

## Medical Research Council trial of treatment of hypertension in older adults: principal results

MRC Working Party

### Abstract

**Objective**—To establish whether treatment with diuretic or  $\beta$  blocker in hypertensive older adults reduces risk of stroke, coronary heart disease, and death.

**Design**—Randomised, placebo controlled, single blind trial.

**Setting**—226 general practices in the MRC general practice research framework.

**Subjects**—4396 patients aged 65-74 randomised to receive diuretic,  $\beta$  blocker, or placebo. Patients had mean systolic pressures of 160-209 mm Hg and mean diastolic pressures <115 mm Hg during an eight week run in and were not taking antihypertensive treatment.

**Intervention**—Patients were randomised to atenolol 50 mg daily; hydrochlorothiazide 25 mg or 50 mg plus amiloride 2.5 mg or 5 mg daily; or placebo. The regimens were adjusted to achieve specified target pressures. Mean follow up was 5.8 years.

**Main outcome measures**—Strokes, coronary events, and deaths from all causes.

**Results**—Both treatments reduced blood pressure below the level in the placebo group. Compared with the placebo group, actively treated subjects (diuretic and  $\beta$  blocker groups combined) had a 25% (95% confidence interval 3% to 42%) reduction in stroke ( $p=0.04$ ), 19% (-2% to 36%) reduction in coronary events ( $p=0.08$ ), and 17% (2% to 29%) reduction in all cardiovascular events ( $p=0.03$ ). After adjusting for baseline characteristics the diuretic group had significantly reduced risks of stroke (31% (3% to 51%)  $p=0.04$ ), coronary events (44% (21% to 60%),  $p=0.0009$ ), and all cardiovascular events (35% (17% to 49%),  $p=0.0005$ ) compared with the placebo group. The  $\beta$  blocker group showed no significant reductions in these end points. The reduction in strokes was mainly in non-smokers taking the diuretic.

**Conclusion**—Hydrochlorothiazide and amiloride reduce the risk of stroke, coronary events, and all cardiovascular events in older hypertensive adults.

### Introduction

Hypertension in older adults confers increased risk of cardiovascular diseases especially stroke.<sup>1,4</sup> When the Medical Research Council trial was set up in 1981, published reports of controlled trials of antihypertensive treatment in the primary or secondary prevention of cardiovascular diseases had included only small numbers of subjects and events from adults aged 60 or over at entry<sup>5-9</sup> or were age specific subgroup analyses of larger trials.<sup>10-14</sup> The consequences of hypertension and treatment in older adults might differ from those in younger people. We therefore decided to compare two current major forms of treatment with a placebo. The

Medical Research Council mild hypertension trial in subjects aged 35-64<sup>15</sup> had established a national network of collaborating general practices, and this formed the basis for the present trial of the effects of antihypertensive treatment in men and women aged 65-74. The trial was supervised by an MRC working party and coordinated by the MRC Epidemiology and Medical Care Unit at Northwick Park Hospital, Harrow.

The trial aimed at establishing whether antihypertensive treatment in men and women aged 65-74 years reduces mortality and morbidity due to stroke and coronary heart disease and mortality from all causes. Secondary aims were to compare the effects of the two active drugs and to see whether responses to treatment differed between men and women. The results of a substudy on the effects of lowering blood pressure on cognitive performance had been reassuring.<sup>16</sup>

### Patients and methods

It was estimated<sup>3</sup> that the trial would require 5000 men and women aged 65-74 years followed up for five years to provide a power of 90% to detect a 30% reduction in the rate of stroke (fatal and non-fatal) between the active and placebo groups at a significance level of 2%.

#### RECRUITMENT AND SCREENING FOR RUN IN PERIOD

Recruitment took place between March 1982 and March 1987 through the Medical Research Council's general practice research framework.<sup>17</sup> The population was identified from the age-sex registers of 226 group practices throughout England, Scotland, and Wales: 184 653 invitations for screening were sent and 125 861 people (68%) attended. Systolic blood pressure was the main criterion because it is more strongly related to the risk of stroke than diastolic pressure in people aged over 60.<sup>1,3</sup> Throughout the trial blood pressure was measured with a Hawksley random zero sphygmomanometer (diastolic phase V). Three sitting blood pressure measurements were recorded by the research nurse. The mean of the second and third readings was then calculated and the person was either reassured (systolic pressure <160 mm Hg), referred to his or her general practitioner (systolic pressure >209 mm Hg or diastolic pressure >115 mm Hg, or both), or entered into the run in stage (systolic pressure 160-209 mm Hg; diastolic pressure <115 mm Hg).

#### RUN IN PERIOD AND CRITERIA FOR ENTRY INTO MAIN TRIAL

In all, 20 389 subjects (16% of those attending screening) were suitable for the first, second, and third run in visits made about one, four, and eight weeks after screening. At each visit, the sitting blood pressure was measured three times by the nurse and the mean of the second and third readings was calculated. If

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the overall mean of the three mean run in systolic blood pressures was 160-209 mm Hg, and the mean diastolic blood pressure was 114 mm Hg or less, the subjects (8832) attended to have their blood pressures confirmed by a doctor. If the mean of the doctor's two readings was 159 mm Hg or less the subject was reassured. Those who had a mean pressure of 160-209 mm Hg were given a further appointment for an entry examination for the main trial by the doctor. Those who had a mean of 210 mm Hg or more were asked to attend on a further occasion and two more readings were taken by the doctor. If the mean of all four of the doctor's readings was 160-209 mm Hg the subject was given an appointment for an entry examination for the main trial. Subjects with a mean systolic pressure of 210 mm Hg or more on the doctor's readings were ineligible for the trial and further management was left to their general practitioners. According to these rules, 4961 subjects were suitable for the entry examination.

