

Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial

Lennart Hansson, Lars H Lindholm, Leo Niskanen, Jan Lanke, Thomas Hedner, Anders Niklason, Kimmo Luomanmäki, Björn Dahlöf, Ulf de Faire, Claes Mörlin, Bengt E Karlberg, P O Wester, Jan-Erik Björck, for the Captopril Prevention Project (CAPPP) study group*

Summary

Background Angiotensin-converting-enzyme (ACE) inhibitors have been used for more than a decade to treat high blood pressure, despite the lack of data from randomised intervention trials to show that such treatment affects cardiovascular morbidity and mortality. The Captopril Prevention Project (CAPPP) is a randomised intervention trial to compare the effects of ACE inhibition and conventional therapy on cardiovascular morbidity and mortality in patients with hypertension.

Methods CAPPP was a prospective, randomised, open trial with blinded endpoint evaluation. 10 985 patients were enrolled at 536 health centres in Sweden and Finland. Patients aged 25–66 years with a measured diastolic blood pressure of 100 mm Hg or more on two occasions were randomly assigned captopril or conventional antihypertensive treatment (diuretics, β -blockers). Analysis was by intention-to-treat. The primary endpoint was a composite of fatal and non-fatal myocardial infarction, stroke, and other cardiovascular deaths.

Findings Of 5492 patients assigned captopril and 5493 assigned conventional therapy, 14 and 13, respectively, were lost to follow-up. Primary endpoint events occurred in 363 patients in the captopril group (11.1 per 1000 patient-years) and 335 in the conventional-treatment group (10.2 per 1000 patient-years; relative risk 1.05 [95% CI 0.90–1.22], $p=0.52$). Cardiovascular mortality was lower

with captopril than with conventional treatment (76 vs 95 events; relative risk 0.77 [0.57–1.04], $p=0.092$), the rate of fatal and non-fatal myocardial infarction was similar (162 vs 161), but fatal and non-fatal stroke was more common with captopril (189 vs 148; 1.25 [1.01–1.55], $p=0.044$).

Interpretation Captopril and conventional treatment did not differ in efficacy in preventing cardiovascular morbidity and mortality. The difference in stroke risk is probably due to the lower levels of blood pressure obtained initially in previously treated patients randomised to conventional therapy.

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See Commentary page ???

Introduction

Angiotensin-converting-enzyme (ACE) inhibitors are used widely in the treatment of high blood pressure. Guidelines for the management of hypertension issued by WHO and the International Society of Hypertension, class ACE inhibitors as suitable for first-line treatment, along with diuretics and β -blockers. Guidelines issued by the Joint National Committee in the USA used to state the same thing, but more recent versions of these guidelines have not recommended ACE inhibitors as first-line treatment. This change reflects the fact that no data from prospective and randomised trials in hypertensive patients have shown that ACE inhibitor treatment protects against cardiovascular morbidity and mortality.

There has been concern about the safety of newer antihypertensive agents and whether they give the same benefits as diuretics and β -blockers; such concern has focused on calcium antagonists but not ACE inhibitors. The Captopril Prevention Project (CAPPP) was designed as a prospective intervention trial to compare the potential benefits to cardiovascular morbidity and mortality of a regimen based on the ACE inhibitor captopril with a conventional antihypertensive regimen of diuretics or β -blockers. For ethical reasons, a long-term comparison with placebo was not done.

The scientific background and rationale of the CAPPP study have been reported elsewhere.⁵ Observations on intermediary endpoints, which were available when the study was planned in the late 1980s, suggested that an antihypertensive regimen based on an ACE inhibitor might offer benefits equal to or greater than those of conventional antihypertensive treatment with diuretics, β -blockers, or both.⁶ ACE inhibitors help to reverse left-ventricular hypertrophy,^{7,8} itself a powerful indicator of cardiovascular risk,^{9,10} improve cardiac function in patients with left-ventricular dysfunction,^{11,12} have

