Application of Ambulatory Blood Pressure Monitoring in Differentiating Between Antihypertensive Agents

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PURPOSE: This multicenter, double-blind, parallel group study assessed the usefulness of the ambulatory blood pressure monitoring (ABPM) technique in differentiating between the once-daily administration of the β blockers bisoprolol (10 to 20 mg) and atenolol (50 to 100 mg) in terms of efficacy and duration of action.

PATIENTS AND METHODS: The study population consisted of 659 patients with essential hypertension and an average office diastolic blood pressure (BP) between 95 and 115 mm Hg after 4 weeks of placebo treatment. Office BPs were recorded at the end of the 24-hour dosing interval (trough). ABPM was performed in 11 of the 28 institutions participating in this study in a total of 203 patients. These procedures were performed at the end of the placebo phase and again after 8 weeks of active treatment.

RESULTS: With the use of conventionally measured office BPs, the two drugs significantly ($p < 0.001$) decreased trough systolic and diastolic BPs to a similar extent. By 24-hour monitoring, bisoprolol demonstrated a 33% greater reduction in whole-day average diastolic BP than did atenolol (11.6 ± 0.7 mm Hg versus 8.7 ± 0.8 mm Hg, $p < 0.01$). Significant treatment differences in systolic ($p < 0.05$) and diastolic ($p < 0.01$) BPs were also noted for bisoprolol compared with atenolol during the final 4 hours of the dosing interval (−13.2 ± 1.5/−10.9 ± 1.0 mm Hg versus −8.9 ± 1.6/−7.3 ± 1.1 mm Hg, respectively), and over the time period 6:00 AM to noon (−14.2 ± 1.3/−11.5 ± 0.9 mm Hg versus −9.9 ± 1.4/−7.7 ± 0.9 mm Hg).

CONCLUSION: Whereas conventional BP measurements did not detect differences in the antihypertensive effects of the β blockers bisoprolol and atenolol, ABPM revealed significant treatment differences in both the efficacy and duration of action of these two agents. These findings indicate the power of this technique to discriminate potentially important differences between apparently similar antihypertensive drugs.

The durations of action of antihypertensive drugs have been conventionally assessed by office blood pressure (BP) measurements at the end of the dosing interval or by predictions based on the plasma half-lives of the drugs. Each of these methods can be misleading in predicting clinical effects [1]. The development of ambulatory blood pressure monitoring (ABPM) techniques has provided a more accurate means to assess both the efficacy [2] and duration of action [3] of antihypertensive agents.

Recent attention has focused on the increased frequency of cardiovascular events occurring in the early morning hours [4–6]. Because antihypertensive drugs administered once daily are typically taken upon arising, the end of their dosing intervals (trough effect) tends to coincide with the early-morning rapid increase in BP. Thus, observations of the efficacy of these agents during the important morning hours might provide potentially relevant clinical information.

In this study, we have used both ambulatory and office measurements of BP to directly compare the antihypertensive effects of two β-blocking agents each administered once daily, the widely used β blocker atenolol and the newer agent bisoprolol. The study design has provided an opportunity to test the usefulness of ABPM in differentiating be-

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tween the efficacy of apparently similar antihypertensive agents, especially toward the end of their dosing intervals. Bisoprolol is a beta-1–selective β blocker with a plasma half-life of 9 to 12 hours [7]; atenolol, also a beta-1–selective β blocker, has a plasma half-life of 6 to 9 hours [8]. Despite the apparent similarity of the two agents when tested using conventional BP measurements, potentially important differences in antihypertensive efficacy were revealed by the ABPM technique.

PATIENTS AND METHODS

This multicenter study was performed in 659 patients with mild to moderate essential hypertension (diastolic BP 95 to 115 mm Hg). Essential hypertension was diagnosed by the exclusion of secondary causes of hypertension by conventional clinical criteria. All patients signed an informed consent document approved by the respective Institutional Review Boards of the participating institutions.

The protocol for the 28-center study was of double-blind, randomized, parallel group design. After an initial screening period, patients with sitting diastolic BPs between 95 and 115 mm Hg entered a 4-week single-blind placebo period. Patients in whom the average diastolic BPs at Weeks 3 and 4 of the placebo period were between 95 and 115 mm Hg (measured conventionally) were randomized to receive 10 mg of bisoprolol once daily or 50 mg of atenolol once daily. If after 4 or 6 weeks of this treatment the diastolic BP was greater than 90 mm Hg, the dosages were doubled for the remainder of the study (total active treatment phase of 8 weeks).

