Antihypertensive Treatment Based on Blood Pressure Measurement at Home or in the Physician’s Office
A Randomized Controlled Trial

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Context Self-measurement of blood pressure is increasingly used in clinical practice, but how it affects the treatment of hypertension requires further study.

Objective To compare use of blood pressure (BP) measurements taken in physicians’ offices and at home in the treatment of patients with hypertension.

Design, Setting, and Participants Blinded randomized controlled trial conducted from March 1997 to April 2002 at 56 primary care practices and 3 hospital-based outpatient clinics in Belgium and 1 specialized hypertension clinic in Dublin, Ireland. Four hundred participants with a diastolic BP (DBP) of 95 mm Hg or more as measured at physicians’ offices were enrolled and followed up for 1 year.

Interventions Antihypertensive drug treatment was adjusted in a stepwise fashion based on either the self-measured DBP at home (average of 6 measurements per day during 1 week; n=203) or the average of 3 sitting DBP readings at the physician’s office (n=197). If the DBP guiding treatment was above (>89 mm Hg), at (80-89 mm Hg), or below (<80 mm Hg) target, a physician blinded to randomization intensified antihypertensive treatment, left it unchanged, or reduced it, respectively.

Mean Outcome Measures Office and home BP levels, 24-hour ambulatory BP, intensity of drug treatment, electrocardiographic and echocardiographic left ventricular mass, symptoms reported by questionnaire, and costs of treatment.

Results At the end of the study (median follow-up, 350 days; interquartile range, 326-409 days), more home BP than office BP patients had stopped antihypertensive drug treatment (25.6% vs 11.3%; P<.001) with no significant difference in the proportions of patients progressing to multiple-drug treatment (38.7% vs 45.1%; P=.14). The final office, home, and 24-hour ambulatory BP measurements were higher (P<.001) in the home BP group than in the office BP group. The mean baseline-adjusted systolic/diastolic differences between the home and office BP groups averaged 6.8/3.5 mm Hg, 4.9/2.9 mm Hg, and 4.9/2.9 mm Hg, respectively. Left ventricular mass and reported symptoms were similar in the 2 groups. Costs per 100 patients followed up for 1 month were only slightly lower in the home BP group (€3875 vs €3522 [$4921 vs $4473]; P=.04).

Conclusions Adjustment of antihypertensive treatment based on home BP instead of office BP led to less intensive drug treatment and marginally lower costs but also to less BP control, with no differences in general well-being or left ventricular mass. Self-measurement allowed identification of patients with white-coat hypertension. Our findings support a stepwise strategy for the evaluation of BP in which self-measurement and ambulatory monitoring are complementary to conventional office measurement and highlight the need for prospective outcome studies to establish the normal range of home-measured BP.

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Few prospective cohort studies on the association between cardiovascular outcome and self-measured BP have been published.6-9 Consensus guidelines7,8 propose diagnostic thresholds for the clinical application of self-measured BP, but these are based on observational studies6-15 and have never been tested in large-scale randomized clinical trials. The primary objective of the Treatment of Hypertension Based on Home or Office Blood Pressure (THOP) trial16 was to compare self-measurement and conventional office measurement of BP as guides to initiate and titrate antihypertensive drug treatment. The THOP trial extends our previous research on ambulatory monitoring of BP.1

METHODS
Study Design and Interventions

The ethics committees of the University of Leuven, Leuven, Belgium, and the Beaumont Hospital, Dublin, Ireland, approved the protocol of the THOP trial,16 which was conducted according to the Helsinki declaration17 at 36 primary care practices and 3 hospital-based outpatient clinics in Belgium and 1 specialized hypertension clinic in Dublin, Ireland. At an initial screening, patients gave written informed consent. Men and women with hypertension and a minimum age of 18 years were eligible if they were either untreated or being treated with no more than 2 different antihypertensive agents. Potential candidates were invited for 2 further run-in visits, 2 to 4 weeks apart, while their treatment status and medications were held constant. They could be randomized if the last of 3 consecutive readings of diastolic BP (DBP) obtained in the sitting position at each of the 2 run-in visits averaged 95 to 114 mm Hg. Patients with higher DBP also qualified but were re-examined at shorter intervals. Women of reproductive age had to practice a reliable contraception method. The exclusion criteria encompassed heart failure, unstable angina pectoris, stage 3 or 4 hypertensive retinopathy, a history of myocardial infarction or stroke within 1 year of enrollment, severe noncardiovascular disease (eg, cancer or liver cirrhosis), serum creatinine concentration higher than 177 μmol/L (2.0 mg/dL), mental disorders, and substance abuse. Patients working night shifts also could not be enrolled.

