Resistant hypertension (RH) is defined as uncontrolled office blood pressure (BP), despite the use of ≥3 antihypertensive drugs, ideally including a diuretic.1 Even with a reported prevalence as high as 30% of general hypertensives,1–4 RH is still an understudied clinical condition with a high cardiovascular morbidity and mortality.1,5 In whom the performance of ambulatory BP monitoring (ABPM) is mandatory to diagnose 2 different groups, those with true and white-coat resistant hypertension. Patients are found to change categories between controlled/uncontrolled ambulatory pressures without changing their office blood pressures. In this way, ABPM should be periodically repeated. The aim of this study was to evaluate the most appropriate time interval to repeat ABPM to assure sustained blood pressure control in patients with white-coat resistant hypertension. This prospective study enrolled 198 patients (69% women; mean age: 68.9 ± 9.9 years) diagnosed as white-coat resistant hypertension on ABPM. Patients were submitted to a second confirmatory examination 3 months later and repeated twice at 6-month intervals. Statistical analyses included Bland-Altman repeatability coefficients and multivariate logistic regression. Mean office blood pressure was 163 ± 20/84 ± 17 mm Hg, and mean 24-hour blood pressure was 118 ± 8/66 ± 7 mm Hg. White-coat resistant hypertension diagnosis presented a moderate reproducibility and was confirmed in 144 patients after 3 months. In the third and fourth ABPMs, 74% and 79% of patients sustained the diagnosis. In multivariate regression, a daytime systolic blood pressure ≤115 mm Hg in the confirmatory ABPM tripled the chance of white-coat resistant hypertension status persistence after 1 year. In conclusion, a confirmatory ABPM is necessary after 3 months of the first white-coat–resistant hypertension diagnosis, and the procedure should be repeated at 6-month intervals, except in patients with daytime systolic blood pressure ≤115 mm Hg, in whom it may be repeated annually. (Hypertension. 2012;59[part 2]:384-389.)

Key Words: ambulatory blood pressure monitoring ■ resistant hypertension ■ white-coat effect ■ reproducibility

Subjects and Baseline Procedures
This was a longitudinal observational study with 198 consecutive patients diagnosed as WC-RH on the first ABPM, enrolled from January 2006 to May 2010, entering a cohort of resistant hypertensive patients in the hypertension outpatient clinic of a university hospital. All of the participants gave a written informed consent, and the local ethics committee had previously approved the study protocol. Compliance to antihypertensive treatment was evaluated in the first interview by a validated standard questionnaire.15 Only patients considered moderate or highly adherent to treatment were
enrolled. In clinical interview, demographic and anthropometric characteristics (sex, age, race, weight, height, and waist circumference), cardiovascular risk factors (diabetes mellitus, dyslipidemia, smoking, physical inactivity, and obesity), and target-organ damage (coronary heart disease, heart failure, cerebrovascular disease, advanced retinopathy, and peripheral arterial disease) were recorded.2

**BP Measurements**

Office BP was measured twice in the sitting position by the assisting physician using a digital oscillometric BP monitor (HEM-907 XL, Omron Healthcare, Kyoto, Japan) with a suitably sized cuff, and the physician using a digital oscillometric BP monitor (HEM-907 XL, Omron Healthcare, Kyoto, Japan) with a suitably sized cuff, and the 24-hour, daytime, and nighttime SBP and DBP, as well as the magnitude of the white-coat effect (WCE), estimated as the difference between office and ambulatory daytime measurements. The repeatability coefficients (twice the SDs of the differences between duplicate measurements)17 for office and ambulatory BPs and for the magnitude of the white-coat effect (WCE) were calculated.2

The study was divided into 2 phases (Figure 1). At the first phase, all of the patients diagnosed as WC-RH repeated ABPM after 3 months to confirm the diagnosis. On the second phase, all of the patients with confirmed WC-RH diagnosis repeated the procedure twice in intervals of 6 months. All of the patients used the same antihypertensive therapeutic regimen during the whole study. Patients who became true RH on any follow-up ABPM had their antihypertensive treatment immediately intensified and were dropped from the following ABPMs.

