DIHYDROPYRIDINE CALCIUM-CHANNEL BLOCKERS FOR ANTIHYPERTENSIVE TREATMENT IN OLDER PATIENTS — EVIDENCE FROM THE SYSTOLIC HYPERTENSION IN EUROPE TRIAL

Jan A Staessen, Lutgarde Thijs, Hilde Celis, Jerzy Gasowski, Ji G Wang, Robert H Fagard, for the Systolic Hypertension in Europe Trial Investigators (the Syst-Eur Trial)

Objective. The Syst-Eur study investigated whether active antihypertensive treatment could reduce cardiovascular complications in elderly patients with isolated systolic hypertension.

Design. Randomised, placebo-controlled, double-blind outcome trial.

Setting. Hypertension clinics or general practitioners' surgeries in 198 centres in 23 Western and Eastern European countries.

Subjects. Patients aged ≥ 60 years with sitting systolic blood pressure (BP) 160 - 219 mmHg and sitting diastolic BP < 95 mmHg during run-in phase.

Methods and Results. Four thousand, six hundred and ninety-five patients were randomly assigned to active treatment (N = 2 398), i.e. nitrendipine, with the possible addition of enalapril and hydrochlorothiazide, or to matching placebos (N = 2 297). In the intention-to-treat analysis, the between-group difference in blood pressure (BP) amounted to 10.1/4.5 mmHg ($P < 0.001$). Active treatment reduced the incidence of fatal and non-fatal stroke (primary endpoint) by 42% ($P = 0.003$). On active treatment all cardiac endpoints decreased by 26% ($P = 0.03$) and all cardiovascular endpoints by 31% ($P < 0.001$). Cardiovascular mortality was slightly lower on active treatment (–27%, $P = 0.07$), but all-cause mortality was not influenced (–14%, $P = 0.22$). For total ($P = 0.009$) and cardiovascular mortality ($P = 0.09$), the benefit of antihypertensive treatment weakened with advancing age, and for total mortality it decreased with lower systolic BP at entry ($P = 0.05$). The benefits of active treatment were not independently related to sex or to the presence of cardiovascular complications at entry. The antihypertensive regimen was more effective in patients with diabetes than in those without diabetes at entry. Further analyses also suggested benefit in patients who were taking nitrendipine as the sole therapy. The per-protocol analysis largely confirmed the intention-to-treat results. Active treatment reduced all strokes by 44% ($P = 0.004$), all cardiac endpoints by 26% ($P = 0.05$) and all cardiovascular endpoints by 32% ($P < 0.001$). Total mortality was reduced by 26% ($P = 0.05$), but a similar reduction in cardiovascular mortality did not reach statistical significance in this analysis. Compared with placebo, active treatment also reduced the incidence of dementia by 50%.

Conclusion. Stepwise antihypertensive drug treatment, starting with the dihydropiridine calcium-channel blocker nitrendipine, improves prognosis in elderly patients with isolated systolic hypertension.

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By 1988 several major outcome trials on antihypertensive drug treatment had been published.[1-5] However, at that time the findings in the elderly still left a wide margin of uncertainty, as evidenced by the borderline significance of the effects of therapy on fatal endpoints.[6] Indeed, the results of the early trials[1-5] demonstrated that antihypertensive drug treatment reduced all cardiovascular deaths by 28% ($P = 0.02$) and stroke mortality by 41% ($P = 0.03$), while the decreases in coronary (–28%, $P = 0.14$) and all-cause mortality (–14%, $P = 0.07$) had not reached statistical significance.[6] Furthermore, until 1988, all outcome trials in hypertension had used diastolic blood pressure (DBP) as the main criterion to recruit patients and to adjust treatment. This was in contrast to the growing insight gained from many cross-sectional and longitudinal studies that in older patients systolic blood pressure (SBP) is an important cardiovascular risk factor, whereas DBP is not associated — or may even be inversely correlated — with cardiovascular outcome.[7] In addition, the prevalence of isolated systolic hypertension rises curvilinearly with age. It averages 8% in sexagenarians and exceeds 25% beyond 80 years.[7] Thus, isolated systolic hypertension affects a considerable proportion of all older subjects.

Against this background, in 1989, the European Working Party on High Blood Pressure in the Elderly started the placebo-controlled double-blind Syst-Eur (Systolic Hypertension in Europe) Trial.[8] Active treatment was initiated with the dihydropyridine calcium-channel blocker nitrendipine,[9] with the possible addition of enalapril, hydrochlorothiazide or both drugs. In 1991 the Systolic Hypertension in the Elderly (SHEP) Trial[10] demonstrated that diuretic-based treatment prevented non-fatal stroke, myocardial infarction

Corresponding author: **Jan A Staessen,** MD, PhD
Studiecoördinatiecentrum, Laboratorium Hypertensie, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium

(MI) and congestive heart failure (CHF). In view of the remaining uncertainties with regard to the treatment of isolated systolic hypertension in the elderly,[11-15] the Syst-Eur Trial continued after the publication of the SHEP results.[10] Furthermore, the controversy over the role of calcium-channel blockers as first-line antihypertensive agents[16-19] highlighted the lack of evidence that these drugs also reduce cardiovascular risk.

