Prognostic Influence of Office and Ambulatory Blood Pressures in Resistant Hypertension

Gil F. Salles, MD, PhD; Claudia R. L. Cardoso, MD, PhD; Elizabeth S. Muxfeldt, MD, PhD

**Background:** The prognostic value of office and ambulatory blood pressures (BPs) in patients with resistant hypertension is uncertain.

**Methods:** This prospective study investigates the importance of office and ambulatory BPs as predictors of cardiovascular morbidity and mortality. At baseline, 556 resistant hypertensive patients underwent clinical-laboratory and 24-hour ambulatory BP monitoring examinations. Primary end points were a composite of fatal and nonfatal cardiovascular events and all-cause and cardiovascular mortalities. Multiple Cox regression was used to assess associations between BP and subsequent end points.

**Results:** After median follow-up of 4.8 years, 109 patients (19.6%) reached the primary end point, and 70 all-cause deaths (12.6%) occurred (46 had cardiovascular causes). After adjustment for age, sex, body mass index, diabetes mellitus, smoking, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine level, and number of antihypertensive drugs in use, no office BP showed any prognostic value. After further adjustment for office BP, higher mean ambulatory BPs were independent predictors of the composite end point. The hazard ratios associated with a 1-SD increment in daytime and nighttime systolic BP were 1.26 (95% confidence interval, 1.04-1.53) and 1.38 (1.13-1.68), respectively; the corresponding values for diastolic BP were 1.31 (1.05-1.63) and 1.36 (1.10-1.69). Ambulatory systolic and diastolic BP were equivalent predictors, and both were better than pulse pressure; nighttime BP was superior to daytime BP. For all-cause mortality, only the ambulatory BP monitoring diagnosis of true resistant hypertension was an independent predictor.

**Conclusion:** Higher ambulatory BP predicts cardiovascular morbidity and mortality in resistant hypertensive patients, whereas office BP has no prognostic value.

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**RESISTANT HYPERTENSION** (RH), defined as the failure to control office blood pressure (BP) despite optimal treatment with at least 3 antihypertensive drugs in full dosages, always including a diuretic, is a common, but generally understudied, clinical condition. Its prevalence ranges from 10% to almost 30% of general hypertensive patients in different series. In our general outpatient clinic, the prevalence of RH was 17%, and in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 27% of uncontrolled hypertensive patients were using 3 or more drugs, with an estimated prevalence of RH of at least 15%. Ambulatory BP monitoring (ABPM) has become increasingly important in the management of hypertensive patients, and one of its established indications is RH, mainly because of the possibility that an exaggerated white-coat effect underlies the failure to control office BP levels, so-called white-coat RH.

Several studies in general populations and in hypertensive individuals have shown that ambulatory BP is a better predictor of cardiovascular morbidity and mortality than is office BP, although some controversy on the additive prognostic value of ambulatory BP still exists. In patients with RH, only 1 previous study investigated the prognostic value of ABPM variables. Nevertheless, this pioneering study, with a few patients and events, did not comprehensively explore the relationships between ambulatory BP and the incident cardiovascular morbidity and mortality.

Therefore, the objectives of the present prospective study, with a large number of patients with RH followed up for up to 9 years, were to investigate the prognostic importance of ambulatory BP, during daytime and nighttime, for the future occurrence of fatal and nonfatal cardio-
vascular events and, particularly, to verify whether ambulatory BP levels provide a better estimate of cardiovascular risk above and beyond office BP and other traditional cardiovascular risk factors.

METHODS

PATIENTS AND BASELINE PROCEDURES

This was a prospective follow-up study with 556 patients with RH (mean [SD] known hypertension duration, 18 [12] years) enrolled between January 1, 1999, and December 31, 2004, in the hypertension outpatient clinic of University Hospital Clementino Fraga Filho, Rio de Janeiro, Brazil. All the participants gave written informed consent, and the Research Ethics Committee of Medical School and University Hospital Clementino Fraga Filho had previously approved the study protocol. The enrollment criteria, baseline protocol, and diagnostic definitions have been detailed previously. In brief, all hypertensive patients referred who fulfilled the criteria for RH (office systolic BP [SBP] ≥140 mm Hg or diastolic BP [DBP] ≥90 mm Hg, using 2 or more antihypertensive drugs in full doses [always including a diuretic], and considered at least moderately adherent using a standard validated questionnaire) were submitted to a standard protocol that included a complete clinical examination (with particular attention to the presence of cardiovascular risk factors and target organ damage), laboratory evaluation, standard 12-lead electrocardiography, 2-dimensional echocardiography, and 24-hour ABPM.