**Statistical Analysis**

The statistical analyses were performed in SPSS 19.0. Continuous variables were described as means (SDs) when normally distributed or as medians (range) when asymmetrically distributed. The first phase of the study evaluated the reproducibility of the diagnosis of WC-RH in the first 2 ABPM exams. The use of correlation coefficients for this purpose is misleading.17 So, we used the Bland and Altman graphic approach and calculated the repeatability coefficients (twice the SDs of the differences between duplicate measurements)17 for office and ambulatory BPs and for the magnitude of systolic and diastolic WCEs. The repeatability coefficients were also expressed as a percentage of nearly maximal variation, that is, the interval encompassing 4 times the SD of the averaged duplicate measurements.17,18 Patients who confirmed or not the diagnosis of WC-RH on the second ABPM were compared by unpaired t test, Mann-Whitney test, or χ² test, when appropriate. The second phase of the study evaluated who among those with confirmed WC-RH would sustain this diagnosis after 2 additional ABPMs performed at 6-month intervals and which were the office and ambulatory BP cutoff values on the confirmatory ABPM that best predict the persistence of the WC-RH diagnosis after 1 year. BP measurements on the second ABPM were compared between patients who sustained or not the WC-RH diagnosis at the end of the study by unpaired t test. Office and ambulatory SBPs and DBPs of the second ABPM (the confirmatory one) were categorized at the mean BP.
value found in patients who sustained WC-RH diagnosis at the end of the study, office SBP and DBP (155 and 80 mm Hg, respectively) and ambulatory SBP and DBP (24-hour BP: 115 and 65 mm Hg; daytime BP: 115 and 65 mm Hg; nighttime BP: 105 and 60 mm Hg, respectively). Multivariate logistic regression analysis was performed to evaluate the association of each BP measurement and the diagnosis of WC-RH at the end of the study (the dependent variable). It was adjusted for age, sex, and number of antihypertensive drugs in use, which is a surrogate for hypertension severity.

**Results**

At the first phase, 198 patients (68.7% women; mean age: 68.9 years; SD: 9.8 years) with a first ABPM diagnosis of WC-RH were included in the study, and 144 (73%) confirmed the WC-RH status on a second ABPM performed 3 months later (Figure 1). From the 54 patients with true RH on the second ABPM, 9% had isolated daytime hypertension, 37% had isolated nocturnal hypertension, and 54% had both daytime and nighttime uncontrolled hypertension. The baseline characteristics of patients grouped according to the diagnosis of WC-RH or true RH on the confirmatory second ABPM are outlined in Table 1. Patients who became true RH were younger, more frequently diabetics and current smokers, and had higher office and ambulatory BPs than those with confirmed WC-RH.

The second ABPM presented higher mean BPs in the 3 periods but lower office BPs and, consequently, lower extent of the WCE in comparison with the first ABPM (Table 2). Figure 2 showed Bland and Altman graphics for 24-hour BP. The second ABPM had a mean 5-mm Hg higher 24-hour SBP (95% of the differences were between −19 and 29 mm Hg [2 SDs]) and a 3-mm Hg higher 24-hour DBP (95% of the differences: −13 and 18 mm Hg). As determined by correlation coefficients, SBPs were less reproducible than DBPs, and the magnitude of WCEs showed a poor reproducibility. However, correlation coefficients may not accurately assess reproducibility. Assessing the agreement between the 2 exams with Bland-Altman repeatability coefficients corrected for near-maximal variability, both SBPs and DBPs presented moderate agreement between the first and second ABPMs. A lower reproducibility was observed in the magnitude of systolic WCEs, similar to office BPs (Table 2). Very low and nonsignificant correlations between differences and mean values of 24-hour SBPs and DBPs were found (0.034 for SBP, \( P = 0.63 \), and −0.066 for DBP, \( P = 0.35 \)).

A total of 144 patients continued on the second phase. In the third and fourth ABPMs, 74% and 79% of patients sustained the WC-RH diagnosis, respectively. Twenty-nine patients did not perform 1 of the follow-up ABPMs (Figure 1). These patients had lower prevalence of dyslipidemia and physical inactivity, but they had other characteristics similar to those who completed the study, including office and ambulatory BPs (data not shown). Patients who sustained the WC-RH diagnosis on the fourth ABPM had lower office and ambulatory SBPs on the confirmatory ABPM than those who became true RH (Table 3). Number and class of antihypertensive drugs in use were the same during the whole study. In multivariate regression analysis, we found that a daytime SBP \( \leq 115 \) mm Hg in the confirmatory second ABPM was the best predictor of WC-RH status persistence; its presence triplicated the chance of WC-RH persistence after 1 year (Table 4). Based on these results we proposed an algorithm to guide the follow-up of WC-RH patients (Figure 3).

### Discussion

The main finding of our study is the proposal of an algorithm with great clinical applicability to follow-up white-coat re-
sistant hypertensives, an understudied subgroup of patients, for ascertaining the persistence of optimal BP control. A confirmatory ABPM is necessary after at most 3 months of the first diagnosis, and the procedure should be repeated at every 6-month intervals, except in patients with daytime SBP ≤115 mm Hg, who can repeat it annually. Moreover, more than half of the patients with a first ABPM diagnosis of white-coat RH became true RH after a 15-month period, indicating that white-coat RH patients should not be considered less severe hypertensives but at high risk of developing true RH over a relatively short time period.

