Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial

Jan A. Staessen[a], Lutgarde Thijs[a], Robert Fagard[a], Hilde Celis[a], Willem H. Birkenhäger[b], Christopher J. Bulpitt[c], Peter W. de Leeuw[d], Astrid E. Fletcher[e], Françoise Forette[f], Gastone Leonetti[g], Patricia McCormack[h], Choudomir Nachev[i], Eoin O'Brien[h], José L. Rodicio[j], Joseph Rosenfeld[k], Cinzia Sarti[l], Jaakko Tuomilehto[l], John Webster[m], Yair Yodfat[n] and Alberto Zanchetti[g], for the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators

Background **To assess the impact of immediate versus delayed antihypertensive treatment on the outcome of older patients with isolated systolic hypertension, we extended the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial by an open-label follow-up study lasting 4 years.**

Methods **The Syst-Eur trial included 4695 randomized patients with minimum age of 60 years and an untreated blood pressure of 160–219 mmHg systolic and below 95 mmHg diastolic. The double-blind trial ended after a median follow-up of 2.0 years (range 1–97 months). Of 4409 patients still alive, 3517 received open-label treatment consisting of nitrendipine (10–40 mg daily) with the possible addition of enalapril (5–20 mg daily), hydrochlorothiazide (12.5–25 mg daily), or both add-on drugs. Non-participants ($n = 892$) were also followed up.**

Results **Median follow-up increased to 6.1 years. Systolic pressure decreased to below 150 mmHg (target level) in 2628 participants (75.0%). During the 4-year open-label follow-up, stroke and cardiovascular complications occurred at similar frequencies in patients formerly randomized to placebo and those continuing active treatment. These rates were similar to those previously observed in the active-treatment group during the double-blind trial. Considering the total follow-up of 4695 randomized patients, immediate compared with delayed antihypertensive treatment reduced the occurrence of stroke and cardiovascular complications by 28% ($P = 0.01$) and 15% ($P = 0.03$), respectively, with a similar tendency for total mortality (13%, $P = 0.09$). In 492 diabetic patients, the corresponding estimates of long-term benefit ($P < 0.02$) were 60, 51 and 38%, respectively.**

Conclusions **Antihypertensive treatment can achieve blood pressure control in most older patients with isolated systolic hypertension. Immediate compared with delayed treatment prevented 17 strokes or 25 major cardiovascular events per 1000 patients followed up for 6 years. These findings underscore the necessity of early treatment of isolated systolic hypertension.** ***J Hypertens*** **22:847–857 © 2004 Lippincott Williams & Wilkins.**

Journal of Hypertension 2004, **22**:847–857

Keywords: calcium-channel blocker, clinical trial, isolated systolic hypertension, outcome, myocardial infarction, stroke

[a]Department of Molecular and Cardiovascular Research, University of Leuven, Belgium; [b]Erasmus University, Rotterdam, The Netherlands; [c]Division of Geriatric Medicine, Department of Medicine, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK; [d]Department of Internal Medicine, University Hospital Maastricht, The Netherlands; [e]Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London, UK; [f]Department of Geriatrics, Hôpital Broca, CHU Cochin, University of Paris V, Paris, France; [g]Centro di Fisiologia Clinica e Ipertensione, Ospedale Maggiore, University of Milan and Istituto Auxologico Italiano, Milan, Italy; [h]Beaumont Hospital, Dublin, Ireland; [i]Department of Internal Medicine, Alexandrov's University Hospital, Sofia, Bulgaria; [j]Hospital 12de Octubre, Madrid, Spain; [k]Sackler School of Medicine, Tel Aviv, Israel; [l]Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland; [m]Clinical Pharmacology Unit, Aberdeen Royal Infirmary, Scotland, UK; [n]Department of Family Medicine, Hadassah Medical School, Hebrew University of Jerusalem, Jerusalem, Israel.

Sponsorship: The Syst-Eur trial was a concerted action of the BIOMED Research Programme sponsored by the European Union. The trial was carried out in consultation with the World Health Organization, the International Society of Hypertension, the European Society of Hypertension and the World Hypertension League. Bayer AG (Wuppertal, Germany) sponsored the study. Bayer AG and Merck Sharpe and Dohme Inc. (West Point, Pennsylvania, USA) donated the study medications.

Conflicts of interest: Authors and members of the Syst-Eur management committees have received travel grants or honoraria from Bayer AG.

Correspondence and requests for reprints to Jan A. Staessen, M.D., Ph.D., Studiecoördinatiecentrum, Laboratorium Hypertensie, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Tel: +32 16 34 7104; fax: +32 16 34 7106, +32 16 34 5763; e-mail: jan.staessen@med.kuleuven.ac.be

Received 2 July 2003 **Revised** 1 December 2003
Accepted 5 December 2003

See editorial commentary page 689

0263-6352 © 2004 Lippincott Williams & Wilkins

DOI: 10.1097/01.hjh.0000098286.36684.27

Introduction

In older subjects, isolated systolic hypertension is by far the predominant type of blood pressure elevation and carries a high risk of cardiovascular complications [1]. Intervention trials in patients with isolated systolic hypertension demonstrated that lowering systolic blood pressure by approximately 10 mmHg reduces the incidence of stroke by 30%, and that of all cardiovascular complications by 25% [2–5]. Isolated systolic hypertension requires lifelong treatment, but the median follow-up in these trials was only 3.8 years [4]. Furthermore, increased systolic blood pressure is the main cause of uncontrolled hypertension, of which the prevalence among hypertensive patients often exceeds 50% [6,7]. Estimates of the relative and absolute shortfalls in cardiovascular outcomes due to the delayed administration of antihypertensive treatment are currently unavailable.

Because of a 42% decrease in the risk of stroke, the double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial [3] stopped prematurely in February 1997 after the patients had been followed up for a median of 2 years. We extended the double-blind trial by an open-label study. All Syst-Eur patients, who were still available for follow-up, received active treatment based on the dihydropyridine nitrendipine for a further 4 years. In this article, we compared the effects of early and delayed blood pressure-lowering therapy on their long-term outcome.

