

# Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension

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## Summary

**Background** Isolated systolic hypertension occurs in about 15% of people aged 60 years or older. In 1989, the European Working Party on High Blood Pressure in the Elderly investigated whether active treatment could reduce cardiovascular complications of isolated systolic hypertension. Fatal and non-fatal stroke combined was the primary endpoint.

**Methods** All patients ( $\geq 60$  years) were initially started on masked placebo. At three run-in visits 1 month apart, their average sitting systolic blood pressure was 160–219 mm Hg with a diastolic blood pressure lower than 95 mm Hg. After stratification for centre, sex, and previous cardiovascular complications, 4695 patients were randomly assigned to nitrendipine 10–40 mg daily, with the possible addition of enalapril 5–20 mg daily and hydrochlorothiazide 12.5–25.0 mg daily, or matching placebos. Patients withdrawing from double-blind treatment were still followed up. We compared occurrence of major endpoints by intention to treat.

**Findings** At a median of 2 years' follow-up, sitting systolic and diastolic blood pressures had fallen by 13 mm Hg and 2 mm Hg in the placebo group ( $n=2297$ ) and by 23 mm Hg and 7 mm Hg in the active treatment group ( $n=2398$ ). The between-group differences were systolic 10.1 mm Hg

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(95% CI 8.8–11.4) and diastolic, 4.5 mm Hg (3.9–5.1). Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1000 patient-years (42% reduction;  $p=0.003$ ). Non-fatal stroke decreased by 44% ( $p=0.007$ ). In the active treatment group, all fatal and non-fatal cardiac endpoints, including sudden death, declined by 26% ( $p=0.03$ ). Non-fatal cardiac endpoints decreased by 33% ( $p=0.03$ ) and all fatal and non-fatal 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 ( $-14\%$ ;  $p=0.22$ ).

**Interpretation** Among elderly patients with isolated systolic hypertension, antihypertensive drug treatment starting with nitrendipine reduces the rate of cardiovascular complications. Treatment of 1000 patients for 5 years with this type of regimen may prevent 29 strokes or 53 major cardiovascular endpoints.

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## Introduction

The prevalence of isolated systolic hypertension increases with age. Among people aged 70 and older the prevalence is 8%, and it rises to more than 25% among those aged 80 years or older.<sup>1</sup> In 1989, the European Working Party on High Blood Pressure in the Elderly started a placebo-controlled double-blind trial—Systolic Hypertension in Europe (Syst-Eur).<sup>2</sup> Active treatment was started with the calcium-channel blocker nitrendipine,<sup>3</sup> with the possible addition of enalapril, hydrochlorothiazide, or both. In 1991, the Systolic Hypertension in the Elderly (SHEP) trial showed that diuretic-based treatment prevented stroke, myocardial infarction, and congestive heart failure.<sup>4</sup> Because of the remaining uncertainties about the treatment of isolated systolic hypertension in the elderly,<sup>5,6</sup> the Syst-Eur trial continued after the SHEP results were published.<sup>4</sup> Furthermore, controversy about calcium-channel blockers as first-line antihypertensive agents<sup>7,8</sup> highlighted the lack of evidence that these drugs reduce cardiovascular risk.

We report the morbidity and mortality results of the Syst-Eur trial. We stopped the trial on Feb 14, 1997, after the second interim analysis because we had reached the primary endpoint of a significant benefit for stroke.<sup>2</sup>

## Methods

The protocol of this trial<sup>2</sup> was approved by the ethics committees of the University of Leuven and the participating centres. We used the principles outlined in the Helsinki declaration.<sup>11</sup>

Patients were recruited from 198 centres in 23 countries across western and eastern Europe. Each centre kept a register of screened patients. Eligible patients were at least 60 years old. On

masked placebo during the run-in phase, their sitting systolic blood pressure ranged from 160 mm Hg to 219 mm Hg, their sitting diastolic blood pressure was below 95 mm Hg, and their standing systolic blood pressure was at least 140 mm Hg. All patients consented to be enrolled, and were available for long-term follow-up. We based the blood-pressure measurements for entry on the averages of six sitting and six standing readings—two in each position at three baseline visits, 1 month apart. Patients were not eligible if systolic hypertension was secondary to a disorder that needed specific medical or surgical treatment. Other exclusion criteria were: retinal haemorrhage or papilloedema; congestive heart failure; dissecting aortic aneurysm; a serum creatinine concentration at presentation of 180  $\mu\text{mol/L}$  or more; a history of severe nose bleeds, stroke, or myocardial infarction in the year before the study; dementia; substance abuse; any disorder prohibiting a sitting or standing position; and any severe concomitant cardiovascular or non-cardiovascular disease.