The primary hypothesis tested was that in older patients with isolated systolic hypertension, active treatment could reduce fatal and non-fatal stroke. The secondary endpoints included total and cardiovascular mortality, all cardiovascular endpoints and fatal and non-fatal cardiac endpoints. This review article reports the morbidity and mortality results for the 4 695 randomised Syst-Eur patients. The trial stopped on 14 February 1997 after the second of four planned interim analyses. According to the predefined stopping rules, a significant benefit for stroke, the primary endpoint of the trial,[8] had been reached.

Patients and methods

The protocol of the multicentre Syst-Eur Trial[8] was approved by the Ethics Committees of the University of Leuven and the participating centres. The trial was conducted according to the principles outlined in the Helsinki Declaration.[20]

Patients were recruited from 198 centres in 23 countries across western and eastern Europe. Each centre kept a register of screened patients. Patients were eligible: (*i*) if they were at least 60 years old; (*ii*) if on single-blind placebo treatment during the run-in phase their sitting SBP ranged from 160 to 219 mmHg, with DBP below 95 mmHg; (*iii*) if their standing SBP was 140 mmHg or more; (*iv*) if they consented to be enrolled; and (*v*) if long-term follow-up was possible. The BP criteria for entry were based on the average of 6 sitting and 6 standing readings, i.e. 2 in each position at 3 baseline visits 1 month apart. Patients could not be enrolled if the systolic hypertension was secondary to a condition for which specific medical or surgical treatment was indicated. The other exclusion criteria included retinal haemorrhage or papilloedema; CHF; dissecting aortic aneurysm; a serum creatinine concentration at presentation of 180 µmol/l (2 mg/dl) or higher; a history of severe nose bleeds, stroke or MI within 1 year of randomisation; dementia or substance abuse; any condition prohibiting a sitting or standing position; and any severe concomitant cardiovascular or non-cardiovascular disease.

Eligible patients were stratified by centre, sex and previous cardiovascular complications and randomised to double-blind treatment with active medication or placebo. Active treatment was initiated with nitrendipine (10 - 40 mg/day). If necessary, the calcium-channel blocker was combined with or replaced by enalapril (5 - 20 mg/day) or hydrochlorothiazide (12.5 - 25 mg/day) or both drugs. The study medications were stepwise titrated and combined in an attempt to reduce the sitting SBP by 20 mmHg or more to less than 150 mmHg.[8]

To facilitate the intention-to-treat analysis, patients withdrawing from double-blind treatment were maintained in open follow-up.[8] For patients withdrawing from double-blind treatment, and for whom regular follow-up was impossible, information on vital status, the incidence of major endpoints and other events and the use of antihypertensive medications were collected annually (non-supervised open follow-up).

Morbidity and mortality results in the intention-to-treat analysis[21,22]

At randomisation the patients in the placebo (N = 2 297) and active-treatment (N = 2 398) groups had similar characteristics (Table I). In the intention-to-treat analysis the median follow-up of the 4 695 patients was 2.0 years. At 2 years, nitrendipine or matching placebo was the only treatment administered to 597 (58.9%) and 343 (39.6%) patients, respectively. Among the patients in open follow-up at 2 years, 65 (36.5%) of those randomised to active treatment and 157 (58.1%) of those in the placebo group were on antihypertensive drugs, while treatment status with regard to hypertension was undocumented in 88 (49.4%) and 81 (30.0%) patients, respectively. The between-group differences in the sitting BP averaged 10.1/4.5 mmHg (95% confidence interval (CI) 8.8 - 11.4/3.9 - 5.1 mmHg) at 2 years and 10.7/4.7 mmHg (CI 8.8 - 12.5/3.7 - 5.6 mmHg) at 4 years. The differences in heart rate were –0.1 beats per minute (CI –0.8 - 0.6 beats/min) and –06 beats/min (CI – 1.7 – 0.5 beats/min), respectively.

Cardiovascular mortality tended to be lower on active treatment (–27%, CI –48 - 2%, P = 0.07), but all-cause mortality was not significantly changed (–14%, CI –33 - 0%, P = 0.22). Fatal or non-fatal stroke was observed in 77 patients randomised to placebo and in 47 of the active-treatment group. The cumulative rates were 13.7 and 7.9 strokes per 1 000 patient-years (Table II). Active treatment reduced the occurrence of total stroke by 42% (P = 0.003) and that of non-fatal stroke by 44% (P = 0.007). In the active-treatment group, non-fatal cardiac endpoints decreased by 33% (P = 0.03). All fatal and non-fatal cardiac endpoints, including sudden death, declined by 26% (P = 0.03). A similar trend was observed for non-fatal heart failure (–36%, P = 0.06), for all cases of heart failure (–29%, P = 0.12) and for fatal and non-fatal MI (–30%, P = 0.12, Table II). Active treatment reduced all fatal and non-fatal cardiovascular endpoints by 31% (P < 0.001). The incidence of fatal and non-fatal cancer (–15%, CI –38 - 16%, P = 0.29) and bleeding (not including cerebral and retinal haemorrhages) (–10%, CI –52 - 69%, P = 0.74), was similar in the two treatment groups. In terms of absolute benefit, at the rates observed in the placebo group, treating 1 000 elderly

patients with isolated systolic hypertension for 5 years could prevent 29 strokes or 53 major cardiovascular events.

