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Syst-Eur—A Multicenter Trial on the Treatment of Isolated Systolic Hypertension in the Elderly: First Interim Report

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Summary: Syst-Eur is a multicenter placebo-controlled outcome trial designed by the European Working Party on High Blood Pressure in the Elderly to investigate the effect of antihypertensive treatment on the incidence of stroke in elderly patients with isolated systolic hypertension (ISH). Eligible patients must be at least 60 years old and have a systolic blood pressure averaging 160–219 mm Hg with a diastolic blood pressure <95 mm Hg. The present paper is an interim report on the first 316 patients randomized into this trial. The placebo (n = 170) and active treatment (n = 146) groups were similar at randomization with respect to age (73 ± 8 years; mean ± SD), sitting blood pressure (178 ± 12 mm Hg systolic: 85 ± 7 mm Hg diastolic), percentage of men (34%), and percentage of patients with cardiovascular complications (29%). After randomization blood pressure fell more ($p < 0.001$) in patients on active treatment than in those in the placebo group (19 ± 20 mm Hg systolic; 6 ± 10 mm Hg diastolic vs. 7 ± 19 and 1 ± 10 mm Hg for sitting blood pressure). This first interim report on the Syst-Eur trial demonstrates that a multinational trial in elderly patients with ISH is feasible and that a significant blood pressure difference between the two treatment groups can be achieved and maintained. New centers are being recruited in order to randomize a total of 3,000 patients.
Key Words: Clinical trial—Elderly—Isolated systolic hypertension—Pilot study.

Several major intervention trials on the treatment of hypertension have been published during the last two decades. Most of these trials have recruited young and middle-aged patients with combined systolic and diastolic hypertension, but some trials also included patients 60 years or older [for review see (1)]. The results in elderly patients with combined systolic and diastolic hypertension demonstrate that antihypertensive treatment on average reduces cardiovascular mortality by 28%, mainly through a decrease in the incidence of stroke (−41%) (1).

In most countries systolic blood pressure contin-

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Syst-Eur is a concerted action of the European Community's Medical and Health Research Programme. The trial is carried out in consultation with the World Health Organisation, the International Society of Hypertension, the European Society of Hypertension, and the World Hypertension League.

ues to rise beyond the age of 50 years, while diastolic blood pressure decreases in the elderly, leading to a widening of the pulse pressure (2–4). This explains the increase in the prevalence of isolated systolic hypertension (ISH) in the elderly, averaging 0.1% at 40 years, 0.8% at 50, 5.0% at 60, 12.6% at 70, and 23.6% at 80 years of age (5). Although systolic blood pressure elevation is a well-known cardiovascular risk factor in the elderly (6–11), at present only one trial, namely, the recently published Systolic Hypertension in the Elderly Program (SHEP) (12–18), reported that treating ISH in elderly patients may reduce the incidence of nonfatal stroke and nonfatal myocardial infarction. However, in contrast to the previous intervention studies in patients with combined systolic and diastolic hypertension (1), the SHEP trial (18) did not demonstrate a significant beneficial effect of antihypertensive treatment on any of the cardiovascular mortality endpoints.

In 1989 the European Working Party on High Blood Pressure in the Elderly (EWPHE), which had already published an intervention study in elderly patients with combined systolic and diastolic blood pressure elevation (19–21), decided to undertake Syst-Eur (22), a therapeutic trial on isolated systolic hypertension conducted in several European countries. This paper is an interim report on the first 316 subjects randomized into this study.

METHODS

The protocol of the Syst-Eur trial has been published in detail elsewhere (22). The entry criteria for the patients include: (a) age of at least 60 years and (b) sitting blood pressure of 160–219 mm Hg systolic with a diastolic pressure <95 mm Hg on placebo during a run-in period. After a single-blind run-in period on placebo and after stratification by center, sex, and the presence or absence of cardiovascular complications, the patients are randomized to double-blind treatment with either active drugs or matching placebos. The following conditions lead to stratification into the subgroups with cardiovascular complications: myocardial infarction >1 year prior to randomization; previous episodes of congestive heart failure; a history of thromboembolic stroke without lasting sequelae; a previous transient ischemic attack and the presence of left ventricular hypertrophy or nondissecting aneurysm (22).

Active treatment consists of nitrendipine (10–40 mg/day) combined with enalapril (5–20 mg/day) and hydrochlorothiazide (12.5–25 mg/day), as necessary. The patients of the control group receive matching placebos. The active drugs (or matching placebos) are titrated in a stepwise manner and combined in order to reach the goal pressure. The latter is defined as a sitting systolic blood pressure <150 mm Hg with a reduction in the sitting systolic blood pressure following randomization by at least 20 mm Hg.