After stratification by center, the study manager at the coordinating office used a computerized random number function to assign patients to treatment based on their BP measured at home vs at the physician's office. For the measurements at home, patients used validated18 oscillometric Omron HEM-705CP devices (Omron Inc, Kyoto, Japan), which the manufacturer calibrated before use in the trial. The self-measured BP was the average of all readings collected during the 7 days prior to each follow-up visit. After 5 minutes of rest in the sitting position, patients performed 3 consecutive self-measurements of BP twice daily, in the morning between 6 and 10 AM and in the evening between 6 and 10 PM. They recorded and printed the values of BP and pulse rate along with the time of day. The office BP was the average of 3 consecutive BP readings taken by the physician during the day during usual practice hours, after patients had rested for 5 minutes in the sitting position. The investigators’ terminal digit preference was monitored every 6 months. Regardless of randomization, both the home and office BP were available at each visit. In addition, at randomization, at 6 months, and at the last follow-up visit, patients underwent 24-hour ambulatory monitoring. Validated18 oscillometric SpaceLabs 90207 recorders (SpaceLabs Inc, Redmond, Wash) were programmed to obtain BP readings at 15-minute intervals from 8 AM to 10 PM and at 30-minute intervals otherwise. Day and night BP measurements were time-weighted means computed for fixed clock-time intervals of 10 AM to 8 PM and from midnight to 6 AM, respectively.

After randomization, follow-up visits were scheduled at 1 and 2 months and thereafter at 2-month intervals for up to 1 year. Depending on randomization and in agreement with the treatment goals used in our previous trial of ambulatory BP monitoring,1 the target for both the office- and home-based BP measurement groups was a DBP of 80 to 89 mm Hg. To attain this goal, physicians implemented a standardized drug regimen. After randomization, all patients began or switched to monotherapy with lisinopril, 10 mg/d (step 1). At later visits, treatment could be stepwise intensified by doubling lisinopril to 20 mg/d (step 2); by combining lisinopril with hydrochlorothiazide, 25 mg/d, or amlodipine, 5 mg/d (step 3); and, finally, by adding amlo-dipine, 5 mg/d, in patients taking the combination of lisinopril and hydrochlorothiazide or prazosin, up to 6 mg/d, in other patients (step 4). In patients with known contraindications to angiotensin-converting enzyme inhibitors, lisinopril could be substituted by atenolol, 50 mg/d (step 1) or 100 mg/d (step 2).

Immediately after each visit, the clinical investigators transferred all relevant information to the coordinating center in Leuven, including the home and office BP values, current treatment, symptoms, signs, and new diagnoses. One physician at the coordinating center who was blinded with regard to randomization made all treatment decisions. He received only the values of either the office or the self-measured BP, depending on the allocation of patients. The field investigators subsequently implemented his treatment decisions. If the DBP level guiding treatment was above the target (>89 mm Hg), medical treatment was intensified by step 1. If the DBP level was within the target range (80-89 mm Hg), medical treatment was left unchanged. If the DBP level guiding treatment was below the target (<80 mm Hg), medical treatment was reduced by 1 step, which for patients receiving step 1 treatment meant discontinuation of antihypertensive drug treatment. The ambulatory BP values were disclosed only after completion of the trial and were not considered in any treatment decision.

Other Clinical and Technical Measurements

At enrollment, at 2 and 6 months, and at the last visit, patients completed a questionnaire to express their symptoms on a 5-point scale, using as quali-
fiers “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 complaints, including sexual dysfunction, changes in menstrual cycle, and disturbed micturition; various symptoms related to the upper and lower gastrointestinal tract; and disturbances of the upper and lower airways, including cough. The 33 questions were combined into 1 overall and several organ-specific symptom scores by averaging the answers to the individual questions.

The intensity of antihypertensive drug treatment was evaluated by assigning a score proportional to the dose of each of the study medications, with values set at 1 for the maximum daily dose (20 mg of lisinopril, 100 mg of atenolol, 25 mg of hydrochlorothiazide, 5 mg of amldipine, or 6 mg of prazosin) and to 0 in untreated patients. For each patient and each visit, the scores of all medications were summed. Patients’ compliance with therapy was assessed by tablet counts.

Left ventricular mass was noninvasively measured at the beginning and end of follow-up. The R wave in lead aVL, the Sokolow-Lyon index, the Cornell index, and the Cornell product were determined from electrocardiograms. Four hospital-based clinics took part in imaging and Doppler echocardiography. Mean left ventricular wall thickness, echocardiographic left ventricular mass index, 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 and formulas. For analysis, 3 to 5 heart cycles were averaged.

Monetary rates of the Belgian health insurance system were applied to estimate the costs of antihypertensive treatment based on home and office BP measurements. Physicians’ fees amounted to €30 per visit. In 2002, 1 month of treatment with 20 mg/d of lisinopril, 100 mg/d of atenolol, 25 mg/d of hydrochlorothiazide, 5 mg/d of amldipine, and 6 mg/d of prazosin necessitated expenditures of €25, €15, €3, €26, and €6, respectively (€1 = US $1.27 on January 25, 2004). Home BP measurement is not yet reimbursed by the Belgian health care system and was therefore budgeted at the rate of depreciation of the Omron recorders during the trial (€6.6 for 1 week of measurements). Because treatments could begin to diverge only at the first follow-up visit, the calculations disregarded earlier expenses. Two assumptions were made. First, if starting from any visit a patient’s BP remained well controlled and treatment remained unchanged until the end of follow-up, we presumed that from this visit onward, the same treatment schedule would be continued for a further 6 months without any reassessment. Second, we assumed that physicians would reexamine their patients after 2 months if the BP at the last study visit still exceeded the target range. These intervals were chosen because they are in line with current practice at most specialized hypertension clinics in Belgium.