After stratification by centre, sex, and previous cardiovascular complications, we randomly assigned eligible patients treatment with active medication or placebo by means of a computerised random function. Active treatment was started with nitrendipine and, if necessary, this drug was combined with or replaced by enalapril, hydrochlorothiazide, or both. We aimed to reduce the sitting systolic blood pressure by at least 20 mm Hg to less than 150 mm Hg.<sup>2</sup> We used tablets of 20 mg nitrendipine, 10 mg enalapril, and 25 mg hydrochlorothiazide. The dosage steps for nitrendipine were 10 mg in the evening, then 10 mg twice daily, then 20 mg twice daily. For enalapril the dosage steps were 5 mg, then 10 mg, then 20 mg in the evening, and for hydrochlorothiazide, 12.5 mg, then 25 mg in the morning. Placebo tablets were identical to the study drugs, with a similar schedule. For intention-to-treat analysis we maintained open follow-up of the patients who withdrew from treatment.<sup>2</sup> During treatment and supervised open follow-up, clinic visits were scheduled every 3 months. For patients who withdrew from treatment for whom regular follow-up was not possible, we annually collected information on vital status, occurrence of major endpoints and other events, and the use of antihypertensive medications (non-supervised open follow-up). Patients without any report within the year before the trial stopped were counted as lost to follow-up.

Our original sample-size calculations assumed a rate of stroke in the placebo group of 17.0 events per 1000 patient-years. 15 000 patient-years (ie, 3000 patients with an average follow-up of 5 years) were required to detect a 40% change in the overall rate of stroke with a two-tailed significance of 1% and 90% power.<sup>2</sup> On Aug 18, 1995, the projected number of patients had been recruited (figure 1). However, because in the early phase of the study the stroke rate in the placebo group was only 13.6 events per 1000 patient-years, the steering committee decided in January, 1996, to continue recruitment through 1996 or until at least 4000 patients had been randomly assigned treatment.

The main endpoints were death, stroke, retinal haemorrhage or

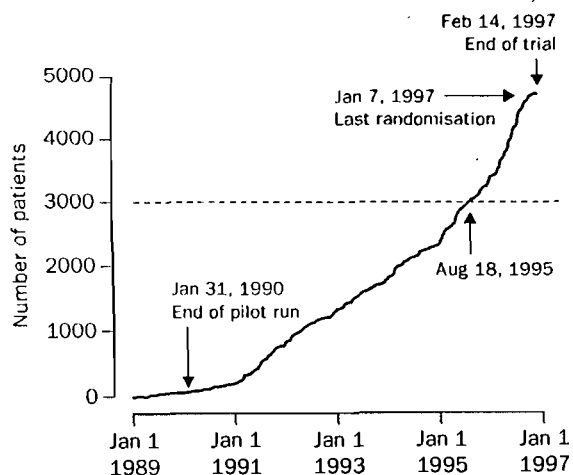


Figure 1: Numbers of patients randomly assigned treatment

exudates, myocardial infarction, congestive heart failure, dissecting aortic aneurysm, and renal insufficiency. The endpoint committee, which was unaware of the patients' treatment status, identified all major endpoints by reviewing the patients' files and other source documents, or by requesting detailed written information from the investigators, or by both approaches. Endpoints were coded according to the ninth (1975) revision of the International Classification of Diseases.<sup>13</sup>

Stroke, our primary endpoint, was defined as a neurological deficit with symptoms continuing for more than 24 h or leading to death with no apparent cause other than vascular. Acute myocardial infarction was defined as two of the following three disorders: typical chest pain, electrocardiographic changes, or increased cardiac enzymes.<sup>2</sup> Myocardial infarction did not include silent myocardial infarction. Congestive heart failure required the presence of three disorders—symptoms, such as dyspnoea, clinical signs, such as ankle oedema or crepitations, and the necessity of treatment with diuretics, vasodilators, or antihypertensive drugs. Sudden death included any death of unknown origin occurring immediately or within 24 h of the onset of acute symptoms, as well as unattended death for which no likely cause could be established by necropsy or medical history. Cardiac events included fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction, and sudden death. Renal insufficiency was diagnosed if at two consecutive visits the serum creatinine concentration reached or exceeded 360  $\mu\text{mol/L}$  or doubled compared with the concentration at randomisation.

All other events were checked at the coordinating office by doctors who were unaware of the treatment-group status. Transient ischaemic attack was defined as focal cerebral dysfunction lasting for less than 24 h, did not lead to withdrawal from double-blind treatment, and was not, therefore, an endpoint.<sup>2</sup> Angina pectoris was diagnosed from chest pain, with or without electrocardiographic signs of coronary ischaemia, the need for coronary revascularisation in the absence of acute myocardial infarction, or the indication to start nitrates. Diseases of the large (non-coronary) arteries were ICD-9 codes 433.0-433.9, 440.0-440.9, 442.0-442.9, 443.1, 443.9-444.9, and 447.0-447.9,<sup>13</sup> and included surgical or angioplastic procedures on these arteries, but not dissecting aortic aneurysm. Intercurrent diseases were non-fatal non-cardiovascular disorders leading to hospital admission or withdrawal of double-blind treatment or supervised open follow-up. Bleeding disorders excluded cerebral and retinal haemorrhage.

Uncontrolled hypertension was a sitting blood pressure of more than 219 mm Hg systolic or 99 mm Hg diastolic at three consecutive visits while the patients were on the maximum tolerated treatment dose. In January, 1996, on the ethics committee's recommendation, the upper admissible sitting systolic blood pressure at randomisation became 200 mm Hg, but the maximum value during treatment remained 219 mm Hg.

