Antihypertensive Treatment Based on Conventional or Ambulatory Blood Pressure Measurement

A Randomized Controlled Trial

Jan A. Staessen, MD, PhD; Geert Byttebier, MSc; Frank Buntinx, MD, PhD; Hilde Celis, MD; Eoin T. O'Brien, MD, FRCP; Robert Fagard, MD, PhD; for the Ambulatory Blood Pressure Monitoring and Treatment of Hypertension Investigators

Context.—Ambulatory blood pressure (ABP) monitoring is used increasingly in clinical practice, but how it affects treatment of blood pressure has not been determined.

Objective.—To compare conventional blood pressure (CBP) measurement and ABP measurement in the management of hypertensive patients.

Design.—Multicenter, randomized, parallel-group trial.

Setting.—Family practices and outpatient clinics at regional and university hospitals.

Participants.—A total of 419 patients (≥18 years), whose untreated diastolic blood pressure (DBP) on CBP measurement averaged 95 mm Hg or higher, randomized to CBP or ABP arms.

Interventions.—Antihypertensive drug treatment was adjusted in a stepwise fashion based on either the average daytime (from 10 AM to 8 PM) ambulatory DBP (n=213) or the average of 3 sitting DBP readings (n=206). If the DBP guiding treatment was above (>89 mm Hg), at (80-89 mm Hg), or below (<80 mm Hg) target, 1 physician blinded to the patients' randomization intensified antihypertensive treatment, left it unchanged, or reduced it, respectively.

Main Outcome Measures.—The CBP and ABP levels, intensity of drug treatment, electrocardiographic and echocardiographic left ventricular mass, symptoms reported by questionnaire, and cost.

Results.—At the end of the study (median follow-up, 182 days; 5th to 95th percentile interval, 85-258 days), more ABP than CBP patients had stopped antihypertensive drug treatment (26.3% vs 7.3%; $P<.001$), and fewer ABP patients had progressed to sustained multiple-drug treatment (27.2% vs 42.7%; $P<.001$). The final CBP and 24-hour ABP averaged 144.1/89.9 mm Hg and 129.4/79.5 mm Hg in the ABP group and 140.3/89.6 mm Hg and 128.0/79.1 mm Hg in the CBP group. Left ventricular mass and reported symptoms were similar in the 2 groups. The potential savings in the ABP group in terms of less intensive drug treatment and fewer physician visits were offset by the costs of ABP monitoring.

Conclusions.—Adjustment of antihypertensive treatment based on ABP monitoring instead of CBP measurement led to less intensive drug treatment with preservation of blood pressure control, general well-being, and inhibition of left ventricular enlargement but did not reduce the overall costs of antihypertensive treatment.

JAMA. 1997;278:1065-1072

AMBULATORY MONITORING makes it possible to record the blood pressure (BP) throughout the whole day in patients engaged in their normal activities and to provide within 24 hours a reliable estimate of their BP.[1] To acquire the same information, conventional measurements must be repeated at intervals of a few weeks.[2] Furthermore, ambulatory monitoring is characterized by high reproducibility,[3] is not subject to digit preference and observer bias,[4] and avoids the so-called white coat effect,[5,6] ie, the transient rise of a patient's BP in response to the clinic surroundings or the presence of the observer.[7]

For editorial comment see p 1110.

The growing consensus on diagnostic thresholds[8] and the production of national guidelines[9] have paved the way for the more frequent use of ambulatory monitoring in clinical practice, although

From the Hypertensie en Cardiovasculaire Revalidatie Eenheid, Departement voor Moleculair en Cardiovasculair Onderzoek, Katholieke Universiteit Leuven (Drs Staessen, Celis, and Fagard), and Academisch Centrum voor Huisartsgeneeskunde, Katholieke Universiteit Leuven (Dr Buntinx), Leuven, Belgium; Hypertension Unit, Beaumont Hospital, Dublin, Ireland (Dr O'Brien); and ZENECA NV, Destelbergen, Belgium (Dr Byttebier).

A complete list of participants in the Ambulatory Blood Pressure Monitoring and Treatment of Hypertension group appears at the end of this article.

Reprints: Jan A. Staessen, MD, PhD, Klinisch Laboratorium Hypertensie, Inwendige Geneeskunde-Cardiologie, U. Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium (e-mail: jan.staessen@med.kuleuven.ac.be).

at present there is no evidence that patient care would be improved. The Ambulatory Blood Pressure Monitoring and Treatment of Hypertension (APTH) trial,[10] a randomized study coordinated in Belgium, tested the hypothesis that ambulatory monitoring would lead to less intensive antihypertensive drug treatment with fewer adverse effects, while preserving BP control during the whole day and, hence, the reduction of left ventricular mass.

METHODS

General Design

The protocol of the multicenter APTH trial[10] was approved by the Ethics Committee of the University of Leuven. The trial was conducted according to the Helsinki Declaration.[11] At 47 family practices and 9 clinics run by internists, the investigators screened possible participants among the treated and untreated hypertensive patients. At an initial screening visit, informed consent was obtained and all antihypertensive drugs were gradually discontinued and replaced by 1 placebo tablet, prescribed once daily in a single-blind fashion. Approximately 4 and 8 weeks later, the patients were reexamined. They were eligible to be randomized if, at these 2 visits, the last of 3 consecutive conventional diastolic blood pressure (DBP) readings in the sitting position averaged 95 through 114 mm Hg. Patients with a higher DBP also qualified but were reexamined at shorter intervals depending on the degree of elevation. The other selection criteria were a minimum age of 18 years, effective contraception in women of reproductive age, and the possibility of regular follow-up during the intended study period.

Patients were excluded if stopping antihypertensive drug treatment was contraindicated; for example, if patients had overt heart failure, unstable angina pectoris, hypertensive retinopathy stage III or IV, or if they had a history of myocardial infarction or cerebrovascular accident within 1 year, severe noncardiovascular diseases such as cancer or liver cirrhosis, a serum creatinine concentration exceeding 133 μmol/L (1.5 mg/dL), mental disorders, or addiction to narcotic agents or alcohol. Patients working night shifts also were not enrolled.

After stratification by center, eligible patients were randomized at the coordinating office by means of a computerized random number function. Treatment allocation was balanced per block of 10 patients followed at the same center. Patients were randomized to be treated based on the average daytime (from 10 AM to 8 PM) ambulatory blood pressure (ABP group) or the average of 3 sitting readings obtained by conventional sphygmomanometry (CBP group). At randomization, all patients were started on 10 mg per day of lisinopril (step 1). Follow-up visits after randomization were scheduled at 1, 2, 4, and 6 months. At each visit, all patients had both conventional blood pressure (CBP) and ABP measured. The clinical investigators recorded the CBP readings, current treatment, symptoms, signs, and new diagnoses on the study form and transferred the ABP readings onto a memory card. Immediately after each visit, these paper and electronic documents were mailed to the coordinating office, where the CBP readings were averaged and the memory card was decoded. In both groups, the same standardized treatment regimen was applied with the goal to reach the same target range of DBP, ie, 80 through 89 mm Hg.[10] The possible treatment steps at visits 1 through 4 involved increasing lisinopril to its standard daily dose of 20 mg (step 2), the addition of 12.5 mg of hydrochlorothiazide in the morning (step 3), and the addition of 5 mg of amlodipine per day (step 4). In patients with known contraindications to angiotensin-converting enzyme inhibitors, 50 mg (step 1) or 100 mg (step 2) of atenolol per day was used instead of lisinopril. If the DBP guiding treatment was above target (>89 mm Hg), medical treatment was intensified by 1 step. If the DBP was within the target range (80-89 mm Hg), medical treatment was left unchanged. If the DBP guiding treatment was below target (<80 mm Hg), medical treatment was reduced by 1 step. In both treatment groups, the level of the target BP and the treatment steps were the same. This made it possible for 1 physician at the coordinating office to make all treatment decisions in a blinded fashion.