Subjects had 12 lead electrocardiography and completed a questionnaire concerning cardiovascular and other symptoms, smoking, and treatment for hypertension, gout, asthma, or diabetes. Urine was tested for glucose and protein and blood was taken for measuring total serum cholesterol, urea, creatinine, electrolyte, and glucose concentrations.

Subjects were excluded from the trial if they had known or suspected secondary hypertension; were taking antihypertensive drugs; had cardiac failure or any other accepted indication for antihypertensive treatment; were receiving treatment for angina pectoris; had a history of myocardial infarction or stroke within the preceding three months; had impaired renal function; were diabetic; had asthma; had any serious intercurrent disease, including malignancy known to be present at the time of examination; or had a serum potassium concentration of 3.4 mmol/l or less or >5.0 mmol/l. A total of 4396 subjects gave informed consent and were entered into the main trial (3.5% of those screened).

#### RANDOMISATION AND TREATMENT REGIMENS

All trial entrants were randomly allocated in equal proportions to one of four treatment categories: (a) a potassium sparing diuretic regimen (amiloride, hydrochlorothiazide); (b) matching placebo tablets; (c) the  $\beta$  blocker atenolol; and (d) matching placebo tablets. Randomisation was in stratified blocks of eight within each sex and clinic. The trial was single blind: patients did not know which treatment group they were in, but the doctors and nurses did. An early substudy assessed blood pressure control and the biochemical effects of two different dose regimens of diuretic—that is, 5 mg amiloride and 50 mg hydrochlorothiazide or 2.5 mg amiloride and 25 mg hydrochlorothiazide, each in a single tablet once daily.<sup>18</sup> As a result all patients were transferred to the lower dose in 1985. Those randomly allocated to the  $\beta$  blocker received 50 mg atenolol once daily. Each patient was assigned a target systolic blood pressure (150 or 160 mm Hg), which depended on the mean systolic pressure after the run in period (mean <180 mm Hg, target  $\leq$ 150 mm Hg; mean  $\geq$ 180 mm Hg, target  $\leq$ 160 mm Hg). Drug regimens for those on active treatment were modified if blood pressure had not responded after 12 weeks or if target pressure had not been achieved after six months. The most common change necessary was an increase in atenolol to 100 mg daily (225 patients). When further control was necessary the other trial drug was used to supplement the drug allocated by randomisation. After this, the calcium channel blocker nifedipine was used in doses of up to 20 mg daily. Any other supplementary drugs were also allowed at this stage (further details on request).

#### FOLLOW UP

Patients who entered the trial were followed up fortnightly for one month, then monthly up to three months, and three monthly thereafter. At each visit, the nurse measured blood pressure twice. If the mean blood pressure at any visit during the main trial reached or exceeded 115 mm Hg diastolic or 210 mm Hg systolic, the patient was recalled two weeks later. If either of these pressures were sustained on active trial treatment the general practitioner managed further treatment outside the trial protocol. For patients receiving placebo, active treatment was started and this was required in 11% of patients. Patients whose blood pressure equalled or exceeded the upper limits on any three non-consecutive occasions were similarly managed.

#### TRIAL TERMINATING EVENTS

A patient's participation in the trial ended with stroke, whether non-fatal or fatal; coronary events, defined as sudden death thought to be due to a coronary cause, death known to be due to a myocardial infarction, and non-fatal myocardial infarction; other cardiovascular events, including deaths due to hypertension and to rupture or dissection of an aortic aneurysm; and death from any other cause. The records of all patients were "flagged" at Southport NHS central register to ensure notification of death. The diagnostic evidence for each terminating event was assessed by an arbitrator, blind to the treatment regimen. World Health Organisation criteria for classification of strokes and coronary events were used.<sup>19, 20</sup> All available documentation was reviewed, including copies of general practitioners' notes, hospital in-patient or outpatient notes, electrocardiographic recordings, necropsy findings, and death certificates.

If a patient had a non-fatal event followed by a fatal event in the same category, only the fatal event was included in the analyses (19 strokes and 22 coronary events). If a person had two events in different categories (13 patients)—for example, a non-fatal stroke then a coronary event (fatal or non-fatal)—both were included. Data on terminating events were analysed after every 5000 patient years and were reviewed by an independent monitoring and ethics committee.

#### STATISTICAL MANAGEMENT

The primary results are based on a comparison of groups according to their randomised treatment—that is, on an intention to treat basis. In all analyses the two placebo groups have been combined. The effect of treatment modification in subgroups was formally tested by examining interactions between treatment groups and subgroups rather than by considering differences within each subgroup separately. A significant interaction would indicate that relative risks potentially differed between the subgroups. The *p* values associated with subgroup analyses should be interpreted conservatively as numerous comparisons have been made and selection by interest might have occurred.

The relation of several baseline characteristics and treatment with primary event outcomes were further investigated by logistic regression.

#### Results

Table I shows the characteristics of patients at entry and confirms that the three treatment groups were comparable. The original aim was to accrue 25 000 patient years of observation by recruiting 5000 patients and following them for five years. In the event 4396 patients were recruited, and so the average follow up time was extended to 5.8 years, thus achieving 25 355 patient years of observation.

TABLE 1—Characteristics of treatment groups at entry to trial

	Men			Women		
	Diuretic (n=454)	β Blocker (n=456)	Placebo (n=926)	Diuretic (n=627)	β Blocker (n=646)	Placebo (n=1287)
Mean years of observation	5.6	5.6	5.6	6.0	5.9	5.9
Mean age (years)	70.2	70.3	70.2	70.4	70.4	70.4
Mean body mass index (kg/m <sup>2</sup> )	26.1	26.4	26.4	26.8	26.8	26.6
Mean systolic blood pressure (mm Hg)	183	183	183	186	186	186
Mean diastolic blood pressure (mm Hg)	92	91	91	90	91	90
Mean serum cholesterol (mmol/l)	5.9	6.0	5.9	6.9	6.9	6.8
Mean serum potassium (mmol/l)	4.2	4.2	4.2	4.2	4.2	4.2
Mean serum urate (μmol/l)	376	374	374	318	311	313
Mean serum sodium (mmol/l)	141	141	141	142	142	142
Mean serum urea (mmol/l)	6.1	6.2	6.0	5.9	5.7	5.8
% Cigarette smokers	22	21	24	14	15	13
% With ischaemic electrocardiographic changes*	18	17	18	17	14	15

\*1<sub>1-3</sub> 4<sub>1-3</sub> 5<sub>1-2</sub> on Minnesota code (one or more code present).

