Ambulatory pressure decreases on long-term placebo treatment in older patients with isolated systolic hypertension

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Objective: This long-term study investigated the widely accepted hypothesis that ambulatory pressure does not decrease in patients given placebo.

Methods: One hundred and twelve older (≥60 years) outpatients with isolated systolic hypertension were recruited. Treatment consisted of a placebo during a 3-month baseline period and long-term follow-up.

Results: At baseline, on placebo treatment, clinic systolic/diastolic (SBP/DBP) blood pressure (±SD) averaged 176±12/86±7 mmHg and 24-h SBP/DBP 151±15/81±10 mmHg. These pressures were unaltered in 51 patients in whom the baseline measurements were repeated after a further month on placebo. After the 112 patients had received placebo for 1 year (median), clinic SBP/DBP fell by 6.6±15.9 ($P<0.001$)/1.4±7.4 ($P=0.06$) mmHg and 24-h SBP by 2.4±10.7 mmHg ($P<0.05$), whereas 24-h DBP did not change significantly. The 24-h SBP decreased more with higher baseline level and longer follow-up (5–21 months).

Conclusions: These findings in older patients with isolated systolic hypertension suggest that in long-term studies the ambulatory pressure may slightly but significantly decrease on a placebo. Like those using conventional sphygmomanometry, long-term studies using non-invasive ambulatory monitoring require a placebo-controlled design.

Journal of Hypertension 1994, 12:1035–1039

Keywords: Ambulatory blood pressure, conventional blood pressure, placebo.

Introduction

Blood pressure measurements made by conventional sphygmomanometry have guided patient recruitment and therapy in most hypertension studies, including all outcome trials [1]. Despite their record, conventional blood pressure readings are subject to the so-called placebo effect [2], often attributed to a gradual weakening of the alerting reaction [3] and to a regression-to-the-mean phenomenon [4–7].

Ambulatory blood pressure monitoring attenuates the white-coat effect [3,8], and produces measurements that are more reproducible than those produced by conventional sphygmomanometry [5–7,9]. Intra-arterially measured ambulatory pressure did not alter when hyper-

Sponsorship: Coordination of the Syst-Eur Trial at the European level was supported between 1991 and 1992 by a grant from the European Union. The study is also supported by the National Fund for Scientific Research, Brussels, Belgium, and Bayer AG, Wuppertal, Germany.

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Date of receipt: 3 March 1994; revised: 18 May 1994; accepted: 19 May 1994.

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tensive patients were put on a placebo for 6 weeks [10]. Similarly, in a 6-week study using a non-invasive recording technique [11], the ambulatory pressure fell only slightly during the initial recording hours, such that the average pressure over 24 h remained unaffected. On balance, most publications now favour the hypothesis that ambulatory pressure is not subject to a placebo effect [4–7,10–22]. However, long-term studies are not yet available and the debate continues, fuelled in part by the far-reaching implications for the design of clinical trials. The Syst-Eur Study [23] is a double-blind outcome trial in older patients with isolated systolic hypertension, in which half of the patients are being randomized to placebo. The present study took advantage of this ongoing trial to determine the extent to which the conventional and ambulatory pressures had changed over 1 month and 1 year of follow-up on placebo.

Methods

The protocol of the multicentre Syst-Eur trial [23] and its side-project on ambulatory monitoring [24] has been published elsewhere. After discontinuation of all antihypertensive drugs, the participants (≥60 years) first entered a single-blind period on placebo, during which eligible patients on conventional measurement maintained a sitting systolic blood pressure (SBP) of 160–219 mmHg and a diastolic blood pressure (DBP) <95 mmHg.

One hundred and twelve patients, randomized into the placebo arm of the Syst-Eur Trial [23], were included in the present analysis. Their ambulatory pressure had been recorded on a placebo at baseline as well as during follow-up. Properly validated [25,26] monitors had been programmed to measure at intervals not greater than 30 min. In a subgroup of 51 patients, ambulatory monitoring had been repeated during the baseline period [24]. The clinic pressure corresponding to each recording was the average of two conventional readings in the sitting position.

Editing of the recordings according to published criteria [21] was considered but ultimately not put into practice because the editing procedure did not affect the blood pressure means and could be viewed as a possible source of bias. For analysis all ambulatory recordings were truncated at 24 h [27]. The within-participant means of the ambulatory pressures were weighted by the time interval between consecutive readings [27]. Daytime was the interval 10.00–20.00 h and night-time was midnight to 6.00 h. The initial two recording hours were analysed separately because monitoring is usually begun in hospital, where the white-coat effect could still be of influence [2,11]. Means were compared using Student's t-test. Significant correlates of the blood pressure during long-term follow-up were traced by stepwise multiple regression.

