

Clinical trials with ambulatory blood pressure monitoring: fewer patients needed?

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Summary

We have tested the concept that fewer patients are needed in trials of antihypertensive treatment if blood pressure is measured by ambulatory monitoring rather than by conventional sphygmomanometry.

233 patients (≥ 60 years old) with isolated systolic hypertension were randomly allocated placebo ($n=119$) or active treatment ($n=114$). Blood pressure measurements were compared by Wilcoxon's test and blood pressure profiles by ANOVA. With either method of measurement, the same number of patients (40 in each treatment group) was required to show a reduction after 1 year in clinic (13/8 mm Hg) or average blood pressure over 24 h (9/5 mm Hg). To detect that the decrease in systolic pressure was not steadily maintained through the day, 40 patients in each treatment group were needed for blood pressure profiles made up of 4-hourly or 2-hourly means and 60 for profiles of 1-hourly means. For diastolic pressure, the corresponding numbers were 80, 100, and more than the number of available patients, respectively.

We conclude that parallel group trials focusing on the average blood pressure over 24 h, rather than on conventionally measured blood pressure, cannot economise on sample size. Moreover, trials studying the full course of blood pressure throughout the day, require more—not fewer—patients than studies of only the conventional or average 24 h blood pressure.

Lancet 1994; **344**: 1552–56

Introduction

The search for long-acting antihypertensive agents is on, because once-daily dosing is thought to enhance patient compliance.^{1,2} Ambulatory monitoring is often used to prove that a once-daily regimen controls blood pressure over 24 h. A 1991 consensus document suggested that clinical trials could economise on sample size if antihypertensive treatment were assessed by ambulatory rather than by conventional blood pressure measurement.³ In view of the variability of the diurnal blood pressure curve,^{4,5} we have tested this idea by analysis of ambulatory recordings from patients with isolated systolic hypertension who had been enrolled in the Syst-Eur Trial.^{6,7}

Methods

Study design

The protocol of the Syst-Eur Trial has been described elsewhere.⁶ Eligible patients were at least 60 years old and had on placebo treatment systolic pressure when seated of 160–219 mm Hg and diastolic pressure below 95 mm Hg as well as systolic pressure on standing of 140 mm Hg or more. These blood pressure criteria were based on the averages of six seated and six standing readings (two in each position at three baseline visits with intervals of 1 month).

After stratification by sex and the presence or absence of cardiovascular complications, patients were randomly assigned double-blind treatment with active medication or placebo. Active treatment consisted of nitrendipine (10–40 mg per day), combined with enalapril (5–20 mg per day) or hydrochlorothiazide (12.5–25.0 mg per day), or both. Patients in the control group received matching placebos. The study medication was titrated in a stepwise manner and combined to reduce the systolic pressure when seated by 20 mm Hg or more to 150 mm Hg or lower.⁶

Ambulatory monitoring

Syst-Eur centres opting to take part in ambulatory monitoring were asked to make recordings at baseline, at 6 and 12 months, and annually thereafter.⁷ Validated^{8,9} monitors were programmed to obtain measurements with intervals no greater than 30 min. The clinic pressures corresponding to the recordings were the averages of the seated measurements (ie, six readings at baseline and two at follow-up).

For this analysis, 251 patients were selected because their ambulatory pressure had been recorded before and after randomisation. The recording nearest to the 1-year follow-up visit was chosen for analysis. Of the 251 patients, 18 were excluded because the baseline or follow-up registration did not cover 24 h or consisted of 1 h intervals without valid readings.