COURSE OF BLOOD PRESSURE

For patients entering the trial, doctors' confirmatory systolic and diastolic blood pressure measurements were higher than the mean run in values (fig 1). The doctors' measurements were on average 10 mm Hg higher for systolic pressure and 3 mm Hg higher for diastolic pressure.

The systolic and diastolic pressures fell immediately in all groups, with the greatest systolic fall being seen in the diuretic group in the first three months. After two years, however, the treatment groups had similar systolic and diastolic pressures (fig 1). More patients randomised to receive β blocker required supplementary drugs than those randomised to diuretic (52% β blocker v 38% diuretic at five years). This partly explains the narrowing in the differences in blood pressure between diuretic and β blocker groups.

WITHDRAWALS FROM RANDOMISED TREATMENT

Compared with the placebo group, the diuretic group had significantly more withdrawals for impaired glucose tolerance (6.9 (diuretic group) v 2.7 (placebo group) per 1000 patient years), gout (4.4 v 0.1), skin disorders (3.9 v 1.1), muscle cramp (5.2 v 0.1), nausea (7.4 v 1.1), and dizziness (7.4 v 1.2). Those receiving β blocker were withdrawn significantly more often than those on placebo for impaired glucose tolerance (5.8 (β blocker) v 2.7 (placebo) per 1000 patient years), Raynaud's phenomenon (11.3 v 0.3), dyspnoea (22.9 v 1.1), lethargy (19.1 v 2.0), nausea (4.1 v 1.1), dizziness (10.6 v 1.2), headache (7.2 v 1.1), and low pulse rate (28.0 v 0.0). Those receiving β blocker were withdrawn significantly more often than those receiving diuretic because of Raynaud's phenomenon (11.3 (β blocker) v 0.6 (diuretic) per 1000 patient years), dyspnoea (22.9 v 0.8), lethargy (19.1 v 4.1), headache (7.2 v 2.5), and low pulse rate (28.0 v 0.0) and significantly less often because of gout (0.0 v 4.4) and muscle cramp (1.0 v 5.2). Overall, the β blocker group had significantly more withdrawals than the diuretic group, for both suspected major side effects and inadequate blood pressure control: over five years the diuretic group had 160 withdrawals for major side effects and one for inadequate control; the β blocker group, 333 for side effects and 12 for inadequate control; and placebo group, 82 for side effects and 175 for inadequate control.

Over the five and a half years about 25% of people were lost to follow up. The cumulative percentages of people who stopped taking their randomised treatment, including both those withdrawn but continuing on follow up and those lost to follow up, were 48% of the diuretic group, 63% of the β blocker group, and 53% of the placebo group. There were about 6300 patient years in each of the four randomly allocated treatment groups. In the diuretic group, treatment accounted for 69% of the patient years, including supplementation by the β blocker for 11% of the time. Corresponding

percentages for those allocated to the β blocker were 55% and supplementation with diuretic for 16%. In the placebo groups 69% of the patient years were spent on placebo treatment, with 6% of the time on either of the active treatments.

PRIMARY RESULTS

Stroke—The number of strokes (fatal and non-fatal) was significantly reduced in people randomised to receive active treatment (101 v 134 receiving placebo, p=0.04) with a reduction in rates of 25% (95% confidence interval 3% to 42%) (table II, fig 2). There

