

ANTIHYPERTENSIVE THERAPY IN PATIENTS ABOVE AGE 60 WITH
SYSTOLIC HYPERTENSION

A progress report* of the European Working Party on
High blood pressure in the Elderly (EWPHE)

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ABSTRACT

1. Although systolic blood pressure elevation is responsible for increased incidence of cardiovascular accidents in old people, the preventive benefit of lowering systolic hypertension in elderly has not been confirmed.
2. A double blind study comparing the effects of a placebo and of an active regimen (hydrochlorothiazide-triamterene with or without methyldopa) in people over 60 years with isolated systolic hypertension has been undertaken by the European Working Party on High blood pressure in the Elderly (EWPHE).
3. The actively treated group shows a lowered sitting blood pressure (-15/6 mm Hg), a mild increase of serum creatine, serum uric acid and blood glucose and a mild decrease of serum potassium after two years of treatment when compared to the spontaneous changes observed in the placebo treated group.

4. The study is continuing to evaluate if the blood pressure reduction prevents or reduces the incidence of cardiovascular accidents, although some biochemical changes were provoked by the treatment.

INTRODUCTION

It has been shown that the distribution of blood pressure values has a unimodal Gaussian distribution (16) and that systolic and diastolic blood pressure values increase progressively with age up to 60 years. If we assume, as suggested by the WHO (9), the value of 160/95 mm Hg as the upper limit of normal blood pressure, a significant number of people over 60 years can be classified as hypertensive patients. Many studies have shown that the incidence of cerebrovascular (hemorrhage, thrombosis), cardiac (angina pectoris, myocardial infarction, cardiac failure) and renovascular (nephro-angiosclerosis) diseases is directly correlated with the severity of blood pressure elevation. According to Kannel et al. (14) there is an increase of the atherothrombotic brain infarction of about 30% for each 10 mm Hg rise of systolic blood pressure.

On the contrary it is still controversial if the blood pressure reduction can prevent these cardiovascular complications. Indeed the problem is very complex and the results may be very different according to the parameters examined. Hoobler et al. (10) found no significant benefit of antihypertensive treatment in the recurrence of cerebrovascular strokes in hypertensive patients when compared to placebo treated patients (with exception of decreased incidence of cardiac failure).

While there has been no doubt on the advantages of treating patients with more severe hypertension (19), only recently some studies have shown the usefulness of

treatment in mild and moderate forms of arterial hypertension (11-13).

However, the practitioners find it often more difficult to accept the idea of antihypertensive treatment in elderly than in younger patients. This might perhaps be due to the very important side effects of the first available antihypertensive drugs as mecamlamine, exametonium, pentolinium etc. with their orthostatic hypotension; also in the past the systolic high blood pressure was not considered so dangerous as the diastolic blood pressure elevation. More recently it has been recognized that the systolic blood pressure elevation "per se" is a major risk factor for cardiovascular disease. Furthermore, the discovery of new antihypertensive drugs as diuretics, alphas-methyldopa, clonidine, etc. has allowed to achieve a better control of blood pressure without important side effects.

Controlled trials with these hypotensive agents in elderly patients have so far revealed no increased mortality nor morbidity with the active treatment and suggested either no difference or even some possible benefit. A recent paper of the Hypertension Detection and Follow-up Program (HDFP) (11,12) showed a decrease (-17%) in mortality of hypertensive patients treated with stepped care when compared to the regular care group both in the total population and in the subgroup of patients between 60 and 69 years, although the blood pressure reduction was only 5 mm Hg greater in the stepped care group. The simultaneous improvement of non-cardiovascular deaths in the stepped care group, casts some doubts on the hypotensive reduction as the only cause of mortality decrease. Also in the Australian therapeutic trial in mild hypertension 582 subjects

were between 60 and 69 years at entry and a separate analysis of this subgroup showed a 39% reduction in trial end-points in the active treatment group compared to the placebo group (17).

