Antihypertensive Therapy in Patients Above Age 60

Fifth interim report of the European Working Party on High blood pressure in the Elderly (EWPHE)

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1. Five hundred and sixty three hypertensive patients above the age of 60 have entered the double-blind multicentre trial of the European Working Party on High blood pressure in Elderly (EWPHE). Half were treated with one 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 of methyldopa/day.

2. No significant differences between the groups were present prior to randomization. A significant blood pressure difference of 25/10 mm Hg was obtained between the groups and maintained during five years of follow-up. No major disturbances in serum potassium or serum sodium were noted.

3. 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 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, but were independent of the change in creatinine; the serum uric acid was on average 1 mg higher in the actively treated than in the placebo group.

4. Fasting blood glucose did not change significantly in the placebo treated group, but it did so in the active treatment group.

5. A favourable influence on prognosis by active treatment can be expected on the basis of the blood pressure reduction and in the absence of major electrolytes 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.

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INTRODUCTION

High blood pressure is a major risk factor for stroke[1] and coronary heart disease both for middle age subjects, and persons over the age of 60.[2] However, the presence of a relationship between increased pressure and increased morbidity and mortality does not necessarily imply that the latter will be diminished by decreasing the arterial pressure using hypotensive agents. Attempts have been made to study the outcome of elderly hypertensive patients treated with or without hypotensive agents.

Controlled trials with hypotensive agents in these patients failed to reveal an increased mortality or morbidity with active treatment and suggested either no difference[3, 4] or some possible, but not statistically significant, benefit.[5, 6, 7]

Because of this uncertainty, the European Working Party on High blood pressure in Elderly (EWPHE) started to study this problem using a protocol[8] for a double-blind multicentre trial. Previous interim reports dealing with the pilot trial,[9] the two years follow-up,[10] the four years follow-up,[11] glucose intolerance[12] and serum uric acid[13] have been published.

The present paper reports changes in blood pressure and biochemical measurements observed up to March 1979 for a 5 years follow up. This paper only deals with treatments effects, which are not end-points for the study. Mortality and stroke morbidity are deliberately omitted since the trial is continuing in all the centres and interim results are known only to the co-ordinating office.

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 initial record form is sent to the co-ordinating office after he has been followed for a run-in period on placebo capsules.

The *positive (selection) criteria* are as follows: (1) age of 60 years or more on admission into the study; (2) sitting blood pressure (average of readings on three separate visits) on placebo during the run-in period within certain limits: 160-239 mm Hg for systolic and 90-119 mm Hg (90-114 mm Hg diastolic in one centre) for diastolic blood pressure, and (3) the patients' willingness to co-operate and to be followed-up regularly (informed consent).

The *negative (exclusion) criteria* are as follows: (1) certain specific causes of blood pressure elevation: all patients with hyperthyroidism or phaeochromocytoma, coarctation of the aorta, Cushing's or Conn's syndrome, or renovascular hypertension who may be treated by surgery; (2) certain complications of hypertension: hypertensive retinopathy grade III or IV, congestive heart failure, enlarging aortic aneurysm, severe renal failure *(serum creatinine above 2.4 mg%)*, past history of cerebral or subarachnoid haemorrhage, and (3) certain other diseases: active hepatitis or active cirrhosis, life-threatening diseases, gout.

The patients are *stratified* for each collaborating centre into 1 of 8 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- or placebo-treated 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 (s)he 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 one capsule containing either 25 mg of hydrochlorothiazide and 50 mg of triamterene, or a matching placebo. The dosage may be increased, after not less than 2 weeks, to two capsules per day.

If the blood pressure remains high after 1 month, alphamethyldopa or a matching placebo can be added; first half a tablet of 500 mg and later one 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 may end the study for one of the following reasons: (1) by completion of 7 years' observation; (2) by being lost to follow-up; (3) by interruption of all study treatment for more than 3 months, or (4) by the following study terminating events: (a) death; (b) cerebral or subarachnoid haemorrhage; (c) papilloedema, retinal haemorrhage or retinal exudates; (d) enlarging or dissecting aortic aneurysm; (e) congestive heart failure requiring diuretics or antihypertensive drugs; (f) hypertensive encephalopathy; (g) increase in left ventricular hypertrophy (certain radiographic and electrocardiographic definitions); (h) rise in blood pressure exceeding certain defined limits; and (i) angina requiring long-term adrenergic beta receptor blocking drugs.

Specific non-terminating events are also recorded, such as myocardial infarction, and at certain centres measurements are being made of symptomatic well-being (quality of life), plasma catecholamines and renin levels.

The study lasts up to 7 years per patient; the data are recorded and sent to the co-ordinating office every 3 months by using a short quarterly record form, yearly by using a more detailed annual 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

A. *Characteristics on admission*

In March 1979, a total number of 563 patients have been admitted into the trial.

