PAPERS AND SHORT REPORTS

MRC trial of treatment of mild hypertension: principal results

MEDICAL RESEARCH COUNCIL WORKING PARTY

Abstract

The main aim of the trial was to determine whether drug treatment of mild hypertension (phase V diastolic pressure 90-109 mm Hg) reduced the rates of stroke, of death due to hypertension, and of coronary events in men and women aged 35-64 years. Subsidiary aims were: to compare the course of blood pressure in two groups, one taking bendrofluazide and one taking propranolol, and to compare the incidence of suspected adverse reactions to these two drugs. The study was single blind and based almost entirely in general practices; 17 354 patients were recruited, and 85 572 patient years of observation have accrued. Patients were randomly allocated at entry to take bendrofluazide or propranolol or placebo tablets.

The primary results were as follows. The stroke rate was reduced on active treatment: 60 strokes occurred in the treated group and 109 in the placebo group, giving rates of 1·4 and 2·6 per 1000 patient years of observation respectively ($p<0·01$ on sequential analysis). Treatment made no difference, however, to the overall rates of coronary events: 222 events occurred on active treatment and 234 in the placebo group (5·2 and 5·5 per 1000 patient years respectively). The incidence of all cardiovascular events was reduced on active treatment: 286 events occurred in the treated group and 352 in the placebo group, giving rates of 6·7 and 8·2 per 1000 patient years respectively ($p<0·05$ on sequential analysis). For mortality from all causes treatment made no difference to the rates. There were 248 deaths in the treated group and 253 in the placebo group (rates 5·8 and 5·9 per 1000 patient years respectively).

Several post hoc analyses of subgroup results were also performed but they require very cautious interpretation. The all cause mortality was reduced in men on active treatment (157 deaths versus 181 in the placebo group; 7·1 and 8·2 per 1000 patient years respectively) but increased in women on active treatment (91 deaths versus 72; 4·4 and 3·5 per 1000 patient years respectively). The difference between the sexes in their response to treatment was significant ($p=0·05$). Comparison of the two active drugs showed that the reduction in stroke rate on bendrofluazide was greater than that on propranolol ($p=0·002$). The stroke rate was reduced in both smokers and non-smokers taking bendrofluazide but only in non-smokers taking propranolol. This difference between the responses to the two drugs was significant ($p=0·03$). The coronary event rate was not reduced by bendrofluazide, whatever the smoking habit, nor was it reduced in smokers taking propranolol, but it was reduced in non-smokers taking propranolol. The rate of all cardiovascular events was not reduced by bendrofluazide, whatever the smoking habit, or in smokers taking propranolol but was reduced in non-smokers taking propranolol. The difference between the two drugs in this respect was significant ($p=0·01$).

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Introduction

The Medical Research Council's trial of drug treatment of mild hypertension began in 1977, after a successful pilot study.[1] By that time controlled trials had shown that treatment was

effective in reducing the incidence of events related to hypertension, such as stroke, in severely hypertensive men,[2] in hypertensive men with phase IV diastolic pressures exceeding 115 mm Hg,[3] and in survivors of strokes[4]; and there was some suggestion that men with phase V diastolic pressures of 90-114 mm Hg might also benefit.[5] There was, however, no definite evidence that drug treatment would reduce the rates of stroke or other cardiovascular events in men with phase V diastolic pressures below 110 mm Hg, and there were no controlled trial data at all on the value of treatment for women with mild hypertension.

AIMS

This trial was therefore set up, under the guidance of an MRC working party responsible for all major scientific decisions, to establish whether drug treatment of mild hypertension (phase V diastolic pressure 90-109 mm Hg) would be associated with a 40% reduction in the number of deaths due to stroke (*International Classification of Diseases* (eighth revision) 430-438) and hypertension (ICD 400-404) and in the number of non-fatal strokes (power 95%, significance level 1%). It was appreciated that there would also be large enough numbers of fatal (ICD 410-414) and non-fatal coronary events to assess the effects of treatment on this category.

The two subsidiary objectives were: (*a*) to compare the course of blood pressure in two groups of participants, one taking the thiazide diuretic bendrofluazide and one taking the β blocking agent propranolol; and (*b*) to compare the incidence of suspected adverse reactions to these two drugs.

Patients and methods

STUDY SIZE

Calculations based on epidemiological data[6] and on the Registrar General's mortality statistics[7] suggested that 18 000 men and women aged 35-64 years, each to be followed up for five years (giving a total of 90 000 person years of observation), would be needed to achieve the main aim of the trial with regard to stroke. This size was likely to be at least adequate for assessing a similar effect of treatment on the rate of coronary events, which were expected to occur more frequently than stroke. It was recognised that even this study size would not permit separate analyses for men and women and was unlikely to permit separate analyses for stroke and coronary event rates in people in the two individual active drug groups. The drug groups were kept separate as far as possible, and the two drugs were only exceptionally used as supplements to one another, so that if the results eventually showed that any comparisons of event rates by randomised drug were feasible these would not be invalidated.

RECRUITMENT AND SCREENING

Recruiting took place over nine years from March 1973 to February 1982, starting slowly during the pilot phase and proceeding rapidly from 1977 onwards. The pilot study showed that clinics specially established in general practice were at least as satisfactory as similar clinics based in industrial organisations or in large screening projects. Since mild hypertension is usually managed in general practice, general practice clinics were used for most of the main phase of the study. More practices than could be included applied to take part. One of the factors determining a practice's suitability was the availability of space for screening (carried out sometimes within the practice rooms and sometimes in one of the MRC's mobile screening caravans) and for trial clinics. In consequence disproportionate numbers of practices from areas such as small towns were enlisted. By reducing the participation of practices in inner city areas this selection process has probably affected the social class structure of the trial population, biasing it towards the upper socioeconomic groups. The population screened was almost entirely identified from the age-sex registers of 176 group practices distributed throughout England, Scotland, and Wales: 695 000 invitations to attend for screening were sent out, and 515 000 (74%) were accepted.

The blood pressure criteria for entry to the trial were: at screening, diastolic (phase V) pressures of 90-109 mm Hg together with a systolic pressure below 200 mm Hg. Screening pressure was defined as the mean of four readings taken on two separate occasions and confirmed by the mean of two later readings still in this range ("entry pressure"). A total of 46 350 (9% of those screened) had blood pressures in the trial range; 25 750 (5%), however, had some exclusion factor (secondary hypertension; taking antihypertensive treatment; normally accepted indications for antihypertensive treatment (such as congestive cardiac failure) present; myocardial infarction or stroke within the previous three months; presence of angina, intermittent claudication, diabetes, gout, bronchial asthma, serious intercurrent disease, or pregnancy). Of the 20 600 (4%) eligible, 16 410 (almost 80%) agreed to participate, giving signed informed consent. Together with 944 people identified at other screening centres, this gave the total of 17 354 participants; the follow up period was extended to five and a half years.

