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Use of Dihydropyridines for Antihypertensive Treatment in Older Patients: Evidence from the Systolic Hypertension in Europe Trial

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

Patients (≥ 60 years) were randomly assigned to active treatment ($n = 2398$), ie, nitrendipine, with the possible addition of enalapril and hydrochlorothiazide, or to matching placebos ($n = 2297$). In the intention-to-treat analysis, the between-group difference in blood pressure amounted to 10.1/4.5 mmHg ($p < 0.001$). Active treatment reduced the incidence of fatal and nonfatal 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 blood pressure 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 %.

Stepwise antihypertensive drug treatment, starting with the dihydropyridine calcium-channel blocker nitrendipine, improves prognosis in elderly patients with isolated systolic hypertension. *J Clin Basic Cardiol 2000; 3: 15–21.*

Key words: calcium-channel blocker, dementia, diabetes mellitus, dihydropyridine, elderly, isolated systolic hypertension, nitrendipine.

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 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 is an important cardiovascular risk factor, whereas diastolic blood pressure 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 demonstrated that diuretic-based treatment prevented nonfatal stroke, myocardial infarction and congestive heart failure [10]. 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 on 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 nonfatal stroke. The secondary endpoints included total and cardiovascular mortality, all cardiovascular endpoints and fatal and nonfatal cardiac endpoints. This review article reports the morbidity and mortality results in the 4695 randomized Syst-Eur patients. The trial stopped on February 14th, 1997 after the second of 4 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 multicenter Syst-Eur trial [8] was approved by the Ethics Committees of the University of Leuven and the participating centers. The trial was conducted according to the principles outlined in the Helsinki declaration [20].

Patients were recruited from 198 centers in 23 countries across western and eastern Europe. Each center kept a register of screened patients. Patients were eligible, (1) if they

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were at least 60 years old, (2) if on single-blind placebo treatment during the run-in phase their sitting systolic blood pressure ranged from 160 to 219 mmHg with diastolic blood pressure below 95 mmHg, (3) if their standing systolic pressure was 140 mmHg or more, (4) if they consented to be enrolled, and (5) if long-term follow-up was possible. The blood pressure criteria for entry were based on the averages of 6 sitting and 6 standing readings, ie, 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, congestive heart failure, dissecting aortic aneurysm, a serum creatinine concentration at presentation of 180 mmol/l (2 mg/dl) or higher; a history of severe nose bleeds, stroke or myocardial infarction within 1 year of randomization, dementia or substance abuse, any condition prohibiting a sitting or standing position and any severe concomitant cardiovascular or noncardiovascular disease.

Eligible patients were stratified by center, sex and previous cardiovascular complications and randomized to double-blind treatment with active medication or placebo. Active treatment was initiated with nitrendipine (10–40 mg per day). If necessary, the calcium-channel blocker was combined with or replaced by enalapril (5–20 mg per day) or hydrochlorothiazide (12.5–25 mg per day) or both drugs. The study medications were stepwise titrated and combined in an attempt to reduce the sitting systolic blood pressure 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, in whom regular follow-up was impossible, information on vital status, the incidence of major endpoints and other events and the use of antihypertensive medications was collected annually (nonsupervised open follow-up).

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

At randomization the patients in the placebo (n = 2297) and active-treatment (n = 2398) groups had similar characteristics (Table 1). In the intention-to-treat analysis the median follow-up of the 4695 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 randomized 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 blood pressure averaged 10.1/4.5 mmHg (95 % confidence interval [CI]: 8.8 to 11.4/3.9 to 5.1 mmHg) at 2 years and 10.7/4.7 mmHg (CI: 8.8 to 12.5/3.7 to 5.6 mmHg) at 4 years. The differences in heart rate were –0.1 beats per minute (CI: –0.8 to 0.6 beats per minute) and –0.6 beats per minute (CI: –1.7 to 0.5 beats per minute), respectively.

