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MORTALITY AND MORBIDITY RESULTS FROM THE EUROPEAN WORKING PARTY ON HIGH BLOOD PRESSURE IN THE ELDERLY TRIAL*

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Summary A double-blind randomised placebo-controlled trial of antihypertensive treatment was conducted in patients over the age of 60. Entry criteria included both a sitting diastolic blood pressure on placebo treatment in the range 90–119 mm Hg and a systolic pressure in the range 160–239 mm Hg. 840 patients were randomised either to active treatment (hydrochlorothiazide + triamterene) or to matching placebo. If the blood pressure remained raised, methyldopa was added to the active regimen and matching placebo in the placebo group. An overall intention-to-treat analysis, combining the double-blind part of the trial and all subsequent follow-up, revealed a non-significant change in total mortality rate (−9%, p=0·41) but a significant reduction in cardiovascular mortality rate (−27%, p=0·037). The latter was due to a reduction in cardiac mortality (−38%, p=0·036) and a non-significant decrease in cerebrovascular mortality (−32%, p=0·16). In the double-blind part of the trial, total mortality rate was not significantly reduced (−26%, p=0·077). Cardiovascular mortality was reduced in the actively treated group (−38%, p=0·023), owing to a reduction in cardiac deaths (−47%, p=0·048) and a non-significant decrease in cerebrovascular mortality (−43%, p=0·15). Deaths from myocardial infarction were reduced (−60%, p=0·043). Study-terminating morbid cardiovascular events were significantly reduced by active treatment (−60%, p=0·0064). Non-terminating cerebrovascular events were reduced (−52%, p=0·026), but the non-terminating cardiac events were not (+3%, p=0·98). In the patients randomised to active treatment there were 29 fewer cardiovascular events and 14 fewer cardiovascular deaths per 1000 patient years during the double-blind part of the trial.

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Introduction

HYPERTENSION is one of the major risk factors for stroke and coronary heart disease in elderly subjects.[1,2] However, such an association does not necessarily imply that morbidity and mortality are reduced when blood pressure is lowered by antihypertensive drugs. Controlled trials with antihypertensive agents in elderly subjects have shown either no difference or some possible, but not statistically significant, benefit.[3-9]

In view of the uncertainties regarding treatment in aged people, the European Working Party on High Blood Pressure in the Elderly initiated a trial to assess the effects of antihypertensive drug therapy in patients above the age of 60 years. The double-blind multicentre trial started in 1972.

The present paper reports overall morbidity and mortality results in 840 randomised patients. The trial was brought to an end in the summer of 1984 when the Steering Committee reported that some preset trial end-points had been reached.

Patients and Methods

Study Protocol

The protocol has already been published in detail.[10] In brief, elderly patients with high blood pressure were admitted to the trial if they fulfilled certain criteria during a run-in period on placebo. The inclusion criteria were: (1) age 60 years or more at admission to the study; (2) sitting blood pressure on placebo during the run-in period within the limits 160–239 mm Hg for systolic and 90–119 mm Hg for diastolic blood pressure; (3) patient's willingness to cooperate and to be followed-up regularly (informed consent). The exclusion criteria were: (1) curable causes of high blood pressure; (2) certain complications of hypertension, ie, retinopathy grade III or IV, congestive heart failure, history of cerebral or subarachnoid haemorrhage; (3) concurrent diseases such as hepatitis or cirrhosis, gout, malignancy, and diabetes mellitus requiring insulin treatment.

Patients were randomly allocated to an active treatment or placebo treatment group. At first, all patients received daily one diuretic capsule containing either 25 mg hydrochlorothiazide and 50 mg triamterene or a placebo. The dosage could be increased, after at least two weeks, to two capsules per day. If the blood pressure remained high after one month, methyldopa tablets (500 mg) could be added to the active treatment group and placebo tablets in the placebo group, starting with half a tablet a day and increasing eventually to four tablets daily. Placebo capsules and tablets were identical in shape, taste, and colour to the active treatment medication.

