

Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study

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Summary

Background The efficacy of new antihypertensive drugs has been questioned. We compared the effects of conventional and newer antihypertensive drugs on cardiovascular mortality and morbidity in elderly patients.

Methods We did a prospective, randomised trial in 6614 patients aged 70–84 years with hypertension (blood pressure ≥ 180 mm Hg systolic, ≥ 105 mm Hg diastolic, or both). Patients were randomly assigned conventional antihypertensive drugs (atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily) or newer drugs (enalapril 10 mg or lisinopril 10 mg, or felodipine 2.5 mg or isradipine 2–5 mg daily). We assessed fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease. Analysis was by intention to treat.

Findings Blood pressure was decreased similarly in all treatment groups. The primary combined endpoint of fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease occurred in 221 of 2213 patients in the conventional drugs group (19.8 events per 1000 patient-years) and in 438 of 4401 in the newer drugs group (19.8 per 1000; relative risk 0.99 [95% CI 0.84–1.16], $p=0.89$). The combined endpoint of fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, and other cardiovascular mortality occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (0.96 [0.86–1.08], $p=0.49$).

Interpretation Old and new antihypertensive drugs were similar in prevention of cardiovascular mortality or major events. Decrease in blood pressure was of major importance for the prevention of cardiovascular events.

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Introduction

The benefits of treating hypertension in elderly people through decrease of cardiovascular morbidity and mortality have been well documented in prospective intervention studies.^{1–7}

In the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) study,⁴ a double-blind, randomised, controlled trial, 1627 elderly patients with hypertension were assigned active antihypertensive treatment (one of three β -blockers or a fixed-ratio combination of hydrochlorothiazide and amiloride) or placebo. Active treatment lowered endpoint rates significantly compared with placebo: fatal and non-fatal strokes by 47%, major cardiovascular events (all strokes, all myocardial infarctions, and other cardiovascular mortality) by 40%, and total mortality by 43%.

Before publication of the results of STOP-Hypertension in 1991, questions had been raised about the usefulness of newer antihypertensive drugs, specifically angiotensin-converting-enzyme (ACE) inhibitors and calcium antagonists, in the prevention of cardiovascular morbidity in elderly patients with hypertension. We therefore designed the STOP-Hypertension-2 study^{8,9} to compare cardiovascular mortality during treatment with conventional antihypertensive drugs (diuretics, β -blockers, or both) with that during treatment with newer drugs (ACE inhibitors or calcium antagonists). We did not include a long-term placebo control group for ethical reasons. We aimed also to compare the three treatments for effect on cardiovascular mortality.

Patients and methods

Study population

From Sept 1, 1992, to Dec 30, 1994, we enrolled 6628 men and women in 312 health centres in Sweden (figure 1) who had