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	Baseline		Follow-up	
	Placebo (n=119)	Active (n=114)	Placebo (n=119)	Active (n=114)
Systolic pressure				
Clinic	175 (12)	178 (14)	168 (21)	155 (18)*
24 h	150 (15)	150 (16)	149 (15)	139 (14)*
Day	155 (16)	155 (17)	153 (17)	146 (16)*
Night	138 (16)	138 (19)	137 (17)	126 (17)*
Diastolic pressure				
Clinic	86 (7)	85 (6)	85 (9)	77 (10)*
24 h	81 (10)	80 (10)	80 (10)	75 (10)*
Day	85 (11)	85 (11)	84 (11)	80 (11)*
Night	72 (11)	70 (13)	70 (11)	65 (13)*

Values are mean (SD).

Daytime=1000-2000 h; night-time=0000-0600 h.

*p<0.01 for difference between baseline and follow-up.

Table 1: Effect of treatment on conventionally measured and ambulatory blood pressure

Statistical analysis

If ambulatory recordings were longer than 24 h, only the first 24 h was used for analysis, but the recordings stayed unedited. Diurnal profiles were drawn by averaging blood pressure over 1 h, 2 h, or 4 h periods. The 24 h, daytime, and night-time pressures were weighted for the time between consecutive readings.¹⁰ As a consequence of patient selection, the distribution of the clinic pressure was truncated; Wilcoxon's test was therefore used to compare blood pressures. The diurnal blood pressure profiles were contrasted by repeated measures ANOVA,¹¹ with treatment allocation (active vs placebo) and time of day as main effects. To establish whether the antihypertensive action was steady over 24 h, the model also tested for a treatment-time interaction. To find out whether the results would be different in patients with raised 24 h pressure, we repeated the analyses for only subjects with 24 h systolic pressures above 133 mm Hg, the 95th percentile in normotensive subjects.¹²

The net treatment effect, the double-delta of pressure,¹¹ was calculated by subtracting the mean change from baseline on placebo from the corresponding change on active treatment. The 95% CI about the net treatment effect showed the times during the day when the pressure reduction was significant.

