Short- and Long-Term Incidence of Stroke in White-Coat Hypertension

Paolo Verdecchia, Gian Paolo Reboldi, Fabio Angeli, Giuseppe Schillaci, Joseph E. Schwartz, Thomas G. Pickering, Yutaka Imai, Takayoshi Ohkubo, Kazuomi Kario

Abstract—White-coat hypertension (WCH) has been associated with a low risk for stroke, but long-term data are scanty. We analyzed individual data from 4 prospective cohort studies from the United States, Italy, and Japan that used comparable methodology for 24-hour noninvasive ambulatory blood pressure monitoring (ABPM). Overall, 4406 subjects with essential hypertension and 1549 healthy normotensive controls who were untreated at the time of initial ABPM were followed for a median of 5.4 years up to censoring or occurrence of a first stroke. At entry, mean age of subjects was 56 years (range 18 to 97). Prevalence of WCH was 9%. During follow-up, there were 213 new cases of stroke. Stroke rate (×100 person years) was 0.35 in the normotensive group, 0.59 in the WCH group, and 0.65 in the group with ambulatory hypertension. In a multivariate analysis, the adjusted hazard ratio for stroke was 1.15 (95% confidence interval [CI], 0.61 to 2.16) in the WCH group (P=0.66) and 2.01 (95% CI, 1.31 to 3.08) in the ambulatory hypertension group (P=0.001) compared with the normotensive group. After the sixth year of follow-up, the incidence of stroke tended to increase in the WCH group, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of follow-up. In conclusion, WCH was not associated with a definitely increased risk of stroke during the total follow-up period. However, WCH might not be a benign condition for stroke in the long term. (Hypertension. 2005;45:203-208.)

Key Words: blood pressure monitoring, ambulatory ■ stroke ■ blood pressure

Methods

The International Collaborative Study of the Prognostic Utility of ABPM was initiated to examine the relationship between ambulatory BP and the risks of cardiovascular disease using individual data from a pooled sample of large observational cohorts that contain ambulatory BP measurements. The aims of the study, the structure of the database, and all analytic and publication aspects were discussed and agreed on in advance. The study from the United States was the New York Prognostic Effects of ABPM (NYPEAP)14; the study from Italy was the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA)5,11; and the studies from Japan were the Ohasama study12 and the Jichi Medical School (JMS)-ABPM Study, Wave 1.6,13 Details regarding inclusion and exclusion criteria in the single studies have been published previously.5,6,10-13

The majority of subjects in the NYPEAP (83%), PIUMA (88%), and JMS-ABPM (88%) cohorts had a clinic BP ≥140 mm Hg systolic BP (SBP) or 90 mm Hg diastolic BP (DBP) at entry compared with only 27% in the Ohasama community sample. Subjects on antihypertensive medications in NYPEAP, PIUMA, and Tochigi, but not Ohasama, were withdrawn from medications for a minimum of 2 weeks before ABPM. In NYPEAP, PIUMA, and JMS-ABPM, clinically normotensive subjects (ie, those with office BP <140 mm Hg SBP and 90 mm Hg DBP) were generally healthy volunteers recruited from the hospital staff or asymptomatic subjects without medical problems referred to the hospital facility for various reasons.

Received July 15, 2004; first decision July 30, 2004; revision accepted October 28, 2004.
From the Dipartimento Malattie Cardiovascolari (P.V., F.A.), Ospedale R. Silvestrini, Perugia, Italy; Dipartimento Medicina Interna (G.P.R.), Università degli Studi di Perugia, Italy; Medicina Interna (G.S.), Angiologia e Malattie da Arteriosclerosi, Università degli Studi di Perugia, Italy; Department of Psychiatry and Behavioral Science (J.E.S.), State University of New York, Stony Brook; Behavioral Cardiovascular Health and Hypertension Program PH-9 946 (T.G.P.), Columbia University College of Physicians and Surgeons, New York, NY; Department of Clinical Pharmacology and Therapeutics (Y.I., T.O.), Tohoku University Graduate School of Medicine and Pharmaceutical Science, Sendai, Japan; and Department of Cardiology (K.K.), Jichi Medical School, Tochigi, Japan.
Correspondence to Paolo Verdecchia, MD, FACC, Dipartimento Malattie Cardiovascolari, Ospedale R. Silvestrini, 06100 Perugia, Italy. E-mail verdec@tin.it

Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000151623.49780.89
Subjects with overt cardiac or cerebrovascular disease, cancer, or hepatic or renal disease at enrollment were excluded. Subjects with diabetes, defined by a fasting glucose of 7.8 mmol/L or use of an oral hypoglycemic agent or insulin, were included. All subjects provided informed consent to be included in each of the 4 studies, which were approved by local ethical committees.

**BP Measurement**

Details regarding the procedures for clinic BP and ABPM in the NYPEAP, PIUMA, Ohasama, and JMS-ABPM cohorts have been published previously. Clinic BP was taken at the time of enrollment into the study. In the NYPEAP study, a BP taken by the physician was available for 85% of participants. When missing, the clinic BP taken by a nurse was substituted.

In all 4 studies, ABPM was carried out at entry. In the PIUMA study, the monitor (SpaceLabs 5200, 90202, or 90207; SpaceLabs) was set to measure BP every 15 minutes during the entire 24-hour period. In the NYPEAP study, readings were taken either: (1) every 15 minutes between 6 AM and 12 PM and at 30-minute intervals between 12 PM and 6 AM using either a Del Mar Avionics P2 or P3 or a SpaceLabs 5200 (first 672 subjects); or (2) every 15 minutes between 8 AM and 10 PM and at 30-minute intervals between 10 PM and 8 AM using a SpaceLabs 90202 monitor (last 341 subjects).

In the Ohasama study, readings were taken at 30-minute intervals. Well-trained public health nurses visited each participant on a weekday morning to attach the ABPM device and to detach it the next morning. The participants kept a diary to record daily activities. Ambulatory BP was monitored using the ABPM-630 (Nippon Colin), preset to measure BP every 15 minutes. In the JMS-ABPM, noninvasive ABPM was performed on a weekday with 1 of 3 automatic devices (ABPM-630; Nippon Colin; TM-2421 or TM-2425, Ad&D Co., Inc.), which recorded BP and pulse rate every 30 minutes for 24 hours.

Using self-reports of the times participants went to sleep and woke up, ambulatory BP readings were aggregated to create a mean of all readings taken while awake and the mean of all readings taken during sleep. This was done separately for SBP and DBP and for pulse pressure (PP), the difference between SBP and DBP.

**White-Coat Hypertension**

WCH was defined by an average awake ambulatory BP <130 mm Hg SBP and 80 mm Hg DBP. We also determined the risk of stroke associated with a definition of WCH based on an awake ambulatory BP <135/85 mm Hg.

**Follow-Up**

Follow-up was based on telephone contacts or periodical clinical visits at the referring facility or through the Regional Stroke Registration System. Stroke was defined as a focal central nervous system lesion considered vascular in origin and having clinical sequelae lasting ≥24 hours. Fatal and nonfatal strokes were included. Transient ischemic attacks were excluded from the present analysis.

**Data Analysis**

Statistical analysis was performed using SPSS (SPSS) and SAS-Stat (SAS Institute). One-way ANOVA and multiple comparisons with the Tukey test when appropriate were performed to compare the study sites and the 3 groups with clinical normotension, WCH, and ambulatory hypertension. We report the number of strokes that were recorded in each study, the total number of person years of follow-up for that event, and the unadjusted incidence rate. For survival analyses, event-free curves were estimated using Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. For subjects who experienced multiple events, analysis was restricted to the first event. The independent effect of several prognostic factors on survival was tested by stepwise Cox model.