Throughout the study, the patients were encouraged to take their medication as closely as possible to 10:00 AM. BP was measured with a mercury sphygmomanometer just before dosing for assessment of conventional office BP using standardized techniques [9]. At each visit during the placebo and treatment periods, three consecutive (2 minutes apart) sitting systolic and diastolic (Korotkoff phase V) BPs were measured by the same observer using the same arm and an appropriately sized cuff. The recorded BP measurement at each visit was the average of the three measurements. All patients qualified for the study based on office measurements.

Prior to the study, a subgroup of investigators with experience in the technique of ABPM were selected to perform this procedure as part of the protocol. Thus, at 11 of the 28 study sites, ABPM was performed at the end of the placebo phase (baseline) and again at the end of active treatment. BP was obtained at 15-minute intervals throughout the 24-hour monitoring period. The monitoring device was attached immediately after dosing and was removed 24 hours later. The SpaceLabs 90207 system (SpaceLabs Inc, Redmond, WA) was used for the monitoring. This device uses a standard cuff that was programmed in this study to inflate automatically at 15-minute intervals throughout the monitoring period. BP is measured by an oscillometric method. Previously we have shown that this instrument, as well as a comparable auscultatory device, each provided values that showed a close concordance with values obtained simultaneously with a mercury sphygmomanometer or by direct intra-arterial measurements [10]. Data were processed according to methods described previously [11]. Briefly, BP averages were calculated during each of the 12 2-hour monitoring periods of the whole day. Actual clocktime was used as the basis for determining time intervals. No smoothing procedures (e.g., fourier transformation, spline) were utilized.

To compare efficacy of the two drugs, 24-hour systolic and diastolic average BPs, areas under the curves, and loads were calculated for each agent at baseline and at the end of the active treatment phase. Areas under the BP curves were determined by plotting the recorded systolic and diastolic BPs for the 24-hour period and then calculating the entire area under the curve to a value of 0 mm Hg [12]. Systolic and diastolic loads were determined by calculating the percentage of systolic BPs above 140 mm Hg and diastolic BPs above 90 mm Hg for the 24-hour period. An alternative load calculation based on a criterion of 140/90 mm Hg during the day and 120/80 mm Hg at night was performed. Daytime, nighttime, and the last 4 hours of the dosing interval were defined *a priori* as time segments of interest. Therefore, to more precisely compare durations of action of the two agents, average BPs were calculated for the following four separate time intervals: daytime hours (6:00 AM to 10:00 PM), nighttime hours (10:00 PM to 6:00 AM), the period 6:00 AM to 12 noon, and the last 4 hours of the dosing interval.

The primary efficacy analysis was performed on all patients who completed active treatment without protocol violations. To prevent potential biases of excluding patients, an intent-to-treat analysis was conducted on all randomized patients who had at least one baseline BP reading and one postbaseline reading regardless of protocol violations. All patients were included in the analysis of safety, which was evaluated by reports of adverse drug experiences, laboratory results, and 12-lead electrocardiograms.

Statistical analysis of the study data consisted of between-treatment comparisons of changes in BP from baseline values. BP and heart rate data were

TABLE I

Clinical Characteristics and Demographics of Study Population and Patients Randomized to Ambulatory Blood Pressure Monitoring

	Bisoprolol*		Atenolol*	
	Study Population	Ambulatory BP Patients	Study Population	Ambulatory BP Patients
No.	308	107	298	96
Sex (%)				
Male	61	56	65	59
Female	39	44	35	41
Race (%)				
Non-black	80	79	80	86
Black	20	21	20	14
Age (y)				
Mean	54	52	55	53
Range	21–84	21–74	23–82	23–78
Weight (kg)				
Mean	84	85	85	82
Range	50–141	50–141	44–125	48–118
Mean baseline sitting diastolic BP (mm Hg)†	100.8 ± 0.3	100.5 ± 0.4	100.7 ± 0.3	100.1 ± 0.4
Mean baseline sitting systolic BP (mm Hg)†	151.9 ± 0.9	150.6 ± 1.4	151.4 ± 0.9	150.4 ± 1.5
Mean baseline sitting heart rate (beats/min)†	75.4 ± 0.5	74.8 ± 0.7	75.2 ± 0.6	74.1 ± 0.7

BP = blood pressure.
*No significant differences ($p > 0.05$) between treatment groups or between study population and patients randomized to ambulatory blood pressure monitoring.
†Data are presented as mean ± SEM.