Methods

Study design

The Ethics Committees of the University of Leuven and the participating institutions approved the protocols of the double-blind trial [3] and the follow-up study [8]. The Helsinki declaration for investigation in human subjects served as standard for the implementation of the Syst-Eur project. Participants were recruited in 198 centres in 23 countries across eastern and western Europe [3]. They were at least 60 years old. During the run-in period on placebo, they had, when seated, a systolic pressure of 160–219 mmHg with diastolic blood pressure below 95 mmHg. The entry blood pressure was the mean of six readings – two at three baseline visits, 1 month apart. After stratification by centre, sex and previous cardiovascular complications, a computerized random function without blocking or minimization algorithm assigned patients to double-blind treatment with either active medication or placebo. After termination of the double-blind trial on 14 February 1997, all patients who were still visiting follow-up clinics were invited to continue, or to start, antihypertensive therapy with the same study medications as used previously in the active-treatment arm. Patients originally assigned to nitrendipine are referred to as the active-treatment group and those originally assigned to placebo as the placebo group.

Follow-up

The goal of treatment was to lower systolic pressure (the mean of two readings obtained in the sitting position) to below 150 mmHg. Doctors attempted to reach the target blood pressure by stepwise titration of nitrendipine (10–40 mg daily), the first-line medication, with the possible addition of enalapril (5–20 mg daily) or hydrochlorothiazide (12.5–25.0 mg daily), or both add-on drugs. If side-effects occurred, study medications could be back-titrated or stopped and replaced by another study drug. In treatment-resistant patients, the open-label study medication could be associated with, or replaced by, any other antihypertensive drug. During the double-blind trial and during the first year of the open-label study, clinic visits were scheduled every 3 months. From the second year of the open-label follow-up onwards, reports were due every 6 months. For patients who withdrew from the study or who could not be followed up as planned, investigators collected information, at yearly intervals, on vital status, occurrence of diseases and the use of antihypertensive medications. The extended follow-up stopped on 31 December 2001. Patients without any report within the year before this date were counted as lost to follow-up.

The endpoint committee, whose members were unaware of randomization groups, reviewed the outcomes defined in the study protocols [3,8], which included death, stroke, retinal haemorrhage or exudates, myocardial infarction, congestive heart failure, dissecting aortic aneurysm and renal insufficiency. Stroke did not include transient ischaemic attack. Cardiac events consisted of myocardial infarction, heart failure and sudden death. Renal insufficiency was diagnosed if at two consecutive visits the serum creatinine concentration reached or exceeded 360 μmol/l or doubled compared with the concentration at randomization. To investigate the adverse outcomes attributed by some investigators to the use of calcium-channel blockers [9–12], we compared the incidence of myocardial infarction, benign neoplasm, cancer and haemorrhagic complications between patients on short-term (placebo group) versus long-term treatment with active nitrendipine. In addition, we introduced the use of active nitrendipine as a time-dependent covariable in multiple Cox regression.

Statistical analysis

For database management and statistical analysis, we used SAS version 8.1 (SAS Institute, Cary, North Carolina, USA). The data were entered in duplicate at the coordinating office (Leuven, Belgium) with systematic quality checks every 3 months. The data-monitoring committee conducted the statistical analysis by intention to treat using two-sided tests. Means and

proportions were compared by the standard normal z test and χ^2 analysis, respectively. We plotted survival curves using Kaplan–Meier estimates. Unadjusted and adjusted between-group comparisons of disease outcomes relied on the log-rank test and Cox regression, respectively. In Cox regression, we adjusted the time to an event for patient characteristics at randomization with proven impact on outcome [13], including sex, age, previous cardiovascular complications, systolic blood pressure, smoking status and residence in western versus eastern Europe. We used appropriate interaction terms in Cox regression to test the homogeneity of the treatment effects in subgroups delineated by stratification [3] or other criteria used in previous analyses [13,14]. Diabetes was defined, by the criteria of the World Health Organization [15], as a history of diabetes mellitus, treatment with antidiabetic drugs or a fasting or non-fasting blood glucose concentration equal to or greater than 7.8 or 11.1 mmol/l, respectively [15].

Role of the funding source

The Syst-Eur investigators initiated, designed and conducted the study independent of the sponsor. The study-coordinating centre processed the data and prepared all scientific reports.

Results

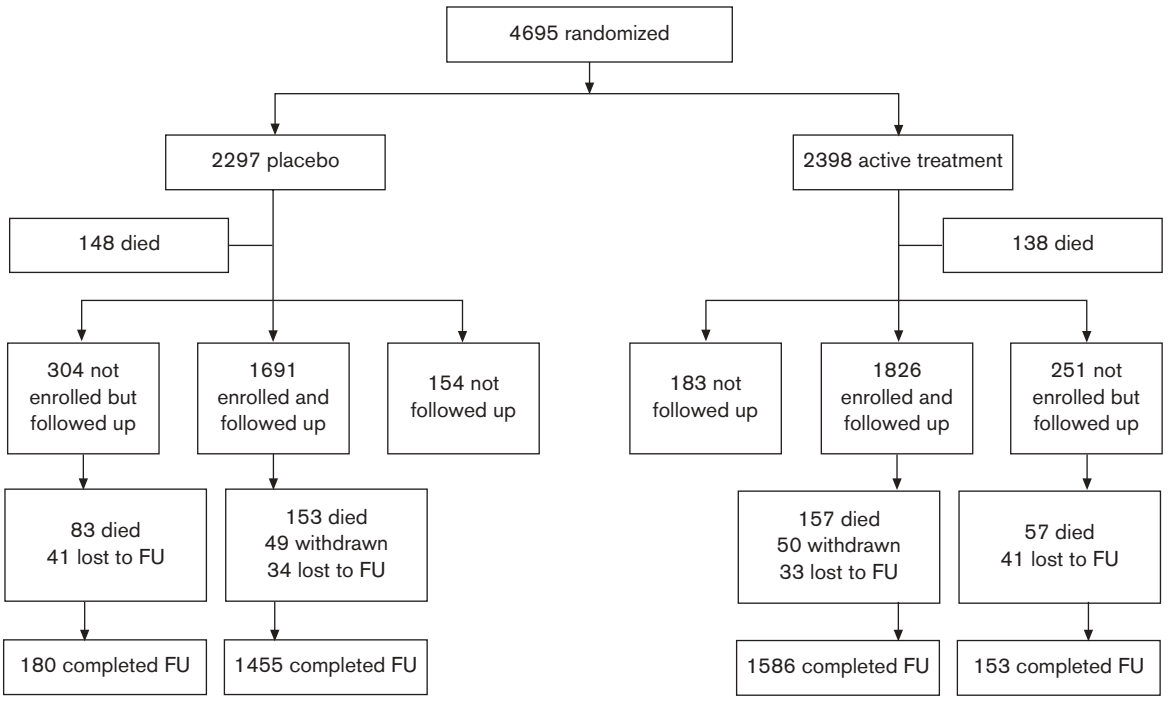
Study profile

At the end of the double-blind trial [16], of 2297 patients originally randomized to placebo and 2398 allocated to active treatment, 148 (6.4%) and 138 (5.8%) had died. Of the patients who were still alive and available for follow-up ($n = 4409$), 1691 of the former placebo group and 1826 of the active-treatment group consented to be enrolled in the open-label study. The participation rate was 92.2 and 94.0%, respectively. Of the patients not enrolled in the open-label study, 304 randomized to placebo and 251 allocated to active treatment could be followed up. For 154 and 183 patients, respectively, only information collected during the double-blind trial was available for analysis (Fig. 1).