Patients remained in the double-blind part of the trial until the summer of 1984, unless one of the following events occurred: (1) loss to follow-up; (2) interruption of all study treatment for more than three months; (3) one of the specific study terminating events, including death, non-fatal cerebral or subarachnoid haemorrhage, development of hypertensive retinopathy grade III or IV, dissecting aneurysm, congestive heart failure not controllable without diuretics or antihypertensive drugs, hypertensive encephalopathy, severe increase in left ventricular hypertrophy, and a rise in blood pressure exceeding the defined limits.[10]

TABLE I—EXPERIENCE DURING DOUBLE-BLIND PART OF TRIAL

Time	SBP/DBP $\bar{x}\pm$SD (n)		
	Placebo	Active	p
Randomisation	182±16 / 101± 7 (424)	183±17 / 101± 7 (416)	0·65 / 0·98
After 1 yr	172±23 / 95±12 (287)	151±17 / 88± 9 (300)	<0·001
3 yr	172±25 / 94±11 (171)	149±16 / 85± 9 (187)	<0·001
5 yr	171±25 / 95± 9 (93)	150±20 / 85± 9 (108)	<0·001
7 yr	167±22 / 90± 9 (27)	148±18 / 85±10 (39)	<0·001

SBP = sitting systolic blood pressure in mm Hg; DBP = sitting diastolic blood pressure in mm Hg.

Data were sent to the coordinating office every three months on specially designed forms and deaths and other terminating events were classified independently by two investigators into previously agreed categories.[10] These investigators were not aware of the treatment group to which the patients had been assigned. After leaving the double-blind part of the trial the surviving patients were followed up until July 1984, but only date and cause of death were recorded.

Statistical Methods

Both analyses on randomised treatment in the double-blind part of the trial (on-randomised-treatment or per-protocol analysis) and an overall intention-to-treat analysis were performed.[10] The latter was confined to mortality owing to the difficulty in determining morbidity outside the period of double-blind follow-up. Life tables were computed by means of the BMDP IL survival program.[11] For non-terminating events, patients could be included more than once if they had different events, but only once for any single event. When both a non-terminating and a terminating event occurred in the same patient, the life-table analysis considered the first event as the end-point, when both types of events were analysed together. When a life table for one particular event was constructed, terminating from another cause led to censoring of the data at that

TABLE II—DEATHS IN THE INTENTION-TO-TREAT ANALYSIS

Causes of death	Placebo group n=424		Active group n=416		Percentage change† for active treatment		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
All causes	149	76	135	69	−9	−28 to +15	0·41
Non-cardiovascular non-renal	54	28	61	31	+14	−21 to +64	0·48
All cardiovascular	93	47	67	34	−27	−46 to −1	0·037
Cerebrovascular	31	16	21	11	−32	−61 to +19	0·16
Cardiac	47	24	29	15	−38	−61 to −1	0·036
Other cardiovascular	15	8	17	9	NC	NC	NC
Renal	1	NC	4	2	NC	NC	NC
Unknown	1	NC	3	2	NC	NC	NC

*Rates are the number of patients having an event per 1000 patient years of observation and include all deaths up to July 1, 1984, whether or not the patients were still in the double-blind part of the trial. In 24 patients the life/death status was not known on July 1, 1984, but survival was known to an earlier date. 12 of these persons were in the actively treated group and 12 in the placebo group.

†This mean and the 95% confidence limits were calculated for the actively treated group, placebo rate = 100%.

‡Comparison of both treatment groups with Mantel-Cox statistics from life-table analysis.

NC = not calculated, since the rate in the placebo group was less than 10 per 1000 patient years.

TABLE III—TERMINATING FATAL EVENTS ON RANDOMISED TREATMENT

—	Placebo group		Active group		Percentage change† for active treatment		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
All causes	89	70	73	52	−26	−45 to +1	0·077
Non-cardiovascular, non-renal (total)	28	22	30	21	−3	−42 to +62	0·96
Cardiovascular (total)	61	48	42	30	−38	−58 to −8	0·023
Cerebrovascular	19	15	12	9	−43	−72 to +18	0·15
Cardiac (total)	29	23	17	12	−47	−71 to −3	0·048
Myocardial infarction	16	13	7	5	−60	−84 to −4	0·043
Others (including sudden death)	13	10	10	7	−30	−69 to +59	0·44
Pulmonary embolism and/or infarction	7	6	8	6	NC	NC	NC
Others	6	5	5	4	NC	NC	NC
Renal	0	0	1	1	NC	NC	NC

*Rates are number of patients having an event per 1000 patient years under observation.
†Percentage change is calculated from the rates, placebo rate = 100%.
‡Comparison of both treatment groups with Mantel-Cox statistics from life-table analysis.
NC = not calculated, since the rate in the placebo group was less than 10.

