Ambulatory Monitoring Uncorrected for Placebo Overestimates Long-term Antihypertensive Action

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Abstract This study compares blood pressure (BP) changes during active antihypertensive treatment and placebo as assessed by conventional and ambulatory BP measurement. Older patients (≥60 years, n=337) with isolated systolic hypertension by conventional sphygmomanometry at the clinic were randomized to placebo or active treatment consisting of nitrendipine (10 to 40 mg/d), with the possible addition of enalapril (5 to 20 mg/d) and/or hydrochlorothiazide (12.5 to 25 mg/d). At baseline, clinic systolic/diastolic BP averaged 175/86 mm Hg and 24-hour and daytime ambulatory BPs averaged 148/80 and 154/85 mm Hg, respectively. After 13 months (median) of active treatment, clinic BP had dropped by 22.7/7.0 mm Hg and 24-hour and daytime BPs by 10.5/4.5 and 9.7/4.3 mm Hg, respectively ($P<.001$ for all). However, clinic (9.8/1.6 mm Hg), 24-hour (2.1/1.1 mm Hg), and daytime (2.9/1.0 mm Hg) BPs decreased also during placebo ($P<.05$, except for daytime diastolic BP); these decreases represented 43%/23%, 20%/24%, and 30%/23% of the corresponding BP fall during active treatment. After subtraction of placebo effects, the net BP reductions during active treatment averaged only 12.9/5.4, 8.3/3.4, and 6.8/3.2 mm Hg for clinic, 24-hour, and daytime BPs, respectively. The effect of active treatment was also subject to diurnal variation ($P<.05$). Changes during placebo in hourly systolic and diastolic BP means amounted to (median) 21% (range, −1% to 42%) and 25% (−3% to 72%), respectively, of the corresponding changes during active treatment. In conclusion, expressed in millimeters of mercury, the effect of antihypertensive treatment on BP is larger with conventional than with ambulatory measurement. Regardless of whether BP is measured by conventional sphygmomanometry or ambulatory monitoring, a substantial proportion of the long-term BP changes observed during active treatment may be attributed to placebo effects. Thus, ambulatory monitoring uncorrected for placebo or control observations, like conventional sphygmomanometry, overestimates BP responses in clinical trials of long duration. (***Hypertension.* 1996;27[part 1]:414-420.**)

Key Words • blood pressure monitoring, ambulatory • antihypertensive therapy • clinical trials • blood pressure monitoring • placebo

The SYST-EUR Trial is a double-blind, placebo-controlled outcome trial in older patients with isolated systolic hypertension that the European Working Party on High Blood Pressure in the Elderly is currently conducting in Western and Eastern Europe and in Israel.[1] Presently, the 3000 patients originally planned for have been randomized. In accordance with current clinical practice,[2] only conventional sphygmomanometric BP readings by an auscultating observer determine a patient's eligibility for randomization and guide the stepwise adjustments of treatment during the double-blind phase of the trial.[1]

In addition to conventional sphygmomanometry, ambulatory BP monitoring is increasingly used in clinical trials to evaluate the magnitude and duration of the BP-lowering action of antihypertensive agents. SYST-EUR centers can opt to monitor their patients in an attempt to evaluate whether the ambulatory BP, over and above the clinic BP, is helpful in predicting cardiovascular events.[3] This article builds on the data collected so far in the SYST-EUR Trial[1] and contrasts the effects of antihypertensive treatment and placebo as assessed by conventional sphygmomanometry and ambulatory monitoring. It extends the findings of a previous article that was limited to the placebo arm of the trial.[4]

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Methods

Study Design

The protocol of the SYST-EUR Trial has been published elsewhere.[1] It was approved by the Ethics Committee of the Faculty of Medicine at the University of Leuven as well as by the institutional review committees of all participating centers. Patients were eligible (1) if they were at least 60 years old; (2) if, on a placebo during the run-in phase, their sitting SBP ranged from 160 to 219 mm Hg with a DBP below 95 mm Hg; (3) if their standing SBP was 140 mm Hg or higher; and (4) if, after having been informed, they voluntarily consented to be enrolled. The BP criteria for entry rested on the averages of six sitting and six standing readings, ie, two in each position at three baseline visits 1 month apart.