Characteristics of participants and non-participants

Table 1 summarizes the characteristics at randomization of the 3517 patients enrolled in the open-label study, and those of the 892 non-participants. Participants compared with non-participants were younger (69.0 versus 72.6 years), more obese (27.3 versus 26.4 kg/m^2) and had lower systolic pressure (173.4 versus 174.7 mmHg), higher diastolic pressure (85.7 versus 85.2 mmHg) and lower heart rate (72.8 versus 73.7 beats per minute). Female sex (66.6 versus 70.0%), smoking (6.5 versus

Fig. 1



Study profile. FU indicates follow-up.

Table 1 Clinical features of treatment groups at randomization

Characteristic	Patients enrolled in the open follow-up study			Patients not enrolled in open follow-up study	
	Placebo ($n = 1691$)	Active ($n = 1826$)		Placebo ($n = 458$)	Active ($n = 434$)
Mean (SD) of entry characteristic					
Age (years)	69.0 ± 6.0	69.0 ± 5.9	***	72.6 ± 6.7	72.6 ± 6.9
Systolic pressure (mmHg)	173.4 ± 9.5	173.3 ± 9.4	***	174.6 ± 11.1	174.8 ± 11.0
Diastolic pressure (mmHg)	85.6 ± 5.7	85.7 ± 5.7	*	85.4 ± 6.0	84.9 ± 6.2
Pulse rate (beats per minute)	72.8 ± 8.0	72.8 ± 7.9	**	73.1 ± 8.0	74.4 ± 7.8
Body mass index (kg/m^2)	27.3 ± 4.0	27.3 ± 4.2	***	26.7 ± 4.2	26.2 ± 4.0
Total cholesterol (mmol/l)	6.05 ± 1.16	5.99 ± 1.16		6.09 ± 1.19	6.00 ± 1.43
HDL cholesterol (mmol/l)	1.40 ± 0.46	1.42 ± 0.48		1.38 ± 0.41	1.39 ± 0.46
Serum creatinine (μmol/l)	88.3 ± 18.6	87.8 ± 18.3	***	84.9 ± 17.6	86.1 ± 19.2
Number (%) with entry characteristic					
Women	1121 (66.3)	1121 (66.9)		317 (69.2)	307 (70.7)
Previous antihypertensive treatment	774 (45.8)	813 (44.5)	**	220 (48.0)	225 (51.8)
Cardiovascular complications	489 (28.9)	544 (29.8)		136 (29.7)	99 (22.8)
Diabetes mellitus[a]	170 (10.1)	190 (10.4)		43 (9.4)	44 (10.1)
Recruited in western Europe	788 (46.6)	895 (49.0)	***	396 (86.5)	388 (89.4)
Current smokers	106 (6.3)	121 (6.6)	*	35 (7.6)	40 (9.2)
Drinking ⩾ 1 unit alcohol/day	181 (10.7)	176 (9.6)	***	69 (15.1)	60 (13.8)

Placebo and active refer to patients originally randomized to placebo or active treatment. [a]Diagnosis based on the criteria of the World Health Organization [15]. *$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$, for comparison of means (normal z test) or proportions (χ^2 statistic) between patients enrolled versus not enrolled in the open follow-up study.

8.4%) and daily intake of alcohol (10.2 versus 14.5%) were slightly less prevalent among participants than non-participants (Table 1).

Among participants and non-participants, patients in the placebo and active-treatment groups had similar entry characteristics (Table 1).

Antihypertensive therapy

During the double-blind trial [3], the proportion of patients progressing to combination therapy with study medications, either placebos or active study drugs, increased faster in the placebo than in the active-treatment group (59.9 versus 40.6% at the last visit on double-blind treatment, $P < 0.0001$). In contrast, at the last visit of the open-label study, the proportion of participants having proceeded to combination therapy was similar in those formerly randomized to placebo (52.1%) and in those continuing active treatment (51.3%). Of 1691 participants originally randomized to placebo, at the last visit, 1282 (75.8%) took nitrendipine either in monotherapy ($n = 572$, 33.8%) or in combination with enalapril, hydrochlorothiazide or other antihypertensive drugs ($n = 710$, 42.0%), 73 (4.3%) and 16 (0.9%) were on monotherapy with enalapril or hydrochlorothiazide, respectively, and 87 (5.1%) were not treated for hypertension. Among 1826 patients continuing active treatment, at the last visit, 1385 (75.8%) took nitrendipine, either alone ($n = 631$, 34.6%) or in combination with other drugs ($n = 754$, 41.3%); 86 (4.7%) and 42 (2.3%) were on monotherapy with enalapril or hydrochlorothiazide, respectively; and 74 (4.1%) were not treated. At the last visit, the mean (± SD) daily doses of the study drugs in the participants first randomized to placebo were 31.1 ± 11.4 mg ($n = 1264$) for nitrendipine, 15.7 ± 5.6 mg for enalapril ($n = 723$) and 23.8 ± 9.6 mg ($n = 369$) for hydrochlorothiazide. In the participants continuing active treatment, these doses were 31.4 ± 11.1 mg ($n = 1374$), 15.8 ± 5.7 mg ($n = 826$) and 24.0 ± 8.5 mg ($n = 445$), respectively.