Their characteristics are given in the tables.

Both groups are comparable at the start of the trial: the average was 72 (Table 1) and patients up to 97 years of age were admitted into the trial.

TABLE 1
SOME PATIENT CHARACTERISTICS ON ADMISSION

	Placebo	Active
— Total number (n)	280	283
— Age (in years)	72 ± 0.5	72 ± 0.5
— Sex: male (n)	89	92
female (n)	191	191
— Body weight (in kg)	67.3 ± 0.8	66.9 ± 0.8
— Height (in cm)	159 ± 0.6	158 ± 0.6
— Recumbent blood pressure (in mmHg)		
— systolic	182 ± 1.1	183 ± 1.1
— diastolic (ph 5)	100 ± 0.5	100 ± 0.6
— Recumbent pulse rate (in beats/min)	78 ± 0.7	78 ± 0.6
— Eye fundus		
- grade I (n)	91	98
- grade II (n)	110	106
- lens opacity (n)	20	13
- normal (n)	43	53
- unknown (n)	16	13
— Central nervous system disturbances present (n)	52	49

In this and the following tables the mean ± standard error of the mean are given.

Only one in three of the patients were males. Obesity was not a major problem since their mean body weight was 67 kg for an average height of 1.59 m. The cardiothoracic ratio averaged 52.2%, which could be considered as high in a middle aged population, but normal in a population over age 60.[14]

The cause of the hypertension was not determined in the majority of cases, since in most patients investigations such as a renal arteriogram were not performed (Table 2). Renal parenchymal disease was considered as the cause in about one out of ten cases. In some cases, a probable aetiological diagnosis was made and an additional possible diagnosis suggested.

B. *Drug intake*

The drug intake in the actively treated patients is given in Table 3. The intake of the diuretic was relatively constant over the total trial period; only a few patients were taking methyldopa after 3 months, while after one to five years the methyldopa intake averaged around 300 mg daily.

TABLE 2
DIAGNOSIS ON ADMISSION

	Placebo	Active
— Functional diagnosis of hypertension		
- hypertension		
(a) without organ involvement	178	184
(b) with only left ventricular hypertrophy	45	46
(c) with myocardial infarction or angina pectoris	16	13
(d) with only central nervous system involvement	10	13
(e) with only renal involvement	6	7
(f) with eye fundus grade III only	0	0
(g) with multiple organ involvement	25	20
— Aetiological diagnosis of hypertension		
- essential	268	273
- renal parenchymal	21	17
- possible renovascular	1	1
- other secondary causes	6	4

TABLE 3
AVERAGE DRUG INTAKE IN THE ACTIVE TREATMENT GROUP
(in mg)

	Hydrochlorothiazide	** Triamterene	*** Methyldopa
After 1 year	39 ± 1.1	77 ± 2.2	275 ± 40
After 5 years	41 ± 4.6	81 ± 9.2	468 ± 269

hydrochlorothiazide — Dichlotride, Esidrex
** triamterene — Dytac
*** methyldopa — Aldomet

C. Blood pressure

The changes in sitting systolic and diastolic (phase 5) blood pressure are illustrated in Table 4.

In the placebo group, both the systolic and diastolic blood pressure fell significantly ($p<0.001$) between the initial measurement and the measurement after 3 months; subsequent changes in pressure were small.

In the actively treated group, the fall in blood pressure during the first three months was 24/10 mm Hg and at 3 months the fall in blood pressure was significantly larger in the actively treated group; this difference was mainly due to the administration of the diuretic.

After 3 months the systolic and diastolic blood pressures continue to decrease in the actively treated group probably as a consequence of the administration of methyldopa.

At 5 years, the average sitting blood pressure was 26/17 mm Hg higher in the placebo group than in the actively treated group.

TABLE 4
SITTING BLOOD PRESSURE (in mm Hg)

	Placebo	Active
During run-in period	182 ± 1.0	183 ± 1.0
	101 ± 0.5 (280)	101 ± 0.5 (283)
After 1 year	171 ± 2.1	150 ± 1.4***
	95 ± 1.0 (133)	88 ± 0.9*** (143)
After 3 years	163 ± 3.5	143 ± 2.7***
	90 ± 2.3 (37)	83 ± 1.5* (38)
After 5 years	172 ± 13.1	146 ± 5.7
	99 ± 7.5 (7)	82 ± 3.0 (8)

Note: Numbers in brackets denote patient numbers. The far smaller numbers of one year and subsequently is due to continuing enrolment and follow-up as well as from loss of defaulters.