Clinical and Technical Measurements

The CBP (phase V diastolic) was the average of 3 consecutive readings taken after the patients had been seated for 5 minutes.[2] Three additional standing readings were obtained to exclude orthostatic hypotension. Digit preference was monitored every 6 months. For the ambulatory measurements, the clinical investigators used SpaceLabs (Redmond, Wash) equipment, consisting of validated[12,13] oscillometric 90207 monitors and 90239A data interface units, of which the printing function was disabled. The ambulatory readings were programmed at 15-minute intervals from 8 AM to 10 PM and at 30-minute intervals otherwise. Day and night were defined using fixed-clocktime[11] periods, ranging from 10 AM to 8 PM and from midnight to 6 AM. Immediately after each patient had completed the study, the clinical investigator received the printouts of all ambulatory recordings, the corresponding BP statistics, and guidelines for their interpretation.[8]

Using a self-administered questionnaire, the patients expressed their symptoms on a 5-point scale, using as qualifiers "never," "a little," "moderately," "fairly," and "very." The questionnaire covered neurosensory symptoms, such as dizziness, troubled vision, sleep disturbances, and headache; circulatory symptoms, such as palpitations, hot flashes, and ankle edema; urogenital disturbances, including sexual dysfunction, changes of the menstrual cycle, and disturbed micturition; various complaints related to the upper and lower gastrointestinal tracts; and disturbances of the upper and lower airways, including cough. The 32 questions were combined into 1 overall and several organ-specific symptom scores by averaging the marks of the individual questions.

The intensity of antihypertensive drug treatment was evaluated by assigning a score of 0.5 to a daily dose of 10 mg of lisinopril, 50 mg of atenolol, or 12.5 mg of hydrochlorothiazide; a score of 1 to a daily dose of 20 mg of lisinopril, 100 mg of atenolol, or 5 mg of amlodipine; and a score of 0 to untreated patients. Three larger centers located at an academic center, a regional hospital, and a family practice were considered to be representative for the 3 levels of health care at which the study was conducted. These 3 centers assessed patient compliance from tablet counts.

Left ventricular mass was measured noninvasively at the beginning and end of follow-up. The R wave in lead aVl and the Sokolow-Lyon index[15] were measured from electrocardiograms. For imaging and Doppler echocardiography, the physicians referred their patients to regional clinics or to the University Hospital in Leuven, Belgium.[16,17] Mean left ventricular wall thickness, echocardiographic left ventricular mass, fractional shortening, and the ratio of the peak left ventricular inflow velocities in early diastole (E) and at the atrial contraction (A) were determined according to established conventions[18] and formulae.[16,17,19] For analysis, 3 to 5 heart cycles were averaged.

Cost-benefit Analysis

The rates of the Belgian health insurance system were used to estimate the cost-effectiveness of ABP monitoring in comparison with CBP measurement. Costs and charges are given in US dollars using a conversion rate of 35 Belgian francs to US $1. Physicians' fees averaged $25 per visit. One month of daily treatment with 20 mg of lisinopril, 100

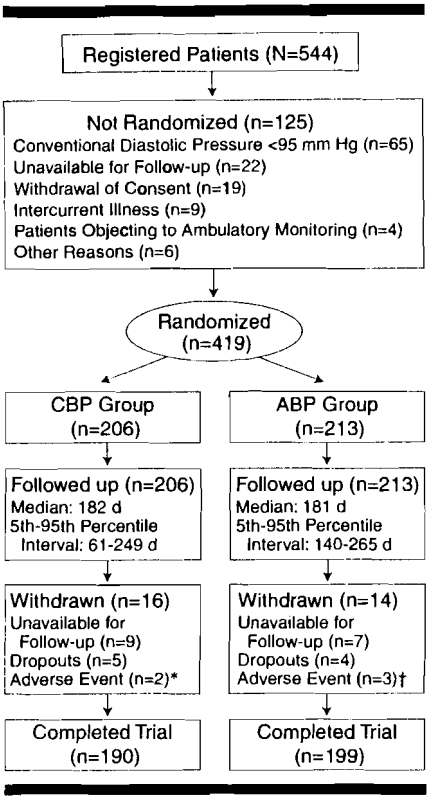

Figure 1.—Flowchart of the patients. The Ambulatory Blood Pressure Monitoring and Treatment of Hypertension trial was a blinded randomized comparison of antihypertensive drug treatment based on conventional blood pressure (CBP) or ambulatory blood pressure (ABP) measurement. Asterisk indicates that 1 patient experienced a nonfatal myocardial infarction, and 1 patient underwent abdominal surgery because of persistent urachus complicated by paralytic ileus. Dagger indicates that 3 ABP patients withdrew because of heart failure from uncontrolled hypertension, acute myocardial infarction, or depression.

mg of atenolol, 12.5 mg of hydrochlorothiazide, or 5 mg of amlodipine were priced at $38, $21, $2, and $32, respectively. The ABP monitoring, not yet reimbursed by the Belgian health insurance system, was budgeted at $30 per recording, ie, the average charge in Western European countries.[9]

Because only at the first follow-up visit treatments could start to diverge, the calculations disregarded all earlier expenses. The other trial visits and the ABP recordings, in contrast with usual clinical care, were scheduled regardless of whether BP was well controlled or not. Therefore, 2 assumptions were made. First, if at any visit a patient's BP remained well controlled so that no further treatment adjustment was necessary, the last treatment adjustment was assumed to be continued for 6 months without further reassessment. Second, the calculations presumed that patients whose BP at the end of the trial still exceeded the target range would be reexamined 2 months later. These intervals were chosen because they are in line with current practice at the University Hospital in Leuven as well as with the median follow-up in the trial (6 months) and the median interval between visits (2 months), respectively.