After the publication of the main outcome results on 13 September 1997,[21] efforts to locate all patients continued and the database was updated.[22] The number of patients lost to follow-up decreased from 116 to 61 (2.7%) in the placebo group and from 121 to 63 (2.6%) in the active-treatment group; the number of patient-years accumulated increased from 5 709 to 5 844 and from 5 995 to 6 140, respectively. However, the slightly greater number of endpoints available for analysis[22] did not affect the conclusions of the initial Syst-Eur report.[21]

Table I. Clinical features of the treatment groups at randomisation

Characteristic	Placebo (N = 2 297)	Active treatment (N = 2 398)
Age in years (mean (SD))	70.2 (6.7)	70.3 (6.7)
BP in mmHg (mean (SD))		
Sitting SBP (mmHg)	173.9 (10.1)	173.8 (9.9)
Sitting DBP (mmHg)	85.5 (5.9)	85.5 (5.8)
Standing SBP (mmHg)	169.2 (12.1)	168.8 (12.4)
Standing DBP (mmHg)	87.4 (7.7)	87.3 (7.7)
Sitting heart rate, beats/min (mean (SD))	73.0 (8.1)	73.3 (7.9)
Body mass index, kg/m² (mean (SD))		
Men	26.3 (3.1)	26.6 (3.5)
Women	27.5 (4.4)	27.2 (4.5)
Serum cholesterol, mmol/l (mean (SD))		
Total cholesterol	6.0 (1.2)	6.0 (1.2)
High-density lipoprotein cholesterol	1.4 (0.5)	1.4 (0.5)
Characteristic present at baseline (N (%))		
Female	1 520 (66.2%)	1 618 (67.5%)
Previous antihypertensive medication	1 083 (47.1%)	1 104 (46.0%)
Cardiovascular complications	697 (30.3%)	705 (29.4%)
Diabetes mellitus	240 (10.4%)	252 (10.5)
Never smokers	1 705 (74.2%)	1 763 (73.5%)
Past smokers	427 (18.6%)	454 (18.9%)
Current smokers	164 (7.1%)	179 (7.5%)
Abstaining from alcohol	1 674 (72.9%)	1 724 (71.9%)
Drinking < 1 unit alcohol per day	355 (15.5%)	414 (17.3%)
Drinking ≥ 1 unit alcohol per day	267 (11.1%)	258 (10.8%)

* Defined according to the criteria of the World Health Organisation.[31]
SD = standard deviation, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure.

Table II. Non-fatal endpoints alone and combined with fatal endpoints

Nature of endpoint	Rate per 1 000 patient-years (number of endpoints)		Relative difference with rate in placebo group	
	Placebo (N = 2 297)	Active (N = 2 398)	% rate (95% CI)	P
Non-fatal endpoints				
Stroke	10.1 (57)	5.7 (34)	–44 (–63, –14)	0.007
Retinal exudates	0.0 (0)	0.2 (1)	–	–
Cardiac endpoints	12.6 (70)	8.5 (50)	–33 (–53, –3)	0.03
Heart failure	7.6 (43)	4.9 (29)	–36 (–60, 2)	0.06
Myocardial infarction	5.5 (31)	4.4 (26)	–20 (–53, 34)	0.40
Renal failure	0.4 (2)	0.5 (3)	–	–
Fatal and non-fatal endpoints				
Stroke	13.7 (77)	7.9 (47)	–42 (–60, –17)	0.003
Cardiac endpoints*	20.5 (114)	15.1 (89)	–26 (–44, –3)	0.03
Heart failure	8.7 (49)	6.2 (37)	–29 (–53, 10)	0.12
Myocardial infarction	8.0 (45)	5.5 (33)	–30 (–56, 9)	0.12
All cardiovascular endpoints	33.9 (186)	23.3 (137)	–31 (–45, –14)	< 0.001

* Non-fatal and fatal cardiac endpoints included fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction and sudden death.

SUBGROUP ANALYSIS ACCORDING TO TREATMENT INTENTION[23]

In the intention-to-treat analysis, male sex and cardiovascular complications were positively and independently correlated with cardiovascular risk, but the relative risk reduction was similar in men and women and was not influenced by the presence of cardiovascular complications at entry. In multiple Cox regression analysis, the *P*-values for the interactions with treatment ranged from 0.62 to 0.86 for sex and from 0.26 to 0.87 for cardiovascular complications.

Age was a strong predictor of outcome. In Cox regression with adjustment applied for significant covariates, the treatment-by-age interaction term was significant ($P = 0.009$) for total mortality and nearly significant ($P = 0.09$) for cardiovascular mortality, indicating that the benefit of treatment was lost after the age of about 75 years. In contrast, the treatment-by-age interaction terms for the combined fatal and non-fatal events were not statistically significant. Similar analyses revealed that the effect of treatment on total mortality was more prominent at higher initial SBP ($P = 0.05$), but this was not the case for combined endpoints.