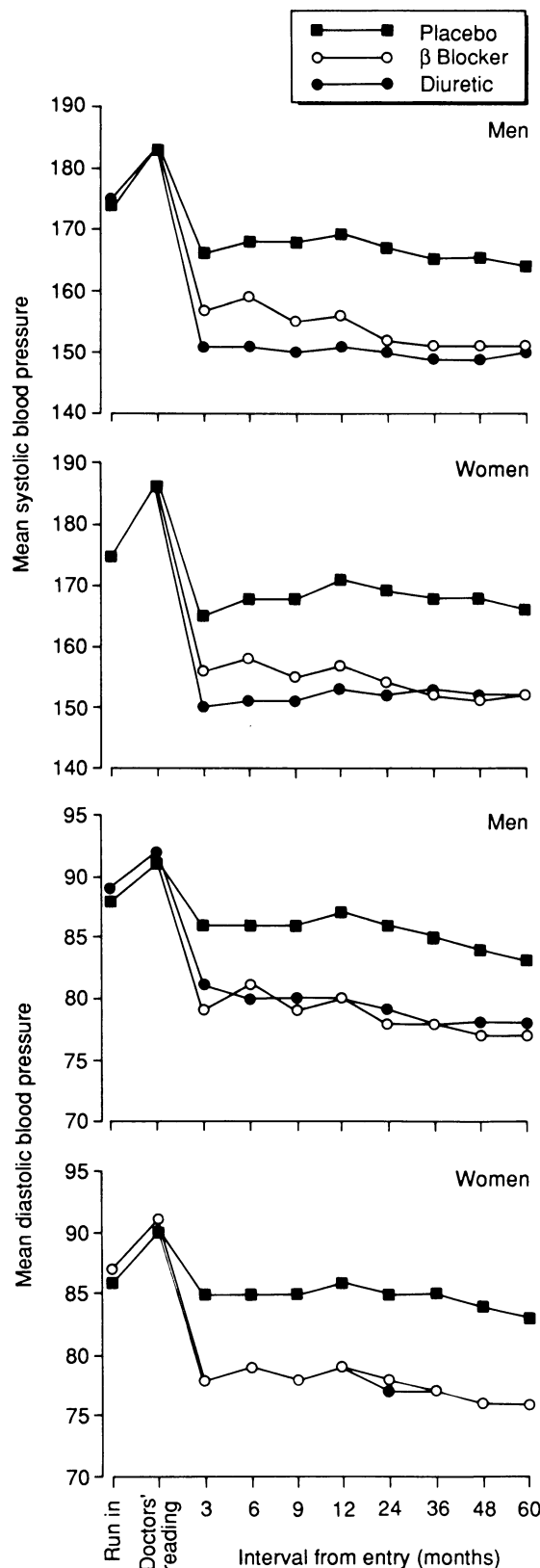


FIG 1—Mean level of blood pressure by sex and randomised treatment

TABLE II—Main events and rates of events (per 1000 patient years) by randomised treatment group

	Diuretic (6290 patient years)*		β Blocker (6330 patient years)*		Total active treatment (12 620 patient years)*		Placebo (12 735 patient years)*		% Difference (95% Confidence interval)†	Absolute difference per 1000 patient years (95% Confidence interval)†
	No of events	Rate	No of events	Rate	No of events	Rate	No of events	Rate		
Strokes:										
Fatal	16	2.5	21	3.3	37	2.9	42	3.3	12 (-37 to 44)	0.4 (-1.0 to 1.8)
Non-fatal	29	4.7	35	5.6	64	5.2	92	7.4		
Total	45	7.3	56	9.0	101	8.1	134	10.8	25 (3 to 42)	2.7 (0.3 to 5.1)
Coronary events:										
Fatal	33	5.2	52	8.2	85	6.7	110	8.6	22 (-4 to 41)	1.9 (-0.2 to 4.0)
Non-fatal	15	2.4	28	4.5	43	3.4	49	3.9		
Total	48	7.7	80	12.8	128	10.3	159	12.7	19 (-2 to 36)	2.4 (-0.2 to 5.0)
All cardiovascular events	107	17.4	151	24.6	258	21.0	309	25.2	17 (2 to 29)	4.2 (0.5 to 7.9)
All cardiovascular deaths	66	10.5	95	15.0	161	12.8	180	14.1	9 (-12 to 27)	1.3 (-1.5 to 4.1)
Non-cardiovascular deaths	68	10.8	72	11.4	140	11.1	135	10.6	-5 (-33 to 17)	-0.5 (-3.1 to 2.1)
Cancer deaths	49	7.8	59	9.3	108	8.6	99	7.8	-10 (-45 to 16)	-0.8 (-3.0 to 1.4)
All deaths	134	21.3	167	26.4	301	23.9	315	24.7	3 (-14 to 18)	0.8 (-3.0 to 4.6)

\*Patient years for stroke, coronary events, and cardiovascular events are slightly less. †Differences between total active group and placebo group.

TABLE III—Principal events and rates of events (per 1000 patient years) by sex

	Men				Women			
	Active treatment (5075 patient years)*		Placebo (5192 patient years)*		Active treatment (7545 patient years)*		Placebo (7543 patient years)*	
	No of events	Rate	No of events	Rate	No of events	Rate	No of events	Rate
Strokes	55	11.1	71	14.1	46	6.2	63	8.5
Coronary events	69	13.8	100	19.7	59	7.9	59	7.9
All cardiovascular events	142	29.1	182	36.9	116	15.7	127	17.3
All cardiovascular deaths	89	17.5	115	22.1	72	9.5	65	8.6
Non-cardiovascular deaths	94	18.5	65	12.5	46	6.1	70	9.3
Cancer deaths	74	14.6	47	9.1	34	4.5	52	6.9
All deaths	183	36.1	180	34.7	118	15.6	135	17.9

\*Patient years for stroke, coronary events, and cardiovascular events are slightly less.

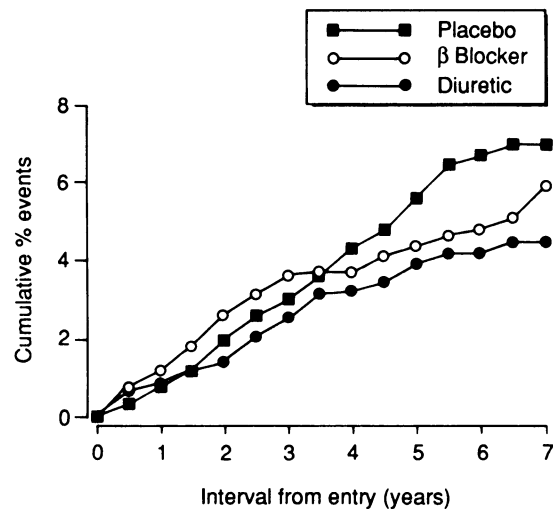


FIG 2—Cumulative percentage of patients experiencing stroke by randomised treatment

was no evidence that this effect differed in the two sexes (table III).

Coronary events were less common in those allocated to active treatment (128 events) than in those receiving placebo (159;  $p=0.08$ ) with a reduction in rates of 19% (-2% to 36%) (table II, fig 3). Coronary events were reduced in men only, but this sex difference was not significant (interaction test  $p=0.12$ ) (table III).

All cardiovascular events—The number of events was significantly reduced on active treatment (258 v 309 placebo,  $p=0.03$ ) with a 17% (2% to 29%) reduction in rates (table II). Of these events, 235 (41%) were strokes and 287 (51%) were coronary episodes. Once again, sex did not seem to influence this treatment effect (table III).