Table 1.—Baseline Characteristics of Patients Randomized to Antihypertensive Drug Treatment Based on Conventional Blood Pressure (CBP) or Ambulatory Blood Pressure (ABP) Measurements

Characteristics	CBP Group (n=206)	ABP Group (n=213)	P
Age, mean (SD), y	51.3 (11.9)	53.8 (10.8)	.03
Body mass index, mean (SD), kg/m^2	28.5 (4.8)	28.2 (4.4)	.39
Women, No. (%)	102 (49.5)	124 (58.2)	.07
Receiving oral contraceptives, No. (%)*	14 (13.7)	10 (8.1)	.17
Receiving hormonal substitution, No. (%)*	19 (18.6)	19 (15.3)	.51
Previous antihypertensive treatment, No. (%)†	134 (65.0)	139 (65.3)	.95
Diuretics, No. (%)*	47 (35.1)	59 (42.4)	.26
β-Blockers, No. (%)*	65 (48.5)	80 (57.6)	.17
Calcium channel blockers, No. (%)*	45 (33.6)	38 (27.3)	.32
Angiotensin-converting enzyme inhibitors, No. (%)*	50 (37.3)	48 (34.5)	.72
Multiple-drug treatment, No. (%)*	62 (46.3)	65 (46.8)	.97
Smokers, No. (%)	42 (20.5)	35 (16.4)	.29
Alcohol use, No. (%)	115 (55.8)	102 (47.9)	.10
Serum creatinine, mean (SD), μmol/L‡	85.75 (15.91)	88.4 (16.80)	.25
Serum total cholesterol, mean (SD), mmol/L‡	6.00 (1.03)	6.10 (1.19)	.32

*Percentages and values of *P* computed considering only women receiving antihypertensive drug treatment before their enrollment.
†Defined as antihypertensive drug treatment within 6 months before the screening visit.
‡Divide creatinine by 88.4 and cholesterol by 0.02586 to convert milligrams per deciliter.

Statistical Analysis

Database management and statistical analyses were performed with SAS software, version 6.11 (SAS Institute Inc, Cary, NC). Serial measurements were analyzed using the difference between the entry and the last available measurement as the main outcome variable.[20] The between-group differences in continuous measurements were calculated by subtracting the mean changes from baseline in the CBP group from those in the ABP group. Between-group comparisons involved the Mann-Whitney rank-sum test for nonnormally distributed data and a *t* test and analysis of covariance for normally distributed variables. Proportions were compared using the χ^2 statistic and longitudinal changes in treatment status by Kaplan-Meier survival function estimates[21] and the log-rank test. The probability that treatment could be stopped was correlated with several explanatory variables using multiple logistic regression. Stopping treatment was defined as the discontinuation of drug treatment at 1, 2, or 4 months until the end of the study, because the conventional (CBP group) or the daytime (ABP group) DBP was less than 80 mm Hg and thereafter remained at or below the target level (80-89 mm Hg).

RESULTS

Flow of Patients

Of 544 patients enrolled at 56 centers, 419 (77.0%) met the entry criteria and were randomized (Figure 1). The CBP patients (n=206) were on average 2.5 years younger ($P=.03$) than the ABP patients (n=213) and tended to include fewer women (49.5% vs 58.2%; $P=.07$), but otherwise the 2 groups had similar characteristics (Table 1) and BP values at entry (Table 2). Of the 2029 ambulatory registrations, 89.5% were recorded on weekdays, 9.0% on Saturdays, and 1.5% on Sundays.

Sixteen CBP patients (7.8%) and 14 ABP patients (6.6%) did not complete the study because they dropped out (n=9), experienced an adverse event (n=5, Figure 1), or missed 1 or more follow-up visits (n=16). In the 419 randomized patients, the median follow-up was 182 days (5th to 95th percentile interval, 85-258 days).

Treatment Intensity and BP Control

More ABP patients than CBP patients could stop antihypertensive drug treatment for the duration of the trial (Figure 2) because their DBP was less than 80 mm Hg and thereafter stabilized below or at the target range (26.3% vs 7.3%; 4.7 vs 1.3 patients per 100 followed for 1 month; $P<.001$). The opposite trend was observed for patients proceeding to sustained multiple-drug treatment (27.2% vs 42.7%; 4.8 vs 8.3 patients per 100 followed for 1 month; $P<.001$). From the second follow-up visit on, drug treatment became more intense ($P<.001$) in the CBP group than the ABP group, although patients who continued to receive antihypertensive drug treatment received similar daily doses (Table 3). At the 3 centers that recorded tablet counts, the CBP patients (n=53) and ABP patients (n=50) took the same fraction of the prescribed doses (89.3% vs 90.1%; $P=.90$).

Table 2.—Blood Pressure at Randomization and at End of Follow-up in the 2 Treatment Groups*

Blood Pressure	CBP Group (n=206)	ABP Group (n=213)	Difference	P
Conventional pressure				
Systolic, mm Hg				
Randomization	164.4 (20.3)	164.9 (20.3)	0.5 (−3.4 to 4.4)	.79
Adjusted changes	−24.1 (1.2)	−20.8 (1.2)	3.3 (−0.1 to 6.7)	.06
Diastolic, mm Hg				
Randomization	104.0 (9.4)	102.9 (8.9)	−1.1 (−2.8 to 0.7)	.24
Adjusted changes	−14.4 (0.7)	−13.0 (0.7)	1.4 (−0.5 to 3.3)	.16
24-h pressure				
Systolic, mm Hg				
Randomization	143.9 (16.3)	142.5 (15.5)	−1.4 (−4.5 to 1.6)	.36
Adjusted changes	−15.9 (0.8)	−13.1 (0.8)	2.8 (0.6 to 5.1)	.02
Diastolic, mm Hg				
Randomization	89.7 (11.1)	88.5 (10.4)	−1.2 (−3.3 to 0.8)	.24
Adjusted changes	−10.6 (0.5)	−9.0 (0.5)	1.6 (0.2 to 3.0)	.03
Daytime pressure				
Systolic, mm Hg				
Randomization	150.7 (16.4)	148.9 (15.9)	−1.8 (−4.9 to 1.3)	.25
Adjusted changes	−15.6 (0.9)	−13.0 (0.9)	2.6 (0.2 to 5.0)	.04
Diastolic, mm Hg				
Randomization	95.6 (11.5)	93.8 (11.1)	−1.9 (−4.0 to 0.3)	.10
Adjusted changes	−10.3 (0.6)	−8.8 (0.6)	1.5 (−0.0 to 3.0)	.06
Nighttime pressure				
Systolic, mm Hg				
Randomization	131.4 (18.5)	129.9 (17.1)	−1.5 (−4.9 to 2.0)	.41
Adjusted changes	−16.7 (1.0)	−13.2 (1.0)	3.5 (0.8 to 6.3)	.01
Diastolic, mm Hg				
Randomization	79.1 (12.5)	78.5 (11.8)	−0.6 (−2.9 to 1.7)	.62
Adjusted changes	−11.3 (0.6)	−9.4 (0.6)	1.9 (0.2 to 3.6)	.03

*CBP and ABP indicate conventional and ambulatory blood pressure measurement. Mean between-group differences are given with a 95% confidence interval and a *P* value. Adjusted change refers to the mean changes from randomization (SE) to the last follow-up visit adjusted for baseline value, sex, and age. All within-group changes were significant ($P \leq .001$).