*Members listed at end of paper

Department of Public Health and Social Sciences, University of Uppsala, Uppsala, Sweden (Prof L Hansson MD); **Department of Public Health and Clinical Medicine** (Prof L H Lindholm MD) and **Department of Medicine** (Prof P O Wester MD), **Umeå University Hospital, Umeå, Sweden**; **Department of Medicine, Kuopio University Hospital, Kuopio, Finland** (Prof L Niskanen MD); **Department of Statistics, Lund University, Lund, Sweden** (Prof J Lanke PhD); **Department of Clinical Pharmacology, Sahlgrenska University Hospital, Gothenburg, Sweden** (Prof T Hedner MD); **Bristol-Myers Squibb, Stockholm, Sweden** (A Niklason MB, C Mörlin MD, J-E Björck MB); **Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland** (Prof K Luomanmäki MD); **GU Clinical Research Institute, Gothenburg, Sweden** (B Dahlöf MD); **Department of Cardiovascular Research, Karolinska Hospital, Stockholm, Sweden** (Prof U de Faire MD); and **Department of Medicine, University Hospital, Linköping, Sweden** (Prof B E Karlberg MD)

Correspondence to: Prof Lennart Hansson, Division of Clinical Hypertension Research, Department of Public Health and Social Sciences, University of Uppsala, Box 609, S-751 25 Uppsala, Sweden

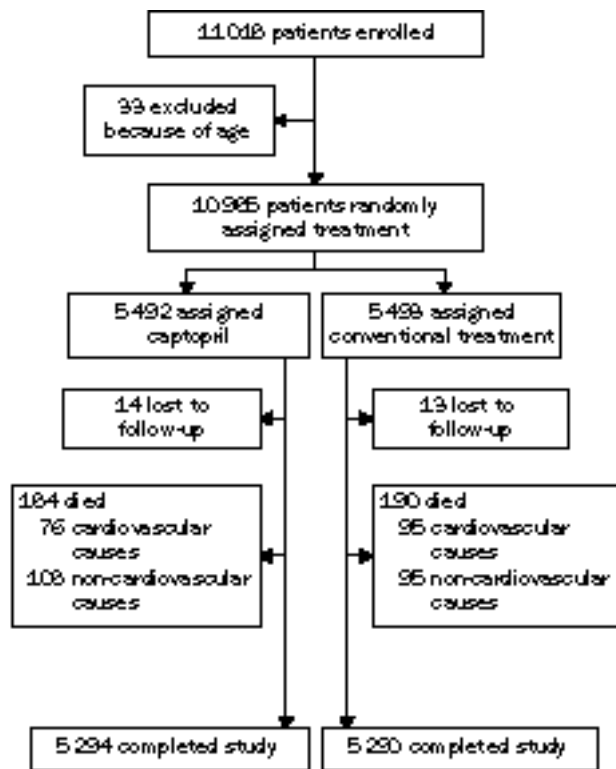


Figure 1: Trial profile

favourable metabolic effects,¹³ and help to maintain quality of life.¹⁴ More recently, benefits of ACE inhibition have been shown in patients with diabetic nephropathy¹⁵ and in diabetic patients in general.¹⁶ ACE inhibitors also maintain renal function in patients with primary hypertension,^{17,18} which strengthens the hypothesis that a therapeutic regimen based on ACE inhibitors in the treatment of primary hypertension could reduce the risk of cardiovascular morbidity and mortality.

Methods

Study population

The CAPPP trial, at 536 health centres in Sweden and Finland, used the design of the PROBE study¹⁹ (Prospective Randomised

Characteristic	Captopril treatment (n=5492)	Conventional treatment (n=5493)
Demographic		
M/F	3016/2476	2858/2635
Age (years)*	52.4 (8.3)	52.7 (8.4)
Clinical		
Weight (kg)*	81.6 (15.2)	80.6 (15.1)
Height (cm)*	170.8 (9.0)	170.1 (9.1)
Supine systolic blood pressure (mm Hg)*	161.8 (19.9)	159.6 (20.1)
Supine diastolic blood pressure (mm Hg)*	99.8 (9.9)	98.1 (10.1)
Serum creatinine ($\mu\text{mol/L}$)*	86.5 (15.2)	86.1 (15.0)
Serum cholesterol (mmol/L)*	6.20 (1.19)	6.16 (1.16)
Fasting blood glucose (mmol/L)*	5.22 (1.38)	5.23 (1.36)
Previously untreated	2640	2605
Smokers	1217	1214
Medical history		
Myocardial infarction	40	55
Ischaemic heart disease	64	81
Stroke	50	39
Transient ischaemic attacks	43	35
Atrial fibrillation	36	34
Congestive heart failure	19	10
Cardiovascular complications	219	213
Diabetes mellitus	309	263

Data are number of patients or *mean (SD).