All cause mortality was similar in the treated and placebo groups (23.9 (treated) v 24.7 (placebo) per 1000 patient years) (table II). There was no sex difference in this respect (table III). Deaths from cardiovascular causes were slightly fewer in the active

treatment group than the placebo group (161 v 180 placebo), but both groups had similar numbers of deaths from non-cardiovascular causes (140 v 135) and from cancer (108 v 99). There was a difference between the sexes in deaths from cancer; 74 men receiving active treatment and 47 receiving placebo died of cancer compared with 34 women receiving active treatment and 52 receiving placebo (interaction test  $p=0.002$ ). Twenty one of these patients had a history of cancer at entry to the trial (four receiving diuretic; six β blocker; and 11 placebo), their hypertension at the time being an additional and legitimate clinical concern. Omitting these cases did not substantially alter the interaction between treatment and sex ( $p=0.003$ ).

#### SUBGROUP RESULTS

Table II shows the main events for the two treatment groups separately. The rates of stroke were not

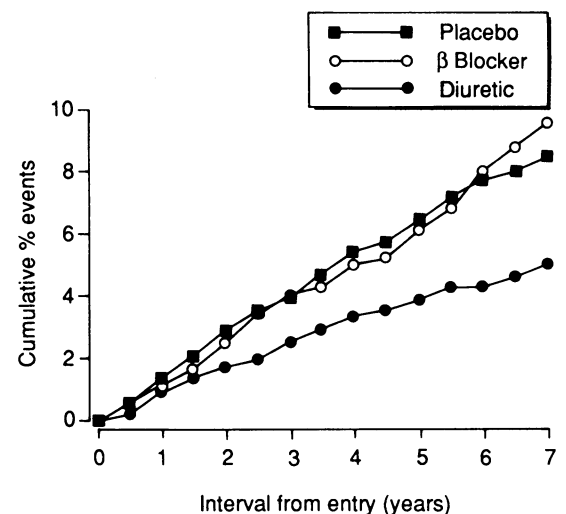


FIG 3—Cumulative percentage of patients experiencing coronary events by randomised treatment

significantly different in the two active treatment groups ( $p=0.33$ ) but the rate of coronary events in the diuretic group was significantly lower than that in the  $\beta$  blocker group ( $p=0.006$ ). For all cardiovascular events the rate was also significantly lower in the diuretic than in the  $\beta$  blocker group ( $p=0.007$ ).

The difference between the total number of deaths in the diuretic and  $\beta$  blocker groups was marginally significant ( $p=0.07$ ), with a 19% (95% confidence interval -2% to 36%) reduction in mortality in the diuretic group (table II). This difference was due to deaths from cardiovascular causes (66 in diuretic group *v* 95 in  $\beta$  blocker group;  $p=0.03$ ).

The main category of non-cardiovascular death was cancer. The apparent excess of men dying of cancer was more pronounced in the  $\beta$  blocker group than the diuretic group ( $p=0.19$ ; table IV). When comparing the  $\beta$  blocker with the placebo group there was a significant interaction between sex and treatment ( $p=0.002$ ; table IV), the death rate in the treatment group being 17 per 1000 patient years in men and 4.2 in women. As previously, exclusion of patients with cancers at entry to the trial did not alter the interaction ( $p=0.002$ ). Classification of the deaths by site of cancer and randomised treatment group showed no organ or system clustering, except that 14 men randomised to  $\beta$  blocker had cancers of the lung or bronchus compared with eight in the diuretic group and 11 in the placebo group, giving rates per 1000 patient years of 5.5, 3.1, and 2.1 respectively.

The rates of events for every end point were raised in smokers compared with non-smokers (table V), and there is some evidence that smokers and non-smokers differed in their response to active treatment with

respect to stroke events (interaction test  $p=0.04$ ) and to all cardiovascular events ( $p=0.03$ ). In both cases the reduction in events in patients receiving active treatment seemed to be confined to non-smokers, and this held for both men and women. For coronary events and deaths from all causes, however, response to active treatment did not differ between smokers and non-smokers. The effect of the  $\beta$  blocker on deaths from all causes was significantly modified by smoking when compared with the effect of the diuretic ( $p=0.04$ ). There was no suggestion of an interaction for cause specific end points.

There was no evidence that systolic blood pressure at entry (160-179 mm Hg or 180-209 mm Hg), diastolic pressure at entry (<90 mm Hg or  $\geq 90$  mm Hg), or age (65-69 or 70-74) influenced response to treatment. This applied to both the average of the three runs in blood pressures and the doctors' confirmatory pressures.

#### ON TREATMENT ANALYSES

All results so far have been on the intention to treat principle. This approach is unbiased, but it has the disadvantage that possible drug effects might be diluted by the substantial proportion of patient years in which the assigned treatment was not followed. An additional analysis is therefore presented for deaths from cardiovascular causes and cancer in relation to actual treatment received. For cardiovascular events, deaths rather than non-fatal events are used since non-fatal events were less reliably reported once patients had been lost to follow up. This analysis should be viewed as secondary as the fact that changes in treatment may be related to the patient's risk of death cannot be corrected for. The on treatment results included only those deaths and patient-years on randomised treatment. For diuretic and  $\beta$  blocker groups this included any periods in which patients received either an altered dose of their randomised drug or the randomised drug in combination with other drugs (including the other trial drug).

