Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Learn and Live℠

Prognostic Value of Ambulatory Blood Pressure Monitoring in Refractory Hypertension : A Prospective Study

Josep Redon, Carlos Campos, Maria L. Narciso, Jose L. Rodicio, Jose M. Pascual and Luis M. Ruilope

Hypertension 1998;31;712-718

Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Prognostic Value of Ambulatory Blood Pressure Monitoring in Refractory Hypertension

A Prospective Study

Josep Redon, Carlos Campos, Maria L. Narciso, Jose L. Rodicio, Jose M. Pascual, Luis M. Ruilope

Abstract—The objective of this study was to establish whether ambulatory blood pressure offers a better estimate of cardiovascular risk than does its clinical blood pressure counterpart in refractory hypertension. This prospective study assessed the incidence of cardiovascular events over time during an average follow-up of 49 months (range, 6 to 96). Patients were referred to specialized hypertension clinics (86 essential hypertension patients who had diastolic blood pressure >100 mm Hg during antihypertensive treatment that included three or more antihypertensive drugs, one being a diuretic). Twenty-four-hour ambulatory blood pressure monitoring (ABPM) was performed at the time of entrance. End-organ damage was monitored yearly, and the incidence of cardiovascular events was recorded. Patients were divided into tertiles of average diastolic blood pressure during activity according to the ABPM, with the lowest tertile <88 mm Hg (LT, n=29), the middle tertile 88 to 97 mm Hg (MT, n=29), and the highest tertile >97 mm Hg (HT, n=28). While significant differences in systolic and diastolic ambulatory blood pressures were observed among groups, no differences were observed at either the beginning or at the time of the last evaluation for office blood pressure. During the last evaluation, a progression in the end-organ damage score was observed for the HT group but not for the two other groups. Twenty-one of the patients had a new cardiovascular event; the incidence of events was significantly lower for the LT group (2.2 per 100 patient-years) than it was for the MT group (9.5 per 100 patient-years) or for the HT group (13.6 per 100 patient-years). The probability of event-free survival was also significantly different when comparing the LT group with the other two groups (LT versus MT log-rank, $P<.04$; LT versus HT log-rank, $P<.006$). The HT group was an independent risk factor for the incidence of cardiovascular events (relative risk, 6.20; 95% confidence interval, 1.38 to 28.1, $P<.02$). Higher values of ambulatory blood pressure result in a worse prognosis in patients with refractory hypertension, supporting the recommendation that ABPM is useful in stratifying the cardiovascular risk in patients with refractory hypertension. **(*Hypertension*. 1998;31:712-718.)**

Key Words: blood pressure monitoring, ambulatory ■ hypertension, refractory ■ cardiovascular risk ■ prognosis

Hypertensive patients whose clinical BP remains persistently high despite being prescribed appropriate multiple medications present a relatively common clinical problem. These patients, so-called resistant or refractory, account for 10% of hypertensive subjects referred to specialized clinics and frequently have changes in their medications, including the addition of other antihypertensive drugs.[1] Attempts have been made to classify refractory hypertension according to its cause. It may be due to a specific identifiable disorder (secondary hypertension) associated with exogenous substances that raise BP or interfere with the action of antihypertensive agents (ie, nonsteroidal anti-inflammatory drugs), attributable to complicating biological factors (obesity and hyperinsulinemia), ascribable to inappropriate or inadequate treatment, or due to noncompliance with a prescribed medical regimen. In many cases, however, it is not possible to find a potentially correctable cause of the elevated BP, even though the patient's compliance to medication seems to be adequate.[1]

In some cases this may be the result of genuine refractory hypertension, while interesting that in others it may be simply the consequence of an exaggerated white-coat effect. For instance, evaluation of these patients requires BP measurements outside the clinical environment in order to exclude the existence of the latter.[2] Monitoring ambulatory BP with a noninvasive device[3,4] provides more representative values of BP than clinic BP does, and the behavior of BP during the activity and sleep periods is observable. Target-organ damage in essential hypertension correlates better with ambulatory than with clinical BP,[5,6] and for any given value of clinical BP, target-organ damage is directly related to the mean levels and variability of ambulatory BP. Moreover, it has been claimed that values obtained in 24-hour monitoring are better predictors of cardiovascular risk than data obtained in casual measurements.[7–9]

Published consensus has established that one of the major uses for ABPM is in the evaluation of refractory hyperten-

Received August 4, 1997; first decision September 2, 1997; revision accepted September 29, 1997.

From the Hypertension Clinic, Hospital Clínico, University of Valencia (Spain) (J.R., M.L.N.); Hypertension Clinic, 12 de Octubre Hospital, Madrid (C.C., J.L.R., L.M.R.); and Internal Medicine, Hospital of Sagunto (Spain) (J.M.P.).

Correspondence to Josep Redon, MD, Hypertension Clinic, Internal Medicine, Hospital Clinico, University of Valencia, Avda Blasco Ibañez 10, 46010 Valencia, Spain.