Table 1: Baseline characteristics

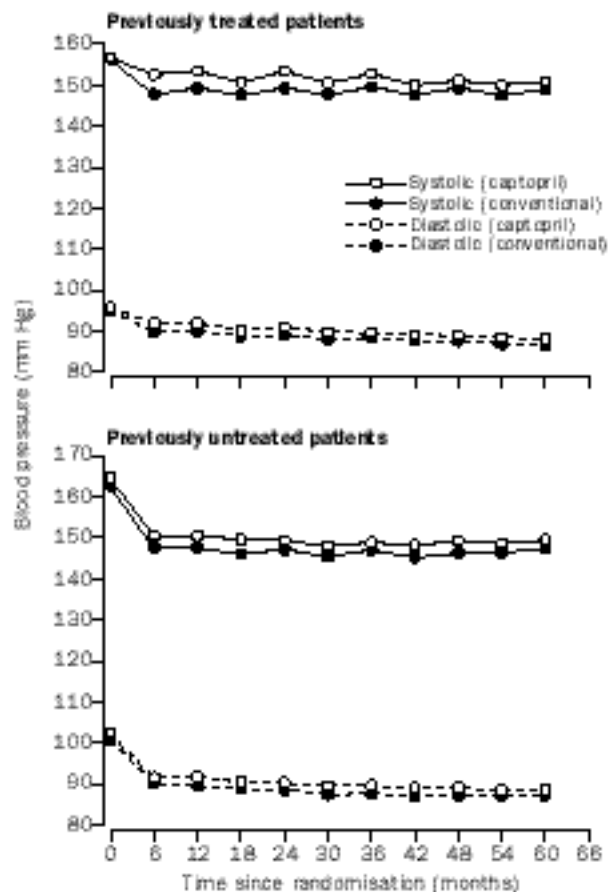


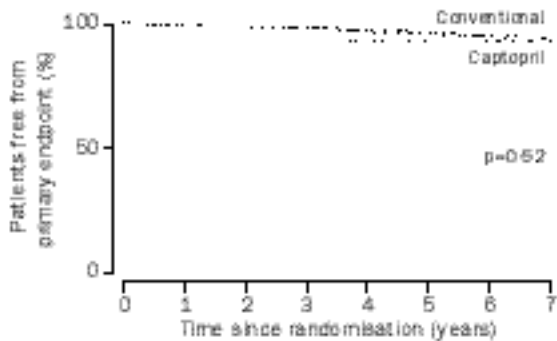
Figure 2: Blood pressure during study

Open Blinded Endpoint), which is similar to routine clinical practice. Men and women aged 25–66 years who had treated or untreated primary hypertension were included in the trial if their diastolic blood pressure was 100 mm Hg or higher on two separate occasions. Exclusion criteria were secondary hypertension, serum creatinine concentration of more than 150 $\mu\text{mol/L}$, and disorders that required treatment with β -blockers. Eligible patients were randomly assigned captopril treatment or conventional antihypertensive treatment with diuretics, β -blockers, or both. The initial dose of captopril was 50 mg daily given in one or two doses. In the group receiving conventional treatment, atenolol and metoprolol were the most commonly used β -blockers, and hydrochlorothiazide and bendrofluazide the most common diuretics. The initial dose of atenolol and metoprolol was 50–100 mg once daily.

Characteristic	Previously untreated (n=5245)		Diabetes (n=572)	
	Captopril (n=2640)	Conventional (n=2605)	Captopril (n=309)	Conventional (n=263)
Demographic				
M/F	1499/1141	1403/1202	196/113	158/105
Age (years)*	51.3 (8.4)	51.7 (8.5)	55.0 (7.6)	55.7 (7.4)
Clinical				
Weight (kg)*	80.9 (15.4)	80.6 (15.0)	90.4 (16.7)	88.8 (15.9)
Height (cm)*	171.3 (9.1)	170.7 (9.0)	171.6 (8.9)	171.1 (8.8)
Supine systolic blood pressure (mm Hg)*	166.6 (19.5)	163.3 (19.8)	163.6 (18.8)	163.3 (20.6)
Supine diastolic blood pressure (mm Hg)*	103.6 (8.6)	101.2 (9.6)	97.1 (9.6)	97.3 (10.1)
Previously untreated	2640	2605	113	99
Medical history				
Cardiovascular complications	77	80	33	19
Diabetes mellitus	113	99	309	263

Data are number of patients or *mean (SD).