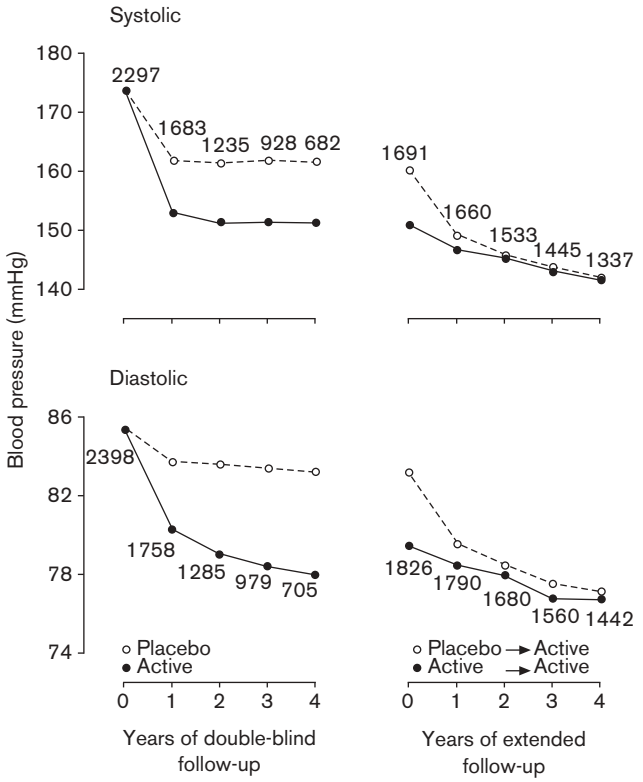
Among non-participants, information on therapy was available for 210 patients randomized to placebo and 191 allocated to active treatment, of whom 174 (82.9%) and 145 (75.9%) were on antihypertensive drug treatment.

Blood pressure control

From randomization to the last visit of the double-blind trial (Fig. 2), systolic blood pressure decreased from 173.9 ± 10.1 to 162.4 ± 17.2 mmHg in the placebo group and from 173.8 ± 9.9 to 150.8 ± 14.7 mmHg in the active-treatment group. Diastolic blood pressure changed from 85.5 ± 5.9 to 83.5 ± 8.3 mmHg and from 85.5 ± 5.8 to 79.4 ± 8.4 mmHg, respectively. Thus, at the end of the double-blind trial, the blood pressure differences between the two treatment groups averaged 11.6 mmHg (95% CI 10.7–12.5) systolic and 4.1 mmHg (95% CI 3.6–4.6) diastolic. Compared with placebo, more patients allocated to active treatment had reached a systolic pressure below 150 mmHg (21.1 versus 50.1%, $P < 0.0001$).

From enrolment into the open-label study to the last visit of the extended follow-up, systolic blood pressure fell from 160.4 ± 16.2 to 143.5 ± 13.9 mmHg in the former placebo group and from 151.0 ± 14.6 to 142.9 ± 14.2 mmHg in the active-treatment group. Diastolic blood pressure declined from 83.4 ± 7.8 to 77.2 ± 7.9 mmHg and from 79.6 ± 7.8 to 76.7 ± 8.4 mmHg,

Fig. 2



Systolic and diastolic blood pressures in patients initially assigned to placebo or active treatment. Results are given separately for 4695 patients randomized in the double-blind trial (left) and for 3517 participants subsequently enrolled in the open-label study (right).

respectively. Thus, the systolic differences averaged 9.4 mmHg (95% CI 8.3–10.4) at enrolment in the open follow-up study and 0.7 mmHg (95% CI −0.3–1.6) at the last visit. The corresponding diastolic differences were 3.8 mmHg (3.3–4.3) and 0.5 mmHg (−0.1–1.0), respectively. The differences between the placebo and active-treatment groups in the proportion of patients whose systolic pressure was lower than 150 mmHg decreased from enrolment (25.7 versus 50.5%, $P < 0.001$) to the last visit (74.0 versus 76.0%, $P = 0.17$). Most of the improvement in systolic blood pressure control occurred within 12 months of the switch from randomized to open-label treatment (Fig. 2).

Outcome results

We tabulated outcome results for mortality (Table 2), fatal and non-fatal cardiovascular events (Table 3), and other fatal and non-fatal outcomes (Table 4). Outcomes are presented for the double-blind trial [3,16], the patients enrolled in the open-label follow-up study, non-participants maintained in non-supervised follow-up, and for the overall follow-up of all randomized patients. The Syst-Eur patients were recruited over 8 years [3]. Median follow-up in the double-blind study was 24 months, with follow-up of individual patients ranging from 1 to 97 months [3]. During the double-blind trial, 12 115 patient-years accrued (placebo 5908 plus active treatment 6207), 15 676 during the open-label study (7530 plus 8146), 2105 during non-supervised follow-up (1150 plus 955) and 29 896 overall (14 588 plus 15 308).

The present study allowed us to complete information on outcomes, which had occurred before the end of the double-blind trial (14 February 1997) in patients classified as lost to follow-up in previous reports [3,16]. In this slightly updated analysis of the double-blind trial, active treatment reduced the rate of fatal and non-fatal stroke (Table 3) from 14.0 to 8.5 events per 1000 patient-years (39% reduction, $P = 0.004$) and the incidence of all cardiovascular complications (Table 3) from 34.7 to 25.0 events per 1000 patient-years (28%, $P = 0.002$). All cardiac endpoints decreased by 24% (Table 3). Non-fatal stroke, excluding transient ischaemic attack, declined by 43% ($P = 0.006$). In contrast, total and cardiovascular mortality (Table 2) and deaths from specific cardiovascular disorders (data not shown) were not significantly reduced.

During the extended follow-up on open-label treatment, the rates of fatal and non-fatal stroke (Table 3 and Fig. 3), all cardiovascular complications (Table 3) and cardiovascular mortality (Table 1) in patients formerly randomized to placebo and in those continuing active treatment were similar to those observed on active treatment during the double-blind trial. This resulted in a persistent advantage for patients originally allocated to active treatment (Fig. 3). During the open-label follow-up, no differences occurred in any of the disease outcomes between the patients formerly randomized to placebo and those continuing active treatment. Considering total follow-up, early compared with delayed therapy significantly lowered the rates of fatal and non-fatal stroke (28% reduction, Table 3 and Fig. 3) and all cardiovascular complications (15%, Table 3), with a similar tendency for total mortality (13%, Table 2). In absolute terms, early compared with delayed treatment prevented 17 strokes or 25 major cardiovascular events per 1000 patients followed up for 6 years.

During all study phases, mortality from non-cardiovascular diseases (Table 2) and the incidence of fatal and non-fatal cancer, benign neoplasms, and haemorrhagic complications (Table 4) were similar in patients on short-term (placebo group) and long-term (active-treatment group) therapy with nitrendipine. These conclusions remained unaltered when we introduced the use of active nitrendipine as a time-dependent covariable in Cox regression models adjusted for the patient characteristics at randomization.