Statistical Analyses
The primary efficacy measure of BP control was the 24-hour level. With significance set at 5% and power at 85%, approximately 200 patients per treatment group had to be randomized to detect BP differences of 5 mm Hg for systolic BP (SBP) or 2 mm Hg for DBP, assuming standard deviations of 15 mm Hg and 10 mm Hg, respectively.

Database management and statistical analyses were performed with SAS software, version 8.1 (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 office BP group from those in the home BP group. Between-group comparisons involved the Mann-Whitney rank sum test for non-normally distributed data and the t test and analysis of covariance for normally distributed variables. Proportions were compared by the χ² statistic and longitudinal changes in treatment status by Kaplan-Meier survival function estimates and the log-rank test. The probability that treatment could be stopped was modeled in relation to several explanatory variables using multiple logistic regression. Treatment stoppage was defined as discontinuation of drug treatment until the end of the study because the office or home DBP was less than 80 mm Hg and thereafter remained at or below the target level (80-89 mm Hg).

RESULTS
Flow of Patients
As shown in Figure 1, 400 (66.0%) of 606 patients enrolled at the 60 centers met the entry criteria and were randomized. Of the patients screened and randomized, 554 (91.4%) and 373 (93.2%) were Belgian and 52 (8.6%) and 27 (6.8%) were Irish. At randomization, the
TREATMENT BASED ON HOME VS OFFICE BLOOD PRESSURE MEASUREMENT

office BP (n = 197) and home BP (n = 203) groups had similar characteristics (Table 1) and BP values (Table 2). Twenty-six office BP patients (13.2%) and 27 home BP patients (13.3%) did not complete the study because they dropped out (n = 30), experienced an adverse event (n = 2; Figure 1) or missed 1 or more follow-up visits (n = 21). Among the 400 randomized patients, the median follow-up was 350 days (interquartile range [IQR], 327-406 days). In the office BP group, the median follow-up was 352 days (IQR, 323-411 days) and for the home BP group, it was 350 days (IQR, 327-406 days).

Treatment Intensity and BP Control

More home BP than office BP patients could permanently stop antihypertensive drug treatment (Figure 2) because their DBP was less than 80 mm Hg and thereafter stabilized at or below the target range (25.6% vs 11.3%; 2.2 vs 1.0 patients per 100 followed up for 1 month; log-rank P < .001). The opposite trend was observed for patients proceeding to multiple-drug treatment (38.7% vs 45.1%; 3.3 vs 3.8 patients per 100 followed up for 1 month; log-rank P = .14).

Further analyses explored whether sex, age, previous antihypertensive treatment, and diastolic office BP or home BP at randomization could predict the permanent discontinuation of antihypertensive drug treatment. In home BP patients, the probability of stopping drug treatment increased 2.1-fold for each 5-mm Hg decrement in the diastolic home BP at randomization (95% confidence interval [CI], 1.6 to 2.8; P < .001). After accounting for the diastolic office BP at randomization (P = .42), sex (P = .64), age (P = .86), and previous antihypertensive treatment (P < .001), the odds ratio was 1.2 (95% CI, 1.1-1.3; P < .001). Thus, in the home BP group, lower home DBP at entry and the lack of previous treatment independently predicted permanent cessation of antihypertensive drug therapy during follow-up. In the office BP group, the office DBP at randomization did not predict discontinuation of treatment. The odds ratios associated with a 5-mm Hg lower office DBP at entry were 1.3 (95% CI, 0.8-2.1; P = .21) before any adjustment and 1.1 (95% CI, 0.9-1.2; P = .23) with adjustment for home DBP at randomization (P = .67), sex (P = .62), age (P = .62), and previous antihypertensive treatment (P = .004). Thus, in the office BP group, only lack of previous treatment predicted stoppage of antihypertensive treatment during follow-up.

The office, home, and ambulatory BPs decreased (P < .001) after randomization (Table 2). At the first follow-up visit (Figure 1), these decreases were similar in both treatment groups, averaging 12/8.2 mm Hg for office BP and 8.4/5.2 mm Hg for home BP. After the 1-month follow-up visit, drug treatment became more intense (P < .001) in the office BP than home BP group, although patients who continued antihypertensive drug treatment used similar daily doses (Table 3). At the 2-month visit, SBP and DBP were significantly higher in the home BP than office BP group (P = .02) with a similar trend for DBP at 4 months (P = .01). At 6 months (Figure 3), the decreases in BP were of similar magnitude in the 2 randomized groups: 19.1/12.8 mm Hg for office BP, 14.3/8.6 mm Hg for home BP, and 11.6/7.5 mm Hg for the daytime ambulatory BP. Thereafter, as summarized in Table 2 and Figure 3, the BP reductions became consistently and significantly greater in office BP than home BP patients. After adjustment for baseline BP, sex, age, and body mass index, the final differences between the 2 treatment groups ranged from 4.8 to 6.8 mm Hg for SBP and from 2.9 to 3.5 mm Hg for DBP (Table 2). Further adjustment for previous antihypertensive treatment did not materially alter these estimates. Of the 51 home BP patients who could stop drug treatment, 33 (64.7%) maintained a home DBP below 85 mm Hg. Office BP patients (n = 159) and home BP patients (n = 169) with available pill counts took similar percentages of the prescribed dosages of the study medications (89.3% vs 90.1%; P = .90).