At randomisation, the median daily use of tobacco was 15 cigarettes in 231 male smokers (P_5 - P_{95} interval (PI) 3 - 50 cigarettes) and 10 cigarettes (PI 2 - 30 cigarettes) in 112 female smokers. Both before and after adjustment for significant covariates, smoking predicted total and cardiovascular mortality and the combined fatal and non-fatal cardiovascular and cardiac endpoints. With adjustments applied for significant covariates, Cox regression for stroke showed a significant interaction ($P = 0.01$) between treatment and smoking. The relative hazard rate of active versus placebo treatment was 0.47 (CI 0.32 - 0.69) in non-smokers, but 2.75 (CI 0.73 - 10.4) in smokers. At randomisation, 393 men and 132 women consumed at least one unit of an alcoholic beverage per day, i.e. one glass of beer, wine, aperitif, fortified wine or liquor. Their median daily consumption of alcohol was 19 g (PI 10 - 54 g) and 14 g (PI 10 - 36 g), respectively. Alcohol intake at entry and the alcohol-by-treatment interaction terms were not correlated with outcome before or after adjustment for covariates.

Of the 4 695 patients, 1 994 (42 5%) had been recruited in eastern Europe. However, because of the longer follow-up of the western European patients (median 3.4 versus 1.1 years), approximately 75% of the endpoints were noticed in western Europeans. In terms of relative risk reduction, the outcome results were similar in eastern and western European patients.

PER-PROTOCOL ANALYSIS

In the per-protocol analysis, i.e. the analysis of the patients on double-blind medication, the number of patient-years in the placebo and active treatment groups amounted to 4 508 and 5 166, respectively (83% of the total number of patient-years). Median follow-up was 1.7 years. The between-group differences in the sitting SBP and DBP then averaged 11.6 mmHg and 5.3 mmHg, respectively. In the patients remaining on double-blind medication, active treatment significantly reduced total mortality by 26% ($P = 0.05$). Similar though non-significant trends were observed for cardiac (–20%, $P = 0.34$) and cerebrovascular (–31%, $P = 0.36$) mortality.

The per-protocol analysis of the combined fatal and non-fatal endpoints produced results similar to those in the intention-to-treat approach. Active treatment reduced cardiovascular, cardiac and cerebrovascular events by 32% ($P < 0.001$), 26% ($P = 0.05$) and 44% ($P = 0.004$), respectively. In terms of absolute benefit, the per-protocol analysis suggested that treating 1 000 patients for 5 years would prevent 24 deaths, 29 strokes, 25 cardiac endpoints or 54 major cardiovascular events. In general, the results were remarkably similar in the intention-to-treat and per-protocol analyses.

CALCIUM-CHANNEL BLOCKADE AND CARDIOVASCULAR PROGNOSIS[24]

In the Syst-Eur Trial, active treatment was initiated with the dihydropyridine calcium-channel blocker nitrendipine.[9] The controversy about possible adverse effects of calcium-channel blockers arose only in 1995[18] and was not considered in 1991 or 1992, when the Ethics Committee of the Syst-Eur Trial and the review boards of the participating centres decided to continue the trial. However, in view of the persistent concerns about the use of calcium-channel blockers as first-line antihypertensive drugs,[18,19,25-29] further analyses addressed the question whether treatment with nitrendipine[9] alone could influence prognosis.

At 6 months, 1 517 patients of the placebo group (66.0%) and 1 829 of those randomised to active treatment (76.3%) were still on monotherapy with the first-line study medication. The net BP reduction in the active-treatment group was 7.7 mmHg SBP and 3.3 mmHg DBP. At this early moment in the trial, when most patients were still on the first-line medication, active treatment reduced all cardiovascular endpoints by 55% (CI 20 - 75%, $P = 0.005$), all cardiac endpoints by 62% (CI 21 - 82%, $P = 0.007$), total mortality by 60% (CI 17 - 81%, $P = 0.01$) and cardiovascular mortality by 62% (CI 14 - 83%, $P = 0.02$). In contrast, the 37% (CI –78 - 77%) reduction in fatal and non-fatal stroke was not yet significant. The relative reduction in all cardiovascular endpoints at 6 months was of the same order of magnitude as at 1, 2, or 4 years of follow-up, when more patients had proceeded to combined therapy (Fig. 1).