Tables VI and VII show that for cardiovascular causes and cancer, on treatment death rates were lower than the corresponding intention to treat rates. This is because death rates were higher after patients had

TABLE IV—Deaths from cancer by treatment and sex; intention to treat analysis

	Men		Women	
	No of deaths	Rate/1000 patient years	No of deaths	Rate/1000 patient years
Diuretic	31	12.2	18	4.8
$\beta$ Blocker	43	17.0	16	4.2
Placebo	47	9.1	52	6.9

TABLE V—Principal events and rates (per 1000 patient years) by smoking habit at entry and randomly allocated drug treatment

	Smokers								Non-smokers							
	Diuretic (1298 patient years)*		$\beta$ Blocker (1300 patient years)*		Total active (2598 patient years)*		Placebo (2707 patient years)*		Diuretic (4985 patient years)*		$\beta$ Blocker (5030 patient years)*		Total active (10015 patient years)*		Placebo (10023 patient years)*	
	No of events	Rate	No of events	Rate	No of events	Rate	No of events	Rate	No of events	Rate	No of events	Rate	No of events	Rate	No of events	Rate
Strokes	17	13.5	17	13.5	34	13.5	29	10.9	28	5.7	39	7.9	67	6.8	105	10.7
Coronary events	13	10.1	28	21.9	41	16.0	46	17.4	35	7.1	52	10.5	87	8.8	113	11.4
All cardiovascular events	37	29.6	55	44.4	92	37.0	84	32.2	70	14.3	96	19.6	166	17.0	225	23.3
Non-cardiovascular deaths	17	13.1	28	21.5	45	17.3	37	13.7	51	10.2	44	8.7	95	9.5	98	9.8
All deaths	39	30.0	68	52.3	107	41.2	98	36.2	95	19.1	99	19.7	194	19.4	217	21.6

\*Patient years for stroke, coronary events, and cardiovascular events are slightly less.

TABLE VI—On treatment analysis of deaths from cardiovascular causes by treatment group

	Diuretic	$\beta$ Blocker	Placebo
No of deaths	28	40	87
No of person years	4302	3477	8783
Death rate/1000 person years	6.5	11.5	9.9

TABLE VII—On treatment analysis of deaths from cancer by treatment group and sex

	Men			Women		
	Diuretic	$\beta$ Blocker	Placebo	Diuretic	$\beta$ Blocker	Placebo
No of deaths	12	22	19	8	6	32
No of person years	1745	1391	3584	2557	2086	5199
Death rate/1000 person years	6.9	15.8	5.3	3.1	2.9	6.2

withdrawn from randomised trial treatment or had lapsed from follow up. However, the differences in mortality from cardiovascular causes and cancer in the on treatment analysis follow the same pattern as previously described for the intention to treat analysis.

#### RISK FACTORS

Logistic regression analyses have been used to relate entry data, including randomised treatment, to the risk of subsequent major events (table VIII). For stroke the beneficial effect of diuretic is estimated as a significant 31% reduction (95% confidence interval 3% to 51%) in risk, after allowing for baseline factors. The estimated 18% (-14% to 40%) reduction in the  $\beta$  blocker group was not significant. The baseline factors of value in predicting risk of stroke were diastolic blood pressure,

TABLE VIII—Contribution of baseline variables to risk of major events (based on multiple logistic regression)

	Stroke			Coronary heart disease			Cardiovascular event			Cardiovascular deaths			Total deaths		
	Relative risk	95% Confidence interval	p Value	Relative risk	95% Confidence interval	p Value	Relative risk	95% Confidence interval	p Value	Relative risk	95% Confidence interval	p Value	Relative risk	95% Confidence interval	p Value
Systolic blood pressure* (10 mm Hg increase)	1.03	0.93 to 1.15	0.56	1.02	0.92 to 1.12	0.76	1.01	0.94 to 1.09	0.72	1.01	0.92 to 1.11	0.76	1.03	0.96 to 1.11	0.41
Diastolic blood pressure* (5 mm Hg increase)	1.07	1.01 to 1.14	0.03	1.03	0.97 to 1.09	0.33	1.06	1.02 to 1.11	0.005	1.03	0.97 to 1.08	0.34	1.01	0.97 to 1.05	0.79
Age (5 year increase)	1.30	1.02 to 1.67	0.04	1.20	0.96 to 1.51	0.11	1.28	1.08 to 1.51	0.005	1.44	1.16 to 1.78	0.0008	1.35	1.14 to 1.59	0.0004
Male v female	1.49	1.11 to 2.00	0.008	2.41	1.83 to 3.17	<0.0001	2.04	1.67 to 2.50	<0.0001	2.23	1.72 to 2.88	<0.0001	1.90	1.56 to 2.31	<0.0001
Smoker v non-smoker	1.21	0.89 to 1.66	0.23	1.41	1.07 to 1.87	0.02	1.55	1.26 to 1.91	<0.0001	1.96	1.53 to 2.52	<0.0001	1.71	1.41 to 2.09	<0.0001
Ischaemic v non-ischaemic electrocardiographic changes	1.40	1.01 to 1.95	0.05	1.50	1.11 to 2.03	0.01	1.62	1.30 to 2.03	<0.0001	1.92	1.47 to 2.51	<0.0001	1.70	1.37 to 2.11	<0.0001
Cholesterol (1 mmol/l increase)	0.94	0.84 to 1.06	0.35	1.27	1.14 to 1.41	<0.0001	1.12	1.04 to 1.21	0.005	1.19	1.08 to 1.32	0.0005	0.94	0.87 to 1.02	0.12
Diuretic v placebo	0.69	0.49 to 0.97	0.04	0.56	0.40 to 0.79	0.0009	0.65	0.51 to 0.83	0.0005	0.71	0.52 to 0.96	0.03	0.84	0.67 to 1.05	0.13
β Blocker v placebo	0.82	0.60 to 1.14	0.25	0.97	0.73 to 1.30	0.85	0.96	0.77 to 1.19	0.69	1.06	0.81 to 1.39	0.66	1.08	0.88 to 1.34	0.46

\*Values at entry to trial.

TABLE IX—Number of patients required to be treated with diuretic for five years to avoid one event in three types of hypertensive patient with differing cardiovascular risk profiles\*

	Men			Women		
	Profile A	Profile B	Profile C	Profile A	Profile B	Profile C
Stroke	83	71	22	111	100	29
Coronary events	37	35	13	83	76	24
Cardiovascular events	30	26	11	54	47	13

\*A: Aged 65 with diastolic pressure 85 mm Hg and systolic pressure 160 mm Hg, non-smoker, no ischaemic electrocardiographic changes, and total serum cholesterol 6.47 mmol/l (median trial level).

