

# Treatment of isolated systolic hypertension in the elderly: further evidence from the SYST-EUR trial

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**Aims** The SYST-EUR study investigated whether active antihypertensive treatment could reduce cardiovascular complications in elderly patients with isolated systolic hypertension.

**Methods and results** Patients ( $\geq 60$  years of age) were randomly assigned to active treatment ( $n=2398$ ) with nitrendipine, with the possible addition of enalapril and hydrochlorothiazide, or matching placebos ( $n=2297$ ). In the intention-to-treat analysis, the between-group difference in blood pressure was  $10.1/4.5$  mmHg ( $P<0.001$ ). Active treatment reduced the total incidence of stroke as the primary end-point by 42% ( $P=0.003$ ), of all cardiac end-points by 26% ( $P=0.03$ ), and of all cardiovascular end-points combined by 31% ( $P<0.001$ ). Cardiovascular mortality was slightly lower on active treatment ( $-27\%$ ;  $P=0.07$ ), but all-cause mortality was not influenced ( $-14\%$ ;  $P=0.22$ ). The benefit of antihypertensive treatment weakened with advancing age for both total ( $P=0.009$ ) and cardiovascular mortality ( $P=0.09$ ); for total mortality it decreased with higher systolic blood pressure at entry ( $P=0.05$ ). The benefits of active treatment were not independently related to gender or to the presence of

cardiovascular complications at entry. The antihypertensive regimen was at least as effective in patients with diabetes as in those without diabetes at entry. Further analyses also suggested a 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 end-points by 26% ( $P=0.05$ ) and all cardiovascular end-points by 32% ( $P<0.001$ ). Total mortality was reduced by 26% ( $P=0.05$ ) although the similar reduction in cardiovascular mortality did not reach statistical significance in this analysis.

**Conclusion** It can be concluded that stepwise antihypertensive drug treatment, starting with the dihydropyridine calcium channel blocker nitrendipine, improves prognosis in elderly patients with isolated systolic hypertension. (*Eur Heart J Supplements* 1999; 1 (Suppl M): M2–M5)

**Key Words:** Isolated systolic hypertension, elderly, nitrendipine, calcium channel blocker, diabetes, cardiovascular disease.

## Introduction

Isolated systolic hypertension occurs in about 15% of people aged 60 years or more and is a significant risk factor for cardiovascular events, particularly for stroke<sup>[1]</sup>. The question whether elderly patients with isolated systolic hypertension would benefit from antihypertensive treatment is, therefore, of paramount importance in public health. In 1991, the Systolic Hypertension in the Elderly (SHEP) trial<sup>[2]</sup> showed that diuretic-based therapy prevented stroke, myocardial

infarction and congestive heart failure. The Systolic Hypertension in Europe Trial (SYST-EUR)<sup>[3]</sup>, in which treatment was initiated with the calcium channel blocker nitrendipine, confirmed the benefit of lowering blood pressure in elderly patients with isolated systolic hypertension<sup>[4]</sup>. The present review will summarize the main findings<sup>[4]</sup> and the results from further analyses of the SYST-EUR data<sup>[5–7]</sup>.

## Patients and methods

Patients at least 60 years old were recruited from 198 centres in 23 countries across Western and Eastern Europe. Sitting systolic blood pressure ranged from 160 mmHg to 219 mmHg for masked placebo during the run-in phase and sitting diastolic pressure was below

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\*A complete list of the participants in the SYST-EUR trial appears in reference<sup>[4]</sup>.

**Table 1** Difference in risk for fatal and non-fatal events and for fatal events between the active-treatment group and the placebo group

Nature of event	Fatal and non-fatal events		Fatal events	
	Rate (%) (95% CL)	<i>P</i>	Rate (%) (95% CL)	<i>P</i>
All causes	—	—	-14 (-33 to +9)	0.22
Cardiovascular	-31 (-54 to -14)	<0.001	-27 (-48 to +2)	0.07
Cardiac	-26 (-44 to -3)	0.03	-27 (-51 to +11)	0.14
Heart failure	-29 (-53 to +10)	0.12	-24 (-70 to +93)	0.57
Myocardial infarction	-30 (-56 to +9)	0.12	-56 (-82 to +9)	0.08
Sudden death	—	—	-12 (-49 to +52)	0.65
Stroke	-42 (-60 to -17)	0.003	-27 (-62 to +39)	0.33
Non-cardiovascular	—	—	-1 (-31 to +41)	0.95
Cancer	-15 (-38 to +16)	0.29	-31 (-63 to +26)	0.22

