Antihypertensive therapy in patients above age 60 years. Eighth Interim Report of the European Working Party on High Blood Pressure in the Elderly (EWPHE)

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Summary

Seven hundred and ninety-two hypertensive patients above the age of 60 years have entered the double-blind multicentre trial of the European Working Party on High Blood Pressure in the Elderly (EWPHE). Half were treated with 1 capsule daily containing 25 mg hydrochlorothiazide and 50 mg triamterene and half were given placebo. If blood pressure control was not adequate in those receiving active treatment, a second capsule was given and, if necessary, up to 2 g methyldopa/day. No significant differences between the groups were present prior to randomization. A significant blood pressure difference of 20/8 mmHg was obtained between the groups and maintained during 5 years of follow-up. No major disturbances in serum potassium or serum sodium were noted. On the other hand, during the initial phase an increase in serum creatinine and serum uric acid was noted in the actively-treated group which was maintained during the later

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years. This increase in serum creatinine was related to the decrease in sitting systolic blood pressure. Also, changes in serum uric acid correlated with changes in serum creatinine both in the placebo and in the actively-treated group; the serum uric acid was on average 1 mg higher in the actively-treated than in the placebo-group. Fasting blood glucose did not change significantly in the placebo-treated group, but it did so in the active-treatment group. A favourable influence of active treatment on prognosis can be expected on the basis of the blood pressure reduction and in the absence of major electrolyte disturbances. However, the balance between this decreased risk and the increase produced by the rise in blood glucose and the other treatment effects remains to be determined. The trial continues and more patients are being admitted.

Key words: Hypertension — aged — antihypertensive agents — hydrochlorothiazide — triamterene — methyldopa

Introduction

Hypertension is a major risk factor for stroke[16] and coronary artery disease in both middle aged and elderly subjects.[11] An association between increased blood pressure and increased morbidity and mortality does not necessarily imply, however, that lowering the blood pressure with antihypertensive drugs will necessarily modify the risks in elderly subjects. Controlled trials of antihypertensive agents in elderly patients have not shown an increased mortality or morbidity associated with active treatment and have suggested either no difference[13,15,18] or some possible but not necessarily statistically significant benefits.[17,19-21]

In 1973, the European Working Party on High Blood Pressure in the Elderly (EWPHE) started to study the effects of antihypertensive drug therapy in the elderly using a protocol for a double-blind, multicentre trial.[8] Previous interim reports of the pilot trial,[4] the 2-year follow-up,[3] the 4-year follow-up,[2] 5-year follow-up,[9,10] glucose intolerance,[5] serum uric acid[6] and changes in renal and cardiac function[1] have been published.

The present paper reports changes in blood pressure and biochemical measurements observed up to January 1982. This report deals only with treatment effects that are not end-points for the study. Mortality and morbidity data will only be published on completion of the study.

Patients and methods

Study protocol

Elderly patients with high blood pressure are admitted to the study if they fulfil certain criteria. Before final admission of a patient, his or her initial record form is sent to the Co-ordinating Office after a run-in period on placebo capsules.

The positive (selection) criteria are as follows: (i) age of 60 years or more on admission into the study; (ii) sitting blood pressure (average of readings on three separate visits) on placebo during the run-in period within certain limits: 160 to 239 mmHg for systolic and 90 to 119 mmHg for diastolic blood pressure; and (iii)

the patients' willingness to co-operate and to be followed-up regularly (informed consent).

The negative (exclusion) criteria are as follows: (i) certain specific causes of blood pressure elevation, i.e. all patients with hyperthyroidism or phaeochromocytoma, coarctation of the aorta, Cushing's or Conn's syndrome, or renovascular hypertension who might be treated by surgery; (ii) certain complications of hypertension, i.e. hypertensive retinopathy Grade III or IV, congestive heart failure, enlarging aortic aneurysm, severe renal failure, past history of cerebral or subarachnoid haemorrhage; and (iii) certain other diseases, i.e. active hepatitis or active cirrhosis, life-threatening diseases, gout, etc.