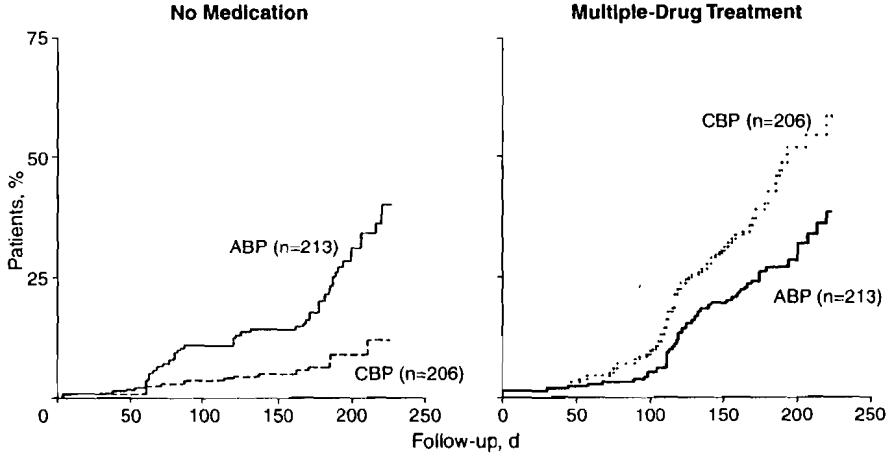

Figure 2.—Kaplan-Meier estimates[21] modeling the probability that during follow-up patients would permanently stop antihypertensive drug treatment or would proceed to sustained multiple-drug treatment. The differences between the patients randomized to conventional blood pressure (CBP) or ambulatory blood pressure (ABP) measurement were significant ($P<.001$).

Further analyses explored whether sex, age, or the CBP or ABP at randomization could predict the permanent discontinuation of antihypertensive drug treatment. In the ABP patients, the probability of stopping drug treatment increased 1.9 times for each 5 mm Hg that the daytime DBP was lower at randomization (95% confidence interval [CI], 1.6-2.4; $P<.001$). After accounting for the CBP at baseline, sex, and age, the odds ratio was still 1.8 (95% CI, 1.5-2.3; $P<.001$). In the latter regression model, female sex was also associated with a 2.6 times (95% CI, 1.2-5.6; $P=.02$) higher probability of stopping treatment, but age and the CBP did not significantly predict the cessation of antihypertensive drug treatment. In the CBP group, the odds ratio associated with a 5 mm Hg lower conventional DBP at entry was 1.0 (95% CI, 0.7-1.4; $P=.99$), regardless of whether the model accounted for the daytime DBP, sex, and age. Of the latter 3 covariates, none reached statistical significance. Thus, only daytime ABP and female sex independently predicted the cessation of antihypertensive drug treatment in the ABP group.

The CBP and ABP decreased ($P<.001$) after randomization (Table 2). At the first follow-up visit, the decreases were the same in the 2 treatment groups, averaging 16.5/10.2 mm Hg for the CBP and 11.2/7.5 mm Hg for the ABP. Thereafter, the BP reduction tended to be slightly greater in CBP patients than in ABP patients (Figure 3). After adjustment for the baseline BP, sex, and age, the final average differences between the 2 treatment groups ranged from 2.6 to 3.3 mm Hg for systolic blood pressure (SBP) and from 1.4 to 1.9 mm Hg for DBP (Table 2). Of the 56 ABP patients in whom drug treatment was stopped, 33 (58.9%) maintained a daytime DBP below 85 mm Hg

Complaints, Adverse Events, and Left Ventricular Mass

During the follow-up, the average (SD) symptom score fell ($P<.001$) on a 5-point scale from 1.62 (0.42) to 1.42 (0.3) in the CBP group and from 1.61 (0.43) to 1.43 (0.35) in the ABP group. The between-group differences were small, averaging 0.01 (95% CI, −0.04 to 0.06) at the last visit. The scores for dizziness, headache, palpitations, ankle edema, and organ-specific symptoms (see "Methods") also showed similar trends in the treatment groups. Major adverse events occurred in 7 CBP patients and 9 ABP patients ($P=.66$). Three patients (CBP vs ABP, 1 vs 2) sustained a nonfatal myocardial infarction, 2 patients (1 vs 1) developed heart failure, 6 patients (4 vs underwent noncardiovascular surgery and 3 patients (1 vs 2) suffered from relapsing depression. In the ABP group patient developed a rash and another suffered from peptic ulcerations.

Electrocardiograms and imaging and Doppler echocardiograms of sufficient quality were available at the beginning and end of the study in 353, 309, and 2 patients, respectively (Table 4). At baseline, the R amplitude in lead aVI and the E:A ratio were slightly larger in the ABP group than in the CBP group. However, after adjustment for the baseline values, sex, and age, the between-group differences in the changes in the electrocardiographic and echocardiographic variables were small and statistically insignificant (Table 4). The echocardiographic results were not materially altered when the analyses were confined to the 24 ABP patients and the 25 CBP patients who

Table 3.—Antihypertensive Medications in the 2 Treatment Groups*

Score and Medications	First Visit	Second Visit	Third Visit	Last Visit
Treatment score				
CBP	0.54 (0.14)	0.77 (0.34)	1.00 (0.48)	1.18 (0.75)
ABP	0.53 (0.16)	0.62 (0.40)†	0.75 (0.55)†	0.84 (0.76)†
Lisinopril, mg/d (%)				
CBP	10.0 (95.1)	20.0 (88.9)	20.0 (81.9)	20.0 (79.1)
ABP	10.0 (95.3)	10.0 (74.2)†	20.0 (68.9)‡	20.0 (61.0)†
Atenolol, mg/d (%)				
CBP	50.0 (3.4)	50.0 (7.0)	50.0 (12.4)	100.0 (14.1)
ABP	50.0 (4.7)	100.0 (7.7)	50.0 (12.1)	50.0 (14.1)
HCTZ,§ mg/d (%)				
CBP	25.0 (0.5)	12.5 (5.0)	12.5 (33.7)	12.5 (40.8)
ABP	12.5 (1.4)	12.5 (2.9)	12.5 (22.3)‡	12.5 (25.8)†
Amlodipine, mg/d (%)				
CBP	5.0 (1.0)	5.0 (1.0)	5.0 (3.6)	5.0 (17.5)
ABP	0.0 (0.0)	5.0 (0.5)	5.0 (1.9)	5.0 (9.9)‖

*CBP and ABP indicate the groups randomized to antihypertensive drug treatment based on conventional or ambulatory blood pressure measurement. The intensity of antihypertensive treatment was scored by assigning a value of 1 to equipotent daily doses of various drugs. Values for treatment scores are mean (SD).
†$P \leq .001$.
‡$P \leq .01$.
§HCTZ indicates hydrochlorothiazide.
‖$P \leq .05$.