Data base management and statistical analyses were performed using SAS software (23). The average differences between the blood pressure at randomization and the last available measurement within the first 9 months following randomization were compared for the active treatment and placebo groups (24). Means were compared using Student's *t* test, and the proportion of patients reaching goal pressure were compared with the chi-square statistic. Mortality, morbidity, and adverse events are being monitored, but this paper deals only with the effects of randomized treatment on blood pressure.

RESULTS

Characteristics of the patients on admission

On March 1, 1991, 517 patients from 11 countries had been entered into the placebo run-in period of the trial. Of these 316 had been randomized; 160 patients who did not comply with the entry criteria had been removed from follow-up, and 41 patients were still progressing through the run-in period.

The characteristics of the 316 patients randomized into the double-blind trial are given in Table 1. Age averaged 73 ± 8 years (mean ± SD) and ranged from 60 to 96 years. Only 34% of the randomized patients were men, and 29% showed cardiovascular complications at entry.

Follow-up

The maximum follow-up varied because the patients had been entered over a period of several months. A total of 152 patients had been followed for at least 3 months. A follow-up of 9 months was attained in 82 patients.

Blood pressure during double-blind treatment

In the placebo group the fall in sitting systolic blood pressure over the initial 6 months following randomization averaged 5 ± 18 mm Hg, and the change in the sitting diastolic blood pressure averaged 0 ± 9 mm Hg (Fig. 1). In the patients assigned active treatment, the sitting systolic blood pressure

TABLE 1. *Patient characteristics at randomization*

	Placebo	Active treatment
Number	170	146
Sex (M/F)	63/107	43/103
Age (year)	73 ± 7	74 ± 8
Weight (kg)	70 ± 13	67 ± 12
Height (cm)	162 ± 10	160 ± 10
Body mass index (kg/m^2)	27 ± 4	26 ± 4
Systolic pressure (mm Hg)		
Supine	182 ± 14	179 ± 13
Sitting	178 ± 12	177 ± 13
Standing	174 ± 15	175 ± 14
Diastolic pressure (mm Hg)		
Supine	86 ± 7	86 ± 8
Sitting	86 ± 8	84 ± 7
Standing	87 ± 9	86 ± 9
Pulse rate (beats/min)	74 ± 9	75 ± 8
Cardiovascular complications (%)	32	25

Values are means ± SD.