The patients are stratified for each collaborating centre into one of eight categories according to age, sex, and the presence or absence of cardiovascular complications of their high blood pressure. After stratification, the patients are randomly allocated to an active-treatment or placebo-treatment group for the duration of the study. The corresponding drugs are sent to the different centres where the patient can be admitted into the study if he or she continues to fulfil the admission criteria. Treatment randomization is restricted so that, in each of the categories for a participating centre, approximately the same number of patients will receive active or placebo treatment (restricted randomization per centre and per category).

At first, all patients receive 1 capsule containing either 25 mg hydrochlorothiazide and 50 mg triamterene, or a matching placebo. The dosage may be increased, after not less than 2 weeks, to 2 capsules per day. If the blood pressure remains high after 1 month, alpha-methyldopa in the treated group or matching placebo in the placebo group can be added; first, half a tablet of 500 mg and later 1 tablet, increasing eventually to four 500 mg tablets daily. Both capsules and tablets are identical in shape, taste, and colour to their matching placebo.

All patients data are recorded and sent to the Co-ordinating Office every 3 months by using a short quarterly record form and annually by using a more detailed record form.

Statistical methods

A paired t-test was used for within-group changes and a standard unpaired t-test for comparison between the active and placebo groups.

Results

Patient characteristics on admission

By 1st January 1982, a total number of 792 patients had been admitted into the trial. Their characteristics are given in Table I. No significant differences between the active and placebo groups were found on admission and, therefore, both groups were comparable at the start of the trial.

The average age was 72 years (range 60 to 97 years). Only 30% of the patients were males. In the total study population, obesity was not a major problem, although the mean body weight was 66.8 kg for an average height of 1.59 m. The cardio-thoracic ratio averaged 52.3% which might be considered to be high in a

Table I. Patient characteristics on admission

Patients	Placebo group		Active-treatment group	
Total no. studied	398		394	
Age (years)	72.1±0.40		71.8±0.41	
Sex: Male	117		122	
Female	281		272	
Body weight (kg)	67.0±0.6 (n=391)		66.5±0.6 (n=388)	
Height (cm)	159±0.5 (n=381)		159±0.5 (n=376)	
Sitting blood pressure (mmHg):				
Systolic	183±0.8 (n=398)		183±0.9 (n=394)	
Diastolic (Phase 5)	101±0.4 (n=398)		101±0.4 (n=394)	
Sitting pulse rate (beats/min):	79.6±0.5 (n=383)		80.6±0.5 (n=385)	
	Right (n=395)	*Left* (n=395)	*Right* (n=388)	*Left* (n=388)
Eye fundus:				
Grade I	128	124	142	136
Grade II	160	164	151	153
Lens opacity	27	25	18	19
Normal	58	60	62	64
Unknown	22	22	15	16
Central nervous system disturbances present	69 (n=397)		70 (n=394)	

Note: values are given as the mean (±S.E.M.) for the number of patients in the two groups given in parentheses

middle-aged population but which is frequently present in the population over 60 years of age.[14]

The cause of hypertension was not determined in most patients (Table II) because, in most cases, investigations such as renal arteriography were not performed. Renal parenchymal disease was considered to be the cause in 56 (7%) and renovascular hypertension was suspected in 13 patients. In some patients, a probable primary diagnosis was made and additional possible diagnoses suggested. The total number of aetiological diagnoses therefore exceeds the number of patients in the study. No significant differences between the two treatments for functional or aetiological diagnoses were observed at randomization.

Drug intake

The drug intake in the actively treated group is given in Table III. The intake of diuretic was relatively constant over the total trial period. Only a few patients

Table II. Diagnosis on admission of the patients studied: number of patients

Diagnosis	Placebo group	Active-treatment group
Functional diagnosis of hypertension		
Hypertension with organ involvement	249	247
Hypertension with only left ventricular hypertrophy	70	66
Hypertension with myocardial infarction or angina pectoris	25	21
Hypertension with only central nervous system involvement	16	23
Hypertension with only renal involvement	6	9
Hypertension with eye fundus Grade III only	0	0
Hypertension with multiple organ involvement	32	28
Aetiological diagnosis of hypertension		
Essential	384	384
Renal parenchymal hypertension	30	26
Possible renovasacular hypertension	6	7
Other secondary causes	7	6

were taking methyldopa after 3 months but after 1 year almost one-third required this drug, in addition to the diuretic (methyldopa average dosage 254 mg daily).