TABLE II

Analyses of Whole-Day Blood Pressure By Three Different Methods: Mean Changes From Baseline to End of Treatment

Blood Pressure	Change From Baseline After Treatment With		Treatment Difference Between Drugs (%)
	Bisoprolol	Atenolol	
Average (mm Hg)			
Systolic	−15.0 ± 1.3*	−11.9 ± 1.4*	26
Diastolic	−11.6 ± 0.7†	−8.7 ± 0.8†	33
Areas under the curve (mm Hg · h)			
Systolic	−360 ± 30*	−285 ± 33*	26
Diastolic	−280 ± 17†	−209 ± 19†	34
Load (%)‡			
Systolic	−28 ± 2*	−22 ± 2*	27
Diastolic	−28 ± 2†	−21 ± 2†	33
Alternative load (%)§			
Systolic	−31 ± 3‖	−24 ± 3	29
Diastolic	−33 ± 2†	−24 ± 2†	37

*$p = 0.09$.
†$p < 0.01$.
‡Percent readings > 140/90 mm Hg over the 24-hour period.
§Percent readings > 140/90 mm Hg daytime (6 AM to 10 PM) and 120/80 mm Hg nighttime (10 PM to 6 AM).
‖$p = 0.05$ for comparison of treatment differences within each method of analysis.

evaluated by analysis of covariance using baseline measurements as the covariate; other factors were center, treatment, and center by treatments interaction. There were no statistically significant interactions between centers and treatment. Comparisons of response rates and safety were also performed using χ^2 or Fisher's exact test for categorical variables and analysis of variance for continuous variables. Values are given as mean ± SEM.

RESULTS

Of the 659 patients entering the study, 336 were randomized to receive bisoprolol and 323 to receive atenolol. From this group, 53 patients were excluded from the primary efficacy analysis because of protocol violations (22 patients—nonqualifying baseline BP; 23 patients—concomitant medication interfering with BP determination; 8 patients—poor compliance). Inclusion of the intent-to-treat patients in the data analysis yielded results nearly identical to the primary efficacy analysis. The demographics and clinical characteristics of the remaining 606 patients are outlined in Table I; there were no significant differences between the treatment groups with respect to any demographic or clinical characteristic. At the end of the active phase of the study, 53% of the patients randomized to bisoprolol compared with 64% of the patients randomized to atenolol required dose escalation ($p = 0.01$) (final mean dose: bisoprolol 15.3 mg; atenolol 82.0 mg).

After treatment, in the evaluable study population ($n = 606$), the decrease in conventionally measured office diastolic BP at trough (24 hours after dosing) in patients treated with bisoprolol (11.9 ± 0.5 mm Hg; $n = 308$) was slightly but not significantly ($p = 0.06$) greater than in patients treated with atenolol (10.7 ± 0.5 mm Hg; $n = 298$). The reductions in systolic BP were 12.2 ± 0.9 and 11.8 ± 0.9 mm Hg, respectively. Both bisoprolol and atenolol caused significant ($p < 0.01$) reductions in heart rate (11 ± 1 and 9 ± 1 beats/min). The response rate (diastolic BP less than or equal to 90 mm Hg or a reduction of greater than or equal to 10 mm Hg) was greater in patients treated with bisoprolol compared with atenolol (70% versus 62%, $p = 0.04$).

The clinical characteristics of the patients randomized for ABPM are shown in Table I. These patients were comparable to the overall study population in both demographics and baseline vital signs. The ambulatory BP data were of high quality; fewer than 1% (47 of 4,872) of the 12 2-hour periods of the whole day obtained in the 203 patients lacked data.