Eligible patients were stratified by sex and the presence versus absence of cardiovascular complications and were randomized to double-blind treatment with active medication or placebo. Active treatment consisted of nitrendipine (10 to 40 mg/d), combined with enalapril (5 to 20 mg/d) and/or hydrochlorothiazide (12.5 to 25 mg/d) if necessary. The patients of the control group received matching placebos. The study medication was stepwise titrated and combined in an attempt to reduce the sitting SBP by 20 mm Hg or more to a level of less than 150 mm Hg.[1]

Selected Abbreviations and Acronyms

BP = blood pressure
DBP = diastolic blood pressure
SBP = systolic blood pressure
SYST-EUR = Systolic Hypertension in Europe

BP and Other Measurements

SYST-EUR centers opting to take part in ambulatory monitoring were asked to perform recordings at baseline, at 6 and 12 months, and annually thereafter.[3] Validated[5,6] monitors were programmed to obtain measurements at intervals not greater than 30 minutes. The conventional BP corresponding to each ambulatory recording was the average of the two readings with patients in the sitting position obtained at the nearest clinic visit.

The patients were interviewed at baseline and follow-up concerning their smoking habits, habitual alcohol intake, and activities of daily living.[7,8] In addition, the serum activity of γ-glutamyltranspeptidase was determined as an index of alcohol intake.[9]

Analysis of the Diurnal BP Profile

If the ambulatory recordings were longer than 24 hours, only the first 24 hours was used for analysis. Recordings were excluded whenever the available readings constituted less than 80% of those programmed or covered less than 22 consecutive hours. The editing criteria[10,11] considered for deletion of readings from the recordings were (1) SBP<DBP, (2) SBP >240 or <40 mm Hg, (3) DBP >140 or <40 mm Hg, (4) pulse rate >150 or <40 beats per minute, and (5) pulse pressure <10% of SBP. The 24-hour, daytime, and nighttime pressures and hourly BP means were weighted for the time between consecutive readings.[12]

Daytime was from 10 AM to 8 PM and nighttime from midnight to 6 AM. These definitions of daytime and nighttime have been used in previous studies[10,13] and exclude the transition periods in the morning and evening during which BP changes rapidly. The awake and sleeping periods were determined from diary cards kept by the patients on recording days.[3]

Statistical Analysis

Database management and statistical analyses were performed with the SAS software (SAS Institute Inc).

Statistical methods included Student's t test and linear regression analysis. Diurnal BP profiles, drawn from hourly BP means, were contrasted by repeated measures ANOVA,[14] considering as main effects treatment allocation (active versus placebo) and time of day. For establishment of whether the antihypertensive action was steady over 24 hours, the model also tested for a treatment-time interaction. The net treatment effect, sometimes referred to as the double delta of BP,[15] was calculated by subtracting the mean change from baseline during placebo from the corresponding change during active treatment. The 95% confidence limits about the net treatment effect showed the times during the day when the BP reduction was significant.

The reproducibility of duplicate measurements was studied by the Bland and Altman technique.[16] For comparison of the reproducibility of various BP measurements, the repeatability coefficients were expressed as a percentage of nearly maximal variation, ie, the interval encompassing four times the SD of the averaged duplicate measurements.

Results

Data Available for Analysis

On May 15, 1995, 407 patients had their ambulatory BP recorded during the run-in phase of the trial and at least once after randomization. In 174 of these patients, duplicate recordings had been obtained at baseline. After patients with incomplete recordings were excluded, these numbers were 337 and 118, respectively.

The 792 ambulatory recordings included in the present analysis comprised a total of 51 960 single BP readings, of which only 1.5% complied with at least one of the criteria considered for editing. In 501 recordings (63%), no single reading met the editing criteria. Because editing did not influence the results, only analyses based on unedited recordings are presented.