Selected Abbreviations and Acronyms

ABPM = ambulatory blood pressure monitoring
BP = blood pressure
CI = confidence interval
DBP = diastolic blood pressure
ECG = electrocardiograph
HT = highest tertile
LT = lowest tertile
MT = middle tertile
RR = relative risk
SBP = systolic blood pressure

sion.[10–20] Despite agreement in the use of ABPM with refractory hypertensive subjects, no confirmatory data about the prognostic value of ABPM in this group have been available until now. To establish whether ambulatory BP offers a better estimate of cardiovascular risk than do its clinical BP counterparts, we have conducted a prospective study assessing the incidence of cardiovascular events over time in patients diagnosed as having refractory hypertension.

Methods

Selection of Study Participants

A group of 86 patients were included in the study. Patients were recruited from the outpatient clinic of two hospitals (Hospital of Sagunto and Hospital 12 de Octubre, Madrid) over a 68 month period (January 1989 to December 1994). All patients who fulfilled the inclusion criteria were invited to participate, and written consent was obtained. The inclusion criteria were the following: (a) clinical diastolic BP >100 mm Hg (Korotkoff phase V, sitting position) for three visits at 1-month intervals during the same antihypertensive treatment, which included three or more antihypertensive drugs, one of them being a diuretic; (b) preserved renal function, glomerular filtration rate estimated by endogenous creatinine clearance >60 mL/min per 1.73 m^2. Patients with diabetes mellitus or with secondary hypertension were excluded. The presence of previous cardiovascular events did not constitute an exclusion criteria in subjects maintaining their normal physical and work activities.

At the beginning of the study all patients had a complete clinical workup to rule out secondary hypertension and to assess the presence of end-organ damage. Twenty-four ABPM were performed at the time of entrance. End-organ damage was monitored yearly, and the incidence of cardiovascular events during the time of follow-up was recorded. A minimal 6-months of follow-up was required for being included in the analysis.

Office and Ambulatory Blood Pressure Measurements

BP was measured in a quiet environment with a mercury sphygmomanometer with the patient in a sitting position after 5 minutes of rest, following the recommendations of the British Hypertension Society.[21] SBP and DBP (Korotkoff phase I and phase V, respectively) represented in each visit the mean of three different readings measured at 5-minute intervals.

ABPM was performed with the use of an oscillometric monitor (Spacelabs 90202 or 90207) on a regular working day, during the normal intake of the usual antihypertensive treatment. Following the standard protocol, recording began between 8:30 and 9 AM, with readings every 20 minutes from 6 PM until midnight and every 30 minutes from midnight to 6 AM. Before starting the study, reliability of BP values measured with the monitor were checked against simultaneous measurements with a mercury sphygmomanometer. Differences of <5 mm Hg were allowed. Those patients with recordings showing an error rate in >25% of the total readings were excluded from the study.

Different time periods were defined in the following manner for the analysis of BP values obtained during monitoring: (a) the total 24 hours, (b) a day or activity period running from 8 AM until 10 PM, (c) a night or sleep period running from midnight to 6 AM, and (d) hourly periods over the 24 hours. The average of SBP, DBP, and mean blood pressure were calculated for every one of the periods. The ratio between the averages of BP during the day period and during the night period, day/night ratio, was calculated as an estimate of circadian variability.

Patients were divided into tertiles of average DBP during activity according to the ABPM, with the LT <88 mm Hg (n=29), the MT 88 to 97 mm Hg (n=29), and the HT >97 mm Hg (n=28).

Clinical Score of End-Organ Damage

The presence of end-organ damage attributed to hypertension, estimated at the beginning of the study and yearly, was reported as a modification of a previously published score.[22] This score was calculated with the use of data derived from each patient's history, physical examination, and laboratory investigations such as ECG, chest radiograph, fundus oculi, urinalysis, and plasma creatinine. History questions were asked to establish the presence (1 point) or absence (0 points) of ischemic heart disease, heart failure, cerebrovascular insufficiency, and peripheral arterial disease. The following ECG abnormalities were considered evidence of target-organ damage: (a) left ventricular hypertrophy (Sokolow criteria) without (1 point) or with strain (2 points); (b) other ECG abnormalities, such as signs of infarction, resting ischemia, left bundle-branch block, ventricular arrhythmias, and atrial fibrillation in absence of other possible causes (1 point). Abnormalities on chest radiograph considered evidence of target-organ damage were (a) moderate, cardiothoracic index 0.50 to 055, (1 point) or (b) marked cardiac enlargement, cardiothoracic index >0.55 (2 points). The abnormalities of the fundus were classified according to the Keith-Wagener criteria: grade II (1 point) and grade III or IV (2 points). Serum creatinine >132 mmol/L (1.5 mg/dL) and/or proteinuria >1 g/24 hours scored 1 additional point. The total score for an individual patient was the sum all item scores and ranged from a minimum of 0 to a maximum of 12.