Results

The 112 participants (45 men and 67 women) were aged (mean±SD) 70±7 years (range, 60–99 years). Before entry into the placebo run-in period, 26 patients had experienced cardiovascular complications. At baseline, clinic SBP and DBP ranged from 160 to 214 and from 49 to 94 mmHg, respectively, and 24-h SBP and DBP from 111 to 196 and from 63 to 107 mmHg, respectively.

Short-term (median, 30 days; range, 14–119 days) placebo treatment in 51 patients was not accompanied by significant changes in clinic and ambulatory pressures (Table 1). During long-term (median, 12 months; range, 5–21 months) follow-up in the 112 patients, clinic SBP and DBP fell on average by 6.6 ($P<0.001$) and 1.4 mmHg ($P=0.06$; Table 1). In the long term the ambulatory pressures tended to decrease; the 2.4 mmHg drop in 24-h SBP was statistically significant on a two-tailed test (Table 1, Fig. 1). Body weight was measured both at baseline and at the long-term follow-up visit in 90 patients, in whom the changes averaged +0.13±3.05 kg ($P=0.68$).

Stepwise multiple regression showed that the clinic and ambulatory pressures during long-term follow-up were positively correlated with the initial pressure (Table 2). The 24-h SBP on double-blind treatment with a placebo increased proportionally to 76% of the baseline pressure, but fell with longer follow-up (Fig. 2). Thus, for a fixed duration of follow-up, the regression model derived for 24-h SBP predicted a greater absolute fall with higher baseline levels. In previously treated (n=58) compared with never-treated (n=54) patients, clinic SBP fell an

Table 1. Baseline blood pressure and subsequent changes.

	Systolic pressure (mmHg)			Diastolic pressure (mmHg)		
	Baseline	Δ 1 month	Δ 1 year	Baseline	Δ 1 month	Δ 1 year
No. patients	112	51	112	112	51	112
Conventional blood pressure	176±12	−2.7±15.9	−6.6±15.9***	86±7	−1.6±7.2	−1.4±7.4†
24-h ABP	151±15	−1.3±8.4	−2.4±10.7*	81±10	−0.4±4.3	−1.1±8.2
Daytime ABP	156±17	−1.8±9.8	−2.6±14.9†	85±11	−0.5±6.3	−0.7±10.2
Night-time ABP	138±16	+0.4±14.4	−1.5±12.3	71±10	−0.2±5.8	−1.6±8.8†
ABP during initial 2 h	162±17	−2.3±13.8	−2.8±17.0	90±13	−1.1±13.5	−1.2±13.2
ABP, excluding initial 2 h	149±15	−0.1±7.8	−2.0±10.5*	80±10	+0.5±4.4	−1.0±8.3

Means±SD. †$0.05 \le P \le 0.07$; *$P<0.05$, **$P<0.01$, ***$P<0.001$ versus baseline.

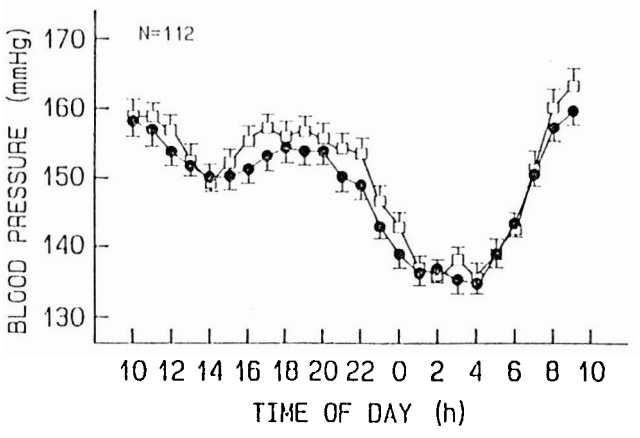

Fig. 1. The 24-h systolic blood pressure at baseline (○) and after a median follow-up of 1 year (●) in 112 patients. Values are hourly means ± SEM.

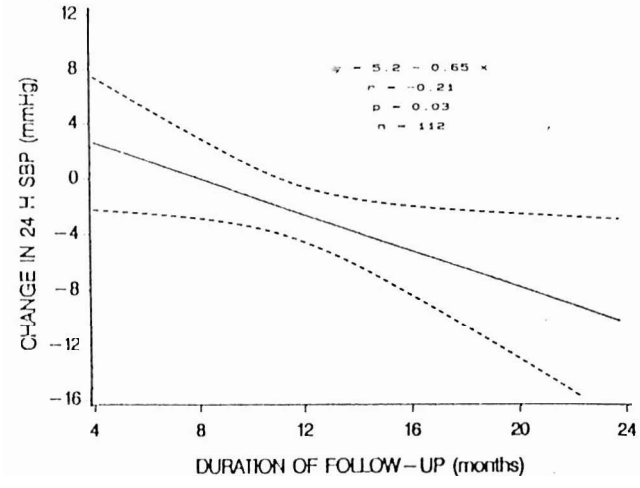

Fig. 2. The 24-h systolic blood pressure (SBP) as a function of the duration of follow-up in 112 patients.

average 6.5 mmHg less and clinic DBP fell an average 2.8 mmHg less (Table 2). During long-term follow-up, 24-h and night-time DBP were lower in older patients; 24-h DBP was 4.6 mmHg lower in patients with cardiovascular complications at baseline and night-time DBP was 3.3 mmHg lower in men than in women (Table 2).

