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ORIGINAL ARTICLE

Systolic Hypertension in Europe (Syst-Eur) Trial Phase 2: objectives, protocol, and initial progress

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The Systolic Hypertension in Europe (Syst-Eur) trial proved that blood pressure (BP) lowering therapy starting with nitrendipine reduces the risk of cardiovascular complications in older (≥60 years) patients with isolated systolic hypertension (systolic BP ≥160 mm Hg and diastolic BP <95 mm Hg). After the completion of the Syst-Eur trial on 14 February 1997, 3506 consenting patients (93.0% of those eligible) were enrolled in phase 2 of the Syst-Eur trial. This open follow-up study aims to confirm the safety of long-term antihypertensive therapy based on a dihydropyridine. To lower the sitting systolic BP below 150 mm Hg (target BP), the first-line agent nitrendipine (10–40 mg/day) may be associated with enalapril (5–20 mg/day), hydrochlorothiazide (12.5–25 mg/day), both add-on study drugs, or if required any other antihypertensive agent. On 1 November 1998, 3248 patients were still being followed, 86 patients had proceeded to non-supervised follow-up, and 43 had died. The median follow-up in Syst-Eur 2 was 14.3 months. At the last available visit, systolic/diastolic BP in the patients formerly randomised to placebo ($n = 1682$) or active treatment ($n = 1824$), had decreased by 13.2/5.2 mm Hg and by 4.6/1.6 mm Hg, respectively, so that the between-group BP difference was 1.7 mm Hg systolic (95% CI: 0.8 to 2.6 mm Hg; $P < 0.001$) and 0.9 mm Hg diastolic (95% CI: 0.4 to 1.5 mm mm Hg; $P < 0.001$). At the beginning of Syst-Eur 2, the goal BP was reached by 25.4% and 50.6% of the former placebo and active-treatment groups; at the last visit these proportions were 55.9% and 63.1%, respectively. At that moment, 45.9% of the patients were on monotherapy with nitrendipine, 29.3% took nitrendipine in combination with other study drugs. Until the end of 2001, BP control of the Syst-Eur 2 patients will be further improved. Cardiovascular complications and adverse events, such as cancer or gastro-intestinal bleeding, will be monitored and validated by blinded experts.

Keywords: calcium-channel blockade; elderly; dihydropyridine; isolated systolic hypertension

Introduction

In 1989 the European Working Party on High Blood Pressure in the Elderly started the placebo-controlled double-blind Systolic Hypertension in Europe trial (Syst-Eur).[1] Active treatment was initiated with the dihydropyridine calcium-channel blocker nitrendipine[2] with the possible addition of enalapril, hydrochlorothiazide or both drugs. The Syst-Eur trial stopped on 14 February 1997 according to predefined rules,[3] because the second of four planned interim analyses had shown a significant benefit for stroke, the primary end-point.[1] At the Syst-Eur investigators meeting in March 1997, the decision was taken to keep the Syst-Eur patients in follow-up. This article summarizes the rationale and protocol of this study, named Systolic Hypertension in Europe Phase 2 (Syst-Eur 2), and aims to present the first progress report.

Rationale and objective of Syst-Eur 2

Calcium-channel blockers had a track record of safe and uneventful use in many cardiovascular indications until in 1995 a meta-analysis of the literature raised the hypothesis that short-acting dihydropyridines could in a dose-dependent fashion provoke rather than prevent myocardial infarction in patients with pre-existing coronary heart disease.[4] This publication[4] heralded the start of a long-lasting and still ongoing debate in the medical community.[5–8]

The Syst-Eur trial proved that antihypertensive treatment starting with the dihydropyridine nitrendipine[2] reduced the risk of fatal and non-fatal stroke and cardiovascular complications in older (≥60 years) patients with isolated systolic hypertension (systolic blood pressure ≥160 mm Hg and diastolic blood pressure <95 mm Hg).[3] Cardiovascular benefit was equally observed in the patients remaining on monotherapy with nitrendipine as in those pro-

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gressing to combined treatment with nitrendipine plus enalapril, hydrochlorothiazide, or both drugs.[9] At the risk observed in the placebo group (intention-to-treat analysis), treating 1000 patients for 5 years could prevent 29 strokes or 53 major cardiovascular events.[3] Similar findings were obtained in two placebo-controlled trials in China, in which antihypertensive treatment was also started with a dihydropyridine.[10,11]

In spite of the positive results in placebo-controlled outcome trials,[3,10,11] the controversy on the use of calcium-channel blockers as first-line antihypertensive agents continues. One of the arguments used is that the median follow-up of the Syst-Eur patients was only 2 years and that therefore they may not have been exposed to nitrendipine[2] for a period sufficiently long to elicit adverse effects, such as cancer,[12,13] gastro-intestinal bleeding,[14] or coronary complications in patients with pre-existing coronary heart disease[4,15,16] or diabetes mellitus.[17–22] In keeping with the expert recommendation[8] that well-conducted observational studies may answer issues of drug safety, the Syst-Eur patients will remain in open follow-up to confirm the safety and, ultimately the cost-effectiveness, of antihypertensive therapy based on a dihydropyridine calcium-channel blocker.

Protocol of Syst-Eur 2

The protocol of Syst-Eur 2 was approved by the Ethics Committees of the University of Leuven and the participating centres. The study is conducted according to the principles outlined in the Helsinki declaration.[23]

Recruitment of patients

In spring 1997, soon after the termination of the Syst-Eur trial,[3] the patients still in follow-up were informed on the risk reduction conferred by the active-treatment regimen. All patients, who withdrew from double-blind treatment, either active or placebo, or who were already in open follow-up, were then offered the possibility to continue or to start antihypertensive therapy with the same drugs as previously used in the active-treatment arm. Patients who granted their informed consent will remain in open follow-up for 5 years until the end of the year 2001. Because medical treatment has been standardized and is the same in all patients, confounding by indication, a major problem in many observational studies[8] can only play a minor role in Syst-Eur 2.