Database management and statistical analysis were done with SAS software, version 6.10. The data were entered in duplicate at the coordinating office (Leuven, Belgium) with systematic quality checks every 3 months. The data were analysed by intention to treat with two-sided tests. We compared means and proportions by standard normal  $z$  test and  $\chi^2$  analysis and survival curves by Kaplan-Meier survival function estimates and the log-rank test.

We expected 250 strokes to occur within 5 years. We planned interim analyses after every 50 strokes<sup>2</sup> to test for beneficial or adverse events occurring before the end of the trial. Asymmetrical monitoring boundaries, drawn according to the O'Brien-Fleming method,<sup>16</sup> allowed us to stop the study for a beneficial effect of active treatment on total stroke at 1% probability or for an adverse effect on any major endpoint at 5%.<sup>2</sup> At the second interim analysis in February, 1997, we found a significant decrease in the occurrence of stroke in the active-treatment group that, according to the predefined stopping rules, led us to stop the trial early.

## Results

Of 8926 screened patients 6403 (71.7%) were eligible for enrolment in the run-in period (figure 2). 1708 patients

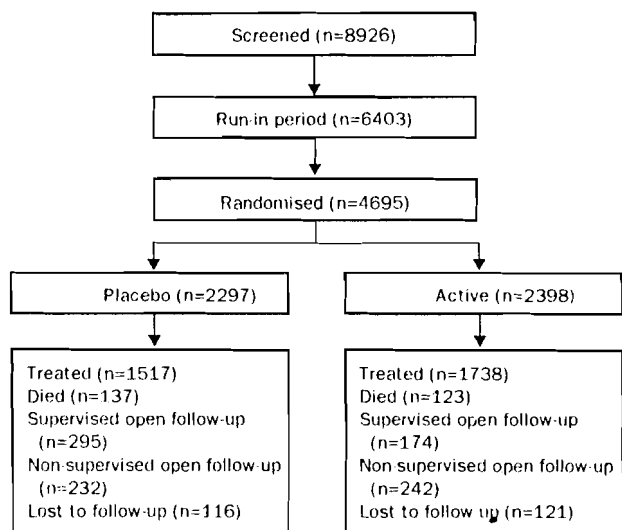


Figure 2: Trial profile  
Number of patients per group shown for each timepoint.

were not included because of blood pressure values outside the recruitment range ( $n=910$  [53.4%]), withdrawal of consent ( $n=439$  [25.7%]), the presence or occurrence of cardiovascular or non-cardiovascular illnesses, prohibiting randomisation ( $n=202$  [11.8%]), symptoms or treatment with masked placebo ( $n=55$  [3.2%]), or for undocumented reasons ( $n=333$  [19.5%]). 1262 (26.9%) of randomised patients were recruited in Finland, 1044 (22.2%) in Bulgaria, 321 (6.8%) in the Russian Federation, 273 (5.8%) in Belgium, 227 (4.8%) in Italy, 213 (4.5%) in Israel, 210 (4.5%) in the UK, 172 (3.7%) in France, 161 (3.4%) in Estonia, 155 (3.3%) in Lithuania, 139 (3.0%) in Spain, 127 (2.7%) in Poland, and 102 (2.2%) in Romania. Fewer than 100 patients were enrolled in each of Belorussia, the Czech Republic, Croatia, Germany, Greece, Ireland, the Netherlands, Portugal, Slovakia, and Slovenia.

At randomisation, patients in the placebo ( $n=2297$ ) and active-treatment ( $n=2398$ ) groups were similar for distribution of sex, age, blood pressure, pulse rate, body-mass index, serum cholesterol, the use of tobacco and alcohol, previous cardiovascular complications, and antihypertensive treatment (table 1). Overall, 343 (7.3%) patients (231 men and 112 women) smoked at randomisation and 525 (11.2%) (393 men and 132 women), consumed at least one unit of alcohol per day.

In the two treatment groups combined, 1402 (29.9%) patients had cardiovascular complications at randomisation. 575 (41.0%) and 103 (7.3%) of these patients had symptoms or signs suggestive of coronary heart disease or cerebrovascular disease, respectively. Electrocardiographic changes compatible with left-ventricular hypertrophy were present in 614 patients (43.8%). 110 (7.8%) patients had a combination of these disorders or other vascular, retinal, or renal lesions. Only 58 (4.1%) of 1402 patients had a history of stroke and 163 (11.6%) a history of myocardial infarction.

Patients were recruited over 8 years and median follow-up was 24 months (range 1–97, figure 1). The numbers of patient-years in the placebo and active-treatment groups were 5709 and 5995. Figure 2 shows the status of all patients on Feb 14, 1997, when the trial was stopped.