95 mmHg. After considering a number of exclusion criteria, 4695 patients were randomly assigned to 10–40 mg of nitrendipine daily, with the possible addition of 5–20 mg of enalapril daily and 12.5–25 mg of hydrochlorothiazide daily ( $n=2398$ ), or to matching placebos ( $n=2297$ ). Patients withdrawing from double-blind treatment were followed up. At randomization, age averaged  $70.2 \pm 6.7$  (SD) years and sitting blood pressure  $173.8 \pm 10/85.5 \pm 5.9$  mmHg; two-thirds of the participants were women. The trial included 1402 patients (29.9% of the total) with mainly mild cardiovascular complications at entry. Only 58 of these had a history of stroke and 163 a history of myocardial infarction. The others had symptoms or signs suggestive of coronary heart disease ( $n=412$ ), symptoms or signs of cerebrovascular disease ( $n=45$ ), electrocardiographic changes compatible with left ventricular hypertrophy ( $n=614$ ) or a combination of these conditions or other vascular, retinal or renal lesions ( $n=110$ ). Furthermore 492 patients (10.5%) had diabetes at baseline. Diabetes was defined as a history of diabetes mellitus, treatment with antidiabetic drugs, a fasting blood glucose level  $\geq 7.8$  mmol.l<sup>-1</sup>, or a non-fasting glucose level  $\geq 11.1$  mmol.l<sup>-1</sup>.

### Analysis by intention-to-treat

The SYST-EUR trial was stopped in February 1997, after the second interim analysis, because the primary end-point of a significant benefit for stroke had been reached. Median follow-up was 24 months and the number of patient-years in the placebo and active-treatment groups were 5709 and 5995, respectively. The between-group differences of blood pressure were 10.1 mmHg for systolic and 4.5 mmHg for diastolic ( $P<0.001$ ). Table 1 shows that the incidence of fatal and non-fatal stroke was reduced by 42% ( $P=0.003$ ), of cardiac events by 26% ( $P=0.03$ ), and of the combined cardiovascular end-points by 31% ( $P<0.001$ ). In terms of absolute benefit, the analysis suggested that at the

rates observed in the placebo group, treatment of 1000 patients for 5 years would prevent 29 strokes and 53 major cardiovascular events<sup>[4]</sup>. All-cause mortality was not influenced ( $P=0.22$ ) whereas cardiovascular mortality was slightly lower on active treatment ( $-27\%$ ;  $P=0.07$ ). Non-cardiovascular mortality and cancer mortality in the two groups were not different.

### Subgroup analysis

The 4695 patients who entered the double-blind phase of the trial were randomized after prospective stratification for centre, gender and previous cardiovascular complications, so as to test the 'a priori' hypotheses that these characteristics had influenced outcome in the SYST-EUR trial. In the analysis by intention-to-treat, 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<sup>[5]</sup>. 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. The results from Eastern and Western Europe were comparable in terms of relative risk reduction. Age was a strong predictor of outcome. In Cox regression analysis with adjustment applied for significant covariates, the treatment-by-age interaction term was significant for total mortality ( $P=0.009$ ) and nearly significant for cardiovascular mortality ( $P=0.09$ ), 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 non-fatal 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 ( $P=0.05$ ), although this was not the case for the combined end-points.