### TABLE 1. Main Characteristics in the Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort (n=5955)</th>
<th>NYPEAP (n=1296)</th>
<th>PIUMA (n=2620)</th>
<th>Ohasama (n=1277)</th>
<th>JMS-ABPM (n=762)</th>
<th>Overall P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56 (14)</td>
<td>50 (13)</td>
<td>51 (12)</td>
<td>61 (10)</td>
<td>72 (10)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>White, %</td>
<td>64.1</td>
<td>92.2</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black, %</td>
<td>1.4</td>
<td>6.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asian, %</td>
<td>34.2</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Other, %</td>
<td>0.3</td>
<td>1.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>50</td>
<td>65</td>
<td>53</td>
<td>34</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.2 (16)</td>
<td>75.1 (14)</td>
<td>75.1 (14)</td>
<td>54.0 (9)</td>
<td>56.0 (10)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.3 (3.8)</td>
<td>25.1 (3.5)</td>
<td>26.8 (3.9)</td>
<td>23.4 (3.0)</td>
<td>24.0 (3.5)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.0</td>
<td>not available</td>
<td>7.6</td>
<td>17.5</td>
<td>11.9</td>
<td>-</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>19.7</td>
<td>10.7</td>
<td>23.6</td>
<td>19.3</td>
<td>20.9</td>
<td>-</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.43 (1.08)</td>
<td>5.85 (1.11)</td>
<td>5.54 (1.09)</td>
<td>4.98 (0.93)</td>
<td>5.17 (0.88)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>87.5 (22)</td>
<td>95.5 (23)</td>
<td>87.5 (21)</td>
<td>not available</td>
<td>79.6 (19)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.50 (1.35)</td>
<td>5.81 (1.18)</td>
<td>5.63 (1.38)</td>
<td>not available</td>
<td>5.33 (1.39)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>149 (23)</td>
<td>150 (21)</td>
<td>154 (20)</td>
<td>131 (18)</td>
<td>160 (22)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>90 (14)</td>
<td>94 (11)</td>
<td>95 (11)</td>
<td>74 (11)</td>
<td>91 (14)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Office PP, mm Hg</td>
<td>59 (17)</td>
<td>56 (18)</td>
<td>58 (17)</td>
<td>57 (14)</td>
<td>69 (16)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Awake SBP, mm Hg</td>
<td>139 (17)</td>
<td>141 (17)</td>
<td>141 (16)</td>
<td>129 (14)</td>
<td>145 (18)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Awake DBP, mm Hg</td>
<td>87 (15)</td>
<td>91 (10)</td>
<td>91 (11)</td>
<td>76 (8)</td>
<td>82 (29)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Awake PP, mm Hg</td>
<td>52 (15)</td>
<td>49 (13)</td>
<td>50 (11)</td>
<td>53 (8)</td>
<td>62 (29)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Sleep SBP, mm Hg</td>
<td>121 (18)</td>
<td>122 (18)</td>
<td>124 (17)</td>
<td>112 (15)</td>
<td>127 (18)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Sleep DBP, mm Hg</td>
<td>72 (11)</td>
<td>76 (11)</td>
<td>75 (11)</td>
<td>64 (8)</td>
<td>72 (11)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Sleep PP, mm Hg</td>
<td>49 (11)</td>
<td>46 (13)</td>
<td>49 (11)</td>
<td>48 (8)</td>
<td>55 (11)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>
Analyses were stratified by study site because of expected differences in stroke rate between the different groups. Several potential confounding variables assessed at entry were considered in the analysis: current smoking status, weight, height, body mass index, total cholesterol, and use of antihypertensive medication, including those titrated off before ABPM. In 2-tailed tests, \( P < 0.05 \) were considered statistically significant.

**Results**

**Cohort Features**

As shown in Table 1, age of the subjects was higher in the JMS-ABPM cohort than in the other cohorts (all \( P < 0.01 \)). Diabetes was more frequent in the Ohasama sample (all \( P < 0.001 \)) compared with each of the others, but information was not available from the NYPEAP cohort. Office SBP and PP were highest in the JMS-ABPM cohort (all \( P < 0.01 \) versus the other cohorts), whereas office DBP was highest in the PIUMA cohort (all \( P < 0.01 \) versus the other cohorts). Comparable differences between the cohorts were found for awake and asleep ambulatory BP.