Diabetes mellitus was diagnosed by means of medical history or by undergoing antidiabetic treatment or by 2 fasting glucose measurements of 126 mg/dL or greater (to convert to millimoles per liter, multiply by 0.0555). Patients were considered physically active if they exercised at least 30 minutes per day, 4 days a week. Current smoking was defined as smoking in the past month. Dyslipidemia was diagnosed by means of history, by being treated with any lipid-reducing drug, or by a baseline total cholesterol level greater than 200 mg/dL, a high-density lipoprotein cholesterol level less than 50 mg/dL in women or less than 40 mg/dL in men, a low-density lipoprotein cholesterol level greater than 130 mg/dL. (to convert all cholesterol levels to millimoles per liter, multiply by 0.0555). Patients were considered adherent using a standard validated questionnaire. First and fifth Korotkoff sounds were the criteria for SBP and DBP, and the BP considered was the mean between the 2 readings. Pulse pressure (PP) was calculated as SBP minus DBP. Two-dimensional echocardiography was performed by the same experienced observer. Left ventricular mass was calculated using the Devereux formula and was indexed to body surface area. The diagnosis of left ventricular hypertrophy was defined by an indexed left ventricular mass greater than 125 g/m² in men and greater than 110 g/m² in women. The ABPM was recorded using Mobil-O-Graph (version 12) equipment approved by the British Society of Hypertension. All the patients used their prescribed antihypertensive medications during ABPM. A reading was taken every 15 minutes throughout the day and every 30 minutes at night. Variables evaluated were mean 24-hour, daytime, and nighttime SBP, DBP, and PP. The nighttime period was ascertained for each individual patient from registered diaries and personal interviews. After ABPM, patients were classified as having either true RH (mean daytime SBP ≥135 mm Hg or DBP ≥85 mm Hg) or white-coat RH (mean daytime SBP <135 mm Hg and DBP <85 mm Hg).

FOLLOW-UP AND END POINTS

The patients were followed up regularly at least 3 to 4 times a year until December 2007. Those who did not present to the hospital were contacted annually to determine vital status. The observation period for each patient was the number of months from the date of the first clinical examination to the date of the last clinical visit in 2007 or the date of the first end point. Thirty-seven patients (6.7%) were lost to follow-up and were considered censored observations at the date of their last hospital visit.

The primary end point was a composite of all fatal and nonfatal cardiovascular events: fatal and nonfatal acute myocardial infarction (AMI) (defined as the presence of ≥2 of the following: typical chest pain, characteristic electrocardiographic alterations [either a 0.1-mV ST-segment deviation or a typical necrosis Q wave], and increased cardiac enzyme levels [either creatinine kinase or its MB fraction had to be higher than 2 times the upper limit of normal]), sudden cardiac death (defined as death occurring instantaneously or within 2 hours after the onset of symptoms without any evidence of trauma or violence or unexplained death) for which no likely cause could be established in a patient known to be previously in a stable condition of health), new-onset heart failure (needing at least hospitalization and echocardiographic confirmation of an ejection fraction <40%), death from progressive heart failure, any myocardial revascularization procedure (surgical or not), fatal and nonfatal stroke (defined as any rapidly developing neurologic deficit lasting for >24 hours or leading to death with no apparent cause other than vascular origin), any aortic or lower limb revascularization procedure (surgical or not), any amputation above the ankle, death from aortic or peripheral arterial disease (including mesenteric ischemia), the beginning of dialysis, and death due to renal failure. New-onset angina, intermittent claudication, and cerebral transient ischemic attacks were not considered end points. All-cause and cardiovascular mortalities were also primary end points. Total CHD events (fatal and nonfatal AMIs, sudden deaths, and myocardial revascularizations) and total fatal and nonfatal strokes were secondary end points. End points were ascertained from medical records (most nonfatal and fatal in-hospital events were attended at University Hospital Clementino Fraga Filho, death certificates, and interviews with attending physicians and patients’ families using a standard questionnaire reviewed by an independent observer.