Patient Characteristics at Randomization

The patients allocated to placebo (n=169) and active treatment (n=168) had the same characteristics at randomization. They comprised 142 men and 195 women. Cardiovascular complications were present in 94 patients. Of the 337 patients, 167 had been treated during the 6 months before they were considered for entry into the trial, 30 with diuretics, 19 with β-blockers, 21 with converting enzyme inhibitors, 33 with calcium entry blockers, and 64 with various other drugs or with a combination of several antihypertensive agents. Previous antihypertensive treatment was usually discontinued 1 month before the first run-in visit during placebo. The median time interval between the latter visit and randomization was 76 days (range, 36 to 300) in the previously treated patients and 70 days (range, 20 to 300) in the other patients.

In all 337 patients, age averaged 70±6 (±SD) years (range, 60 to 100). Body mass index was 26.1±3.3 kg/m^2 in men and 26.5±4.0 kg/m^2 in women. SBP at the clinic averaged 175±12 mm Hg (range, 160 to 217) and DBP 86±6 mm Hg (range, 49 to 94). The corresponding 24-hour pressures were 148±16 mm Hg (range, 110 to 202) and 80±9 mm Hg (range, 58 to 138), respectively. Daytime versus awake and nighttime versus sleeping SBP and DBP did not differ (Table 1).

Reproducibility of Clinic and Ambulatory Pressures at Baseline

In 118 patients, ambulatory monitoring had been repeated during the run-in phase of the trial at a median interval of 33 days (range, 7 to 127). Reproducibility of

TABLE 1. Conventional and Ambulatory BPs at Baseline and Median Follow-up of 1 Year

	Baseline		Follow-up	
	Placebo (n=169)	Active (n=168)	Placebo (n=169)	Active (n=168)
SBP				
Clinic	175±11	175±13	165±20	153±17
24-Hour	148±15	148±15	146±16	138±14
Daytime	154±16	154±17	151±17	144±16
Nighttime	136±17	137±19	134±18	126±16
Awake	154±16	153±16	151±16	143±15
Sleep	136±17	137±19	135±18	126±15
DBP				
Clinic	86±6	85±6	85±9	78±10
24-Hour	80±9	79±8	79±9	75±8
Daytime	85±10	84±10	84±10	80±9
Nighttime	71±10	70±10	70±10	66±11
Awake	85±10	84±9	83±10	79±9
Sleep	71±10	70±10	71±10	66±10

Daytime is 10 AM to 8 PM, and nighttime is midnight to 6 AM. Values are mean±SD and expressed in mm Hg.

the clinic pressure was studied by contrasting the averages of the two readings obtained with patients in the sitting position at two outpatient visits. Group means of the clinic and ambulatory pressures could be reproduced without significant changes in their values, except for the 24-hour, daytime, and awake SBP, which decreased ($P<.05$) by approximately 2 mm Hg, and for the awake DBP, which decreased ($P<.05$) by 1 mm Hg (Table 2).

The intraindividual reproducibility of BP level was studied by expressing the repeatability coefficients as a percentage of nearly maximal variation. On this relative scale, the clinic pressures showed higher repeatability coefficients, signifying lower reproducibility, than the 24-hour, daytime, and awake pressures and to a lesser extent than the nighttime and sleeping pressures (Table 2).

Treatment Effects on Clinic and Ambulatory Pressures

Follow-up averaged 13 months (median) (range, 4 to 30). Of the 337 patients, 310 remained on the first-line medication, ie, nitrendipine (n=151; daily dose, 27±12 mg) or matching placebo (n=159). At the follow-up visit, second- and third-line medications had been started in 49 (14±7 mg) and 21 (22±6 mg) patients on active treatment and in 84 and 47 patients on placebo.