In a recent double blind placebo controlled trial in 91 elderly patients with mild hypertension, Kuramoto et al. (15) found no difference between the active treatment and control group in total mortality (7 in each group), cardiovascular mortality (3 in each group) and a non-significant decrease in non-fatal cerebrovascular events (1 versus 3) or congestive heart failure (0 versus 3). Combining the fatal and non-fatal cardiovascular events no significant difference was found between both groups (4 versus 9); adding the patients, all belonging to the placebo group, who were excluded because of a blood pressure rise exceeding 200/100 mm Hg ($n = 9$), the total number of cardiovascular events was significantly ($p < 0.01$) decreased in the active treatment group (4 versus 19).

Also Sprackling et al. (18) found no significant difference in total mortality and non-fatal cardiovascular events in an open trial where elderly hypertensive patients have been randomly allocated to methyl-dopa treatment and to a regimen without hypotensive drugs.

In all the major trials the patients were selected on the basis of certain diastolic levels: up to now no results are available of large controlled trials on the influence of antihypertensive therapy on morbidity and mortality in patients with isolated systolic blood pressure elevation.

In 1973 the European Working Party on High blood pressure in the Elderly (EWPHE) started to study the influence of antihypertensive therapy on cardiovascular

prognosis in elderly hypertensive patients using a protocol for a double blind multicentre trial. Previous interim reports dealing with the pilot trial, the two-years follow-up, the four-years follow-up, the glucose intolerance, the uric acid levels and changes in renal and cardiac function during the placebo and active drug treatment in patients above age sixty have been already published (1-8).

In the present paper are reported the blood pressure and biochemical changes observed during a 2-years follow-up in a special group of elderly hypertensive patients, namely those with isolated systolic blood pressure elevation, as defined by a diastolic blood pressure below 95 mm Hg and a systolic blood pressure of 160 mm Hg or more. The patients were randomly divided in two subgroups: one was treated with active drug (diuretics with or without methyldopa), while the other received a placebo. Mortality and morbidity are deliberately omitted since the trial is continuing in all the centers.

RESULTS

A. Characteristics on Admission

On January 1, 1980, a total number of 650 patients have been admitted into the EWPHE trial; 132 of these had a sitting diastolic blood pressure between 90 and 94 mm Hg at entry. They will be the subject of the present report. Their characteristics are given in the table 1. No significant differences between the two treatment groups were found on admission and therefore both groups are comparable at the start of the trial.

The average age was 72.9 years (table 1) and patients up to 93 years of age were admitted into the

TABLE 1^o

Some Characteristics on Admission

	Placebo	Active	Probability of between group differences
- Total number (n)	58	74	p > 0.1 for all items
- Age (in years)	73.3 \pm 1.1	72.5 \pm 0.9	
- Sex: male (n)	14	16	
female (n)	44	58	
- Body weight (in kg)	65.6 \pm 1.5	65.3 \pm 1.2	
- Height (in cm)	159 \pm 1.1	158 \pm 0.9	
- Recumbent blood pressure (in mm Hg)	180 \pm 2.7 <hr/> 91 \pm 0.9	181 \pm 2.1 <hr/> 92 \pm 0.6	
- Recumbent pulse rate (in beats/min)	75 \pm 1.3	79 \pm 1.1	
- Eye fundus			
- grade I (n)	11	26	
- grade II (n)	28	32	
- lens opacity (n)	2	2	
- normal (n)	11	8	
- unknown (n)	6	6	

trial. Only 23% of the patients were males. Obesity was not a major problem in these patients, since their mean body weight was 65 kg for an average height of 1.58 m. The cardio-thoracic ratio averaged 52%, which could be considered as high in a middle aged population, but is frequently seen in a population over age 60.

The cause of the hypertension was not fully studied in the majority of cases, since in most patients inves-

tigations such as a renal arteriogram were not performed (table 2). Renal parenchymal disease was considered as the cause in about 8%. Renovascular hypertension was suspected in 4 patients. In some cases, a probable diagnosis was made and an additional possible diagnosis suggested. The total number of etiological diagnoses therefore exceeds the number of patients entered.