The proportion of patients started on multiple-drug treatment or proceeding to open follow-up increased faster ( $p<0.001$ ) in the placebo than in the active treatment

Characteristic	Treatment group	
	Placebo (n=2297)	Active treatment (n=2398)
Mean (SD) age in years	70.2 (6.7)	70.3 (6.7)
Mean (SD) blood pressure in mm Hg		
Sitting systolic	173.9 (10.1)	173.8 (9.9)
Sitting diastolic	85.5 (5.9)	85.5 (5.8)
Standing systolic	169.2 (12.1)	168.8 (12.4)
Standing diastolic	87.4 (7.7)	87.3 (7.7)
Mean (SD) sitting heart rate in beats per min	73.0 (8.1)	73.3 (7.9)
Mean (SD) body-mass index in kg/m <sup>2</sup>		
Men	26.3 (3.1)	26.6 (3.5)
Women	27.5 (4.4)	27.2 (4.5)
Mean (SD) serum cholesterol in mmol/L		
Total cholesterol	6.0 (1.2)	6.0 (1.2)
High density lipoprotein cholesterol	1.4 (0.5)	1.4 (0.5)
Number of patients with characteristic at baseline		
Women	1520 (66.2%)	1618 (67.5%)
Previous antihypertensive medication	1083 (47.1%)	1104 (46.0%)
Cardiovascular complications	697 (30.3%)	705 (29.4%)
Never smokers	1705 (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%)
<1 unit alcohol per day	355 (15.5%)	414 (17.3%)
≥1 unit alcohol per day	267 (11.6%)	258 (10.8%)

Table 1: Clinical features of treatment groups at randomisation

group (table 2). At 2 years, nitrendipine or placebo were the only treatments given to 597 (58.9%) of 1014 and 343 (39.6%) of 866 patients, respectively, who stayed on double-blind medication (table 2). Among the patients in open follow-up at 2 years, 65 (36.5%) of 174 randomly assigned active treatment, and 157 (58.1%) of 270 in the placebo group were on antihypertensive drugs, and treatment status with regard to hypertension was undocumented in 88 (49.4%) and 81 (30.0%) patients, respectively.

At 2 years, in the intention-to-treat analysis, the sitting systolic and diastolic blood pressures had fallen by a mean (SD) of 13 (17) mm Hg and 2 (8) mm Hg in the placebo group, and by 23 (16) mm Hg and 7 (8) mm Hg in the active treatment group (figure 3); standing systolic and diastolic blood pressure had fallen by 10 (18) mm Hg and 2 (8) mm Hg, and 21 (17) mm Hg, and 7 (9) mm Hg, respectively. At median follow-up, 21.4% of patients in the placebo group and 43.5% in the active treatment group had reached the target blood pressure ( $p<0.001$ ). At 2 years, the changes in the sitting pulse rate were 0.3 (9.0) beats per min ( $p=0.25$ ) and 0.2 (8.9) beats per min ( $p=0.54$ ), respectively. We calculated the differences between groups by subtracting the changes from baseline in the placebo group from the corresponding changes in the active-treatment group. For sitting blood pressure mean between-group differences were 10.1 mm Hg (95% CI 8.8–11.4) systolic and 4.5 mm Hg (3.9–5.1) diastolic at 2 years, and 10.7 mm Hg (8.8–12.5) and 4.7 mm Hg (3.7–5.6) at 4 years. The differences in pulse rate were  $-0.1$  beats per min ( $-0.8$  to  $0.6$ ) and  $-0.6$  beats per min ( $-1.7$  to  $0.5$ ), respectively.

Uncontrolled hypertension led 126 (5.5%) patients in the placebo group and 11 (0.5%) patients in the active-treatment group ( $p<0.001$ ) to withdraw from treatment. For 59 and five of these patients, respectively, the blood-pressure criteria applied by the clinical investigator were less stringent than those foreseen by the protocol.

There were fewer deaths from cardiovascular causes in the active treatment group ( $-27\%$  [ $-48$  to  $2$ ],  $p=0.07$ ) than in the placebo group, but all-cause mortality was not

Groups	Number of patients at specified year of follow-up							
	Placebo group (n=2297)				Active-treatment group (n=2398)			
	Year 1	Year 2	Year 3	Year 4	Year 1	Year 2	Year 3	Year 4
<b>Total number</b>	1683	1235	928	682	1758	1285	979	705
<b>Died</b>	31	51	63	61	15	41	54	54
<b>Double-blind follow-up</b>								
All study drugs	1428	866	544	325	1580	1014	677	426
No study drugs	5	2	2	0	2	6	2	2
Only nitrendipine	693	343	178	95	1037	597	385	216
Study drug(s) other than nitrendipine	725	519	358	226	537	405	283	202
Treatment unknown	5	2	6	4	4	6	7	6
<b>Drugs taken</b>								
Nitrendipine*†	1352	800	486	286	1407	856	571	351
Enalapril*†	677	477	330	206	471	330	223	152
Hydrochlorothiazide*†	315	297	226	150	147	164	139	104
Antihypertensive drugs†‡	16	8	6	1	12	10	8	5
<b>Open follow-up</b>								
All open follow-up	193	270	267	253	122	178	190	181
Supervised	133	186	179	162	71	89	90	92
Non supervised	60	84	88	91	51	89	100	89
<b>Antihypertensive treatment</b>								
Antihypertensive drugs	99	157	166	156	41	65	78	86
No antihypertensive drugs	13	32	24	28	15	25	23	26
Treatment unknown	81	81	77	69	66	88	89	69
<b>Lost to follow-up§</b>	28	48	54	43	41	52	58	44

\*In placebo group matching placebos were used. In the active treatment group, mean daily doses (SD) of nitrendipine, enalapril, and hydrochlorothiazide were 28.2 (12.1) mg, 13.5 (6.2) mg, and 21.2 (6.2) mg, respectively.