Table III. Average drug intake (mg/day) in the active-treatment group: mean (±S.E.M.) values

Duration of treatment	No. patients*	Hydrochloro-thiazide	Triamterene	Methyldopa
After 3 months	331	34±0.7	68±1.4	45±11
After 1 year	264	38±0.8	75±1.7	254±28
After 2 years	191	38±0.9	75±1.9	322±40
After 3 years	121	37±1.2	74±2.4	326±52
After 4 years	82	40±1.4	79±2.9	369±65
After 5 years	36	40±2.1	81±4.1	354±93

*In this and the following tables, as well as in the corresponding Figures, the number of patients decreases over time, mainly because patients were admitted to the trial over several years

The presence or absence of thiazide, triamterene and methyldopa were analyzed in 24-hour urine samples from 157 patients. In the active treatment group 86% of the patients complied with the diuretic and 79% with the methyldopa; in the placebo group, diuretics were found in the urine of 2% and methyldopa also in 1% of the patients.

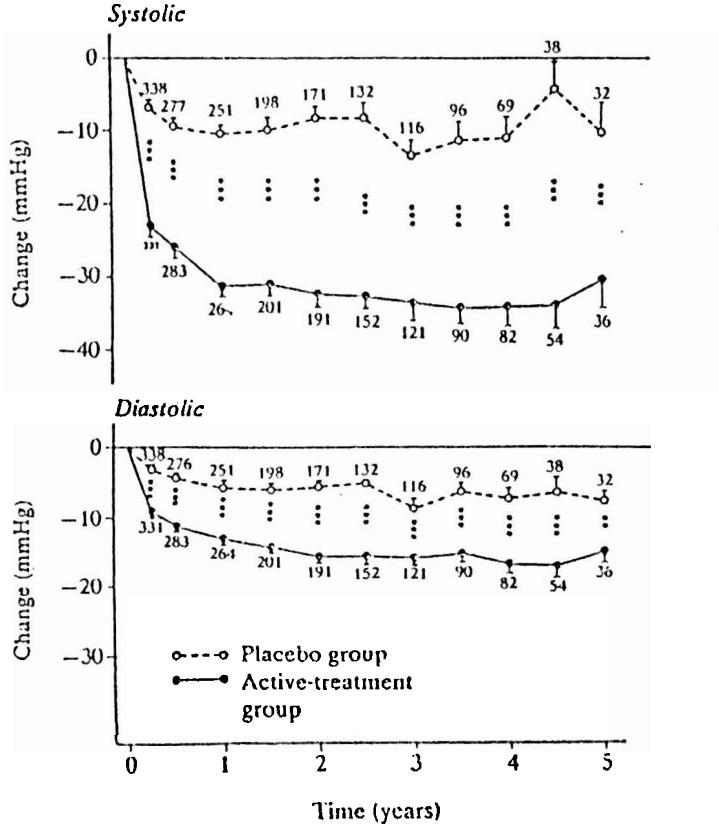
Blood pressure

The sitting systolic and diastolic (Phase 5) blood pressures before and during the study are shown in Table IV and Figure 1.

Table IV. Sitting systolic and diastolic blood pressure (mmHg): mean (±S.E.M.) values

Measurement	Placebo group			Active-treatment group			Probability of between-group differences	
	No. patients	Systolic	Diastolic	No. patients	Systolic	Diastolic	Systolic	Diastolic
During run-in period	398	183±0.8	101±0.4	394	183±0.9	101±0.4	p>0.1	p>0.1
After 3 months	338	175±1.2	97±0.6	331	160±1.1	92±0.6	p<0.001	p<0.001
After 1 year	251	172±1.4	95±0.7	264	151±1.0	88±0.6	p<0.001	p<0.001
After 2 years	171	172±1.8	96±0.9	191	150±1.1	85±0.7	p<0.001	p<0.001
After 3 years	116	166±2.0	92±1.1	121	147±1.4	86±0.9	p<0.001	p<0.001
After 4 years	69	168±2.8	93±1.3	82	147±2.0	86±1.1	p<0.001	p<0.001
After 5 years	32	165±4.0	94±2.0	36	148±3.6	85±1.8	p=0.002	p<0.001