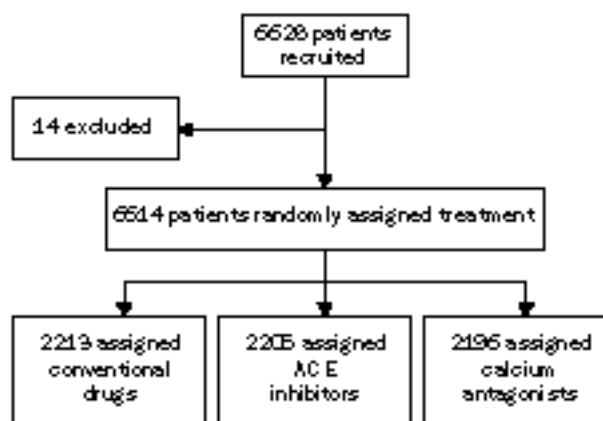


Figure 1: Trial profile

	All patients (n=6614)	Conventional drugs group (n=2213)	ACE inhibitors group (n=2205)	Calcium antagonists group (n=2196)
Patients' characteristics				
Age (years)	76.0	76.0	76.1	75.9
Men/women	2196 (33.2%)/4418 (66.8%)	708 (32.0%)/1505 (68.0%)	743 (33.7%)/1462 (66.3%)	747 (34.0%)/1449 (66.0%)
Recruited from STOP-Hypertension	410 (6.2%)	128 (5.8%)	137 (6.2%)	147 (6.7%)
Clinical characteristics				
Supine blood pressure (mm Hg)	194/98	194/98	194/98	194/98
Standing blood pressure (mm Hg)	187/101	187/101	187/100	187/101
Body-mass index (kg/m ²)	26.7	26.7	26.7	26.7
Serum cholesterol (mmol/L)	6.4	6.4	6.4	6.5
Serum triglycerides (mmol/L)	1.7	1.7	1.7	1.7
Blood glucose (mmol/L)	5.6	5.6	5.6	5.5
Smokers (%)	9.0	8.8	9.4	8.8
History				
Myocardial infarction	205 (3.1%)	73 (3.3%)	60 (2.7%)	75 (3.4%)
Ischaemic heart disease	529 (8.0%)	186 (8.4%)	183 (8.3%)	163 (7.4%)
Stroke	258 (3.9%)	86 (4.0%)	868 (3.9%)	83 (3.8%)
Congestive heart failure	126 (1.9%)	33 (1.5%)	51 (2.3%)	44 (2.0%)
Atrial fibrillation	311 (4.7%)	104 (4.7%)	117 (5.3%)	90 (4.1%)
Other cardiovascular disease	337 (5.1%)	115 (5.2%)	115 (5.2%)	105 (4.8%)
Diabetes mellitus	721 (10.9%)	252 (11.4%)	236 (10.7%)	231 (10.5%)

Data are means unless marked otherwise.

Table 1: Baseline clinical characteristics

hypertension (blood pressure ≥ 180 mm Hg systolic, ≥ 105 mm Hg diastolic, or both), aged 70–84 years. The only difference in inclusion criteria between this trial and the STOP-Hypertension trial was that patients with isolated systolic hypertension could be included in STOP-Hypertension-2, based on previous positive findings in patients with isolated systolic hypertension treated with diuretics³ and calcium antagonists.^{6,7} Patients were followed up until Dec 31, 1998.

Study design

We used a prospective, randomised, open, masked-endpoint trial design,¹⁰ which is similar to routine clinical practice. Patients were randomly assigned treatment with one of three classes of drugs: conventional antihypertensive drugs (diuretics, β -blockers, or both—oral atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg, or fixed-ratio hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily), ACE inhibitors (enalapril 10 mg or lisinopril 10 mg daily), or calcium antagonists (felodipine 2.5 mg or isradipine 2.5 mg daily). The choices of drugs within the groups were not randomised. Patients on β -blockers were given hydrochlorothiazide 25 mg plus amiloride 2.5 mg as additional treatment if the target blood pressure ($<160/95$ mm Hg) had not been reached at the 2-month visit or later. Patients who had started on diuretic treatment or calcium antagonist were given any of the β -blockers in the doses listed, and patients on ACE inhibitors were given hydrochlorothiazide 12.5–25.0 mg.

We measured blood pressure in the supine position after 5 min of rest, with a cuff and a rubber balloon that completely encircled the upper arm, generally with the dimensions 12–13 \times 35 cm, altered as appropriate.

After the initial dose-titration period, we saw patients twice yearly. At each visit, blood pressure and heart rate were measured. We collected information on adverse events by asking patients

whether new symptoms had occurred since the last visit. Laboratory tests and electrocardiography were done routinely once yearly and as needed in relation to new symptoms.

An independent endpoint committee assessed all endpoints according to prespecified criteria.⁸ The members of this committee were masked to the treatment and blood pressures of the patients. A specially appointed auditor randomly selected 16 centres to check their function in the trial and adherence to protocol, which was followed well. Relevant ethics committees approved the study. All patients gave their informed consent to participate.

