Cardiovascular Outcome in White-Coat Versus Sustained Mild Hypertension
A 10-Year Follow-Up Study

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Background—The aim of this study was to compare the risk conferred by white-coat versus sustained mild hypertension for the development of cardiovascular disease.

Methods and Results—Patients (n = 479) who underwent 24-hour intra-arterial ambulatory blood pressure monitoring on the basis of a persistently elevated clinic systolic blood pressure of 140 to 180 mm Hg were followed up for the development of subsequent cardiovascular events during a 9.1±4.2-year period. White-coat hypertension, defined as a clinic systolic blood pressure of 140 to 180 mm Hg associated with a 24-hour ambulatory systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg, was present in 126 patients, and the remainder had sustained mild hypertension. A subgroup of patients without complications underwent follow-up echocardiography and carotid ultrasound. White-coat hypertensives were younger (44±12 versus 52±10 years, respectively; P<0.001) and had a significantly lower incidence of cardiovascular events (1.32 versus 2.56 events per 100 patient-years, respectively; P<0.001) than sustained hypertensives. Multivariate analysis revealed age (P=0.002), sex (P=0.007), race (P=0.001), smoking (P=0.005), and the presence of white-coat hypertension (hazard ratio, 0.29; 95% CI, 0.09 to 0.90; P=0.04) to be independent predictors of subsequent cardiovascular events. Subgroup analysis in patients without complications revealed a lower incidence of left ventricular hypertrophy and lesser degrees of carotid hypertrophy in the white-coat group.

Conclusions—These findings indicate a relatively benign outcome in white-coat hypertension compared with sustained mild hypertension. (Circulation. 1998;98:1892-1897.)

Key Words: hypertension ■ prognosis ■ hypertrophy ■ cardiovascular diseases ■ carotid arteries

Over the past 50 years, it has been increasingly recognized that isolated clinic blood pressure measurements taken by the physician may not be truly representative of the daily blood pressure load away from the medical environment.1,2 Twenty-four-hour ambulatory blood pressure monitoring offers a more valid assessment of an individual’s true blood pressure level by taking frequent readings during routine daily activities.3 Application of this technique has allowed the identification of a subgroup of individuals with a persistently elevated clinic blood pressure but normal ambulatory blood pressure. The term “white-coat hypertension” has been used to describe this phenomenon, and it is thought to occur in ≈20% to 40% of presumed mildly hypertensive patients.4 A recently completed longitudinal study5 and preliminary data from a large ongoing study6 have shown white-coat hypertension to be associated with a lower risk of subsequent cardiovascular events than sustained hypertension. However, comparative cross-sectional data regarding target-organ damage in patients with white-coat versus sustained hypertension are conflicting.7-14 Left ventricular hypertrophy, carotid wall thickening, and atherosclerotic plaques are prognostically significant forms of target-organ damage15,16 and may be considered surrogate markers of overt cardiovascular disease.17

The aim of this study was to compare the risk conferred by white-coat and sustained mild hypertension for the development of subsequent cardiovascular events and for the long-term development of surrogate markers of overt cardiovascular disease in an uncomplicated subgroup of patients.

See p 1834

Methods

The hypertension database in our institution consists of 502 patients with mild hypertension, defined as a clinic systolic blood pressure of 140 to 180 mm Hg, who had undergone 24-hour intra-arterial ambulatory blood pressure monitoring within the period January 1, 1979, to January 1, 1993.18 The diagnosis of hypertension was based on persistently elevated clinic blood pressures taken over a period of weeks to months in a primary-care setting. At the initial hospital visit, a single blood pressure measurement was taken by a nurse or technician, with the patient resting for 5 to 10 minutes in the supine position.
Follow-up

The study patients have been intermittently reviewed over the years to record clinic blood pressure, drug therapy, and the occurrence of interim cardiovascular events. The most recent follow-up was performed during an 18-month period from 1994 to 1996 (Figure 1). Of the 502 study patients, 50 patients had died (dates and certified causes of death obtained from the National Health Service Central Register, Southport, UK), and 244 attended follow-up reevaluation in 1994 to 1996, consisting of a full history, physical examination, clinic blood pressure measurement on usual medication, risk factor profile, blood urea, serum electrolytes and creatinine estimation, total cholesterol level, echocardiography, and carotid ultrasonography. In the remaining 208 patients who failed to respond to 2 written communications, a minimum of 2 years of follow-up data were obtained on 185 of these patients from departmental and hospital records of previous visits. Adequate follow-up data were not available for the remaining 23 patients, which restricted the analysis to 479 of the 502 patients. The racial composition of the group, reflecting the local population of the London boroughs of Harrow, Brent, and Ealing, consisted of 361 white, 86 South Asian (Indian subcontinent), and 32 black subjects.