Figure 1. Change in sitting systolic and diastolic blood pressure (mmHg) during the 5-year treatment period: mean (±S.E.M.) values



Note: figures refer to the number of patients studied at the end of each time period.
***p<0.001, **0.1>p>0.001

In the placebo group, both the systolic and diastolic blood pressures had fallen significantly ($p<0.001$) from the initial levels after 3 months in the trial, but subsequent changes were small and not significant. In the actively-treated group, the reduction in blood pressure during the first 3 months was 23/9 mmHg. During the first 3 months, the blood pressure reduction was significantly greater in the actively-treated group ($p<0.001$). After 3 months, the systolic and diastolic pressures continued to decrease in the actively-treated group, probably as a result of the addition of methyldopa. After 5 years, the average sitting blood pressure was 17/9 mmHg greater in the placebo-treated group than in the actively-treated group.

A minority of patients (9%) has been followed-up for 5 years and not all have been followed-up for 3 months.

Body weight

On admission, the body weight was similar in both groups (Table I); and at no time during the first 5 years was there a significant difference in body weight between the two groups.

Serum creatinine

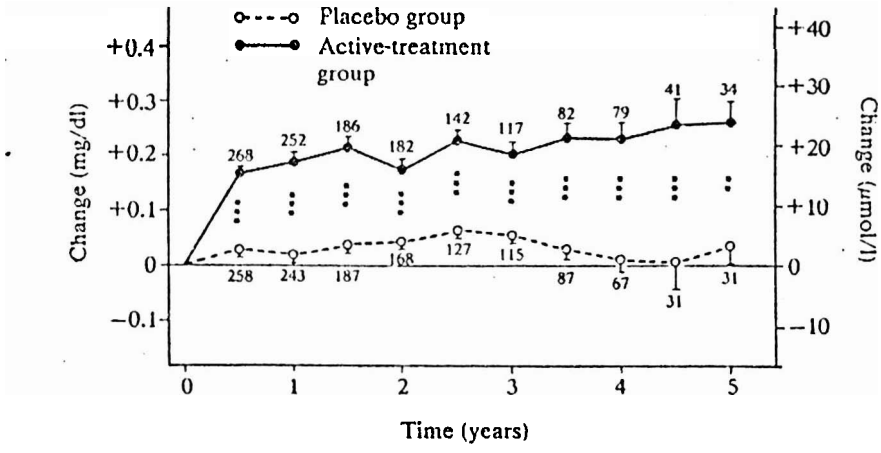
The serum creatinine levels (Table V and Figure 2) were similar in both groups on admission. In the placebo group, the serum creatinine increased slightly but significantly ($p=0.028$) during the first year and later changes were not significant. In the actively-treated group, the increase in serum creatinine was more marked and during the trial the serum creatinine was significantly higher in the actively-treated group than in the placebo group.

In the actively-treated group, changes in sitting blood pressure (both systolic and diastolic) over the first 3 months were correlated significantly with changes in serum creatinine (y). For systolic blood pressure (x), $y=0.087-0.0026\,x$, $n=318$, $r=0.21$, $p=0.00016$; for diastolic blood pressure (x), $y=0.12-0.0028\,x$, $n=318$, $r=0.11$, $p=0.04$. In the placebo group, these correlations were not significant.

Table V. Serum creatinine concentrations (mg/dl): mean (±S.E.M.) values

Measurement	Placebo group		Active-treatment group		Probability of between-group differences
	No. patients	Serum creatinine	No. patients	Serum creatinine	
During run-in period	396	1.02±0.02	390	1.02±0.03	$p>0.1$
After 3 months	321	1.03±0.02	321	1.15±0.02	$p<0.001$
After 1 year	244	1.03±0.02	254	1.17±0.02	$p<0.001$
After 2 years	169	1.00±0.02	184	1.13±0.03	$p<0.001$
After 3 years	115	1.00±0.03	119	1.17±0.04	$p<0.001$
After 4 years	67	0.99±0.04	80	1.17±0.05	$p=0.003$
After 5 years	31	0.97±0.05	35	1.25±0.06	$p<0.001$

Figure 2. Change in serum creatinine levels during the 5-year treatment period: mean (±S.E.M.) values



***p<0.001, **0.01>p>0.001

Serum uric acid

The serum uric acid level (Table VI and Figure 3) was not significantly different between both groups on admission (p=0.079).