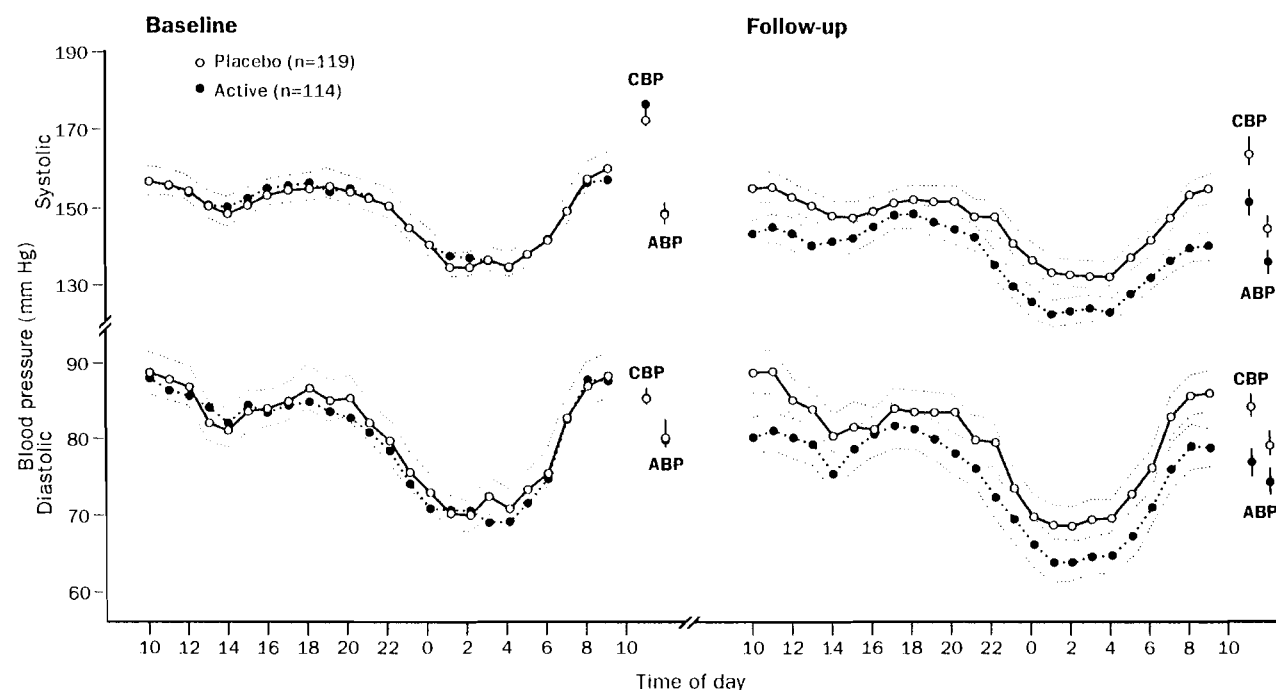


Figure 1: Hourly means (with 95% CI) of systolic and diastolic pressure and average conventional (CBP) and 24 h pressure (ABP) at baseline and follow-up

	p value from ANOVA					
	Baseline			Follow-up		
	1 h	2 h	4 h	1 h	2 h	4 h
Systolic pressure						
Treatment	0.90	0.90	0.93	<0.001	<0.001	<0.001
Treatment-time	0.63	0.80	0.81	0.01	<0.001	<0.001
Diastolic pressure						
Treatment	0.52	0.51	0.48	<0.001	<0.001	<0.001
Treatment-time	0.49	0.85	0.76	0.06	0.006	<0.001

Table 2: ANOVA of diurnal blood pressure profiles—treatment allocation, time of day, and treatment-time interaction

Finally, power calculations were done empirically by random selection of 20, 40, 80, or 100 patients from each treatment group. For each subset of patients, the probability value was calculated for the net reduction in the conventional and 24 h pressure, as well as for the treatment-time interaction.

Results

The 233 participants (84 men, 149 women) had a mean age of 71 years (SD 6; range 60–100). At baseline, the mean conventionally measured systolic blood pressure was 176 (13; 160–217) mm Hg and diastolic 86 (6; 49–94) mm Hg; the 24 h pressures were 150 (15; 110–202) mm Hg and 81 (10; 58–138) mm Hg, respectively.

After median follow-up of 12 (4–25) months, active treatment had decreased the clinic, 24 h, daytime, and night-time blood pressure values ($p<0.01$, table 1). Of the 233 patients, 215 remained on the first-line medication—ie, nitrendipine ($n=102$; daily dose 29 [12] mg) or matching placebo ($n=113$). Second-line and third-line medications were started in 39 (14 [7] mg) and 21 subjects (20 [6] mg) on active treatment, and in 61 and 34 placebo-treated patients.

Diurnal profiles

Both at baseline and at follow-up, time of day was a significant source ($p<0.001$) of blood pressure variation.

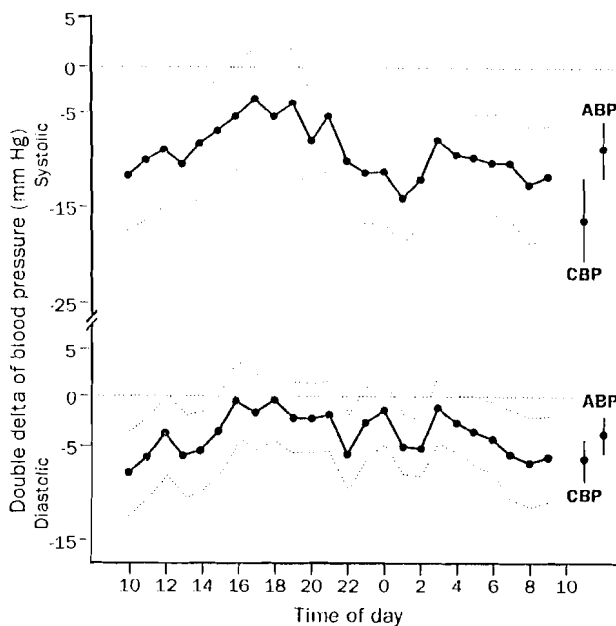


Figure 2: Net effect of treatment on systolic and diastolic blood pressure during the day (1 h intervals) and on average conventional (CBP) and 24 h blood pressure (ABP). Double delta=change from baseline on active treatment minus change from baseline on placebo.