**Differences Between Groups**

Age of the subjects (Table 2) was higher in the WCH group than in the other groups. Subjects with WCH tended to be women more frequently, smokers less frequently, and diabetics more frequently when compared with those with ambulatory hypertension (all \( P < 0.01 \)). In the WCH group, office BP was intermediate between the normotensive group and that with ambulatory hypertension. In contrast, awake SBP and DBP were lower in the group with WCH than in the normotensive group (both \( P < 0.01 \)), whereas sleep SBP and DBP were comparable between the 2 group. Prevalence of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up is reported in Figure 1. A similar proportion of subjects included in the normotensive control group or the WCH group at entry were receiving the 5 classes of antihypertensive drugs (all \( P < NS \)). In contrast, a greater proportion of subjects belonging to the AH group were receiving diuretics, \( \beta \)-blockers, angiotensin-converting enzyme inhibitors or calcium antagonists (\( P < 0.01 \) versus each of the other groups). Frequency of treatment with angiotensin II antagonists did not differ between the groups.

![Image](https://hyper.ahajournals.org/)

**Figure 1.** Percentage of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up. ACE indicates angiotensin-converting enzyme.
TABLE 3. Entry Characteristics of Subjects With and Without Future Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Future Stroke (n=5742)</th>
<th>Future Stroke (n=213)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 (14)</td>
<td>68 (12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>49.3</td>
<td>56.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68 (16)</td>
<td>64 (16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.3 (3.3)</td>
<td>25.0 (4.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10.5</td>
<td>23.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asian ethnic group, %</td>
<td>33.5</td>
<td>53.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>19.3</td>
<td>29.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.43 (1.08)</td>
<td>5.35 (1.06)</td>
<td>0.293</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>86.9 (22)</td>
<td>91.1 (20)</td>
<td>0.028</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.50 (1.3)</td>
<td>5.78 (1.8)</td>
<td>0.021</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>148 (22)</td>
<td>159 (24)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>90 (14)</td>
<td>90 (14)</td>
<td>0.95</td>
</tr>
<tr>
<td>Office PP, mm Hg</td>
<td>59 (16)</td>
<td>69 (19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Awake SBP, mm Hg</td>
<td>139 (17)</td>
<td>149 (19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Awake DBP, mm Hg</td>
<td>87 (15)</td>
<td>87 (12)</td>
<td>0.657</td>
</tr>
<tr>
<td>Awake PP, mm Hg</td>
<td>52 (15)</td>
<td>61 (14)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep SBP, mm Hg</td>
<td>121 (17)</td>
<td>134 (21)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep DBP, mm Hg</td>
<td>72 (11)</td>
<td>76 (12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep PP, mm Hg</td>
<td>49 (11)</td>
<td>58 (14)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Incidence of Stroke

There were 213 new cases of stroke. Overall, the JMS-ABPM cohort showed the highest rate of stroke (6.09/100 person years) followed by the Ohasama cohort (2.12/100 person years), the PIUMA cohort (0.59/100 person years), and the NYPEAP cohort (0.19/100 person years).

At entry (Table 3), subjects with future stroke were older, leaner, and more frequently smokers, diabetics, and of Asian ethnic origin than the subjects without future stroke (all P<0.01). Office and awake SBP and PP, but not DBP, were higher in the group with future stroke than in that without future stroke (all P<0.001). Sleep SBP, DBP, and PP were higher in the group with future stroke (all P<0.001).

The cumulative hazard for stroke (Figure 2) differed between the normotensive group, the group with WCH, and the group with ambulatory hypertension (log-rank test; P value for trend=0.0013). Figure 2 shows that the cumulative hazard for stroke was comparable in the WCH and normotensive groups up to the sixth year of follow-up. However, subsequently, there was an increase in the hazard of stroke in the WCH group, with the corresponding curve diverging from that of the normotensive group and crossing that of the ambulatory hypertension group by the ninth year of follow-up.