Table VI. Serum uric acid concentrations (mg/dl): mean (±S.E.M.) values

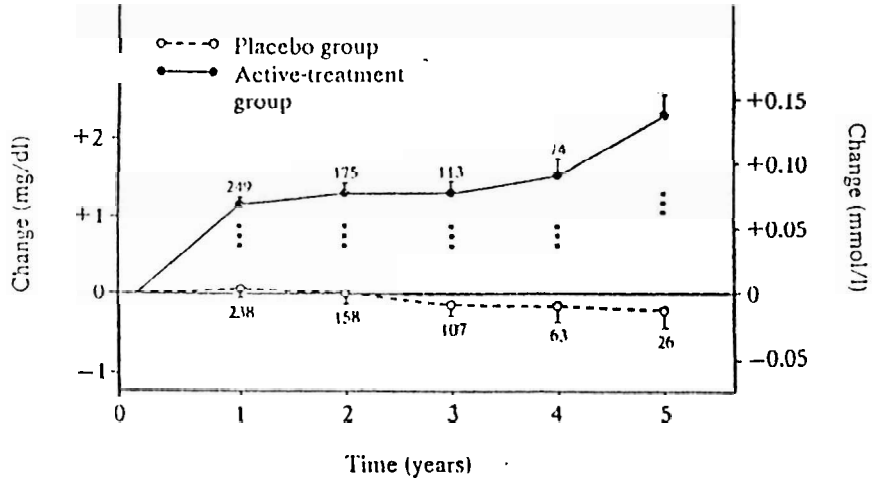
Measurement	Placebo group		Active-treatment group		Probability of between-group differences
	No. patients	Serum uric acid	No. patients	Serum uric acid	
During run-in period	386	5.50±0.07	386	5.33±0.07	p>0.05
After 1 year	245	5.53±0.10	254	6.48±0.11	p<0.001
After 2 years	163	5.44±0.11	176	6.55±0.13	p<0.001
After 3 years	111	5.40±0.12	114	6.57±0.16	p<0.001
After 4 years	64	5.42±0.19	74	6.67±0.22	p<0.001
After 5 years	26	5.21±0.28	27	7.54±0.24	p<0.001

In the placebo group, no significant increase was observed. In the actively-treated group, the serum uric acid increased by 1.18 mg/dl during the first year and remained elevated during the subsequent years. The change in the serum uric acid (y) within the first year was significantly correlated with change in the serum creatinine (x) according to the following equations. In the placebo-treated group, $y=0.003 + 1.39\ x$, $n=232$, $r=0.25$, $p=0.0001$; in the actively-treated group, $y=0.785 + 1.83\ x$, $n=239$, $r=0.315$, $p<0.00001$.

Serum potassium and sodium

The combination of a thiazide diuretic and a potassium-sparing agent produced only small changes in the serum potassium, but the small differences in the

Figure 3. Change in serum uric acid levels during the 5-year treatment period: mean (±S.E.M.) values



***p<0.001

serum potassium levels between the active and placebo-treated groups reached statistical significance (Table VII and Figure 4).