Study medications

The goal of antihypertensive treatment during Syst-Eur 2 is to lower the sitting systolic blood pressure (average of two readings obtained after a 5-min rest) to a level lower than 150 mm Hg. The target blood pressure should be achieved by the stepwise titration of nitrendipine, the first-line study medication, with the possible addition of enalapril, hydrochlorothiazide, or both drugs. The dosage steps for nitrendipine are: half a tablet (10 mg) in the evening and half a tablet and one tablet in the morning and the evening (10 mg and 20 mg twice daily, respectively); for enalapril these steps are half a tablet (5 mg), one tablet (10 mg) and two tablets (20 mg) in the evening; and for hydrochlorothiazide, half a tablet (12.5 mg) and one tablet (25 mg) in the morning. If side effects occur during monotherapy with nitrendipine, the daily dose should first be back-titrated. If side effects persist at this lower dose, nitrendipine may be discontinued and enalapril started. Similarly, the second-line medication may be withdrawn because of side effects, and hydrochlorothiazide started. If required to reach the goal blood pressure in treatment-resistant patients, or to treat cardiovascular disorders in any patient, the doctor may during follow-up in Syst-Eur 2 associate any other antihypertensive or cardiovascular drug with the open-label study medication.

Assessment of events

As before in the Syst-Eur trial,[1,3] the following events will be considered as major complications: death, stroke, retinal haemorrhage or exudates, myocardial infarction, congestive heart failure, dissecting aortic aneurysm and renal insufficiency. A blinded expert committee will ascertain all major events by reviewing the local patient files and other source documents, by requesting detailed written information from the investigators, or by both approaches. Diseases will be coded according to the ninth (1975) revision of the International Classification of Diseases.[24]

Stroke is defined as a neurological deficit with symptoms continuing for more than 24 h or leading to death with no apparent cause other than vascular. Typical chest pain or electrocardiographic changes and/or the increase in cardiac enzymes lead to the diagnosis of acute myocardial infarction, provided that at least two of these three criteria[1] are fullfilled. Myocardial infarction does not include silent myocardial infarction. Congestive heart failure requires the presence of three conditions, namely symptoms, such as dyspnoea, clinical signs, such as ankle oedema or crepitations, and the necessity to initiate treatment with diuretics, vasodilators or antihypertensive drugs. Sudden death encompasses any death of unknown origin occurring instantly or within an estimated 24 h after the onset of acute symptoms as well as unattended death for which no likely cause could be established by autopsy or recent medical history. Cardiac events include fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction and sudden death. Renal insufficiency is diagnosed if at two consecutive visits the serum creatinine concentration reaches or exceeds 360 μmol/l (4.0 mg/dl) or has doubled in comparison with the level at randomisation.

In Syst-Eur phase 2, the blinded expert committee will also validate the following events: the diagnosis of any cancer, which must be backed-up by anatomopathogical confirmation; bleeding; and anaemia defined as a haemoglobin level of less than 10 g/dl.

Follow-up

During the first year of the Syst-Eur 2 study, the investigators have to update the coordinating office on the status of their patients at 3-monthly intervals; from the second year on reports are due every 6 months. Blood pressure, heart rate, the intake of medications, symptoms and signs, intercurrent diseases, and major and minor events are recorded at each visit. Visits at yearly intervals also include a measurement of body weight, the registration of smoking and drinking habits and the activities of daily living, an electrocardiogram, fundoscopy, urinalysis (sediment, albumin and glucose), and routine haematological and biochemical measurements.

One important difference with the Syst-Eur trial proper is that in Syst-Eur 2 the open-label study medication must not be stopped if a patient experiences a major event, unless a study drug is suspected to have played a causal role. Patients, who withdraw from the study and who no longer participate in clinic visits, proceed to the non-supervised follow-up, during which the investigator has to obtain information on their health status at annual intervals via the telephone, via contacts with other doctors or relatives, or via consultation of registries, hospital records or vital statistics.

Statistical analysis

Database management and statistical analysis are performed with the SAS software, version 6.12 (SAS Institute Inc, Carey, NC, USA). The data are entered in duplicate at the coordinating office (Leuven, Belgium) with systematic quality checks at 3-month intervals.

Comparisons of means and proportions will be based on the standard normal z-test and the χ^2-statistic, respectively. The outcome results will be analysed according to an intention-to-treat principle, using two-sided tests. Three interim analyses, respectively after 15, 30 and 45 months, and one final analysis will be performed. The O'Brien–Fleming rule[25] will be employed and the monitoring boundaries will be set at the 1% significance level. Syst-Eur 2 could be stopped, if the age- and sex-adjusted rates for all-cause, cardiovascular or cancer mortality would exceed those observed in the placebo group during the Syst-Eur trial proper. Because non-fatal end-points will not be considered in the interim analyses, and because the required significance level was set at a conservative 1% level, it is unlikely that Syst-Eur 2 will have to be stopped prematurely due to random fluctuation in the occurrence of fatal events.

Other analyses will be based on multiple Cox regression. The exposure variable will be defined as the area under the curve relating in individual patients the consecutive doses of nitrendipine to the duration of intake. The underlying two-sided hypothesis is that the risk of possible adverse events may be influenced in either direction by the intensity of the exposure to nitrendipine. The area under the curve index will be used as a fixed characteristic in Cox regression. Alternatively, the daily dose of nitrendipine may also be considered as the index of exposure, but this measure will be treated as a time-dependent covariate in the Cox model.