Follow-up of the Patients

After the initial evaluation, patients were followed in one of the outpatient clinics and when needed during hospitalization periods by one of the authors. Antihypertensive treatment was monitored by means of frequent office BP measurements, and when appropriate changes in the number, class, and dose of antihypertensive drugs (diuretics, β-blockers, α-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and vasodilators) were made according to clinical criteria (goal of BP control <140/90 mm Hg) in spite of whether treating physicians were or were not aware of the ABPM results. A comparison of the incidence of new cardiovascular events, fatal and nonfatal, between patient groups was made during the follow-up. In subjects experiencing multiple nonfatal events, the analysis included only the first event. Cardiovascular events included myocardial infarction, angina pectoris, coronary revascularization, stroke, transient ischemic attack, sudden death, aortoiliac occlusive disease, progressive heart failure, and hypertensive emergency. Myocardial infarction was diagnosed on the basis of at least two of three standard criteria (typical chest pain, ECG QRS changes, and transient elevation of myocardial enzymes by more than twofold the upper normal laboratory limits). Angina pectoris was defined as chest pain accompanied by typical ischemic changes in the ECG. Stroke was diagnosed on the basis of rapid onset of localizing neurological deficit lasting 24 hours or longer in the absence of any other process that could explain the symptoms. Transient ischemic attack was defined as any sudden focal neurological deficit that cleared completely in less than 24 hours, based on a diagnosis made by a physician. Sudden death was defined as a witnessed death that occurred within 1 hour after the onset of acute symptoms, with no history of violence or accident playing a role in the fatal outcome. Progressive heart failure was defined as symptoms when appearing during the follow-up in patients without previous heart failure symptoms. Hypertensive emergency

TABLE 1. General Characteristics: Office and Ambulatory BPs in Hypertensive Subjects Grouped by Ambulatory BP

	Lowest Tertile, n=29 (Daytime DBP <88 mm Hg)	Middle Tertile, n=29 (Daytime DBP 88-97 mm Hg)	Highest Tertile, n=28 (Daytime DBP >97 mm Hg)
Age, y	55.6±7.5	53.3±11.4	50.8±8.4
Sex, M/F	11/18	8/21	6/22
Body mass index, kg/m^2	28.3±3.9	28.1±4.0	28.3±3.7
Antihypertensive drugs, n	3.3±0.6	3.1±0.6	3.5±0.9
Office BP, mm Hg			
SBP	174.8±20.6	173.8±20.3	182.2±23.8
DBP	105.5±4.7	107.0±5.9	110.9±9.6
Ambulatory BP, mm Hg			
Average 24-hour			
SBP	129.6±17.8	142.2±12.3	161.2±15.0
DBP	77.0±5.0	88.5±4.9	101.7±6.7
Average daytime (8 AM-10 PM)			
SBP	132.1±18.3	145.4±12.1	165.1±14.7
DBP	79.6±4.9	91.9±3.7	105.6±6.8
Average nighttime (midnight-6 AM)			
SBP	121.8±17.3	129.6±17.5	145.9±18.2
DBP	69.2±7.7	76.9±12.3	89.6±11.5
Day/night ratio			
SBP	1.09±0.09	1.13±0.11	1.13±0.11
DBP	1.17±0.11	1.21±0.16	1.19±0.15

Values are mean±SD.

was defined as, and only considered applicable, when symptoms were accompanied by papilledema in funduscopic examination.

Statistical Analysis

For each variable, values are expressed as mean±SD. Differences between groups were sought by using ANOVA for continuous variables and χ^2 for discontinuous variables. Two-way ANOVA was used to analyze changes in the variables (BP and score) over time in the two group of patients.

Event rates for new cardiovascular events, fatal plus nonfatal, during the time of follow-up are presented as the number of events per 100 patient-years, based on the ratio of the observed number of events to the total number of patient-years of exposure. Survival curves were estimated with the Kaplan-Meier product-limit method, and differences between groups were estimated by the log-rank test. The Cox proportional hazard model was used to assess the effect of the prognostic factor on event-free survival. We tested the independent significance of each ABPM tertile group. The covariates included previous cardiovascular events (absent, present), age (<60 years, >60 years), sex, current smoking (absent, present), ECG criteria of left ventricular hypertrophy (absent, present), office BP at beginning and during follow-up, and average of daytime ambulatory SBP as a continuous variable. Adjusted RR for the significant Cox model factors were calculated and expressed along with the 95% CI.

Results

General Characteristics

Eighty-six patients (27 men and 59 women; mean age, 53±9 years), all white, who met the inclusion criteria, were included in the study. The principal clinical characteristics and BP values of the patients in each group are shown in Table 1. No differences in age, sex, or body mass index were observed between groups. Five patients (17%) in the LT group, 6 (21%) in the MT group, and 7 (25%) in the HT group had had at least one previous cardiovascular event.