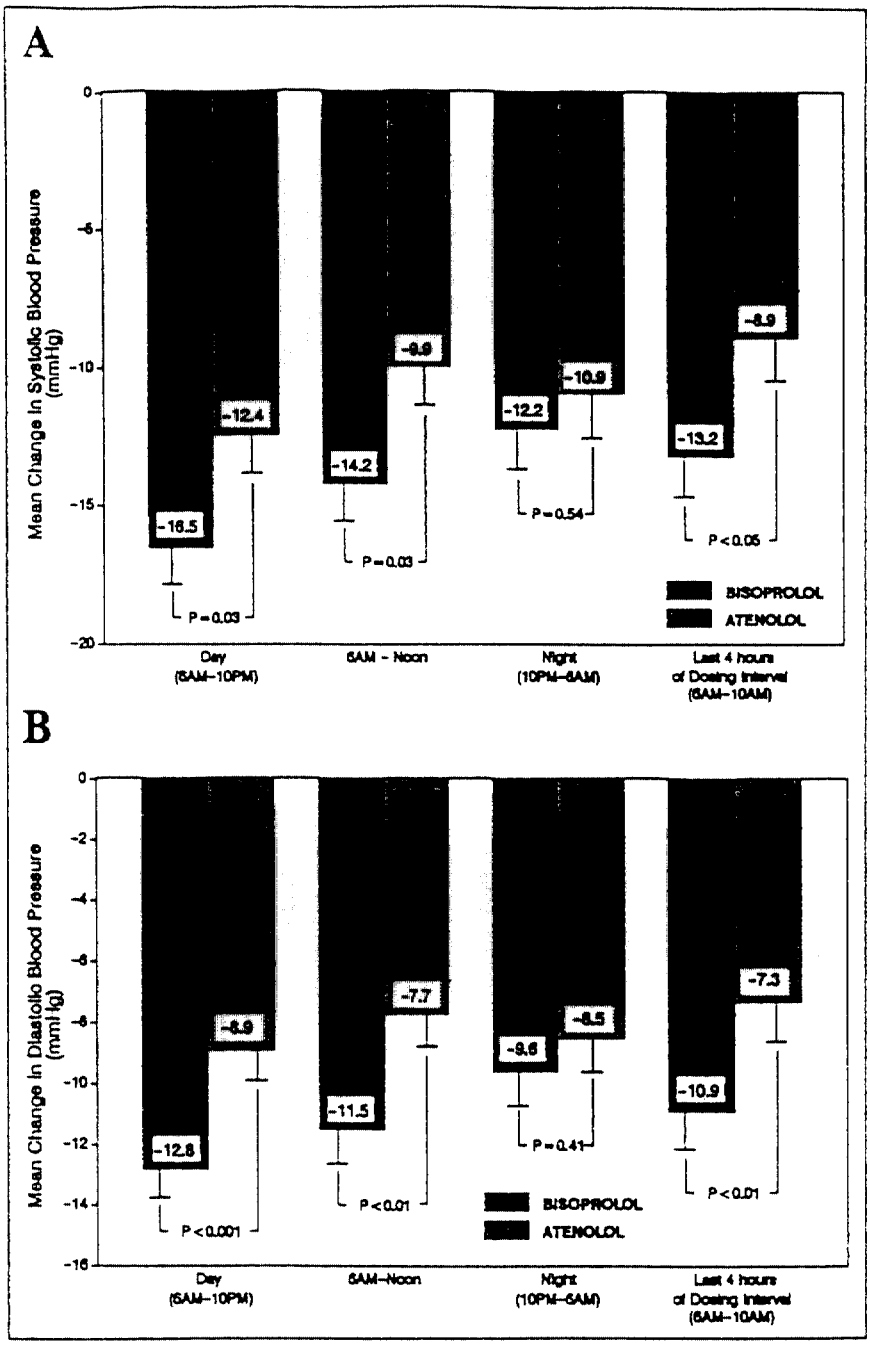

Figure 1. Mean changes from baseline to end of treatment in ambulatory (**A**) systolic and (**B**) diastolic blood pressures over specific time intervals.

Mean whole-day reductions from baseline to the end of treatment in systolic and diastolic BPs are shown in **Table II** (bisoprolol baseline 144 ± 2/90 ± 1 mm Hg; atenolol baseline 146 ± 2/91 ± 1 mm Hg). When the two groups were compared, the average decrease in diastolic BP for the 24-hour period in patients treated with bisoprolol was significantly greater ($p < 0.01$) than that in the patients treated with atenolol. Similarly, the decrease in systolic BP tended to be greater in the patients treated with bisoprolol than in those treated with atenolol, but the difference was of marginal significance ($p = 0.09$).

Two alternative methods of analyzing whole-day BP data are area under the BP curve and load. Mean reductions in systolic and diastolic area under the curve (bisoprolol baseline 3,447 ± 39/2,147 ± 21 mm Hg-h; atenolol baseline 3,526 ± 42/2,199 ± 23 mm Hg-h) and load (bisoprolol baseline 54 ± 3/48 ± 2%; atenolol baseline 61 ± 3/51 ± 3%) are also shown in Table II. The three methods of analysis (whole-day average BP, area under the curve, and load) were compared in terms of their ability to assess differences in the efficacy of the two agents. The magnitude of the differences in efficacy between the two drugs was closely similar with each method.