Finally, the two-sided hypothesis will be tested that outcome in patients on long-term nitrendipine treatment (subjects originally randomised to active treatment) and on short-term nitrendipine treatment (subjects originally randomised to placebo and only switched to active treatment after the termination of the Syst-Eur trial proper[3]) may differ. For potential adverse events in this analysis, such as cancer and gastro-intestinal bleeding, a one-sided test will be used with an overall significance level of 1% and the stopping boundaries at the three interim analyses will be adjusted accordingly. For this type of analysis, survival curves will also be compared using Kaplan–Meier survival function estimates and the log rank test.

First progress report

Study profile

A total of 4695 patients have been randomised in the Syst-Eur trial (Figure 1). On 14 February 1997, the date on which the double-blind trial ended, there were 281 deaths (6.0%), while 126 patients did not have any report within the preceeding year and were therefore considered to be lost to follow-up (2.9%). Obviously, these patients were not eligible for further follow-up in Syst-Eur 2. Furthermore, on 14 February 1997, 522 of 4695 randomised patients (11.1%) had already proceeded to non-supervised follow-up; of these patients, 208 remained in non-supervised follow-up in Syst-Eur phase 2, seventeen patients had died and 297 were lost to follow-up (Figure 1).

Of the remaining 3766 patients (80.2%), 434 were in supervised open follow-up at the end of the Syst-Eur trial and 3332 patients were still on double-blind treatment (Figure 1). Of these 3766 patients, who were eligible for further follow-up in Syst-Eur phase 2, 3506 (93.0%) participated. Among the 260 patients who withdrew from the study, 65 proceeded to non-supervised follow-up, 187 were lost to follow-up (no report within the preceeding year), and eight died. On 1 November 1998, at the time of the preparation of this progress report, 3248 of the 3506 patients enrolled in Syst-Eur 2, were still in follow-up, 86 had proceeded to non-supervised follow-up, 43 had died and 129 were lost to follow-up. Their median follow-up in Syst-Eur 2 was 14.3 months (range: 0.3 to 21.3 months).

Patient characteristics at entry in Syst-Eur 2

The characteristics of the 3506 enrolled patients, of whom 1682 had formerly been randomised to placebo and 1824 to active treatment, are presented in Table 1. Age at entry in Syst-Eur phase 2 averaged (±s.d.) 71.1 ± 6.3 years and ranged from 60 to 97 years. Of the Syst-Eur 2 patients, 66.6% were female, 2.3% had experienced a non-fatal cardiovascular end-point prior to the end of the Syst-Eur trial proper, and 12.2% had been diagnosed as hav-

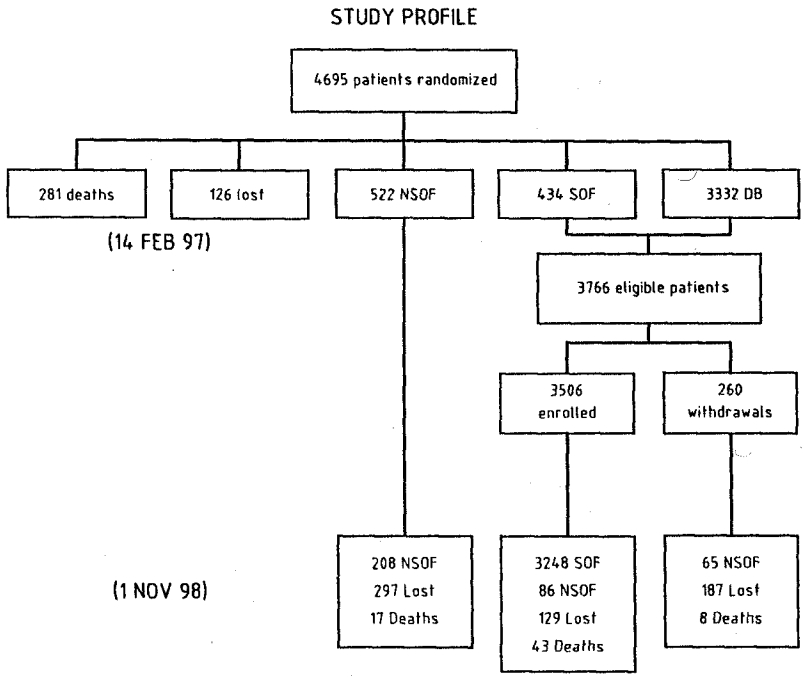

Figure 1 Study profile. DB, NSOF and SOF indicate double-blind, non-supervised open follow-up and supervised open follow-up, respectively. Patients without report within the last year were classified as lost-to-follow-up.

Table 1 Patient characteristics at entry in Syst-Eur 2

Characteristic	*Placebo*[a]	*Active treatment*[a]
Number	1682	1824
Female sex (%)	66.3	66.8
Age (years)	71.1 ± 6.4	71.2 ± 6.3
Sitting systolic blood pressure (mm Hg)	160.5 ± 16.2	151.0 ± 14.6***
Sitting diastolic blood pressure (mm Hg)	83.4 ± 7.8	79.6 ± 7.8***
Sitting heart rate (beats per minute)	72.4 ± 9.1	73.1 ± 8.9*
Standing systolic blood pressure (mm Hg)	157.7 ± 16.7	148.2 ± 15.5***
Standing diastolic blood pressure (mm Hg)	85.1 ± 9.2	81.6 ± 8.9***
Body-mass index (kg/m²)	27.1 ± 4.0	27.1 ± 4.2
Total cholesterol (mmol/l)	5.9 ± 1.1	5.8 ± 1.1
High-density-lipoprotein cholesterol (mmol/l)	1.36 ± 0.40	1.40 ± 0.50*
Cardiovascular end-points in Syst-Eur trial (%)	3.0	1.6**
Diabetes mellitus (%)	11.7	12.7
Current smokers (%)	4.2	4.6
<1 unit of alcohol per day (%)	13.2	14.3
≥ 1 unit alcohol per day (%)	8.3	9.4

Significance of between group differences: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.
[a] Indicates patients formerly randomised to placebo or active treatment.