Blood Pressure at the Beginning of the Study and at the End of the Follow-up Period

Office and ambulatory BP values are shown in Table 1. No differences in office SBP and DBP were present among the groups. Not only the mean values of both 24-hour ambulatory SBP and DBP, but also those values obtained during day and night periods were significantly higher in the HT group ($P<.001$) than in the other groups. Differences between office BP and the average of daytime ambulatory BP were 29.1±24.1 mm Hg for SBP and 15.4±12.2 mm Hg for DBP. Only 6 (8.3%) of the subjects had a daytime ambulatory BP higher than their office BP. The circadian pattern of BP in the three groups is shown in Fig 1. The highest tertile group exhibited the greatest average values of hourly SBP and DBP throughout the day and night periods when compared with the other groups ($P<.01$ for all hourly periods). No differences in the day/night ratio as an estimate of circadian variability were observed among the groups.

The values of office BP achieved at the time of final evaluation were significantly lower than those observed at baseline. The extent of BP reduction, however, did not differ among the three groups for either the SBP (LT group, 17.1 mm Hg; 95% CI, 6.3 to 27.7; MT group, 16.4 mm Hg, 95% CI, 3.8 to 29.1; HT group, 14.5 mm Hg, 95% CI, 0.6 to

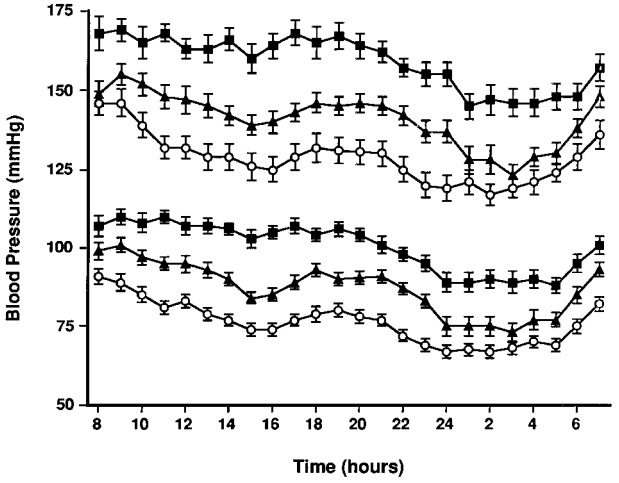

Figure 1. Twenty-four-hour circadian BP profile in patients with resistant hypertension grouped by ambulatory BP: LT group (○, average of ambulatory during the activity DBP <88 mm Hg, n=29), MT group (▲, average of ambulatory during the activity DBP 88 to 97 mm Hg, n=29), and HT group (■, average of ambulatory during the activity DBP >97 mm Hg, n=29). There are significant differences in all hourly averages among groups. Values are mean±SE.

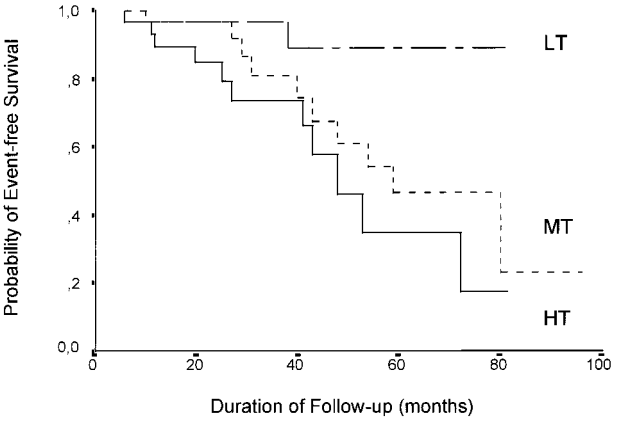

Figure 2. Probability of event-free survival in patients with resistant hypertension grouped by ambulatory BP: LT group (average of ambulatory during the activity DBP <88 mm Hg, n=29), MT group (average of ambulatory during the activity DBP 88 to 97 mm Hg, n=29), and HT group (average of ambulatory during the activity DBP >97 mm Hg, n=29). The comparison of survival curves between the groups shows significant differences between LT and MT groups (log-rank $P<.04$) and LT and HT groups (log-rank $P<.006$). No differences between MT and HT groups were observed (log-rank $P<.26$).

28.3; P=NS) or for the DBP (LT group, 12.0 mm Hg, 95% CI, 7.6 to 16.4; MT group, 9.7 mm Hg, 95% CI, 4.3 to 15.1; HT group, 9.4 mm Hg, 95% CI, 1.8 to 17.0; P=NS). Office DBP persisted at >100 mm Hg for 11 (38%) of the LT group, 12 (41%) of the MT group, and 14 (50%) of the HT group at the last evaluation.