Table 2: Baseline characteristics of previously untreated patients and of patients with diabetes at baseline



Patients at risk	Captopril	Conventional
0	5492	5493
1	5344	5362
2	4911	4970
3	3211	3180

Figure 3: Patients remaining free from primary endpoint

Hydrochlorothiazide was given as 25 mg once daily, and bendrofluzide as 2.5 mg once daily. The randomisation sequence was generated by computer and conveyed to the investigators by means of sealed numbered envelopes, one for each patient, with instructions to use the envelopes in numerical order.

Blood pressure was measured with the patient supine by means of conventional mercury sphygmomanometers. The cuff contained a rubber bladder with dimensions of 12×35 cm. Larger cuffs were used if necessary. We calculated the mean of two measurements of blood pressure made to the nearest 2 mm Hg. The goal of treatment was a supine diastolic blood pressure of 90 mm Hg or less. To reach this goal, the treatment dose could be increased to 100 mg once or twice daily in the captopril group, and if necessary a diuretic was added. In the group that received conventional treatment, an optimum dose of β -blocker or diuretic was used. The investigators were free to choose suitable conventional treatment, and the diuretic and the β -blocker could be combined. A calcium antagonist could be added to the treatment regimen in both treatment groups.

The primary endpoint was the combination of fatal and non-fatal myocardial infarction and stroke, and other cardiovascular deaths. Primary events and most secondary events were assessed by an independent endpoint committee from which the treatment allocation was concealed. Secondary endpoints were new or deteriorated ischaemic heart disease and congestive heart failure, atrial fibrillation, diabetes mellitus, transient ischaemic attacks, and death from all causes. A diagnosis of acute myocardial infarction required that at least two of the following criteria were met: central chest pain for more than 15 min; transient increase in serum concentrations of enzymes indicating myocardial damage; and electrocardiographic changes typical of myocardial infarction. A diagnosis of fatal myocardial infarction required the same criteria as a non-fatal acute myocardial infarction, or a statement of that diagnosis in hospital or necropsy reports. Diagnosis of stroke required typical symptoms or signs of remaining neurological deficit, with sudden onset and persistence for more than 24 h. Diagnosis of transient ischaemic attacks required symptoms and signs of neurological deficit with sudden onset but with a duration of less than 24 h. Diagnosis of fatal stroke required the same criteria as a non-fatal stroke, or a statement of that diagnosis in hospital records or necropsy reports. Diagnosis of diabetes was made according to

Event (n)	Captopril group	Conventional group
Fatal myocardial infarction	27	35
Fatal stroke	20	22
Other cardiovascular deaths	23	24
Sudden death	6	14
Non-fatal myocardial infarction	137	128
Non-fatal stroke	173	127
Ischaemic heart disease	258	251
Atrial fibrillation	117	135
Congestive heart failure	75	66
Diabetes mellitus	337	380
Transient ischaemic attacks	31	25

Table 3: Patients with events during follow-up by treatment group

WHO criteria, and required at least two abnormal fasting glucose values or, if not unequivocal, confirmation by an oral glucose-tolerance test. The CAPP study was approved by ethics committees in Sweden and Finland.

Statistical analysis

Analysis was by intention to treat. The CAPP study was designed to have an 80% power of detecting a 20% reduction in the rate of primary endpoints in a two-sided test at 5% significance. 640 primary events were required in the two groups combined. For each patient, only the first occurrence of primary endpoint was included in the analysis. Cox regression analysis used time since randomisation as a non-parametrically modelled time variable. The model was adjusted for age at randomisation, sex, diabetes, and systolic blood pressure at randomisation. The study group included both previously untreated patients and patients receiving antihypertensive treatment before randomisation, and we did not include a washout period. We therefore had to account for baseline differences in the model. We included baseline systolic blood pressure, a factor 'previously untreated', and the product of these factors in the model. In the on-treatment analysis a patient was classified as on treatment for as long as he or she took the intended medication and no other medication. All calculations used Stata software (version 5).