Table 2 Treatment status at the end of the Syst-Eur trial

	Placebo[a]	*Active*[a]
Total number	1682	1824
Still in double-blind follow-up	1481	1716**
No study drugs	26	29
Nitrendipine only	662	1063**
Study medication other than nitrendipine	793	624**
Drugs taken[bc]		
Nitrendipine	1411	1534
Enalapril	753	556**
Hydrochlorothiazide	398	217**
Open-label antihypertensive drugs[c]	16	10
Supervised open follow-up	182	99**
No antihypertensive drugs	46	26
Open-label antihypertensive drugs	136	73
Treatment unknown	19	9*

Significance of between group differences: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.
[a]Indicates patients formerly randomised to placebo or active treatment.
[b]Because many patients were on combined treatment, numbers do not add up.
[c]To bridge medical emergencies without having to break the code, antihypertensive drugs could be prescribed for up to 3 consecutive months.

ing diabetes mellitus at randomisation or during follow-up.

Treatment

At the end of the Syst-Eur trial (Table 2), significantly ($P = 0.001$) less patients in the active-treatment group than in the control group had proceeded to combined treatment with various double-blind medications and less patients randomised to active treatment ($P = 0.001$) were in open follow-up (Table 2). At the last visit in the Syst-Eur trial, the average daily doses of the active double-blind medications were 28.0 ± 12.2 mg for nitrendipine ($n = 1534$), 13.6 ± 6.1 mg for enalapril ($n = 565$), and 21.4 ± 6.8 mg ($n = 217$) for hydrochlorothiazide; the patients of the control group took placebos equivalent with daily doses of 32.4 ± 11.3 mg for nitrendip-

ine ($n = 1411$), 15.9 ± 6.7 mg for enalapril ($n = 753$) and 24.6 ± 9.7 ($n = 398$) for hydrochlorothiazide.

After their enrolment in Syst-Eur phase 2, the patients formerly randomised to placebo were started on nitrendipine with the possible addition of enalapril or hydrochlorothiazide (Table 3). At the last available visit, 1236 patients of the former placebo group ($n = 1682$) took nitrendipine, either in monotherapy ($n = 793$; 47.1%) or in combination with enalapril, hydrochlorothiazide, or both drugs ($n = 443$; 26.3%). At the last available visit, among the patients of the former active-treatment group ($n = 1824$), 1398 took nitrendipine alone ($n = 815$; 44.7%), or in combination with the other study drugs ($n = 583$; 32.0%).

Sitting blood pressure

At the last visit before entry in Syst-Eur phase 2, 25.4% of the patients randomised to placebo and 50.6% of those in the active-treatment group, had reached the goal blood pressure, namely a systolic level less than 150 mm Hg. At 12 months of follow-up in Syst-Eur 2, these proportions were 55.9% and 63.1%, respectively (Figure 2).

At entry in Syst-Eur phase 2, the mean sitting systolic blood pressure in the patients randomised to placebo was 160.5 ± 16.2 mm Hg and in those of the active-treatment group 151.0 ± 14.6 mm Hg; the corresponding diastolic levels were 83.4 ± 7.8 mm Hg and 79.6 ± 7.8 mm Hg (Table 1). At 3 months of follow-up in Syst-Eur 2, in the patients of the control group ($n = 1080$), the sitting blood pressure had fallen by 6.6 mm Hg systolic (95% CI: 5.7 to 7.5 mm Hg) and by 2.2 mm Hg diastolic (95% CI: 1.8 to 2.6 mm Hg); in the patients previously randomised to active treatment ($n = 1202$), the corresponding blood pressure reductions were 3.6 mm Hg systolic (95% CI: 2.9 to 4.3 mm Hg) and 1.1 mm Hg diastolic (95% CI: 0.7 to 1.6 mm Hg), respectively (Figure 3).

At 12 months, in the patients of the control group ($n = 1355$), the sitting blood pressure had fallen by 11.6 mm Hg systolic (95% CI: 10.7 to 12.5 mm Hg) and by 3.7 mm Hg (95% CI: 3.3 to 4.3 mm Hg) diastolic; in the patients previously randomised to active treatment ($n = 1478$), the corresponding blood pressure reductions were 4.7 mm Hg (95% CI: 4.0 to 5.4 mm Hg) and 1.1 mm Hg (95% CI: 0.7 to 1.5 mm Hg), respectively (Figure 3).