†Because many patients were on combined treatment, numbers may not add up.

‡To bridge medical emergencies without having to break code, antihypertensive drugs could be prescribed during double blind study period for up to 3 consecutive months.

§Patients without follow up data for more than 1 year.

Table 2: Follow-up and treatment status by treatment group and year of follow-up

significantly different (table 3). In the placebo group, the death rate due to stroke, heart failure, myocardial infarction, and sudden death ranged from 1.8 to 4.7 deaths per 1000 patient-years. Although there were fewer deaths from these causes in the active-treatment group, the CIs were wide and did not exclude the possibility of no effect of antihypertensive treatment. Non-cardiovascular and cancer mortality did not differ significantly (table 3).

The primary endpoint was fatal and non-fatal strokes combined. 77 patients on placebo and 47 on active treatment had strokes. The cumulative rates were 13.7 and 7.9 strokes per 1000 patient-years (table 4, figure 4). Active treatment reduced the occurrence of all strokes 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, decreased by 26% ( $p=0.03$ ). We found similar trends of reduction 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 myocardial infarction (30%,  $p=0.12$ ; table 4, figure 4). Active treatment reduced all fatal and non-fatal cardiovascular endpoints by 31% ( $p<0.001$ ).

Transient ischaemic attacks were not significantly influenced by active treatment ( $-12%$ ,  $p=0.62$ ; table 5). The rate of all cerebrovascular events (ie, fatal and non-fatal strokes and transient ischaemic attacks) was 18.0 and 11.8 events per 1000 patient-years (100 cases and 70 cases) in the placebo and active-treatment groups, respectively. Active treatment reduced the rate of all cerebrovascular events by 34% ( $-51$  to  $-11$ ,  $p=0.006$ ).

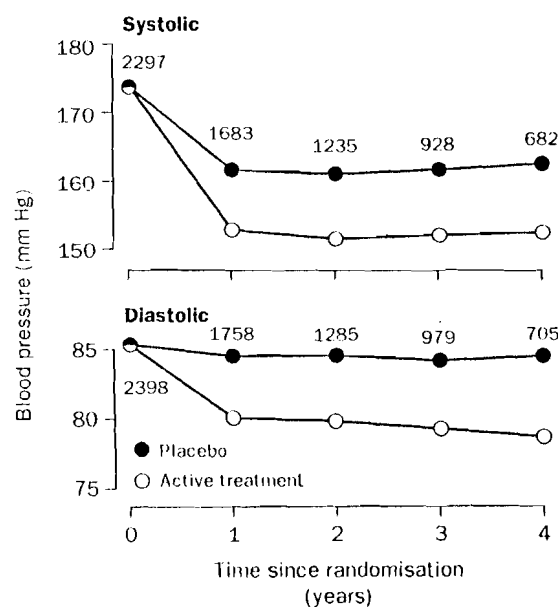


Figure 3: Average sitting systolic and diastolic blood pressure at randomisation and during follow-up

Cause of death	Rate per 1000 patient-years (number of deaths)		Difference (active minus placebo)	
	Placebo (n=2297)	Active (n=2398)	% rate (95% CI)	p
<b>All causes</b>	24.0 (137)	20.5 (123)	-14 (-33 to 9)	0.22
<b>Unknown cause</b>	0.4 (2)	0.7 (4)	..	..
<b>Cardiovascular</b>				
All cardiovascular	13.5 (77)	9.8 (59)	-27 (-48 to 2)	0.07
Stroke	3.7 (21)	2.7 (16)	-27 (-62 to 39)	0.33
Cardiac mortality*	9.1 (52)	6.7 (40)	-27 (-51 to 11)	0.14
Heart failure	1.8 (10)	1.3 (8)	-24 (-70 to 93)	0.57
Coronary mortality†	7.4 (42)	5.3 (32)	-27 (-54 to 15)	0.17
Myocardial infarction	2.6 (15)	1.2 (7)	-56 (-82 to 9)	0.08
Sudden death	4.7 (27)	4.2 (25)	-12 (-49 to 52)	0.65
Dissecting aortic aneurysm	0.4 (2)	0.2 (1)	..	..
Pulmonary embolism	0.2 (1)	0.3 (2)	..	..
Peripheral arterial disease	0.2 (1)	0 (0)	..	..
<b>Non-cardiovascular</b>				
Total	10.2 (58)	10.0 (60)	-1 (-31 to 41)	0.95
Cancer	4.4 (25)	3.0 (18)	-31 (-63 to 26)	0.22

\*Included deaths from heart failure and coronary mortality.  
†Consisted of fatal myocardial infarction and sudden death.