B. Drug Intake

The drug intake in the actively treated patients is given in table 3. The daily intake of hydrochlorothiazide averaged 35 mg over the total trial period; only a few patients were taking methyldopa after 3 months, while from one year on the methyldopa intake averaged 226 mg daily.

C. Blood Pressure

The changes in sitting systolic and diastolic (phase 5) blood pressure are given in table 4 and in figure 1.

In the placebo group, both the systolic and diastolic blood pressure fell slightly during the first year and continued to decrease during the second year. In the actively treated group the fall in blood pressure during the first three months was 20/7 mm Hg. After 3 months the systolic and diastolic blood pressures continued to decrease in the actively treated group probably as a consequence of the administration of methyldopa. At 2 years the average sitting blood pressure was 16/8 mm Hg higher in the placebo treated group than in the actively treated group.

A minority of patients have been followed for two years and not all have been followed for three months.

TABLE 2^o
Diagnosis on Admission

	Placebo	Active	Probability of between group differences
Functional diagnosis of hypertension			p > 0.1 for all items
- hypertension without organ involvement (n)	35	51	
- hypertension with only left ventricular hyper hypertrophy (n)	10	12	
- hypertension with myo- cardial infarction or angina pectoris (n)	3	4	
- hypertension with only central nervous system involvement (n)	4	3	
- hypertension with only renal involvement (n)	0	0	
- hypertension with eye fundus grade III only (n)	0	0	
- hypertension with mul- tiple organ involvement (n)	6	4	
Etiological diagnosis of hypertension			
- essential (n)	55	71	
- renal parenchymal hypertension (n)	2	5	
- possible renovascular hypertension	1	3	
- other secondary causes (n)	1	2	

TABLE 3^o
Average drug intake in the active treatment
group (in mg)

	Hydrochloro- thiazide	Triamterene	Methyldopa
After 1 year	33 \pm 2.0	66 \pm 4.0	232 \pm 70
After 2 years	37 \pm 2.6	74 \pm 5.1	300 \pm 119

TABLE 4^o
Sitting blood pressure (mm Hg)

	Placebo	Active	Probability of between group differences
During run-in-period	178 \pm 2.1	178 \pm 1.8	> 0.1
	91 \pm 0.3	92 \pm 0.2	> 0.1
	(58) [†]	(74)	
After 3 months	167 \pm 2.9	158 \pm 2.6	= 0.03
	87 \pm 1.0	85 \pm 1.4	= 0.15
	(49)	(56)	
After 1 year	170 \pm 4.1	152 \pm 2.1	< 0.001
	90 \pm 1.9	84 \pm 1.2	= 0.006
	(31)	(41)	
After 2 years	166 \pm 5.8	150 \pm 2.6	= 0.02
	85 \pm 2.9	77 \pm 2.1	= 0.04
	(19)	(25)	