AGE RANGE

People in the trial age range, 35-64 years, were expected to experience fewer strokes and coronary events than would an older population; but, because the impact of such events may be greater in younger people, the importance of obtaining evidence about the value of antihypertensive treatment in this age group was considered sufficient to outweigh this disadvantage. People aged less than 35 were not recruited because their event rate would have been so low.

TREATMENT REGIMENS

Patients were randomly allocated at entry to one of four treatments: the thiazide diuretic bendrofluazide; placebo tablets that looked like bendrofluazide; the β blocker propranolol; and placebo tablets that looked like propranolol. The two placebo groups were treated as one in all analyses. Randomisation was in stratified blocks of eight within each sex, 10 year age group, and clinic. Thiazide diuretics and β adrenoceptor blocking drugs were selected because, firstly, at the time the trial was designed these were the most commonly used pharmacological agents for treating mild to moderate hypertension and, secondly, it was hoped to show whether the incidence of coronary events would be reduced by β blockade. There are important differences in the metabolic, hormonal, and haemodynamic effects of these two types of drug, and it was hoped that useful comparative data would be collected in the trial. The drugs selected from these groups were bendrofluazide and propranolol. There was already considerable experience of their use, which made it less likely that serious toxicity would be discovered. The doses chosen, 10 mg daily of bendrofluazide and up to 240 mg daily of propranolol, were in common use and were known to be roughly equipotent in terms of their hypotensive effect.

The target level of blood pressure for those randomised to active treatment was diastolic pressure (phase V) below 90 mm Hg, to be reached within six months of entry to the study. Supplementary treatment was added if blood pressure did not respond satisfactorily to the primary drug. Methyldopa was originally used as a supplement to bendrofluazide and guanethidine as a supplement to propranolol, but later methyldopa was used whatever the primary drug. Only exceptionally was one of the primary trial drugs used to supplement the other (the five and a half year cumulative percentage was 5%, 2% of the total patient years of observation).

A small group of patients (288) was randomly assigned at entry to a fifth treatment regimen of observation only, taking no tablets but otherwise adhering to the standard protocol. The course of blood pressure in this group was indistinguishable from that in the placebo group,[8] and the two groups have been merged in the analyses.

The changes in dosage in the propranolol group and the availability of supplementary treatment in both actively treated groups sometimes necessitated several adjustments of medication in patients whose blood pressure did not easily reach the target level. When the protocol was written it was judged unreasonable to ask general practitioners to undertake such adjustments in a double blind study, and the trial was therefore single blind only.

Doctors were free to use their own judgment in managing obesity and advising on cigarette smoking, exercise, and salt intake, but they were asked to follow a consistent policy for treated and control patients.

DATA COLLECTION AND QUALITY CONTROL

The first four screening measurements and the follow up blood pressure measurements were made by specially trained, and regularly tested, nurses. Confirmatory blood pressure measurements in the later stages of screening and full medical examinations at entry and each year of the trial were performed by the general practitioners. Hawksley random zero sphygmomanometers[9] were used for almost all blood pressure measurements; in only two clinics were London School of Hygiene sphygmomanometers[10] used instead. All forms were checked at the coordinating centre (based in the MRC Epidemiology and Medical Care Unit, Northwick Park Hospital, Harrow), and adherence to the protocol was monitored.

WITHDRAWAL FROM RANDOMLY ALLOCATED TREATMENT

Control patients whose blood pressure rose to levels at which placebo treatment was judged unethical were transferred to the corresponding active drug. The original criteria for transfer were a diastolic pressure of 115 mm Hg or a systolic pressure of 210 mm Hg, or both, at two consecutive or three non-consecutive follow up visits. In September 1980 these levels were reduced to 110 mm Hg for diastolic pressure and 200 mm Hg for systolic pressure. If people on active treatment developed pressures at these levels their doctors were free to use whatever drugs they selected irrespective of the protocol.

Other reasons for withdrawal from randomised treatment included the development of complications necessitating active treatment and suspected adverse drug reactions. All patients whose treatment was changed were asked to continue to attend for all the follow up examinations.

TERMINATION OF PARTICIPATION IN TRIAL

Events terminating a patient's participation were: stroke, whether fatal or non-fatal; coronary events, including sudden death thought to be due to a coronary cause, death known to be due to myocardial infarction, and non-fatal myocardial infarction; other cardiovascular events, including deaths due to hypertension (ICD 400-404) and to rupture or dissection of an aortic aneurysm; and death from any other cause. Clinic staff reported these events to the coordinating centre. The records of all patients who suffered non-fatal terminating events and of any others who lapsed from the trial, whatever the reason, were "flagged" at the Southport NHS central register to ensure notification of death.

ASSESSMENT OF TERMINATING EVENTS

The evidence on which the diagnosis of each terminating event was based was assessed by an arbitrator ignorant of the treatment regimen. All available documentation was reviewed, including copies of general practitioners' notes, hospital inpatient or outpatient notes, electrocardiographic recordings, necropsy findings, and death certificates, and full details were almost always obtained. In virtually all cases classification of fatal events used in the trial analyses was based on this detailed information rather than solely on the wording or coding of the death certificate. The arbitrator used WHO criteria[11,12] for classification. "Definite" and "possible" categories of coronary events were combined, as the distinction between these groups depends not only on the nature of the episode but also on the amount of evidence available.

If a patient had a non-fatal event followed by a fatal event in the same category—for example, a non-fatal and then a fatal stroke—only the fatal event was included in the analyses (38 people were in this group). If a person suffered two events in different categories—for example, a non-fatal stroke and then a coronary event—both were included (six people were in this group).

Data for terminating events were regularly reviewed by the monitoring committee, which prepared reports for the independent ethical committee, whose remit included advising when the trial should stop.

STATISTICAL MANAGEMENT

Primary results—All analyses presented here are based on randomised treatment ("intention to treat") categories. Thus data for all participants are presented as if the individual was still in the treatment group to which he was originally randomised, although substantial percentages of patients (see below) were in fact withdrawn from their randomly allocated regimen during follow up. This method of analysis is the preferred approach for randomised clinical trial data, despite the inevitable contamination of the original treatment groups with results for individuals receiving alternative treatments. Although intention to treat analysis may underestimate effects associated with treatment, it is unlikely to lead to false conclusions due to subsequent selection of the group of patients who remain on a particular treatment regimen. This method may fail to detect the consequences of pharmacological effects present only at the time a drug is taken. In fact, there were only minor differences between the results of the intention to treat and on treatment analyses.

Data for terminating events were analysed sequentially. Results were tested every six months. The incidence of the main endpoints of the trial (strokes, coronary events, all cardiovascular events, and all cause mortality) in the two actively treated groups together was compared with that in the two placebo groups together and tested at a stringent nominal p value (using a χ^2 test without continuity correction) allowing the maintenance of an overall type I (false positive) error rate of 0·01 for the beneficial effects of active treatment with 15 analyses of the data.[13] The corresponding overall type I error rate for the adverse effects of treatment was kept at 0·05. Data for comparisons between the two sexes and between the two active regimens were also kept under review.