Table 2 Mortality

Cause of death	Study phase	Rate per 1000 patient-years (number of events) Placebo	Active	Relative difference (active–placebo) with 95% CI
All causes	DB	25.1 (148)	22.2 (138)	−11 (−30, 12)
	O-FU	20.3 (153)	19.3 (157)	−5 (−24, 19)
	NS-FU	72.2 (83)	59.7 (57)	−17 (−41, 16)
	TOTAL	26.3 (384)	23.0 (352)	−13 (−24, 1)*
Cardiovascular	DB	13.9 (82)	11.0 (68)	−21 (−43, 9)
	O-FU	10.5 (79)	10.4 (85)	−1 (−27, 35)
	NS-FU	34.8 (40)	27.2 (26)	−22 (−52, 28)
	TOTAL	13.8 (201)	11.7 (179)	−15 (−31, 4)
Non-cardiovascular	DB	11.0 (65)	10.5 (65)	−5 (−32, 34)
	O-FU	9.0 (68)	8.5 (69)	−6 (−33, 31)
	NS-FU	31.3 (36)	31.4 (30)	0 (−38, 63)
	TOTAL	11.6 (169)	10.7 (164)	−8 (−25, 15)
Cancer	DB	4.7 (28)	3.1 (19)	−35 (−64, 16)
	O-FU	3.6 (27)	3.9 (32)	10 (−34, 83)
	NS-FU	10.4 (12)	10.5 (10)	0 (−57, 132)
	TOTAL	4.6 (67)	4.0 (61)	−13 (−39, 23)

DB, O-FU, NS-FU and TOTAL, respectively, indicate the double-blind trial, the open follow-up study, the non-supervised follow-up of patients not enrolled in the open-label study, and the overall follow-up of all randomized patients. CI, confidence interval. Placebo and active refer to patients originally randomized to placebo or active treatment. *$P = 0.09$ (log-rank test).

Table 3 Fatal and non-fatal cardiovascular events

Event	Study phase	Rate per 1000 patient-years (number of events) Placebo	Active	Relative difference (active–placebo) with 95% CI
Stroke[a]	DB	14.0 (81)	8.5 (52)	−39 (−57, −14)***
	O-FU	6.4 (48)	5.7 (46)	−11 (−41, 33)
	NS-FU	18.4 (21)	15.9 (15)	−14 (−55, 68)
	TOTAL	10.1 (144)	7.3 (110)	−28 (−44, −7)***
Myocardial infarction	DB	8.2 (48)	6.4 (39)	−23 (−49, 18)
	O-FU	5.6 (42)	6.9 (56)	23 (−17, 84)
	NS-FU	8.8 (10)	6.3 (6)	−28 (−74, 97)
	TOTAL	6.8 (98)	6.6 (100)	−3 (−27, 28)
Myocardial infarction and sudden death	DB	13.2 (77)	10.3 (63)	−22 (−44, 8)
	O-FU	9.6 (72)	10.8 (87)	12 (−18, 53)
	NS-FU	19.3 (22)	9.5 (9)	−51 (−77, 6)*
	TOTAL	11.8 (169)	10.4 (157)	−12 (−29, 10)
Heart failure	DB	9.1 (53)	6.7 (41)	− 27 (−51, 10)
	O-FU	6.2 (46)	7.2 (58)	17 (−21, 72)
	NS-FU	11.4 (13)	21.3 (20)	86 (−7, 274)*
	TOTAL	7.6 (109)	7.6 (115)	0 (−23, 30)
Cardiac events[b]	DB	20.9 (120)	15.9 (97)	−24 (−42, 0)**
	O-FU	14.8 (110)	16.1 (129)	9 (−16, 40)
	NS-FU	29.3 (33)	28.8 (27)	−2 (−41, 64)
	TOTAL	17.9 (253)	16.4 (244)	−9 (−23, 9)
All cardiovascular events	DB	34.7 (196)	25.0 (151)	−28 (−42, −11)***
	O-FU	23.0 (169)	22.8 (181)	−1 (−19, 23)
	NS-FU	51.0 (57)	44.3 (41)	−13 (−42, 30)
	TOTAL	28.5 (394)	24.3 (356)	−15 (−26, −2)

For explanation, see Table 2. [a]Excludes transient ischaemic attack. [b]Includes fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction and sudden death. *$0.08 \leqslant P \leqslant 0.06$, ** $P \leqslant 0.05$, *** $P \leqslant 0.01$, for comparison between placebo and active treatment (log-rank test).

Subgroup analyses

Considering total follow-up, we did not detect any heterogeneity in the effects of treatment according to gender or the patient characteristics at randomization, including previous cardiovascular complications, systolic blood pressure, smoking status, or residence in western versus eastern Europe.

In keeping with previous subgroup analyses of the double-blind trial [13], we noticed in the long-term follow-up of all patients a borderline significant interaction ($P = 0.06$) between treatment allocation and age for all-cause mortality, albeit not for other outcomes. Randomization to active treatment was associated with a decreased relative risk of death in subjects aged 60–

Table 4 Other events

Event	Study phase	Rate per 1000 patient-years (number of events)		Relative difference (active−placebo) with 95% CI[c]
		Placebo	Active	
Transient ischaemic attack	DB	4.5 (26)	3.2 (20)	−27 (−59, 31)
	O-FU	4.3 (32)	4.3 (35)	+1 (−37, 64)
	NS-FU	5.3 (6)	5.3 (5)	0 (−70, 226)
	TOTAL	4.5 (64)	3.9 (59)	−12 (−39, 25)
Renal failure[a]	DB	0.5 (3)	0.6 (4)	–
	O-FU	0.9 (7)	0.5 (4)	–
	NS-FU	0.9 (1)	1.0 (1)	–
	TOTAL	0.8 (11)	0.6 (9)	−22 (−68, 88)
Fatal and non-fatal cancer	DB	14.7 (85)	12.4 (75)	−16 (−38, 15)
	O-FU	11.5 (85)	11.9 (95)	+3 (−23, 39)
	NS-FU	15.7 (18)	18.0 (17)	14 (−41, 122)
	TOTAL	12.8 (182)	11.9 (177)	−7 (−25, 14)
Benign neoplasm	DB	2.7 (16)	4.1 (25)	49 (−20, 180)
	O-FU	6.1 (45)	5.3 (42)	−14 (−43, 32)
	NS-FU	3.6 (4)	2.2 (2)	–
	TOTAL	4.5 (65)	4.6 (69)	+1 (−28, 42)
Fatal and non-fatal haemorrhage[b]	DB	3.6 (21)	3.6 (22)	0 (−45, 81)
	O-FU	2.1 (16)	2.3 (21)	10 (−43, 114)
	NS-FU	2.6 (3)	4.2 (4)	–
	TOTAL	2.8 (40)	2.8 (43)	2 (−33, 58)

For explanation, see Table 2. [a]Serum creatinine concentration having doubled since randomization or exceeding 360 μmol/l (4.0 mg/dl) or death from renal failure. [b]Excludes haemorrhagic stroke and bleeding from haemorrhoids, gums or nose. [c]Statistic not calculated when the number of events was less than five in any group.