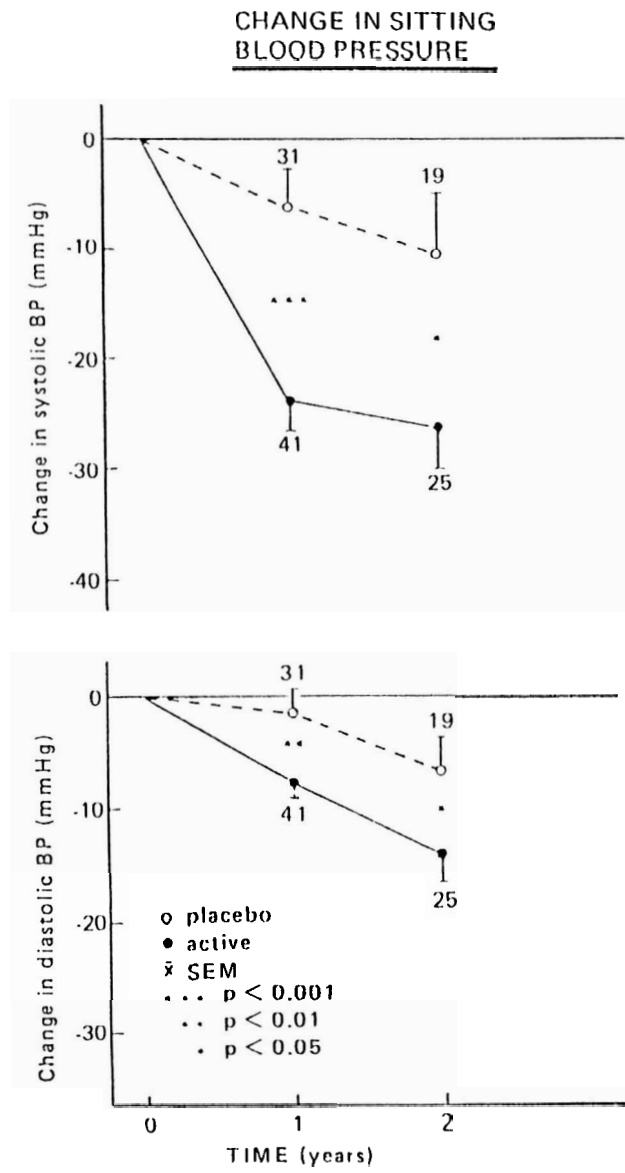


FIGURE 1

D. Body Weight

On admission, the body weight was similar in both groups (table 1); and at no time during the first two years was there a significant difference in body weight between the two groups.

E. Serum Creatinine

The serum creatinine levels (table 5) were similar in both groups on admission. In the placebo group the serum creatinine rose slightly and this rise was significant ($p = 0.04$) after two years. During the trial serum creatinine tended to be higher in the actively treated group than in the placebo group and this difference was significant after one year (figure 2).

TABLE 5^o
Serum Creatinine (mg%)

	Placebo	Active	Probability of between group differences
During run-in-period	1.0 \pm 0.04 (58) [†]	1.0 \pm 0.03 (74)	> 0.1
After 3 months	1.1 \pm 0.04 (48)	1.2 \pm 0.04 (55)	> 0.1
After 1 year	1.1 \pm 0.08 (29)	1.2 \pm 0.05 (38)	> 0.1
After 2 years	1.1 \pm 0.09 (18)	1.2 \pm 0.06 (24)	> 0.1

The increase in serum creatinine was related to the hypotensive effect in the actively treated group at 3 months (figure 3). The decrease of sitting blood pressure in the first three months was significantly correlated with the increase in serum creatinine in this period. In the placebo group, this relationship was not significant ($r = -0.21$ and $p < 0.1$).

F. Serum Uric Acid

The serum uric acid level (table 6) was similar in both groups on admission. In the placebo group a small but insignificant increase was observed (figure 4). In the active treatment group serum uric acid increased by 29% during the first year and remained high during the subsequent years. The changes in serum uric acid (y) within the first year were significantly correlated

TABLE 6^o
Serum Uric Acid (in mg%)

	Placebo	Active	Probability of between group differences
During run-in-period	5.4 ± 0.20 (57) [†]	5.2 ± 0.16 (73)	> 0.1
After 1 year	6.0 ± 0.32 (31)	6.7 ± 0.32 (39)	$= 0.09$
After 2 years	5.7 ± 0.44 (18)	6.6 ± 0.36 (22)	> 0.1