Table 1. Baseline Characteristics of Patients Randomized to Antihypertensive Drug Treatment Based on BP Measurement at the Physician’s Office or at Home

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Office BP Group (n = 197)</th>
<th>Home BP Group (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>52.6 (12.0)</td>
<td>54.2 (12.1)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)†</td>
<td>27.7 (4.4)</td>
<td>28.5 (4.7)</td>
</tr>
<tr>
<td>Women</td>
<td>102 (51.8)</td>
<td>107 (52.7)</td>
</tr>
<tr>
<td>Oral contraceptive use‡</td>
<td>15 (14.7)</td>
<td>9 (8.4)</td>
</tr>
<tr>
<td>Hormone therapy‡</td>
<td>17 (16.7)</td>
<td>19 (17.8)</td>
</tr>
<tr>
<td>Previous antihypertensive treatment</td>
<td>85 (43.2)</td>
<td>97 (47.8)</td>
</tr>
<tr>
<td>Diuretics‡</td>
<td>22 (25.9)</td>
<td>29 (29.9)</td>
</tr>
<tr>
<td>β-Blockers‡</td>
<td>50 (58.8)</td>
<td>53 (54.6)</td>
</tr>
<tr>
<td>Calcium channel blockers‡</td>
<td>16 (18.8)</td>
<td>19 (19.6)</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors‡</td>
<td>20 (23.5)</td>
<td>26 (26.8)</td>
</tr>
<tr>
<td>Other classes of antihypertensive drugs§</td>
<td>11 (12.9)</td>
<td>9 (9.3)</td>
</tr>
<tr>
<td>Multiple-drug treatment‡</td>
<td>33 (38.8)</td>
<td>39 (40.2)</td>
</tr>
<tr>
<td>Enrolled at family practices</td>
<td>151 (76.6)</td>
<td>156 (76.8)</td>
</tr>
<tr>
<td>Smokers</td>
<td>45 (22.8)</td>
<td>42 (20.7)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>124 (62.9)</td>
<td>125 (61.6)</td>
</tr>
<tr>
<td>Serum creatinine, mean (SD), mg/dL</td>
<td>0.98 (0.26)</td>
<td>0.97 (0.19)</td>
</tr>
<tr>
<td>Serum total cholesterol, mean (SD), mg/dL</td>
<td>225 (41)</td>
<td>224 (40)</td>
</tr>
</tbody>
</table>

Abbreviation: BP, blood pressure.

SI conversions: To convert creatinine and cholesterol to µmol/L and mmol/L, respectively, multiply by 88.4 and 0.0259, respectively.

†Body mass index is calculated as weight in kilograms divided by the square of height in meters.

‡Data are expressed as number (percentage) of patients unless otherwise indicated. Between-group comparisons were not statistically significant (P > .06).

§Other classes of antihypertensive drugs include centrally acting drugs, β-blockers, vasodilators, and angiotensin II type 1 receptor antagonists.

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Symptoms, Adverse Events, and Left Ventricular Mass

During the entire follow-up, the mean symptom score decreased (P<.001) on a 5-point scale from 1.52 (SD, 0.36) to 1.40 (SD, 0.32) in the office BP group and from 1.60 (SD, 0.40) to 1.50 (SD, 0.41) in the home BP group. The baseline-adjusted changes in the overall symptom score were similar in both groups at 6 months (−0.07 vs −0.10; P = .39) and at the end of the trial (−0.10 vs −0.10; P = .99). The scores for dizziness, headache, palpitations, and ankle edema and organ-specific symptoms also showed similar trends in the 2 treatment groups. Major adverse events occurred in 13 office BP and 10 home BP patients (P = .52). Five patients experienced major cardiovascular complications (office BP vs home BP, 1 vs 4) involving the coronary (1 vs 2) or cerebrovascular (0 vs 2) circulation; 16 had major noncardiovascular illnesses (10 vs 6) of the gastrointestinal tract (2 vs 0) or the musculoskeletal system (3 vs 2) or required noncardiovascular surgery (1 vs 2); 2 patients developed major depression (2 vs 0).

Serial electrocardiograms and echocardiograms of sufficient quality were available in 355 and 54 patients, respectively (Table 4). After adjustment for baseline values, sex, age, and body mass index, the between-group differences in the changes in most electrocardiographic and echocardiographic measurements were small and statistically nonsignificant (Table 4). At the end of the trial, there was marginal benefit only for the echocardiographic E:A ratio (P = .02) in the office BP compared with the home BP group.