Clinical Score at the Beginning of the Study and at the End of the Follow-up Period

At baseline, mean value of the clinical score was higher in the HT group than in the other groups; however, this difference did not attain statistical significance (LT group, 2.30, 95% CI, 1.45 to 3.14; MT group, 2.41, 95% CI, 1.50 to 3.33; and HT group, 2.64, 95% CI, 1.82 to 3.47; respectively, P=NS).

A statistically significant progression of end-organ damage was observed for the highest ambulatory BP group (3.70, 95% CI, 2.82 to 4.58; $P<.03$), but not for the other groups (LT group, 2.11, 95% CI, 1.36 to 2.86; MT group, 2.93, 95% CI, 1.94 to 3.92; P=NS).

Cardiovascular Morbidity During the Follow-up

Mean time of observation was 49 months, ranging from 6 to 96 months (median, 45 months). During the follow-up, 21 patients had a new cardiovascular event (11 with coronary heart disease, myocardial infarction, or angina pectoris; 5 with cerebrovascular disease, stroke, or transient ischemic attack; 4 with progressive heart failure; 1 with hypertensive emergency). While no statistically significant difference between the two groups with highest ambulatory BP, incidence of events was significantly lower for the LT group (LT group, 2 events, 2.2 per 100 patient-years; MT group, 9 events, 9.5 per 100 patient-years; HT group, 10 events, 13.6 per 100 patient-years). Similar results were observed when the comparison between groups was performed by excluding patients with previous cardiovascular events (LT group, 1 event, 1.3 per 100 patient-years; MT group, 6 events, 8.4 per 100 patient-years; HT group, 7 events, 12.1 per 100 patient-years). The probability of event-free survival is shown in Fig 2. The comparison of survival curves among the groups for the overall population shows significant differences between the LT and MT groups (log-rank $P<.04$), and between the LT and HT groups (log-rank $P<.006$). No differences between MT and HT groups were observed (log-rank $P<.26$). When only patients without previous cardiovascular events were considered, differences among groups remain (LT versus MT, $P<.05$; LT versus HT, $P<.02$; MT versus HT, $P<.37$).

In the Cox analysis, the risk of cardiovascular events was significantly higher for those patients who had previously experienced cardiovascular events (RR, 2.47; 95% CI, 1.05 to 5.78, $P<.04$) and for subjects included in the HT group (RR, 6.20; 95% CI, 1.38 to 28.1, $P<.02$) (Table 4). The prognostic value of ambulatory BP as an independent risk factor remains even when patients who had suffered previous cardiovascular events were removed from the analysis (RR, 8.76; 95% CI, 1.07 to 71.8, $P=.05$). In contrast, age, sex, left ventricular hypertrophy in the ECG, SBP, and DBP office BP at the beginning and at the time of the last evaluation and daytime ambulatory SBP were not independent risk factors for morbid cardiovascular events.

Discussion

In a group of 86 hypertensive patients with refractory hypertension, defined as the finding of an office DBP ≥100 mm Hg during the administration of an adequate combination of three or more antihypertensive drugs, 21 cardiovascular events were recorded during a mean follow-up of 49 months. The risk of a cardiovascular event was significantly higher for the patients who previously had experienced a cardiovascular event and for patients who had a higher ambulatory BP at the time of inclusion. The risk in relation to ambulatory BP values seems to increase progressively from lowest values to highest. What-

TABLE 2. Baseline Clinical End-Organ Damage in Hypertensive Subjects Grouped by Ambulatory BP

	Lowest Tertile, n=29 (Daytime DBP <88 mm Hg)	Middle Tertile, n=29 (Daytime DBP 88-97 mm Hg)	Highest Tertile, n=28 (Daytime DBP >97 mm Hg)
Previous CV events	5 (17)	6 (21)	7 (25)
TIA or stroke	1 (3)	1 (3)	1 (4)
Coronary heart disease	2 (7)	4 (14)	4 (14)
Heart failure	2 (7)	1 (3)	2 (7)
ECG			
Normal	15 (62)	18 (62)	12 (43)
LVH voltage	7 (24)	6 (21)	8 (29)
LVH voltage plus strain	7 (24)	5 (17)	8 (29)
Rx CT index			
<0.50	24 (83)	19 (66)	19 (68)
0.50-0.55	5 (17)	8 (28)	7 (29)
>0.55	0 (0)	2 (7)	1 (4)
Funduscopy (Keith-Wagener)			
0-I	25 (86)	11 (38)	7 (25)
II	4 (14)	14 (48)	20 (71)
III	0 (0)	4 (14)	1 (4)
Serum creatinine			
<132 mmol/L	26 (90)	25 (86)	26 (93)
≥132 mmol/L	3 (10)	4 (14)	2 (7)
Proteinuria			
<1.0 g/24 hours	28 (97)	28 (97)	27 (96)
≥1.0 g/24 hours	1 (3)	1 (3)	1 (4)
Total score*	2.30±2.11	2.41±2.39	2.64±2.13

CV indicates cardiovascular; TIA, transient ischemic attack; LVH, left ventricular hypertrophy; and CT, cardiothoracic index.