Figure 1 shows the effects of the two agents on systolic (A) and diastolic (B) BPs over defined time intervals of the 24-hour monitoring period. For day-

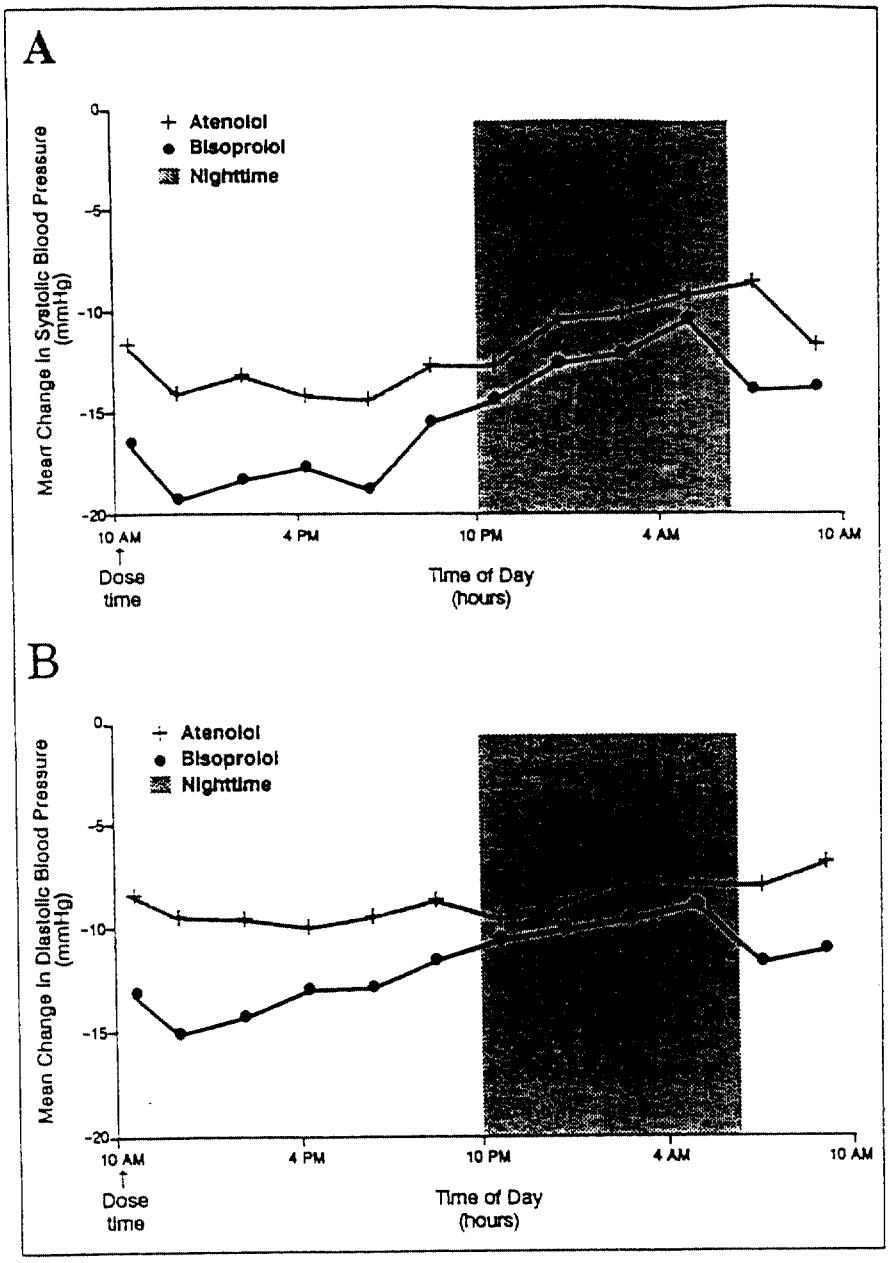

Figure 2. Mean changes from baseline to end of treatment in ambulatory (A) systolic and (B) diastolic blood pressures over the 24-hour monitoring period.

time hours, and the specific time period 6:00 AM to noon, the average decrease in systolic ($p = 0.03$, both time intervals) and diastolic ($p < 0.01$, both time intervals) BPs was greater in patients treated with bisoprolol than in those treated with atenolol. Both drugs effectively lowered nighttime BP to a similar extent ($p < 0.01$ versus baselines, p = NS for treatment differences). The durations of action of the two drugs were compared by BP measurements recorded at the end of the dosing interval. Over the last 4 hours of the dosing interval, bisoprolol was more effective in lowering systolic ($p < 0.05$) and diastolic ($p < 0.01$) BPs compared with atenolol. The effects of the two agents over the entire 24-hour monitoring period in terms of mean changes from baseline values are depicted graphically in Figure 2.