STATISTICAL ANALYSES

Statistical analyses were performed using a software program (SPSS version 13.0; SPSS Inc, Chicago, Illinois). Continuous variables are described as means (SDs). Survival analyses were performed by means of Kaplan-Meier estimation of event-free survival curves and were compared using log-rank tests (with patients categorized as having true or white-coat RH) and multivariate Cox proportional hazards regression. For patients with multiple events, analysis was restricted to the first event under study. Results are given as hazard ratios (HRs) with 95% confidence intervals (95% CIs). The HRs were standardized by calculating them for 1-SD increments of each BP measurement. Each BP measurement was first adjusted for age and sex and then was fully adjusted for all potential risk factors: age, sex, body mass index, diabetes mellitus, dyslipidemia, physical inactivity, current smoking, preexisting cardiovascular diseases, serum cre-
Results

Baseline characteristics and follow-up end points

After median follow-up of 4.8 years (range, 1-103 months), which corresponds to 2678 patient-years of follow-up, 109 patients (19.6%) reached the primary composite end point: there were 44 strokes, 21 AMIs, 15 myocardial revascularizations, 10 new-onset heart failures, 5 sudden deaths, 3 lower limb amputations, and 2 deaths due to aortic or peripheral arterial disease. Seven patients initiated dialysis and 2 died of renal failure. The crude incidence rate of total cardiovascular events was 4.32 per 100 patient-years of follow-up. There were 44 CHD events (23 AMIs, 16 myocardial revascularizations, and 5 sudden deaths) and 46 total fatal and nonfatal strokes. There were 70 all-cause deaths (12.6%, incidence rate of 2.61 per 100 patient-years), 46 from cardiovascular causes (8.3%, incidence rate of 1.72 per 100 patient-years of follow-up). Cardiovascular deaths were due to AMI (14 patients), stroke (13 patients), sudden cardiac death (7 patients), progressive heart failure (5 patients), renal failure (4 patients), and aortic or peripheral arterial events (3 patients). The most frequent causes of noncardiovascular deaths were cancer (8 patients) and infectious diseases (5 patients).

Table 1 provides the baseline characteristics of all the patients enrolled and of those with and without a fatal or nonfatal cardiovascular event during follow-up. Patients used a median of 4 (range, 3-6) antihypertensive drugs at baseline. There was no difference in antihypertensive drug treatment at baseline between patients with and without the composite end point.

Survival analysis

Table 2 provides the results of Cox proportional hazards regression of office and ABPM measurements adjusted for age and sex and fully adjusted for the 3 primary end points under study. No office BP presented any prognostic importance for any of the end points evaluated. Regarding ambulatory BPs, 24-hour, daytime, and nighttime SBPs and DBPs and 24-hour and nighttime PPs provided significant prognostic information for the occurrence of fatal and nonfatal cardiovascular events (the primary end point), above
The ABPM diagnosis of true RH was independent of 24-hour SBP. Although all the interaction terms between ABPM and diabetes mellitus were nonsignificant (P > .20), there was also a trend toward greater HRs in diabetic than in nondiabetic individuals: for nighttime SBP, the HRs were 2.00 (95% CI, 1.29-3.28) and 1.28 (0.99-1.66), and for nighttime DBP, 2.02 (1.36-3.00) and 1.22 (0.93-1.59), respectively.

Figure 2 shows the HRs when 2 ambulatory BP variables were included in the same fully adjusted model for the composite end point. Nighttime BPs were better predictors than were daytime BPs, and SBP was equal to DBP, but both were better than PP as cardiovascular risk predictors. The prognostic value of the diagnosis of true RH was also independent of 24-hour SBP.

Table 3 presents the Cox analysis for the 2 secondary end points. No office BP was a predictor of any of the end points. Ambulatory SBP and DBP, and the ABPM diagnosis of true RH, were predictors of fatal and nonfatal strokes but not of total CHD events.