*Total score is the average of the individual score calculated according the criteria explained in the text.

Values are number of patients and the percentage between parentheses.

ever the case, in the absence or in presence of a previous cardiovascular event, ambulatory BP was an independent marker of risk for new events. The data of the present study show that ABPM is useful in stratifying the risk in patients with refractory hypertension according to office BP measurements, supporting the recommendations from the National and International Consensus Meetings.[10–20]

The persistence of the differences between casual and ambulatory BP observed in this study might be ascribable to the persistence of the so-called "white-coat effect."[23–26] In this sense, Gosse and coworkers[24] retrospectively analyzed data from 154 patients who had taken part in therapeutic trials. These authors reported the presence of the white-coat effect in the same percentage of patients both before and 3 months after treatment. However, the authors stressed the low reproducibility of the magnitude of the white coat in individual patients, where correlation coefficients of 0.45 for systolic and 0.32 for diastolic pressure were shown. This study demonstrated that the white-coat effect persists in hypertensive subjects even after months of therapy and regardless of the class of drug used.

The differences between office and ambulatory BP and the relation to the reduction in clinical BP during antihypertensive treatment have recently been published by Parati and coworkers[25] in 266 patients treated with various antihypertensive drugs and in 116 patients treated with placebo. They have concluded that a considerable difference persists between clinical and ambulatory BPs after several weeks of treatment but that the magnitude of the differences is significantly attenuated with time. Moreover, the reduction in clinical BP during treatment was higher or lower in function to the magnitude of initial differences between office and ambulatory BP. This observation is in agreement with our data, although no statistically significant differences were present among the groups. The data show that patients in LT group, with the greatest difference between office BP and ambulatory BP, tended to exhibit the greatest fall in office BP over time when compared with patients in the other groups.

During the last several years, ABPM has been introduced into hypertension research and in clinical practice on the basis of two lines of evidence. First, that values of ambulatory BP are more reproducible than their office BP counterparts, both in normotensive and in hypertensive subjects, independent of the age of subjects.[27,28] Second, there is a very consistent body of evidence from cross-sectional studies demonstrating that am-

TABLE 3. End-Organ Damage and Cardiovascular Events Developed During the Follow-up Period in Hypertensive Subjects Grouped by Ambulatory BP

	Lowest Tertile, n=29 (Daytime DBP <88 mm Hg)	Middle Tertile, n=29 (Daytime DBP 88-97 mm Hg)	Highest Tertile, n=28 (Daytime DBP >97 mm Hg)
End-organ damage			
ECG LVH	2	2	5
Serum creatinine >132 mmol/L	1	2	5
Proteinuria >1 g/24 hours	1	1	3
Total score	2.11±1.90	2.93±2.61	3.70±2.22
Cardiovascular events			
TIA or stroke	0	2	3
Angina or myocardial infarction	2	4	5
Progressive cardiac failure	0	2	2
Admission for hypertensive emergency	0	1	0
Total events	2	9	10

See Table 2 for abbreviations.

bulatory BP correlates more closely than does office pressure with target organ damage, as represented by left ventricular hypertrophy[5] and microalbuminuria in either hypertensive and normotensive type 1 diabetes mellitus.[29,30] Furthermore, Mancia et al[31] in the SAMPLE study demonstrated that for hypertensive patients with echographic left ventricular hypertrophy and in treatment with lisinopril, the reduction in left ventricular mass was correlated to the fall in ambulatory BP but not to the reduction in casual BP.

Prospective data relating ambulatory BP to cardiovascular prognosis have been limited to two articles. The first, published by Perloff and coworkers,[7] included 751 patients and evaluated daytime ambulatory BP as well as clinical BP measurements during a follow-up of 5 years. This study showed that the combination of ambulatory and clinical BP values was a better predictor of the incidence of cardiovascular events than was clinical BP alone. Although criticized on several grounds, this was the first approach to the prognostic value of ABPM. The second was published by Verdecchia and coworkers,[8] who followed 1187 hypertensive and 205 normotensive men an women for an average of 3.2 years. The event rate observed was similar in the normotensive and white-coat hypertensives and was significantly higher in the sustained hypertensives. The present study adds further information as to the prognostic value of ABPM, in this case in patients with refractory hypertension, a group with high cardiovascular risk.[2]

The results of this study deserve some commentary. First of all, the averages of ambulatory BP at the beginning are a better prognostic marker of cardiovascular events than are such other well-known markers of risk as office BP during follow-up[32] and left ventricular hypertrophy.[33] The persistence of a marked white-coat effect throughout the study and the high prevalence of left ventricular hypertrophy explains this result in our study population. Second, the prognostic value of ambulatory BP predicted not only the incidence of cardiovascular events but also other end-organ damage. Occurrence of left ventricular hypertrophy and/or proteinuria and the increment of plasma creatinine values were more frequently in the HT group than in the other groups during the observation period (Table 3). Finally, ambulatory BP day/night ratio as an estimate of circadian variability was not an independent marker of risk among patients with refractory hypertension. A higher cardiovascular risk has been reported in women with low BP circadian variability, "nondippers," than the risk in those with "normal" BP circadian variability, "dippers."[8] The high BP values maintained during the night, despite the presence of a