The crude rate of stroke (×100 person years) during the entire follow-up period was 0.35 in the normotensive group, 0.59 in the WCH group, and 0.65 in the group with ambulatory hypertension. The corresponding values up to the sixth year of follow-up were 1.06 in the normotensive group, 0.91 in the WCH group, and 1.5 in the ambulatory hypertension group. The unadjusted hazard ratios for stroke, with 95% confidence intervals (CIs), are displayed in Figure 3. Results were comparable using the 130/80 and the 135/85 mm Hg threshold values for definition of WCH.

Multivariate Analysis

In a Cox analysis (Table 4) stratified by center, WCH was associated with a nonsignificant 1.15 hazard ratio for stroke compared with the normotensive group (P=0.658). The no-interaction assumption of the stratified model was evaluated according to Kleinbaum and found acceptable at the <0.01 level. The no-interaction assumption implies that the variables being stratified (ie, center) do not interact with the covariates in the model. When office SBP and awake SBP were forced in the same model, office BP did not yield statistical significance (P=0.322), and the risk of stroke increased by 2% for any 1 mm Hg increase in the awake SBP (95% CI, 1% to 3%; P=0.0001). The 6-year risk factor-adjusted probability of stroke in clinically normotensive individuals and in hypertensive subjects with WCH and ambulatory hypertension is depicted in Figure 4. Estimates have been made in smokers and nonsmokers for either sex.

Discussion

This study is the first to investigate the short- and long-term risk of stroke in subjects with WCH, ambulatory hypertension, and clinical normotension in a large multinational and multiethnic population. WCH was defined by an average daytime ambulatory BP <130 mm Hg SBP and <80 mm Hg DBP because in a previous analysis, the risk of cardiovascular events increased in association with higher ambulatory BP levels. Average daytime levels of BP <130/80 mm Hg have been defined as definitely normotensive.

During the entire follow-up period, the incidence of stroke did not differ between the WCH and the normotensive control groups. However, stroke rate showed a trend to increase after the sixth year of follow-up in the group with WCH, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of observation. Results were consistent among the different cohorts and were independent of age, sex, cigarette smoking, and previous antihypertensive medications.
Clinical Relevance and Prognostic Value of WCH

ABPM has been approved by the US Centers for Medicare and Medicaid Services18 for reimbursement in patients with suspected WCH. Although some outcome-based studies suggested that WCH is associated with a risk of events apparently comparable to that of clinically normotensive subjects and inferior to that of subjects with elevated daytime BP,5–9 other studies focused on target organ damage suggested that patients with WCH may be at intermediate risk between the clinically normotensive individuals and those with ambulatory hypertension.7,8,19–21 Therefore, the important issue of whether WCH should be considered an innocent condition remains open and unresolved.4,22 Unfortunately, only a few data are available on the long-term natural history of WCH. In a longitudinal study, such condition evolved into ambulatory hypertension in 37% of subjects, with an accompanying rise in left ventricular mass.23 In a study, a comparable proportion of subjects with clinical normotension and WCH evolved toward ambulatory hypertension (15% and 22%, respectively).24 In this study, based on 38 100 person years of observation, the highest stroke rate was noted in the clinical-based JMS-ABPM cohort, which included elderly Japanese subjects with hypertension, followed by the Ohasama cohort, which included a general Japanese population, and the PIUMA cohort, which included Italian subjects with essential hypertension.25 Thus, it could be speculated that frequent BP peaks triggered by alerting reactions to stress may contribute to the rise in long-term risk of carotid atherosclerosis and ultimately of stroke in subjects with WCH.