Secondary results—The results of some post hoc subgroup analyses are presented, although such analyses require very cautious interpretation and can be misleading. Those discussed here are biologically plausible, which helps to substantiate their credibility. The results of these analyses have been presented whether or not they reached conventional or arbitrary levels of statistical significance. Some p values are indeed conventionally significant, but, in ascribing importance to these, the large number of comparisons made must be borne in mind.

Predictive characteristics—Logistic regression analysis was used to estimate the relation between treatment, certain entry characteristics, and the probability of subsequently having a terminating event. The entry characteristics considered were: age, sex, cigarette smoking, ischaemic changes on the electrocardiogram (Minnesota codes 1_{1-2}, 4_{1-3}, 5_{1-2} (one or more)), systolic and diastolic blood pressure, serum cholesterol concentration, and Quetelet's body mass index (body weight/height^2 in kg/m^2). The terminating events examined in these analyses were strokes, coronary events, all cardiovascular events, and all cause mortality. Treatment was considered in two ways: firstly, by comparing data for the active and placebo groups and, secondly, by comparing the results for one primary drug with those for the other. Interaction analyses, using the relation between entry variables and treatment defined in both these ways, were used to assess the importance of possible differences in response to treatment which were found between certain subgroups. Such comparisons were outside the original aims of the trial and may have had only a limited ability to detect even moderate differences. The results in individual subgroups were not subjected to significance testing, as this can often be misleading.[14] The logistic regressions used a controlled stepdown procedure (with some categorisation of continuous variables where necessary because of limitations of computer space). The calculations were performed using generalised linear interactive modelling (GLIM).[15] The p values presented in relation to the results of the logistic regression analyses refer to this "once off" testing.

All rates shown have been age standardised to the structure of the total trial population.

Results

NUMBERS, RISK FACTORS, AND PATIENT YEARS OF OBSERVATION

The numbers of patients recruited, certain entry characteristics, and the patient years of observation are shown in table Im, which confirms that there were no obvious imbalances between the groups in terms of major risk factors at entry. The aim was to accrue 90 000 patient years; in the event 85 572 were achieved by the end of the trial. Closely similar percentages of initially smoking patients in the active and the placebo groups gave up smoking during the trial (24·6% of men on active treatment and 23·3% in the control group of men, with corresponding figures for women of 23·4% and 22·5%). Data for changes in body weight during the trial could not usefully be compared, as each of the two active drugs was itself associated with a change in body weight (a reduction on bendrofluazide and an increase

on propranolol) which was significantly different from that in placebo treated subjects. No data for exercise or salt intake were collected.

COURSE OF BLOOD PRESSURE

Average blood pressure fell immediately after entry in all treatment groups (fig 1m), including those taking placebo tablets and those on observation only. The fall was steepest in the first two weeks; it then continued, more gradually, for about three months. From the first anniversary of entry onwards average pressure changed very little.

Average pressure after entry was lower in those taking bendrofluazide than in those taking propranolol. Within the propranolol group pressure control was less effective in older people; the details have been published.[16] The percentages of participants with diastolic pressure at the target level (below 90 mm Hg) were consistently higher in the bendrofluazide group than in the propranolol group (table IIm). The use of supplementary drugs by those randomised to bendrofluazide (fixed dose) consistently exceeded that by patients randomised to propranolol (titratable dose) (table IIIm). The extent of separation between average pressures in actively treated and control groups is shown in table IVm. Annual measurements showed that between one third and one half of all those taking placebo had diastolic pressures below 90 mm Hg; however, different people made up this total at each anniversary. Only 18% (1270) of the 7141 in the placebo group for whom blood pressure measurements at the first three anniversary visits were recorded had diastolic pressures below 90 mm Hg on each of these three occasions; 23% (1657) were in the target range at two of these visits and 27% (1929) at one visit. Only 32% (2285) had no measurements of diastolic pressure below 90 mm Hg at any of these visits.

Altogether 1011 people randomised to placebo treatment and 76 people randomised to active tablets (table Vm) developed blood pressure above the mild range.

WITHDRAWALS FROM RANDOMISED TREATMENT AND LAPSES FROM FOLLOW UP

Numbers and cumulative percentages of people withdrawn from randomised treatment because they developed either suspected adverse reactions to the primary regimen (discussed in detail elsewhere[17]) or levels of blood pressure above the upper limit for the trial are shown in table Vm and fig 2m. The protocol for the follow up routine was the same for these people as for those whose treatment was unchanged.

The five and a half year cumulative percentages of people lapsing from follow up (fig 3m) were about 19% and include losses of about 3·5% due to participants moving house.

The total five and a half year cumulative percentages of men who stopped taking their randomised treatment, including both those withdrawn from their randomly allocated regimen but continuing on follow up and those lapsing from the trial, were 43% of the bendrofluazide group, 42% of the propranolol group, and 47% of the placebo group. For women the figures were 33%, 40%, and 40% respectively. The cumulative percentages of people not taking either primary active drug by five and a half years were smaller: 33% of men originally randomised to bendrofluazide and 34% of men randomised to propranolol and 28% and 31% respectively of women.

PRIMARY RESULTS

The principal findings, directly answering those questions specified at the design stage, were as follows (table VI, fig 4m).

MINIPRINT TABLES I to V and VII

Im

TABLE I—*Numbers, patient years of observation completed, and entry characteristics of treatment groups*

	Men: Bendrofluazide	Men: Propranolol	Men: Placebos	Men: Pooled SD	Women: Bendrofluazide	Women: Propranolol	Women: Placebos	Women: Pooled SD
Number (%):	2238 (25)	2285 (25)	4525 (50)		2059 (25)	2118 (25)	4129 (50)	
Patient years:	10 945	11 184	22 190		10 274	10 508	20 471	
Mean age (years)	51	51	51	8	53	53	53	7
Mean body weight (kg)	82	81	81	12	70	70	70	13
Mean systolic blood pressure (mm Hg)	158	158	158	16	165	165	165	17
Mean diastolic blood pressure (mm Hg)	98	98	98	6	99	99	98	6
Mean serum cholesterol (mmol/l)	6·3	6·3	6·3	1·0	6·7	6·7	6·7	1·2
Mean serum potassium (mmol/l)	4·1	4·1	4·2	0·4	4·1	4·1	4·1	0·4
Mean serum urate (µmol/l)	382	374	373	68	297	293	293	63
Mean serum sodium (mmol/l)	142	142	142	2	142	142	142	3
Mean serum urea (mmol/l)	5·4	5·4	5·4	1·2	5·2	5·1	5·2	1·2
% Cigarette smokers	32	30	32		27	25	27	
% With left ventricular hypertrophy on ECG*	0·4	0·3	0·4		0·2	0·2	0·4	
% With Q wave abnormalities†	1·0	1·2	1·5		1·7	1·7	1·4	
% With history of stroke	0·8	0·7	0·7		0·7	0·7	0·7	

*$3_1, 4_{1-3}, 5_{1-3}$ on Minnesota code. †1_{1-3} on Minnesota code.
Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml. Potassium and sodium: 1 mmol/l ≈ 1 mEq/l. Urate: 1 mmol/l ≈ 17 mg/100 ml. Urea: 1 mmol/l ≈ 6 mg/100 ml.