Documentation of Events

Departmental and hospital records of all patients were scrutinized before follow-up. Events were classified as noncardiovascular death, coronary events, and cerebrovascular events. Coronary events consisted of fatal and nonfatal myocardial infarction, arrhythmic death, congestive heart failure death, and coronary revascularization. Cardiovascular events included fatal and nonfatal stroke. A history of myocardial infarction, stroke, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or peripheral revascularization volunteered by the patient was accepted if documented in the hospital records or if confirmed by the general practitioner.

Intra-Arterial Blood Pressure Monitoring

The methodology of intra-arterial blood pressure recording used in this laboratory has been well documented.\textsuperscript{19,20} Blood pressure was recorded from a fine brachial artery cannula with a specially designed transducer/perfusion unit and an Oxford Medilog Mark I tape recorder. The equipment was designed so that patients were fully ambulant and able to carry out their normal daily activities. The 24-hour tape recordings were analyzed on a custom-built hybrid computer using a program that calculated mean hourly blood pressure and heart rate. Mean systolic and diastolic intra-arterial blood pressures were calculated by averaging the 24-hour systolic and diastolic readings.

Echocardiography

M-mode and 2-dimensional echocardiography were performed by the same investigator using a commercially available machine (ATL Ultramark 9 HDI CV) with a 2- to 3-MHz broad-band transducer. Left ventricular end-diastolic dimensions were obtained from 2-dimensionally guided M-mode tracings according to the recommendations of the American Society of Echocardiography.\textsuperscript{21} Left ventricular mass index was calculated as follows:\textsuperscript{22} $LVMI = \frac{0.8 \times 1.04[(LVVID + PWT + IVST) - LVVID] + 0.6 \times \text{body surface area (g/m}^2\rangle$, where LVVID is the left ventricular internal diameter, PWT the posterior wall thickness, and IVST the interventricular septal thickness. Left ventricular hypertrophy was considered present if LVMI was $\geq 125 \text{ g/m}^2$ for men and $110 \text{ g/m}^2$ for women.

Carotid Ultrasonography

Both carotid arteries were imaged with the high-resolution Kontron Sigma 44 ultrasound system equipped with a mechanical sector probe with a 7.5-MHz annular imaging transducer providing an axial resolution of 0.15 mm. The mid and distal common carotid artery, carotid bulb, and proximal portions of the internal and external carotid arteries were systematically interrogated in short-axis and long-axis views. Three end-diastolic measurements of diffuse carotid intima-media thickness (IMT) were carried out on the far wall of both common carotid arteries, $\pm 1\text{ cm proximal to the carotid bulb in the longitudinal view.}$\textsuperscript{23} The mean of the 6 IMT measurements was used in the analysis. Two-dimensionally guided M-mode tracings of the distal common carotid artery were also obtained to determine lumen diameter (D). This was used to calculate cross-sectional area (CSA) as follows: $\text{PI(2IMT+D/2)^2-PI(D/2)^2}$. Carotid IMT and arterial wall CSA were considered to be markers of carotid hypertrophy. A plaque was defined as a distinct area with an IMT $\geq 50\%$ greater than that of the adjacent wall,\textsuperscript{24} and the maximal IMT measurement (IMT$_{\text{max}}$) was used as a semiquantitative score for carotid atherosclerosis severity. In the absence of atheroma, the greater of the IMT measurements from the far wall of the distal common carotid artery and the carotid bulb were taken as IMT$_{\text{max}}$.

Reproducibility of Left Ventricular and Carotid Artery Measurements

To assess serial intraobserver reproducibility of LVMI and carotid measurements, 30 patients underwent echocardiography and carotid ultrasonography on 2 separate occasions within a period of 2 weeks. Coefficients of variation for IMT, lumen diameter, IMT$_{\text{max}}$, and LVMI were 1%, 2%, 11%, and 14%, respectively.

Statistical Analysis

The clinical variables analyzed included age, sex, race, body mass index, serum cholesterol, smoking, and years of follow-up. Echocardiographic parameters consisted of the presence or absence of left ventricular hypertrophy, and carotid measurements included IMT, CSA, and IMT$_{\text{max}}$. Continuous variables were tested for normality by

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**Figure 1.** Follow-up scheme for 502 study patients.