Active treatment decreased the clinic and ambulatory SBP and DBP, but also during placebo these pressures tended to decline (Table 3, Fig 1). The decreases in the clinic, 24-hour, daytime, and awake SBPs during placebo represented 43%, 20%, 24%, and 30% of the corresponding changes during active treatment; for DBP, these values amounted to 23%, 24%, 23%, and 23% (Fig 2). After subtraction of the BP changes in the placebo group, the net BP reductions during active treatment averaged 12.9 mm Hg for the clinic SBP and 8.3, 6.8, and 7.6 mm Hg for the 24-hour, daytime, and awake SBPs, respectively (Table 3); the corresponding net reductions in DBP amounted to 5.4, 3.4, 3.2, and 3.5 mm Hg.

TABLE 2. Reproducibility of Clinic and Ambulatory BP Levels in 118 Patients

	Change	Consistency	Repeatability
Clinic			
SBP	−0.3	9.0 (0, 50)	31 (50%)
DBP	−1.0	4.3 (0, 21)	15 (52%)
24-Hour			
SBP	−1.8*	5.5 (0, 31)	17 (28%)
DBP	−0.6	3.1 (0, 22)	11 (29%)
Daytime			
SBP	−2.4*	6.3 (0, 34)	21 (33%)
DBP	−1.1	4.7 (0, 19)	14 (35%)
Nighttime			
SBP	−1.4	7.3 (0, 73)	27 (40%)
DBP	−0.1	4.1 (0, 24)	14 (35%)
Awake			
SBP	−2.4*	5.8 (0, 34)	18 (28%)
DBP	−1.1*	3.6 (0, 17)	12 (29%)
Sleep			
SBP	−1.6	5.5 (0, 57)	23 (34%)
DBP	−0.4	3.7 (0, 23)	13 (33%)

Values are expressed in mm Hg. Change shows the mean difference between duplicate recordings (second minus first recording), taking into account the sign of the difference. Consistency shows the median difference between duplicate recordings, disregarding the sign of the difference (range in parentheses). Repeatability shows twice the SD of the changes between repeated recordings (percentage of nearly maximal variation between parentheses; see "Methods" for further explanation).
*$P<.05$.

In the two treatment groups, the regression slopes of the 24-hour pressures at follow-up (fu) versus those at baseline (b) were significantly ($P<.001$) smaller than unity. In the placebo group, the regression equations were $SBP_{fu}=35.8+0.74\ SBP_b$ ($r=.72$) and $DBP_{fu}=23.3+0.70\ DBP_b$ ($r=.73$); in the patients allocated to active treatment, the equations were $SBP_{fu}=59.5+0.53\ SBP_b$ ($r=.59$) and $DBP_{fu}=33.2+0.52\ DBP_b$ ($r=.53$). These equations indicated that in absolute terms, ie, in millimeters of mercury, the 24-hour SBP and DBP decreased more in patients with higher whole-day pressures at baseline.

Over the follow-up period, no significant changes occurred in the patients' body weight (mean change±SD, −0.1±3.4 kg), smoking habits (−0.6±5.3 g tobacco per day), alcohol intake (−0.6±5.3 g/d), serum γ-glutamyltranspeptidase activity (−0.1±0.19%), and score for the activities of daily living (median change, 0; range, −5 to +1). Modifications over the follow-up period in these lifestyle measures and previous antihypertensive treatment were not correlated with the decrease in the ambulatory BP values in the placebo group. The changes in body weight constituted the only possible exception because they tended to be positively associated with the changes in the 24-hour DBP (regression coefficient±SE, 0.29±0.16 mm Hg/kg; $P=.07$) and in the daytime (0.38±0.20 mm Hg/kg, $P=.08$) and nighttime (0.35±0.19 mm Hg/kg, $P=.07$) DBPs.

Treatment Effects on Diurnal BP Profiles

At both baseline and follow-up, time of day was a significant ($P<.001$) source of BP variation. At baseline, treatment allocation ($P=.96$ for SBP, $P=.39$ for DBP) as well as the interaction terms between treatment and time of day were not significant ($P=.75$ and .40, respectively). These results confirmed that during the run-in phase, the diurnal BP profiles were superimposable in the two treatment arms of the trial (Fig 1).