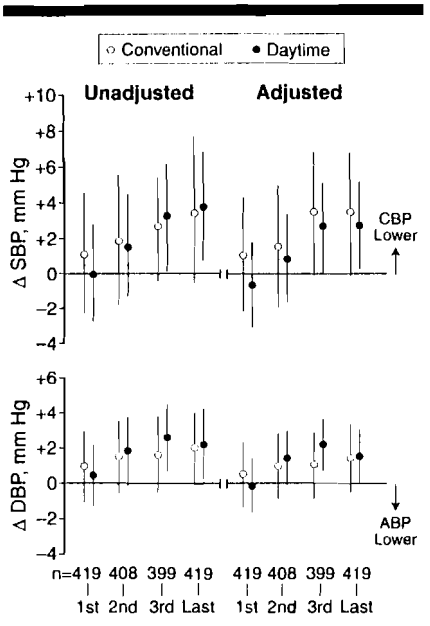

Figure 3.—The differences (Δ) in systolic blood pressure (SBP, top) and diastolic blood pressure (DBP, bottom) between patients randomized to treatment based on conventional blood pressure (CBP) or ambulatory blood pressure (ABP) measurement. Values are mean with 95% confidence interval before (left) or after (right) adjustment for the baseline value, sex, and age. Positive values indicate lower blood pressure levels in the CBP group. N indicates the number of subjects at each follow-up visit in the 2 treatment groups combined.

been examined at the University Hospital in Leuven. In this restricted analysis, left ventricular mass at the end of follow-up tended to be 40 g (95% CI, −80 to 1; $P=.06$) smaller in the ABP patients with a concurrent reduction of mean wall thickness by 1.3 mm (95% CI, −2.5 to −0.1 mm; $P=.05$). Furthermore, in these 49 patients, the between-group differences averaged −1.4 mm (95% CI, −4.7 to 2.0 mm; $P=.44$) for the left ventricular internal diameter, +3.2% (95% CI, −2.4% to 8.8%; $P=.27$) for fractional shortening, and 0.01 (95% CI, −0.28 to 0.29; $P=.97$) for the E:A ratio. The echocardiographic findings in the ABP patients in whom antihypertensive drug treatment could be permanently stopped were also similar to those in the remainder of their group.

Costs of Medications and Follow-up Visits

The costs of the medications amounted to $4188 and $3390 ($P=.001$) per 100 CBP and ABP patients treated for 1 month (Table 5). The fees of the physicians averaged respectively $1008 and $898 per 100 patient-months ($P=.007$). However, the potential savings in the ABP group associated with less intensive drug treatment and fewer physician visits were offset by the charges of ambulatory monitoring. Overall, cost-effectiveness was similar in the 2 treatment groups (Table 5).

COMMENT

In this randomized clinical trial, the final BP values were slightly higher in ABP than in CBP patients. The largest difference (3.5 mm Hg) was observed for SBP at night, probably because more CBP patients than ABP patients were receiving multiple-drug treatment, thereby dividing the intake of their medications over the whole day. In spite of less intensive drug treatment, BP did not increase beyond control in the ABP patients, in whom the 24-hour BP at the last visit averaged 129.4/79.5 mm Hg.

The changes in electrocardiographic and echocardiographic left ventricular mass were small and not different in the 2 treatment groups of the trial. Previous antihypertensive treatment, insufficient duration of active treatment, between-center variability, and regression to the mean in the echocardiographic measurements are unlikely to explain the present findings. Indeed, in hypertensive patients in World Health Organization stages I and II, 16 weeks of antihypertensive drug treatment started after 4 weeks of placebo were shown to reduce left ventricular mass by 20 g ($P<.001$).[22] If, after 1 year of active therapy, antihypertensive drug treatment was interrupted, left ventricular mass rose again in only 3 weeks' time.[22] Furthermore, the present echocardiographic findings were reproducible when the analysis was limited to the 49 patients who were examined at the University Hospital in Leuven. Other studies at the latter center[23] also showed that left ventricular mass index (LVMI) remained on average unchanged when patients were receiving placebo treatment if the echocardiographic examinations were repeated at an interval of 2 to 3 weeks, regardless of whether all patients (average LVMI, 3.05 g/kg) or only those belonging to the highest quartile (average LVMI, 3.99 g/kg) were considered in the analysis. Furthermore, in the present study, left ventricular mass and mean wall thickness at randomization were approximately 15% smaller than in other trials run exclusively at hypertension clinics.[22] It is well known that left ventricular hypertrophy usually regresses more under antihypertensive drug treatment when it is initially more pronounced. Moreover, several investigators found that the left ventricle is not hypertrophied if the awake[24] or daytime[25] BP is less than 133 mm Hg[25] to 138 mm Hg[24] systolic or 86 mm Hg[24] to 89 mm Hg[25] diastolic, ie, the levels observed at entry in approximately 25% of the present patients.

To facilitate extrapolation of results, current guidelines[26-28] for the diagnosis and treatment of hypertension were used. The study subjects were selected and antihypertensive drug treatment was initiated based on CBP rather than ABP measurement. Most patients were recruited at family practices, but specialized hypertension clinics also took part. The choice of the goal BP was another critical point in the design of the trial. Antihypertensive treatment was adjusted according to only DBP because most outcome trials in hypertension[29,30] have implemented this option; until recently, the World Health Organization defined hypertension exclusively on the basis of DBP,[27,28] and moreover, had both SBP and DBP been used, the treatment strategy should have been more complex. For the 2 types of DBP measure-

ment on which treatment was based, the goal level was set at 80 through 89 mm Hg. For conventional sphygmomanometry, this range drop coincides with the recommendations of several expert committees[26-28] and 2 meta-analyses[30,31] as well as with the levels achieved in a number of outcome trials.[29,30] A consensus on operational thresholds for ambulatory monitoring is still growing.[32] In 6 reports,[33-38] the 95th percentile for the daytime DBP in normotensive subjects ranged from 83 mm Hg[37] to 89 mm Hg.[33] Furthermore, if the daytime DBP was less than 88 mm Hg[39] or 90 mm Hg,[40] intensifying antihypertensive drug treatment based on CBP measurements did not reduce the ABP.

By using ABP monitoring, antihypertensive drug treatment may be postponed in 25% of the hypertensive population and multiple-drug treatment avoided in 15%. These findings do not imply that white coat hypertensive patients should be left untreated, but that their initial therapy may consist of hygienic measures and regular follow-up. From a clinical point of view, it would be relevant to identify in advance those hypertensive patients in whom drug treatment would not be immediately required. In an Italian database on ambulatory blood pressure measurement,[35] the probability of white coat hypertension[5,6] rose by 10% for each 10-year increment in age and was 40% to 50% higher in women than in men. For each 10/5 mm Hg rise in the conventionally measured systolic/diastolic BP, the probability of white coat hypertension decreased by 6%/9%.[35] More importantly, if the CBP had been recorded at only 1 visit or if only 2 CBP readings had been averaged to diagnose hypertension, the probability of white coat hypertension rose 2-fold to 4-fold.[35] In the present study, 90% of the patients were 40 to 70 years old. In all patients, the diagnosis of hypertension had been confirmed at the visits at 4 and 8 weeks after initial screening. Under these circumstances, age and the conventionally measured BP did not help in identifying the patients in whom antihypertensive drug treatment would subsequently be interrupted. In the ABP group, only a lower daytime DBP and female sex predicted this condition.