Cardiovascular mortality tended to be less on active treatment (–27 %; CI: –48 to 2 %; p = 0.07), but all-cause mortality was not significantly changed (–14 %; CI: –33 to 9 %; p = 0.22). Fatal or nonfatal stroke were observed in 77 patients randomized to placebo and in 47 of the active-treatment group. The cumulative rates were 13.7 and 7.9 strokes per 1000 patient-years (Table 2). Active treatment reduced the occurrence of total stroke by 42 % (p = 0.003) and that of nonfatal stroke by 44 % (p = 0.007). In the active-treatment group, nonfatal cardiac endpoints decreased by 33 % (p = 0.03). All fatal and nonfatal cardiac endpoints, including sudden death, declined by 26 % (p = 0.03). A similar trend was observed for nonfatal heart failure (–36 %; p = 0.06), for all cases of heart failure (–29 %; p = 0.12) and for fatal and nonfatal myocardial infarction (–30 %; p = 0.12; Table 2). Active treatment reduced all fatal and nonfatal cardiovascular endpoints by 31 % (p < 0.001). The incidence of fatal and nonfatal cancer (–15 %; CI: –38 to 16; p = 0.29) and bleeding (not including cerebral and retinal haemorrhages; –10 %; CI: –52 to 69 %; p = 0.74) was similar in the 2 treatment groups. In terms of absolute benefit, at the rates observed in the placebo group, treating 1000 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 5709 to 5844 and from 5995 to 6140, respectively. However, the slightly greater number of endpoints available for analysis [22] did not affect the conclusions of the initial [21] Syst-Eur report.

Table 1. Clinical features of the treatment groups at randomization

Characteristic	Placebo (n = 2297)	Active treatment (n = 2398)
Mean (SD) age, y	70.2 (6.7)	70.3 (6.7)
Mean (SD) blood pressure, mmHg		
Sitting systolic, mmHg	173.9 (10.1)	173.8 (9.9)
Sitting diastolic, mmHg	85.5 (5.9)	85.5 (5.8)
Standing systolic, mmHg	169.2 (12.1)	168.8 (12.4)
Standing diastolic, mmHg	87.4 (7.7)	87.3 (7.7)
Mean (SD) sitting heart rate, beats/minute	73.0 (8.1)	73.3 (7.9)
Mean (SD) body mass index, kg/m ²		
Men	26.3 (3.1)	26.6 (3.5)
Women	27.5 (4.4)	27.2 (4.5)
Mean (SD) serum cholesterol, mmol/L		
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, No. (%)		
Female	1520 (66.2 %)	1618 (67.5 %)
Previous antihypertensive medication	1083 (47.1 %)	1104 (46.0 %)
Cardiovascular complications	697 (30.3 %)	705 (29.4 %)
Diabetes mellitus*	240 (10.4 %)	252 (10.5 %)
Never smokers	705 (74.2 %)	1763 (73.5 %)
Past smokers	427 (18.6 %)	454 (18.9 %)
Current smokers	164 (7.1 %)	179 (7.5 %)
Abstaining from alcohol	1674 (72.9 %)	1724 (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 Organization (see reference [31]).

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. By contrast, the treatment-by-age interaction terms for the combined fatal and nonfatal events were not statistically significant. Similar analyses revealed that the effect of treatment on total mortality was more prominent at higher initial systolic blood pressure (p = 0.05), but this was not the case for combined endpoints.

At randomization, the median daily use of tobacco was 15 cigarettes in 231 male smokers (P₅-P₉₅ interval [PI]: 3 to 50 cigarettes) and 10 cigarettes (PI: 2 to 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 nonfatal cardiovascular and cardiac endpoints. With adjustments applied for significant covariates, Cox regression showed for stroke 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 to 0.69) in nonsmokers, but 2.75 (CI: 0.73 to 10.4) in smokers. At randomization, 393 men and 132 women consumed at least one unit of an alcoholic beverage per day, ie, one glass of beer, wine, aperitif, fortified wine or liquor. Their median daily consumption of alcohol was 19 g (PI: 10 to 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 4695 patients, 1994 (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 [23]