At follow-up, active treatment shifted ($P<.001$) the diurnal BP profile downward (Fig 1). Moreover, for both SBP ($P=.05$) and DBP ($P=.03$), the treatment-time interaction was significant, indicating that the net treatment effect was subject to diurnal variation (Fig 3). If the changes in the hourly BP means in the patients on placebo were expressed as a percentage of the corresponding changes during active treatment, these averaged (median) 21% for SBP and 25% for DBP (range, −1% to 42% and −3% to 72%, respectively) (Fig 2).

Disparity Between Clinic and Ambulatory Measurements

At baseline, the correlation coefficients between the clinic and daytime measurements were .46 for SBP and .39 for DBP. The corresponding correlation coefficients at follow-up were .57 and .49 in the placebo group and .32 and .35 during active treatment ($P<.001$ for all correlations). Clinic SBP was on all occasions higher ($P<.001$) than daytime SBP, ie, 21±15 mm Hg at baseline, 14±17 mm Hg during placebo at follow-up, and 9±19 mm Hg during active treatment. In contrast, the mean differences between the clinic and daytime DBPs were small, averaging 1±10 mm Hg at baseline as well as during placebo at follow-up and −2±11 mm Hg during active treatment.

Discussion

After approximately 1 year, the net separation in the clinic pressure between the two treatment groups aver-

TABLE 3. BP Changes During Placebo and Active Treatment and Net Treatment Effects After Median Follow-up of 13 Months

	Placebo (n=169)	Active Treatment (n=168)	Net Effect (n=337)
SBP			
Clinic	−9.8 (−12.2, −7.4)‡	−22.7 (−25.1, −20.3)‡	12.9 (9.2, 16.7)‡
24-Hour	−2.1 (−3.8, −0.4)*	−10.5 (−12.4, −8.5)‡	8.3 (5.8, 10.8)‡
Daytime	−2.9 (−5.1, −0.6)*	−9.7 (−11.9, −7.4)‡	6.8 (3.5, 10.2)‡
Nighttime	−1.5 (−3.3, +0.3)	−10.9 (−13.4, −8.5)‡	9.5 (6.0, 13.0)‡
Awake	−2.4 (−4.6, −0.3)*	−10.1 (−12.2, −7.9)‡	7.6 (4.6, 10.6)‡
Sleep	−1.2 (−3.1, +0.6)	−11.5 (−13.9, −9.2)‡	10.3 (7.3, 13.3)‡
DBP			
Clinic	−1.6 (−2.8, −0.4)†	−7.0 (−8.3, −5.7)‡	5.4 (3.9, 6.8)‡
24-Hour	−1.1 (−2.1, −0.1)*	−4.5 (−5.7, −3.3)‡	3.4 (2.2, 4.7)‡
Daytime	−1.0 (−2.3, +0.2)	−4.3 (−5.7, −2.9)‡	3.2 (1.7, 4.8)‡
Nighttime	−1.1 (−2.3, +0.1)	−4.2 (−5.7, −2.6)‡	3.1 (1.5, 4.7)‡
Awake	−1.1 (−2.3, +0.1)	−4.7 (−6.0, −3.3)‡	3.5 (1.7, 5.3)‡
Sleep	−1.0 (−2.2, +0.2)	−4.5 (−6.0, −3.0)‡	3.5 (1.6, 5.5)‡

Daytime is 10 AM to 8 PM, and nighttime is midnight to 6 AM. Values are means, with 95% confidence intervals in parentheses. Within-group BP changes were calculated by subtracting run-in from follow-up measurements. Net treatment effects are the differences between the average BP changes during placebo and those during active treatment.
*$P<.05$, †$P<.01$, ‡$P<.001$.

