2.42)	0.000
Male gender*	1.51 (0.91–2.49)	0.109
Body mass index (kg/m <sup>2</sup> )	0.98 (0.90–1.05)	0.529
Antihypertensive therapy†	0.83 (0.48–1.42)	0.492
Hypertension status‡		0.000§
White-coat hypertension vs. normotension	0.76 (0.16–3.45)	0.724
Sustained hypertension vs. normotension	4.26 (1.28–14.2)	0.018
Sustained hypertension vs. white coat hypertension	5.58 (2.01–15.5)	0.001

\*Female = 0, male = 1; †absence = 0, presence = 1; ‡normotension: D1 = 1, D2 = 0, D3 = 0; white-coat hypertension: D1 = 0, D2 = 1, D3 = 0; sustained hypertension: D1 = 0, D2 = 0, D3 = 1; §global test of significance for differences among three groups.

CI = confidence interval.

**Figure 3.** Stroke-free survival curves.



**Figure 4.** Stroke incidence in the subjects with silent cerebral infarct (SCI) and in those without any SCI. Overall p value is <0.0001 for six group comparisons.

of the population and to the fact that 62% were women, the prevalence of WCHT being higher in women and in the elderly (2,3).

In our baseline data, SCI was found in 36% of NT, 42% of WCHT and 53% of SHT, and multiple SCI ( $\geq 2$  SCIs/person) were found in 24% of NT, 25% of WCHT and 39% of SHT. The prevalence of SCI in elderly normotensive subjects and elderly hypertensive patients in this study is similar to what has been reported in previous studies using brain MRI (41% to 53%) (9,23–25). In this study, there was no significant difference in the prevalence of SCI between the NT and WCHT groups, but it was higher in the SHT group than in either the NT or WCHT group. This finding is consistent with a previous report in a different elderly population (9).

**Table 4.** Relative Risks for Stroke and Silent Cerebral Infarct (n = 585)

Covariates	Relative Risk (95% CI)	p Value
Age (10 years)	1.65 (1.12–2.41)	0.010
Male gender*	1.36 (0.75–2.46)	0.307
Body mass index (kg/m <sup>2</sup> )	0.98 (0.89–1.07)	0.642
Antihypertensive therapy†	0.57 (0.30–1.07)	0.079
Silent cerebral infarct‡	4.63 (2.04–10.5)	0.003
Hypertension status§		0.000
White-coat hypertension vs. normotension	0.66 (0.11–4.04)	0.651
Sustained hypertension vs. normotension	3.82 (0.88–16.7)	0.074
Sustained hypertension vs. white coat hypertension	5.51 (1.75–18.9)	0.004

\*female = 0, male = 1; †absence = 0, presence = 1; ‡absence = 0, presence = 1; §normotension: D1 = 1, D2 = 0, D3 = 0; white-coat hypertension: D1 = 0, D2 = 1, D3 = 0; sustained hypertension: D1 = 0, D2 = 0, D3 = 1; ||global test of significance for differences among three groups.  
 CI = confidence interval.

The total stroke incidence in the WCHT group (0.61/100 person-years) was similar to that seen in the NT group (0.58/100 person-years). Thus, when considered together with the evidence that there was no difference in the prevalence of SCI, WCHT seems to be no more harmful in terms of the risk of stroke than NT, even in an older population. On the other hand, there was a marked difference in the stroke incidence between the WCHT group (0.61/100 person-years) and the SHT group (2.7/100 person-years). After adjustment for age, gender, and BMI, SHT was an independent risk factor, with a RR of stroke of 4.3 in this population, whereas WCHT was unrelated to stroke. Thus, clinically it is worthwhile to distinguish SHT from WCHT in the older hypertensive population.

When we studied the effect of SCI on stroke incidence in the 585 subjects who had both ABPM and brain MRI, we found that SCI is a strong predictor of clinical stroke (RR = 5.9). This risk was slightly lower than the RR of approximately 10 reported in a recent Japanese prospective study of adults with a mean age of 58 years (26). In the present study, the few strokes that occurred in the WCHT were all in those with SCI. Thus, in older WCHT subjects, the stroke incidence may be definitively determined by SCI. Even among the SHT, those without any SCI had a lower stroke incidence than that of the WCHT with SCI. This might suggest that stroke incidence is determined more powerfully by the subclinical target organ damage (SCI) than BP levels per se, especially in the older hypertensives. However, within the older hypertensive subjects with SCI, the stroke incidence of WCHT was still lower than that of SHT (36% of the SHT). Furthermore, when we controlled for the status of SCI in a Cox regression model, the RR of stroke associated with a prior SCI was 4.6 (p = 0.003). The RR of

SHT was 5.8 versus WHT ( $p = 0.004$ ) and 3.8 versus NT ( $p = 0.07$ ), whereas the RR of WCHT was comparable to that of NT. Thus, the difference in the stroke prognosis between SHT and WCHT (or NT) was largely independent of SCI status, indicating that identifying the WCHT versus SHT is prognostically significant even after assessment of SCI.