Results

11 018 patients were enrolled in the study, but 33 were excluded because of their age. Of the remaining 10 985 patients, 5492 were randomly assigned captopril treatment and 5493 were randomly assigned conventional treatment (figure 1). Follow-up lasted for a mean of 6.1 years: a total of 67 239 patient-years were recorded. Only 27 (0.25%) patients were lost to follow-up.

Baseline characteristics (table 1) and effects on blood pressure have been described elsewhere.²⁰ Blood pressure at baseline was higher in the captopril group than in the group that received conventional therapy, both among previously untreated patients (166.6/103.6 vs 163.3/101.2 mm Hg, $p < 0.0001$ in both cases) and among those already on antihypertensive treatment (157.4/96.2 vs 156.2/95.4 mm Hg; $p = 0.025$ and $p = 0.001$, respectively, figure 2). Diabetes mellitus at baseline was more common in the captopril group than in the group that received conventional treatment (table 2).

The primary endpoint (fatal and non-fatal myocardial infarction, stroke and other cardiovascular deaths) did not differ between the two treatment groups (relative risk 1.05; $p = 0.52$, figures 3, 4). Numbers of the individual events are given in table 3.

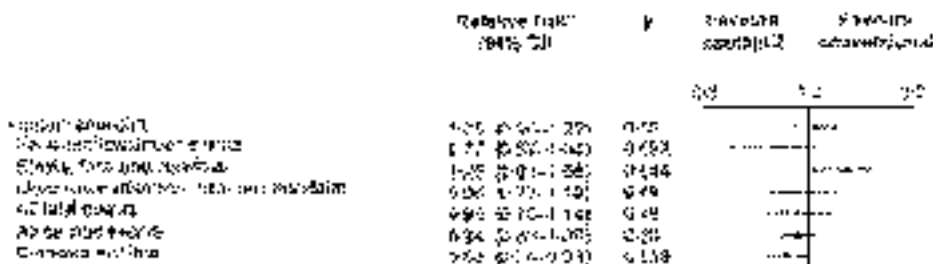


Figure 4: Relative risk of captopril vs conventional therapy

*Adjusted for age, sex, diabetes, systolic blood pressure, and previous treatment.

	Relative risk (95% CI)*	p
Primary endpoint	1.12 (0.94-1.32)	0.20
Fatal cardiovascular events	0.88 (0.62-1.25)	0.47
Stroke, fatal and non-fatal	1.43 (1.12-1.82)	0.004
Myocardial infarction, fatal and non-fatal	0.94 (0.73-1.20)	0.61
All fatal events	1.04 (0.82-1.32)	0.75
All cardiac events	0.94 (0.82-1.07)	0.33
Diabetes mellitus	0.79 (0.67-0.94)	0.007

*Adjusted for age, sex, diabetes, systolic blood pressure, and previous treatment.

Table 4: On-treatment analysis: relative risk of captopril vs conventional therapy

Cardiovascular mortality, defined as fatal stroke and myocardial infarction, sudden death, and other cardiovascular death, was slightly lower in the captopril group than in the conventional group (0.77; $p=0.092$). Fatal and non-fatal strokes were more common in the captopril group (1.25; $p=0.044$). The rates of fatal and non-fatal myocardial infarction were similar in the two treatment groups (0.96, $p=0.68$).

Analyses of secondary outcomes (figure 4) showed that total mortality did not differ between the two treatment groups (0.93; $p=0.49$), and the incidence of diabetes was lower in the captopril group than in the conventional group (0.86; $p=0.039$). The rates of all cardiac events—fatal and non-fatal myocardial infarction, other cardiovascular deaths and sudden deaths, ischaemic heart disease, congestive heart failure, atrial fibrillation—did not differ between the two treatment groups (0.94; $p=0.30$).

On-treatment analysis was also done. No new differences between groups were shown, although the results that were significant by intention-to-treat were more significant in the on-treatment analyses (table 4). There was no difference between groups in blood pressure related to cardiovascular mortality or morbidity, or in comparisons between once-daily and twice-daily doses of captopril.

Separate subgroup analyses were done for patients with diabetes at baseline and for previously untreated patients (figure 5, 6). In both of these groups, captopril was as effective in preventing cardiovascular events as in the whole study population.

Discussion

Our conventional randomisation procedure, using sealed envelopes, resulted in an imbalance between groups at baseline in terms of the blood pressure measurements.