TABLE IV—TERMINATING NON-FATAL CARDIOVASCULAR AND RENAL EVENTS ON RANDOMISED TREATMENT

—	Placebo group		Active group		Percentage change† for active group		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
Non-fatal, morbid cardiovascular terminating events							
Total	25	20	11	8	−60	−88 to −19	0·0064
Cerebral haemorrhage	3	2	4	3	NC	NC	NC
Papilloedema, retinal haemorrhages or exudates	5	4	0	0	NC	NC	NC
Severe congestive heart failure (not controlled by digitalis alone)	17	13	7	5	−63	−85 to −10	0·014
Non-fatal, non-morbid cardiovascular terminating events							
Total	30	24	10	7	−70	−85 to −38	0·0006
Severe increase in BP	19	15	2	1	−90	−98 to −59	0·0001
Therapy required with: Beta-blocker	10	8	6	4	NC	NC	NC
Calcium antagonist	0	0	1	1	NC	NC	NC
Diuretics	0	0	1	1	NC	NC	NC
Severe left ventricular hypertrophy or dilatation	1	1	0	0	NC	NC	NC
Renal: severe increase in creatinine	1	1	4	3	NC	NC	NC

*,†,‡For explanation of symbols, see table III.
NC = not calculated.

point in time. Tests of significance were performed on the life-table analysis with the Mantel-Cox estimate.[12]

The percentage difference in deaths or events was calculated for the actively treated group by taking the rate in the placebo group as 100%. These rates were calculated per 1000 patient years under observation. The confidence intervals (CI) for the percentage reduction in events in the active group were calculated as follows (M. Shipley, personal communication):

1. Let p_2 = rate in active group and d_2 number of events
p_1 = rate in placebo group and d_1 number of events in this group
then the 95% CI for $\mathrm{Ln}(\frac{p_2}{p_1})$ is given by

$$\mathrm{Ln}\left(\frac{p_2}{p_1}\right) \pm 1{\cdot}96 \left[\frac{1}{d_1} + \frac{1}{d_2}\right]^{1/2}$$

2. Let the upper value be x_U and the lower value x_L then the 95% CI for the percentage reduction in events $(\frac{p_2 - p_1}{p_1} \times 100)$ is given by

$$\left[(e^{x_L} - 1) \times 100 \; (e^{x_U} - 1) \times 100\right]$$

The difference in events between the placebo and active treatment group (events saved) was calculated by life-table analysis over 7 years' observation as described elsewhere.[10]

Results

Patients' Characteristics at Randomisation and during Double-blind Part of Trial

The 840 patients were randomised to placebo (n = 424) or active treatment (n = 416). The placebo and active treatment groups were similar in sex ratio (respectively, 70·5% and 69·0% women), age (72±8 in both groups), sitting blood pressure at randomisation (table I), weight (67±13 and 66±12 kg), height (159±10 cm in both groups), and percentage with cardiovascular complications (36% and 35%) on admission to the trial.

During the double-blind part of the trial the blood pressure was lower ($p < 0{\cdot}001$) in the actively treated patients than in those on placebo (table I). In the active treatment group at the end of the double-blind part of the trial, 4% were not taking a diuretic, 51% took a diuretic but less than two capsules a day, and 45% took two or more capsules a day; in the placebo treatment group these values were respectively 2%, 28%, and 70% for the placebo diuretic capsules. In the active treatment group 65% were not taking methyldopa tablets, 26% were taking between half and two tablets a day, and 9% were on more than two tablets a day; in the placebo treatment group, the corresponding percentages were 37, 27, and 36.

Intention-to-treat Analysis (table II)

The most stringent analysis to apply to clinical trial data is an analysis on the basis of the treatment group to which the patient was randomised (intention-to-treat), irrespective of subsequent drop-out or changes in treatment.

The duration of follow-up for the intention-to-treat analysis averaged 4·63 yr in the placebo and 4·69 yr in the active treatment group. The patient years of observation were 1963 in the placebo group and 1950 in the active treatment group.

The intention-to-treat analysis was restricted to the cause and date of death because data on non-fatal events in patients who dropped out from randomised treatment were not available. The small reduction in mortality rate from all causes was not significant (−9%, p=0·41), but the reductions in cardiac mortality (−38%, p=0·036) and all cardiovascular mortality (−27%, p=0·037) were both significant.

Study-terminating Events in the Double-blind Part of the Trial

Further analyses were made on both fatal and non-fatal events that occurred while individual patients were still on randomised treatment. More patients in the placebo group reached a trial end-point, and the duration of follow-up in the double-blind part of the study was consequently shorter in this group (2·99 yr) than in the actively treated group (3·36 yr). The longest follow-up for a single patient was 11 yr.