TABLE 4. Relative Risks for Cardiovascular Morbid Events Assessed by Cox Proportional Hazards Model

	Overall Population (n=85)			Patients Without CV Events (n=67)		
Covariate	**RR**	**95% CI**	***P***	**RR**	**95% CI**	***P***
Previous CV events, present vs absent	2.50	1.02-6.10	.045	...	...	...
Ambulatory BP						
LT vs MT	3.69	0.79-17.33	.098	5.28	0.62-44.65	.127
LT vs HT	6.42	1.39-29.7	.017	8.75	1.06-72.15	.049
Age, <60 y vs ≥60 y	1.28	0.43-3.76	.659	1.19	0.31-4.49	.801
Sex, F vs M	0.80	0.34-1.88	.602	0.94	0.28-3.12	.920
LVH ECG, present vs absent	1.53	0.61-3.88	.367	2.24	0.73-6.87	.156

LT indicates average of ambulatory during the activity DBP <88 mm Hg; MT, average of ambulatory during the activity DBP 88-97 mm Hg; and HT, average of ambulatory during the activity DBP >97 mm Hg. See Table 2 for other abbreviations.

"normal" nocturnal BP fall, overcome the importance of the extent of BP fall in refractory hypertensives.

It should be pointed out that the present study has several its limitations. To begin with, the number of subjects was relatively small, although as the subjects studied are a group with high cardiovascular risk, the number of events recorded is high enough to allow for comparisons between groups. Second, antihypertensive drugs and their combinations were variable during the follow-up because of the special characteristics of the study group. The maintenance of the same treatment during large periods could raise ethical conflicts. Additionally, a lipid profile might help to explain our findings. Nonetheless, only a small number of patients needed lipid-lowering drugs, 3 in each group, and no differences in the values of total cholesterol or triglycerides were present among the groups at the time of inclusion. Finally, one aspect not covered in the study was the performance of regular ABPM during the follow-up to further assess the prognostic value of this technique. It is known that lowering elevated BP results in a remarkable reduction of hypertension-induced morbidity and mortality and that the benefits of treatment are greatest for those patients whose BP had been reduced the most.[32] Whether or not ambulatory BP values throughout a long follow-up period represent a more accurate prognostic tool than office BP in evaluating refractory hypertensive patients needs to be assessed in future studies.

In conclusion, higher values of ambulatory BP result in a more accurate prognosis of future cardiovascular events in patients with refractory hypertension than do casual BP values. Although more studies are needed to better assess the prognostic value of ambulatory BP, the present data support the Consensus Meetings' recommendation that ABPM be used to stratify cardiovascular risk in patients with refractory hypertension.