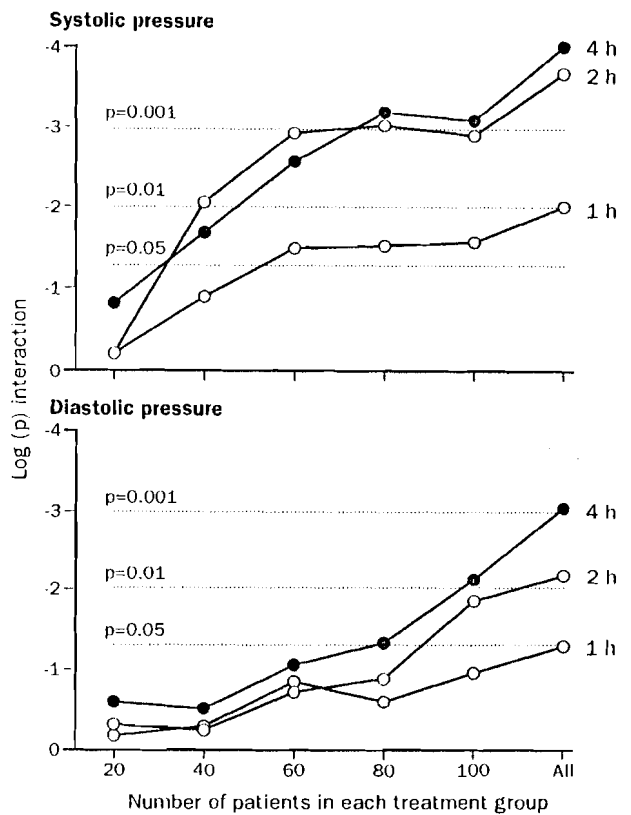


Figure 4: Probability of demonstrating at follow-up a significant treatment-time interaction for systolic and diastolic pressure.

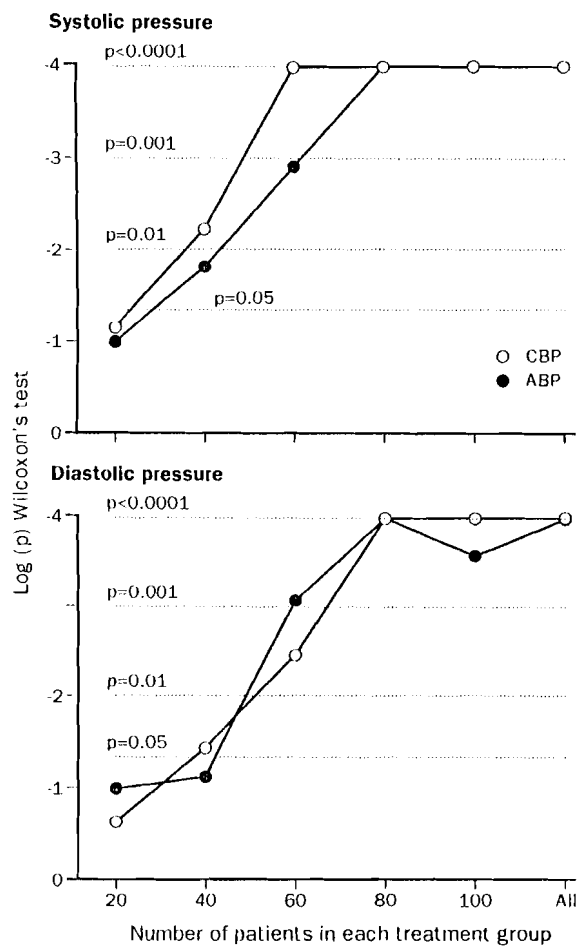


Figure 3: Probability of finding a significant effect of treatment on conventional blood pressure and 24 h systolic and diastolic blood pressure.