IIm

TABLE II—*Percentages of participants with diastolic blood pressure below 90 mm Hg at anniversary visits*

Years since joining trial:	Men 1	Men 2	Men 3	Men 4	Men 5	Women 1	Women 2	Women 3	Women 4	Women 5
Bendrofluazide	66	69	70	72	72	71	75	76	79	78
Propranolol	60	65	66	68	71	64	68	69	73	76
Placebos	38	40	42	43	43	42	44	46	49	50

IIIm

TABLE III—*Cumulative percentages of participants taking supplementary therapy*

Years since joining trial:	Men 1	Men 2	Men 3	Men 4	Men 5	Women 1	Women 2	Women 3	Women 4	Women 5
Bendrofluazide	21	26	30	32	34	15	19	21	23	24
Propranolol	12	18	21	23	25	8	12	14	17	19

IVm

TABLE IV—*Difference (in mm Hg) between mean levels of blood pressure at anniversaries of entry in actively treated people and those on placebo, by sex and drug*

Years since entry:	Men 1	Men 2	Men 3	Men 4	Men 5	Women 1	Women 2	Women 3	Women 4	Women 5
Systolic blood pressure										
Bendrofluazide	13	12	13	13	11	13	14	14	14	15
Propranolol	10	10	10	10	9	8	10	9	9	10
Diastolic blood pressure										
Bendrofluazide	5	6	6	6	6	6	6	7	7	6
Propranolol	4	5	6	5	6	4	5	5	5	4

Vm

TABLE V—*Principal reasons for withdrawal from randomised treatment. Numbers of reports and rates/1000 patient years†*

	Men: Bendrofluazide No	Rate	Men: Propranolol No	Rate	Men: Placebos No	Rate	Women: Bendrofluazide No	Rate	Women: Propranolol No	Rate	Women: Placebos No	Rate
Impaired glucose tolerance	60	7·7***	27	3·4	53	3·3	46	5·9***	16	2·1	31	2·0
Gout‡	100	12·8***	12	1·5	14	0·9	12	1·5***	0		0	
Impotence	98	12·6***	50	6·3***	20	1·3	0		0		0	
Raynaud's phenomenon	0		41	5·1***	3	0·2	2	0·3	34	4·5***	4	0·3
Skin disorder	6	0·8	12	1·5**	5	0·3	3	0·4	9	1·2**	2	0·1
Dyspnoea	1	0·1	57	7·1***	7	0·4	2	0·3	53	7·1***	3	0·2
Lethargy	28	3·6***	42	5·3***	8	0·5	13	1·7***	62	8·3***	4	0·3
Nausea, dizziness, or headache	33	4·2***	33	4·1***	22	1·4	58	7·4***	70	9·4***	27	1·8
Pressure at or above levels requiring change of treatment	8	1·0***	33	4·1***	611	38·2	11	1·4***	24	3·2***	400	26·0

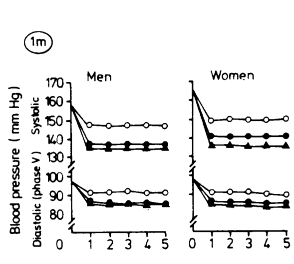
†Patient years of observation relates here only to years accrued before withdrawal of randomised treatment.
‡Defined as symptoms plus serum urate values in excess of 500 µmol/l in men, 450 µmol/l in women.
**$p < 0·01$; ***$p < 0·001$; p values are for comparison of rate on individual active drug with rate on placebos.

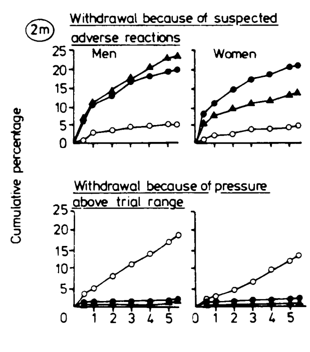
VIIm

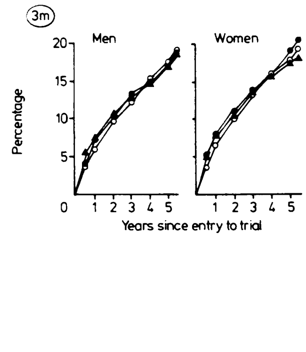
TABLE VII—*Numbers, person years of observation, and principal events by sex and drug regimen at randomisation. Rate=rate/1000 patient years*

	Men: Bendrofluazide		Men: Propranolol		Men: Active treatment		Men: Placebos		Women: Bendrofluazide		Women: Propranolol		Women: Active treatment		Women: Placebos	
No entered:	2 238		2 285		4 523		4 525		2 059		2 118		4 177		4 129	
Patient years:	10 945		11 184		22 129		22 190		10 274		10 508		20 782		20 471	
	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate
Stroke																
Fatal	0	0·0	6	0·5	6	0·3	13	0·6	4	0·4	8	0·8	12	0·6	14	0·7
Non-fatal	11	1·0	20	1·8	31	1·4	52	2·3	3	0·3	8	0·8	11	0·5	30	1·5
Total	11	1·0	26	2·3	37	1·7	65	2·9	7	0·7	16	1·5	23	1·1	44	2·1
Coronary events																
Fatal	50	4·6	38	3·4	88	4·0	87	3·9	9	0·9	9	0·9	18	0·9	10	0·5
Non-fatal	49	4·5	47	4·2	96	4·3	113	5·1	11	1·1	9	0·9	20	1·0	24	1·2
Total	99	9·0	85	7·6	184	8·3	200	9·0	20	1·9	18	1·7	38	1·8	34	1·7
All cardiovascular events	113	10·3	112	10·0	225	10·2	272	12·3	27	2·6	34	3·2	61	2·9	80	3·9
All cardiovascular deaths	56	5·1	48	4·3	104	4·7	112	5·1	13	1·3	17	1·6	30	1·4	27	1·3
Non-cardiovascular deaths	26	2·4	27	2·4	53	2·4	69	3·1	33	3·2	28	2·7	61	2·9	45	2·2
All deaths	82	7·5	75	6·7	157	7·1	181	8·2	46	4·5	45	4·3	91	4·4	72	3·5

MINIPRINT FIGURES 1 to 4







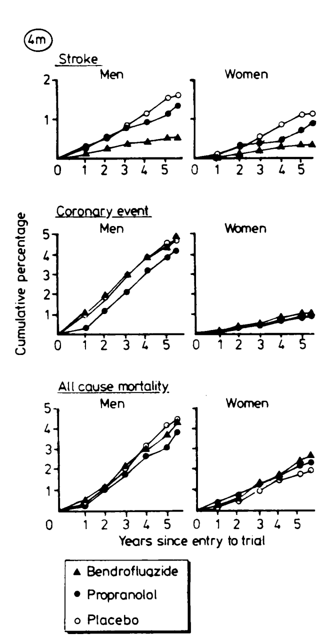


FIG 1—Mean levels of blood pressure by sex and randomised treatment group.