Table 3: Mortality by treatment group

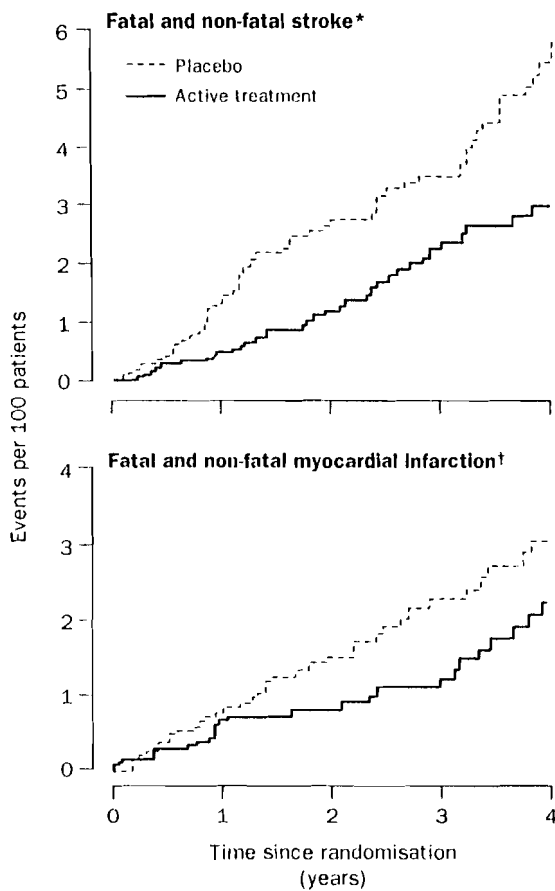


Figure 4: Cumulative rates of fatal and non-fatal stroke and myocardial infarction by treatment group

\* $p=0.003$ . † $p=0.12$ .

The rates of angina pectoris ( $-24\%$ ,  $p=0.04$ ) and peripheral arterial disease ( $-32\%$ ,  $p=0.06$ ) were slightly lower in the patients on active treatment (table 5). The occurrence of cancer, benign neoplasm, and bleeding, excluding cerebral and retinal haemorrhage, was similar in both treatment groups (table 5). The rates of intercurrent diseases of non-cardiovascular origin, which led to admission to hospital, withdrawal from double-blind treatment, or supervised open follow-up were also similar. 137 placebo-group patients were admitted to hospital because of non-cardiovascular disorders compared with 145 in the active-treatment group (25.3 vs 25.4 admissions per 1000 patient-years,  $p=0.95$ ).

## Discussion

The antihypertensive drugs used in our trial were the dihydropyridine calcium-channel blocker nitrendipine, the converting-enzyme inhibitor enalapril, and the thiazide diuretic hydrochlorothiazide. Among elderly patients with isolated systolic hypertension, these drugs reduced the risk of stroke and the occurrence of various other cardiovascular complications. We saw the benefit of active treatment soon after randomisation, when most patients were still on monotherapy with nitrendipine. Endpoints decreased similarly in eastern and western European patients. At the rates seen in the placebo group, treatment of 1000 elderly patients with isolated systolic hypertension for 5 years could prevent 29 strokes or 53 major cardiovascular events.

The benefits of antihypertensive treatment were similar

Nature of endpoint	Rate per 1000 patient-years (number of endpoints)		Difference (active minus placebo)	
	Placebo (n=2297)	Active (n=2398)	% rate (95% CI)	p
<b>Non-fatal endpoints</b>				
Stroke	10.1 (57)	5.7 (34)	-44 (-63 to -14)	0.007
Retinal exudates	0 (0)	0.2 (1)	..	..
Cardiac endpoints	12.6 (70)	8.5 (50)	-33 (-53 to -3)	0.03
Heart failure	7.6 (43)	4.9 (29)	-36 (-60 to 2)	0.06
Myocardial infarction	5.5 (31)	4.4 (26)	-20 (-53 to 34)	0.40
Renal failure	0.4 (2)	0.5 (3)	..	..
<b>Fatal and non-fatal endpoints combined</b>				
Stroke	13.7 (77)	7.9 (47)	-42 (-60 to -17)	0.003
Cardiac endpoints*	20.5 (114)	15.1 (89)	-26 (-44 to -3)	0.03
Heart failure	8.7 (49)	6.2 (37)	-29 (-53 to 10)	0.12
Myocardial infarction	8.0 (45)	5.5 (33)	-30 (-56 to 9)	0.12
All fatal and non-fatal cardiovascular endpoints	33.9 (186)	23.3 (137)	-31 (-45 to -14)	<0.001

\*Included fatal and non-fatal heart failure, fatal and non-fatal myocardial infarction, and sudden death (see table 3).

Table 4: Non-fatal endpoints alone and combined with fatal endpoints

to those in six other trials<sup>17, 22</sup> in older patients with combined systolic and diastolic hypertension. Overall, in these trials antihypertensive treatment reduced fatal stroke by 33% and cardiovascular mortality by 22%.<sup>23</sup> In a subsequent quantitative review,<sup>24</sup> which also included the SHEP trial,<sup>4</sup> the estimates were the same.