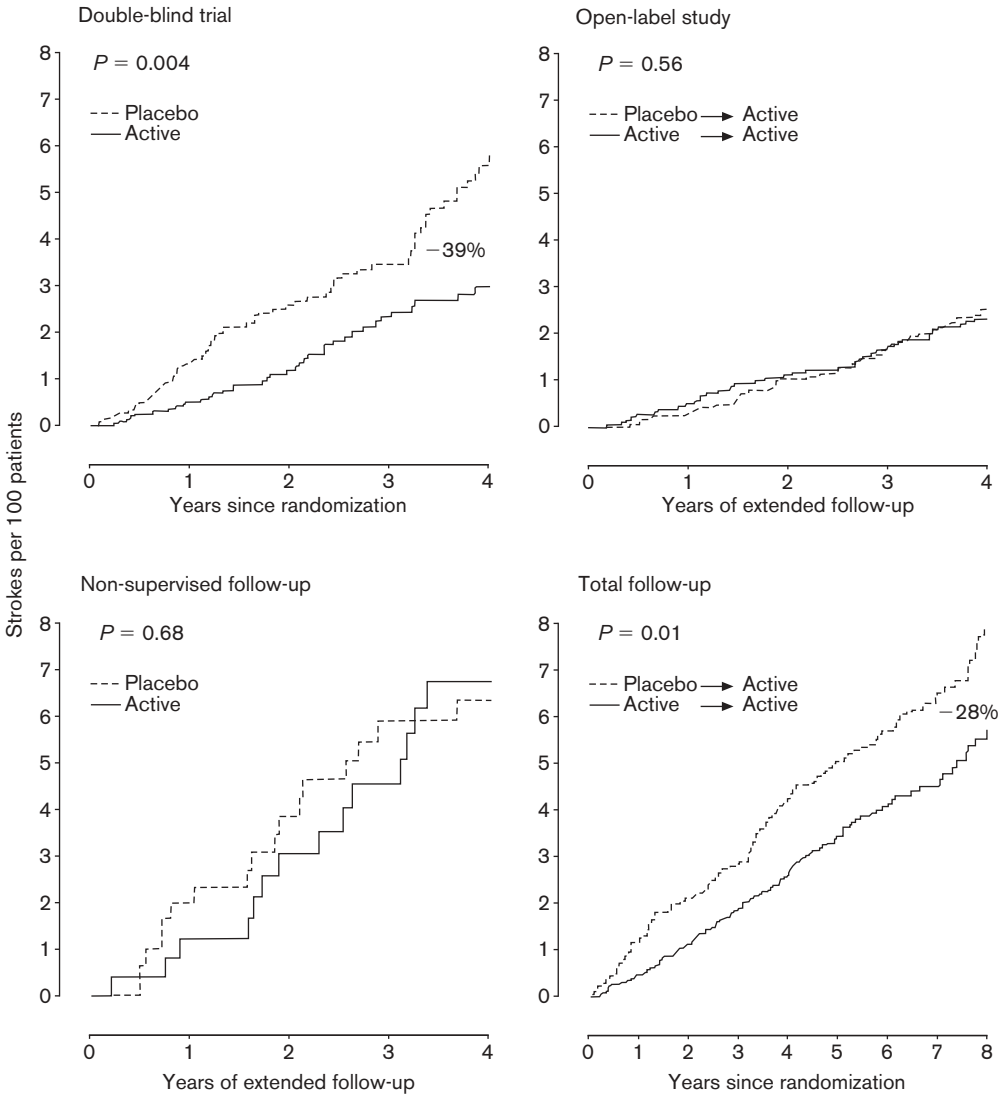
69 years (−29%, 95% CI −4 to −47) or 70–79 years (−19%, −34 to +1), but with a slightly increased risk of death in patients aged 80 years or more (+19%, −8 to +54). Furthermore, analyses stratified for diabetes mellitus at entry and encompassing total follow-up (Fig. 4) demonstrated that assignment to active treatment, compared with initial randomization to placebo, produced relative risk reductions for total mortality (38 versus 5% reduction, $P = 0.04$), all cardiovascular events (51 versus 7% reduction, $P = 0.002$) and fatal and non-fatal stroke (60 versus 20%, $P = 0.04$) which were greater in diabetic than non-diabetic patients, with a similar trend for fatal and non-fatal cardiac events (41 versus 2%, $P = 0.07$).

Discussion

If a trial shows that a new therapeutic approach reduces a predefined endpoint more effectively than the current standard of therapy, the only option left is to close the study. However, if the disease under study requires life-long treatment, the amount of patient-years accumulated is usually small in comparison with the extrapolations made in clinical guidelines. Consequently, the margins of uncertainty in terms of long-term benefit and safety usually remain large. Recently, the investigators of the double-blind Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial addressed this issue by offering all patients still alive 6 years after randomization to placebo or pravastatin, open-label therapy with the active drug for another 2 years [17]. To the best of our knowledge, our study is the first to implement a similar approach in the field of hypertension.

Our key finding was that early compared with delayed blood pressure-lowering therapy reduced the rates of stroke and all cardiovascular complications, with a similar trend for total mortality. As soon as the patients originally allocated to placebo received blood pressure-lowering medications, the rates of these complications rapidly decreased and became similar to those observed throughout follow-up in the active-treatment group. The rates of cardiovascular complications were higher in patients not enrolled in the open follow-up study, but again similar in those randomized to placebo or active treatment. Thus, the relative risk reductions achieved at the end of the whole Syst-Eur study were entirely due to the early benefit in the patients allocated to active treatment. This underscores the necessity of starting blood pressure-lowering therapy soon after isolated systolic hypertension is diagnosed. Failure to comply with this therapeutic guideline [18] is the direct cause of a large number of preventable cardiovascular complications. Indeed, the control rate of isolated systolic hypertension is substantially lower than that of diastolic hypertension [6,7]. Both the medical profession and the public should become aware of the large potential to save lives and improve the quality of life. On the other hand, lowering systolic pressure remained beneficial even after a delayed onset of drug therapy. Our findings are also relevant to health economists, because they allow cost-effectiveness calculations