CHANGE IN SERUM URIC ACID

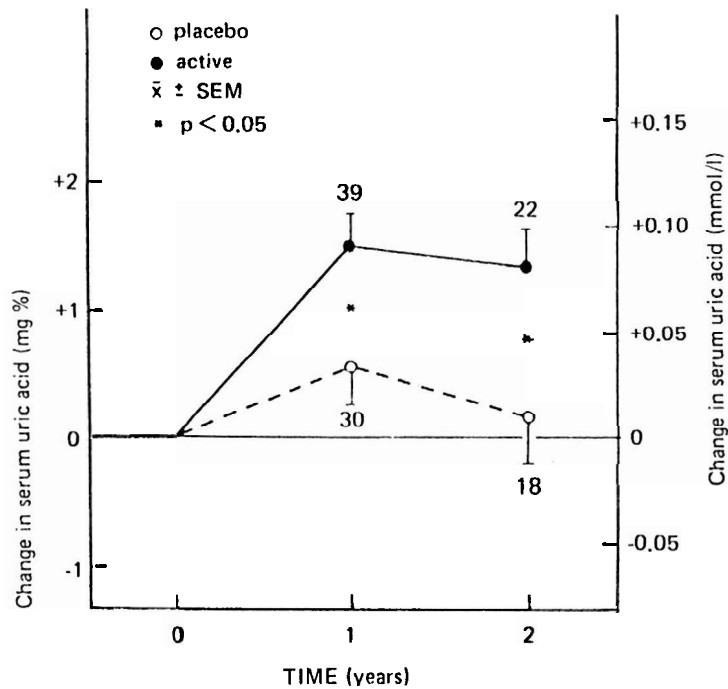


FIGURE 4

with the changes in serum creatinine (x) according to the following formula:

- in the active treatment group: $y = 0.84 + 2.78x$

$n = 37$

$r = 0.496$ and $p = 0.002$

- in the placebo group this relationship ($r = 0.22$) was not significant.

G. Serum Potassium and Sodium

The combination of a thiazide diuretic and a potassium sparing agent provoked only small changes in serum potassium (table 7 and figure 5).

TABLE 7°
Serum Potassium (in mEq/l)

	Placebo	Active	Probability of between group differences
During run-in-period	4.3 \pm 0.05 (58) [†]	4.2 \pm 0.05 (74)	> 0.1
After 3 months	4.3 \pm 0.06 (46)	4.1 \pm 0.06 (55)	= 0.01
After 1 year	4.4 \pm 0.07 (31)	4.2 \pm 0.07 (40)	= 0.07
After 2 years	4.2 \pm 0.08 (19)	4.1 \pm 0.12 (23)	> 0.1

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

H. Blood Glucose

As reported elsewhere (5) the fasting blood glucose level did not change significantly in the placebo treated group during the first year (figure 6). Also in the actively treated group, the rise in blood glucose was not significant; the number of patients was however smaller (n = 38 after one year) than in our previous report.

CHANGE IN POTASSIUM

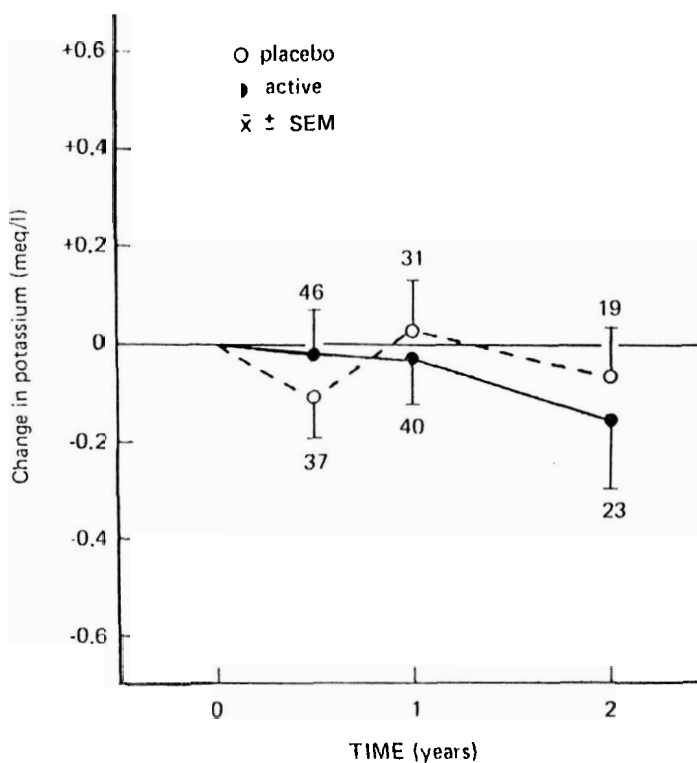


FIGURE 5

DISCUSSION

The reports of the Framingham study have shown an increased incidence of coronary thrombosis, cerebrovascular accidents and cardiac failure in elderly hypertensive patients when compared to normotensive people of the same age; this by itself does not justify antihypertensive therapy. Indeed it must be shown that the antihypertensive therapy prevents the cardiovascular complications of hypertension. On the other side the