## Outcome in diabetic and non-diabetic patients

Compared with the 4203 non-diabetic patients, the 492 patients with diabetes mellitus had higher systolic blood pressure (175.3 vs 173.7 mmHg), lower diastolic blood pressure (84.5 vs 85.6 mmHg), higher mean blood glucose concentrations ( $8.2$  vs  $5.1$  mmol  $\cdot$  l $^{-1}$ ), higher body mass index ( $28.3$  vs  $27$  kg  $\cdot$  m $^{-2}$ ) and lower HDL cholesterol concentrations ( $1.3$  vs  $1.4$  mmol  $\cdot$  l $^{-1}$ )<sup>[6]</sup>. A significantly higher proportion of diabetic patients had previous cardiovascular complications before enrolment, and the rate of cardiovascular complications during the trial was about twice the rate observed in the non-diabetics. Active treatment significantly reduced cardiovascular complications in diabetics. After controlling the statistical analysis for possible confounders, total mortality was found to have been reduced by 55%, cardiovascular mortality by 76%, all cardiovascular end-points by 69%, fatal and non-fatal stroke by 73% and all cardiac end-points by 63%. In the non-diabetic group, active treatment significantly decreased all cardiovascular end-points ( $-26\%$ ) and fatal and non-fatal stroke ( $-38\%$ ). In diabetic patients, compared with non-diabetics, active treatment had a more beneficial effect on total ( $P=0.04$ ) and cardiovascular ( $P=0.02$ ) mortality and on all cardiovascular end-points combined ( $P=0.01$ ). In conclusion, the SYST-EUR trial showed that dihydropyridine-based antihypertensive treatment is particularly beneficial in older diabetic patients with isolated systolic hypertension; for 1000 patients treated for 5 years, such treatment could prevent 178 major cardiovascular end-points in diabetic patients, and 39 in non-diabetic patients.

## The effect of calcium channel blockade

In view of the concerns about the use of calcium channel blockers as first-line antihypertensive therapy, the SYST-EUR investigators explored to what extent nitrendipine administered alone prevented cardiovascular complications<sup>[7]</sup>. Of the 2398 actively treated patients, 1327 took only nitrendipine (average dose  $23.4$  mg  $\cdot$  day $^{-1}$ ) and 1042 progressed to other treatments, including nitrendipine ( $n=757$ ;  $35.7$  mg  $\cdot$  day $^{-1}$ ), enalapril ( $n=783$ ;  $13.4$  mg  $\cdot$  day $^{-1}$ ), and/or hydrochlorothiazide ( $294$ ;  $21.0$  mg  $\cdot$  day $^{-1}$ ). Patients on monotherapy with nitrendipine had 25% fewer cardiovascular end-points compared with the whole placebo group ( $n=2297$ ) ( $P=0.05$ ) and those progressing to other active treatments showed decreases in total mortality (40%), stroke (59%) and all cardiovascular end-points (39%) ( $P<0.01$  in each case). Among the control patients, 863 used only the first-line placebo. Compared with this subgroup; patients on monotherapy with nitrendipine showed a nearly 50% reduction ( $P\leq 0.004$ ) of all types of end-points, including total and cardiovascular mortality. The full relative benefit from

nitrendipine was seen as early as 6 months after randomization. To ascertain that the benefit conferred by the dihydropyridine was not due to selection bias, the 1327 patients remaining on monotherapy with nitrendipine were matched by sex, age, previous cardiovascular complications and systolic blood pressure at entry with an equal number of placebo patients. In this analysis, nitrendipine reduced ( $P<0.05$ ) cardiovascular mortality by 41%, all cardiovascular end-points by 33%, and fatal and non-fatal cardiac end-points by 33%. In spite of the limitations inherent in 'post hoc' analyses, these findings suggest that the calcium channel blocker nitrendipine, given as a single antihypertensive medication, prevents cardiovascular complications in older patients with isolated systolic hypertension.

## Per-protocol analysis

In the per-protocol analysis<sup>[5]</sup>, 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 4508 and 5166, respectively, i.e. 83% of the total number of patient years. The 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 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.

In general, the per-protocol analysis of the combined fatal and non-fatal end-points 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 end-points and 54 major cardiovascular events. In general, the results from the intention-to-treat and per-protocol analyses were remarkably similar.

The SYST-EUR trial, initiated by A. Amery (who died on November 2, 1994), was a concerted action of the BIOMED Research Program 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. 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 Sharpe and Dohme Inc (West Point, PA, U.S.A.).

The authors gratefully acknowledge the secretarial assistance of N. Ausseleos.

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