### Table 2. Results of Cox Survival Analyses for Associations Between BP Measurements and the Primary End Points

<table>
<thead>
<tr>
<th>BP Measurement</th>
<th>Composite End Point (n=109)</th>
<th>All-Cause Mortality (n=70)</th>
<th>Cardiovascular Mortality (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted^a</td>
<td>Multivariate Adjusted^b</td>
<td>Adjusted^a</td>
</tr>
<tr>
<td>Age and Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>1.08 (0.90-1.30)</td>
<td>1.08 (0.90-1.29)</td>
<td>1.00 (0.79-1.27) c 0.99 (0.78-1.25)</td>
</tr>
<tr>
<td>24 h</td>
<td>1.39 (1.15-1.68)c 1.32 (1.09-1.60)d</td>
<td>1.32 (1.04-1.68)c 1.24 (0.97-1.60)</td>
<td>1.39 (1.03-1.86)c 1.25 (0.93-1.69)</td>
</tr>
<tr>
<td>Daytime</td>
<td>1.33 (1.11-1.61)d 1.26 (1.04-1.53)e</td>
<td>1.28 (1.01-1.62)e 1.21 (0.95-1.54)</td>
<td>1.34 (1.00-1.79)e 1.22 (0.91-1.64)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>1.44 (1.20-1.73)c 1.38 (1.13-1.68)d</td>
<td>1.34 (1.05-1.71)e 1.27 (0.98-1.64)</td>
<td>1.38 (1.03-1.85)e 1.27 (0.93-1.74)</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>0.95 (0.77-1.16) 1.03 (0.85-1.26)</td>
<td>0.85 (0.65-1.10) 0.94 (0.73-1.21)</td>
<td>0.83 (0.60-1.15) 0.94 (0.69-1.28)</td>
</tr>
<tr>
<td>24 h</td>
<td>1.26 (1.02-1.56)c 1.33 (1.06-1.66)e</td>
<td>1.13 (0.86-1.48) 1.18 (0.88-1.59)</td>
<td>1.16 (0.83-1.62) 1.18 (0.84-1.68)</td>
</tr>
<tr>
<td>Daytime</td>
<td>1.23 (1.00-1.52) 1.31 (1.05-1.63)e</td>
<td>1.13 (0.87-1.48) 1.23 (0.93-1.83)</td>
<td>1.16 (0.83-1.60) 1.24 (0.88-1.74)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>1.33 (1.09-1.64)d 1.36 (1.10-1.69)d</td>
<td>1.16 (0.89-1.51) 1.17 (0.87-1.56)</td>
<td>1.19 (0.86-1.65) 1.19 (0.84-1.69)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>1.16 (0.96-1.41) 1.09 (0.90-1.32)</td>
<td>1.13 (0.89-1.44) 1.04 (0.81-1.32)</td>
<td>1.26 (0.94-1.70) 1.12 (0.83-1.51)</td>
</tr>
<tr>
<td>24 h</td>
<td>1.35 (1.13-1.61)c 1.22 (1.00-1.48)</td>
<td>1.34 (1.07-1.67)e 1.21 (0.96-1.53)</td>
<td>1.40 (1.07-1.84)e 1.21 (0.91-1.60)</td>
</tr>
<tr>
<td>Daytime</td>
<td>1.31 (1.09-1.58)d 1.17 (0.95-1.44)</td>
<td>1.31 (1.04-1.65)e 1.16 (0.90-1.50)</td>
<td>1.38 (1.04-1.84)e 1.16 (0.85-1.57)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>1.37 (1.14-1.64)c 1.27 (1.04-1.55)e</td>
<td>1.35 (1.08-1.69)e 1.26 (0.98-1.62)</td>
<td>1.37 (1.04-1.81)e 1.24 (0.91-1.68)</td>
</tr>
<tr>
<td>True RH</td>
<td>2.20 (1.40-3.44)c 2.11 (1.34-3.34)c</td>
<td>2.13 (1.21-3.73)c 2.09 (1.02-3.55)c</td>
<td>1.99 (1.01-3.93)e 1.88 (0.93-3.80)</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; RH, resistant hypertension.

^a Hazard ratios for continuous variables were standardized by calculating them for 1-SD increments.

^b Adjusted for sex, age, body mass index, diabetes mellitus, current smoking, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine level (log10 transformed), and number of antihypertensive drugs in use. Ambulatory BPs were further adjusted for their respective office BPs.

^c P < .01.

^d P < .001.

