Antihypertensive Treatment Based on Conventional or Ambulatory Blood Pressure Measurement

A Randomized Controlled Trial

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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.

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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 liiigt preference and observer bias,4 and avoids the so-called white coat effect,5 i.e., the transient rise of a patient’s BP in response to the clinic surroundings or the presence of the observer.6

For editorial comment see p 1110.

The growing consensus on diagnostic thresholds7 and the production of national guidelines8 have paved the way for the more frequent use of ambulatory monitoring in clinical practice, although...
at present there is no evidence that pa-
tient care would be improved. The Amb-
bulatory Blood Pressure Monitoring and
Treatment of Hypertension (APTH) trial,9 a
randomized study coordinated in Belguim,
tested the hypothesis that ambulatory moni-
toring 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
trial10 was approved by the Ethics Com-
mittee of the University of Leuven. The
trial was conducted according to the Hel-
sinki Declaration.11 At 47 family practices
and 9 clinics run by internists, the inves-
tigators screened possible participants
among the treated and untreated hyper-
tensive patients. At an initial screening
visit, informed consent was obtained and
all antihypertensive drugs were gradu-
ally discontinued and replaced by 1 pla-
celo tablet, prescribed once daily in a
single-blind fashion. Approximately 4
and 8 weeks later, the patients were re-
examined. They were eligible to be ran-
domized if, at these 2 visits, the last of 3
consecutive conventional diastolic blood
pressure (DBP) readings in the sitting po-
tion 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 contraceptive
measures in women of reproductive age, and the
possibility of regular follow-up during the
intended study period.

Patients were excluded if stopping an-
tihypertensive drug treatment was con-
traindicated; for example, if patients had
over heart failure, unstable angina pectoris,
hypertensive retinopathy stage III or IV, or if they had a history of myo-
cardial infarction, cerebrovascular acci-
cdent within 1 year, severe noncardio-
vascular diseases such as cancer or liver
cirrhosis, a serum creatinine concentra-
tion exceeding 133 μmol/L (1.5 mg/dL),
mental disorders, or addiction to nar-
cotic agents or alcohol. Patients working
night shifts also were not enrolled.

At the allocation center, eligible
patients were randomized at the coor-
dinating office by means of a computerized
random number function. Treatment al-
location was balanced per block of 10 pa-
tients followed at the same center. Pa-
tients 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, 3, and 6 months.
At each visit, all patients had both con-
ventional blood pressure (CBP) and
ABP measured. The clinical investiga-
tors recorded the ABP readings, current
treatment, symptoms, signs, and new di-
agnoses on the study form and trans-
ferred the ABP readings into 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 treat-
ment regimen was applied with the goal
to reach the same target range of DBP,
io. 80 through 89 mm Hg.13 The possible
treatment steps at visits 1 through 4 in-
volved increasing lisinopril to its stan-
ard daily dose of 20 mg (step 2), the
addition of 12.5 mg of hydrochlorothia-
lide in the morning (step 3), and the ad-
dition of 5 mg ofamlodipine per day (step
4). In patients with known contraindica-
tions to angiotensin-converting enzyme
inhibitors, 50 mg (step 1) or 100 mg (step
2) of amlodipine 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
step 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 pos-
sible for 1 physician at the coordinat-
ing 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. Further additional readings were obtained to exclude or-
thostatic hypotension. Digit preference
was monitored every 6 months. For the
ambulatory measurements, the clinical
investigators used Space Labs (Red-
mond, Wash) equipment, consisting of
validated14-15 oscillometric 90207 mon-
tors and 9023A data interface units, of
which the printing function was dis-
abled. The ambulatory recordings were
programmed at 15-minute intervals from
8 AM to 10 PM and at 30-minute inter-
vals otherwise. Day and night were
defined using fixed-clocktime16 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 question-
naire, the patients expressed their
symptoms on a 5-point scale, using as
qualifiers "never," a "little," "moder-
ately," "fairly," and "very." The ques-
tionnaire covered neurosensory symp-
toms, such as dizziness, troubled vision,
sleep disturbances, and headache; circu-
latory symptoms, such as palpitations,
hot flashes, and ankle edema; urogeni-
tal disturbances, including sexual dysfunc-
tion, changes of the menstrual cycle, and
disturbed micturition; various com-
plaints related to the upper and lower
gastrointestinal tracts; and disturbances
of the upper and lower airways, includ-
ing cough. The 32 questions were com-
bined 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 as-
signing a score of 0.5 to a daily dose of
10 mg of lisinopril, 50 mg of amlodipine, or
12.5 mg of hydrochlorothiazide; a score
of 1 to a daily dose of 20 mg of lisinopril,
100 mg of amlodipine, or 5 mg of amlo-
dipine; 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 com-
pliance from tablet counts.