The present findings spanned a median follow-up of only 6 months and require further validation in long-term prospective studies.[32,41] Reports by Perloff et al,[42] Mann et al[43] and Verdecchia et al[44] have already shown that the awake[42] and 24-hour BPs[43] predict cardiovascular morbidity and mortality, even after adjustment for the CBP. Verdecchia et al[44] found that the incidence of cardiovascular events was similar in normotensive subjects and in white coat hypertensive men and women whose daytime ABP was below 136/87 mm Hg and 131/86 mm Hg, respectively. Further analyses of the same Italian database (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale [PIUMA]) recently confirmed that the difference between the clinic and the daytime ABP, taken as a measure of white coat hypertension, did not predict cardiovascular morbidity and mortality.[6]

Table 4.—Electrocardiographic and Echocardiographic Characteristics at Randomization and at End of Follow-up in the 2 Treatment Groups*

Characteristics	CBP Group	ABP Group	Difference	P
Electrocardiographic voltages, No.	171	182	NA	NA
R wave in lead aVl, mV				
Randomization	0.55 (0.31)	0.62 (0.35)	0.07 (0.00 to 0.14)	.03
Adjusted changes	0.01 (0.03)	−0.03 (0.03)	−0.02 (−0.09 to 0.06)	.67
Sokolow-Lyon index, mV†				
Randomization	2.25 (0.69)	2.37 (0.79)	0.12 (−0.04 to 0.28)	.14
Adjusted changes	−0.16 (0.05)‡	−0.07 (0.05)	0.09 (−0.06 to 0.23)	.25
Echocardiography of the left ventricle, No.	150	159		
Mass, g				
Randomization	203 (60)	196 (59)	−7 (−20.0 to 6.0)	.33
Adjusted changes	−2 (5)	−6 (5)	−4 (−18.0 to 10.0)	.56
Mean wall thickness, mm				
Randomization	11.1 (2.1)	10.9 (2.0)	−0.2 (−0.6 to 0.3)	.42
Adjusted changes	−0.1 (0.2)	−0.3 (0.2)	−0.2 (−0.6 to 0.3)	.48
End-diastolic internal diameter, mm				
Randomization	48.8 (6.2)	48.5 (6.1)	−0.3 (−1.7 to 1.1)	.65
Adjusted changes	0.0 (0.5)	−0.1 (0.5)	−0.2 (−1.5 to 1.2)	.83
Fractional shortening, %				
Randomization	36.1 (9.4)	36.9 (8.5)	0.8 (−1.2 to 2.8)	.41
Adjusted changes	1.5 (0.7)§	2.1 (0.7)‡	0.6 (−1.3 to 2.5)	.54
E:A ratio‖				
Randomization	0.95 (0.31)	1.04 (0.37)	0.09 (0.01 to 0.17)	.02
Adjusted changes	0.10 (0.03)‡	0.03 (0.03)	−0.07 (−0.15 to 0.02)	.15

*CBP and ABP indicate conventional and ambulatory blood pressure measurement. Adjusted change refers to the mean changes from randomization (SE) to the last follow-up visit adjusted for baseline value, sex, and age. Mean between-group differences are presented with a 95% confidence interval and a *P* value. NA indicates not applicable.
†Sum of the S wave in lead V_1 and the tallests of either the R wave in lead V_5 or V_6.[15]
‡$P \leq .01$.
§$P \leq .05$.
‖The ratio of the peak inflow velocities in early diastole (E) and at atrial contraction (A) were available in 146 CBP patients and 143 ABP patients.

Table 5.—Cost-effectiveness Analysis of the Adjustment of Antihypertensive Drug Treatment Based on Ambulatory Blood Pressure (ABP) Instead of Conventional Blood Pressure (CPB) Measurement

	Costs,* $ ($ per 100 Patients Treated for 1 mo)				
Analysis Variables	CBP Group (n=206)	ABP Group (n=213)	Difference, Mean (SE)	Mean Cost-benefit Ratio (95% Confidence Interval)	P
Physician fees	1008 (422)	898 (381)	109 (40)	10.8 (3.0 to 18.7)	<.001
Antihypertensive drugs	4187 (2102)	3390 (2011)	797 (205)	19.0 (9.4 to 28.7)	.001
Lisinopril	2592 (1088)	2238 (1082)	355 (108)	13.7 (5.5 to 22.0)	.001
Atenolol	593 (513)	475 (512)	118 (51)	19.9 (3.0 to 37.0)	.02
Hydrochlorothiazide	82 (75)	59 (71)	23 (7)	28.3 (11.1 to 45.5)	.002
Amlodipine	918 (973)	618 (828)	300 (90)	32.7 (13.3 to 51.9)	.001
Ambulatory monitoring	NA	1078 (457)	−1078 (32)	NA	NA
Total	**5194 (2371)**	**5366 (2567)**	**−172 (247)**	−3.3 (−12.7 to 6.1)	.48

*Absolute costs were converted to US dollars, averaged (SD) per group, and standardized to 100 patients followed up for 1 month. The algorithm assumed that if the blood pressure was well controlled, patients would be followed up at 6-month intervals, and that if the diastolic blood pressure level still exceeded the therapeutic target range at the end of the study, they would be reexamined after 2 months. Values may not sum because of rounding. NA indicates not applicable.

If backed up by long-term prospective outcome studies, these results may have far-reaching implications. In industrialized countries such as the United States[45] or Belgium,[46] the prevalence of definite hypertension after adolescence amounts to nearly 15% of the whole population, increases curvilinearly with advancing age,[47] and may exceed 30% beyond 70 years.[47] Among the hypertensives, the prevalence of white coat hypertension varies from 20%[5,48] to 35%.[35] Extrapolating from the present findings, using ambulatory monitoring as an accessory to conventional sphygmomanometry would make it possible to save in 15% of the population up to 20% of the short-term health care costs spent in treating hypertension. However, the present findings also suggest that the financial gains achieved by postponing or avoiding drug treatment may in the short run be offset by the charges associated with ABP monitoring. In particular, the high costs of the monitoring equipment make it difficult to implement this technique on a wide scale where it would be mostly needed, ie, in family practice, the first line in diagnosing and treating hypertension. However, self-measurement of BP[49,50] using strictly standardized procedures may provide a valid and less expensive alternative. In addition to the cost-benefit ratio, expert committees advising on the clinical application of ABP monitoring would also have to consider other aspects, such as cost-effectiveness in terms of the prevention of cardiovascular complications, the potential of ABP monitoring to enhance the quality of life of white coat hypertensive patients, and the amount of training that would be required to familiarize all levels of the medical profession with an alternative technique of BP measurement.

In conclusion, the present findings suggest that adjustment of antihypertensive treatment based on ABP monitoring instead of conventional sphygmomanometry may lead to less intensive drug treatment with preservation of BP control, general well-being, and inhibition of left ventricular enlargement. On the other hand, ABP monitoring, at the presently applied rates, does not seem to reduce the short-term costs of antihypertensive treatment. Whether these conclusions would still hold true in the long term, especially after accounting for morbidity and mortality, remains to be elucidated.