Costs of Medications and Follow-up Visits

The costs of the medications amounted to £1210 and €1688 (P = .002) per 100 office BP and home BP patients treated for 1 month (Table 5). The mean fees of the physicians were, respectively, €1789 and €1510 per 100 patient-months (P < .001). However, the potential savings in the home BP group associated with less-intensive drug treatment and fewer physician visits were partially offset by the costs of home monitoring. Overall, expenditure was slightly but significantly higher for office BP compared with home BP measurement (Table 5).

COMMENT

In this randomized clinical trial with a duration of 1 year, adjustment of antihypertensive treatment based on home BP instead of office BP led to less intensive drug treatment and marginally lower medical costs but also to less long-term BP control with no differences in general well-being and electrocardiographic or echocardiographic left ventricular mass. On the other hand, compared with repeated assessment of BP at the physician’s office, self-measurement at home allowed the discontinuation of antihypertensive drug treatment in twice as many patients. Thus, self-measurement helped to identify patients with white-coat hypertension. These findings support a step-wise strategy for the evaluation of BP. In keeping with current guidelines, 23 patients with elevated office BP on repeat measurement and either target-organ damage or a high cardiovascular risk profile should start drug treatment. However, when elevated office BP is the only detectable abnormality or when pa-
Patients with a normal office BP show unexplained target-organ damage, self-measurement, ambulatory monitoring, or both must be used to exclude white-coat hypertension (isolated clinic hypertension) or masked hypertension (isolated ambulatory or home hypertension), respectively.

The final differences in SBP and DBP between the randomized groups averaged 6.8 and 3.5 mm Hg on conventional measurement at the physician’s office and 4.9 and 2.9 mm Hg on 24-hour ambulatory monitoring. Blood pressure gradients of this magnitude are clinically relevant for the long-term prognosis. Indeed, in prospective observational studies, a 5- to 6-mm Hg decrease in usual DBP was associated with 35% to 40% less stroke and 20% to 25% less coronary heart disease. A meta-regression analysis of 30 clinical trials in hypertensive or high-risk patients demonstrated that a 5-mm Hg difference in SBP over 3 to 5 years changed the risk of all cardiovascular complications and stroke by 25% to 30%. More recently, the Blood Pressure Lowering Treatment Trialists’ Collaboration confirmed the importance of small BP differences in cardiovascular prognosis.

Figure 2. Kaplan-Meier Estimates of Probability That During Follow-up Patients Would Permanently Stop Antihypertensive Drug Treatment or Proceed to Sustained Multiple-Drug Treatment

Figure 3. Mean Systolic and Diastolic Blood Pressures Measured in Physician’s Office, at Patient’s Home, or by Daytime Ambulatory Monitoring

Error bars indicate SEs. P values are for the differences between patients randomized to treatment based on blood pressure measurement in the physician’s office vs at home. Asterisk indicates P<.05; dagger, P<.01; and double dagger, P<.001.
Table 3. Antihypertensive Medications in the 2 Treatment Groups

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>1 Month</th>
<th>2 Months</th>
<th>6 Months</th>
<th>Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P Value†</td>
<td>P Value†</td>
<td>P Value†</td>
<td>P Value†</td>
</tr>
<tr>
<td>Treatment score, mean (SD)*</td>
<td>0.70 (0.54)</td>
<td>0.78 (0.65)</td>
<td>1.27 (0.99)</td>
<td>1.47 (1.19)</td>
</tr>
<tr>
<td>Office BP group</td>
<td>0.31</td>
<td>0.08</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Home BP group</td>
<td>0.008</td>
<td>1.00</td>
<td>1.03</td>
<td>1.03</td>
</tr>
<tr>
<td>Study medication, % of patients (median dose, mg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>80.7 (10)</td>
<td>69.5 (20)</td>
<td>63.8 (20)</td>
<td>59.8 (20)</td>
</tr>
<tr>
<td>Office BP group</td>
<td>0.24</td>
<td>0.10</td>
<td>0.48</td>
<td>0.02</td>
</tr>
<tr>
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<td>0.29</td>
<td>0.54</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Atenolol</td>
<td>18.3 (50)</td>
<td>17.3 (25)</td>
<td>19.8 (5)</td>
<td>29.0 (25)</td>
</tr>
<tr>
<td>Office BP group</td>
<td>0.57</td>
<td>0.56</td>
<td>0.07</td>
<td>0.07</td>
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<tr>
<td>Home BP group</td>
<td>0.61</td>
<td>0.61</td>
<td>0.15</td>
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<tr>
<td>Hydrochlorothiazide</td>
<td>5.6 (25)</td>
<td>9.0 (25)</td>
<td>19.8 (5)</td>
<td>31.5 (25)</td>
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<tr>
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<td>0.29</td>
<td>0.54</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Home BP group</td>
<td>0.29</td>
<td>0.12</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>4.6 (5)</td>
<td>4.0 (5)</td>
<td>12.4 (5)</td>
<td>29.9 (5)</td>
</tr>
<tr>
<td>Office BP group</td>
<td>0.57</td>
<td>0.56</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
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<td>0.61</td>
<td>0.61</td>
<td>0.15</td>
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<tr>
<td>Prazosin</td>
<td>0.00 (1.5)</td>
<td>2.3 (6)</td>
<td>2.3 (6)</td>
<td>4.0 (3)</td>
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<tr>
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<td>0.15</td>
<td>0.15</td>
<td>0.04</td>
<td>0.04</td>
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<tr>
<td>Home BP group</td>
<td>0.15</td>
<td>0.15</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Abbreviation: BP, blood pressure.