FIG 2—Cumulative percentages withdrawn from randomised treatment.

FIG 3—Cumulative rates of people lapsing from follow up.

FIG 4—Cumulative percentages of people with terminating events (stroke, coronary events, and all cause mortality) by sex and by randomised treatment.

Stroke—The event rate of stroke was significantly reduced in people randomised to receive active treatment. There were 60 strokes in the actively treated group and 109 in the placebo group ($p = 0.0006$ on once off testing, $p < 0.01$ on sequential analysis). The percentage difference between the rates in the treated and placebo groups (1·4 and 2·6 per 1000 patient years respectively) was 45%. The absolute difference was 1·2 strokes per 1000 patient years.

Coronary events—The overall coronary event rate was not significantly affected by treatment (222 in the treated group, 234 in the placebo group, with rates per 1000 patient years of 5·2 and 5·5 respectively).

All cardiovascular events—The cardiovascular event rate was significantly reduced in the actively treated group. There were 286 such events on active treatment and 352 in the placebo group ($p = 0.01$ on once off testing, $p < 0.05$ on sequential analysis). Rates per 1000 patient years were 6·7 and 8·2 respectively, with a percentage difference of 19% between rates for treated and placebo groups and an absolute difference of 1·6 events per 1000 patient years. Results in this category are dominated by figures for coronary events, which considerably exceeded the numbers of strokes.

Analysis also showed that the all cause mortality was almost identical in the two groups. There were 248 deaths in the treated group and 253 in those taking placebo tablets, giving rates of 5·8 and 5·9 per 1000 patient years respectively.

SUBGROUPS

Individual active drug (tables VIIm and VIII)

Stroke—Both drugs were associated with reduced stroke rates. Eighteen strokes occurred in the bendrofluazide group, 42 on propranolol, and 109 on placebo (rates of 0·8, 1·9, and 2·6 per 1000 patient years respectively). The percentage reduction on bendrofluazide was significantly ($p = 0.002$) greater than that on propranolol.

All cardiovascular events—Both drugs were associated with slightly reduced rates (6·6 per 1000 patient years on bendrofluazide, 6·7 on propranolol, and 8·2 on placebo). There was no significant difference between the effects of the individual active drugs ($p = 0.76$).

For *coronary events* and for *all cause mortality* there were no statistically significant differences between the effects associated with bendrofluazide and those associated with propranolol ($p = 0.24$ and 0·71 respectively).

Sex (tables VIIm and IX)

Strokes, coronary events, and all cardiovascular events—There were no statistically significant differences between men and women in their percentage response to active treatment (p values 0·63, 0·45, and 0·62 respectively).

TABLE VI—*Main events for both sexes together. Numbers and rates per 1000 patient years*

	Active treatment†		Placebos		% Difference‡ (95% confidence limits)	Absolute difference/1000 patient years§ (95% confidence limits)
	No	Rate	No	Rate		
Strokes						
Fatal	18	0·4	27	0·6	34	0·2
Non-fatal	42	1·0	82	1·9	49	0·9
Total	60	1·4	109	2·6	45 (25, 60)	1·2 (0·6, 1·7)
Coronary events						
Fatal	106	2·5	97	2·3	−9	−0·2
Non-fatal	116	2·7	137	3·2	16	0·5
Total	222	5·2	234	5·5	6 (−13, 21)	0·3 (−0·7, 1·3)
All cardiovascular events*	286	6·7	352	8·2	19 (5, 31)	1·6 (0·4, 2·7)
All cardiovascular deaths	134	3·1	139	3·3	4 (−22, 24)	0·1 (−0·6, 0·9)
Non-cardiovascular deaths	114	2·7	114	2·7	0 (−29, 23)	0·0 (−0·7, 0·7)
All deaths	248	5·8	253	5·9	2 (−16, 18)	0·1 (−0·9, 1·2)

*Not necessarily equal to the total of strokes plus coronary events because it also includes "other relevant deaths" and death due to other cardiovascular causes such as ruptured aneurysms.
†Randomised either to bendrofluazide or to propranolol.
‡Percentage difference between rates on active and on placebo therapy.
§Absolute difference between rates on active treatment and on placebo therapy.

TABLE VIII—*Principal events by randomly allocated drug, both sexes together**

	Bendrofluazide		Propranolol		Placebos		% Difference		Absolute difference/1000 patient years	
	No	Rate	No	Rate	No	Rate	Bendrofluazide	Propranolol	Bendrofluazide	Propranolol
Strokes	18	0·8	42	1·9	109	2·6	67	24	1·7	0·6
Coronary events	119	5·6	103	4·8	234	5·5	−2	13	−0·1	0·7
All cardiovascular events	140	6·6	146	6·7	352	8·2	20	18	1·7	1·5
Non-cardiovascular deaths	59	2·8	55	2·5	114	2·7	−4	5	−0·1	0·1
All deaths	128	6·0	120	5·5	253	5·9	−2	6	−0·1	0·4

*Apparent discrepancies are due to rounding in the figures presented for the rates.

TABLE IX—*Principal events by sex*

	Active treatment		Placebo treatment			
	No	Rate	No	Rate	% Difference	Absolute difference/1000 patient year
			Men			
Strokes	37	1·7	65	2·9	43	1·3
Coronary events	184	8·3	200	9·0	8	0·7
All cardiovascular events	225	10·2	272	12·3	17	2·1
Non-cardiovascular deaths	53	2·4	69	3·1	23	0·7
All deaths	157	7·1	181	8·2	13	1·1
			Women			
Strokes	23	1·1	44	2·1	48	1·0
Coronary events	38	1·8	34	1·7	−11	−0·2
All cardiovascular events	61	2·9	80	3·9	25	1·0
Non-cardiovascular deaths	61	2·9	45	2·2	−34	−0·8
All deaths	91	4·4	72	3·5	−25	−0·9