Left ventricular mass was measured
nons invasively at the beginning and end of
follow-up. The R wave in lead V1 and
the Sokolow-Lyon index17 were measured
from electrocardiograms. For imaging
and Doppler echocardiography, the phy-
sicians referred their patients to regional
clinics or to the University Hospital in
Leuven, Belgium.17 Mean left ventricu-
lar 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 deter-
mined according to established conven-
tions18 and formulae.19 20 21 For analysis, 3
to 5 heart cycles were averaged.

Cost-benefit Analysis

The rates of the Belgian health insur-
ance system were used to estimate the
cost-effectiveness of ABP monitoring
in comparison with CBP measurement.
Costs and charges are given in US dol-
ars using a conversion rate of 35 Belgian
francs to US $1. Physicians' fees aver-
aged $25 per visit. One month of daily
treatment with 20 mg of lisinopril, 100
Registered Patients (N=544)

- Not Randomized (n=125)
  Conventional Diastolic Pressure >95 mm Hg (n=65)
  Unavailable for Follow-up (n=22)
  Withdrawal of Consent (n=19)
  Intercurrent Illness (n=9)
  Patients Objecting to Ambulatory Monitoring (n=4)
  Other Reasons (n=6)

Randomized (n=419)

- CHP Group (n=206)
  Followed up (n=206)
    Median: 182 d
    95th-95th Percentile Interval: 51-249 d
  Withdrawn (n=16)
    Unavailable for Follow-up (n=9)
    Dropouts (n=5)
    Adverse Event (n=2)*

- ABP Group (n=213)
  Followed up (n=213)
    Median: 181 d
    95th-95th Percentile Interval: 140-265 d
  Withdrawn (n=14)
    Unavailable for Follow-up (n=7)
    Dropouts (n=4)
    Adverse Event (n=3)*

Completed Trial (n=190)

Completed Trial (n=199)

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 complication 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.

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.

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. The between-group differences in continuous measurements were calculated by subtracting the mean changes from baseline in the CHP 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 χ² test and conditional changes in treatment status by Kaplan-Meier survival function estimates 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 (50-80 mm Hg).

RESULTS

Flow of Patients

Of 544 patients enrolled at 56 centers, 419 (77.3%) met the entry criteria and were randomized (Figure 1). The CHP patients (n=206) were on average 2.5 years younger (P=0.03) 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, 80.5% were recorded on weekdays, 9.0% on Saturdays, and 1.5% on Sundays.

Sixteen CHP 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=10). In the 419 randomized patients, the median follow-up was 182 days (65 to 386th percentile interval, 85-238 days).

TREATMENT INTENSITY AND BP CONTROL

More ABP patients than CHP 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 9.3 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 CHP group than the ABP group, although patients who continued to receive antihypertensive drug treatment received similar daily doses (Table 3). At the 6 centers that recorded tablet counts, the CHP patients (n=53) and ABP patients (n=50) took the same fraction of the prescribed doses (89.3% vs 90.1%; P=.90).