The overall stroke incidence in this study of older subjects with a mean age of 72 years was 1.8/100 person-years, five times higher than the incidence of CAD (0.36/100 person-years). In Western countries, even in the elderly population, the incidence of CAD is higher than that of stroke (20,28). This marked difference in the demographics of cardiovascular disease can be attributed to both racial and cultural differences between Japanese (or Asians) and Caucasians. The stroke incidence (0.58/100 person-years) of the NT in this study was lower, but that of patients with hypertension (WCHT + SHT combined: 2.1/100 person-years) was higher than that of the elderly (approximately 1/100 person-years for those  $\geq 70$  years) in the wave-3 population of the Hisayama Study, a community-based prospective Japanese study (29). In the Shanghai Trial Of Nifedipine in the Elderly (30), the stroke incidence in the placebo group of Asian hypertensive patients was 3.7/100 person-years. Although the mean age of these hypertensive subjects was 66, which is five years younger than ours, the stroke incidence was higher than that of our untreated group (2.4/100 person-years). In another recent trial in an elderly Asian population, the Systolic Hypertension in China (Syst-China) trial, the stroke incidence of the placebo group (mean age: 67 years) was 2.08 (31). When we excluded nine hemorrhagic stroke events from the total 59 stroke events in 811 hypertensive subjects (WCHT + SHT), the incidence of ischemic stroke and unknown subtype was 1.8/100 person-years. This is also lower than the incidence of thromboembolic stroke (3.4/100 person-years) in the Japanese-American hypertensive men  $>65$  years from the Honolulu Heart Program (32). These differences in the stroke incidence of the Asian population may be due partly to regional differences in study populations, study design (community-based or clinic-based) or differences in the prevalence of treatment.

The frequency of ECG-LVH tended to be higher in the WCHT group than in the NT group (6.4 vs. 2.7%,  $p = 0.15$ ), although the incidence of cardiovascular events was comparable between the two groups. As LVH carries a worse prognosis, particularly for cardiac events, this may involve a worse prognosis for WCHT compared to NT in Western populations in which cardiac disease is more common than in the Japanese population.

A limitation of this study is that our NT group consisted of those who were recruited at the hospital. However, in a previous study, SCI was detected by brain MRI in 14 of 34 (41%) normotensive healthy Japanese subjects recruited from a rural Japanese community (23). Thus, the prevalence (36%) of SCI in our NT group appears slightly less than

that in the community-dwelling elderly Japanese population. Other limitations are that there were no BP data collected at follow-up and that there were differences in the status of antihypertensive treatment between the WCHT and SHT groups. At the time of the latest follow-up, 32% of the former and 61% of the latter were receiving antihypertensive medication. This difference may partly reflect the impact of our sending the results of the ABPM and brain MRI to the subjects' physicians. Stroke incidence was marginally less common in the treated SHT than in the untreated SHT (7.4 vs. 12.4%,  $p = 0.056$ ), whereas this difference was not significant in WCHT, because of the low stroke incidence (1.3 vs. 2.5%,  $p = 0.56$ ).

In conclusion, in older Japanese subjects the incidence of stroke with WCHT is similar to that of NT and one fourth of the risk with SHT. This pattern persists even after controlling for the strong predictive effect of SCI on stroke.

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**Reprint requests and correspondence:** Dr. Kazuomi Kario, Department of Cardiology, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Kawachi, Tochigi, 329-0498, Japan. E-mail: [kkario@jichi.ac.jp](mailto:kkario@jichi.ac.jp).