Members of the Ambulatory Blood Pressure and Treatment of Hypertension trial: Participating Investigators. In Belgium: Guido Adriaens, MD (Neerwinden); Margriet Beenaerts, MD, Staf Henderickx, MD, Jan-Harm Keijzer, MD, Pim Van den Elzen, MD, Roderick A. Van Der Have, MD (Lommel); Nadine Bernard, MD (Beyne-Heusay); Christian Bertbe, MD (Clinique Notre Dame de Bruyères, Chenée); Hubert Bruggeman, MD (Medisch Centrum Noordoost Limburg, Maaseik); Leszek Bieniaszewski, MD, Hilde Celis, MD, Robert Fagard, MD, Giuliana Ginocchio, MD, Jan A. Staessen, MD, Ji Guang Wang, MD (Hypertensie en Cardiovasculaire Revalidatie Eenheid, Departement voor Moleculair en Cardiovasculair Onderzoek, Katholieke Universiteit Leuven, Leuven); Frank Buntinx, MD, Paul De Cort, MD, Pauwel De Hertogh, MD, Jan Heyrman, MD (Academisch Centrum voor Huisartsgeneeskunde, Katholieke Universiteit Leuven, Leuven); Eduard Cerstelotte, MD (Beringen), Georges Charbel, MD (died on July 13, 1996; Clinique Saint Etienne, Brussels); Jan Claessens, MD, Dirk A. Staessen, MD (Eeuwfeestkliniek, Antwerpen); Veerle De Bock, MD (Kliniek Louise-Marie, Antwerpen); Gerda De Ceuster, MD, Eric Verlinden, MD (Boechout); Eric De Graef, MD (Humbeek); Lutgardis De Groote, MD (Kessel-Lo); Philippe De Jaegher, MD, Ivan Elegeert, MD (Sint Niklaasklinick, Kortrijk), Jozef Dekelver, MD (Maasmechelen); Frank Delvaux, MD (Winksele); Jean-François De Plaen, MD (Clinique Universitaire Saint Luc, Université Catholique de Louvain, Brussels); Michel Deruyver, MD (Leest); Marc Derveaux, MD, Bernadette Vergauwen, MD (Sint Jozefkliniek, Mortsel); André De Vlieger, MD (Koekelare); Luc de Wolf, MD (Heilig Hart Kliniek, Tienen); Vincent Fronville, MD (Namur); Marc Geboers, MD (Sint Jozefziekenhuis, Vilvoorde); Marc Geeraert, MD (Ichtegem); Jan Geurts, MD (Rotem); Yorgo Haralambidis, MD (Brussels); Ann Hauwaert, MD (Sint Katelijne, Waver); Marie-Christine Herregods, MD, Anna Vandeplas, MD (Medisch Centrum der Huisartsen, Leuven); Veerle Immegeers, MD (Heilig Hartziekenhuis, Asse); Simonne Lens, MD, Robert Lins, MD (Stuivenbergziekenhuis, Antwerp); Harry Lesseliers, MD, John Thoeng, MD (Sint Elisabetziekenhuis, Turnhout); Ivan Leunckens, MD (Antwerp); Philip Libaut, MD (Opwijk); Marc Maes, MD (Beverlo); Kristien Mechelmans, MD (Zwartberg); Jan Panneels, MD (Wezembeek-Oppem); Ann Pattyn, MD, Johan Van De Bruaene, MD (Deerlijk); Etienne Philips, MD (Oostende); Erwin Raymenants, MD (Sint Jozefziekenhuis, Mechelen); Serge Rigo, MD (Maasmechelen); Jozef Schurmans, MD (Medisch Centrum, Tessenderlo); Anne-Marie Spaey, MD (Heverlee); Roland Stroobandt, MD (Sint Jozefkliniek, Oostende); Rudi Van Boxstael, MD (Betekom); Kristien Van Cleemput, MD (Eppegem); Dirk Vandenbrande, MD (Brussels); Stan Vanden Bempt, MD (died on February 23, 1996; Veltem); Steven Van Den Noortgate, MD (Wilrijk); Edward Vanderputte, MD (Leut); Stef Van der Vliet, MD (Eppegem); Jan Van De Walle, MD (Boechout); Alberic Van Dorpe, MD (Mariaziekenhuis, Lommel); Filip Van Essche, MD (Tervuren); Lukas Vangeel, MD (Boechout); Michel Van Halewijn, MD (Brussels); Roger Van Hoof, MD (Militair Hospitaal, Brussels); Patrick Vankrunkelsven, MD, Caroline Vanwelden, MD (Laakdal); Jan Vanleeuwe, MD (Tervuren); Fik Van Lint, MD, Jan Van Lint, MD (Arendonk); Walter Van Mieghem, MD (Kliniek André Dumont, Genk); Werner Van Peer, MD (Boechout); Guido Vereeken, MD (Halen); Lode Vermeersch, MD (Tremelo); Ignace Verscheure, MD (Wilsele); Karl Von Kemp, MD (Wemmel); and Herman Willems, MD (Overijse). **In other countries:** Neil Atkins, BSc, Linda Kelly, RN, Fáinsía Mee, RN, Eoin T. O'Brien, MD (Beaumont Hospital, Dublin, Ireland); Peter De Leeuw, MD (Universitair Ziekenhuis Maastricht, Maastricht, The Netherlands); and Peter Frambach, MD (Luxembourg, Luxembourg).

Advisory Board. Belgian members: Antoon Amery, MD (died on November 2, 1994); Frank Buntinx, MD, Robert Fagard, MD, Jan A. Staessen, MD (Leuven); Denis Clement, MD (Gent); Jean-Paul Degaute, MD (Brussels); Jean-François De Plaen, MD (Brussels); Georges Rorive, MD (Liège); and Robert Lins, MD (Antwerp). **Other members:** Peter De Leeuw, MD (Maastricht, the Netherlands); and Eoin T. O'Brien, MD (Dublin, Ireland).

Trial Management: Jan Polfliet, RN (Campus Gasthuisberg, Leuven), and Hilde De Roeck, Wendy Kerselaers, BSc, and Claude Vincent (ZENECA, Destelbergen) helped in monitoring and analyzing the trial. Logistical support was provided by Steven Huysse, MD (ZENECA, Destelbergen), and expert technical and secretarial assistance by Ann Lambein and Mieke De Bosschere (ZENECA, Destelbergen) and Lutgart De Pauw, RN, Paul Drent, RN, Sylvia Van Hulle, RN, and Renilde Wolfs (Campus Gasthuisberg, Leuven).

The Ambulatory Blood Pressure and Treatment of Hypertension (APTH) trial was conducted under the auspices of the Belgian Hypertension Committee. The study was funded by ZENECA Inc (Destelbergen, Belgium). The study medication was donated by ZENECA and Roerig-Pfizer (Brussels, Belgium).

The APTH trial would not have been possible without the collaboration of many patients and the interest of Geert De Vriese, MD, and Thierry Van Hedent, MD (ZENECA), in this project. The authors gratefully acknowledge the critical comments of Willem H. Birkenhäger, MD (Rotterdam, the Netherlands).