* $p < 0.05$
** $p < 0.01$ otherwise no statistically significant difference
*** $p < 0.001$

Not all patients have been followed for five years or eve for three months. Figure 1 gives the sitting pressures as percentage of the pressure of each patient on admissior

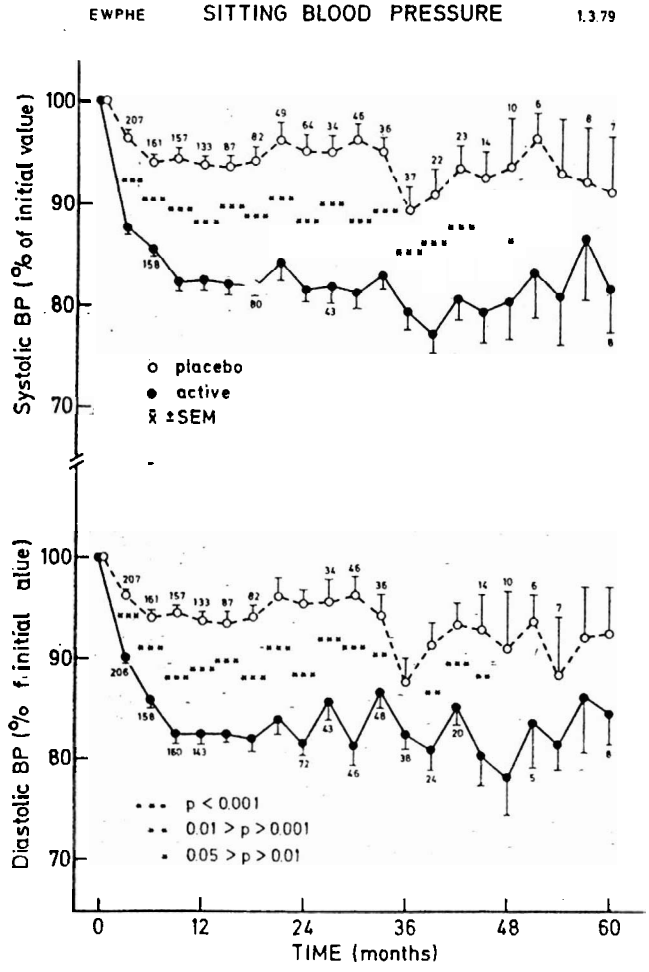

Figure 1

D. Body Weight

At no time was there a significant difference in bod weight between the two groups.

E. Serum creatinine and uric acid

Serum creatinine levels (Table 5) were similar in both groups on admission. In the placebo group, serum creatinine rose slightly but significantly during the first year, but later changes were not significant. In the active treatment group, the increase in serum creatinine was even more pronounced during the first three months; thus, during the trial serum creatinine was significantly higher in the actively-treated group.

The increase in serum creatinine was related to the hypotensive effect in the actively treated group.

The decrease of sitting blood pressure in the first three months correlated significantly with the increase in serum creatinine in this period. In the placebo group, there was no significant correlation.

The serum uric acid level (Table 5) was slightly different in the groups on admission. In the placebo group a slightly higher level was observed. In the active treatment group serum uric acid increased by 30% during the first year and remained high during the subsequent years. The changes in serum uric acid within the first year were significantly correlated with the changes in serum creatinine both in the placebo group and in the actively treated group.

After 1 year the serum uric acid was about 1 mg% higher in the actively treated than in the placebo groups.

F. Serum potassium and sodium

The combination of a thiazide diuretic and a potassium sparing agent provoked only small changes in serum potassium (Table 5).

However, since the potassium level tended to increase in the placebo group and to decrease in the actively treated group, this small difference in serum potassium level did, on occasions, reach statistical significance.

The serum sodium concentrations were similar in both groups on admission and subsequent changes were small.

G. Blood glucose

As reported elsewhere,[12] the fasting blood glucose level did not change significantly in the placebo treated group during the first years, but rose significantly in the actively treated group (Figure 2).

TABLE 5
BIOCHEMICAL PARAMETERS OF PATIENTS

	Placebo	Active
Serum creatinine (mg%)		
— During run-in period	1.02 ± 0.02 (279)	1.01 ± 0.02 (280)
— After 1 year	1.05 ± 0.03 (130)	1.22 ± 0.03*** (134)
— After 3 years	1.03 ± 0.07 (36)	1.29 ± 0.09* (38)
— After 5 years	1.10 ± 0.14 (7)	1.35 ± 0.15 (8)
Serum uric acid (mg%)		
— During run-in period	5.60 ± 0.08 (270)	5.33 ± 0.08* (278)
— After 1 year	5.59 ± 0.13 (131)	6.77 ± 0.15*** (137)
— After 3 years	5.58 ± 0.22 (35)	6.91 ± 0.30 (37)
— After 5 years	5.74 ± 0.68 (7)	7.56 ± 0.56 (7)
Serum Potassium (mEq L)		
— During run-in period	4.22 ± 0.03 (278)	4.17 ± 0.03 (282)
— After 1 year	4.25 ± 0.04 (130)	4.08 ± 0.04** (138)
— After 3 years	4.21 ± 0.07 (37)	4.01 ± 0.08 (36)
— After 5 years	4.39 ± 0.15 (7)	4.14 ± 0.14 (8)