To ascertain that the apparent benefit conferred by nitrendipine was not due to selection bias in the control group, the 1 327 patients who remained on single nitrendipine treatment throughout the entire trial were matched by sex, age (60 - 69, 70 - 79, and ≥ 80 years), previous cardiovascular complications and SBP at entry (within 4 mmHg) with an equal

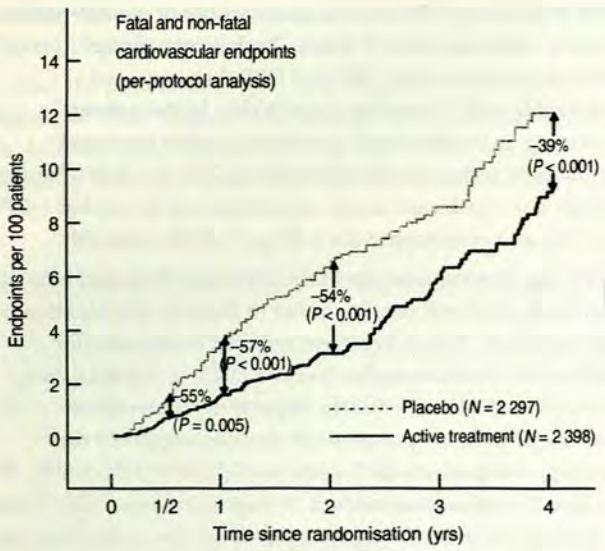

Fig. 1. Cumulative rates of all cardiovascular endpoints in the per-protocol analysis. The between-group differences in the rates are presented for various follow-up intervals. The benefit of active treatment was already significant at 6 months, when most of the 4 695 randomised patients were still on monotherapy with active nitrendipine or matching placebo. (From reference 24, with permission.)

number of placebo patients drawn from the control group, regardless of the type of the placebos taken. At 2 years (median follow-up in the two groups), the net BP reduction in the actively treated patients averaged 13.7 mmHg SBP and 5.4 mmHg DBP. Compared with the matched control group, active nitrendipine reduced cardiovascular mortality by 41% ($P = 0.05$), all cardiovascular endpoints by 33% ($P = 0.01$), fatal and non-fatal cardiac endpoints by 33% ($P = 0.05$), and fatal and non-fatal heart failure by 48% ($P = 0.05$).

OUTCOME IN DIABETIC AND NON-DIABETIC PATIENTS[30]

At randomisation, 492 patients (10.5%) had diabetes mellitus according to the criteria of the World Health Organisation[31] (Table I). At 2 years (median follow-up), the net differences in BP between the placebo and active-treatment groups were 8.6 mmHg SBP and 3.8 mmHg DBP in the diabetic patients; in the 4 203 patients without diabetes, these differences were 10.3 mmHg and 4.6 mmHg, respectively.

In the survival analysis without adjustment for possible confounders, active treatment in the diabetic patients reduced the incidence of total mortality (–41%, CI –69 - 9%, $P = 0.09$), cardiovascular mortality (–70%, CI –89 - –19%, $P = 0.01$), all cardiovascular endpoints (–62%, CI –80 - –19%, $P = 0.002$), fatal and non-fatal stroke (–69%, CI –89 - –14%, $P = 0.02$) and cardiac endpoints (–57%, CI –82 - 6%, $P = 0.06$). In the non-diabetic patients, treatment only decreased the risk of all cardiovascular complications (–25%, CI –41 - 5%, $P = 0.02$) and stroke (–36%, CI –57 - –5%, $P = 0.02$).

In diabetic patients (Fig. 2), with adjustments for possible confounders applied, active treatment reduced all-cause mortality by 55%, cardiovascular mortality by 76%, all cardiovascular endpoints by 69%, fatal and non-fatal stroke by 73% and all cardiac endpoints by 63%. In the non-diabetic patients, active treatment decreased all cardiovascular endpoints 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 endpoints ($P = 0.01$) significantly more in diabetic than in non-diabetic patients.[30]

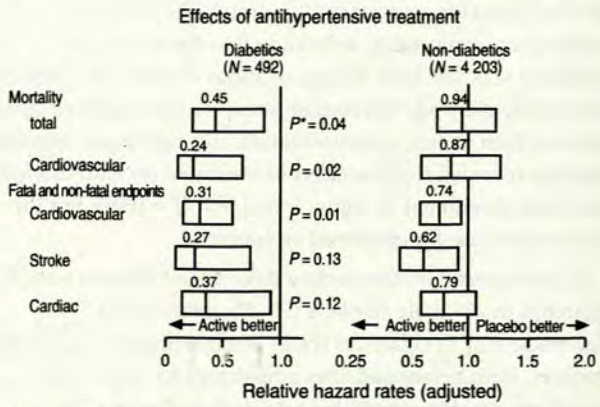

Fig. 2. Relative hazard rates of active treatment versus placebo in diabetic and non-diabetic patients with cumulative adjustments for sex, age, previous cardiovascular complications, systolic blood pressure at entry, smoking, and residence in western Europe. The P-values refer to the treatment-by-diabetes interaction and indicate whether the treatment effect was significantly different according to the presence of diabetes at randomisation. (From reference 30, with permission.)