Study Limitations

Because office and ambulatory BP measurements have been obtained only at entry, no information is available on the prognostic impact of serial changes in these parameters over time. In the Office versus Ambulatory Blood Pressure (OvA) study, in-treatment ambulatory BP predicted cardiovascular events independently of traditional risk factors in treated hypertensive patients.26 However, the OvA study could not compare the predictive value of pretreatment versus in-treatment BP. In the PIUMA study, in-treatment ambulatory BP was more potent tension. The lowest stroke rate was observed in the NYPEAP cohort, recruited in the New York area. In the absence of a significant center-covariate interaction, our findings can be reliably assumed as consistent across the different cohorts.

An unexpected finding in our study was a distinct trend toward an increased incidence of stroke in the WCH group after the sixth year of follow-up. Although substantiated only by a small number of events, these findings raise some concerns about the long-term safety of WCH. Clearly, further long-term studies are needed to clarify this aspect. In this context, it has been noted that the degree of BP rise during mental stress is a predictor of the long-term growth of atherosclerotic plaque independently of age and initial plaque area25 Thus, it could be speculated that frequent BP peaks triggered by alerting reactions to stress may contribute to the rise in long-term risk of carotid atherosclerosis and ultimately of stroke in subjects with WCH.

TABLE 4. Independent Predictors of Stroke

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1 year</td>
<td>1.08</td>
<td>0.000</td>
<td>1.07–1.10</td>
</tr>
<tr>
<td>Sex</td>
<td>Men vs women</td>
<td>1.57</td>
<td>0.003</td>
<td>1.17–2.12</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Yes vs no</td>
<td>1.71</td>
<td>0.001</td>
<td>1.24–2.37</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>Yes vs no</td>
<td>1.63</td>
<td>0.001</td>
<td>1.23–2.18</td>
</tr>
<tr>
<td>Ambulatory BP category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive group</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCH</td>
<td>1.15</td>
<td>0.658</td>
<td>0.61–2.16</td>
<td></td>
</tr>
<tr>
<td>Ambulatory hypertension</td>
<td>2.01</td>
<td>0.001</td>
<td>1.31–3.08</td>
<td></td>
</tr>
</tbody>
</table>

Analysis stratified by center. WCH was defined by an average awake BP <130/80 mm Hg SBP and 80 mm Hg DBP.
than pretreatment ambulatory BP for cardiovascular risk strati-
ification.27 In the present study, a comparable number of subjects
who were clinically normotensive or white-coat hypertensives at
entry were receiving antihypertensive drugs during follow-up.
These data suggest a comparable evolution toward the need of
antihypertensive treatment in subjects with WCH and clinically
normotensive controls. Finally, because data on mortality shortly
after stroke were not available from all cohorts, no separate
analysis could be performed on fatal and nonfatal stroke.
Similarly, analyses on the different types of stroke (ie, lacunar,
embolic, hemorrhagic, etc) were not possible because of insuf-
cient standardization across the different cohorts. A substantial
proportion of strokes in hypertensive subjects are attributable to
lacunar infarction at the base of the brain, where short straight
arteries transmit a substantial BP load from the large arteries
to small resistance arteries over a very short distance.28

Perspectives
The long-term prognostic impact of WCH remains uncertain.
In this multinational outcome-based study, we failed to detect
in the differences in the risk of stroke between subjects with WCH
and clinically normotensive controls. The risk of stroke
remained consistently higher among subjects with ambulatory
hypertension. However, the incidence of stroke showed a trend
to increase in the long run in the group with WCH, with the
 corresponding hazard curve crossing that of the ambulatory
hypertension group by the ninth year of follow-up. These data
raise the hypothesis, to be tested in future studies, that WCH
might not be a benign condition for stroke in the long term.

Acknowledgments
This work was support by grants from the National Heart, Lung,
and Blood Institute, Japan Arteriosclerosis Prevention Fund, and
the Ministry of Japan, Associazione Umbra Cuore e Ipertensione
and Bristol-Myers Squibb Company. We thank Francesca Saveri
for secretarial assistance and Mariano Cecchetti for nursing assistance.