TABLE X—*Principal events by entry smoking habit, both sexes together**

Patient years:	Bendrofluazide				Propranolol				Placebos				% Benefit				Absolute benefit/1000 patient years			
	Smokers 6 206		Non-smokers 14 913		Smokers 6 056		Non-smokers 15 498		Smokers 12 352		Non-smokers 30 152		Bendrofluazide *v* placebos		Propranolol *v* placebos		Bendrofluazide *v* placebos		Propranolol *v* placebos	
	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers	Smokers	Non-smokers
Strokes	6	1·0	12	0·8	26	4·3	16	1·0	48	4·0	60	1·9	75	59	−8	47	3·1	1·1	−0·3	0·9
Coronary events	57	9·3	62	4·1	57	9·5	45	2·9	102	8·5	131	4·3	−9	4	−12	33	−0·8	0·2	−1·0	1·4
All cardiovascular events	65	10·6	75	5·0	84	14·0	61	3·9	157	13·2	193	6·3	20	21	−7	38	2·6	1·3	−0·9	2·4
Non-cardiovascular deaths	17	2·8	40	2·7	19	3·2	36	2·3	51	4·3	63	2·1	35	−30	26	−12	1·5	−0·6	1·1	−0·3
All deaths	47	7·7	79	5·3	54	9·1	66	4·2	119	10·1	134	4·4	23	−20	10	3	2·4	−0·9	1·0	0·1

*Numbers of events do not always tally with those in other tables, because there were 76 people for whom the smoking habit at entry was not recorded and who are not included here.

All cause mortality—There was a benefit associated with treatment in men (157 deaths on active treatment and 181 deaths on placebo (7·1 and 8·2 per 1000 patient years respectively)) but the opposite effect in women (91 deaths in the treated group compared with 72 on placebo, giving rates of 4·4 and 3·5 per 1000 patient years respectively). The difference between the sexes was significant ($p = 0·05$).

Cigarette smoking (table Xm, figs 5 and 6)

Effects of active treatment—When the percentage response to active treatment in non-smokers was compared with that in smokers, no statistically significant differences were found for stroke ($p = 0·19$), for coronary events ($p = 0·08$), or for all cause mortality ($p = 0·19$). For all cardiovascular events the difference between smokers and non-smokers was just statistically significant ($p = 0·05$), with the greater benefit in non-smokers.

Comparison of drugs—Smoking habit did not affect the response to bendrofluazide but was important when the response to propranolol was considered. For *stroke* the event rate was reduced in smokers and in non-smokers on bendrofluazide but only in non-smokers on propranolol and the difference between the two drugs was significant in this respect ($p = 0·03$). For *coronary events* the rate was not affected in smokers or non-smokers on bendrofluazide or in smokers on propranolol. The rate in non-smokers on propranolol was reduced, but the difference between the two drugs was not significant ($p = 0·11$). The event rate for *all cardiovascular events* was not affected in smokers or non-smokers on bendrofluazide or in smokers on propranolol. In non-smokers on propranolol the event rate was reduced. The difference between the two drugs was statistically significant ($p = 0·01$). The rate for *all cause mortality* was not affected by either active drug in either smoking habit group, and the drugs were not statistically significantly different from one another ($p = 0·11$) in this respect.

Non-cardiovascular deaths

There was no evidence to link any treatment regimen with a change in death rates in any category of non-cardiovascular deaths (table XIm).

RISK FACTORS AND THE PREDICTION OF PERSONAL RISK

Logistic regression analyses using entry data showed that the level of systolic blood pressure at entry was significantly associated with the risk of stroke, coronary events, all cardiovascular events, and all cause mortality.

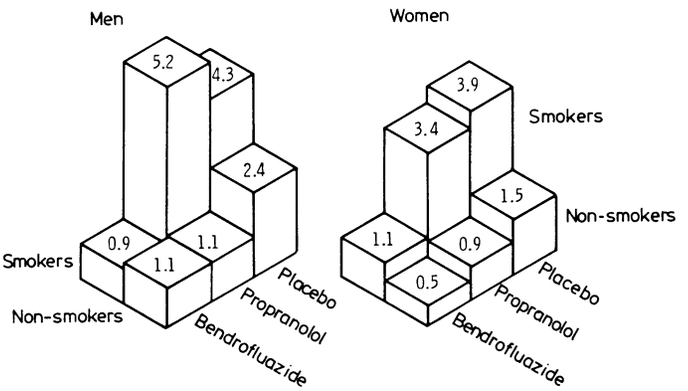


FIG 5—Incidence of stroke per 1000 person years of observation according to randomised treatment regimen and cigarette smoking status at entry to trial.

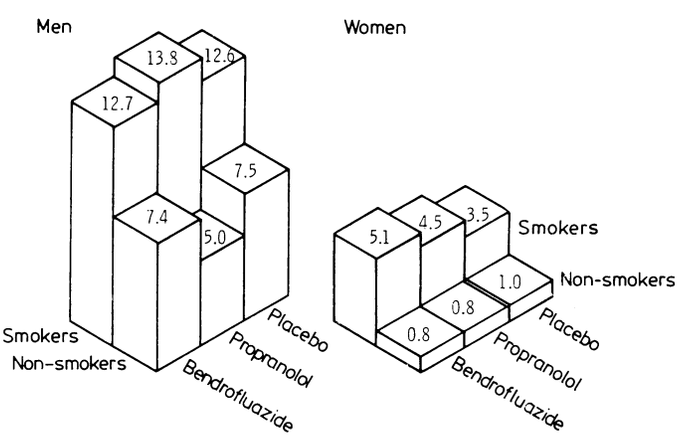


FIG 6—Incidence of coronary events per 1000 person years of observation according to randomised treatment regimen and cigarette smoking status at entry to trial.

MINIPRINT TABLES XI to XIII

XIm

TABLE XI—*Non-cardiovascular deaths*

	Men								Women							
	Bendrofluazide		Propranolol		Active treatment		Placebos		Bendrofluazide		Propranolol		Active treatment		Placebos	
	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate	No	Rate
Malignant*	17	1·6	18	1·6	35	1·6	44	2·4	24	2·3	23	2·2	47	2·3	36	1·8
Infection	2		0		2		4		0		0		0		1	
Pancreatitis	1		0		1		0		1		1		2		2	
Accident	2		5		7		3		1		1		2		1	
Suicide	2		0		2		1		3		0		3		0	
Other not known	2		4		6		7		4		3		7		5	
Total	26	2·4	27	2·4	53	2·4	69	3·1	33	3·2	28	2·7	61	2·9	45	2·2

*Malignant deaths were analysed by site; there was no evidence that any treatment regimen was associated with an excess of tumours at any site.