References

1. The Scientific Committee. Consensus document on non-invasive ambulatory blood pressure monitoring. *J Hypertens.* 1990;8(suppl 6):S135-S140.
2. Petrie JC, O'Brien ET, Littler WA, de Swiet M. Recommendations on blood pressure measurement by a working party of the British Hypertension Society. *BMJ.* 1989;293:611-615.
3. Conway J, Johnston J, Coats A, Somers V, Sleight P. The use of ambulatory blood pressure monitoring to improve the accuracy and to reduce the number of subjects in clinical trials of antihypertensive agents. *J Hypertens.* 1988;6:111-116.
4. Sassano P, Chatellier G, Corvol P, Ménard J. Influence of observer's expectation on the placebo effect in blood pressure trials. *Curr Ther Res.* 1987; 41:305-312.
5. Pickering TG, James GD, Boddie C, Harshfield GA, Blank S, Laragh JH. How common is white coat hypertension? *JAMA.* 1988;259:225-228.
6. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Porcellati C. Prognostic significance of the white coat effect. *Hypertension.* 1997;29:1218-1224.
7. Mancia G, Bertinieri G, Grassi G, et al. Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet.* 1983; 2:695-698.
8. Staessen JA, Bieniaszewski L, O'Brien ET, Fagard R. What is a normal blood pressure on ambulatory monitoring? *Nephrol Dial Transplant.* 1996; 11:241-245.
9. Pickering TG. A review of national guidelines on the clinical use of ambulatory blood pressure monitoring. *Blood Press Monit.* 1996;1:151-156.
10. Staessen J, Amery A. APTH: a trial on ambulatory blood pressure monitoring and treatment of hypertension: objectives and protocol. *Acta Cardiol.* 1993;48:25-42.
11. The 41st World Medical Assembly. Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *Bull Pan Am Health Organ.* 1990;24:606-609.
12. O'Brien E, Mee F, Atkins N, O'Malley K. Accuracy of the SpaceLabs 90207 determined by the British Hypertension Society Protocol. *J Hypertens.* 1991;9:573-574.
13. White WB, Lund-Johansen P, Omvik P. Assessment of four ambulatory blood pressure monitors and measurements by clinicians versus intraarterial blood pressure at rest and during exercise. *Am J Cardiol.* 1990;65:60-66.
14. Fagard R, Brguljan J, Thijs L, Staessen J. Prediction of the actual awake and asleep blood pressures by various methods of 24 h pressure analysis. *J Hypertens.* 1996;14:557-563.
15. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J.* 1949; 37:161-186.
16. Bielen E, Fagard R, Amery A. The inheritance

of left ventricular structure and function assessed by imaging and Doppler echocardiography. *Am Heart J.* 1991;121:1743-1749.
17. Fagard R, Aubert A, Lysens R, Staessen J, Vanhees L, Amery A. Non-invasive assessment of seasonal variations in cardiac structure and function in cyclists. *Circulation.* 1983;67:896-901.
18. Sahn DJ, De Maria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurement. *Circulation.* 1978;58: 1072-1083.
19. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986;57:450-458.
20. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ.* 1990;300:230-235.
21. Altman DG. *Practical Statistics for Medical Research*, New York, NY: Chapman & Hall; 1991:368-371.
22. Bielen E, Fagard RH, Lijnen PJ, Tjandra-Maga TB, Verbesselt R, Amery AK. Comparison of the effects of isradipine and lisinopril on left ventricular structure and function in essential hypertension. *Am J Cardiol.* 1992;69:1200-1206.
23. Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension.* 1997;29: 22-29.
24. Devereux RB, James GD, Pickering TG. What is normal blood pressure? comparison of ambulatory pressure level and variability in patients with normal or abnormal left ventricular geometry. *Am J Hypertens.* 1993;6:211S-215S.
25. Gosse P, Promax H, Durandet P, Clementy J. White coat hypertension: no harm for the heart. *Hypertension.* 1993;22:766-770.
26. The Joint National Committee on Detection Evaluation and Treatment of High Blood Pressure. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med.* 1993;153:154-183.
27. The Guidelines Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee. The 1993 Guidelines for the Management of Mild Hypertension: memorandum from a World Health Organization/International Society of Hypertension meeting. *Hypertension.* 1993;22:392-403.
28. WHO Expert Committee on Hypertension Control. *Hypertension Control: Report of a WHO Expert Committee.* Geneva, Switzerland: World Health Organization; 1996.
29. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease, 2: short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet.* 1990;335:827-838.
30. Thijs L, Fagard R, Lijnen P, Staessen J, Van Hoof R, Amery A. A meta-analysis of outcome trials in elderly hypertensives. *J Hypertens.* 1992;10:1103-1109.
31. Fletcher AE, Bulpitt CJ. How far should blood pressure be lowered? *N Engl J Med.* 1991;326:251-254.
32. Pickering TG. The ninth Sir George Pickering Memorial Lecture: ambulatory monitoring and the definition of hypertension. *J Hypertens.* 1992;10: 401-409.
33. O'Brien E, Murphy J, Tyndall A, et al. Twenty-four hour ambulatory blood pressure in men and women aged 17 to 80 years: the Allied Irish Bank Study. *J Hypertens.* 1991;9:355-360.
34. Imai Y, Nagai K, Sakuma M, et al. Ambulatory blood pressure of adults in Ohasama, Japan. *Hypertension.* 1993;22:900-912.
35. Staessen JA, O'Brien ET, Amery AK, et al. Ambulatory blood pressure in normotensive and hypertensive subjects: results from an international database. *J Hypertens.* 1994;12(suppl 7):S1-S12.
36. Staessen JA, Bieniaszewski L, O'Brien ET, Imai Y, Fagard R. An epidemiological approach to ambulatory blood pressure monitoring: the Belgian population study. *Blood Press Monit.* 1996;1:13-26.
37. Wiinberg N, Hoegholm A, Christensen HR, et al. 24-h ambulatory blood pressure in 352 normal Danish subjects, related to age and gender. *Am J Hypertens.* 1995;8:978-896.
38. Mancia G, Sega G, Bravi C, et al. Ambulatory blood pressure normality: results from the PAMELA study. *J Hypertens.* 1995;13:1377-1390.
39. Fagard R, Bielen E, Staessen J, Thijs L, Amery A. Response of ambulatory blood pressure to antihypertensive therapy guided by clinic pressure. *Am J Hypertens.* 1993;6:648-653.
40. Waeber B, Scherrer U, Petrillo A, et al. Are some hypertensive patients overtreated? a prospective study of ambulatory blood pressure recording. *Lancet.* 1987;2:732-734.
41. Clement DL, De Buyzere M, Duprez D. Prognostic value of ambulatory blood pressure monitoring. *J Hypertens.* 1994;12:857-864.
42. Perloff D, Sokolow M, Cowan R. The prognostic value of ambulatory blood pressures. *JAMA.* 1983; 249:2792-2798.
43. Mann S, Millar Craig MW, Raftery EB. Superiority of 24-hour measurement of blood pressure over clinic values in determining prognosis in hypertension. *Clin Exp Hypertens.* 1985;A7:279-281.
44. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension.* 1994;24:793-801.
45. Burt VL, Cutler JA, Higgins M, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population: data from the Health Examination Surveys, 1960 to 1991. *Hypertension.* 1995;23:60-69.
46. Staessen JA, Roels H, Fagard R, for the Phee-Cad Investigators. Lead exposure and the conventional and ambulatory blood pressure: a prospective population study. *JAMA.* 1996;275:1563-1570.
47. Staessen J, Amery A, Fagard R. Editorial review: isolated systolic hypertension. *J Hypertens.* 1990;8:393-405.
48. Palatini P, Pessina AC. A new approach to define the upper normal limits of ambulatory blood pressure. *J Hypertens.* 1990;8(suppl 6):S65-S70.
49. Julius S, Mejia A, Jones K, et al. 'White coat' versus 'sustained' borderline hypertension in Tecumseh, Michigan. *Hypertension.* 1990;16:617-623.
50. Zaruke KB, Feagan BG, Mahon JL, Feldman RD. A randomized study comparing a patient-directed hypertension management strategy with usual office-based care. *Am J Hypertens.* 1997;10: 58-67.