aged 12.9 mm Hg for SBP and 5.4 mm Hg for DBP. These observations confirm earlier interim reports on the SYST-EUR Trial.[17,18] They are also in keeping with the Systolic Hypertension in the Elderly Program (SHEP) results.[19] The patients in this American outcome trial had an entry SBP ranging from 160 to 219 mm Hg, but their DBP was less than 90 mm Hg. The net treatment effect in the SHEP Trial after 1 year of follow-up averaged 14.0 mm Hg for SBP and 3.9 mm Hg for DBP.[19]

Approximately one third of the patients enrolled in the SYST-EUR Trial undergo ambulatory monitoring, in addition to conventional sphygmomanometry. The net separation between the two treatment arms after a median follow-up of approximately 1 year was considerably smaller for the ambulatory than for the clinic pressures, ie, 4.9/2.0 mm Hg less for the 24-hour pressures and 6.1/2.2 mm Hg less for the daytime pressures. Thus, the differentiation in the clinic pressures between the two treatment groups was 55%/59% larger than observed for the 24-hour pressures and 90%/69% larger than for the daytime pressures. The view[20,21] currently prevails that ambulatory recordings more closely reflect a patient's habitual BP level than the few readings taken by an auscultating observer in the stressful hospital environment.[22,23] The present study therefore suggests that the true BP responses in a long-term randomized clinical trial are overestimated by conventional sphygmomanometry by as much as 50% to 90%. The latter estimate is in agreement with a large meta-analysis of prospective observational studies in the field of hypertension.[24] A correction for regression dilution bias was calculated by introducing the so-called usual BP, defined as an individual's average BP over several years. According to these calculations,[24] a 12 mm Hg difference in the baseline pressure was rescaled into a 7.5 mm Hg contrast in the usual pressure. Thus, BP measurements at a single occasion (baseline) were felt to inflate the gradient in the usual pressure by approximately 60%.

BP measurements by conventional sphygmomanometry have guided patient recruitment and therapy in most clinical trials in the field of hypertension, including all outcome trials.[25] Despite their track record, conventional BP readings are subject to the so-called placebo effect, often attributed to a gradual weakening of the alerting reaction[22,23] and to a regression-to-the-mean phenomenon.[26-29] If conventional and ambulatory measurements are repeated within the same subjects, the latter are characterized by greater reproducibility,[26-28] attributable to the absence of digit preference,[30] ob-

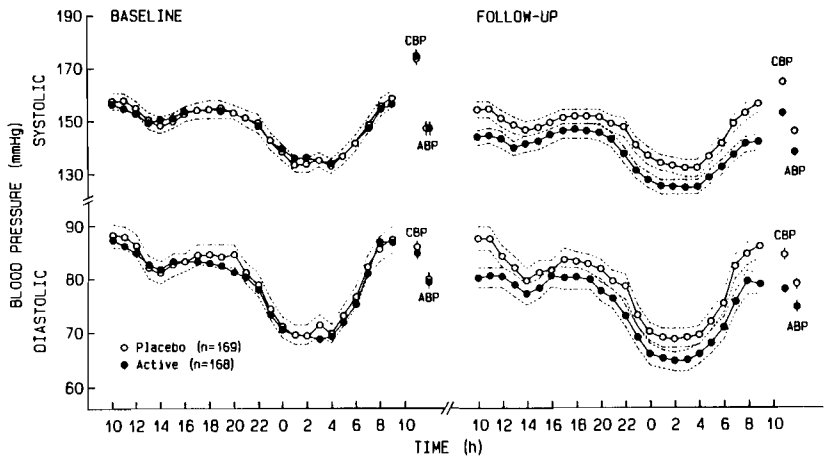

FIG 1. Hourly means of SBP (top) and DBP (bottom) and average conventional (CBP) and 24-hour (ABP) pressures at baseline (left, open symbols) and after a median follow-up of 1 year (right, closed symbols). Means are expressed with 95% confidence interval.