^e P < .05.

and beyond other traditional cardiovascular risk factors, including their respective office BPs. Increases of 1 SD in nighttime SBP (22 mm Hg) and in nighttime DBP (14 mm Hg) were associated with a 38% and a 36%, respectively, higher risk of having a future cardiovascular event. The ABPM diagnosis of true RH was also an independent predictor of the composite end point, with a fully adjusted HR of 2.11. Further adjustment for the presence of echocardiographic left ventricular hypertrophy did not change the results. For all-cause mortality, only the ABPM diagnosis of true RH had independent prognostic importance, whereas no ambulatory BP variable was independently associated with cardiovascular mortality after full statistical adjustment. Excluding the renal events (beginning of dialysis and death from renal failure) from the composite end point and from cardiovascular mortality did not change the results. For example, the fully adjusted HRs of nighttime SBP and DBP for the composite end point were 1.40 (95% CI, 1.14-1.72) and 1.35 (1.08-1.70), respectively, and that of true RH was 2.30 (1.42-3.74), whereas office BPs remained nonsignificantly associated with the end points. Also, on Kaplan-Meier analysis, the diagnosis of true RH distinguished 2 subgroups of patients with significantly different prognoses regarding the occurrence of any cardiovascular event and of all-cause and cardiovascular mortalities (Figure 1). Of the other covariates, age, diabetes mellitus, smoking, body mass index, serum creatinine level, and number of antihypertensive drugs in use were predictors of end points to various extents in different Cox models.

Of the several interactions tested, the only one significant for the composite end point was that between diabetes mellitus and the ABPM diagnosis of true RH (P=.04), with the prognostic value of true RH being much stronger in diabetic patients (HR, 3.45; 95% CI, 2.25-5.13; P<.001) than in nondiabetic individuals (1.45; 0.82-2.54; P=.20) in the fully adjusted analysis. Although all the interaction terms between ambulatory BPs and diabetes mellitus were nonsignificant (P > .20), there was also a trend toward greater HRs in diabetic than in nondiabetic individuals: for nighttime SBP, the HRs were 2.00 (95% CI, 1.29-3.28) and 1.28 (0.99-1.66), and for nighttime DBP, 2.02 (1.36-3.00) and 1.22 (0.93-1.59), respectively.

Figure 2 shows the HRs when 2 ambulatory BP variables were included in the same fully adjusted model for the composite end point. Nighttime BPs were better predictors than were daytime BPs, and SBP was equal to DBP, but both were better than PP as cardiovascular risk predictors. The prognostic value of the diagnosis of true RH was also independent of 24-hour SBP.

Table 3 presents the Cox analysis for the 2 secondary end points. No office BP was a predictor of any of the end points. Ambulatory SBP and DBP, and the ABPM diagnosis of true RH, were predictors of fatal and nonfatal strokes but not of total CHD events.

## COMMENT

This prospective study with a large group of patients with RH followed up for up to 9 years demonstrates that ambulatory BPs (SBP and DBP) are important prognostic risk markers for future cardiovascular morbidity and mortality, independent of office BPs and other traditional car-

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diovascular risk factors; office BPs have no prognostic value. Furthermore, it shows that nighttime BPs are stronger risk markers than are daytime BPs, that SBP and DBP are equally effective as predictors of future cardiovascular events and that both are better than PP, and that ambulatory BPs seem to be stronger risk factors in diabetic than in nondiabetic RH patients. Finally, it shows that the simple ABPM diagnosis of true or white-coat RH at baseline provides useful independent prognostic information for cardiovascular morbidity and for all-cause mortality.

Since the classic study by Perloff et al\textsuperscript{20} in 1983, the finding that ambulatory BPs are better cardiovascular risk predictors than are office BPs has been consistently demonstrated in hypertensive patients (treated,\textsuperscript{12} untreated,\textsuperscript{11,13} or both\textsuperscript{14}), in diabetic patients,\textsuperscript{21} and in population-based cohorts,\textsuperscript{8-10} but the superiority of ambulatory BP over office BP is not generally accepted.\textsuperscript{15} In RH patients, there is only 1 previous prospective study,\textsuperscript{16} published a decade ago. This pioneering study, possibly due to the few patients enrolled (n=86) and, consequently, the reduced number of events (n=21) observed during mean follow-up of 49 months, did not completely explore the relationships between ambulatory BP levels and cardiovascular outcome. Nevertheless, it demonstrated that RH patients in the highest tertile group of daytime DBP (≥97 mm Hg) were at increased risk for future cardiovascular events and of progressing target organ damage in relation to those in the lowest tertile group after adjusting for age, sex, smoking, previous cardiovascular diseases, left ventricular hy-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Kaplan-Meier estimates of incident total fatal and nonfatal cardiovascular event curves (A), all-cause mortality curves (B), and cardiovascular mortality curves (C) in patients grouped according to ambulatory blood pressure monitoring diagnosis of true or white-coat resistant hypertension (RH). The number of patients at risk data applies to B and C.