At baseline, the treatment-time interaction was not significant (table 2), which confirms that the diurnal profiles were the same in the two treatment groups (figure 1).

Active treatment reduced blood pressure during the day (figure 1). For systolic pressure, there was a significant treatment-time interaction irrespective of the time interval used for resolution of the profiles (table 2). For diastolic pressure, a significant interaction was observed only when the profiles were calculated from 2 h or 4 h measurements. Results were the same when the analysis was confined to the 205 patients with raised (>133 mm Hg) 24 h systolic pressure.

The size of the treatment-time interaction depended on the resolution of the diurnal profiles. With 1 h intervals (figure 2), the difference between the largest and smallest pressure reduction through the day averaged 10.7 mm Hg for systolic pressure (ie, 14.0 [1-2 h] vs 3.3 mm Hg [17-18 h]) and 7.6 mm Hg for diastolic pressure (ie, 8.0 [10-11 h] vs 0.4 mm Hg [16-17 h]). These differences averaged 8.5 and 6.0 mm Hg for profiles with 2 h intervals, and 7.3 and 5.9 mm Hg, respectively, for profiles with 4 h intervals.

Sample size

To show a net reduction ($p < 0.05$) in the conventional or 24 h pressure a sample of 40 subjects randomly selected from each group was sufficient. Compared with conventional measurements, 24 h monitoring did not confer any benefit in terms of a smaller sample size (figure 3).

The number of patients required to demonstrate a significant treatment-time interaction in systolic pressure rose from 40 in each treatment group for 2 h or 4 h intervals to 60 for 1 h intervals (figure 4). For diastolic

pressure, 80 patients in each treatment group sufficed for 4 h intervals and 100 for 2 h intervals, but for 1 h intervals, even all available patients were not adequate. Thus, the probability of finding a treatment-time interaction rose as the sample size increased and as the resolution of the profiles was smoothed from 1 h to 4 h.

Discussion

If conventional and ambulatory measurements are repeated within the same subjects, the latter are characterised by greater reproducibility.¹⁴⁻¹⁶ This effect can be explained by the absence of digit preference,¹⁷ observer bias,¹⁷ and the "white coat" reaction,¹⁸⁻²⁰ but mostly by the greater number of readings averaged to calculate the ambulatory values.²¹ Compared with equivalent trials that use conventional sphygmomanometry, the better within-subject reproducibility means that cross-over trials with ambulatory monitoring, in which the averages of at least twenty readings are being compared, need to enrol fewer patients than trials with conventional blood pressure measurement.¹⁴⁻¹⁶ Our findings in this study emphasise that, by contrast with what is often perceived,^{1,22} the advantage of the higher reproducibility of ambulatory monitoring is lost in trials with a parallel-group design when between-subject variability, rather than within-subject variability is driving the test statistic, and when effects on the full course of blood pressure through the day are being examined.

In trials with a parallel-group design, the same number of patients is required for comparisons of clinic or average 24 h pressure (figure 3). This finding is not surprising, because the 24 h blood pressure showed a similar SD to clinic measurements and a smaller reduction on active treatment (table 1). As a consequence of the criteria used for patient recruitment, the assumption of normality was violated for the clinic pressure, and the non-parametric Wilcoxon's rank-sum test was therefore used. However, our results (figure 3) could be duplicated with Student's *t* test, which assumes normality of the underlying distributions.