Stepwise multiple regression analysis was also performed in the subgroup of 90 patients, in whom long-term changes in body weight were available for analysis. The covariates entered into the regression models in this subgroup were not different from those listed in Table 2. After adjustment for these covariates, the partial regression coefficients between the long-term changes in blood pressure and body weight were −0.024 ± 0.61 mmHg/kg (P=0.97) for clinic SBP and +0.34 ± 0.25 mmHg/kg (P=0.18) for clinic DBP. The corresponding partial regression coefficients for the 24-h pressures were +0.46 ± 0.35 mmHg/kg (P=0.19) and +0.81 ± 0.24 mmHg/kg (P=0.001), respectively.

Discussion

In these patients, who all had an elevated clinic SBP, the 24-h SBP fell by 2.4 mmHg during long-term follow-up on a placebo. Although this amounted to only one-third of the concurrent reduction in the clinic SBP, these findings suggest that in contrast to the prevailing view in the literature [4–7,10–22], the ambulatory pressure may not be entirely devoid of a placebo effect. To explain this discrepancy, various mechanisms must be considered, such as the technique of blood pressure determination, measurement artefacts, the statistical power of the published reports, the duration of follow-up, and patient age.

The intra-arterial technique does not involve compression of the arm and could therefore be less disturbing for the participant and free of a placebo effect [10]. Some investigators did not use an automated method of ambulatory recording [14]; others used stationary [12,13] or ambulatory monitors in a hospital. Some studies showing a non-existent placebo effect with ambulatory monitoring are hard to interpret because they do not report

Table 2. Correlates of blood pressure during long-term follow-up on placebo.

	Systolic pressure (mmHg)			Diastolic pressure (mmHg)		
	Clinic	24-h	Night	Clinic	24-h	Night
R^2	0.52	0.54	0.55	0.36	0.54	0.47
Intercept	−46.7	+41.4	+32.2	+19.8	+56.1	+46.9
Regression coefficients						
Sex (men 1, women 0)	NS	NS	NS	NS	NS	+3.28*
Age (years)	NS	NS	NS	NS	−0.27**	−0.25*
Complications	NS	NS	NS	NS	+4.55**	NS
Initial pressure (mmHg)	+1.21***	+0.76***	+0.81**	+0.74***	+0.59***	+0.65***
Length of follow-up (months)	NS	−0.63*	−0.71*	NS	−0.54**	−0.62**
Previous treatment (0, 1)	+6.54*	NS	NS	+2.85*	NS	NS

In addition to the duration of follow-up, the following characteristics, determined at baseline, were considered for entry into the model: sex, age, body mass index, initial blood pressure, pulse rate, presence of cardiovascular complications, intake of antihypertensive drugs before entry into the trial, and smoking and drinking habits (coded 1 or 0 for condition present or absent). Significance of the regression coefficients: NS, not significant; *$P \leq 0.05$, **$P < 0.01$, ***$P \leq 0.001$ versus baseline.

concurrent changes in clinic pressure [4,12,17]. Furthermore, non-invasive ambulatory monitoring, as used in the present study, may not be entirely free of measurement artefacts. A recently published report [28] showed that the blood pressure, continuously measured by the Peñaz method [29] at a finger of the contralateral arm, rose transiently during inflation of the cuff of two types of auscultatory ambulatory monitors. Thus, the present decrease in 24-h SBP over time may also, at least to some extent, represent a weakening of such an artefactual increase in pressure.

In general, few reports had enough statistical power to demonstrate or exclude small changes in the ambulatory pressure. Assuming that the standard deviation of the within-participant blood pressure differences is roughly four times larger than the mean change in pressure (Table 1), studies setting out to find a 5% significant result on a two-tailed test would require 63–295 participants, depending on whether the desired power was 50 or 99% [30]. In agreement with these sample size calculations [30], the present change in 24-h SBP was not significant when the long-term analysis was restricted to the 51 patients for whom short-term data were also available.