![Figure 2](https://example.com/figure2.png)

**Figure 2.** Hazard ratios (95% confidence intervals [CIs]) when 2 ambulatory blood pressure monitoring variables were included simultaneously in the same multivariate Cox models for prediction of the composite end point. All the models were further adjusted for sex, age, body mass index, diabetes mellitus, current smoking, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine level (log\textsubscript{10} transformed), number of antihypertensive drugs in use, and office blood pressures. *P*<.05. DBP indicates diastolic blood pressure; PP, pulse pressure; RH, resistant hypertension; and SBP, systolic blood pressure.
pertently on electrocardiography, and office BP. This study confirms this finding and further advances it by examining the relative prognostic values of daytime vs nighttime BPs and of SBP vs DBP vs PP. Regarding the prognostic importance of the ABPM diagnosis of true or white-coat RH, there is also only 1 previous study that addressed this issue.\textsuperscript{23} This study evaluated 276 patients with RH (although not all of them were using a diuretic), 130 with true RH, and reported that after mean follow-up of 5 years, true RH patients had a 2.4-fold (95% CI, 1.0- to 5.8-fold) increased risk of having a fatal or nonfatal cardiovascular event compared with white-coat RH patients after adjusting for age, smoking, low-density lipoprotein cholesterol level, diabetes mellitus, left ventricular hypertrophy on echocardiography, and office SBP. The present study corroborates this observation, with a very similar relative risk (2.1; 95% CI, 1.3-3.3), and advances it by demonstrating that true RH status is also an independent predictor of all-cause mortality and that its predictive value is additive to 24-hour ambulatory BP. The complete lack of any prognostic value of daytime BP has been previously demonstrated in these 2 previous studies\textsuperscript{10,22} and confirmed in the present study. This finding reinforces the recommendation that antihypertensive drug treatment in RH patients should be driven by ABPM results and not by office BP measurements.

The finding that nighttime BPs are the best predictors of cardiovascular morbidity and mortality compared with daytime BPs has been previously demonstrated in some studies,\textsuperscript{10,11,13-15} and verified in the present one, but not in other studies.\textsuperscript{8,9,12} It seems that the superiority of nighttime over daytime BPs is especially evident in hypertensive patients,\textsuperscript{11,13,14} particularly in treated patients,\textsuperscript{10} suggesting that antihypertensive drug treatment is, at least in part, responsible for attenuating the prognostic value of daytime BP. This observation is plausible because most antihypertensive drug treatment is directed toward controlling office BP, that is, during the daytime period. Beyond the effect of antihypertensive drug treatment, other hypotheses for explaining the better predictive performance of nighttime BP have been raised. First, the higher variability in daytime BPs, due to the effect of physical and psychoemotional stress, may weaken its prognostic power, whereas the greater uniformity resulting from sleeping may help increase the prognostic strength of nighttime BPs.\textsuperscript{10,11} Second, higher nighttime BPs and increased cardiovascular risk may be linked to common pathophysiologic mechanisms, such as autonomic cardiovascular imbalance favoring augmented sympathetic tonus or increased salt sensitivity or renal dysfunction that needs higher nighttime BPs to sustain natriuresis.\textsuperscript{10,11} Third, during the night, reduction of arteriolar tonus allows greater transmission of BP from the large arteries to microcirculation, enhancing its damaging effects on heart, kidney, and vascular structures.\textsuperscript{15} Fourth, higher nighttime BPs and antihypertensive drug treatment resistance may be associated with secondary causes of hypertension,\textsuperscript{3} such as obstructive sleep apnea syndromes\textsuperscript{13} and primary aldosteronism,\textsuperscript{14} both associated with worse cardiovascular prognoses.\textsuperscript{15,16} These potential mechanisms are not mutually exclusive and are operative to different extents in each patient.