We corrected our data for imbalance in blood pressure at baseline, sex, and the prevalence of diabetes in the analyses. Centralised randomisation by fax²¹ would have been preferable, but this procedure was not standard 10 years ago, when this study was planned.

The proportion of patients lost to follow-up (0.25%) is not as low as that of the STOP-Hypertension trial (0),²² but much lower than that of the MRC study in older patients (25%).²³ The small number of patients lost to follow-up could not have affected the results of our study, since the loss was evenly distributed between the two treatment groups (14 vs 13). Complete information on primary events was available for the remaining patients.

The two treatment regimens had virtually the same effect on blood pressure, although blood pressure measurements were slightly but significantly higher in the captopril group throughout the study (figure 2). Almost all of the previously treated patients had been taking diuretics, β -blockers, or both, and were accustomed to that kind of therapy, whereas captopril was in most instances a new therapy. Target blood pressure (diastolic blood pressure 90 mm Hg) was more rapidly achieved in the conventionally treated group than in the captopril group during the first 6-12 months of the study (figure 2), although this effect was not noted for previously untreated patients. Our study would have been improved if we had included only previously untreated patients, but recruitment of a large enough sample would have been difficult.

Almost equal numbers of patients began captopril treatment once daily (48%) and twice daily (52%), but patients were switched between these two regimens during the trial. Moreover, patients were not randomly assigned once-daily or twice-daily treatment. These factors preclude meaningful analysis of outcomes in relation to captopril dosage.

The treatment regimens did not differ in terms of prevention of the primary endpoint, but the risk of stroke was lower with conventional than with captopril therapy. This finding could be the result of non-adjustment for high blood pressure measurements at baseline and throughout the study in the captopril group, or a more frequent history of stroke and transient ischaemic attacks in that group than in the group assigned conventional treatment. A difference of 2 mm Hg could account for a

15% difference in risk of stroke and transient ischaemic attack.²⁴ In diabetic patients blood pressure measurements at baseline were identical in the two treatment groups and the incidence of stroke was the same in the two groups. The number of fatal strokes did not differ significantly in the two treatment groups (20 captopril vs 22 conventional): if there really was an increased risk of stroke in the captopril group, there should have been a proportional increase in both fatal and non-fatal strokes. Long-

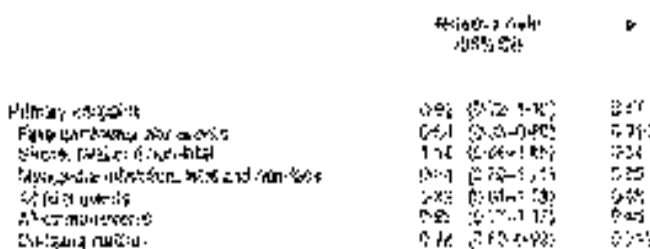


Figure 5: Relative risk in previously untreated patients (n=5245)

*Adjusted for age, sex, diabetes, and systolic blood pressure.

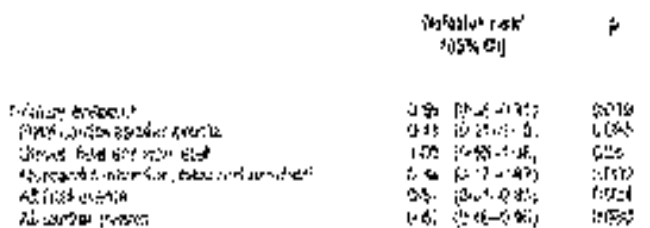


Figure 6: Relative risk in patients with diabetes mellitus at baseline (n=572)

*Adjusted for age, sex, systolic blood pressure, and previous treatment.

term follow-up data from the Glasgow Blood Pressure Clinic showed that the reduction in fatal stroke associated with ACE inhibitors was at least as good as that associated with non-ACE inhibitors.²⁵ Further discussion of this issue can be expected when the results of the STOP-Hypertension-2 study become available,²⁶ in which hypertensive patients were randomly assigned one of the three therapeutic options: conventional treatment (diuretics, β -blockers), calcium antagonists, or ACE inhibitors, with cardiovascular mortality as the primary endpoint.