In the per-protocol analysis, ie, the analysis of the patients on double-blind medication, the number of patient-years in the placebo and active treatment groups amounted to 4508 and 5166, respectively (83 % of the total number of patient-years). Median follow-up was 1.7 years. The between-group differences in the sitting systolic and diastolic blood pressures then averaged 11.6 mmHg and 5.3 mmHg, respectively. In the patients remaining on double-blind medication, active treatment significantly reduced total mortal-

ity by 26 % (p = 0.05). Similar though nonsignificant 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 nonfatal endpoints produced results similar to those in the intention-to-treat approach. Active treatment reduced cardiovascular, cardiac and cerebrovascular events by, respectively, 32 % (p < 0.001), 26 % (p = 0.05) and 44 % (p = 0.004). In terms of absolute benefit, the per-protocol analysis suggested that treating 1000 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 did not arise until 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 centers 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, 1517 patients of the placebo group (66.0 %) and 1829 of those randomized to active treatment (76.3 %) were still on monotherapy with the first-line study medication. The net blood pressure reduction in the active-treatment group was 7.7 mmHg systolic and 3.3 mmHg diastolic. 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 to 75 %; p = 0.005), all cardiac endpoints by 62 % (CI: 21 to 82 %; p = 0.007), total mortality by 60 % (CI: 17 to 81 %; p = 0.01) and cardiovascular mortality by 62 % (CI: 14 to 83 %; p = 0.02). In contrast, the 37 % (CI: -78 to 77 %) reduction in fatal and nonfatal 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 (Figure 1).

To ascertain that the apparent benefit conferred by nitrendipine was not due to selection bias in the control

Table 2: Nonfatal endpoints alone and combined with fatal endpoints

Nature of endpoint	Rate per 1000 patient-years (Number of endpoints)		Relative difference with rate in placebo group	
	Placebo (n = 2297)	Active (n = 2398)	% rate (95 % CI)	p
Nonfatal 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 nonfatal 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

* Nonfatal and fatal cardiac endpoints included fatal and nonfatal heart failure, fatal and nonfatal myocardial infarction and sudden death

group, the 1327 patients who remained on single nitrendipine treatment throughout the whole trial, were matched by sex, age (60–69, 70–79, and ≥ 80 years), previous cardiovascular complications and systolic blood pressure at entry (within 4 mmHg) with an equal 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 2 groups), the net blood pressure reduction in the actively treated patients averaged 13.7 mmHg systolic and 5.4 mmHg diastolic. 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 nonfatal cardiac endpoints by 33 % ($p = 0.05$), and fatal and nonfatal heart failure by 48 % ($p = 0.05$).

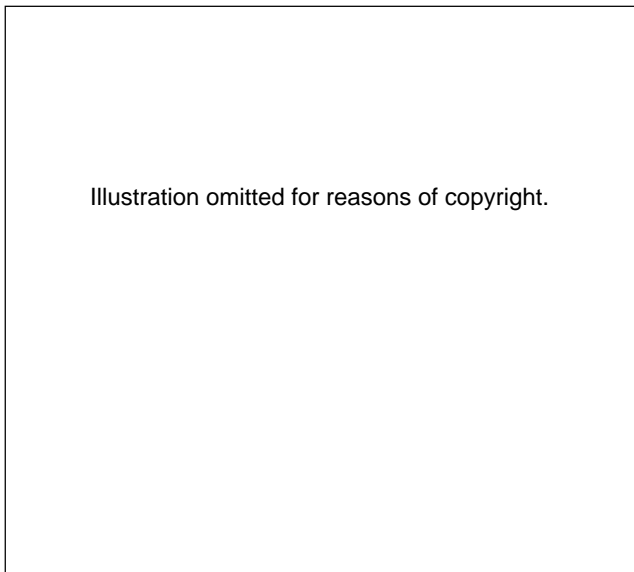


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Figure 1. Cumulative rates of all cardiovascular endpoints in the per-protocol analysis. The between-group differences in the rates are presented for various follow-up intervals. The benefit of active treatment was already significant at 6 months, when most of the 4695 randomized patients were still on monotherapy with active nitrendipine or matching placebo. From reference [24]; with permission