*The intensity of antihypertensive treatment was scored by assigning a value of 1 to equipotent daily doses of various study medications.
†P values are for the comparison between the office BP and home BP groups in treatment score or percentage of patients receiving specific drugs. Median daily doses of study medications were similar in the 2 groups with the exception of those for prazosin at the last visit (P = .04).

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Office BP Group</th>
<th>P Value for Within-Group Change</th>
<th>Home BP Group</th>
<th>P Value for Within-Group Change</th>
<th>Between-Group Difference, Mean (95% CI)†</th>
<th>P Value for Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic voltages, No.</td>
<td>172</td>
<td>0.09</td>
<td>183</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R in lead aVL, mV</td>
<td>Randomization</td>
<td>0.60 (0.38)</td>
<td>0.59 (0.35)</td>
<td>-0.01 (−0.09 to 0.07)</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>-0.02 (0.02)</td>
<td>-0.01 (−0.09 to 0.07)</td>
<td>2.20 (0.03)</td>
<td>2.20 (0.03)</td>
<td>0.10 (−0.06 to 0.25)</td>
<td>.22</td>
</tr>
<tr>
<td>Sokolow-Lyon index, mV‡</td>
<td>Randomization</td>
<td>2.17 (0.69)</td>
<td>2.26 (0.76)</td>
<td>0.10 (−0.06 to 0.25)</td>
<td>.22</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>-0.12 (0.03)</td>
<td>-0.09 (−0.11 to 0.01)</td>
<td>2.20 (0.03)</td>
<td>2.20 (0.03)</td>
<td>0.10 (−0.06 to 0.25)</td>
<td>.22</td>
</tr>
<tr>
<td>Cornell voltage, mV§</td>
<td>Randomization</td>
<td>2.05 (0.75)</td>
<td>2.08 (0.66)</td>
<td>0.03 (−0.12 to 0.17)</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>-0.14 (0.03)</td>
<td>-0.12 (−0.10 to 0.06)</td>
<td>2.08 (0.66)</td>
<td>2.08 (0.66)</td>
<td>0.03 (−0.05 to 0.10)</td>
<td>.54</td>
</tr>
<tr>
<td>Cornell product, µV × s H²</td>
<td>Randomization</td>
<td>167 (67)</td>
<td>173 (64)</td>
<td>5 (−3 to 9)</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>-13 (3)</td>
<td>-12 (−3 to 9)</td>
<td>5 (−3 to 9)</td>
<td>5 (−3 to 9)</td>
<td>1 (−2 to 9)</td>
<td>.84</td>
</tr>
<tr>
<td>Left ventricular echocardiography, No.</td>
<td>27</td>
<td>0.007</td>
<td>27</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass index, g/m²</td>
<td>Randomization</td>
<td>101 (32)</td>
<td>108 (32)</td>
<td>8 (−0.3 to 0.2)</td>
<td>.19</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>-8 (4)</td>
<td>-16 (−3 to 2)</td>
<td>8 (−0.3 to 0.2)</td>
<td>8 (−0.3 to 0.2)</td>
<td>1 (−2 to 9)</td>
<td>.84</td>
</tr>
<tr>
<td>Mean wall thickness, mm</td>
<td>Randomization</td>
<td>10.9 (2.2)</td>
<td>11.2 (2.2)</td>
<td>0.3 (−0.9 to 1.5)</td>
<td>.66</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>-0.7 (0.3)</td>
<td>-1.2 (−1.3 to 0.2)</td>
<td>10.9 (2.2)</td>
<td>10.9 (2.2)</td>
<td>0.3 (−0.9 to 1.5)</td>
<td>.66</td>
</tr>
<tr>
<td>End-diastolic left ventricular internal diameter, mm</td>
<td>Randomization</td>
<td>46.5 (4.1)</td>
<td>48.5 (4.4)</td>
<td>2.0 (−0.3 to 4.4)</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>0.1 (0.0)</td>
<td>0.0 (−0.1 to 0.1)</td>
<td>48.5 (4.4)</td>
<td>48.5 (4.4)</td>
<td>2.0 (−0.3 to 4.4)</td>
<td>.09</td>
</tr>
<tr>
<td>E:A ratio</td>
<td>Randomization</td>
<td>1.14 (0.53)</td>
<td>1.11 (0.42)</td>
<td>0.03 (−0.30 to 0.23)</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Adjusted change</td>
<td>0.15 (0.06)</td>
<td>0.07 (−0.06)</td>
<td>1.14 (0.53)</td>
<td>1.14 (0.53)</td>
<td>0.03 (−0.30 to 0.23)</td>
<td>.80</td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; CI, confidence interval.