This study has several limitations. First, we used baseline office and ambulatory BPs for the analyses, so changes in BP during follow-up were not considered. Moreover, changes in antihypertensive drug treatment, which were at the discretion of each hypertension clinic physician according to the ABPM results of each patient, were not evaluated; also, possible fluctuations in patients’ adherence to

### Table 3. Results of Cox Survival Analyses for Associations Between BP Measurements and the Secondary End Points

<table>
<thead>
<tr>
<th>BP Measurement</th>
<th>Total CHD Events (n=44)</th>
<th>Stroke (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age and Sex Adjusted</td>
<td>Multivariate Adjusted\textsuperscript{a}</td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>1.04 (0.78-1.40)</td>
<td>1.08 (0.80-1.46)</td>
</tr>
<tr>
<td>24 h</td>
<td>1.21 (0.89-1.63)</td>
<td>1.18 (0.86-1.61)</td>
</tr>
<tr>
<td>Daytime</td>
<td>1.16 (0.86-1.57)</td>
<td>1.13 (0.83-1.54)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>1.27 (0.94-1.71)</td>
<td>1.26 (0.92-1.73)</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>0.85 (0.61-1.18)</td>
<td>0.98 (0.70-1.38)</td>
</tr>
<tr>
<td>24 h</td>
<td>0.93 (0.66-1.30)</td>
<td>1.00 (0.70-1.42)</td>
</tr>
<tr>
<td>Daytime</td>
<td>0.93 (0.67-1.30)</td>
<td>1.01 (0.72-1.43)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>1.01 (0.73-1.41)</td>
<td>1.10 (0.78-1.55)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>1.21 (0.89-1.63)</td>
<td>1.12 (0.82-1.52)</td>
</tr>
<tr>
<td>24 h</td>
<td>1.38 (1.04-1.83)\textsuperscript{d}</td>
<td>1.27 (0.93-1.72)</td>
</tr>
<tr>
<td>Daytime</td>
<td>1.33 (0.99-1.80)</td>
<td>1.21 (0.87-1.69)</td>
</tr>
<tr>
<td>Nighttime</td>
<td>1.40 (1.08-1.76)\textsuperscript{d}</td>
<td>1.31 (0.96-1.81)</td>
</tr>
<tr>
<td>True RH</td>
<td>1.34 (0.71-2.54)</td>
<td>1.46 (0.75-2.83)</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CHD, coronary heart disease; RH, resistant hypertension.

\textsuperscript{a}Hazard ratios for continuous variables were standardized by calculating them for 1-SD increments.

\textsuperscript{b}Adjusted for sex, age, body mass index, diabetes mellitus, current smoking, physical inactivity, dyslipidemia, previous cardiovascular diseases, serum creatinine level (log\textsubscript{10} transformed), and number of antihypertensive drugs in use. Ambulatory BPs were further adjusted for their respective office BPs.

\textsuperscript{c}P < .05.

\textsuperscript{d}P < .01.

\(P < .05\).
treatment during follow-up could not be accounted for. The fact that office BPs were obtained during only 1 visit may have limited their predictive performance. Second, the relatively few cardiovascular deaths and CHD events probably contributed to the failure to demonstrate the prognostic value of ambulatory BPs for these end points owing to insufficient statistical power. Third, this study enrolled only patients with RH, which is a common but usually understood subgroup of general hypertensive patients. Hence, these results may not be generalized to other, less severe hypertensive individuals.

This study has important clinical implications. First, it reinforces the importance of ABPM performance in RH patients. Furthermore, ABPM should be performed during the whole 24 hours, with separate analyses of the daytime and nighttime periods, because it seems that nighttime BPs are better cardiovascular risk factors than are daytime BPs. Second, it raises the question of whether therapeutic interventions directed specifically at controlling nighttime hypertension will be able to improve cardiovascular prognosis compared with the traditional approach of controlling daytime BP levels. In this regard, a recent study showed that a bedtime dosing of antihypertensive medications was capable of controlling nighttime hypertension and restoring the nondipping pattern in RH patients. Whether this improved nocturnal BP control translates into better cardiovascular outcomes is presently unknown. This important clinical question should be addressed in future prospective interventional studies.

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