XIIm

TABLE XII—*Stroke rates and percentage benefit associated with treatment by (a) entry systolic pressure and (b) entry diastolic pressure, both sexes together*

	Entry systolic pressure mm Hg					Entry diastolic pressure mm Hg			
	<150	150-159	160-169	170-179	≥180	<95	95-99	100-104	≥105
Strokes 1000 patient years									
Bendrofluazide	0·6	1·0	0·4	0·8	1·2	0·2	1·3	1·0	1·1
Propranolol	1·2	1·0	2·6	2·2	2·3	1·5	2·4	2·2	1·6
Active treatment	0·9	1·0	1·7	1·5	1·7	0·8	1·8	1·6	1·4
Placebos	1·4	1·8	2·5	3·2	3·9	1·4	2·3	3·1	4·4
% Benefit									
Bendrofluazide	60	46	83	75	70	88	44	68	75
Propranolol	19	46	−16	29	42	−9	−6	31	65
Active treatment	39	46	33	52	56	40	18	50	69

XIIIm

TABLE XIII—*Contribution of baseline variables to risks of developing a terminating event in the trial*

	Systolic blood pressure—10 mm Hg increase	Diastolic blood pressure—4 mm Hg increase	Age—5 year increase	Women men	Smokers non-smokers	Ischaemic ECG non-ischaemic ECG*	Cholesterol 6·5 6·5 mmol l	Quetelet index—3·0 kg m² increase	Placebo active	Propranolol bendrofluazide
Stroke										
p value	0·02	0·003	<10⁻⁴	0·002	<10⁻⁴	0·06	0·43	0·19	0·0006	0·002
RR 95% CL	1·14	1·21	1·46	0·60	2·29	1·65	1·14	0·91	1·74	2·30
	(1·02-1·28)	(1·07-1·37)	(1·26-1·66)	(0·43-0·83)	(1·66-3·13)	(1·00-2·69)	(0·83-1·56)	(0·80-1·05)	(1·26-2·40)	(1·33-3·99)
Coronary events										
p value	0·001	0·71	<10⁻⁴	<10⁻⁴	<10⁻⁴	<10⁻⁴	<10⁻⁴	0·008	0·60	0·24
RR 95% CL	1·10	1·02	1·32	0·15	2·27	2·13	1·76	1·13	1·05	0·65
	(1·03-1·18)	(0·94-1·10)	(1·23-1·43)	(0·11-0·19)	(1·87-2·76)	(1·56-2·90)	(1·45-2·14)	(1·03-1·23)	(0·87-1·27)	(0·64-1·11)
Cardiovascular events										
p value	0·001	0·05	<10⁻⁴	<10⁻⁴	<10⁻⁴	<10⁻⁴	<10⁻⁴	0·19	0·01	0·76
RR 95% CL	1·11	1·07	1·38	0·23	2·36	1·94	1·60	1·05	1·23	1·04
	(1·04-1·17)	(1·00-1·14)	(1·29-1·47)	(0·19-0·28)	(2·01-2·79)	(1·48-2·54)	(1·35-1·89)	(0·98-1·13)	(1·05-1·46)	(0·81-1·32)
All deaths										
p value	0·03	0·82	<10⁻⁴	<10⁻⁴	<10⁻⁴	<10⁻⁴	0·005	0·78	0·86	0·71
RR 95% CL	1·07	1·01	1·41	0·41	1·99	2·27	1·31	1·01	1·02	0·95
	(1·01-1·14)	(0·94-1·09)	(1·31-1·52)	(0·34-0·50)	(1·66-2·40)	(1·72-3·00)	(1·09-1·58)	(0·93-1·10)	(0·85-1·22)	(0·73-1·23)

RR = relative risk CL = confidence limits
*1, 4, 5, one or more code present

Although the level of entry systolic pressure was significantly associated with the subsequent stroke rate, it was not significantly related to the percentage benefit associated with active treatment (table XIIm). For the sake of simplicity table XIIm shows results for stroke only, but the general finding applies similarly to the other categories of events: although entry systolic pressure was a risk factor for the development of coronary events, all cardiovascular events, and all cause mortality, it was not significantly associated with any percentage changes in rates conferred by active treatment in comparison with the placebo regimen. The level of diastolic pressure at entry was less clearly associated with the risk of subsequent events. The level of systolic pressure at six months was significantly related to subsequent development of stroke in patients on any of the three treatment regimens, of coronary events in the placebo group, of all cardiovascular events in the propranolol and placebo groups, and of all cause mortality in the placebo group. The percentage benefit due to active treatment, however, in any category of events, was not related to the level of pressure at six months. The level of diastolic pressure was less clearly related to the subsequent development of events and was not related to the percentage benefit associated with treatment.

Age, male sex, and cigarette smoking were also significantly related to the subsequent development of stroke, coronary events, all cardiovascular events, and all cause mortality (table XIIIm). The presence of an ischaemic pattern on the electrocardiogram and a high serum cholesterol concentration were risk factors for coronary events, all cardiovascular events, and all cause mortality. Quetelet's body mass index was a risk factor for coronary events only.

The value of these logistic regressions, using all entry data including blood pressure, in identifying those individuals who would suffer any event was then assessed, using data for the placebo group. Risk scores were calculated, based on multiple logistic regressions; there was considerable overlap between scores for event and non-event groups. If 80% of people in the (relatively small) group who experienced a coronary event were to be correctly identified using entry data at least 38% of the (much larger) group who did not have a coronary event would have been incorrectly classified. Discrimination of people likely to develop stroke was even less precise, so that overall there is no method which would enable a doctor to give a useful prediction to an individual patient.

Discussion

In answer to the principal questions specified at the design stage these results provide clear evidence that active treatment was associated with a reduction in stroke rate in this mildly hypertensive population and show no clear overall effect on the incidence of coronary events. Active treatment had no evident effect on the overall all cause mortality, but there was a beneficial effect in men and an adverse effect in women. With this exception, there is no clear evidence that the effects of treatment differed in the two sexes.

The reduction in the stroke rate attributable to antihypertensive treatment both confirms and adds to the results of earlier national studies.[18] In this predominantly white population the reduction was shown in both sexes. Since the percentage reduction was not related to pressure level at entry, the finding seems to apply equally to the complete range of pressure studied. The result is, of course, specific to the trial population. Extrapolation from these results to pressures outside the range, or to older people, would need further evidence.

This reduction in stroke rate due to active treatment first became evident in 1983 ($p < 0.01$ on the sequential analysis), but the reduction in stroke rate had to be balanced against possible adverse effects of active treatment on other event rates, and since the overall mortality rates were no different in treated and placebo groups it was thought impossible to use the results as a basis for definitive recommendations about the management of mild hypertension, and the study was continued.

Comparison of the results for the individual active drugs is inextricably linked with what is perhaps the most interesting aspect of these analyses, the difference between results for non-smokers and for smokers.

Bendrofluazide, which reduced stroke rates in both non-smokers and smokers, was associated with a greater reduction in the stroke rate than was propranolol, which reduced the stroke rate in non-smokers only. Bendrofluazide was not associated with a reduction in the coronary event rate either in non-smokers or in smokers, but propranolol reduced this rate in non-smokers. Blood pressure control was also better in the bendrofluazide group (fig 1m, table IIm). The dose of bendrofluazide was fixed and, if this did not reduce pressure to target level within a specified period, supplementary therapy was immediately introduced. The results suggest that, for the groups overall, the simple regimen of a fixed dose proceeding automatically to the addition of supplementary therapy if necessary may have been more effective in achieving target pressure than the more complicated propranolol regimen, which necessitated increasing the dose before adding a supplementary drug. The diminished antihypertensive efficacy of propranolol in smokers when compared with non-smokers[19] presumably also contributed to this difference in pressure control.