*Adjusted change refers to the mean changes (SE) from randomization to the last follow-up visit, adjusted for baseline value, sex (for all variables except the Cornell voltage and Cornell product), age, and body mass index (for all variables except left ventricular mass index).
†Values for differences between the office and home BP groups may not sum because of rounding.
‡Sum of the S wave in lead V1 and the tallest of either the R wave in lead V5 or V6.
§Sum of the R wave in lead aVL and the S wave in lead V3, adjusted for sex by the addition of 0.8 mV for women.
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Furthermore, in the Systolic Hypertension in Europe Trial, with adjustments applied for antihypertensive treatment, sex, age, cardiovascular complications at entry, and current smoking, each 5-mm Hg increment in 24-hour SBP at randomization was significantly and independently associated with increases in the risks of all cardiovascular events and fatal and nonfatal stroke by 9% and 18%, respectively.

To facilitate extrapolation of our results, most THOP patients were recruited at family practices and antihypertensive treatment was either initiated or continued on the basis of hypertensive treatment. Patients were followed up at 6-month intervals without a change in their treatment regimen, whereas if the diastolic blood pressure still exceeded the therapeutic target range at the end of the trial, they would be reexamined within 2 months. Values may not sum because of rounding.

In a meta-analysis of the summary statistics of published articles, the self-recorded BP averaged 115/71 mm Hg in normotensive persons and 119/74 mm Hg in untreated persons not selected on the basis of their BP. In an international database of self-recorded BPs, the 95th percentile in 2401 normotensive persons was 136/85 mm Hg for measurements taken in the morning, 139/86 mm Hg for readings obtained in the evening, and 137/85 mm Hg when the time of day was disregarded. Other experts proposed thresholds approximately ranging from 125 to 140 mm Hg for SBP and from 80 to 90 mm Hg for DBP. To the best of our knowledge, only 2 published studies with a prospective design addressed the relation between cardiovascular risk and self-recorded BP. In a population-based study in Ohasama, Japan, the self-measured BP was a better predictor of total mortality than the BP measured at screening by a nurse. A retrospective analysis of the baseline data of the SHEAF study (Self-measurement of Blood Pressure at Home in the Elderly: Assessment and Follow-up) suggested that older patients (≥60 years) with white-coat hypertension (isolated clinic hypertension) had fewer cardiovascular risk factors and a lower prevalence of previous cardiovascular complications than those with isolated home hypertension or uncontrolled hypertension. The patients were followed up from February 1998 until early 2002. The results of the prospective SHEAF component have not yet been fully published, but preliminary analyses confirmed that self-measurement at home improved the prognostic accuracy of office BP. Multiple standardized office BP readings might predict target organ damage with accuracy similar to that of automated techniques of BP assessment. One limitation of the Japanese and French studies is the small number of office BP readings (1 reading at a single visit and 2 readings at each of 2 visits, respectively) used for the comparison of prognostic precision with home BP.

The APTH trial compared treatment strategies for hypertension based on office BP and the average daytime ambulatory BP. In the present study, ambulatory BP values were only disclosed after completion of the trial and were not used to adjust treatment. Nevertheless, the similarity between the APTH and THOP trials with regard to protocol, conduct and settings, and baseline characteristics of the patients, as well as the intended matching of the target ranges of DBP on 3 types of BP measurement, en-

### Table 5. Cost-effectiveness Analysis of the Adjustment of Antihypertensive Drug Treatment Based on Home BP Instead of Office BP Measurement

<table>
<thead>
<tr>
<th></th>
<th>Office BP Group (n = 197)</th>
<th>Home BP Group (n = 203)</th>
<th>Difference, Mean (SE)</th>
<th>Cost Benefit, % (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician fees</td>
<td>1759 (347)</td>
<td>1510 (493)</td>
<td>249 (43)</td>
<td>11.4 (7.1 to 15.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>2120 (1711)</td>
<td>1688 (1520)</td>
<td>432 (163)</td>
<td>20.4 (5.9 to 31.9)</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1142 (924)</td>
<td>1066 (948)</td>
<td>75 (94)</td>
<td>6.6 (−10.9 to 20.5)</td>
<td>.39</td>
</tr>
<tr>
<td>Atenolol</td>
<td>321 (527)</td>
<td>205 (437)</td>
<td>115 (49)</td>
<td>35.8 (7.7 to 53.3)</td>
<td>.006</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>160 (301)</td>
<td>114 (254)</td>
<td>46 (28)</td>
<td>28.6 (8.1 to 49.9)</td>
<td>.05</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>476 (892)</td>
<td>296 (714)</td>
<td>179 (81)</td>
<td>37.7 (5.4 to 56.3)</td>
<td>.003</td>
</tr>
<tr>
<td>Prazosin</td>
<td>22 (144)</td>
<td>5 (64)</td>
<td>17 (11)</td>
<td>75.8 (−19.9 to 171.5)</td>
<td>.12</td>
</tr>
<tr>
<td>Home monitoring</td>
<td>333 (108)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total 3875 (1723) 3522 (1747) 353 (175) 9.1 (0.2 to 16.9) .04

Abbreviations: BP, blood pressure; CI, confidence interval.