Fig. 3

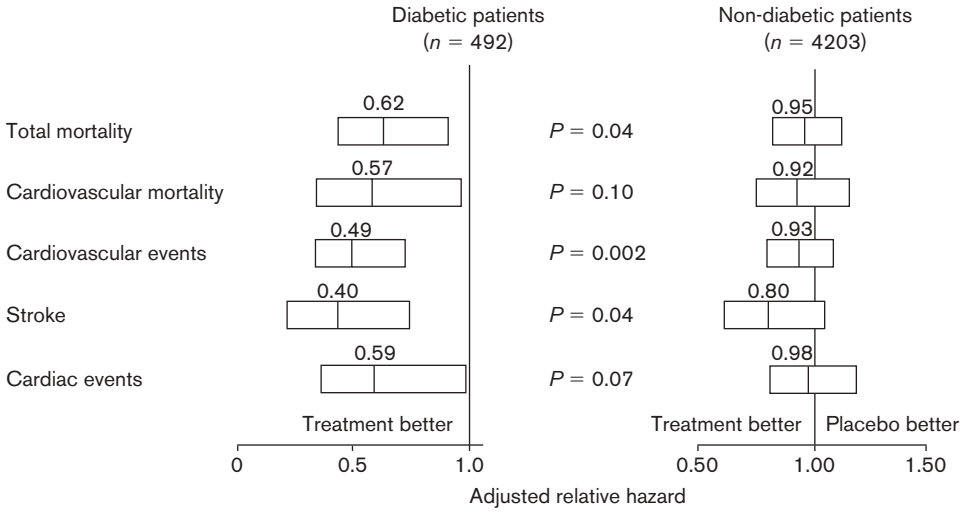


Cumulative rates of fatal and non-fatal stroke by original randomization. Results are given separately for the double-blind trial ($n = 4695$), the open-label study ($n = 3517$), subjects not enrolled in the open-label study but maintained in non-supervised follow-up ($n = 892$), and for the total follow-up of all patients ($n = 4695$).

for early compared with delayed antihypertensive therapy.

Cardiovascular benefit in our study was neither offset nor diluted by increases in the rates of myocardial infarction, cancer, gastrointestinal haemorrhage or dementia [19]. In line with our findings, the Swedish Trial in Old Patients with Hypertension [20] revealed no difference in the cancer risk between patients randomized to old drugs, calcium-channel blockers, or angiotensin-converting enzyme (ACE) inhibitors. More recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) proved that the rates of coronary heart disease, including or excluding coronary revascularization and hospitalized angina, and the incidence of total and cardiovascular mortality, were similar on chlorthalidone and amlodipine [21]. Moreover, the risks of cancer, gastrointestinal bleeding and end-stage renal disease were comparable on both drugs, with a 12% ($P = 0.02$) lower incidence of non-cardiovascular mortality in the amlodipine group [21]. These effects of amlodipine, relative to those of chlorthalidone, were consistent across all ALLHAT subgroups, including black and white, younger and older (≥65 years) patients, and diabetics and non-diabetics [21]. Thus, the calcium-

Fig. 4



Relative hazard rates associated with long-term active treatment in diabetic and non-diabetic patients. Relative hazard rates are for the total follow-up and were adjusted for sex and characteristics at randomization, including previous cardiovascular complications, age, systolic blood pressure, smoking status and residence in western versus eastern Europe. Bars indicate 95% confidence intervals. The numbers above the bars are point estimates. *P* values are for the interaction between randomization group and the presence of diabetes at enrolment.

channel-blocker syndrome, consisting of a wide variety of seemingly unrelated adverse effects [9–12], was not borne out when tested prospectively. Moreover, the Syst-Eur and the ALLHAT findings [21], along with those of other trials [4,5], support the guideline to initiate antihypertensive drug therapy in older patients with isolated systolic hypertension, either with thiazide diuretics or long-acting dihydropyridines [18].

During the double-blind Syst-Eur trial [14], the beneficial effects of nitrendipine-based antihypertensive treatment on overall mortality, cardiovascular mortality and all cardiovascular events were significantly greater in patients with diabetes at randomization than in those without diabetes. The present study corroborated these observations [14]. In other trials in which hypertensive patients were started on a dihydropyridine, diabetic patients also showed the largest reduction in cardiovascular risk [22], or had outcomes similar to those observed in groups allocated to conventional therapy [23] or ACE inhibitors [23]. The pathophysiology of isolated systolic hypertension rests on the stiffening of the central arteries [1], a process that is accelerated and potentiated by diabetes. Dihydropyridines increase arterial compliance, delay and reduce reflected arterial waves and restore the abnormality of the pulsatile component of the blood pressure wave [24]. Moreover, in diabetic Syst-Eur patients, nitrendipine-based therapy reduced the incidence of proteinuria by 71% [25]. Thus, in older diabetic patients with isolated systolic hypertension and normal renal function, long-acting dihydropyridines can be used to initiate blood pressure-lowering therapy.

In absolute terms, early compared with delayed treatment prevented 17 strokes or 25 major cardiovascular events per 1000 patients followed up for 6 years. These estimates are likely to be higher in unselected or high-risk patients. On the other hand, the selection of surviving patients and the differential enrolment in the open-label study and non-supervised follow-up are factors potentially limiting the external validity of our findings. However, Cox regression with adjustments for the main characteristics of our patients at randomization produced confirmatory results. Furthermore, the levels of systolic blood pressure at which we initiated therapy ($\geqslant$160 mmHg) and which we used as the target of treatment ($<$150 mmHg) were respectively 20 mmHg and 10 mmHg higher than those currently recommended in most guidelines [18]. The number of patients it is necessary to treat in order to prevent one event is likely to be higher when systolic pressure is only borderline elevated. Nevertheless, because of the continuous nature of the relationship with cardiovascular risk [26], and because 30–50% of untreated older Europeans have a systolic blood pressure in the high-normal or borderline elevated range [27], therapeutic strategies with intervention at these lower systolic thresholds might prevent more complications than the high-level approach used in our study, albeit at

lower cost-effectiveness. This hypothesis remains to be tested in placebo-controlled outcome trials in older subjects without prior history of cardiovascular complications or additional risk factors.

In conclusion, antihypertensive therapy can achieve blood pressure control in most patients with isolated systolic hypertension. Failure to institute therapy soon after isolated systolic hypertension is diagnosed is a cause of preventable cardiovascular complications and human suffering. Long-acting dihydropyridine calcium-channel blockers are safe to use for the long-term treatment of isolated systolic hypertension, and reduce cardiovascular risk mainly via an immediate decrease in the stroke rate.