References
How common is white-coat hypertension? J Am Med Assoc. 1988;259:
225–228.
2. White WB, Schulman P, McCabe EJ, Dey HM. Average daily blood
pressure, not office pressure, determines cardiac function in patients with
Society of Hypertension guidelines for the management of hypertension.
Palatini P; European Society of Hypertension Working Group on Blood
Pressure Monitoring. When can the practicing physician suspect white
coat hypertension? Statement from the Working Group on Blood Pressure
Silent and clinically overt stroke in older Japanese subjects with white-coat
7. Owens PE, Lyons SP, Rodriguez SA, O’Brien ET. Is elevation of clinic
blood pressure in patients with white coat hypertension who have normal
ambulatory blood pressure associated with target organ changes? J Hum
8. Owens P, Atkins N, O’Brien E. Diagnosis of white coat hypertension by
Leeuw PW, Dobovisek J, Jaaskivi M, Leontetti G, O’Brien E, Palatini P,
Parati G, Rodicio JL, Vanhanen H, Webster J. Response to antihyper-
tensive therapy in older patients with sustained and nonsustained systolic
hypertension. Systolic Hypertension in Europe (Syst-Eur) Trial Investi-
M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboli G.
Ambulatory blood pressure: an independent predictor of prognosis in
Hisansuchi I, Imai Y. Prediction of stroke by ambulatory blood pressure
monitoring versus screening blood pressure measurements in a general
Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood
pressure as a predictor of silent and clinical cerebrovascular disease in elderly
15. Pickering TG for an American Society of Hypertension Ad Hoc Panel.
Recommendations for the use of home (self) and ambulatory blood pressure
187–220.
1996.
18. CMS. Centers for Medicare and Medicaid Services. Medicare Coverage
Policy—Decisions. Ambulatory blood pressure monitoring (#CAG-
19. Grandi AM, Broggi R, Colombo S, Santillo R, Imperiale D, Bertolini A,
Guardi L, Venco A. Left ventricular changes in isolated office hyper-
tension. A blood pressure-matched comparison with normotension and
Valagussa F, Bombelli M, Giannattasio C, Zanchetti A, Mancia G. Alter-
ations 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). Circa-
Pessina AC. Target-organ damage in stage I hypertensive subjects with
white coat and sustained hypertension: results from the HARVEST study.
22. Moser M. White-coat hypertension—to treat or not to treat. A clinical
Guerrieri M, Comparato E, Porcellati C. Identification of subjects with
white-coat hypertension and persistently normal ambulatory blood
24. Polonia H, Santos AR, Gama GM, Bost F, Bettencourt PM, Martins LR.
Follow-up clinic and ambulatory blood pressure in untreated white-coat
hypertensive patients (evaluation after 2–5 years). Blood Press Monit.
25. Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress
and the progression of carotid artery disease. J Hypertens. 1997;15:
49–55.
DA, Faghri RH, Gheeraert PJ, Missault LH, Braun JJ, Six, RO, Van Der
Niepen P, O’Brien E; Office Versus Ambulatory Blood Pressure Study Investi-
gators. Prognostic value of ambulatory blood pressure recordings in
M, Angeli F, Norgiolini S, Ambrosio A. Risk of cardiovascular disease in
relation to achieved office and ambulatory blood pressure control in
28. Spence JD. Cerebral consequences of hypertension. In: Laragh JH,
Branner BM, eds. Hypertension: Pathophysiology, Diagnosis and Man-
Short- and Long-Term Incidence of Stroke in White-Coat Hypertension
Paolo Verdecchia, Gian Paolo Reboli, Fabio Angeli, Giuseppe Schillaci, Joseph E. Schwartz, Thomas G. Pickering, Yutaka Imai, Takayoshi Ohkubo and Kazuomi Kario

Hypertension. 2005;45:203-208; originally published online December 13, 2004;
doi: 10.1161/01.HYP.0000151623.49780.89
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/45/2/203