Statistical analysis

We designed the study to have a statistical power of 90% to detect a 25% difference in cardiovascular mortality in a two-sided test at 5% significance between conventional and newer drugs. 540 events were required to show this difference and, according to data from official Swedish statistics and the STOP-Hypertension study, we estimated that 6600 patients needed to be recruited and followed up over the 4 years of the study. In addition, this number would provide a statistical power of about 80% to detect a 25% difference in cardiovascular mortality in a two-sided test at 5% significance between any two of the three treatment groups.

Analysis was by intention to treat and of only the first occurrence of each event in question. Cox's regression analysis used time since randomisation as non-parametrically modelled time variable. The model was adjusted for sex and baseline age, diastolic blood pressure, diabetes, and smoking status. An on-treatment analysis is planned for the future. We did all calculations on Stata software (version 5).

Results

14 patients were excluded because they were outside the age range of 70–84 years (figure 1). The mean number of patients per trial centre was 21.2; more than 150 centres randomised 25 patients or more. No patient was lost to follow-up and no patient refused to continue in the study. 33 249 patient-years were accumulated, 11 150 in the conventional drugs group, 11 048 in the ACE inhibitors

	STOP-Hypertension-2 (n=6614)	STOP-Hypertension (n=1627)
Patients' characteristics		
Males	33%	37%
Smokers	9.0%	7.8%
Mean body-mass index (kg/m ²)	26.7	26.6
History		
Myocardial infarction	3.1%	2.0%
Stroke	3.9%	4.2%
Diabetes mellitus	10.9%	7.8%
Age-groups		
70–74 years	41%	44%
75–79 years	37%	40%
80–84 years	22%	17%

Table 2: Comparison of selected STOP-Hypertension-2 and STOP-Hypertension baseline characteristics

	Conventional drugs group	ACE inhibitors group	Calcium antagonists group
Randomisation	194/98	194/98	194/98
1 month	173/88	174/89	172/88
6 months	165/85	167/86	167/85
12 months	165/85	167/86	167/85
24 months	163/84	164/84	165/84
36 months	161/83	163/83	163/82
48 months	161/82	162/82	162/82
54 months	158/81	159/81	159/80

Table 3: Supine blood pressure (mm Hg)

	Conventional drugs group (%)	ACE inhibitors group (%)	Calcium antagonists group (%)
Shortness of breath	11.8	7.3	8.5
Palpitations	2.9	5.3	7.9
Flushing	1.6	2.2	9.7
Headaches	5.7	7.7	10.0
Cold hands and feet	9.1	3.3	2.5
Slow pulse	3.7	0.8	1.4
Nightmares	5.8	1.4	2.0
Dry mouth	4.4	2.0	2.7
Ankle oedema	8.5	8.7	25.5
Insomnia	4.3	1.8	2.3
Dry cough	3.7	30.1	5.7
Dizziness	27.8	27.7	24.5

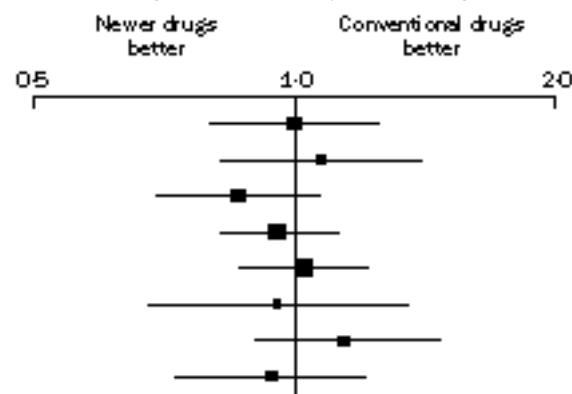
Table 4: Proportions of patients reporting 12 most common adverse events

group, and 11 051 in the calcium antagonists group; 369, 380, and 362 patients respectively, died. Baseline values