PREVENTION OF DEMENTIA[32,33]

Systolic hypertension increases the risk of dementia in ageing people. The Vascular Dementia Project,[32-34] set up in the framework of the Syst-Eur Trial, investigated whether antihypertensive drug treatment could reduce the incidence of dementia. At baseline and follow-up, cognitive function was assessed by the Mini Mental State Examination (MMSE).[35] If the MMSE score was 23 or less, then the diagnosis of dementia was ascertained based on the *DSM-III-R* criteria.[36] In dementia cases the Modified Ischaemic Score,[37] including a computerised tomography (CT) brain scan, served to differentiate vascular from degenerative disease. If a brain scan could not be performed, then the Hachinski Score[38] replaced the Modified Ischaemic Score[37] to establish the cause of dementia.

In total, 2 418 patients were enrolled in the dementia study. Median follow-up in the intention-to-treat analysis was 2.0

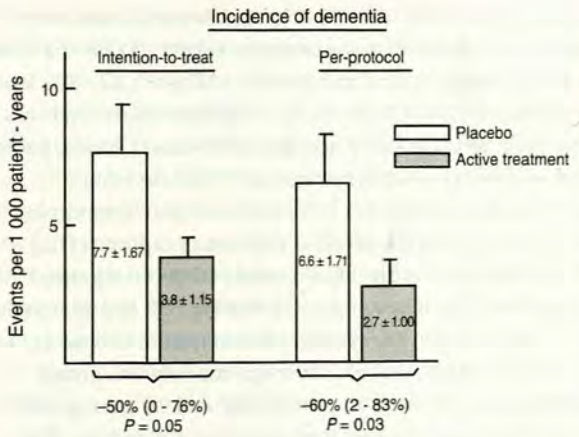

Fig. 3. Incidence of dementia by treatment group in the intention-to-treat and per-protocol analyses.

years. Compared with placebo (N = 1 180), active treatment (N = 1 238) reduced the incidence of dementia by 50% (CI –76 - 0%, P = 0.05) from 7.7 to 3.8 cases per 1 000 patient-years (Fig. 3). In the per-protocol analysis, active treatment decreased the rate by 60% (CI –83 - – 2%, P = 0.03). Active treatment prevented mainly degenerative dementia (8 v. 15 cases in the intention-to-treat analysis), but also vascular (0 v. 2) and mixed (3 v. 4) dementias. At the risk observed in the placebo group , treating 1 000 hypertensive patients for 5 years could prevent 19 cases of dementia.

PROGNOSTIC VALUE OF CONVENTIONAL AND AMBULATORY BLOOD PRESSURE[39-41]

Within the framework of the Syst-Eur Trial, the Study on Ambulatory Blood Pressure Monitoring was set up to compare the prognostic accuracy of conventional and ambulatory BP measurements.[39-41] Follow-up of the placebo group also made it possible to validate proposed diagnostic thresholds[42,43] for BP monitoring in terms of morbidity and mortality. Of 198 Syst-Eur centres, 46 opted to enrol their patients.

Interim reports on the Study on Ambulatory Blood Pressure Monitoring showed: (*i*) that the daytime SBP decreased by 2 - 3 mmHg on long-term placebo treatment;[43,44] (*ii*) that in parallel-group trials or in clinical experiments focusing on the BP profile during the whole day, ambulatory BP monitoring does not allow for economising on sample size;[45] and (*iii*) that it is possible to calculate the trough-to-peak ratio in parallel-group trials while fully accounting for placebo effects as well as interindividual variability.[46]

In the main analysis of the Study on Ambulatory Blood Pressure Monitoring,[41] 29 (3.5%) of 837 randomised patients with a 24-hour BP recording at baseline, were excluded because less than 80% of the required readings were available. SBP and DBP were on average 22.0 mmHg and 2.0 mmHg higher (P < 0.001) on conventional than on daytime (from 10h00 to 20h00)[47] ambulatory measurement.

With cumulative adjustments applied for sex, age, previous cardiovascular complications, smoking and residence in western Europe,[23] a higher SBP at randomisation predicted a worse prognosis (Fig. 4), whereas the association between DBP and outcome was not significant. In the placebo group (N = 393), the 24-hour, daytime and nighttime (from midnight to 06h00) systolic ambulatory BPs predicted the incidence of cardiovascular complications even after further adjustment for the conventional BP. The nighttime SBP behaved as a more accurate predictor of endpoints than the daytime level (except for stroke). The 24-hour level and the night-to-day ratio of SBP were significantly and independently correlated with the incidence of all cardiovascular endpoints in the placebo group. The relative hazard rates associated with a 10 mmHg increase in the 24-hour BP and with a 10% higher night-to-day ratio were 1.23 (CI 1.03 - 1.46, P = 0.02) and 1.41 (CI 1.03 - 1.94, P = 0.03), respectively. In the placebo group, the cardiovascular risk conferred by a conventional SBP of 160 mmHg at randomisation was similar to those associated with a 24-hour, daytime or nighttime SBP of 142 mmHg, 145 mmHg or 132 mmHg, respectively. In the active-treatment group (N = 415), SBP at randomisation did not significantly predict cardiovascular risk, regardless of the technique of BP measurement. This again confirmed that nitrendipine-based treatment substantially reduced the excess risk conferred by the increased SBP at randomisation.