The total picture, then, is that the incidence of stroke was reduced on active treatment with either drug but, whereas bendrofluazide was equally effective in smokers and in non-smokers, propranolol seemed to be relatively ineffective in smokers. For coronary events rates were unaffected by treatment overall, but within subgroups propranolol apparently reduced the coronary event rate in non-smokers though not in smokers. At one stage during the earlier part of the trial there was a trend towards an excess of fatal coronary events in men randomised to bendrofluazide, and concern about this suggestion of a serious drug adverse effect prompted the setting up of a substudy of the relationship between bendrofluazide and ventricular ectopic beats.[20] The numbers of events were small and no firm evidence of an association between bendrofluazide and coronary death has been established. The Multiple Risk Factor Intervention Trial Research Group also referred to the possibility, suggested by a subgroup analysis, that hypertensive men who had abnormal baseline electrocardiograms and were randomised to the active intervention group experienced an excess of fatal coronary events.[21] The authors did warn, however, that these data should not be overemphasised, and a statistical discussion of subgroup analyses subsequently stated that there were inadequate grounds for supposing that the intervention group had been harmed by the active regimen.[14] In the MRC trial the non-cardiovascular causes of death give no evidence that either drug altered the incidence of carcinoma, but numbers are small and the time which has elapsed since patients first took the drug is short. No other non-cardiovascular cause of death is clearly associated with either active drug. The overall all cause mortality rate was unaffected by treatment.

About one eighth of those randomised to the placebo group needed active treatment because their blood pressures rose above the limit considered permissible. Higher associated levels of morbidity and mortality might have been expected had the pressure in these people been allowed to rise further, but, because they form a selected group and because the effects of randomisation have been lost, it is not possible to arrive at valid comparative figures for event rates in this group.

There have been two other large trials which have a considerable bearing on the treatment of mild hypertension. The first is the Australian National Blood Pressure Study,[22] which has the greatest similarities with the MRC trial, since it was based on the comparison of actively treated and placebo groups of subjects, and the second is the US Hypertension Detection and Follow-up Program,[23] which was unlike the other two trials in that it compared a group of subjects treated with the greatest care to ensure compliance in a hospital clinic (stepped care) with a comparable group referred back to their own physicians for treatment (referred care).

In its design, therefore, the Australian trial is the one that first needs comparative assessment. The numbers included were much smaller and the decision to stop the trial was made after about 14 000 patient years of observation, which may be contrasted with the nearly 90 000 patient years of observation in the MRC trial. This is in part because the Australian trial was

stopped when the results were just of marginal statistical significance, so that the number of morbid events was quite small. Nevertheless, the main conclusion was that there was a reduction in the incidence of stroke in the treated group.

The Hypertension Detection and Follow up Program trial cannot be directly compared with either of these two trials, since it had a completely different design and compared one form of treatment with another without a placebo group. Its final conclusions were that in the more intensively treated group (stepped care) there was a reduction in both cardiovascular and non-cardiovascular mortality. This latter finding is different from that of the Australian and MRC trials. A further obvious difference is that the populations studied were dissimilar, not only in the number of blacks in the US trial but in the degree of cardiovascular morbidity in the populations studied. This is brought out by comparison of the mortality rates in the various trials. The Australian and MRC trials are very alike, but mortality from stroke was nearly three times greater among the appropriate part (stratum I) of the referred care group of the US trial than among the placebo group of the MRC trial, mortality from coronary heart disease over two times greater, and all cause mortality also nearly three times greater.[18] Various aspects of the US trial have received comment[24 25]; because of the quite different aims of the MRC and the US trials, and because they involved quite different types of medical care, it would be inappropriate to extrapolate from the Hypertension Detection and Follow up Program in considering what advice should be given to patients with mild hypertension in Britain.

Can advice be based on conclusions drawn from the present MRC trial?

Conclusions

The trial has shown that if 850 mildly hypertensive patients are given active antihypertensive drugs for one year about one stroke will be prevented. This is an important but an infrequent benefit. Its achievement subjected a substantial percentage of the patients to chronic side effects, mostly but not all minor. Treatment did not appear to save lives or substantially alter the overall risk of coronary heart disease. More than 95% of the control patients remained free of any cardiovascular event during the trial.

Neither of the two drug regimens had any clear overall advantage over the other. The diuretic was perhaps better than the β blocker in preventing stroke, but the β blocker may have prevented coronary events in non-smokers.

For all categories of events, and in both treated and placebo groups, rates were lower in non-smokers than in smokers, adding to previous evidence that starting smoking considerably increases the risk of cardiovascular disease. For stroke and also for all cardiovascular events the difference between rates in smokers and non-smokers was greater than the effect of drug treatment.

The working party thanks the general practitioners and nurses who joined the research framework and without whose efforts the trial would have been impossible; this framework was established by Dr W E Miall with the help of Mrs G R Barnes and maintained from 1983 onwards by Dr G Greenberg with the help of Mrs C W Browne; Professor H D Tunstall Pedoe for his work in arbitrating on the assessment of all terminating events; Professor T P Whitehead and Mr P M G Broughton and the staff of the Wolfson Research Laboratories, Queen Elizabeth Medical Centre, Birmingham, for carrying out the biochemical analyses; Duncan, Flockhart and Co Ltd for tablets of bendrofluazide and placebo; Imperial Chemical Industries Ltd for financial support and for tablets of propranolol and placebo; CIBA Laboratories for supplies of guanethidine; and Merck Sharp and Dohme Ltd for a mobile screening unit, funds for its staffing, and supplies of methyldopa.

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If you please to make experience of my Rules, they are very plain and easie enough; neither are they so many that they will burden your brain, nor so few that they will be insufficient for your necessity. If you make use of them, you will find your work easie, you need not call for the help of a Man Midwife, which is a disparagement, not only to your selves, but also to your Profession. And let me tell you this (and I'll tell you but the truth) to your knowledge, care and skill is committed, both the being, and well-being of Women in labor. The Creator of Heaven and Earth, the God of all the world, the great first being of all things, commits the life of every Child of his to your charge, even to the very first minute that he allots it to draw its breath, and at your hands will he have an account of it another day. Oh! What manner of woman ought a Midwife to be? With what knowledge, skill, care, industry and sincerity ought she to perform her office? Let every honest Woman that takes this charge upon her, take notice of it; and when she comes to deliver a Woman, let her know, that for that day or night's work she must another day give account before JEHOVAH, the Lord JESUS CHRIST, and all the ANGELS.

(Nicholas Culpeper (1616-54)
Directory for Midwives, 1671)