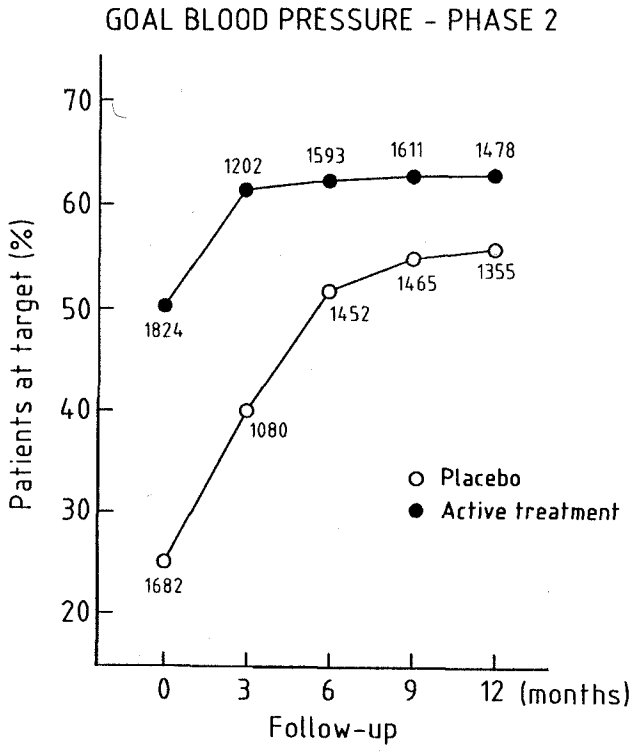

Figure 2 Proportion of patients reaching the goal systolic blood pressure (<150 mm Hg) at entry in Syst-Eur phase 2 and at 3, 6, 9 and 12 months of open-label follow-up. Open and closed symbols indicate the patients formerly randomised to placebo or active treatment, respectively; the total number of patients at each follow-up visit is presented for the two arms of the trial, separately.

If for all patients whose blood pressure had been measured during follow-up in Syst-Eur phase 2, the most recent visit was taken, the sitting blood pressure had fallen by 13.2 mm Hg systolic (95% CI: 12.4 to 14.0 mm Hg) and by 4.6 mm Hg (95% CI: 4.2 to 5.0 mm Hg) diastolic in the patients of the control group ($n = 1682$); in the patients previously randomised to active treatment ($n = 1824$), the corresponding blood pressure reductions were 5.2 mm Hg (95% CI: 4.5 to 5.9 mm Hg) and 1.6 mm Hg (95% CI: 1.2 to 1.8 mm Hg), respectively.

Table 3 *Antihypertensive drug treatment during Syst-Eur 2*

	Formerly randomised to placebo				*Formerly randomised to active treatment*			
	month 3	*month 6*	*month 12*	*last visit*	*month 3*	*month 6*	*month 12*	*last visit*
Total number of patients	1083	1457	1357	1673	1210	1593	1481	1817
On antihypertensive drugs	954	1363	1299	1585	1181	1565	1452	1769
Only nitrendipine	716	898	684	793	657	808	678	815
Study drugs other than nitrendipine	134	317	489	628	467	657	675	833
Only other antihypertensive drugs	104	148	126	164	57	100	99	121
Drugs taken[a]								
Nitrendipine	811	1123	1022	1236	994	1286	1149	1398
Enalapril	132	307	454	571	420	599	609	745
Hydrochlorothiazide	21	55	120	185	162	230	265	363
Other antihypertensive drugs	121	181	185	245	71	125	148	193
No antihypertensive drugs	129	94	58	88	29	28	29	48
Treatment unknown	NA	NA	NA	9	NA	NA	NA	7

[a]Because many patients were on combined treatment, numbers do not add up.

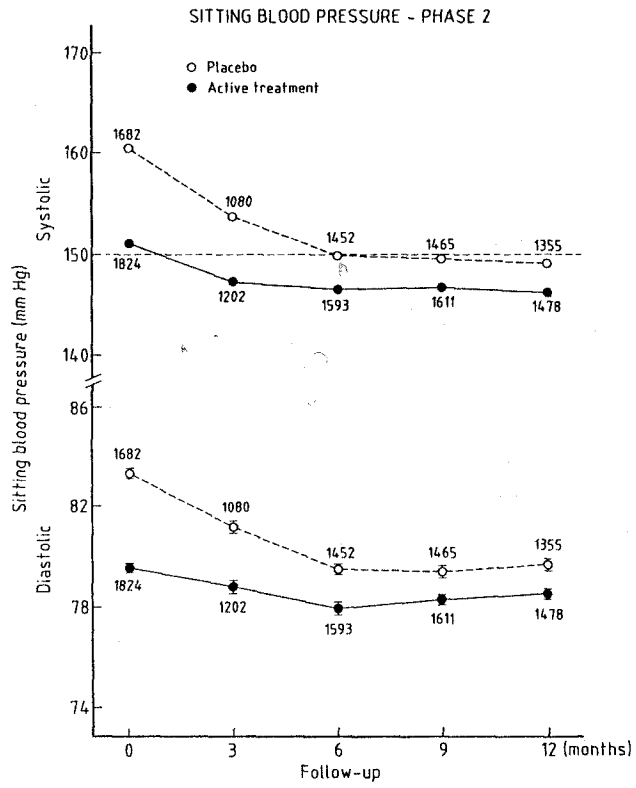

Figure 3 Sitting systolic blood pressure at entry in Syst-Eur 2 and at 3, 6, 9 and 12 months of follow-up. Open and closed symbols indicate the patients formerly randomised to placebo or active treatment, respectively; the total number of patients at each follow-up visit is presented for the two arms of the trial, separately.

At the start of Syst-Eur 2, the net between-group differences in systolic and diastolic blood pressure (placebo minus active-treatment group) were 9.5 mm Hg (95% CI: 8.5 to 10.5 mm Hg) and 3.8 mm Hg (95% CI: 3.3 to 4.3 mm Hg), respectively. At 3 months, these differences were 6.6 mm Hg (95% CI: 5.5 to 7.7 mm Hg) and 2.4 mm Hg (95% CI: 1.8 to 3.1 mm Hg), at 12 months 3.0 mm Hg (95% CI: 2.5 to 3.5 mm Hg) and 1.2 mm Hg (95% CI: 0.6 to 1.8 mm Hg), and at the last available visit 1.7 mm Hg (95% CI: 0.8 to 2.6 mm Hg) and 0.9 mm Hg (95% CI: 0.4 to 1.5 mm Hg).