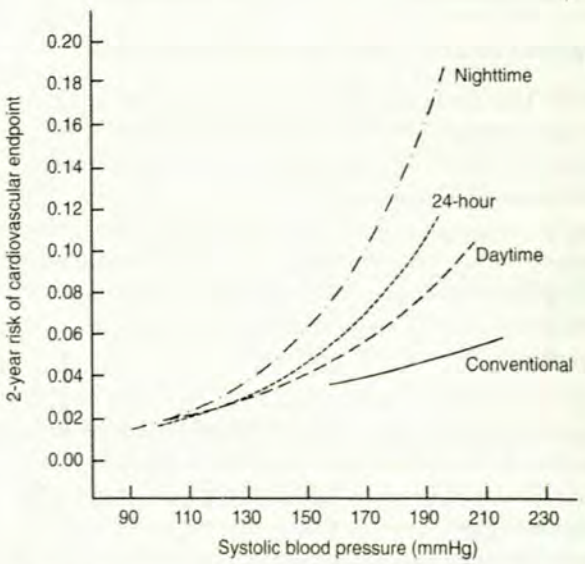

Fig. 4. Systolic blood pressure on conventional, 24-hour, daytime, and nighttime measurement at randomisation as predictors of the 2-year incidence of cardiovascular endpoints in the placebo group. The Cox models were standardised to female sex, 69.6 years (mean age), no previous cardiovascular complications, non-smoking and residence in western Europe. (From reference 41, with permission.)

DISCUSSION

Stepwise antihypertensive drug treatment in the Syst-Eur Trial consisted of the dihydropyridine calcium-channel blocker nitrendipine, the converting-enzyme inhibitor enalapril and the thiazide diuretic hydrochlorothiazide. In elderly patients with isolated systolic hypertension, these drugs reduced the risk of stroke, the primary endpoint in the Syst-Eur Trial, as well as the incidence of various other cardiovascular complications and dementia.

Syst-Eur, a trial in isolated systolic hypertension

The benefits of antihypertensive treatment in the Syst-Eur study were, in relative terms, similar to those in six other trials[1,2,4,5,48,49] in older patients with combined systolic and diastolic hypertension. Overall, in these studies, antihypertensive treatment reduced fatal stroke by 33% and cardiovascular mortality by 22%.[50] In a subsequent quantitative review,[51] which also included the SHEP Trial,[10] but not the small Japanese study by Kuramoto,[5] these pooled estimates were also the same, i.e. 33% and 22%. In the intention-to-treat analysis, the Syst-Eur results with regard to the number of prevented strokes were in close agreement with those reported by the SHEP investigators.[10] In relative terms the percentage reduction in stroke incidence amounted to 42% and 36%,[10] respectively, while in both trials approximately 35 patients had to be treated for 5 years to prevent one stroke. For cardiovascular mortality, the relative benefit in the intention-to-treat analysis amounted to 27% and 20%,[10] respectively, while 5 000 patient-years of treatment prevented 18 and 10 cardiovascular deaths.[10]

Syst-Eur as a calcium-channel blocker trial

Shortly after the first publication of the morbidity and mortality results of the Syst-Eur Trial, the question arose whether the observed beneficial effects of active treatment could be ascribed to any of the drugs used in this trial. Further analyses suggested that the dihydropyridine calcium-channel blocker nitrendipine, independent of the other associated antihypertensive drugs, prevented cardiovascular complications in older patients with isolated systolic hypertension.[24]

Several studies[52-54] investigated the effects of dihydropyridine calcium-channel blockers in Chinese hypertensive patients. The Shanghai Trial of Nifedipine in the Elderly (STONE) was a single-blind trial, in which 1 797 patients were alternatingly assigned to nifedipine (10 - 60 mg/day) or placebo with the possible addition in both treatment groups of active captopril (20 - 50 mg/day) or hydrochlorothiazide (25 mg/day).[53] Patients whose DBP exceeded 110 mmHg were re-allocated to nifedipine. A total of 165 patients were excluded from analysis, but all endpoints were blindly assessed. In an intention-to-treat analysis, total stroke incidence decreased by 57% (CI –23 - –76%). In the nifedipine group, total mortality tended to decline by 45% (CI –71 - 3%). No significant changes were observed in cardiovascular mortality (–26%, CI –66 - 62%) and in the incidence of fatal and non-fatal MI (–6%, CI –87 - 566%) and cancer (–76%, CI –95 - 13%).[53] The Syst-China Trial was a placebo-controlled study in older (≥ 60 years) Chinese patients with isolated systolic hypertension.[54-56] The first-line antihypertensive agent in this study was also nitrendipine (10 - 40 mg/day), with the possible addition of captopril (12.5 - 50 mg/day) and hydrochlorothiazide (12.5 - 50 mg/day). At entry the sitting BP averaged 171 mmHg SBP and 86 mmHg DBP, age averaged 66.5 years, and total serum cholesterol was 5.1 mmol/l. At 2 years of follow-up, the between-group differences in BP were 9.1 mmHg SBP and 3.2 mmHg DBP. Active treatment reduced total stroke by 37% (CI 14 - 53%, $P = 0.01$), all-cause mortality by 39% (CI 16 - 57%, $P = 0.003$), cardiovascular mortality by 39% (CI 4 - 61%, $P = 0.03$), stroke mortality by 58% (CI 14 - 80%, $P = 0.02$), and all fatal and non-fatal cardiovascular endpoints by 37% (CI 14 - 53%, $P = 0.004$).[54]