- n = 502 patients
- n = 244 followed-up in 1994-96 (echo + carotid data)
- n = 185 with follow-up data from previous visits
- n = 479 study patients
- n = 23 without follow-up data

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TABLE 1. Comparison of the Demographic Data in Patients With White-Coat Hypertension Versus Sustained Hypertension

<table>
<thead>
<tr>
<th></th>
<th>White-Coat (n=126)</th>
<th>Sustained (n=353)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>44±12</td>
<td>52±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>57</td>
<td>67</td>
<td>NS</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>99 (78)</td>
<td>262 (74)</td>
<td>NS</td>
</tr>
<tr>
<td>Asian</td>
<td>19 (15)</td>
<td>67 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>8 (7)</td>
<td>24 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.9±4.8</td>
<td>26.7±4.1</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history, %</td>
<td>37%</td>
<td>42%</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.0±1.4</td>
<td>6.0±1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up period, y</td>
<td>9.0±4.0</td>
<td>9.2±4.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

The Shapiro-Francia test. A log₁₀ transformation was used for IMT, CSA, and IMT_max to improve the assumption of normality; all other continuous variables conformed to a normal distribution. A comparison between the groups with white-coat and sustained mild hypertension was made by use of 2 sample t tests and Fisher’s exact test for continuous and categorical variables, respectively. Cox’s survival analysis was performed to determine the independent predictors of time to the first cardiovascular event with respective hazard ratios, 95% CIs, and P values. The continuous variables included in the Cox model were age, body mass index, initial clinic systolic blood pressure, and cholesterol level; hazard ratios reflected the risk associated with a unit increase in these variables. Categorical variables consisted of sex, race, smoking, and white-coat hypertension; hazard ratios represented the risk of a first event in men relative to women, South Asians relative to whites, smokers relative to nonsmokers, and white-coat hypertensives relative to sustained hypertensives, respectively. Because Afro-Caribbeans constituted only a small proportion of the study population, this group was not included in the analysis of race. Multivariate analysis was performed on a subgroup of patients without complications with white-coat versus sustained mild hypertension to assess whether there was a significant difference in left ventricular and carotid artery parameters between these 2 groups, after adjustment for clinical variables. A value of P<0.05 was considered significant.

Results

Demographic Data

Of the 479 patients analyzed, 126 were designated as having white-coat hypertension, and 353 had sustained mild hypertension. As shown in Table 1, the white-coat hypertension group were significantly younger than those with sustained hypertension (44±12 versus 52±10 years, respectively; P<0.001) but otherwise demonstrated similar demographic characteristics. Details of preevent antihypertensive drug therapy were available for 112 of 126 patients with white-coat hypertension and 317 of 353 patients with sustained hypertension.

TABLE 2. Comparison of Preevent Antihypertensive Drug Therapy in Patients With White-Coat Hypertension and Sustained Hypertension

<table>
<thead>
<tr>
<th>Antihypertensive Drugs</th>
<th>White-Coat (n=112), %</th>
<th>Sustained (n=317), %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>18</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>54</td>
<td>47</td>
<td>NS</td>
</tr>
<tr>
<td>Multiple therapy</td>
<td>28</td>
<td>47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

A comparison of the blood pressure data is given in Figure 2. In accordance with the definition, 24-hour ambulatory systolic and diastolic blood pressures were considerably lower in the group with white-coat hypertension than in those with sustained hypertension. Initial clinic systolic and diastolic blood pressures, although elevated, were also significantly lower in the white-coat hypertension group, but follow-up clinic blood pressures were similar in both groups.

Comparison of Events

In the white-coat hypertension group, 15 first events were recorded, consisting of 4 noncardiovascular deaths, 5 cardiovascular deaths, 3 myocardial infarctions, and 3 coronary revascularizations. These occurred over a period of 9.0±4.0 years for the 126 patients, yielding an event rate of 1.32 events per 100 patient-years. In comparison, 83 first events occurred in the 353 sustained hypertensives during a 9.2±4.3-year follow-up period, giving a significantly higher event rate of 2.56 events per 100 patient-years (P<0.001) for the latter group. These events included 13 noncardiovascular deaths, 16 cardiovascular deaths, 10 strokes, 31 myocardial infarctions, 12 coronary revascularizations, and 1 peripheral revascularization. Figure 3 shows the frequency distribution of noncardiovascular death, coronary events, and cerebrovascular events in the 2 groups of patients. Whereas the prevalence of noncardiovascular death in the 2 groups was similar, those with sustained hypertension had approximately twice the risk of coronary events and at least 4
times the risk of a cerebrovascular event compared with white-coat hypertensives.