Standing blood pressure

At entry in Syst-Eur 2, the mean standing systolic blood pressure in the patients formerly randomised to placebo was 157.7 ± 16.7 mm Hg and in those of the active-treatment group 148.2 ± 15.5 mm Hg (Table 1). In the placebo and active-treatment groups, the mean reductions in the standing systolic blood pressure were 6.9 mm Hg (95% CI: 6.0–7.8 mm Hg) and 3.6 mm Hg (2.8–4.4 mm Hg) at 3 months, 11.9 mm Hg (95% CI: 11.0–12.8 mm Hg) and 4.5 mm Hg (3.7–5.3 mm Hg) at 12 months, and 12.9 mm Hg (95% CI: 12.0–13.8 mm Hg) and 5.1 mm Hg (4.4–5.8 mm Hg) at the last follow-up visit. The between-group differences in the standing systolic blood pressure (placebo minus active-treatment group) were 9.5 mm Hg (95% CI: 8.4 to 10.6 mm Hg) at baseline, 6.4 mm Hg (95% CI: 5.2 to 7.6 mm Hg) at 3 months, 2.4 mm Hg (95% CI: 1.3 to 3.5 mm Hg) at 12 months, and 1.7 (95% CI: 0.7 to 2.7 mm Hg) at the last follow-up visit.

At 12 months, 2.0% of the patients randomised to placebo ($n = 27$) and a similar percentage of those randomised to active treatment (1.9%; $n = 28$) showed upon changing from the sitting to the standing position a fall in their systolic blood pressure of 20 mm Hg or more; these proportions were similar to those observed at entry into Syst-Eur 2 (2.2%; $n = 37$ and 2.3%; $n = 41$, respectively).

Pulse rate

In the patients formerly randomised to placebo, the within-group changes in pulse rate (follow-up minus baseline) averaged 0.3 beats per minute (bpm) at 3 months (95% CI: −0.2 to 0.8 bpm; $n = 1080$), 1.0 bpm at 12 months (95% CI: 0.5 to 1.5 bpm; $n = 1355$), and 0.7 bpm at the last available visit (95% CI: 0.2 to 1.2 bpm; $n = 1682$). In the patients formerly randomised to active treatment, these changes were −0.2 bpm at 3 months (95% CI: −0.7 to 0.3 bpm; $n = 1202$), 0.4 bpm at 12 months (95% CI: −0.1 to 0.9 bpm; $n = 1478$), and 0.1 bpm at the last available visit (95% CI: −0.3 to 0.5 bpm; $n = 1824$).

The between-group differences in pulse rate (placebo minus active-treatment group group) were significant at baseline (95% CI: −1.3 to −0.1 bpm), but not significant at 3 months (95% CI: −0.4 to 1.0 bpm), at 12 months (−0.6 to 0.6 bpm), or at the last available follow-up visit in Syst-Eur 2 (95% CI: −0.5 to 0.7 bpm).

Discussion

After termination of the double-blind phase of the Syst-Eur trial, the ethics committee recommended that the coordinating office should do everything possible to ensure continuity of treatment for the patients in the actively treated group and to offer active treatment to those in the placebo group. Furthermore, the patients initially randomised to placebo had to be followed on open-label antihypertensive medication to ascertain that their blood pressure would become adequately controlled. In keeping with these ethical recommendations, most of the Syst-Eur patients, after informed consent had been renewed, were enrolled in the open follow-up study. Within 6 months of the start of Syst-Eur 2, the mean systolic blood pressure in the patients formerly randomised to placebo diminished to a level below 150 mm Hg. The finding that systolic blood pressure also decreased further in the patients formerly randomised to active treatment was rather unexpected. This may be due to the fact that the evidence produced by the Syst-Eur trial[3] was convincing and motivated the investigators to further uptitrate treatment to achieve optimal blood pressure control and greater risk reduction in their patients.

The study medication and treatment strategy used in Syst-Eur 2 are in keeping with the recent recommendations of the Joint National Committee on the Prevention, Detection, Evaluation, and Treat-

ment of High Blood Pressure (JNC VI).[26] According to these guidelines, diuretics and long-acting dihydropyridine calcium-channel blockers should be preferred as first-line treatment in older patients with isolated systolic hypertension. The advice to consider the latter disorder as an indication for long-acting dihydropyridines was largely based on the Syst-Eur results. Indeed, in the intention-to-treat analysis,[3] active treatment decreased the overall stroke rate from 13.7 to 7.9 end-points per 1000 patient-years (–42%; $P = 0.003$) and the incidence of all cardiovascular complications from 33.9 to 23.3 end-points per 1000 patient-years (–31%; $P < 0.001$).[3] At the rates observed in the placebo group, treating 1000 patients for 5 years could prevent 29 strokes or 53 major cardiovascular end-points.[3] Whereas analysis by intention-to-treat reduces bias due to selective withdrawals, it may underestimate the true effects of treatment by including all end-points in the calculations, regardless of whether they occurred on randomised therapy or on open-label medication. In the per-protocol analysis of the Syst-Eur trial,[27] active treatment reduced total mortality by 24% ($P = 0.05$), all fatal and non-fatal cardiovascular end-points by 32% ($P < 0.001$), all strokes by 44% ($P = 0.004$), non-fatal stroke by 48% ($P = 0.005$) and all cardiac end-points, including sudden death, by 26% ($P = 0.05$). With regard to Syst-Eur 2, it is important to note that the cardiovascular benefit in the Syst-Eur trial was equally observed in the patients remaining on monotherapy with nitrendipine as in those progressing to combined treatment with nitrendipine plus enalapril, hydrochlorothiazide, or both drugs.[9]