There were fewer major cardiovascular events in the captopril group, in line with our expectation of the effect of captopril on intermediate endpoints.^{5,15-18} Significantly fewer patients developed diabetes in the captopril group than in the conventional group. This effect may be attributed to the positive effect of captopril on insulin sensitivity during long-term antihypertensive treatment,¹³ although studies of other ACE inhibitors have not confirmed this finding.²⁷⁻²⁹ The lower incidence of diabetes in the captopril group should have positive implications for long-term cardiovascular prognosis.

Patients with diabetes at baseline had a significantly lower rate of the primary endpoint and of fatal cardiovascular events in the captopril group than in the conventional group. There was a 66% lower rate of fatal and non-fatal myocardial infarctions in the captopril group than in the conventional group. The frequency of all cardiac events and total mortality was also significantly lower in the captopril group than in the conventional group. These findings are similar to those of the subgroup analysis of the ABCD (Appropriate Blood Pressure Control in Diabetes) study,¹⁶ and they strengthen the impression that an antihypertensive regimen based on ACE inhibitors is particularly appropriate for the treatment of diabetic patients with hypertension.

On the other hand, the UK Prospective Diabetes Study (UKPDS 39)³⁰ showed no advantage for captopril over atenolol in lowering of the risk of macrovascular and microvascular diabetic complications. This finding suggests that lowering of blood pressure per se may be more important than the choice of antihypertensive agent, although captopril was better tolerated than atenolol by most patients.³¹ The effective lowering of blood pressure in the UKPDS 39 trial was highly beneficial in diabetic patients, which confirms observations in the HOT study²¹ in which the excess risk associated with diabetes was negligible in patients in whom diastolic blood pressure was lowered to 80 mm Hg or less.

Captopril was more effective in lowering the risk of cardiovascular events, particularly fatal events, in the previously untreated group than in the study population as a whole. One factor that may help to explain the variation in findings between previously treated and previously untreated patients is a difference in compliance between captopril and the conventional regimen. We did not investigate this factor, but Monane and colleagues³² showed that therapy with an ACE inhibitor had 1.9 times better compliance than therapy with diuretics in a large group of hypertensive patients. The UKPDS 39 trial also showed better compliance with captopril than with atenolol (78% compliance with captopril, 65% atenolol, $p < 0.0001$).³⁰ In our study, among previously treated patients well used to taking antihypertensive treatment, a difference in compliance

between regimens might not be apparent. By contrast, among those previously untreated, both regimens would be new to the patients and the difference in compliance found by previous studies^{30,32} might have favoured captopril.

The overall results of the CAPPP study suggest that an antihypertensive regimen based on ACE inhibitors is as effective as conventional treatment with diuretics, β -blockers, or both in prevention of cardiovascular morbidity and mortality, possibly less effective in the prevention of stroke, and most probably more effective in the prevention of diabetes. This finding is of particular importance because recent studies have emphasised that both therapies have the same total treatment cost.³³⁻³⁵

CAPPP Study Group

Steering committee—L Hansson, J-E Björck, B Dahlöf, U de Faire, T Hedner, B E Karlberg, J Lanke, L H Lindholm, K Luomanmäki, C Mörlin, L Niskanen, P O Wester.

Endpoint committee—G Härtel, P Siltanen, K Swedberg, A Terent.

Endpoint secretary—A Holmner.

Safety committee—L Erhardt, M Kupari, T Thulin, P-O Bendahl

(statistician).

Data management—B Slaug.

Coordinators

Sweden—P-O Andersson, J Asplund, A Dahlqvist, B Fagerberg, G Frithz,

B-G Hansson, A Hägg, S A Jonsen, T Kahan, B Carlberg, B E

Kristensson, J Kuylentierna, H Larsson, B Lindström, I Mattiasson,

B-H Möller, O R Nilsson, H Stakeberg, A Svensson, K Tolagen,

L Weiner, B Åström, J Östergren.

Finland—A Lehtonen, M Lilja, M Nikkilä, J Partanen.