Table VII. Serum potassium concentrations (mmol/l): mean (±S.E.M.) values

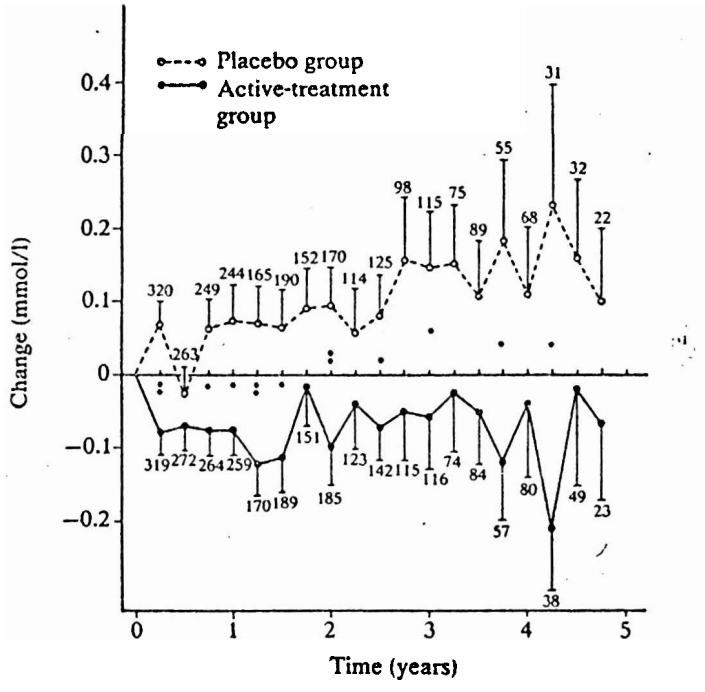
Measurement	Placebo group		Active-treatment group		Probability of between-group differences
	No. patients	Serum potassium	No. patients	Serum potassium	
During run-in period	394	4.22±0.02	393	4.16±0.02	p>0.1
After 3 months	320	4.22±0.02	319	4.09±0.03	p<0.001
After 1 year	244	4.25±0.03	259	4.09±0.03	p<0.001
After 2 years	170	4.24±0.03	185	4.05±0.04	p<0.001
After 3 years	115	4.30±0.04	116	4.07±0.05	p<0.001
After 4 years	66	4.32±0.06	80	4.07±0.06	p=0.003
After 5 years	32	4.35±0.06	36	4.05±0.10	p=0.01

The serum sodium concentrations were similar in both groups on admission and subsequent changes were small and not significant.

Blood glucose

The fasting blood glucose level did not change significantly in the placebo-treated group throughout the 5 years (Table VIII and Figure 5). In the actively-treated group, the mean blood glucose increased significantly in the first 2 years and this increase averaged 11.8 mg/dl after 3 years. The mean blood glucose remained high throughout the 5-year study period.

Figure 4. Change in serum potassium levels during the 5-year treatment period: mean (±S.E.M.) values



**0.01>p>0.001, *0.05>p>0.01

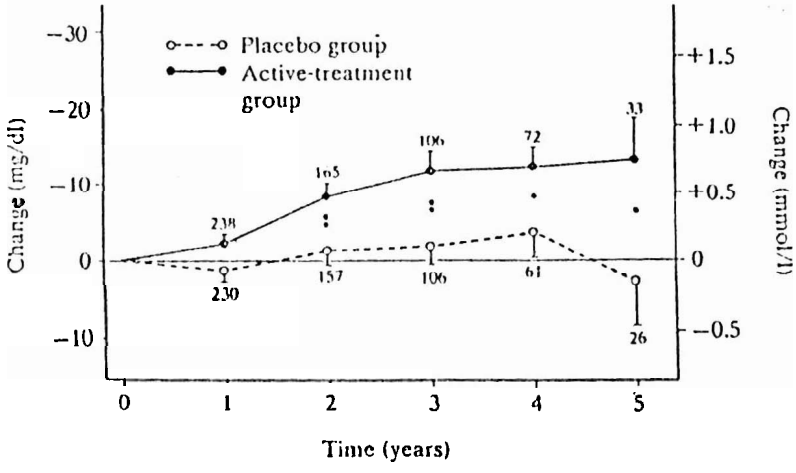
Table VIII. Fasting blood glucose concentrations (mg/dl): mean (±S.E.M.) values

Measurement	Placebo group		Active-treatment group		Probability of between-group differences
	No. patients	Blood glucose	No. patients	Blood glucose	
During run-in period	382	92.0±1.1	373	92.7±1.3	p>0.1
After 1 year	234	89.9±1.1	250	92.5±1.4	p>0.1
After 2 years	163	91.8±1.3	178	97.0±2.1	p=0.041
After 3 years	109	92.1±1.5	112	98.6±2.9	p=0.045
After 4 years	64	94.7±2.5	76	96.3±2.8	p>0.1
After 5 years	28	91.0±2.4	34	100.5±4.4	p>0.05

Serum cholesterol

The serum cholesterol level was similar during the run-in period in both groups: 246 mg/dl (Table IX). It decreased in the placebo group over time and a similar trend was seen in the active-treatment group. Thus, apparently the thiazide-methyldopa treatment did not alter the spontaneous decrease in serum cholesterol which seems to occur at that age.[7]