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## REFERENCES

1. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA* 1988;259:225-8.
2. Pickering TG, Coats A, Mallion JM, Mancia G, Verdecchia P. Task force V: white-coat hypertension. *Blood Press Monit* 1999;4:333-41.
3. Martínez MA, García-Puig J, Martín JC, et al. Frequency and determinants of white coat hypertension in mild to moderate hypertension. *Am J Hypertens* 1999;12:251-9.
4. Julius S, Mejia A, Jones K, et al. "White coat" versus "sustained" borderline hypertension in Tecumseh, Michigan. *Hypertension* 1990;16:617-23.
5. Kuwajima I, Suzuki Y, Fujisawa A, Kuramoto K. Is white coat hypertension innocent? Structure and function of the heart in the elderly. *Hypertension* 1993;22:826-31.
6. Weber MA, Neutel JM, Smith DH, Graettinger WF. Diagnosis of mild hypertension by ambulatory blood pressure monitoring. *Circulation* 1994;90:2291-8.
7. Palatini P, Mormino P, Santonastaso M, et al. Target-organ damage in stage I hypertensive subjects with white coat and sustained hypertension: results from the HARVEST study. *Hypertension* 1998;31:57-63.
8. White WB, Schulman P, McCabe EJ, Dey HM. Average daily blood pressure, not office blood pressure, determines cardiac function in patients with hypertension. *JAMA* 1989;261:873-7.
9. Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension* 1990;16:692-9.
10. Verdecchia P, Schillaci G, Boldrini F, Zampi I, Porcellati C. Variability between current definitions of "normal" ambulatory blood pressure. Implications in the assessment of white coat hypertension. *Hypertension* 1992;20:555-62.
11. Cavallini MC, Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB. Is white coat hypertension associated with arterial disease or left ventricular hypertrophy? *Hypertension* 1995;26:413-9.
12. Kario K, Matsuo T, Kobayashi H, et al. Factor VII hyperactivity and endothelial cell damage are found in elderly hypertensives only when concomitant with microalbuminuria. *Arterioscler Thromb Vasc Biol* 1996;16:455-61.
13. Pickering TG. White coat hypertension: time for action. *Circulation* 1998;98:1834-6.

14. Pickering TG. Blood pressure measurement and detection of hypertension. *Lancet* 1994;344:31-5.
15. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA* 1983;249:2792-8.
16. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994;24:793-801.
17. Ohkubo T, Imai Y, Tsuji I, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens* 1997;15:357-64.
18. Redon J, Campos C, Narciso ML, Rodicio JL, Pascual JM, Ruilope LM. Prognostic value of ambulatory blood pressure monitoring in refractory hypertension: a prospective study. *Hypertension* 1998;31:712-8.
19. Khattar RS, Senior R, Lahiri A. Cardiovascular outcome in white-coat versus sustained mild hypertension: a 10-year follow-up study. *Circulation* 1998;98:1892-7.
20. Staessen JA, Thijs L, Fagard R, et al. Predicting cardiovascular risk using conventional vs. ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *JAMA* 1999;282:539-46.
21. Fagard RH, Staessen JA, Thijs L, et al. Response to antihypertensive therapy in older patients with sustained and nonsustained systolic hypertension. *Circulation* 2000;102:1139-44.
22. Marmot MG, Smith GD. Why are the Japanese living longer? *Br Med J* 1989;299:1547-51.
23. Kawamoto A, Shimada K, Matsubayashi K, Nishinaga M, Kimura S, Ozawa T. Factors associated with silent multiple lacunar lesions on magnetic resonance imaging in asymptomatic elderly hypertensive patients. *Clin Exp Pharmacol Physiol* 1991;18:605-10.
24. Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. *Hypertension* 1996;27:130-5.
25. Kario K, Matsuo T, Kobayashi H, Asada R, Matsuo M. "Silent" cerebral infarction is associated with hypercoagulability, endothelial cell damage, and high Lp(a) levels in elderly Japanese. *Arterioscler Thromb Vasc Biol* 1996;16:734-41.
26. Kobayashi S, Okada K, Koide H, Bokura H, Yamaguchi S. Subcortical silent brain infarction as a risk factor for clinical stroke. *Stroke* 1997;28:1932-9.
27. Pickering TG, Kaplan NM, Krakoff L, et al., and the American Society of Hypertension Expert Panel. Conclusions and recommendations on the clinical use of home(self) and ambulatory blood pressure monitoring. *Am J Hypertens* 1996;9:1-11.
28. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. *JAMA* 1996;276:1886-92.
29. Fujishima M. Cardiovascular disease in the elderly—the Hisayama study. *Nippon Ronen Igakkai Zasshi (Japanese)* 1999;36:16-21.
30. Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens* 1996;14:1237-45.
31. Wang J-G, Staessen JA, Gong L, Liu L. Chinese trial on isolated systolic hypertension in the elderly. *Arch Intern Med* 2000;160:211-20.
32. Curb JD, Abbott RD, MacLean CJ, et al. Age-related changes in stroke risk in men with hypertension and normal blood pressure. *Stroke* 1996;27:819-24.