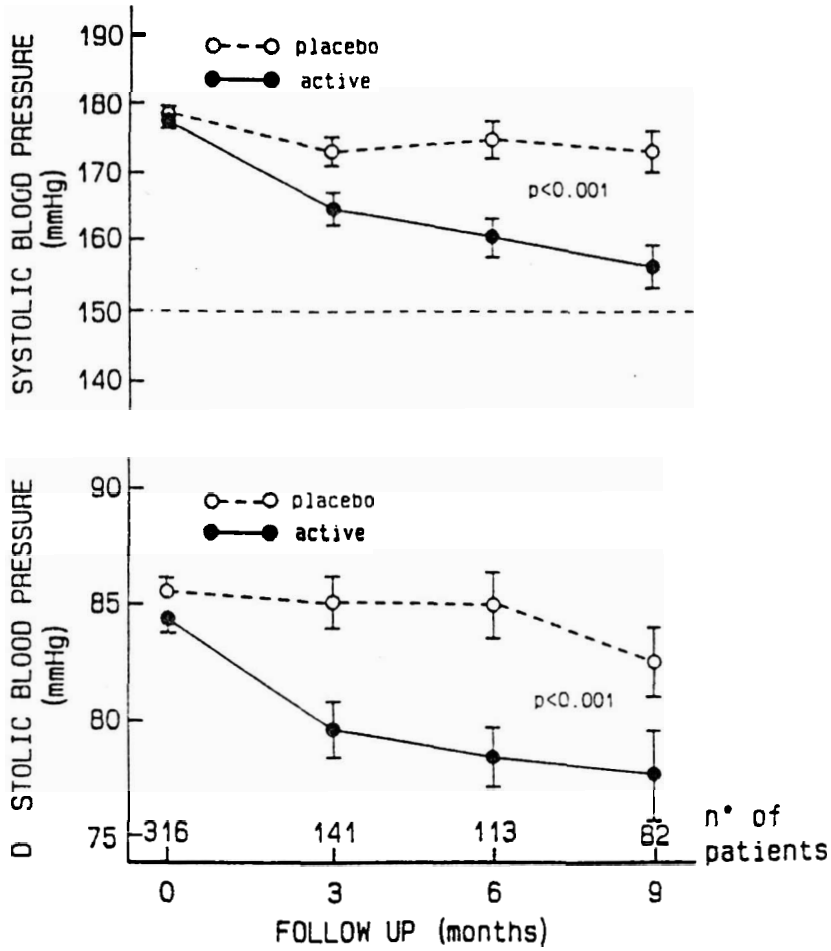

FIG. 1. The sitting systolic and diastolic blood pressures at randomization and at various follow-up visits on double-blind treatment. Values are means ± SE. The difference between the two treatment groups became significant at the 3-month visit, and a significant difference was maintained thereafter. The number of patients with blood pressure readings at a particular follow-up visit is given at the bottom of the figure for the two treatment groups combined.

fell by 15 ± 21 mm Hg and the sitting diastolic pressure by 5 ± 11 mm Hg during the initial 6 months of double-blind treatment (Fig. 1).

The changes in the standing blood pressure during the initial 6 months of placebo treatment averaged −4 ± 17 mm Hg systolic and 1 ± 9 mm Hg diastolic. At 6 months on active treatment the standing blood pressure had fallen by 14 ± 21 mm Hg systolic and 6 ± 12 mm Hg diastolic. At the 6-month visit 11% of the patients assigned to the placebo group showed a fall in their standing systolic blood pressure by ≥20 mm Hg. This was the case in 12% of the patients on active treatment.

The fall in blood pressure from randomization to the last available measurement within the first 9 months following randomization was greater on active treatment than on placebo: 19 ± 20 mm Hg systolic; 6 ± 10 mm Hg diastolic vs. 6 ± 19 and 1 ± 10 mm Hg for sitting blood pressure, and 18 ± 19 and 7 ± 11 mm Hg vs. 4 ± 20 and 0 ± 11 mm Hg for standing blood pressure ($p < 0.01$ for all comparisons).

A total of 152 patients were examined at least on one occasion following randomization. Of these, 12% in the placebo and 31% in the active treatment group had attained the target blood pressure. The percentage of patients reaching the target blood pressure during double-blind follow-up was significantly greater with active treatment than placebo (Fig. 2).

Treatment administered during the double-blind period

The number of study drugs (placebo or active) taken by the patients at the 9-month visit is given in Table 2, according to achievement of the target blood pressure. In the patients randomized to active treatment and taking a specific drug, the daily dose of nitrendipine at the 9-month visit averaged 34 ± 11 mg (n = 28), the dose of enalapril averaged 13 ± 7 mg (n = 18), and the dose of hydrochlorothiazide averaged 19 ± 7 mg (n = 12). Patients randomized to placebo took a number of placebo tablets corresponding to a daily dose of 33 ± 11 mg nitrendipine (n = 48), 17 ± 5 mg enalapril (n = 25), and 23 ± 5 mg hydrochlorothiazide (n = 20).

DISCUSSION

The EWPHE decided to undertake the Syst-Eur trial (22) (a) because ISH affects 13–15% of all subjects over age 60 (5), (b) because ISH constitutes an important cardiovascular risk indicator in the elderly (5), and (c) because in 1989, when the Syst-Eur trial was initiated, there was no experimental evidence showing that the complications of ISH would