In 1995, a case-control study raised the possibility that calcium-channel blockers prescribed to patients with hypertension may increase the risk of myocardial infarction.[15] In a quantitative review of 16 randomised secondary prevention trials, the use of short-acting nifedipine in patients with coronary heart disease was found to be associated with a 16% (95% CI: 1 to 33%) higher mortality.[4] Furthermore, a prospective cohort study observed that the intake of verapamil and diltiazem, but not nifedipine, was correlated with a greater risk of gastro-intestinal haemorrhage in hypertensive persons over 67 years old.[14] Other findings in the same cohort suggested that treatment with calcium-channel blockers would be associated with a general increased risk of cancer.[12,13] These observational reports[4,12–15] left a large margin of uncertainty. With regard to myocardial infarction confounding by indication could not be excluded. One report[13] associating the use of calcium-channel blockers with cancer was based on 47 exposed cases spread over a wide variety of cancer sites and only provided information on exposure to calcium-channel blockers at baseline. In the same cohort patients taking calcium-channel blockers were more likely to be on treatment with warfarin (6.0% *vs* 2.6%; $P < 0.001$) or aspirin (37.3% *vs* 29.7%; $P < 0.001$),[13] which may have confounded the issue of gastro-intestinal bleeding.[14] A nested case-control analysis based on the information taken from the General Practice Research Database in the United Kingdom collected full information on exposure time, but did not find an increased cancer risk in users of calcium-channel blockers or angiotensin-converting enzyme inhibitors relative to the patients on beta-blockers.[28]

The Appropriate Blood Pressure Control in Diabetes (ABCD) Trial[18] enrolled 570 diabetic patients and reported after 67 months of study a significantly higher incidence of fatal and non-fatal myocardial infarction (25 *vs* 5) in the patients randomised to nisoldipine than among those treated with enalapril. However, the ABCD trial was designed to study changes in the creatinine clearance. Myocardial infarction was only one of the secondary end-points.[18] Treatment status and the doses of the double-blind study medications at the time of the infarcts were not reported. Because more diuretics (119 *vs* 93; $P = 0.02$) and beta-blockers (95 *vs* 89; $P = 0.04$) were prescribed in the enalapril group, and because the study medication was stopped slightly more frequently in the nisoldipine group (142 *vs* 129; $P = 0.22$), overall, medical cardiovascular protection could have been unbalanced in favour of the enalapril group. Any cardiovascular event may be the forerunner of myocardial infarction. For this reason, a first-ever-event analysis could have been helpful to correctly interpret the ABCD results, but was not presented.[18] In the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET),[17] the patients receiving fosinopril had a significantly lower risk of the combined outcome of acute myocardial infarction, stroke, or hospitalized angina pectoris than those receiving amlodipine (14/189 *vs* 27/191 events). However, the FACET trial had an open design and events were monitored by 'asking' the patients if they had been hospitalized or had experienced any other event. In contrast to the ABCD trial,[18] the worse outcome on amlodipine compared with the converting-enzyme inhibitor was not due to myocardial infarction (13 *vs* 10), but was driven by hospitalized angina (4 *vs* 0) and stroke (10 *vs* 4). The interpretation of the FACET results[17] is also rendered difficult, because 58 patients randomised to fosinopril (30.7%) and 50 of the amlodipine group (26.2%) crossed over and received the combination of both drugs. A recent subgroup analysis of the Syst-Eur trial[29] showed that in patients with diabetes mellitus active treatment reduced all-cause mortality by 55%, cardiovascular mortality by 76%, all cardiovascular end-points by 69%, fatal and non-fatal stroke by 73% and all cardiac end-points by 63%. In the non-diabetic patients, active treatment decreased all cardiovascular end-points by 26% and fatal and non-fatal stroke by 38%. Active treatment reduced total mortality ($P = 0.04$), cardiovascular mortality ($P = 0.02$) and all cardiovascular end-points ($P = 0.01$) significantly more in the diabetic than the non-diabetic Syst-Eur patients.[29]

In spite of the evidence produced by the Syst-Eur trial[3,9,27,29] and other placebo-controlled outcome studies in hypertension,[10,11] the controversy about the use of calcium-channel blockers as first-line drugs for the treatment of hypertension is still alive. Several arguments fuel the debate. The median follow-up of 2 years in the Syst-Eur trial[3] may have been too short to reveal the suspected adverse effects

of dihydropyridines, such as cancer,[12,13] gastrointestinal bleeding,[14] or coronary complications in patients with pre-existing coronary heart disease[4,15,16] or diabetes mellitus.[17–22] Syst-Eur 2 will answer these reservations. Of the patients enrolled, 2.3% already experienced a major cardiovascular complication prior to the end of the Syst-Eur trial proper, and 12.2% have diabetes mellitus. In contrast to the earlier observational studies, the hypotheses, the procedures to be followed, and the timing of the interim and final analyses have been stated '*a priori*.' Because in Syst-Eur 2 antihypertensive drug treatment is standardized and the same in all patients, confounding by indication can only play a minor role. A blinded expert committee will validate all major cardiovascular complications and possible adverse events, such as cancer, gastro-intestinal bleeding, or anaemia. One important difference with the Syst-Eur trial proper is that in Syst-Eur 2 the open-label study medication must not be stopped if the patients experience a major event, unless the study drugs are suspected to have played a causal role. In case of major complication adequate treatment may be administered without stopping the study medication. Some cardiovascular events, such as stroke or congestive heart failure, may actually require that the study medication be up-titrated to tighten blood pressure control or to support left-ventricular function.