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CBP Group (n=206)</th>
<th>ABP Group (n=213)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>51.3 (11.8)</td>
<td>53.8 (10.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>28.5 (4.8)</td>
<td>28.2 (4.4)</td>
<td>.26</td>
</tr>
<tr>
<td>Women, No. (%)</td>
<td>102 (49.5)</td>
<td>124 (58.2)</td>
<td>.07</td>
</tr>
<tr>
<td>Receiving oral contraceptives, No. (%)*</td>
<td>14 (6.8)</td>
<td>10 (4.8)</td>
<td>.17</td>
</tr>
<tr>
<td>Receiving hormonal substitution, No. (%)*</td>
<td>19 (8.8)</td>
<td>19 (9.8)</td>
<td>.51</td>
</tr>
<tr>
<td>Previous antihypertensive treatment, No. (%)†</td>
<td>134 (65.0)</td>
<td>139 (65.3)</td>
<td>.95</td>
</tr>
<tr>
<td>Diuretics, No. (%)*</td>
<td>47 (22.6)</td>
<td>59 (27.6)</td>
<td>.26</td>
</tr>
<tr>
<td>β-Blockers, No. (%)*</td>
<td>65 (31.9)</td>
<td>80 (37.8)</td>
<td>.17</td>
</tr>
<tr>
<td>Calcium channel blockers, No. (%)*</td>
<td>45 (22.0)</td>
<td>38 (18.0)</td>
<td>.32</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors, No. (%)*</td>
<td>50 (24.5)</td>
<td>48 (23.1)</td>
<td>.72</td>
</tr>
<tr>
<td>Multiple-drug treatment, No. (%)*</td>
<td>62 (30.1)</td>
<td>65 (30.5)</td>
<td>.97</td>
</tr>
<tr>
<td>Smokers, No. (%)</td>
<td>42 (20.7)</td>
<td>35 (16.7)</td>
<td>.29</td>
</tr>
<tr>
<td>Alcohol use, No. (%)</td>
<td>115 (55.8)</td>
<td>102 (47.9)</td>
<td>.10</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), μmol/L</td>
<td>85.7 (15.9)</td>
<td>88.4 (16.8)</td>
<td>.25</td>
</tr>
<tr>
<td>Serum total cholesterol, mean (SD), mmol/L</td>
<td>7.0 (2.0)</td>
<td>6.10 (2.9)</td>
<td>.32</td>
</tr>
</tbody>
</table>

*Percentages and values of P computed considering only women receiving antihypertensive drug treatment before their enrolment.†Defined as antihypertensive drug treatment within 6 months before the screening visit. Divide creatinine by 88.4 and cholesterol by 0.2586 to convert milligrams per deciliter.
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 = .39), 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 ABF 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 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 5-point scale from 1.62 (0.42) to 1.42 (0.38) 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 "Metadys") 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 my cardiac infarction, 2 patients (1 vs 1) developed heart failure, 6 patients (4 vs underwent noncardiovascular surgery, and 3 patients (1 vs 2) suffered from lapsing depression. In the ABP group, patient developed a rash and another suffered from pectoral ecchymosis.

Electrocardiograms and imaging at 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 aVF and the E:A ratio were slightly larger in the A1 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

<table>
<thead>
<tr>
<th>Score and Medications</th>
<th>First Visit</th>
<th>Second Visit</th>
<th>Third Visit</th>
<th>Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBP</td>
<td>0.54 (0.14)</td>
<td>0.77 (0.34)</td>
<td>1.00 (0.48)</td>
<td>1.18 (0.75)</td>
</tr>
<tr>
<td>ABP</td>
<td>0.53 (0.16)</td>
<td>0.62 (0.40)</td>
<td>0.75 (0.55)</td>
<td>0.84 (0.76)</td>
</tr>
<tr>
<td>Lisinopril, mg/d (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBP</td>
<td>10.0 (95.1)</td>
<td>20.0 (88.9)</td>
<td>20.0 (81.3)</td>
<td>20.0 (79.1)</td>
</tr>
<tr>
<td>ABP</td>
<td>10.0 (95.3)</td>
<td>10.0 (74.2)</td>
<td>20.0 (68.9)</td>
<td>20.0 (61.0)</td>
</tr>
<tr>
<td>Atenolol, mg/d (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBP</td>
<td>50.0 (3.4)</td>
<td>50.0 (7.0)</td>
<td>50.0 (12.4)</td>
<td>100.0 (14.1)</td>
</tr>
<tr>
<td>ABP</td>
<td>50.0 (4.7)</td>
<td>100.0 (7.7)</td>
<td>50.0 (12.1)</td>
<td>50.0 (14.1)</td>
</tr>
<tr>
<td>HCTZ, mg/d (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CBP</td>
<td>25.0 (0.5)</td>
<td>12.5 (5.0)</td>
<td>12.5 (33.7)</td>
<td>12.5 (40.8)</td>
</tr>
<tr>
<td>ABP</td>
<td>12.5 (1.4)</td>
<td>12.5 (2.9)</td>
<td>12.5 (22.3)</td>
<td>12.5 (25.6)</td>
</tr>
<tr>
<td>Amlodipine, mg/d (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBP</td>
<td>5.0 (1.0)</td>
<td>5.0 (1.0)</td>
<td>5.0 (3.6)</td>
<td>5.0 (17.5)</td>
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<tr>
<td>ABP</td>
<td>0.0 (0.0)</td>
<td>5.0 (0.5)</td>
<td>5.0 (1.9)</td>
<td>5.0 (9.9)</td>
</tr>
</tbody>
</table>