Figure 5. Change in fasting blood glucose levels during the 5-year treatment period: mean (±S.E.M.) values



**0.01>p>0.001, *0.05>p>0.01

Table IX. Serum cholesterol concentrations (mg/dl): mean (±S.E.M.) values

Measurement	Placebo group		Active-treatment group		Probability of between-group differences
	No. patients	Serum cholesterol	No. patients	Serum cholesterol	
During run-in period	389	247±3	387	246±3	p>0.1
After 1 year	241	244±3	252	249±3	p>0.1
After 2 years	165	242±4	182	242±4	p>0.1
After 3 years	114	238±4	116	232±5	p>0.1

Discussion

The ultimate aim of antihypertensive therapy is to reduce mortality and morbidity while maintaining the quality of life. The purpose of the present multicentre trial is to evaluate this aim, but a definite answer cannot yet be given since it was decided in the study protocol that: (i) these data should not be communicated during the course of the trial, and (ii) the trial should be terminated when significant results are found. The rules for stopping the trial have been agreed on. The pilot trial[4] has already shown, however, that initiation of hypotensive therapy can produce a slow, progressive reduction in pressure without an excess of terminating events in the actively-treated group as compared with the placebo group.

A blood pressure difference of about 20/8 mmHg between the two groups was maintained during the 5 years of observation. In the actively-treated group, the diastolic blood pressure was maintained in the normal range of around 85 mmHg against 95 mmHg in the placebo group. The systolic blood pressure was main-

tained around 170 mmHg in the active-treatment group and around 150 mmHg in the placebo group. According to Kannel *et al.*,[16] for each 10 mmHg increase in systolic blood pressure the risk of an atherothrombotic brain infarction increases about 30 percent. Therefore, the present trial might be expected to detect a difference in stroke incidence. However, it is not clearly established how long such a difference in blood pressure has to be maintained or whether a reduction in pressure from a previously high level has the same beneficial effect as that calculated from observed casual blood pressure differences in epidemiological studies not involving intervention.

The serum creatinine increased during the first 3 months of active treatment (Table V and Figure 2), and thereafter the creatinine concentration in the active-treatment group exceeded that of the placebo group. This increase in serum creatinine was associated with the hypotensive effect, due either to a non-specific effect of blood pressure reduction leading to a decrease in glomerular filtration rate or to a direct effect of diuretics on renal secretory function.

In the placebo group there was little change in the serum creatinine concentration (Figure 2) or the serum uric acid level (Figure 4). On the contrary, in the active-treatment group, the serum uric acid level was increased by 1 mg/dl even when the serum creatinine concentration remained constant. When the serum creatinine level increased or decreased, a parallel change in uric acid level was observed, the uric acid level being maintained at a level 1 mg/dl higher in the active-treatment group than in the placebo group. As previously reported, the change in serum uric acid level with diuretic treatment does not only reflect the changes in serum creatinine level.[12]

With the drugs used in the present trial, the reduction in pressure was maintained without major disturbances in the serum potassium level. Although the serum sodium decreased slightly during the first months, the average concentration was maintained at a normal level thereafter.

Glucose intolerance is also a major risk factor for coronary artery disease. In this study, the thiazide diuretics did enhance this risk factor. Therefore, the balance between the possible increased risk related to an increase in blood glucose and a presumed decreased risk associated with blood pressure reduction remains to be determined. The overall result of this trial should provide this information.

Conclusions

The Steering Committee (C. Dollery, J. V. Joossens, T. Strasser and the co-ordinators A. Amery and A. De Schaepdryver) has reviewed the present data and also all the terminating and non-terminating events reported in the Co-ordinating Office by the different collaborating centres up to 1st January 1982. This group decided that the study should continue without any change to the protocol. The patients already in the study should continue and new patients should be recruited. The group also considered the ethical aspects and concluded that it is ethical to continue the trial; they felt that it would be inappropriate to stop the trial and that

it might be unethical to discontinue it at this stage. The study should end in December 1987 unless it crosses a pre-set ending point before that date; therefore yearly evaluations will continue.

These recommendations were accepted by the members of the EWPHE and the trial is therefore continuing.

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