Although the relative benefit of antihypertensive treatment is constant for a wide range of risks, absolute benefit varies according to the risk of events seen in the placebo group.<sup>24</sup> Of seven intervention trials,<sup>4, 17, 19, 21, 22, 25</sup> the smallest absolute benefit was seen in the Medical Research Council trial in young hypertensive patients with diastolic hypertension<sup>25</sup> and the largest in the Swedish Trial in Old Patients with Hypertension (STOP).<sup>19</sup> Per 1000 patients treated for 5 years, the number of strokes and cardiovascular deaths prevented in those two trials ranged from two to 27 and from six to 67, respectively. The absolute number of strokes prevented by active treatment in our trial was similar to that in the STOP trial, whereas the number of cardiovascular deaths potentially prevented was half-way between the Medical Research Council and STOP results. Our results for stroke and myocardial infarction were similar to those of the SHEP trial.<sup>4</sup> Active treatment with a thiazide combined with atenolol or reserpine decreased these endpoints by 36% and 27%, respectively.<sup>4</sup>

We recruited patients from eastern and western Europe. Of 8926 screened patients, 4695 (52.6%) were randomised. We recruited patients by population

Nature of event	Rate per 1000 patient-years (number of events)		Difference (active minus placebo)	
	Placebo (n=2297)	Active (n=2398)	% rate (95% CI)	p
<b>Non-fatal cardiovascular events</b>				
Transient ischaemic attack	5.1 (29)	4.5 (27)	-12 (-48 to 49)	0.62
Angina pectoris	23.9 (131)	18.1 (105)	-24 (-41 to -2)	0.04
Peripheral arterial disease	10.2 (57)	6.9 (41)	-32 (-54 to 2)	0.06
<b>Non-cardiovascular events</b>				
Fatal and non-fatal cancer	14.7 (82)	12.4 (73)	-15 (-38 to 16)	0.29
Benign neoplasm	3.0 (17)	4.0 (24)	35 (-28 to 151)	0.35
Intercurrent disease*	31.4 (168)	33.1 (186)	5 (-15 to 90)	0.63
Bleeding†	3.5 (20)	3.2 (19)	-10 (-52 to 69)	0.74

\*Intercurrent disease refers to non-fatal non-cardiovascular disorders requiring admission to hospital, withdrawal of double-blind treatment, or supervised open follow-up.

†Bleeding excludes cerebral and retinal haemorrhage.

Table 5: Other events

screening, from family practices,<sup>26</sup> and at primary and secondary referral centres. We included only 1.2% of patients with previous myocardial infarction and 3.5% with a history of stroke. The exclusion of patients with major cardiovascular complications and the selection of individuals likely to comply with long-term follow-up and treatment are factors that must be taken into account when the results are extrapolated. In the SHEP trial,<sup>4</sup> 447 921 individuals were contacted, mainly by mass mailing and community screening. Of these 11.6% met the initial criteria, 2.7% completed the baseline visit, and 1.1% (n=4736) were randomly assigned treatment. Among those patients the maximum diastolic blood pressure at randomisation was 5 mm Hg lower than in our study. Despite these differences in recruitment and selection criteria, total and cardiovascular mortality in the placebo groups of the SHEP trial and our trial were similar (ie, 23 vs 24 deaths and 10 vs 13 deaths per 1000 patient-years).

The role of the newer classes of antihypertensive drugs in the pharmacological treatment of uncomplicated hypertension continues to be debated.<sup>27,28</sup> According to the 1993 guidelines in the USA,<sup>29</sup> diuretics and  $\beta$ -blockers are the only types of drugs that have been used in long-term controlled clinical trials and shown to reduce morbidity and mortality. These drugs have been, therefore, recommended as first-choice agents unless they are contraindicated or unacceptable or there are special indications for other agents.<sup>29</sup> By contrast, a joint committee of WHO and the International Society of Hypertension<sup>30,31</sup> believed that, although most clinical trials tested diuretics, centrally acting drugs, vasodilators, or  $\beta$ -blockers, often in combination, no evidence was available that the benefits were due to any particular class of antihypertensive drug rather than to the lowering of blood pressure per se. The committee recommended that several drugs may be prescribed as first-line treatment of mild sustained hypertension. They listed the drugs in order of proven benefit on morbidity and mortality as: diuretics,  $\beta$ -blockers, and converting-enzyme blockers, calcium-channel blockers, and  $\alpha$ -adrenoceptor-blocking drugs.<sup>30,31</sup> Although both sets of guidelines differed in their approach to designating first-line antihypertensive agents, they both recognised the urgent need to assess the efficacy of calcium-channel blockers and converting-enzyme inhibitors in reducing long-term morbidity and mortality in the treatment of hypertension. We provide evidence that the newer antihypertensive drugs also improve prognosis in a large subset of the hypertensive population.