	Relative risk (95% CI)*	p
Cardiovascular mortality	0.99 (0.84-1.16)	0.89
All myocardial infarction	1.04 (0.86-1.26)	0.69
All stroke	0.89 (0.76-1.04)	0.13
All major cardiovascular events	0.96 (0.86-1.08)	0.49
Total mortality	1.01 (0.89-1.14)	0.92
Frequency of diabetes mellitus	0.96 (0.75-1.23)	0.77
Frequency of atrial fibrillation	1.09 (0.92-1.31)	0.32
Frequency of congestive heart failure	0.95 (0.79-1.14)	0.55

Figure 2: Relative risk of cardiovascular mortality and morbidity for all newer drugs vs conventional drugs

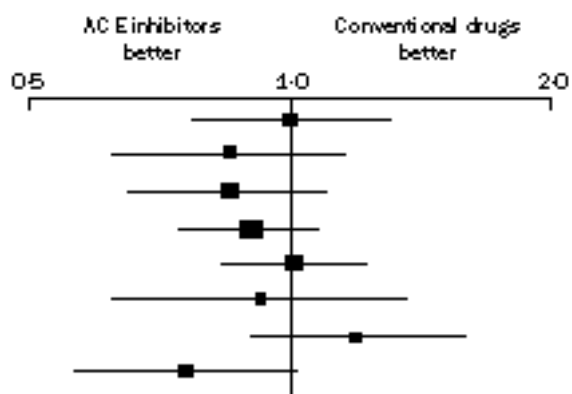
*Adjusted for age, sex, diabetes, diastolic blood pressure, and smoking.



	Relative risk (95% CI)*	p
Cardiovascular mortality	1.01 (0.84-1.22)	0.89
All myocardial infarction	0.90 (0.72-1.13)	0.38
All stroke	0.90 (0.74-1.08)	0.24
All major cardiovascular events	0.94 (0.82-1.07)	0.32
Total mortality	1.02 (0.89-1.18)	0.76
Frequency of diabetes mellitus	0.96 (0.72-1.27)	0.77
Frequency of atrial fibrillation	1.15 (0.94-1.41)	0.18
Frequency of congestive heart failure	0.83 (0.67-1.03)	0.096

Figure 3: Relative risk of cardiovascular mortality and morbidity for ACE inhibitors vs conventional drugs

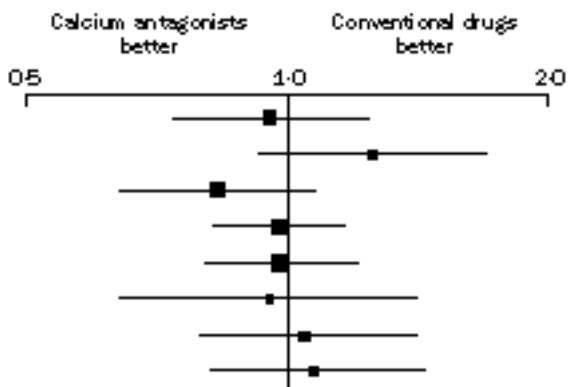
*Adjusted for age, sex, diabetes, diastolic blood pressure, and smoking.



	Relative risk (95% CI)*	p
Cardiovascular mortality	0.97 (0.80-1.17)	0.72
All myocardial infarction	1.18 (0.95-1.47)	0.13
All stroke	0.88 (0.73-1.06)	0.16
All major cardiovascular events	0.99 (0.87-1.12)	0.85
Total mortality	0.99 (0.86-1.15)	0.90
Frequency of diabetes mellitus	0.97 (0.73-1.29)	0.83
Frequency of atrial fibrillation	1.04 (0.85-1.28)	0.68
Frequency of congestive heart failure	1.06 (0.87-1.31)	0.56

Figure 4: Relative risk of cardiovascular mortality and morbidity for calcium antagonists vs conventional drugs

*Adjusted for age, sex, diabetes, diastolic blood pressure, and smoking.



are given in table 1 and some data are compared with STOP-Hypertension data in table 2.