B: The same characteristics as in A but with a diastolic pressure of 95 mm Hg.

C: Aged 74 with diastolic pressure 110 mm Hg and systolic pressure 190 mm Hg, smoker, ischaemic electrocardiographic changes, and serum cholesterol 6.47 mmol/l (median trial level).

This assumes the same proportional effect on risk reduction in all diuretic treated subjects.

sex, age, and ischaemic changes on electrocardiography. Because this and the other logistic models are based on the whole trial population, the association between blood pressure at entry and end points may be attenuated as active treatment reduced blood pressure during the trial. This would probably apply to systolic pressure in particular.

For coronary heart disease there was a highly significant 44% (21% to 60%) reduction in risk in the diuretic group compared with the placebo group after allowing for baseline factors, whereas the β blocker group showed no difference from the placebo group. The key baseline factors in predicting risk of a major coronary event were sex, cholesterol concentration, ischaemic electrocardiographic changes, and smoking. Similarly, the diuretic group showed a significant reduction in risk of all cardiovascular events of 35% (17% to 49%) and cardiovascular deaths of 29% (4% to 48%) compared with the placebo group, but the β blocker group did not (table VIII). The predominant risk predictors for both end points were male sex, smoking, ischaemic changes on electrocardiography, age, and cholesterol concentration.

For total deaths the key predictors were sex, age, smoking, and ischaemic changes on electrocardiography. A non-significant inverse association was observed with cholesterol concentration suggesting that low cholesterol may be associated with an increased risk of death from non-cardiovascular causes. Because diuretic treatment was not associated with a reduction in such deaths, the 16% (−5% to 33%) reduction in total mortality in the diuretic group after allowing for baseline factors did not reach significance.

### Discussion

The overall results of this trial show that active treatment led to a significant reduction in cardiovascular events in men and women aged 65-74 with sustained mild to moderate hypertension.

The observed differences between the active drugs in preventing cardiovascular morbidity and mortality stem primarily from the apparent effectiveness of the diuretic in reducing coronary events and deaths.

This interesting finding is contrary to expectations as diuretics have adverse metabolic effects including raising low density lipoprotein and therefore total cholesterol concentrations.<sup>21,22</sup> The increases in total cholesterol concentration averaged over the period from three months after entry to the end of follow up were identical and small (0.1 mmol/l) in all three randomised groups. Larger increases occurred in the mean serum urate concentrations in the active treatment groups (343 at entry/388 in trial, 337/372, 338/342 μmol/l for diuretic, β blocker, and placebo groups respectively), but these did not prevent the reduction of cardiovascular events by the diuretic. The diuretic group experienced a more rapid and greater control of blood pressure compared with the β blocker group (fig 1), and this may have contributed to the differences in effectiveness with regard to coronary events.

All cause mortality was not significantly affected by active treatment (table II). However, death rates from cancer were apparently increased in men, but not women, randomised to active treatment, and when individual active treatments were compared with placebo, men randomised to the β blocker had a significantly increased cancer mortality. No explanation for this finding can be given; however, cancer was not a primary end point in this trial, and the finding is subject to all the uncertainties of post hoc and subgroup analysis. Diagnoses of cancer were not adjudicated in the same formal way as were the primary trial end points. The results may be a chance finding, and substantial evidence would be needed to justify further action.

### RESULTS OF OTHER TRIALS

An overview of 14 randomised trials of antihypertensive treatment, combining trials using different active drugs and different age ranges, reported a significant average 14% reduction in events due to coronary heart disease in those receiving active treatment.<sup>23</sup> Our trial, like other individual trials,<sup>15,24,25</sup> found no primary cardioprotective effect of β blockers, even though the effectiveness of acute and long term β blockade in reducing mortality after myocardial infarction has been shown.<sup>26-30</sup> The lack of a clear primary cardioprotective effect of β selective β blockers when directly compared with a diuretic regimen has previously been reported in middle aged men in the heart attack primary prevention in hypertension (HAPPHY) trial,<sup>25</sup> whose procedures ensured that both the β blocker and diuretic groups attained equal reductions in diastolic blood pressure. To examine whether the lack of a cardioprotective effect of the β blocker in our trial could be due to the greater lowering of systolic blood pressure in the diuretic group a further logistic regression model of in trial risk factor values was fitted for cardiovascular events, the treatment term comparing the diuretic with the

$\beta$  blocker. This found that even after adjusting for blood pressure changes, the diuretic was associated with a lower risk of cardiovascular events ( $p=0.01$ ) compared with the  $\beta$  blocker, again raising the possibility<sup>15</sup> that the diuretic confers benefit through another mechanism besides blood pressure lowering.

While our trial was in progress four randomised controlled trials of antihypertensive drug treatment in men and women aged 60 and over were reported.<sup>31-34</sup> In the European working party on high blood pressure in the elderly (EWPHE) trial<sup>31</sup> there were comparable and significant reductions in deaths from cardiac and cardiovascular causes and a non-significant reduction in fatal stroke.

Coope and Warrender recruited 884 hypertensive patients (30% men) aged 60 to 79 years in 13 general practices and followed them for 4.4 years.<sup>32</sup> Active treatment was started with atenolol 100 mg daily and was then supplemented with bendrofluzide 5 mg daily, if necessary. The combined regimen accounted for most of the active treatment in this trial, followed by atenolol on its own. The results showed a beneficial effect of treatment on stroke. Coronary events were not affected. An excess of cancers among those on active treatment was not significant. The Swedish trial in old patients (STOP)<sup>33</sup> reported large reductions in stroke, coronary disease, and deaths from all causes attributable to active treatment, which consisted mainly of amiloride and hydrochlorothiazide together with a  $\beta$  blocker.