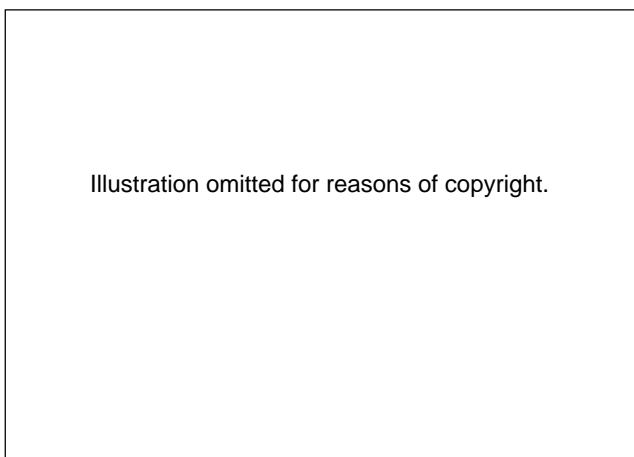


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Figure 2. Relative hazard rates of active treatment versus placebo in diabetic and nondiabetic patients with cumulative adjustments for sex, age, previous cardiovascular complications, systolic blood pressure at entry, smoking, and residence in western 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 randomization. From reference [30]; with permission

Outcome in diabetic and nondiabetic patients [30]

At randomization, 492 patients (10.5 %) had diabetes mellitus according to the criteria of the World Health Organization [31] (Table 1). At 2 years (median follow-up), the net differences in blood pressure between the placebo and active-treatment groups were 8.6 mmHg systolic and 3.8 mmHg diastolic in the diabetic patients; in the 4203 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 reduced in the diabetic patients the incidence of total mortality (–41 %; CI: –69 to 9 %; $p = 0.09$), cardiovascular mortality (–70 %; CI: –89 to –19 %; $p = 0.01$), all cardiovascular endpoints (–62 %; CI: –80 to –19 %; $p = 0.002$), fatal and nonfatal stroke (–69 %; CI: –89 to –14 %; $p = 0.02$) and cardiac endpoints (–57 %; CI: –82 to 6 %; $p = 0.06$). In the nondiabetic patients, treatment only decreased the risk of all cardiovascular complications (–25 %; CI: –41 to –5 %; $p = 0.02$) and stroke (–36 %; CI: –57 to –5 %; $p = 0.02$).

In diabetic patients (Figure 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 nonfatal stroke by 73 % and all cardiac endpoints by 63 %. In the nondiabetic patients, active treatment decreased all cardiovascular endpoints by 26 % and fatal and nonfatal 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 nondiabetic patients [30].

Prevention of dementia [32, 33]

Systolic hypertension increases the risk of dementia in aging people. The Vascular Dementia Project [32–34] set up in the framework of 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, the diagnosis of dementia was ascertained based on the DSM-III-R criteria [36]. In de-

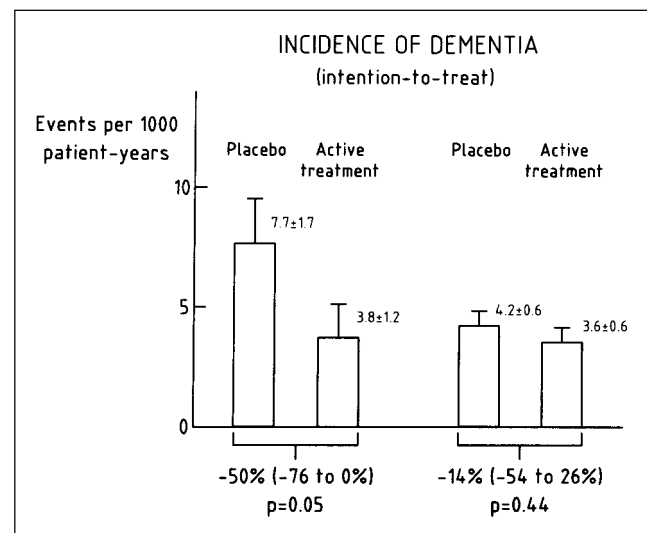


Figure 3. Incidence of dementia by treatment group in the intention-to-treat and per-protocol analyses

mentia cases the Modified Ischemic Score [37], including a computerized tomographic brain scan, served to differentiate vascular from degenerative disease. If a brain scan could not be performed, the Hachinski Score [38] replaced the Modified Ischemic Score [37] to establish the cause of dementia.