The overall incidence and type of adverse events and frequency of early withdrawals from therapy were similar for the two agents (p = NS). The most common treatment-related adverse events for bisoprolol and atenolol, respectively, were fatigue (7% versus 7%), headache (3% versus 4%), dizziness (3% versus 3%), somnolence (2% versus 2%), insomnia (2% versus 1%), impotence (2% versus 2%), decreased libido (1% versus 2%), bradycardia (2% versus 1%), edema (1% versus 1%), dyspnea (1% versus 1%), and bronchospasm (0% versus 1%). Thirty-two patients withdrew from the bisoprolol group (15 patients—adverse drug reactions; 3 patients—uncontrolled BP; 14 patients—lost to follow-up) and 25 patients discontinued atenolol therapy (12 patients—adverse drug reactions; 2 patients—uncontrolled BP; 11 patients—lost to follow-up).

COMMENTS

This study has allowed us to assess the usefulness of ABPM in discriminating between the efficacy and duration of action of two effective antihypertensive agents. Interestingly, in the overall study population, no significant differences were found between the two drugs when using BPs measured by the conventional sphygmomanometer. In contrast, a significant treatment difference of 33% was demonstrated by ABPM in diastolic BP for the day as a whole. Moreover, there were differences of between 43% and 49% in the efficacy of bisoprolol and atenolol for both systolic and diastolic BPs during the time period 6:00 AM and noon and over the last 4 hours of the dosing interval. These observations underscore the usefulness and power of the monitoring technique in discriminating differences in efficacy and duration of action.

The early-morning rapid rise in BP is a period during which control of BP may be important. However, data from the major trials demonstrating reductions in hypertensive complications with antihypertensive therapy were derived from office BP measurements [13–15]. A difference of approximately 5 mm Hg measured in the office in diastolic BP has a major impact on hypertensive complications, as shown in a recent pooled analysis of 9 prospective observational studies [16] and a second pooled analysis of 14 randomized trials [17]. The long-term cardiovascular consequences of treatment differences in BP determined by ABPM are not yet firmly established. Nevertheless, we found that bisoprolol therapy reduced ambulatory systolic and diastolic BPs by 43% and 49%, respectively, more than atenolol during these morning hours. This finding may have potential clinical importance in patients receiving long-term antihypertensive therapy.

BP in both normotensive and hypertensive individuals follows a circadian pattern, decreasing at night [18]. Nocturnal BP reduction, therefore, might be an appropriate goal of antihypertensive therapy; however, concern has been expressed that excessive lowering of BP at night could result in myocardial ischemia, especially in patients with underlying coronary artery disease [19,20]. Of note, as shown in Figure 2, while significant treatment differences were observed in daytime efficacy, the two agents produced similar decreases in BP during the nighttime hours.

In addition to assessing durations of action of individual drugs, whole-day BP monitoring is useful for comparing the overall efficacy of antihypertensive agents. Several different methods of analysis of 24-hour BP have been reported, but there is no agreement as to which method should be used [12,21,22]. For example, one study [23] reported that load correlated more closely than whole-day mean BP with left ventricular mass index. In the present study, we have compared three different methods of analysis (whole-day average BPs, BP areas under the curve, and systolic and diastolic BP loads). We found that the three methods gave closely similar results in comparing the efficacy of the drugs.

Finally, in addition to the usefulness of ABPM in determining the efficacy and duration of action of antihypertensive therapy, studies have correlated whole-day BP more closely than office BP with target organ damage [24–27]. Whole-day average BP has also been shown to be a better predictor of cardiovascular events than conventional BP recordings in the office [28]. Therefore, ABPM appears to be a valuable tool for assessing both the effects of elevated BP and the effectiveness of antihypertensive therapy. Further studies are needed to determine whether BP effects measured by whole-day monitoring are predictive of cardiovascular protective effects.

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