Two previous studies investigated the effects of nifedipine in Chinese hypertensive patients, but followed unorthodox designs.<sup>32,33</sup> The Cheng-Du nifedipine trial was a prospective placebo-controlled trial of 683 hypertensive patients.<sup>33</sup> During the 6 years of follow-up, the rate of cardiovascular events decreased from 14.0% to 5.2% ( $p=0.05$ ). The Shanghai Trial of Nifedipine in the Elderly (STONE) was a single-blind trial in which 1797 patients were assigned either nifedipine (20–60 mg/day) or placebo, with the possible addition in both treatment groups of active captopril (20–50 mg/day) or hydrochlorothiazide (25 mg/day).<sup>32</sup> Patients whose diastolic blood pressure exceeded 110 mm Hg were reassigned nifedipine. Total stroke incidence decreased by 57% (95% CI –23 to –76). In the nifedipine group total mortality declined by 45% (–71 to 3). No significant changes were seen in cardiovascular mortality (–26% [–66 to 62]) and in the rate of fatal and non-fatal myocardial infarction (–6% [–87 to 566]) or

cancer (–76% [–95 to 13]).<sup>32</sup> The Syst-China trial studied Chinese patients aged 60 years or older with isolated systolic hypertension.<sup>34</sup> The first-line antihypertensive agent in that study was also nitrendipine with the possible addition of captopril and hydrochlorothiazide. That population had a lower frequency of atherosclerosis than western populations (unpublished).

The safety of short-acting calcium-channel blockers as first-line antihypertensive agents has been questioned in case-controlled and observational studies, which, according to the investigators' interpretation,<sup>10,13</sup> left a margin of uncertainty, for example, because confounding by indication could not be excluded. We used nitrendipine, which is of the dihydropyridine class with a terminal plasma half-life of 12 h.<sup>3</sup> The median duration of exposure in the active-treatment group was 1.7 years (per-protocol analysis). Compared with the placebo group, no differences occurred in non-cardiovascular death and the rate of cancer and bleeding. After termination of the trial on Feb 14, 1997, all patients were offered nitrendipine, enalapril, and hydrochlorothiazide. Patients in our trial will remain in open follow-up to confirm the safety of dihydropyridines in the long-term management of isolated systolic hypertension.

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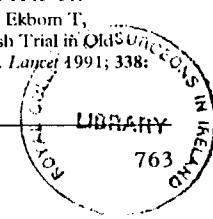
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## A case-control study of measles vaccination and inflammatory bowel disease

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### Summary

**Background** The cause of inflammatory bowel disease (IBD) remains to be established. Evidence has linked measles infection in early childhood with the subsequent risk of developing IBD, particularly Crohn's disease. A cohort study raised the possibility that immunisation with live attenuated measles vaccine, which induces active immunity to measles infection, might also predispose to the later development of IBD, provoking concerns about the safety of the vaccine.

**Method** We report a case-control study of 140 patients with IBD (including 83 with Crohn's disease) born in or after 1968, and 280 controls matched for age, sex and general practitioner (GP) area, designed to assess the influence of measles vaccination on later development of IBD. Documentary evidence of childhood vaccination history was sought from GP and community health records.

**Findings** Crude measles vaccination rates were 56.4% in patients with IBD and 57.1% among controls. Matched odds ratios for measles vaccination were 1.08 (95% CI 0.62-1.88) in patients with Crohn's disease, 0.84 (0.44-1.58) in patients with ulcerative colitis, and 0.97 (0.64-1.47) in all patients with IBD.

**Interpretation** These findings provide no support for the hypothesis that measles vaccination in childhood predisposes to the later development of either IBD overall or Crohn's disease in particular.

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### Introduction

The possibility that the inflammatory bowel diseases (IBDs)—ulcerative colitis and Crohn's disease—are caused by a transmissible agent such as a virus is an attractive hypothesis.<sup>1</sup> Wakefield and colleagues have suggested that Crohn's disease might be the late result of measles virus infection at a critical time during early childhood. This "measles hypothesis" is based on a series of pathological and epidemiological studies.<sup>2-4</sup>

Wild-type measles infection is associated with substantial morbidity and mortality. In the developed world, complications occur in about one in 15 infections, and most deaths result from the development of pneumonia, acute encephalitis, or the rare but relentlessly progressive subacute sclerosing panencephalitis.<sup>5,6</sup> Live attenuated measles vaccine was introduced in the UK in 1968, and as a result of the vaccination campaign the incidence of measles infection and complications has fallen strikingly.<sup>5,6</sup>

The measles hypothesis has been embellished with evidence from a cohort study suggesting an increased risk of IBD in individuals given live attenuated measles vaccine in early childhood.<sup>7</sup> This report has led to concern about the safety of measles vaccination and resulted in some parents declining an effective vaccine. Counselling has been particularly difficult because the evidence on which to base reassurance on this issue is very limited.<sup>8</sup>

The present investigation was devised to assess the risk of IBD associated with vaccination against measles in early childhood. A case-control design was used because of the relative rarity of the disease and the frequency of vaccine exposure in the population.<sup>9,10</sup> The study focuses on the period between 1968 and 1991, during which measles vaccination was routinely offered and immunisation status documented in the UK by general practitioners (GPs) and community health services within the National Health Service. National uptake rates for measles vaccination ranged from 34% in 1968 to 90% in 1991.<sup>11</sup>

### Method

This case-control study was done in East Dorset, UK, with the approval of the local research ethics committee. 164 patients with a definite diagnosis of IBD on the basis of standard clinical