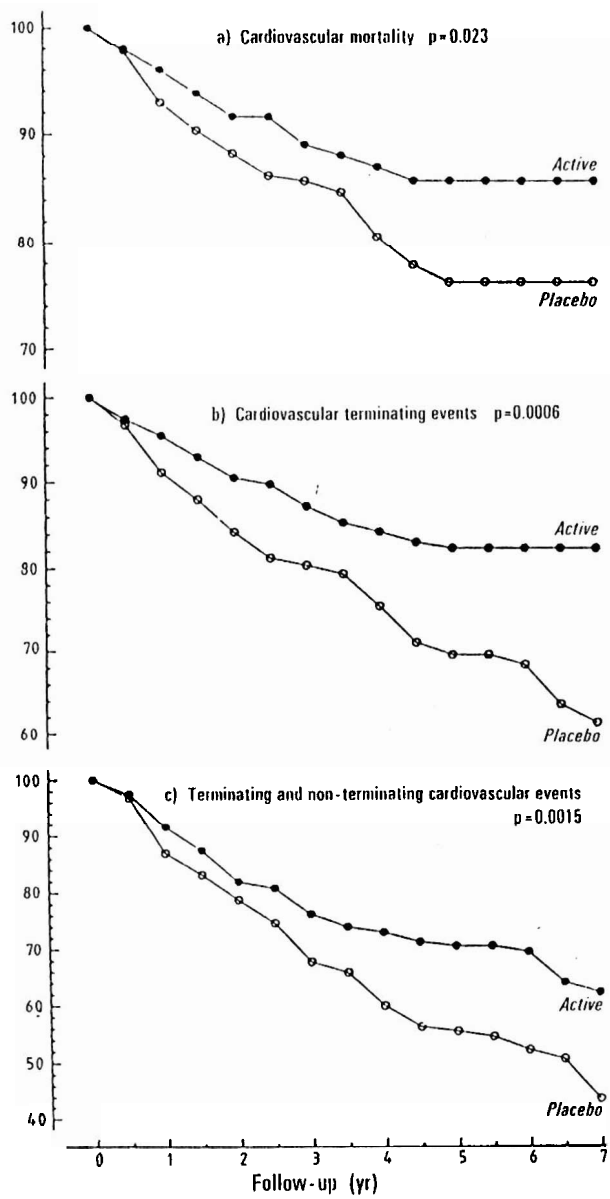
Mortality (table III).—The total death rate was 70/1000 patient years in the placebo group and 52/1000 patient years in the actively treated group while on their randomised treatment. This reduction was not statistically significant (−26%, p=0·077). Total cardiovascular mortality rate was significantly reduced (−38%, p=0·023; see figure). The effect on overall cardiovascular mortality was due mainly to the fall in the cardiac mortality rate (−47%, p=0·048). The fall in cerebrovascular mortality was not significant (−43%, p=0·15). The actively treated group had 14 fewer cardiovascular deaths per 1000 patient years. There was no difference in non-cardiovascular, non-renal mortality rate (−3%, p=0·96).

Non-fatal study-terminating events (table IV).—Non-fatal morbid cardiovascular terminating events (group A, table IV) occurred at a rate of 20/1000 patient years in the placebo group and 8/1000 patient years in the actively treated group. This reduction (−60%, p=0·0064) was mainly accounted for by a 63% reduction in severe congestive heart failure (not controlled by digitalis alone). Progression to malignant or accelerated hypertension did not occur in the actively treated group but occurred in 5 patients of the placebo group. There were 21 fewer study-terminating non-fatal morbid cardiovascular events per 1000 patient years in the actively treated patients. Terminating events, fatal and non-fatal morbid (group A) events combined, were reduced in the active treatment group, both cardiac (−54%, p=0·0016) and cerebrovascular (−46%, p=0·058).

Non-fatal non-morbid cardiovascular terminating events (group B, table IV) included a severe rise in blood pressure to a level that was defined as unacceptable and the need for therapy with beta-adrenoceptor blocking drugs or calcium-entry blocking drugs given for reasons other than the treatment of hypertension (usually for angina). The non-morbid cardiovascular terminating event rate was reduced (−70%, p=0·0006), but these events were not employed in calculating the total cardiovascular event rate since they constituted either less hard data or were not true morbid events (eg, rise in blood pressure). 4 patients were withdrawn from active treatment and 1 from placebo because of a severe increase in serum creatinine.