Table 3 summarizes the results of the Cox survival analysis for predicting the time to a first event. Age ($P=0.002$), sex ($P=0.007$), race (South Asians relative to whites, $P=0.001$), smoking ($P=0.005$), and the presence of white-coat hypertension ($P=0.04$) were independent predictors of subsequent cardiovascular events.

**Target-Organ Status**

Of the 244 patients who attended follow-up evaluation, 32 were excluded because of a history of overt cardiovascular disease, and 15 had suboptimal echocardiographic views. Therefore, a subgroup of 197 patients without complications were assessed for cardiovascular target-organ damage at a mean follow-up period of 10.1 ± 3.4 years; 65 had white-coat hypertension, and 132 were sustained hypertensives. There was no statistically significant difference in the demographic and blood pressure data of the white-coat and sustained hypertensives in this subgroup compared with the original study population.

As outlined in Table 4, LVMI and the prevalence of left ventricular hypertrophy were significantly lower in those with white-coat hypertension. Similarly, IMT and CSA were also significantly lower in the latter group than in those with sustained hypertension. Although the proportion of patients with detectable carotid atherosclerotic plaques in the 2 groups was similar, IMT$_{max}$ was significantly lower in those with white-coat hypertension. After adjustment for clinical variables, the prevalence of manifest left ventricular hypertrophy was significantly lower in the white-coat hypertension group (11% versus 38%, $P<0.001$; odds ratio, 0.45; 95% CI, 0.2 to 0.9; $P=0.02$). Similarly, IMT and CSA were also significantly lower in the group with white-coat hypertension (Table 5). A nonsignificant trend toward a lower IMT$_{max}$ in the white-coat hypertension group was also observed.

**Discussion**

The intra-arterial method of ambulatory blood pressure monitoring is a powerful research tool and remains the reference standard by which noninvasive monitors are validated. It provides beat-to-beat measurements of blood pressure over a 24-hour period in truly ambulant patients and therefore represents the most authentic measure of the daily hemodynamic burden imposed by blood pressure. In comparison, noninvasive auscultatory and oscillometric monitors rely on intermittent recordings at predetermined time intervals, and these may not be accurate during unrestricted physical activity. The present study provides the first longitudinal data on white-coat hypertension by the intra-arterial technique. Mild hypertension was defined on the basis of a clinic systolic blood pressure of 140 to 180 mm Hg and did not take into account the level of clinic diastolic blood pressure. The use of this definition was influenced by cross-sectional evidence showing systolic blood pressure to be more strongly correlated to target-organ damage than diastolic blood pressure and because of the increasingly more common view that systolic blood pressure, except possibly in younger patients, may play the predominant role in the development of cardiovascular morbidity and mortality.

Our findings showed age, sex, race, smoking, and the presence of white-coat hypertension to be independent predictors of subsequent cardiovascular events in patients with mild hypertension based on conventional clinic blood pressure readings. South Asians were at a higher risk of cardio-

**Table 4.** Comparison of Left Ventricular and Carotid Artery Parameters in Patients With White-Coat Versus Sustained Hypertension

<table>
<thead>
<tr>
<th>Parameter</th>
<th>White-Coat (n=65)</th>
<th>Sustained (n=132)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVMI, g/m$^2$</td>
<td>95.5±27.6</td>
<td>111.6±31.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>LVH, %</td>
<td>11</td>
<td>38</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IMT, mm</td>
<td>0.055±0.15</td>
<td>0.060±0.014</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CSA, cm$^2$</td>
<td>0.12±0.04</td>
<td>0.15±0.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IMT$_{max}$, cm</td>
<td>0.12±0.07</td>
<td>0.16±0.10</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy.