*Absolute costs were calculated in mean euros (SD) per group and standardized to 100 patients followed up for 1 month. The algorithm assumed that if diastolic blood pressure was well controlled, patients would be followed up at 6-month intervals without a change in their treatment regimen, whereas if the diastolic blood pressure still exceeded the therapeutic target range at the end of the trial, they would be reexamined within 2 months. Values may not sum because of rounding.

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able comparison of the results of both trials. In the APTH study,1 a strategy guided by ambulatory monitoring instead of office BP measurement, after a median follow-up of 6 months, led to less intensive drug treatment with preservation of general well-being and inhibition of left ventricular hypertrophy, but without cost savings in the group randomized to ambulatory monitoring. In the APTH trial, the final between-group differences in SBP and DBP also tended to be in favor of the office BP group. They averaged 3.3 mm Hg (95% CI, –0.1 to 6.7 mm Hg; P = .06) and 1.4 mm Hg (95% CI, –0.5 to 3.3 mm Hg; P = .16) for office BP measurement and 2.8 mm Hg (95% CI, 0.6–5.1 mm Hg; P = .02) and 1.6 mm Hg (95% CI, 0.2–3.0 mm Hg; P = .03) for the 24-hour ambulatory BP. In the present trial, median follow-up increased from 6 to 12 months with less BP control at the final visit in patients randomized to self-measurement than observed in APTH patients randomized to ambulatory monitoring. One might speculate that had follow-up in the APTH trial been longer, the BP gradient between the randomized groups might have been larger. We reported the APTH trial with the conclusion that these small between-group differences in BP control, albeit statistically significant, probably did not matter in terms of prognosis because there were no differences in left ventricular mass between the randomized groups. In view of more recent evidence from prospective population studies27,28 and outcome trials,29,30 this point of view is no longer tenable. Thus, if automated BP measuring techniques are used to initiate or adjust antihypertensive treatment, lower BP targets must be pursued, which should probably be below 130 mm Hg SBP and 80 mm Hg DBP. At these levels, the incidence of cardiovascular complications is similar in patients with white-coat hypertension diagnosed by daytime ambulatory monitoring and normotensive controls.34 Physical activity and the stress of daily life raise the level of the daytime ambulatory BP in comparison with the BP measured at home, so that the operational threshold proposed for daytime ambulatory monitoring cannot be extrapolated to self-measurement.35

The present study must be interpreted within the context of its limitations. We did not record the time of day at which the field investigators measured the office BP. General practitioners recruited most patients, and about half of those randomized were taking antihypertensive drugs. This might explain why the changes in electrocardiographic and echocardiographic left ventricular mass were small. However, a substudy of left ventricular mass in the Losartan Intervention for Endpoint Reduction (LIFE) trial36 demonstrated that prior treatment was neither associated with greater left ventricular mass at entry nor with a lesser degree of mass reduction during follow-up. More importantly, long-term outcome studies should firmly establish the advantage of further integrating self-measurement and ambulatory monitoring into the routine care of hypertensive patients. Until such evidence becomes available, conventional sphygmomanometry at the physician’s office executed according to published guidelines3 remains key to the diagnosis and treatment of hypertension. Ambulatory BP monitoring and self-measurement are useful to confirm the diagnosis and to diagnose white-coat hypertension or masked hypertension.32 In keeping with the THOP procedures and recent recommendations,7,8 the clinical application of self-measurement requires the use of validated and properly calibrated devices (excluding error-prone wrist devices), patient education, a standardized protocol, at least 3 days of observation,37,38 a printed or electronic report of the readings, and medical supervision. We scheduled self-measurement during the week preceding clinic visits because BP responses to changes in antihypertensive treatment reach their full magnitude only after several days to weeks and because home BP and office BP measurements taken within a short interval are less likely to be confounded by factors affecting the long-term BP variability and can therefore be more readily compared.

In conclusion, adjustment of antihypertensive treatment based on home BP instead of office BP led to less-intensive drug treatment and marginally lower costs but also to less BP control, with no differences in general well-being or left ventricular mass. Self-measurement helps to identify patients with white-coat hypertension. Our findings support a stepwise strategy for the evaluation of BP in which self-measurement and ambulatory monitoring are complementary to conventional office measurement. They highlight the need of prospective studies to establish the normal range of home BP, including the operational thresholds at which drug treatment should be instituted or can be discontinued. Until such prospective data become available, management of hypertension exclusively based on home BP cannot be recommended.

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Author Contributions: Dr Staessen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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TREATMENT BASED ON HOME VS OFFICE BLOOD PRESSURE MEASUREMENT

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