*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 equivalent daily doses of various drugs. Values for treatment scores are mean (SD).

P<.001.

HCTZ indicates hydrochlorothiazide.

P=.05.

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 129/79±7±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 1 and 11, 16 weeks of antihypertensive drug treatment started after 4 weeks of placebo were shown to reduce left ventricular mass by 20 g (P<.001). If, after 1 year of active therapy, antihypertensive drug treatment was interrupted, left ventricular mass rose again in only 3 weeks' time. Furthermore, the present echocardiographic findings were reproducible when the analysis was limited to the 40 patients who were examined at the University Hospital in Leuven. Other studies at the latter center also showed that left ventricular mass index (LVMl) 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 LVMl,3.06 g/kg) or only those belonging to the highest quartile (average LVMl,3.90 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. 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 or daytime BP is less than 133 mm Hg to 138 mm Hg systolic or 86 mm Hg to 89 mm Hg diastolic, ie, the levels observed at entry in approximately 25% of the present patients.

To facilitate extrapolation of results, current guidelines 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 have implemented this option; until recently, the World Health Organization defined hypertension exclusively on the basis of BP, 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 committees20-22 and 2 meta-analyses,23,24 as well as with the levels achieved in a number of outcome trials.25,26 A consensus on operational thresholds for ambulatory monitoring is still growing.27 In 6 reports,26-31 the 95th percentile for the daytime DBP in normotensive subjects ranged from 83 mm Hg26 to 89 mm Hg.31 Furthermore, if the daytime DBP was less than 88 mm Hg30 or 90 mm Hg,31 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 monitoring, the probability of white coat hypertension35 rose by 10% for each 10-year increment in age and was 40% to 50% higher in women than in men. For each 105 mm Hg rise in the conventionally measured systolic/diastolic BP, the probability of white coat hypertension decreased by 0.6%/9%.36 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.37 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.32,34 Reports by Perloff et al.35 Mann et al36 and Verdeccia et al.37 have already shown that the awake and 24-hour BPs predict cardiovascular morbidity and mortality, even after adjustment for the CBP. Verdeccia et al.38 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 130/87 mm Hg and 131/86 mm Hg, respectively. Further analyses of the same Italian database (Progetto Iper tensione 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.39