The blood-pressure-lowering effects were similar in the three treatment groups. Among patients who survived at least 24 months, the decrease in blood pressure from baseline to the last visit was 34.8/16.6 mm Hg in the conventional drugs group, 34.5/16.2 mm Hg in the ACE inhibitors group, and 34.5/17.5 mm Hg in the calcium antagonists group (table 3). At the last visit, 46.0% of all patients were receiving more than one antihypertensive drug. 62.3% of patients in the conventional drugs group were still taking their randomised treatment at the last visit, compared with 66.2% in the calcium antagonists group and 61.3% in the ACE inhibitors group.

Adverse events are reported as the proportion of patients in each treatment group who, at any time during the trial,

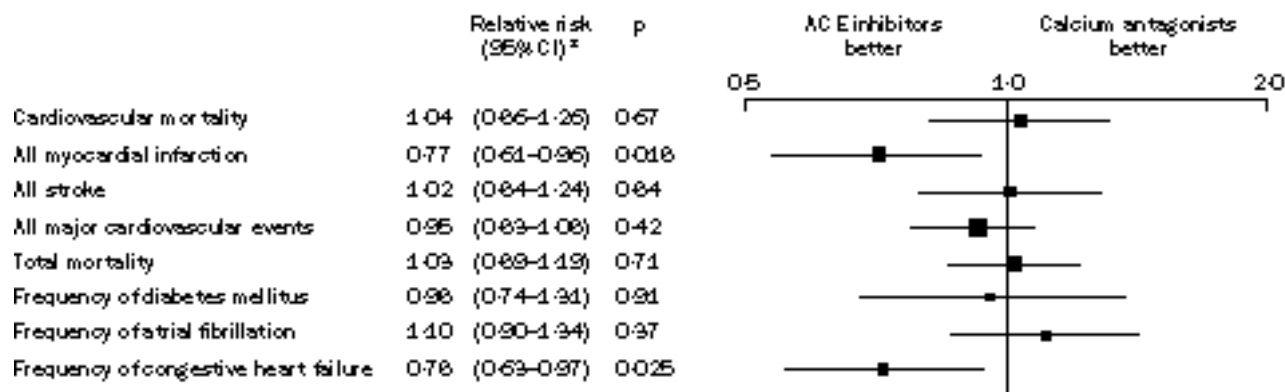


Figure 5: Relative risk of cardiovascular mortality and morbidity for ACE inhibitors vs calcium antagonists

*Adjusted for age, sex, diabetes, diastolic blood pressure, and smoking.

reported an event. We report only the 12 most frequently reported adverse events or symptoms (table 4). Symptoms present at the time of randomisation were not included unless they reappeared at the 6-month visit or later.

More primary endpoints occurred than expected, which gave the study a power of 94.6% for the principal analysis. Conventional and newer drugs lowered blood pressure equally well. The prevention of cardiovascular death, the primary endpoint, was similar in all groups. The relative risks for comparisons of the treatments were between 0.97 and 1.04 with narrow CI. Fatal cardiovascular events occurred in 221 patients in the conventional drugs group (19.8 per 1000 patient-years), and in 438 in the newer drugs group (19.8 per 1000 patient-years; relative risk 0.99 [95% CI 0.84-1.16], $p=0.89$; figure 2).

226 of the fatal cardiovascular events occurred in patients taking ACE inhibitors (20.5 per 1000 patient-years; relative risk compared with conventional drugs 1.01 [0.84-1.22], $p=0.89$; figure 3) and 212 in patients on calcium antagonists (19.2 per 1000; 0.97 [0.80-1.17], $p=0.72$; figure 4). The relative risk in the ACE inhibitors group compared with the calcium antagonists group, was 1.04 (0.86-1.26, $p=0.67$; figure 5). Kaplan-Meier curves for all groups are shown in figure 6.