**Table 5.** Comparison of the Differences in Carotid Artery Structure in White-Coat Hypertension Versus Sustained Hypertension After Adjustment for Clinical Variables

<table>
<thead>
<tr>
<th>% Difference</th>
<th>White-Coat vs Sustained</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMT</td>
<td>−7.5</td>
<td>−13.2 to −1.4</td>
<td>0.02</td>
</tr>
<tr>
<td>CSA</td>
<td>−11.4</td>
<td>−19.1 to −2.9</td>
<td>0.02</td>
</tr>
<tr>
<td>IMT$_{max}$</td>
<td>−13.6</td>
<td>−26.2 to 1.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; and WCHT, white-coat hypertension.
vascular complications than their white counterparts. This finding is consistent with epidemiological data from the United Kingdom showing that South Asians are particularly susceptible to coronary heart disease and also have a higher mortality from cerebrovascular disease than white subjects.18

White-coat hypertension was associated with a relatively benign outcome compared with sustained mild hypertension. This is substantiated by a significantly lower risk of subsequent cardiovascular events in the white-coat group and evidence of lesser degrees of prognostically significant target-organ damage compared with sustained hypertensives in the subset of patients without overt cardiovascular manifestations. Whereas the incidences of noncardiovascular deaths in the 2 groups were similar, sustained hypertensives had twice the incidence of subsequent coronary events and a 4-fold increased risk of cerebrovascular events compared with the white-coat hypertension group. It is notable, however, that the majority of patients with white-coat hypertension were being treated with antihypertensive drugs at follow-up. Blood pressure management during the interim period was based on clinic blood pressure readings as part of standard clinical practice and largely governed by the family practitioner. It is perhaps not surprising, therefore, that a large proportion of designated white-coat hypertensives received interim antihypertensive treatment because of persistently elevated clinic blood pressures. For ethical reasons, it was not possible to repeat intra-arterial ambulatory blood pressure monitoring to assess blood pressure control or influence further management.

Two previous longitudinal studies addressing the prognostic significance of white-coat hypertension, using intermittent noninvasive ambulatory blood pressure monitoring, have similarly found white-coat hypertension to be associated with a more benign outcome than ambulatory hypertension.5,6 It has also been observed that patients with a lower-than-predicted ambulatory blood pressure, derived from a regression line between ambulatory blood pressure and clinic blood pressure, have a lower risk of subsequent fatal or nonfatal cardiovascular events than patients with more elevated ambulatory blood pressure.29 These findings confirm the incremental prognostic value of ambulatory blood pressure monitoring for the stratification of cardiovascular risk in patients with presumed essential hypertension.

In the representative subgroup of patients without overt cardiovascular disease, white-coat hypertension was associated with a significantly lower long-term prevalence of left ventricular hypertrophy and lesser degrees of carotid hypertrophy compared with the sustained hypertension group, even after adjustment for clinical variables. IMTmax was 13.6% lower in the white-coat hypertension group after adjusted analysis, indicating a tendency toward less advanced carotid atherosclerotic changes compared with sustained hypertension. However, this difference failed to reach statistical significance because of a wide 95% CI. This may be attributed in part to the relatively small sample size, the important influence of age, and other atherogenic factors not taken into account in this study, such as lipoprotein levels and hemostatic factors. Previous cross-sectional studies comparing target-organ status of white-coat hypertensives with sustained hypertensives have provided conflicting data.7–24 Nonetheless, in accordance with our findings, the only cross-sectional studies assessing both left ventricular and carotid artery structure found LVMI and carotid IMT to be lower in white-coat hypertensives than in sustained hypertensives.30–32

In the absence of universally accepted limits of normal ambulatory blood pressure, the cutoff points used to dichotomize white-coat and sustained hypertensives in previous studies have been largely arbitrary. In the present study, we used a 24-hour ambulatory blood pressure cutoff point of 140/90 mm Hg, for many reasons. First, intra-arterial ambulatory blood pressure monitoring became an established technique at our institution in the late 1970s, at a time when there were few data on the normal range of ambulatory blood pressure. Therefore, for clinical purposes, for those in whom 24-hour ambulatory systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥90 mm Hg, antihypertensive treatment was generally advocated, whereas for those with lower readings, the recommendations were more conservative. Second, because intra-arterial monitoring allows the continuous measurement of blood pressure in truly ambulant patients, it has been suggested that average intra-arterial readings may be higher than those obtained by intermittent, noninvasive monitoring.35 Moreover, adopting this relatively high ambulatory blood pressure cutoff point could only have served to challenge the contention that white-coat hypertension is benign by including higher levels of ambulatory blood pressure in the white-coat group, thereby dampening any differences between those with white-coat and sustained hypertension.

This study did not include a normotensive control group for comparison because an insufficient number of normotensives have undergone intra-arterial monitoring at our institution. Therefore, it was not possible to evaluate the clinical significance of white-coat hypertension in relation to normotension. However, it can be stated on the basis of our findings that in a group of individuals with mild hypertension as defined by clinic blood pressure measurement, the outcome in white-coat hypertension as presently managed is relatively benign compared with sustained hypertension.

Acknowledgments

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