Trials on the comparison of effects on the full course of blood pressure during the day, for example, to find out the duration of action of antihypertensive drugs, should recruit more—not fewer—patients than studies in which only the clinic pressure or the average 24 h pressure is subject to investigation (figure 4). There is no standard approach for comparison of diurnal blood pressure profiles. Analysis of variance¹¹ has the advantage of accounting in the same model for treatment, time of day, and treatment-time interaction, which provides a straightforward test to explore whether the observed effects are steady over 24 h. If necessary, the model may also accommodate other factors, such as patient characteristics or the baseline pressure.

Many studies of antihypertensive drugs for which a once-daily dosing scheme is advocated rely on the demonstration that the mean 24 h blood pressure is reduced, but fail to prove that the reduction is maintained throughout the 24 h.²³ In fact, the latter can be verified only by measuring blood pressure regularly over 24 h, shorter intervals and more readings per interval resulting in greater precision. Most studies on long-acting calcium entry blockers have recruited fewer patients than found to be necessary in this study.²³ Readers unaware of this problem may mistakenly conclude that certain

antihypertensive agents, given once daily, lower blood pressure over 24 h. Ultimately, the power of a study to exclude a significant treatment-time interaction depends on the study design (cross-over *vs* parallel group), the number of subjects randomised, the time over which pressure readings have been averaged (eg, 1 *vs* 4 h), the number of readings averaged per interval, the standardisation of the measurement technique and the treatment regimen (eg, timing of drug intake), and the size of the treatment-time interaction that should be detectable (roughly the difference between the diurnal maximum and minimum pressure reduction). The technical aspects of the sample size calculations applicable to detect a treatment-time interaction by repeated measures ANOVA have been described elsewhere.²⁴

If a significant treatment-time interaction is detected, the diurnal pattern of blood pressure should be reviewed in more detail. In general, a baseline adjustment is thereby desirable, because diurnal profiles consist of highly variable blood pressure means.^{5,25} In this study, the baseline correction was carried out by subtracting the mean pressure change from baseline on placebo from the corresponding change on active treatment. Alternatively, a baseline adjustment can be made by entering the baseline pressure as a covariate in the model. Contrasts may also be generated between the blood pressure reduction at a given time (eg, the time of peak plasma concentration) and the blood pressure changes at all other times.

It has also been suggested that ambulatory monitoring may facilitate the conduct of clinical trials by the early identification and exclusion of subjects whose blood pressure is raised only in the clinic environment (white coat reactors).^{19,26} This feature may be especially important to trials with ambulatory monitoring, because in patients who have raised conventional blood pressure but normal¹² ambulatory pressure, antihypertensive treatment reduces only the former.^{27,28} Nevertheless, excluding the white coat reactors from our analysis did not affect the outcome.

In this study we found a difference between active and placebo treatment. Active treatment consisted of varying combinations of three different antihypertensive agents. Many reports concentrate on a single antihypertensive agent and attempt to find out its trough-to-peak ratio. Some regulatory agencies have proposed a desirable range for this ratio and recommend that it be adjusted for placebo effects.²⁹ Our findings show that the apparent trough-to-peak ratio can be manipulated by changing the resolution of the diurnal profile. Moreover, not only the point estimate of the ratio is relevant. Its error term and confidence interval are rarely reported, and yet reflect the precision by which advisory boards may need to be guided.

Trials setting out to identify effects on the full course of blood pressure through the day require more—certainly not fewer—patients than studies focusing only on the conventional or the average 24 h pressure.

The Syst-Eur Trial is carried out in consultation with the WHO, the International Society of Hypertension, the European Society of Hypertension, and the World Hypertension League. The trial committees and participating centres are listed in a progress report (*J Hum Hypertens* 1993; 7: 265-71). From 1991 to 1992, the European Union provided a grant for coordination at the European level. The trial is supported by Bayer AG (Wuppertal, Germany) and the National Fund for Scientific Research (Brussels, Belgium). Study medication is donated by Bayer AG and Merck Sharpe and Dohme Inc (West Point, Pennsylvania, USA).

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