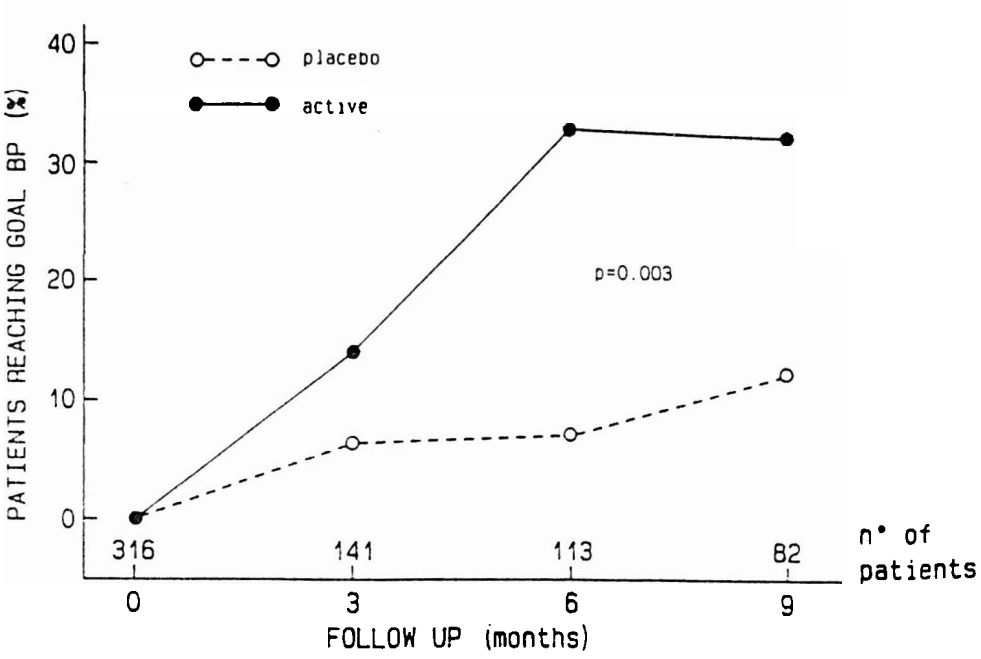

FIG. 2. Percentage of patients reaching the target pressure at various follow-up visits on double-blind treatment. Target pressure was defined as a sitting systolic blood pressure <150 mm Hg with a reduction following randomization by at least 20 mm Hg.

be prevented by medical treatment. In 1985 EWPHE had already concluded a clinical trial on the antihypertensive treatment of elderly patients with combined systolic and diastolic hypertension (19–21). The expertise and structures ensuing from this previous trial (19–21) were very helpful for organizing Syst-Eur because they provided the framework within which the new trial was conceived.

Two trials in elderly hypertensive patients, published before 1989, included a subgroup of ISH patients (9,25) but failed to demonstrate a significant treatment effect on outcome events, possibly because of the small number of patients with ISH (9,25). Besides the present study (22), at least two other double-blind placebo-controlled trials are addressing the hypothesis that antihypertensive treatment is beneficial, specifically in elderly patients with ISH, namely the SHEP (12–18) in the United States, and a trial in China (Lisheng Liu, personal communication).

The mortality and morbidity results of the SHEP trial consist of a significant reduction of nonfatal stroke (37%), nonfatal myocardial infarction (33%), and left ventricular failure (54%) in the active treatment group compared with placebo, whereas the decrease in transient ischemic attacks was not significant (18). Total mortality and mortality from cerebrovascular and coronary causes were also not significantly changed by active treatment (18). In contrast to the previous intervention studies in elderly patients with both systolic and diastolic hypertension (19–21,25), fatal stroke and total cardiovascular mortality did not significantly decrease on active treatment in SHEP (18). However, when nonfatal- and fatal-outcome events in the SHEP trial were combined, the 5-year cumulative incidence rate of total stroke was reduced by 36% ($p = 0.0003$). Adverse reactions were more often observed in the active treatment than in the placebo group with, for instance, significant increases in faintness on standing, falls, loss of consciousness, memory troubles, sexual dysfunction, change in bowel habits, and ankle swelling (18). None of the subjective complaints reported in the SHEP publication was more frequently noticed in the placebo group (18).

In SHEP 447,921 subjects were screened to enroll up to 4,736 participants (18). A conservative estimate based on published prevalence figures for ISH in the elderly (5) is that a population with a similar age distribution and size as those screened for SHEP would probably include close to 60,000 cases. Thus, the subjects randomized into the SHEP trial are a selected subgroup, and may not be entirely representative of the majority of patients with ISH in the population at large.

After publication of the SHEP results, Syst-Eur's ethics and with the European Community liaison committees decided that it was ethical to continue the Syst-Eur trial, but that full consultation of all

TABLE 2. *Study medications at the 9-month visit following randomization*

	Placebo (n = 48)	Active treatment (n = 34)
Patients reaching target pressure		
Patients on 1 drug	3	4
Patients on 2 or 3 drugs	3	7
Total	6	11
Patients not reaching target pressure		
Patients on 1 drug	14	9
Patients on 2 or 3 drugs	28	14
Total	42	23

Syst-Eur investigators is indicated. Syst-Eur's ethics committee believed that the following points are relevant: (a) SHEP is the first randomized controlled trial to assess the value of treating ISH in the elderly. In view of the lack of a significant effect upon mortality and the broad implications of treating ISH, there is a need for the SHEP results to be confirmed in a different population. (b) Elderly patients are now commonly treated with calcium entry blockers or converting-enzyme inhibitors. The value of these drugs has not yet been assessed in any published outcome trial.