The combined endpoint of fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, and other cardiovascular mortality occurred in 460 patients in the conventional drugs group and in 887 patients in the newer drugs group (table 5, figure 2). 437 of these patients were taking ACE inhibitors and 450 were taking calcium antagonists (table 5, figures 3-5).

We compared this combined endpoint with the same endpoint in the STOP-Hypertension trial. The three

groups did not differ in frequency of fatal and non-fatal stroke combined, nor was there any difference in the frequency of myocardial infarction when conventional drugs were compared with the other two regimens separately. There were, however, significantly fewer fatal and non-fatal myocardial infarction during treatment with ACE inhibitors than during calcium antagonist treatment (figure 5, table 5). Moreover, the frequency of congestive heart failure was significantly lower in the ACE inhibitors group than in the calcium antagonists group.

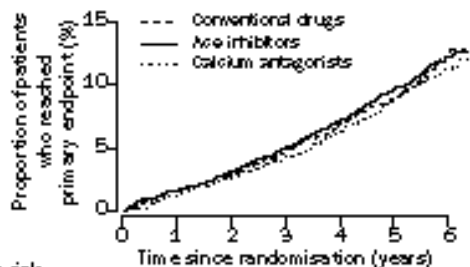
In the 719 patients who had diabetes at baseline (table 6), treatment effects did not differ significantly for frequency of the primary endpoint.

Discussion

This trial was longer than and recruited more than four times as many patients as the STOP-Hypertension study.⁴ The treatment groups in the two studies were similar for all important features, which makes comparisons justified.

All three therapies showed similar efficacy in prevention of cardiovascular mortality and major morbidity; this finding accords with those of Captopril Prevention Project (CAPPP).¹¹ In CAPPP, there was some suggestion that an ACE-inhibitor-based regimen might be less protective against stroke than conventional treatment with diuretics, β -blockers, or both. Although a plausible explanation of this result was provided, it is reassuring that no difference between the three therapeutic regimens in their protective effects against stroke was found in this trial.

The similarity in efficacy of calcium antagonists to diuretics or β -blockers in prevention of cardiovascular events is a new observation. Previous intervention trials in hypertension, in which calcium antagonists have decreased cardiovascular morbidity, have compared drugs with



Patients at risk	0	1	2	3	4	5	6
Calcium antagonists	2196	2156	2094	2029	1950	1422	976
ACE inhibitors	2205	2159	2104	2042	1958	1405	952
Conventional drugs	2213	2169	2118	2057	1979	1425	968

Figure 6: Kaplan-Meier curves of proportion of patients in each group who reached primary endpoint

	Conventional drugs group	ACE inhibitors group	Calcium antagonists group
Total mortality	33.1 (369)	34.4 (380)	32.8 (362)
Cardiovascular mortality	19.8 (221)	20.5 (226)	19.2 (212)
Fatal myocardial infarction	4.9 (55)	4.3 (48)	5.3 (59)
Fatal stroke	4.6 (51)	4.5 (50)	4.2 (46)
Sudden death	4.8 (53)	5.3 (59)	4.7 (52)
Other cardiovascular mortality	5.6 (62)	6.2 (69)	5.0 (55)
Other mortality and morbidity			
All myocardial infarction	14.1 (154)	12.8 (139)	16.7 (179)
All stroke	22.2 (237)	20.2 (215)	19.5 (207)
All major cardiovascular events	44.1 (460)	41.9 (437)	43.6 (450)
Frequency of diabetes mellitus	10.0 (97)	9.6 (93)	9.9 (95)
Frequency of atrial fibrillation	16.4 (176)	19.0 (200)	17.1 (181)
Frequency of congestive heart failure	16.4 (177)	13.9 (149)	17.5 (186)