The Syst-Eur Trial invalidated the circumstantial evidence,[16-19,29,57-61] initially raised by a meta-analysis and several purely observational studies, for potentially dangerous side-effects of calcium-channel blockers. These observational reports[16-19,57] left a large margin of uncertainty. With regard to MI, confounding by indication could not be excluded. One report[17] 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% v. 2.6%, $P < 0.001$) or aspirin (37.3% v. 29.7%, $P < 0.001$),[17] which may have confounded the issue of gastrointestinal bleeding.[16]

Recently, the controversy over the use of calcium-channel blockers found new life in a series of articles[29,58-61] and comments[62] suggesting that calcium-channel blockers, including second-generation dihydropyridines such as amlodipine[58] or nisoldipine,[29] might be harmful, particularly in hypertensive patients with diabetes mellitus. The Syst-Eur Trial is the first double-blind placebo-controlled outcome study to prove that antihypertensive treatment starting with a dihydropyridine calcium-channel blocker is particularly beneficial in diabetic patients.[30,63] Cardiovascular benefit was observed equally in the patients remaining on monotherapy with nitrendipine and in those progressing to combined treatment with nitrendipine plus enalapril, hydrochlorothiazide, or both drugs.[30,63]

Prevention of dementia

In older patients with isolated systolic hypertension, active treatment starting with the dihydropyridine calcium-channel blocker nitrendipine halved the rate of dementia from 7.7 to 3.8 cases per 1 000 patient-years.[33]

The primary hypothesis tested in the Syst-Eur project on cognitive function was that a reduction in BP would protect against vascular dementia.[32] The prevention of Alzheimer's disease was unexpected, although recent studies indicate that vascular factors, particularly hypertension, may play a role in the development of degenerative dementias as well as vascular dementia proper.[64] On the other hand, the observation that antihypertensive treatment with a thiazide did not protect against cognitive impairment in the SHEP Trial[10] argues against the prevention of dementia by just lowering the BP. In vascular and degenerative dementias the calcium-channel blocker nimodipine, compared with placebo, slightly improved the MMSE scores.[65] Thus, an additional or alternative explanation, albeit still unproven, could involve specific neuroprotection conferred by calcium-channel blockade.[65-67] Indeed, the ageing brain loses its ability to regulate intracellular calcium, leading to a cascade of cellular impairments and, ultimately, to cell death.[66-68] The hypothesis of a possible central nervous action of nitrendipine is also supported by the observation that this drug crosses the blood-brain barrier and reduces the turnover of monoamine neuro-transmitters,[69] many of which are deficient in degenerative dementias.[67] Nitrendipine-binding in the rat brain also occurs mainly at those sites primarily affected by Alzheimer's disease, such as the superficial cortex, thalamus and hippocampus, and not in areas with low synaptic density.[70]

The potential reduction by 50% of the incidence of dementias by antihypertensive drug treatment initiated with the dihydropyridine calcium-channel blocker nitrendipine may have important public health implications in view of the increasing longevity of populations worldwide. At the rate observed in the placebo group, treating 1 000 hypertensive patients for 5 years could prevent 19 cases, a benefit which could even be larger in unselected higher risk groups. This beneficial outcome is in addition to the 53 major cardiovascular endpoints similarly prevented by the active drugs used in the Syst-Eur Trial.[21]

Conclusions

In summing up the Syst-Eur Trial, four conclusions emerge. First, this trial confirmed the SHEP findings[10] that antihypertensive treatment of older patients with isolated systolic hypertension prevents or postpones cerebrovascular and other cardiovascular complications.[21,23] Second, the newer antihypertensive drug classes, exemplified by the calcium-channel blocker nitrendipine, with the possible addition of enalapril, are at least equipotent to conventional drugs and may well serve as substitutes for the prevention of cardiovascular complications.[24,63] Third, long-acting dihydropyridine calcium-channel blockers may be particularly indicated in patients with isolated systolic hypertension who also have diabetes mellitus[30] or who are at risk of dementia.[33] Finally, the circumstantial evidence[16-19,29,57-61] for potentially dangerous side-effects of calcium-channel blockers has not been borne out when put to the more rigorous test of a double-blind placebo-controlled prospective trial with a median follow-up of 2 years.

The Syst-Eur Trial, initiated by Antoon Amery (died on 2 November 1994), was a concerted action of the European Community's Medical and Health Research Programme. The trial was carried out in consultation with the World Health Organisation, the International Society of Hypertension, the European Society of Hypertension and the World Hypertension League. The trial was sponsored by Bayer AG (Wuppertal, Germany). The National Fund for Scientific Research (Brussels, Belgium) provided additional support. Study medication was donated by Bayer AG and Merck Sharp and Dohme Inc (West Point, Pa., USA).

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