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CHANGE IN FASTING BLOOD GLUCOSE

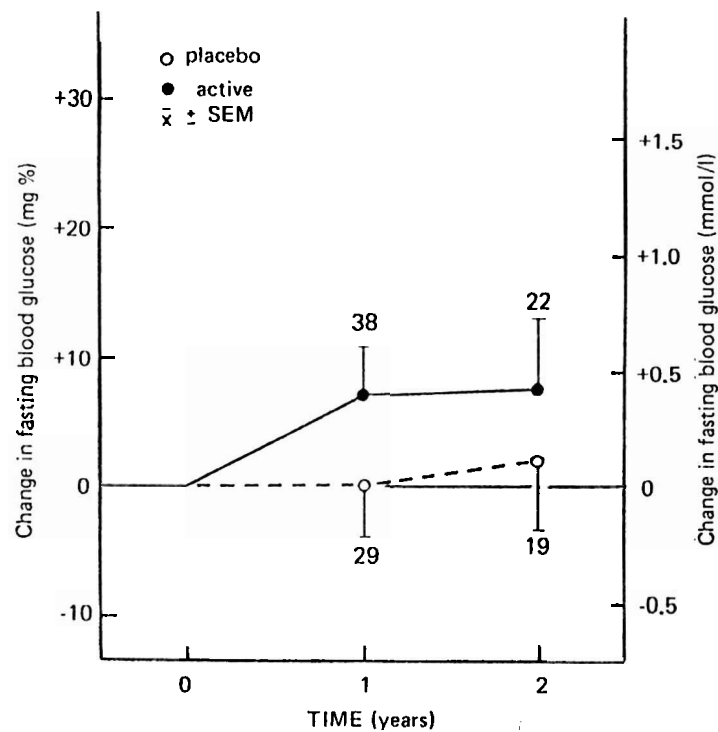


FIGURE 6

antihypertensive treatment must be given for the whole life and is not without side effects especially in old people when many fundamental functions are naturally worsened as the hemodynamic one. Indeed renal, coronary and cerebral blood flows decrease with age and the baroreflex function too is altered: this complication calls for extreme caution in the antihypertensive treatment of elderly.

The aim of reducing mortality and morbidity through the reduction of elevated blood pressure in hyperten-

sive patients without interfering on the quality of the life was evaluated in our patients with diuretics with or without methyldopa. A pilot study with these drugs, allowed to show that this treatment can produce a slow progressive fall in pressure without an excess of terminating events in the actively treated group when compared to the placebo group. It was therefore decided that 1) the results of morbidity and mortality should not be communicated during the course of the trial and 2) the latter should be terminated only when significant results will be available. Also the rules for stopping the trial have been agreed on.

Although a definite answer cannot be given the results on blood pressure changes and the simultaneous biochemical modifications are available up to 2 years of follow-up.

The antihypertensive treatment caused a greater blood pressure reduction of about 15/6 mm Hg in the treated group when compared to the placebo group, although a spontaneous blood pressure decrease of about 11/4 mm Hg was observed in the untreated patients after 3 months of study which persisted throughout the study. In the actively treated group the systolic blood pressure was maintained in the range of 153 mm Hg against 167 mm Hg in the placebo group. If the blood pressure reduction in our study had a similar effect as the effect shown for the blood pressure in the population by Kannel (14), the blood pressure changes observed in our study would cause a significant decrease in cerebrovascular strokes. 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 levels has the same beneficial effect as that calculated from

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observed casual blood pressure differences in epidemiological studies not involving intervention.

The possibility of comparing a placebo and a treated group is important to correctly identify the side effects of drugs because in the old people there are some natural changes which may be erroneously attributed to the antihypertensive therapy.