In the present study, the patients were followed for up to 9 months. The sitting blood pressure fell on average 13/5 mm Hg more on active treatment than on placebo. In the SHEP pilot study (17), after 1 year of treatment the differences between the two treatment groups were 17 mm Hg systolic and 6 mm Hg diastolic. However, in the fifth year of follow-up, when 44% of the SHEP patients assigned to the placebo group were actually receiving drugs with known antihypertensive action, the difference was 12 mm Hg systolic and 4 mm Hg diastolic (18).

In most controlled trials on the efficacy of antihypertensive drugs in elderly patients with predominant systolic hypertension diuretics were the first-line medication (9,12,26–30). The reduction in systolic blood pressure in the actively treated patients as compared with the control group averaged 12 mm Hg; the 95% confidence interval for the mean reduction in systolic blood pressure ranged from 5 to 20 mm Hg (5). The mean effect in these studies (9,12,26–30) on diastolic pressure was a reduction of 3 mm Hg, with a 95% confidence interval ranging from 0 to 6 mm Hg.

The goal pressure in the present study was defined as a sitting systolic blood pressure <150 mm Hg, with a reduction following randomization by at least 20 mm Hg (22). The target pressure is to be achieved by the stepwise titration and combination of nitrendipine, enalapril, and hydrochlorothiazide or matching placebos in the control group. Three months after randomization, the target systolic blood pressure was reached in 7% of the patients randomized to placebo and 14% of the patients on active treatment; after 6 months these figures were 7 and 33%, respectively. It was indeed planned that the target blood pressure would be reached progressively over several months in order to avoid side effects in these elderly patients or an excessive, sudden fall in blood pressure, possibly leading to orthostatic hypotension. As follow-up is extended, randomized treatment will be further adjusted so that an even larger proportion of the patients on active treatment will achieve the target blood pressure.

In conclusion, this first interim report on the Syst-Eur trial demonstrates that a significant difference in systolic blood pressure between the two treatment arms can be achieved and maintaine New centers are now being recruited in order randomize a total of 3,000 patients.

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The interrelations of blood pressure levels, circadian pressure alterations and left ventricular mass in mild to moderate hypertension in human subjects

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Left ventricular hypertrophy in hypertensive patients is an important predictor of cardiovascular morbidity and mortality. Blood pressure follows a circadian rhythm, elevated levels usually occurring during the day, and a trough at night. Some studies have suggested that hypertensive patients with more pronounced circadian blood pressure changes may have a lower prevalance of left ventricular hypertrophy. The aim of this study was to determine the interrelations between blood pressure levels, circadian pressure alterations and left ventricular mass in patients with mild to moderate hypertension.

Thirty-seven previously untreated hypertensive patients underwent 24 hour ambulatory BP monitoring and M-mode echocardiography. Mean 24 hour BP, crest and trough levels (mean BP of the 6 hour periods with highest and lowest average BP levels respectively), were calculated from the ambulatory profile, using a cumulative sums technique. Circadian alteration magnitude (CAM) was defined as the difference between crest and trough levels. Left ventricular mass (LVM) was calculated from echocardigraphic measurements according to the Penn Convention. LVM-index was calculated by dividing LVM by body surface area. The data were analysed using linear regression analysis (Table 1), and Student's unpaired t test

Table 1. The associations between BP levels and both CAM and LVM-index. BP units are mmHg; LVM-index units are g/m^2; β = regression line slope; r = correlation coefficient; * indicates $P < 0.05$.

Independent variable	Dependent variable	Systolic		Diastolic	
		β	r	β	r
Mean 24 hour BP	CAM	+0.36 *	0.45 *	+0.36 *	0.38 *
Crest BP	CAM	+0.45 *	0.69 *	+0.52 *	0.69 *
Trough BP	CAM	+0.04	0.05	+0.09	0.08
Mean 24 hour BP	LVM-index	+0.87 *	0.47 *	+0.83	0.35
Crest BP	LVM-index	+0.76 *	0.50 *	+0.77 *	0.39 *
Trough BP	LVM-index	+0.89 *	0.45 *	+0.64	0.26

In addition, LVM-index was significantly greater in those hypertensive subjects whose CAM was greater than the median value in comparison with those whose CAM was less than the median value (systolic, 119.1 *versus* 102.6 g/m^2, $P < 0.05$; diastolic, 118.6 *versus* 103.1 g/m^2, $P < 0.05$).

The extent of the circadian BP change increased with increasing mean 24 hour and crest BP levels, but CAM was independent of trough BP. Left ventricular mass was positively associated with systolic mean 24 hour, crest and trough BP, and also with diastolic crest BP. In contrast to previous studies, we found that patients with more pronounced circadian blood pressure alterations had increased left ventricular mass, in comparison with patients who had similar trough blood pressure levels, but attenuated circadian pressure changes.