Other Reasons for Stopping Randomised Treatment (table V)

During randomised treatment 128 patients defaulted from follow-up and 52 refused to continue their randomised treatment for various reasons but continued to attend. 38 patients were withdrawn from randomised treatment because of serious intercurrent illnesses (mainly neoplasms). Withdrawal was less frequent in the actively treated group (p=0·022). One centre with 21 patients withdrew from the trial before its end. In another centre the double-blind phase was terminated in 29 patients, each followed for 5 yr, because this was the duration to which the patients had agreed. 11 patients were withdrawn from randomised treatment by the



Cumulative percentage of survivors without events calculated for the patients on randomised treatment by life-table method.[11]

Cardiovascular trial-terminating events include deaths and morbid events (group A of table IV). Cardiovascular non-terminating events are defined in table VI.

local investigators owing to a moderate increase in blood pressure that did not, however, reach the previously established study-terminating criteria. Similarly, 17 patients were withdrawn by the local investigators on discovery that the patients were no longer hypertensive during a brief period without treatment. In 6 patients the treatment code was broken—eg, at the request of an anaesthetist. 2 patients had treatment stopped in error and 2 others were withdrawn because the double-blind drug supply was not available. There were 291 patients still in the double-blind part of the trial when it was stopped in the summer of 1984.

Non-terminating Events

Cardiovascular events that did not necessitate withdrawal from the trial were reduced by 25% (p=0·12) in the actively treated group (table VI). This was due mainly to a reduction of cerebrovascular events (−52%, p=0·026), while the non-terminating cardiac event rate (+3%, p=0·98) was unchanged.

The total cardiovascular event rate was computed, consisting of cardiovascular deaths (table III) plus the non-fatal morbid cardiovascular terminating events (group A, but not group B of table IV) and the non-terminating cardiovascular events (table VI).

Life-table analysis, illustrated in the figure, shows a reduction in both cardiovascular terminating events (−45%, p=0·0006) and cardiovascular terminating plus non-terminating events (−36%, p=0·0015).

In the patients on active, randomised treatment, there were 29 fewer total cardiovascular events per 1000 patient years than in the placebo group.

Discussion

There are many patients over the age of 60 years with high blood pressure but, until now, little scientific evidence has been produced to justify antihypertensive drug treatment. The present trial was initiated 12 yr ago and the range of blood pressure accepted was wide—namely, 160–239/90–119 mm Hg. However, relatively few patients with pressures in the upper part of this range[10] were selected and the mean±SD of blood pressure at randomisation was 183±17/101±7. Thus, the blood pressure levels are typical of those who might be considered for treatment today.

The trial was of long duration and only 35% of the 840 randomised patients were still in the double-blind part when it was terminated; 19% of the patients had died, 4% had had a trial-terminating morbid cardiovascular event, 5% had had a terminating non-morbid event, and 36% had left the double-blind part prematurely for other reasons. Those who left the double-blind part discontinued their randomised treatment. A proportion of those on active treatment will have stopped antihypertensive treatment and a proportion in the placebo group will have been started on active treatment. For this reason the intention-to-treat analysis would be expected to give a lower level of statistical significance than an analysis confined to those patients who continued their randomised

TABLE V—OTHER REASONS FOR STOPPING RANDOMISED TREATMENT

—	Placebo group		Active group		Percentage change† for active treatment		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
Premature stopping							
Total	157	124	149	107	−14	−31 to +8	0·18
Lost to follow-up	69	54	59	42	−23	−45 to +10	0·18
Stopping of trial medication (>3 mo)	22	17	30	21	+23	−29 to +114	0·39
Non-fatal intercurrent disease	25	20	13	9	−53	−76 to −8	0·022
Centre stopped trial	11	9	10	7	NC	NC	NC
Patients stopped after 5 yr in study	11	9	18	13	NC	NC	NC
Moderate increase in blood pressure	11	9	0	0	NC	NC	NC
Low blood pressure off randomised treatment	2	2	15	11	NC	NC	NC
Breaking treatment code required	3	2	3	2	NC	NC	NC
Failure of drug supply	2	2	0	0	NC	NC	NC
Stopping for unknown reason	1	1	1	1	NC	NC	NC
Termination of the trial in summer, 1984	122		169				

*,†,‡For explanation of symbols, see table III. NC = not calculated.