References

1 Staessen J, Amery A, Fagard R. Editorial review. Isolated systolic hypertension in the elderly. *J Hypertens* 1990; **8:**393–405.
2 SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 1991; **265:**3255–3264.
3 Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997; **350:**757–764 [erratum published in the *Lancet* 1997; **350:**1636].
4 Staessen JA, Gąsowski J, Wang JG, Thijs L, Den Hond E, Boissel JP, *et al.* Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet* 2000; **355:**865–872.
5 Wang JG, Staessen JA, Gong L, Liu L, for the Systolic Hypertension in China (Syst-China) Collaborative Group. Chinese trial on isolated systolic hypertension in the elderly. *Arch Intern Med* 2000; **160:**211–220.
6 Fagard RH, Van den Enden M, Leeman M, Warling X. Survey on treatment of hypertension and implementation of World Health Organization/International Society of Hypertension risk stratification in primary care in Belgium. *J Hypertens* 2002; **20:**1297–1302.
7 Mancia G, Bombelli M, Lanzarotti A, Grassi G, Cesana G, Zanchetti A, *et al.* Systolic vs diastolic blood pressure control in the hypertensive patients of the PAMELA population. Pressioni Arteriose Monitorate E Loro Associazioni. *Arch Intern Med* 2002; **162:**582–586.
8 Gąsowski J, Staessen JA, Celis H, Fagard RH, Thijs L, Birkenhäger WH, *et al.* Systolic Hypertension in Europe (Syst-Eur) Trial Phase 2: objectives, protocol and initial progress. *J Hum Hypertens* 1999; **13:**135–145.
9 Pahor M, Guralnik JM, Furberg CD, Carbonin P, Havlik RJ. Risk of gastrointestinal haemorrhage with calcium antagonists in hypertensive persons over 67 years old. *Lancet* 1996; **347:**1061–1065.
10 Furberg CD, Psaty BM, Meyer JV. Nifedipine. Dose-related increase in mortality in patients with coronary heart disease. *Circulation* 1995; **92:**1326–1331.
11 Pahor M, Guralnik JM, Ferrucci L, Corti MC, Salive ME, Cerhan JR, *et al.* Calcium-channel blockade and incidence of cancer in aged populations. *Lancet* 1996; **348:**493–497.
12 Heckbert SR, Longstreth WT Jr, Psaty BM, Murros KE, Smith NL, Newman AB, *et al.* The association of antihypertensive agents with MRI white matter findings and the Modified Mini-Mental State Examination in older adults. *J Am Geriatr Soc* 1997; **45:**1423–1433.
13 Staessen JA, Fagard R, Thijs L, Celis H, Birkenhäger WH, Bulpitt CJ, *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.
14 Tuomilehto J, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, *et al.* Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. *N Engl J Med* 1999; **340:**677–684.
15 Report of a WHO Study Group. Definition, classification and diagnostic criteria. *Prevention of Diabetes Mellitus*. Geneva, Switzerland: World Health Organization; 1994, pp. 16–18.
16 Staessen JA, Thijs L, Birkenhäger WH, Bulpitt CJ, Fagard R, on behalf of the Syst-Eur Investigators. Update on the Systolic Hypertension in Europe (Syst-Eur) Trial. *Hypertension* 1999; **33:**1476–1477.
17 The LIPID Study Group. Long-term effectiveness and safety of pravastatin in 9014 patients with coronary heart disease and average cholesterol concentrations: the LIPID trial follow-up. *Lancet* 2002; **359:**1379–1387.
18 Guidelines Committee. 2003 European Society of Hypertension/European Society of Cardiology Guidelines for the Management of Arterial Hypertension. *J Hypertens* 2003; **21:**1011–1053.
19 Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, *et al.* The prevention of dementia with antihypertensive treatment. New evidence from the Systolic Hypertension in Europe (Syst-Eur) Study. *Arch Intern Med* 2002; **162:**2046–2052. [erratum published in *Arch Intern Med* 2003; **163:**241].
20 Lindholm LH, Anderson H, Ekbom T, Hansson L, Lanke J, Dahlöf B, *et al.* Relation between drug treatment and cancer in hypertensives in the Swedish Trial in Old Patients with Hypertension 2: a 5-year, prospective, randomised, controlled trial. *Lancet* 2001; **358:**539–544.
21 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288:**2981–2997.
22 Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, *et al.* Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; **351:**1755–1762.
23 Hansson L, Lindholm LH, Ekbom T, Dahlöf B, Lanke J, Scherstén B, *et al.* Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; **354:**1751–1756.
24 Ting CT, Chen JW, Chang MS, Yin FCP. Arterial hemodynamics in human arterial hypertension. Effects of the calcium channel antagonist nifedipine. *Hypertension* 1995; **25:**1326–1332.
25 Voyaki SM, Staessen JA, Thijs L, Wang JG, Efstratopoulos AD, Birkenhäger WH, *et al.* Follow-up of renal function in treated and untreated older patients with isolated systolic hypertension. *J Hypertens* 2001; **19:** 511–519.
26 Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360:**1903–1913.
27 Tikhonoff V, Casiglia E, Nawrot T, Staessen JA. Should high-normal blood pressure be treated? *J Hypertens* 2002; **20:**1028–1030.

Appendix

Contributors

Jan Staessen designed the extended follow-up study, negotiated the contract with the sponsor and wrote the first draft of the manuscript. Lutgarde Thijs organized the database and performed the statistical analysis. All named authors took part in the interpretation of the results and prepared the final version of the manuscript.

Trial coordinators

R. Fagard, J.A. Staessen.

Data monitoring committee

C.J. Bulpitt, A.E. Fletcher, J.A. Staessen, L. Thijs.

Endpoint committee

P. de Leeuw, R. Fagard, G. Leonetti, J. Petrie (deceased), C. Sarti and H. Vanhanen (associated members for Finland).

Ethics committee

W.H. Birkenhäger, C.T. Dollery, R. Fagard.

Publication committee

W.H. Birkenhäger, C.J. Bulpitt, J.A. Staessen, A. Zanchetti.

Steering committee

G.G. Arabidze (deceased), P. De Cort, R. Fagard, F. Forette, K. Kawecka-Jaszcz, G. Leonetti, C. Nachev, E. O'Brien, J. Rodicio, J. Rosenfeld, J. Tuomilehto, J. Webster, Y. Yodfat.

Coordination of general practices

H. Celis in collaboration with J. Heyrman, G. Stibbe, M. Van den Haute, Y. Yodfat.

Coordinating office

N. Ausloos, H. Celis, L. De Pauw, P. Drent, J. Gąsowski, R. Fagard, H. Fan, V. Mariën, J.A. Staessen, L. Thijs, S. Vandenreyken, S. Van Hulle, R. Wolfs.

Clinical centres

Clinical investigators are listed in reference [8].