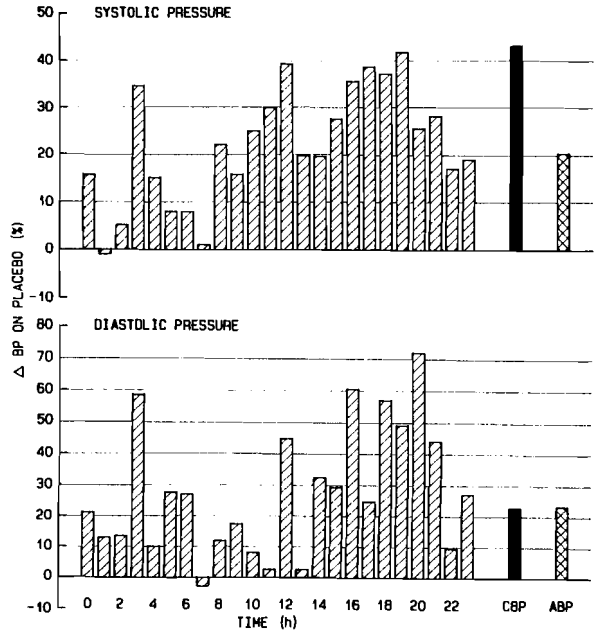

FIG 2. Changes in SBP (top) and DBP (bottom) observed after 1 year of placebo but expressed as a percentage of the corresponding BP changes during active treatment. Results are presented for 1-hour intervals through the day and for the average conventional (CBP) and 24-hour (ABP) pressures.

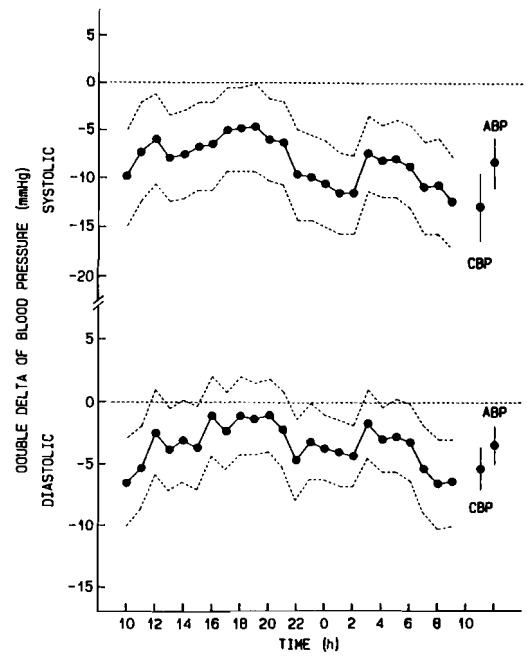

FIG 3. Net effect of treatment on SBP (top) and DBP (bottom) through the day (1-hour intervals) and on the average conventional (CBP) and 24-hour (ABP) pressures. Values, with 95% confidence interval, were computed by subtracting the mean change from baseline during placebo from the corresponding change during active treatment.

server bias,[30] and the white coat reaction[22,23,31] but foremost to the greater number of readings averaged for calculation of the ambulatory values.[32] This was confirmed in the present study, in which the clinic pressures during the placebo run-in period showed higher repeatability coefficients, signifying lower intraindividual reproducibility, than the 24-hour and daytime pressures.

Debate continues over whether ambulatory BP measurements decrease during placebo. The intra-arterially measured ambulatory pressure has been demonstrated to remain at the same level when hypertensive patients were put on a placebo for 6 weeks.[33] Along similar lines, in a 6-week study with a noninvasive recording technique,[34] the ambulatory pressure fell only slightly during the initial recording hours, such that the average BP over 24 hours stayed unaffected. On balance, most publications currently favor the view that the ambulatory pressure is not subject to a placebo effect.[13,18,26-29,33-45] However, few long-term studies on this subject have been published. A previous SYST-EUR publication[4] based on 112 patients and limited to the placebo arm of the trial showed that after a median follow-up of 1 year the clinic SBP fell by 6.6 mm Hg ($P<.001$) and the 24-hour and daytime SBPs by 2.4 ($P<.05$) and 2.6 mm Hg ($P=.06$), respectively. The corresponding decreases in DBP were smaller, averaging only 1.4 ($P=.06$), 1.1, and 0.7 mm Hg.[4] These estimates were of the same order of magnitude as in the present analysis, in which, because of the larger number of patients, the changes during placebo in the clinic and 24-hour DBPs also reached a level of statistical significance.