The duration of follow-up is another important confounder. In keeping with the present findings, no placebo effect was found when monitoring was repeated after 1 month in older patients with isolated systolic hypertension [21]. The long-term follow-up in the present study ranged from 5 to 21 months; 24-h SBP decreased with longer follow-up. In most published reports [4,5,7,10–12,14–17,21] the follow-up was short, not exceeding 6 weeks. A study with a 3-month follow-up in middle-aged mildly hypertensive patients reported no change (0.1/0.7 mmHg) in 24-h pressures [18]. Two longer-term studies [13,20] were unable to demonstrate any fall in ambulatory or clinic pressure. One of these long-term studies consisted of only four hypertensive patients, followed for an average of 66 days; two of the patients dropped out [13]. The other long-term study [20] recruited only normotensive people, who did not take placebo, but after a median interval of 350 days underwent repeat conventional and ambulatory measurements.

Regression to the mean occurs when the baseline pressure is high, and is therefore likely to have contributed to the fall in clinic SBP in the present patients [7]. Familiarization with the clinic environment and with the observer measuring the blood pressure are known to reduce the sympathetically-mediated defence reaction [2]. It is however unlikely that the latter mechanism affected the observed decrease in 24-h SBP to any great extent. Indeed, such a mechanism would be equally applicable to the 24-h SBP and DBP. Moreover, in contrast to a previous report [11], the fall in 24-h SBP was not appreciably reduced when the initial 2 h, during which most patients stayed in the hospital, were removed from the ambulatory recordings.

The more advanced age of the present patients also may have contributed to the decrease in 24-h SBP on a placebo. A first ambulatory recording may be perceived by patients as a more stressful event than later registrations. It could therefore cause a small rise in the blood pressure, which in older patients with stiffer arteries [31] and less efficient baroreflexes [32] may be less effectively buffered than in younger patients. However, in 27 patients with mild to moderate hypertension whose age averaged 44 years (range, 18–68 years), Mutti *et al.* [11] also found a fall in ambulatory pressure during the initial eight recording hours. This report [11] was therefore not dissimilar from the present findings in older patients, although it is generally referred to as a study refuting a placebo effect. Changes in lifestyle during follow-up could also be implicated in the present findings. As in the HARVEST study [22], a direct relationship was demonstrated between the long-term changes in 24-h DBP and body weight, although in the present study neither decreased significantly during the median follow-up of 1 year.

The reproducibility of ambulatory blood pressure means is usually better than that of conventional blood pressure measurements [4–7]. However, from the standard deviations in the present study (Table 1), this was not apparent for all long-term differences in the ambulatory blood pressure. For the initial 2 h of the recordings, the limited reproducibility may be related to the lower number of blood pressure measurements making up these means [4–7]. Considering the daytime blood pressure, the patients' activities influencing the ambulatory pressure readings and the high degree of standardization of the clinic measurements could be involved. Moreover, most reproducibility data have been collected in short-term studies. The present findings are in agreement with those obtained in a long-term population-based study [20], in which the interval between the repeated measurements averaged 350 days (range, 254–430 days), and in which the conventional blood pressure was measured at home in a highly standardized fashion. For the systolic pressure, the repeatability coefficient, expressed as a fraction of the maximal variability, was 36% for the sphygmomanometric readings, 37% for the 24-h average, and 41 and 49% for the day- and night-time averages, larger coefficients indicating poorer reproducibility. The corresponding estimates of the repeatability coefficients for DBP were 65, 47, 55 and 53%, respectively [20].

Ambulatory monitoring is increasingly proposed as an instrument of choice in blood pressure research, particularly in studies where the presumed effects on blood pressure are small, such as in lifestyle interventions [33]. In this context, a 2 mmHg decrease in 24-h SBP on a placebo cannot be deemed trivial. A consensus document [34] suggested that ambulatory monitoring would render a placebo control unnecessary. If this were true, two ambulatory recordings, at the beginning and end of an experimental intervention, would suffice to evaluate a presumed effect on blood pressure. However, the present findings in older patients with isolated systolic hypertension suggest that in the long term ambulatory pressure

is characterized by a small decrease on placebo. Thus, in order to obtain a precise estimate of any intervention on blood pressure, long-term studies using non-invasive ambulatory monitoring, no less than those using conventional sphygmomanometry, require a placebo-controlled design. In addition, such a design is also indispensable to evaluate other aspects of antihypertensive treatment, such as adverse effects and quality of life.

Acknowledgements

The Syst-Eur Trial is carried out in consultation with the World Health Organization, the International Society of Hypertension, the European Society of Hypertension and the World Hypertension League. The Trial Committees and the participating centres are listed in the second progress report, published in *J Hum Hypertens* 1993, 7:265–271. The study medication is donated by Bayer AG, Wuppertal, Germany, and Merck, Sharpe and Dohme, West Point, Pennsylvania, USA.

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