#### IMPLICATIONS OF RESULTS

Our subgroup analyses in smokers and non-smokers were post hoc and so should be interpreted cautiously.<sup>35</sup> Active treatment prevented strokes and all cardiovascular events only in non-smokers. In both the present trial and the earlier MRC trial<sup>15</sup> control of blood pressure was poorer in smokers, especially in those randomised to the  $\beta$  blocker (atenolol and propranolol respectively).

In all, 1879 (43%) of randomised participants had a systolic pressure equal to or exceeding 160 mm Hg and a diastolic pressure below 90 mm Hg, and there is no reason to doubt the applicability of the overall trial results to those with isolated systolic hypertension. This conclusion is supported by the recently published systolic hypertension in the elderly programme (SHEP), which showed a significant 37% reduction in stroke risk in men and women randomised to a stepped care regimen (chlorthalidone step 1; atenolol step 2) compared with a placebo group.<sup>34</sup> Risk of myocardial infarction and cardiovascular events (which included coronary bypass grafting and angioplasty) were reduced (by 33% and 32% respectively) in the active treatment group compared with placebo. The SHEP trial did not report any excess deaths from cancer in the active treatment group.

The main difference between the MRC trial of treatment of mild hypertension in middle aged adults<sup>15</sup> and this trial in older people is the effectiveness of the diuretic in reducing coronary events in this trial. Differences in the diuretics used or in the nature of hypertension and responses to treatment with age are possible explanations.

The clinical decision to use drugs to treat asymptomatic older people who have levels of sustained hypertension in the range considered here should be informed by the effectiveness of the treatment policy, the absolute and relative risks for the individual patient, the adverse drug reactions, and the non-pharmacological alternatives.<sup>37</sup> Table IX shows how the numbers to be treated for five years to avoid one event decrease as the number of risk factors carried by the individual increases, illustrating the importance of considering the cardiovascular risk profile and not

simply the level of hypertension presented by patients. The present trial has not addressed the complex question of whether there are patients in whom lowering blood pressure too much actually increases risk, the so called J shaped curve phenomenon.<sup>38-40</sup>

With regard to all cause mortality this trial, in common with others of similar size,<sup>35</sup> did not have sufficient power to detect small effects of treatment. Overall this trial suggests that treatment of hypertension with the diuretic combination reduces the risk of strokes and all cardiovascular events, at least in non-smokers. Furthermore, there is strong evidence that in this age group the diuretic combination confers considerable benefits by reducing rates of coronary events.

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## Management of elderly patients with sustained hypertension

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### Abstract

**Objective**—To assess the clinical benefits of treating hypertension in elderly patients and to derive practical guidelines regarding indications, goals, and forms of treatment.

**Design**—Review of six published randomised trials.

**Results**—Active treatment of hypertension in elderly patients was associated with significant improvements in several indices of cardiovascular morbidity and mortality, particularly the incidence of fatal and non-fatal strokes. On the basis of the trial data, combined systolic and diastolic hypertension was defined as a sustained systolic pressure >160 mm Hg and diastolic pressure >90 mm Hg. There is convincing evidence that efforts should be made to reduce both systolic and diastolic pressures to below these levels in patients up to the age of 80 years. Isolated systolic hypertension was defined as a systolic pressure >160 mm Hg in the presence of a diastolic pressure <90 mm Hg. Two trials reported benefit from the treatment of isolated systolic hypertension in patients up to the age of 80, and further trials are underway to support or refute this recommendation. Diuretics have an established role in the management of hypertension in elderly patients;  $\beta$  adrenoceptor antagonists have given variable results, and the benefits are less impressive than with diuretic based regimens. Newer agents show promise in the treatment of elderly patients, particularly in the presence of coexisting disease, but their effects on morbidity and mortality have not been evaluated in large randomised trials.

**Conclusions**—Diuretics rather than  $\beta$  blockers are the treatment of choice for patients with uncomplicated hypertension, but combinations of drugs may be required in as many as 50% of patients.

### Introduction

A wealth of clinical evidence supports the need to treat hypertension in patients under the age of 65 years. The strong predictive power of raised blood pressure

for cardiovascular disease—in particular coronary heart disease, heart failure, and stroke—is firmly established, and many trials have confirmed the benefits of drug treatment. There has, however, been a persistent reluctance to treat hypertension in older patients. This has stemmed partly from a lack of evidence of benefit from large controlled trials and partly from fears that efforts to reduce blood pressure in elderly patients might do more harm than good. Treating hypertension in elderly patients presents many theoretical and practical problems. They are a group of survivors who may have taken years to "track" to hypertensive levels of blood pressure or who may have renal artery stenosis or other forms of secondary hypertension. Moreover, they often have relatively low diastolic pressures; it has been proposed that they may respond differently to treatment, and it is widely believed that they are more prone to side effects than younger patients.

Until recently, few trials had specifically looked at the clinical implications of treating elderly hypertensive patients,<sup>1-3</sup> but in the past few months, however, the results of another three major studies have been published.<sup>4-6</sup> The present article reviews currently available trial data to derive practical guidelines for the assessment and management of hypertension in elderly patients, particularly the indications for treatment, goals of treatment, and choice of appropriate antihypertensive agents.

### Materials and methods

We looked at three trials published in the 1980s: the Australian trial of treatment of mild hypertension in the elderly (1981),<sup>1</sup> the European working party on high blood pressure in the elderly (EWPHE) trial (1985),<sup>2</sup> and Coope and Warrender's trial of treatment of hypertension in elderly patients in primary care (1986);<sup>3</sup> and three trials published in the past few months: the systolic hypertension in the elderly programme (SHEP),<sup>4</sup> the Swedish trial in old patients with hypertension (STOP-Hypertension),<sup>5</sup> and the Medical Research Council (MRC) trial of hypertension in older adults.<sup>6</sup>

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