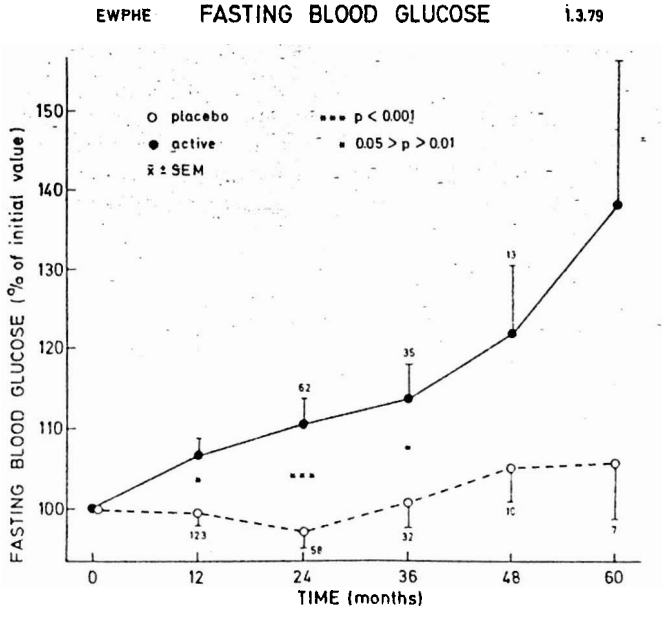

Figure 2

DISCUSSION AND CONCLUSIONS

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 with diuretic ± methyldopa treatment in an elderly population.

A definite answer cannot yet be given since it was decided in the study protocol (a) that these data should not be communicated during the course of the trial, and (b) that the latter should be terminated when significant results are found. The rules for stopping the trial have been agreed.

The pilot trial[9] has already shown, however, that initiation of hypotensive therapy can produce a slow progressive fall in pressure without an excess of terminating events in the actively treated group as compared with the placebo group.

A blood pressure difference of 25/10 mm Hg between the two groups was maintained during the 5 years (Table 4).

In the actively treated group, the diastolic blood pressure was maintained in the normal range of around 85 mm Hg against 95 mm Hg in the placebo group. According to Kannel et al.[1] for each 10 mm increase in systolic blood pressure the risk of an atherothrombotic brain infarction increases by about 30%. Therefore, the present trial may 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 of 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.

On the other hand, glucose intolerance is also a major risk factor for coronary artery disease and the thiazide diuretics did enhance this risk factor.

Therefore, the balance between an increased risk of the rise in blood glucose and the decreased risk brought about by blood pressure reduction remains to be determined.

The overall result of the EWPHE trial should provide this information.

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

Serum creatinine rose during the first 3 months of active treatment (Table 5), 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 where there was no alteration in serum creatinine concentration, the serum uric acid level also remained unchanged. On the contrary, in the active treatment group the serum uric acid level was increased by 1 mg% 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 % higher in the active treatment than in the placebo group. As previously reported, the change in serum acid level with diuretic treatment does not only reflect the changes in serum creatinine level[15].

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EDITORIAL SUMMARY TABLE

TREATMENT OF HYPERTENSION IN THE ELDERLY

(a) Number in groups: Treated 283, Placebo 280.
Age: 72 years. Sex: F/M = 2:1
Recumbent BP: 183/100 mm Hg
Eye Fundus: 2/3 had grade I or II changes

(b) About 2/3 had no organ involvement.
Nearly 1/5 had Left Ventricular Hypertrophy only.
While 1/10 had multiple organ involvement.
90% Essential Hypertensives, 7% with renal parenchymal disease.

(c) Drug intake in Active Treatment group (mg per day)

At 5 years:	
hydrochlorothiazide	41
triamterene	81
methyldopa	468

(d) BP Levels Achieved (mm Hg)

	RUN-IN	1 YR	3 YRS	5 YRS
Placebo	182/101	171/95	163/90	172/99
Active	183/101	150***/88***	143***/83*	146/82

(e) Biochemical Changes:

	Serum Creatinine (mg%)		Serum Uric Acid (mg%)		Serum Potassium (mEq/L)	
	Placebo	Active	Placebo	Active	Placebo	Active
RUN-IN	1.02	1.01	5.60	5.33	4.22	4.17
3 YRS	1.03	1.29*	5.58	6.91	4.21	4.01

Asterisks indicate significant difference between initial levels and those achieved on active treatment.
* $p<0.05$ (significant)
*** $p<0.001$ (highly significant)