Investigators

Sweden—H Aagaard, G Abrahamsson, T Ahlberg, H Åhlander, N Ahlén,

G Ahlepl, E Ahlzén, L-G Ahnell, K Aljaderi, G Almqvist, M Alvin,

B Andersson, G Andersson, H Andersson, I Andersson, M André,

A Anglemo, S Anker, C Appelgren, K Arman, G Asplund, B Atmer,

C Aurelius, G Bartfay, E Basilier, L Berg, M Berg, M Bergfeldt,

A Berglund, B Bergman, B-M Bergman, B Bergstad, R Bergström,

J-E Billner, L Björkman, I Björkvald, S Blanking, U Blomqvist,

B Bodegård, S Bojesen, I Boman, O Borgholst, M Boström,

G Bredmose-Hansen, M Brian, J Brun, B Bystritski, S Byström,

E Bög-Hansen, S-M Carlsson, M Cech, B Christensen, O Christensen,

A Dahl, G Dahlberg, G Dahlén, C Dahlin, A Dahlman, M Dalemar,

L Duca, T Dyrborn, R Dziamski, Å Edlund, C Edström, M Edward,

A Egilsson, T Ehn, M Ehnebo, M Ekberg, K Ekenbratt, S Ekesrydh,

T Ekman, H Ekström, A Elfstrand, T Elfstrand, M Elm, K-G Enander,

M Enander, J Engborg, C Engstrand, G Engström, U-B Ericsson,

V Eriksen, S Eriksson, U Eriksson, C Eskilsson, C Fabian, L Falk,

P Filipsson, B-C Flensner, C Floom, I Fogelberg-Abrah, R Forrest,

P-G Franke, B Franzén, C Frederiksen, S Fredlund, G Frenkner,

J Frithiof, K Fröstrom, B Furunes, B Gebre-Georgies, A Gidlöf,

D Gilstring, A Gonn, U Grandell, P Grangaard, R Grenholm,

V D Gräslund, L Grönquist, C-L Gustafsson, P Gustafsson, P Hansson,

P Hajsjund-Hansen, H Hallberg, C Hallendal, L Hallin, G Hansen,

B Hansson, B Hansson, T Havland, M Hedlund, I-L Hegstrand,

S Hellerstedt, P Hellke, P Hellman, M Hellqvist, T Hermansson,

C Hersvall, K Hertell, O Herterich, M Hessel, C Heyman, H Hirsch,

L Hjelmæus, I Hjärke, S Hofvendahl, B Hofverberg, S Hollenberg,

U Hollertz, R Hollsten, G Holmberg, F Holmer, A Holmgren, A-L Hult,

A Hult, A Hägerfors, C Höglund, T Höglund, J Höjer, B-G Idh,

S Ingelög, H Isaksson, M Ivermark, G Jansson, R Jansson, J Jarl,

B-O Johansson, B Johansson, E Johansson, G Johansson, H Johansson,

L-Å Johansson, N-E Johansson, Y Johansson, Å Johansson, B Johnson,

L Jonsson, K Juul, C Jägerström, C Jägerén, H J Jörgensen, C Karkow,

E Karlsson, T Kjellström, G Klemetz, L Klockhoff, R Klötz, P Koritz,

H Kristoferson, P Kronmann, B Kuylentierna, H Landström, I Lantz,

A-K Larsson, G Larsson, K Larsson, M Larsson, R Larsson, R Larsson,

Å Larsson, L Leander, K Leetmaa, B Lenngren, M Lind, I Lindahl,

R Lindbergh, H O Lindbergsson, U Lindblad, B Lindborg, P Linde,

L Lindén, T Lindén, B Linder, B Linder, H Lindfors, I Lindgren,

A Lindh, B-Å Lindhe, A-C Lindman, E Ljungberg, L Ljungdahl,

P Lorenzon, V Lukic, U Lundahl, N Lundström, C Lyden, J Löfgren,

T Löfgren, L Lönneborg, B Lönner, F Löngqvist, B Magnusson,

P-O Magnusson, K Malmlöf, B Malmros, K Marcus, K Marits,

S-E Mattisson, R Melefors, K Mokhtar, J Munch, J Månsson,

C Mårtensson, L Måwe, A-M Möller, C-M Mólstad, H Nerell,

E Neremo-Lindqvist, P Nicol, E Nielsen, B Nilsson, C Nilsson, H Nilsson,

I R Nilsson, I Nilsson, L Nilsson, S Nilsson, Ö Nilsson, D Norberg,

E Norberg, A Nordenström, U Nordström, I Norén, A-B Nyberg,

B Nyman-Ericsson, J Näsström, B Odeberg, M Ögland, C Öhlund,

U-K Öhlund, T Öhrn, I Örstig, B Östberg, L Östling, R Östlund,

B Olerud, L Olofsson, H Olsson, P M Ollson, P Ollson, S Palm, E Pavek,

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