Finally, the vascular dementia project, set up in the framework of the Syst-Eur trial,[30–32] investigated whether antihypertensive drug treatment could reduce the incidence of dementia. Compared with placebo ($n = 1180$), active treatment ($n = 1238$) reduced the rate of dementia by 50% from 7.7 to 3.7 cases per 1000 patient-years (21 *vs* 11 patients in the intention-to-treat analysis, $P = 0.05$).[32] In Syst-Eur 2, the dementia project[30–32] will be continued. The hypothesis will be tested that long-term treatment with the dihydropyridine nitrendipine[2] (patients originally randomised to active treatment) would provide better protection against dementia than short-term treatment (patients originally randomised to placebo, in whom nitrendipine was only started at the beginning of Syst-Eur 2). In view of the increasing longevity of populations worldwide, confirmation of the initial results on the prevention of dementia[32] may have important public health implications.

In conclusion, Syst-Eur phase 2 is an open follow-up study, which aims to confirm the long-term safety of antihypertensive therapy based on a dihydropyridine. Of 3766 eligible patients, 3506 patients (93.0%) were enrolled, and 2664 (76.0%) were started or continued on nitrendipine as first-line antihypertensive agent. The study is expected to stop after 5 years and to report its results in the year 2002.

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References

1 Amery A *et al.* Syst-Eur. A multicentre trial on the treatment of isolated systolic hypertension in the elderly: objectives, protocol, and organization. *Aging Clin Exp Res* 1991; **3**: 287–302.
2 Goa KL, Sorkin EM Nitrendipine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of hypertension. *Drugs* 1987; **33**: 123–155.
3 Staessen JA *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension [correction published in *Lancet* 1997, volume 350, 29 November, p 1636]. *Lancet* 1997; **350**: 757–764.
4 Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; **92**: 1326–1331.
5 Frohlich ED, Zanchetti A. Antihypertensive therapy: safety and efficacy of drugs and publications. *Hypertension* 1996; **27**: 317–318.
6 Opie LH, Messerli FH. Nifedipine and mortality. Grave defects in the dossier *Circulation* 1995; **92**: 1068–1073.
7 McMurray J, Murdoch D. Calcium-antagonist controversy: the long and short of it? *Lancet* 1997; **349**: 585–586.
8 Walker JF, Stampfer MJ. Observational studies of drug safety. *Lancet* 1997; **348**: 489.
9 Staessen JA *et al.* Calcium channel blockade and cardiovascular prognosis in the European trial on isolated systolic hypertension. *Hypertension* 1998; **32**: 410–416.
10 Gong L *et al.* Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens* 1996; **14**: 1237–1245.
11 Liu L, Wang JG, Gong L, Liu G, Staessen JA, for the Systolic Hypertension in China (Syst-China) Collaborative Group: Comparison of active treatment and placebo for older patients with isolated systolic hypertension. *J Hypertens* 1998; **16**: 1823–1829.
12 Pahor M *et al.* Do calcium channel blockers increase the risk of cancer? *Am J Hypertens* 1996; **9**: 695–699.
13 Pahor M *et al.* Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; **348**: 493–497.
14 Pahor M *et al.* Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; **347**: 1061–1065.
15 Psaty BM *et al.* The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA* 1995; **274**: 620–625.
16 Alderman MH, Cohen H, Roqué R, Madhavan S. Effect of long-acting and short-acting calcium antagonists on cardiovascular outcomes in hypertensive patients. *Lancet* 1997; **349**: 594–598.
17 Tatti P *et al.* Outcome results of the Fosinopril versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in patients with hypertension and NIDDM. *Diabetes Care* 1998; **21**: 597–603.
18 Estacio RO *et al.* The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N Engl J Med* 1998; **338**: 645–652.
19 Alderman M, Madhavan S, Cohen H. Calcium antagonists and cardiovascular events in patients with hypertension and diabetes. *Lancet* 1998; **351**: 216–217.
20 Byington RP, Craven TE, Furberg CD, Pahor M. Isradipine, raised glycosylated haemoglobin, and risk of cardiovascular events. *Lancet* 1998; **350**: 1075–1076.
21 Pahor M, Kritchevsky, SB, Zuccala G, Guralnik JM. Diabetes and risk of adverse events with calcium antagonists. *Diabetes Care* 1998; **21**: 193–194.
22 Pahor M, Psaty BM, Furberg CD. Treatment of hypertensive patients with diabetes. *Lancet* 1998; **351**: 689–690.
23 41st World Medical Assembly: Declaration of Helsinki: recommendations guiding physicians in biomedical research involving human subjects. *Bull Pan Am Health Organ* 1990; **24**: 606–609.
24 World Health Organization. International Classi-

fication of Diseases. Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Based on the Recommendations of the Ninth Revision Conference, 1975, and Adopted by the Twenty-Ninth World Health Assembly. Volume 1. Geneva, Switzerland, World Health Organization, 1977.

25 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35**: 549–556.

26 The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997; **157**: 2413–2446.

27 Staessen JA *et al.* Subgroup and per-protocol analysis of the randomized European trial on isolated systolic hypertension in the elderly. *Arch Intern Med* 1998; **158**: 1681–1691.

28 Jick H *et al.* Calcium-channel blockers and risk of cancer. *Lancet* 1997; **349**: 525–528.

29 Tuomilehto J *et al.* Cardiovascular prognosis in older diabetic and nondiabetic patients treated or untreated for isolated systolic hypertension. *N Engl J Med* 1998 (submitted for publication).

30 Forette F *et al.* Is prevention of vascular dementia possible? The Syst-Eur Vascular Dementia Project. *Aging Clin Exp Res* 1991; **3**: 373–382.

31 Seux ML *et al.* Correlates of cognitive status of old patients with isolated systolic hypertension: the Syst-Eur Vascular Dementia Project. *J Hypertens* 1998; **16**: 963–969.

32 Forette F *et al.* Prevention of dementia in the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet* 1998; **352**: 1347–1351.