References

1. Setaro JF, Black HR. Refractory hypertension. *N Engl J Med*. 1992;327:543–547.
2. Pickering TG. Blood pressure monitoring outside the office for the evaluation of patients with resistant hypertension. *Hypertension*. 1988;11(suppl II):II-96-II-100.
3. Mancia G, Parati G, Pomidossi G, de Rienzo M. Validity and usefulness of noninvasive ambulatory blood pressure monitoring. *J Hypertens*. 1985;3(suppl 2):S5–S11.
4. Pickering TG, Harshfield GA, Kleinert HD, Blank S, Laragh JH. Blood pressure during normal daily activities, sleep and exercise. *JAMA*. 1982;247:992–996.
5. Hoegholm A, Kristensen KS, Bang LE, Nielsen JW, Nielsen WB, Madsen NH. Left ventricular mass and geometry in patients with established hypertension and white-coat hypertension. *Am J Hypertens*. 1993;6:282–286.
6. White WB, Schulmen P, McCabe EJ, Dey HM. Average daily blood pressure, not office pressure, determines cardiac function in patients with hypertension. *JAMA*. 1989;261:873–877.
7. Perloff D, Sokolow M, Cowan RM, Juster RP. Prognostic value of ambulatory blood pressure measurements: further analysis. *J Hypertens*. 1989;7(suppl 3):S3–S10.
8. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension*. 1994;24:793–801.
9. Frattola A, Parati G, Cuspidi C, Albini F, Mancia G. Prognostic value of 24-hour blood pressure variability. *J Hypertens*. 1993;11:1133–1138.
10. National High Blood Pressure Education Program Coordinating Committee. National High Blood Pressure Education Program Working Group Report on ambulatory blood pressure monitoring. *Arch Intern Med*. 1990;159:2270–2280.
11. Fifth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. Publication No. 93–1088. National Institute of Health, Washington, DC. 1993.
12. Enrégistrement ambulatoire de la pressión artèrielle. Document consensus 1991 ètabli par l'Association suisse contre l'hypertension artèrielle. *Schweiz Rundsch Med Prax*. 1992;81:204–205.
13. American College of Physicians. Automated ambulatory blood pressure monitoring devices: their role in the diagnosis and management of hypertension. *Ann Intern Med*. 1993;118:889–892.
14. Poggi L, Mallion JM, Renucci JF, Vaisse B, de Gaudemaris R, Chanudel X, Asmar R, Tcherdakoff P. Mesure ambulatoire non invasive de la pression artèrielle: Recommandations du groupes de la mesure de la societè francaise d'hypertension artèrielle. *Arch Mal Coeur*. 1993;86:1137–1142.
15. I Consenso Brasillero para o uso da monitorização ambulatorial da pressão arterial. *Arq Bras Cardiol*. 1993;60:129–134.
16. Sheps SG, Clement DL, Pickering TG, Krakoff LR, White WB, Messerli FH, Weber MA, Perloff D. ACC position statement: ambulatory blood pressure monitoring. *J Am Coll Cardiol*. 1994;23:1511–1513.
17. Staessen JA, Fagard R, Thijs L, Amery A. A consensus view on the technique of ambulatory blood pressure monitoring. *Hypertension*. 1995;26:912–918.
18. Blood pressure measurement section of the Deutsche Liga zur Bekämpfung des höhen Blutdruckes e V (German Hypertension League). *J Hum Hypertens*. 1995;7:777–779.
19. Parati G, Bosi S, Castellano M, Cristofari M, Di Rienzo M, Lattuada S, Mormino P, Mos L, Omboni S, Palatini P, Ravogli A, Rizzoni D, Verdecchia P, Zito M. Guidelines for 24-h non-invasive ambulatory blood pressure monitoring: report from the Italian Society of Hypertension. *High Blood Pressure*. 1995;4:168–174.
20. Pickering TH, for an American Society of Hypertension Ad Hoc Panel. Recommendations for the use of home (self) and ambulatory blood pressure monitoring. *Am J Hypertens*. 1995;9:1–11.
21. Petrie JC, O'Brien ET, Littler WA, de Swiet M. British Hypertension Society. Recommendations on blood pressure measurement. *BMJ*. 1986;293:611–615.
22. Parati G, Pomidossi G, Albini F, Malaspina D, Mancia G. Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension. *J Hypertens*. 1987;5:93–98.
23. Porchet M, Bussien JP, Waeber B, Nusberger J, Brunner HR. Unpredictability of blood pressures recorded outside the clinic in the treated hypertensive patients. *J Cardiovasc Pharmacol*. 1988;8:332–335.
24. Gosse PH, Bougaleb M, Egloff OH, Lemetayer PH, Clementy J. Clinical significance of white-coat hypertension. *J Hypertens*. 1994;12(suppl 8):S43–S47).
25. Parati G, Omboni S, Mancia G. Difference between office and ambulatory blood pressure and response to antihypertensive treatment. *J Hypertens*. 1996;14:791–797.
26. Gandia MC, Redon J, Lozano JV, Morales-Olivas F, Rubio E. Evaluation of the control of antihypertensive treatment by the use of outpatient blood pressure monitorization [in Spanish]. *Med Clin*. 1994;103:331–334.
27. Lurbe E, Aguilar F, Gomez A, Tacons J, Alvarez V, Redon J. Reproducibility of ambulatory blood pressure monitoring in children. *J Hypertens*. 1993;11(suppl 5):S288–S289.
28. Staessen J, Bulpitt CHJ, O'Brien E, Cox J, Fagard R, Stanton A, Thijs L, Van Hulle S, Vyncke G, Amery A. The diurnal blood pressure profile: a population study. *Am J Hypertens*. 1992;5:386–392.
29. Redon J, Miralles A, Liao Y, Lozano JV, Pascual JM, Cooper RS. Circadian variability and microalbuminuria in essential hypertension. *J Hypertens*. 1994;12:947–954.
30. Lurbe A, Redon J, Pascual JM, Tacons J, Alvarez V, Battle DC. Altered blood pressure during sleep in normotensive subjects with type I diabetes. *Hypertension*. 1993;21:227–235.
31. Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, De Cesaris R, Fogari R, Pessino A, Porcellati C, Salvetti A, Trimarco B. Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy. *Circulation*. 1997;95:1464–1470.
32. Isles CG, Walker LM, Beevers GD, Brown I, Cameron HL, Clarke J, Hawthorne V, Hole D, Lever AF, Robertson JW, et al. Mortality in patients of the Glasgow Blood Pressure Clinic. *J Hypertens*. 1986;4:141–156.
33. Kannel WB, Abbot RD. A prognostic comparison of asymptomatic left ventricular hypertrophy and unrecognized myocardial infarction in the Framinghan Study. *Am Heart J*. 1986;111:391–397.