The WCE was described in 1983 as a phenomenon that occurs in normotensive and hypertensive subjects when BP increases immediately in the presence of a doctor. Large differences between individuals were observed, and the repeated visits with the same doctor did not seem to attenuate the pressure response.19 The physiological, psychological, and behavioral factors involved in the white-coat phenomenon are still controversial.2,20 The prevalence of the WCE ranges from 18% to 60% according to different definitions,2,21–23 and many studies showed that WCH has lower cardiovascular risk than sustained hypertension but higher than sustained normotensives.22,24,25 Resistant hypertensive patients have a high cardiovascular risk5,10–12 and usually present a large magnitude of the WCE, reaching ≤50 mm Hg,7 and also a high prevalence of masked hypertension,26 emphasizing the need to repeat ABPM frequently to ensure BP control.

The principal question to establish the clinical significance of the WCE is defining whether it is a persistent condition or whether it becomes attenuated over time. In some studies, a progressive reduction of office BP was observed and consequently a decrease in the WCE,21,27–29 suggesting that isolated office hypertension could be only a transitional prehypertensive state.28 Otherwise, in a longitudinal study with a median follow-up of 2.5 years evaluating 83 individuals with WCH, 37% shifted to the ambulatory hypertension category without changing office BPs but increasing left ventricular mass.25 Similar to our study, the principal determinant of progression to uncontrolled ambulatory hypertension was average daytime BP levels.25 However, it was suggested that these findings may merely be a regression toward the mean and that the definition of WCH is subject to selection bias.30 In this study, 90 patients with WCH underwent 2 ABPMs 3 months apart.

### Table 3. Comparisons of BP Measurements on the Confirmatory ABPM in Patients Who Persisted or Not With WC-RH at the End of the Study

<table>
<thead>
<tr>
<th>BP Parameters</th>
<th>Patients Who Persisted WC-RH (n=65)</th>
<th>Patients Who Became True RH (n=50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office SBP, mm Hg</td>
<td>156 (17)</td>
<td>162 (18)</td>
<td>0.04</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>79 (16)</td>
<td>80 (13)</td>
<td>0.81</td>
</tr>
<tr>
<td>24-h SBP, mm Hg</td>
<td>115 (9)</td>
<td>119 (7)</td>
<td>0.004</td>
</tr>
<tr>
<td>24-h DBP, mm Hg</td>
<td>64 (7)</td>
<td>66 (7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Daytime SBP, mm Hg</td>
<td>117 (10)</td>
<td>122 (8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Daytime DBP, mm Hg</td>
<td>66 (7)</td>
<td>68 (8)</td>
<td>0.09</td>
</tr>
<tr>
<td>Nighttime SBP, mm Hg</td>
<td>106 (8)</td>
<td>109 (8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Nighttime DBP, mm Hg</td>
<td>58 (7)</td>
<td>61 (8)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Values are mean (SD). BP indicates blood pressure; WC-RH, white-coat resistant hypertension; RH, resistant hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; ABPM, ambulatory blood pressure monitoring.

### Table 4. Multivariate Logistic Regression Analysis for Ambulatory Blood Pressure Monitoring Parameters Associated With Persistence of the White-Coat Resistant Hypertension Diagnosis After 1 y

<table>
<thead>
<tr>
<th>Covariates</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.76</td>
<td>0.32–1.77</td>
<td>0.51</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.02</td>
<td>0.98–1.06</td>
<td>0.40</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>0.76</td>
<td>0.48–1.20</td>
<td>0.25</td>
</tr>
<tr>
<td>Office SBP ≤155 mm Hg</td>
<td>2.19</td>
<td>0.97–4.96</td>
<td>0.06</td>
</tr>
<tr>
<td>24-h SBP ≤115 mm Hg</td>
<td>2.15</td>
<td>0.11–3.92</td>
<td>0.64</td>
</tr>
<tr>
<td>Daytime SBP ≤115 mm Hg</td>
<td>3.19</td>
<td>1.36–7.46</td>
<td>0.007</td>
</tr>
<tr>
<td>Nighttime SBP ≤105 mm Hg</td>
<td>1.88</td>
<td>0.73–4.90</td>
<td>0.19</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; SBP, systolic blood pressure.
most 3 months and repeating the procedure afterward in short intervals of 6 months for most of resistant hypertensive patients, except for those with low daytime SBP levels (≤ 115 mm Hg), who can repeat ABPM on an annual basis.

**Perspectives**

This study provides a useful algorithm to guide clinical practice on the appropriate diagnostic and therapeutic approach for white-coat RH patients to ensuring sustained ambulatory BP control. However, repeating ABPM periodically is costly and uncomfortable for patients, resulting in low cost-effectiveness and low acceptance. So, other methods of out-of-office BP assessment should be evaluated in RH management, such as home BP monitoring. Furthermore, serial changes in office and ambulatory BPs during follow-up of RH patients should be addressed in future prospective studies to evaluate whether this tight BP control in WC-RH patients would translate into better cardiovascular outcomes.

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**Disclosures**

None.

**References**


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