TABLE VI—NON-TERMINATING CARDIOVASCULAR EVENTS ON RANDOMISED TREATMENT

—	Placebo group		Active group		Percentage change† for active group		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
Total	60	52	51	39	−25	−48 to +9	0·12
Cerebrovascular (total)	24	20	13	9	−52	−76 to −7	0·026
Cerebral thrombosis	12	10	5	4	−62	−87 to +7	0·053
Cerebral embolism	2	2	2	2	NC	NC	NC
Transient ischaemic attack	15	12	8	6	−53	−80 to +11	0·081
Cardiac (total)	37	31	42	32	+3	−34 to +61	0·98
Myocardial infarction	12	9	19	14	NC	NC	NC
Moderate congestive heart failure	6	5	12	9	NC	NC	NC
Arrhythmias	8	7	16	12	NC	NC	NC
Heart block	15	12	14	10	−16	−60 to +73	0·57
Other vascular	5	4	5	4	NC	NC	NC

*Number of patients who had an event is indicated. A patient who had different types of events was entered more than once, but a patient who had the same event several times was entered only once.
†,‡For explanations see table III and text. NC = not calculated.

treatment. For ethical reasons, the stopping rules for the trial were based on the more sensitive on-randomised-treatment analysis. In the event, cardiovascular deaths were reduced by 38% in the on-randomised-treatment analysis and by 27% in the intention-to-treat analysis. Morbidity was not reported outside the double-blind part of the study since such data may have been subject to considerable bias.

During the double-blind part of the trial a reduction in cardiovascular terminating plus non-terminating events (−36%) was observed. This result is similar to those in patients aged over 60 both in the Veterans Administration Co-operative Study Group Trial[9] and the Australian Therapeutic Trial in Mild Hypertension[6] (−59% and −39%, respectively).

The cardiac mortality rate (including sudden death) was significantly reduced by treatment but non-fatal myocardial infarction tended to be more frequent in the treated group. Thus, one of the main effects of treatment seemed to be to reduce the case-fatality rate in patients with myocardial infarction, as suggested in the Framingham Study.[13] In the Australian Therapeutic Trial in Mild Hypertension there was only a slight and non-significant reduction in ischaemic heart disease trial end-points.[6,14]

Active treatment reduced the incidence of severe congestive heart failure but not of mild congestive heart failure. This finding suggests that treatment did not alter the myocardial disease leading to cardiac failure but reduced its severity by lowering left ventricular work.

Previous trials of antihypertensive therapy[7-9,14,15] have demonstrated a reduction in the incidence of stroke. In the present trial cerebrovascular mortality was reduced, although the difference was not statistically significant. Non-terminating cerebrovascular events were significantly reduced. As far as can be ascertained, the management of the two groups throughout the double-blind part of the trial was comparable in all respects except the antihypertensive medication. This was achieved by the use of the double-blind technique.

Some methodological aspects of the trial must be further discussed—the effects of "repeated-looks" on the level of statistical significance; the desirability of subgroup analyses; and the success of randomisation. In such a long-term trial the steering committee must have repeated looks at the data for ethical reasons. Because of these repeated looks the level of statistical significance required to stop the trial should be increased. The stopping rules for the trial allowed for up to ten repeated examinations of the data (seven were actually done), and required a 1% level of significance on any one occasion. Such a level of significance is equivalent to an overall level of about 5%.[16] The intention-to-treat analysis was not performed on each of these occasions. Subgroup analyses are not reported here but will be made available in due course. However, the percentage change in cardiovascular terminating events in the active group was −37% (95% confidence limits from −62 to +5) for the patients with diastolic pressure at randomisation between 90 and 99 mm Hg (mild hypertension) and −50% (95% confidence limits from −68 to −21) for those with diastolic pressure between 100 and 119 mm Hg (moderate hypertension). Although a greater benefit from treatment might be anticipated in the moderate than in the mild hypertension group, the 95% confidence limits revealed a major overlap between these two subgroups. At randomisation the patients in the two groups were similar in age, sex ratio, blood pressure, body weight, and height and in the frequency of cardiovascular complications.

Most of the patients in this trial were recruited from clinics rather than by population screening. Caution must be exercised when extrapolating the results to the generality of elderly people with raised blood pressures. However, the patients were drawn from a wide variety of sources—community, general medical, and geriatric services in different European countries[10]—so the findings should have wider application than data generated from a single country. The main benefits identified were a reduction in fatal myocardial infarction, severe congestive heart failure, and stroke. Non-cardiovascular mortality was not affected by active treatment. Minor adverse effects included a decrease in glucose tolerance[17] and an increase in serum uric acid[18] and creatinine[19] in patients treated with diuretics. Overall, the balance sheet favoured active treatment in the patients who were included in the trial.

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