Table 5: Frequency of events per 1000 patient-years

	All patients (n=719)	Conventional drugs group (n=253)	ACE inhibitors group (n=235)	Calcium antagonists group (n=231)
Patients' characteristics				
Age (years)	75.8	76.0	75.8	75.7
Men/women	286 (39.8%)/433 (60.2%)	109 (43.1%)/144 (56.9%)	92 (39.1%)/143 (60.9%)	85 (36.8%)/146 (63.2%)
Recruited from STOP-Hypertension	55 (7.6%)	22 (8.7%)	15 (6.4%)	18 (7.8%)
Clinical characteristics				
Supine blood pressure (mm Hg)	195/96	195/97	196/96	196/97
Standing blood pressure (mm Hg)	190/99	190/99	189/98	190/99
Body-mass index (kg/m ²)	27.8	27.2	28.2	27.9
Serum cholesterol (mmol/L)	6.1	6.0	6.2	6.1
Serum triglycerides (mmol/L)	2.0	2.0	2.0	2.0
Blood glucose (mmol/L)	8.7	8.8	8.8	8.4
Smokers (%)	48 (6.7%)	12 (4.7%)	21 (8.9%)	15 (6.5%)
History				
Myocardial infarction	30 (4.2%)	17 (6.7%)	7 (3.0%)	6 (2.6%)
Ischaemic heart disease	67 (9.3%)	24 (9.5%)	25 (10.6%)	18 (7.8%)
Stroke	36 (5.0%)	18 (7.1%)	10 (4.3%)	8 (3.5%)
Congestive heart failure	21 (2.9%)	7 (2.8%)	7 (3.0%)	7 (3.0%)
Atrial fibrillation	45 (6.3%)	22 (8.7%)	10 (4.3%)	13 (5.6%)
Other cardiovascular disease	40 (5.6%)	14 (5.5%)	16 (6.8%)	10 (4.3%)

Data are means unless shown otherwise.

Table 6: Baseline characteristics of patients with diabetes mellitus

placebo.^{6,7,12} The adverse events we reported were based on any report of an adverse event, at any time during the trial, with no reference to duration or severity.

In this study, more patients than in STOP-Hypertension had had myocardial infarction (3.1 vs 2.0%) and had diabetes mellitus (10.9 vs 7.8%) at baseline. This difference could explain the higher frequency of cardiovascular events in STOP-Hypertension-2. Similarities between the two trials, however, permitted comparison of the event rate in this trial with that in the placebo group in the STOP-Hypertension trial.

The frequency of endpoints was higher in this study than in the actively treated group in the STOP-Hypertension trial, despite the similar systolic blood pressures throughout the two trials. This similarity can be attributed to the higher prevalence of previous myocardial infarction, stroke, and diabetes mellitus, and the longer duration of this study (60 vs 25 months), which meant that patients became older than in the STOP-Hypertension study.

The frequencies of myocardial infarctions and of congestive heart failure were significantly lower in patients treated with ACE inhibitors than in those receiving calcium antagonists in this trial. The differences in the frequency of myocardial infarction support the results from the substudy of the Adequate Blood Pressure Control in Diabetes study.¹³ However, our results should be interpreted with some caution, since 48 statistical comparisons were done. Calcium antagonists were not, however, less effective in any other way in the prevention of cardiovascular events than conventional drugs or ACE inhibitors, which accords with current opinion about safety of calcium antagonists when used appropriately.^{14,15}

Our present results add information to the already accepted view that elderly patients with hypertension benefit from antihypertensive treatment through lowering of cardiovascular morbidity and mortality rates. Older and newer antihypertensive drugs are equally useful. The choice of treatment will, therefore, be related to other factors such as cost, side-effects, and coexisting disorders. We showed that the decrease in blood pressure was very important for the prevention of fatal and non-fatal cardiovascular events in elderly patients with hypertension. This finding is in agreement with the results of the Hypertension Optimal Treatment study.¹⁵ We could not substantiate our hypothesis that some classes of

antihypertensive drugs would provide advantages over others in this population of elderly hypertensive patients.⁸

STOP-Hypertension-2 study group

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