The decline in the ambulatory BP values, amounting to approximately 2 mm Hg, may seem trivial and negligible. However, in relative terms they represented 43%/23%, 20%/24%, and 30%/23% of the corresponding reductions in the clinic, 24-hour, and daytime SBPs/DBPs during active treatment. As far as the clinic pressure is concerned, the thesis that BP changes in a randomized clinical experiment need to be corrected for control observations, eg, during placebo, cannot be refuted and is part of the established culture among trialists. If this rule is true for the clinic pressure, then in opposition to the prevailing view in the literature,[13,18,26-29,33-45] it also needs to be applied for the ambulatory pressure, of which a substantial fraction may be explained by placebo-like effects. This reasoning not only involves the average 24-hour and daytime pressures but also the hourly BP means, which represent the treatment effects through the whole day. In the present study, the decreases in the hourly BP values during placebo constituted up to 70% of what was observed during active treatment.

In the present study, the reduction in the clinic SBP during placebo may have been influenced by the 160 mm Hg threshold used to select the patients and by a subsequent regression-to-the-mean phenomenon. However, other mechanisms are also likely to have been at play because decreases during placebo were observed in the clinic DBP, which in all patients was lower than 95 mm Hg, as well as in the ambulatory measurements, which were not used to select the patients. Familiarization with the hospital environment or the procedure of ambulatory monitoring could be examples of such mechanisms. In addition, the present analysis demonstrated that changes in lifestyle were unlikely to be involved to a major extent.

The clinic SBP was 21 mm Hg higher than the daytime pressure at baseline but only 14 and 9 mm Hg higher at follow-up during placebo and active treatment, respectively. These findings suggest that the white coat effect wears off as time goes by. It may also be attenuated by antihypertensive treatment, which probably dampens the BP surges caused by sympathetic arousal to the

observer measuring the BP. Furthermore, the decreases in the ambulatory measurements during placebo and active treatment were proportional to the BP level at baseline. The regression equations derived in the present study predicted that the 24-hour SBP would decrease by only 3.0 mm Hg during active treatment in patients whose 24-hour SBP at entry was 135 mm Hg, ie, the 95th percentile in normotensive subjects.[46] Thus, in agreement with a previous report,[47] prescribing antihypertensive medications to patients with a high clinic but low ambulatory pressure would not result in a substantial reduction of the habitual BP through the day.

The issue of whether ambulatory measurements need to be corrected for placebo is not without importance, as it inherently touches on the design of clinical trials in the field of hypertension. Some experts[48] feel that ambulatory monitoring eliminates only observer bias and expectation[49] and does not remove regression-to-the-mean and patient-related factors that contribute to the placebo effect. Other researchers defend the point of view that ambulatory monitoring would make control observations during placebo superfluous.[50] If this were true, trials making use of the new technique could investigate antihypertensive interventions just by comparing the BP levels before and after therapy. The present findings suggest that the latter approach may lead to an overestimation of the true antihypertensive effect and should therefore be abandoned at least in long-term trials. A correction for placebo may even be warranted in short-term trials because the reproducibility data in this study showed that after a median interval of 1 month the average 24-hour and daytime SBPs decreased during placebo by 1.8 and 2.4 mm Hg, respectively. Thus, clinical trials relying on ambulatory monitoring should adhere to the same design standards as those making use of conventional sphygmomanometry. Despite these limitations, ambulatory monitoring, compared with conventional BP readings, offers the advantage of providing information on BP control through the whole day and makes it possible to economize on sample size in cross-over but not parallel group trials.[51]

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