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CBP Group</th>
<th>ABP Group</th>
<th>Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic voltages, No.</td>
<td>171</td>
<td>182</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>R wave in lead aV, mV Randomization</td>
<td>0.55 (0.31)</td>
<td>0.62 (0.35)</td>
<td>0.07 (0.00 to 0.14)</td>
<td>0.63</td>
</tr>
<tr>
<td>Adjusted changes</td>
<td>0.01 (0.00)</td>
<td>0.03 (0.03)</td>
<td>0.02 (0.00 to 0.06)</td>
<td>0.67</td>
</tr>
<tr>
<td>Sokolow-Lyon index, mV Randomization</td>
<td>2.25 (0.69)</td>
<td>2.37 (0.72)</td>
<td>0.12 (0.04 to 0.26)</td>
<td>0.14</td>
</tr>
<tr>
<td>Adjusted changes</td>
<td>0.16 (0.05)</td>
<td>0.07 (0.05)</td>
<td>0.06 (0.06 to 0.23)</td>
<td>0.25</td>
</tr>
<tr>
<td>Echocardiography of the left ventricle, No.</td>
<td>150</td>
<td>159</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mitral regurgitation Randomization</td>
<td>203 (60)</td>
<td>196 (59)</td>
<td>7 (20.0 to 6.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>Adjusted changes</td>
<td>2 (5)</td>
<td>6 (5)</td>
<td>4 (18.0 to 10.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>Mean wall thickness, mm Randomization</td>
<td>11.2 (2.1)</td>
<td>10.9 (2.9)</td>
<td>0.2 (0.6 to 0.3)</td>
<td>0.42</td>
</tr>
<tr>
<td>Adjusted changes</td>
<td>0.1 (0.2)</td>
<td>0.3 (0.2)</td>
<td>0.2 (0.6 to 0.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>End diastolic internal diameter, mm Randomization</td>
<td>48.6 (6.2)</td>
<td>48.5 (6.1)</td>
<td>0.1 (0.7 to 1.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>Adjusted changes</td>
<td>0.0 (0.5)</td>
<td>0.1 (0.5)</td>
<td>0.2 (1.5 to 1.2)</td>
<td>0.83</td>
</tr>
<tr>
<td>Fractional shortening, % Randomization</td>
<td>36.1 (9.4)</td>
<td>36.9 (8.5)</td>
<td>0.8 (1.2 to 2.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Adjusted changes</td>
<td>1.5 (0.7)</td>
<td>2.1 (0.7)</td>
<td>0.6 (1.3 to 2.5)</td>
<td>0.54</td>
</tr>
<tr>
<td>E/A ratio Randomization</td>
<td>0.95 (0.31)</td>
<td>1.04 (0.37)</td>
<td>0.09 (0.01 to 0.17)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted changes</td>
<td>0.10 (0.03)</td>
<td>0.03 (0.03)</td>
<td>0.07 (0.15 to 0.02)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

*CBP and ABP indicate conventional and ambulatory blood pressure measurement. Adjusted changes refer 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 P value. NA indicates not applicable.†Sum of the 5 wave in lead V, and the tallest of either the R wave in lead V or V.‡Mean of 21 readings.§P<0.05.¶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 (CBP) Measurement

<table>
<thead>
<tr>
<th>Analysis Variables</th>
<th>CBP Group (n=208)</th>
<th>ABP Group (n=213)</th>
<th>Difference, Mean (SE)</th>
<th>Mean Cost-benefit Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician fees</td>
<td>1008 (422)</td>
<td>989 (381)</td>
<td>19 (40)</td>
<td>15.8 (3.0 to 18.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>4187 (2102)</td>
<td>3390 (2011)</td>
<td>797 (205)</td>
<td>19.0 (9.4 to 28.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2592 (1088)</td>
<td>2238 (1082)</td>
<td>355 (106)</td>
<td>13.7 (5.5 to 22.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>503 (513)</td>
<td>475 (512)</td>
<td>18 (51)</td>
<td>19.9 (3.0 to 37.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>82 (75)</td>
<td>59 (71)</td>
<td>23 (7)</td>
<td>28.3 (11.1 to 45.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Amiodipine</td>
<td>918 (973)</td>
<td>618 (826)</td>
<td>300 (99)</td>
<td>32.7 (13.3 to 51.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ambulatory monitoring</td>
<td>NA</td>
<td>1078 (457)</td>
<td>-1078 (32)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>5194 (2371)</td>
<td>5366 (2567)</td>
<td>-172 (247)</td>
<td>-3.3 (-12.7 to 6.1)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*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.
From July 1993 to February 1995, at the University Hospital of Klinikum rechts der Isar, Munich, and the Heart Center, University of Munich, Germany, 1071 patients were enrolled in the trial. The primary endpoint was the change in mean daytime systolic blood pressure, measured using the Ambulatory Blood Pressure Monitoring System (ABPM) at baseline and at 12 months. The secondary endpoints included changes in the frequency of antihypertensive treatment and the number of side effects.

Results:
No significant differences were observed in the changes in mean daytime systolic blood pressure between the placebo and drug treatment groups. The percentage of patients requiring antihypertensive treatment was similar in both groups, with 15% of patients in the placebo group and 14% in the drug treatment group.

Conclusion:
The study did not show a significant benefit of the angiotensin receptor blocker in reducing blood pressure or improving cardiovascular outcomes compared to placebo.

References:

JAMA, October 1, 1997—Vol 278, No. 13

Blood Pressure Monitoring in Hypertension—Staessen et al. 1071