In total, 2418 patients were enrolled in the dementia study. Median follow-up in the intention-to-treat analysis was 2.0 years. Compared with placebo ($n = 1180$), active treatment ($n = 1238$) reduced the incidence of dementia by 50 % (CI: -76 to 0 %; $p = 0.05$) from 7.7 to 3.8 cases per 1000 patient-years (Figure 3). In the per-protocol analysis, active treatment decreased the rate by 60 % (CI: -83 to -2 %; $p = 0.03$). Active treatment prevented mainly degenerative dementia (8 *versus* 15 cases in the intention-to-treat analysis), but also vascular (0 *versus* 2) and mixed (3 *versus* 4) dementias. At the risk observed in the placebo group, treating 1000 hypertensive patients for 5 years could prevent 19 cases.

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 6 other trials [1, 2, 4, 5, 39, 40] 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 % [41]. In a subsequent quantitative review [42], which also included the SHEP trial [10], but not the small Japanese study by Kuramoto [5], these pooled estimates were also the same, ie, 33 % and 22 %. In the intention-to-treat analysis, the Syst-Eur results with respect 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 5000 patient-years of treatment prevented 18 and 10 [10] cardiovascular deaths.

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 [43–47] 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 1797 patients were alternately 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). [44] Patients whose diastolic blood pressure ex-

ceeded 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: -76 to -23 %). In the nifedipine group total mortality tended to decline by 45 % (CI: -71 to 3 %). No significant changes were observed in cardiovascular mortality (-26 %; CI: -66 to 62 %) and in the incidence of fatal and nonfatal myocardial infarction (-6 %; CI: -87 to 566 %) and cancer (-76 %; CI: -95 to 13 %) [44]. The Syst-China trial was a placebo-controlled study in older (≥ 60 years) Chinese patients with isolated systolic hypertension [45–47]. The first-line antihypertensive agent in this study was also nitrendipine (10 to 40 mg/day) with the possible addition of captopril (12.5 to 50 mg/day) and hydrochlorothiazide (12.5 to 50 mg/day). At entry the sitting blood pressure averaged 171 mmHg systolic and 86 mmHg diastolic, 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 blood pressure were 9.1 mmHg systolic and 3.2 mmHg diastolic. Active treatment reduced total stroke by 37% (CI: 14 to 53 %; $p = 0.01$), all-cause mortality by 39 % (CI: 16 to 57 %; $p = 0.003$), cardiovascular mortality by 39 % (CI: 4 to 61 %, $p = 0.03$), stroke mortality by 58 % (CI: 14 to 80 %; $p = 0.02$), and all fatal and nonfatal cardiovascular endpoints by 37 % (CI: 14 to 53 %; $p = 0.004$) [54].

The Syst-Eur trial invalidated the circumstantial evidence [16–19, 29, 48–52], 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, 48] left a large margin of uncertainty. With regard to myocardial infarction 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 % *versus* 2.6 %; $p < 0.001$) or aspirin (37.3 % *versus* 29.7 %; $p < 0.001$) [17], which may have confounded the issue of gastrointestinal bleeding [16].

Recently, the controversy on the use of calcium-channel blockers found new life in a series of articles [29, 49–52] and comments [53], suggesting that calcium-channel blockers, including second-generation dihydropyridines, such as amlodipine [49] 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 which proved that antihypertensive treatment starting with a dihydropyridine calcium-channel blocker was particularly beneficial in diabetic patients [30, 54]. Cardiovascular benefit 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 [30, 54].

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 1000 patient-years [33].

The primary hypothesis tested in the Syst-Eur project on cognitive function was that a reduction in blood pressure 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 [55]. 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 just by lowering the blood pressure. In vascular and degenerative dementias the calcium-channel blocker nimodipine, compared with placebo, slightly improved the MMSE-scores [56]. Thus, an additional or alternative explanation, albeit still unproven, could involve specific neuroprotection conferred by calcium-channel blockade [56–58]. Indeed, the aging brain loses its ability to regulate intracellular calcium, leading to a cascade of cellular impairments and, ultimately, to cell death [57–59]. 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 neurotransmitters [60], of which many are deficient in degenerative dementias [58]. Nitrendipine-binding in the rat brain also occurs mainly at those sites which are primarily affected by Alzheimer's disease, such as the superficial cortex, thalamus and hippocampus, and not in areas with low synaptic density [61].

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 1000 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 4 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, 54]. 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, 48–52] 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.

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