The serum creatinine showed a slight increase in the placebo group during our study, but in the actively treated patients the serum creatinine rise was more consistent. In the treated group the serum creatinine increase was directly correlated to the reduction of systolic levels, while this correlation was not found in the placebo treated patients. These results may suggest that either the degree of blood pressure reduction in the placebo group was not enough to reduce renal blood flow and glomerular filtration rate or that there was a direct effect of diuretics on renal excretory function.

On the contrary serum uric acid levels were unchanged in the placebo group while there was a significant rise in the actively treated patients: these modifications were proportionally correlated to serum creatinine changes.

With the association of the potassium sparing drug triamterene and the potassium depleting hydrochlorothiazide used in the present trial the reduction in blood pressure was obtained without clinically relevant disturbances in serum potassium levels.

In the present trial the diuretic treatment caused a reduced glucose tolerance test, which may be considered a possible risk for coronary artery disease: however the difference between the active and placebo treated group was not statistically significant.

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The number of patients (132) and the duration of follow-up (2 years) does not allow generalized and conclusive statements. However it is interesting to compare the results of this group of elderly people with isolated systolic hypertension with what has been found in the total population of the EWPHE study including 650 patients with systolic and/or diastolic blood pressure elevation and followed for a longer period (5 years). During the run-in period the diastolic blood pressure, as it is expected, was significantly higher in the whole population than in our subgroup, while systolic blood levels and all the other characteristics (body weight, age, years, etc.) were not statistically different (table 8).

TABLE 8^o
Blood pressure before and during active treatment (mm Hg)

	EWPHE subgroup with systolic hypertension	Total EWPHE population
Placebo	178 ± 1.8	182 ± 1
	92 ± 1	101 ± 1
3 months	158 ± 2	159 ± 1
	85 ± 1	91 ± 1
1 year	152 ± 2	150 ± 1
	84 ± 1	87 ± 1
2 years	150 ± 3	149 ± 1
	77 ± 2	85 ± 1

During the active chronic treatment the systolic blood pressure values had similar reductions at 3 months, 1 and 2 years, while the diastolic values remained on the average slightly higher in the whole population. We can assume therefore that it will be possible to maintain in our subgroup of patients a significant reduction of systolic blood pressure in the follow-up, as it has been observed for the whole population.

The pattern of serum creatinine, uric acid and serum potassium was similar in both groups and the fact that the potassium decrease did not reach a statistically significant level in the systolic hypertensive patients as in the whole population is probably due to the smaller number.

TABLE 9^o

Average daily drug intake in the total EWPHE population and in the subgroup with systolic hypertension.

		Hydrochloro- thiazide mg/day	Triamterene mg/day	Methyldopa mg/day
Systolic hypertension	3 months	-	-	-
	1 year	33	66	232
	2 years	37	74	300
Total EWPHE population	3 months	34 \pm 0.7	68 \pm 1	47 \pm 11
	1 year	38 \pm 0.9	76 \pm 2	250 \pm 29
	2 years	37 \pm 1.0	74 \pm 2	302 \pm 44

TABLE 10

Uric Acid, Serum Creatinine and Serum Potassium Changes during Active Therapy in the total EWPHE Population and in the Subgroup with Systolic Hypertension.

		Placebo	3 months	1 year	2 years
Uric Acid mg%	systolic	5.2 ± 0.16	-	6.7 ± 0.32	6.6 ± 0.36
	whole group	5.32 ± 0.07	-	6.51 ± 0.11	6.48 ± 0.14
Creatinine mg%	systolic	1.0 ± 0.03	1.2 ± 0.04	1.2 ± 0.05	1.2 ± 0.06
	whole group	1.00 ± 0.01	1.15 ± 0.02	1.18 ± 0.02	1.14 ± 0.03
Potassium mEq/l	systolic	4.2 ± 0.05	4.1 ± 0.06	4.2 ± 0.07	4.1 ± 0.12
	whole group	4.16 ± 0.01	4.09 ± 0.03	4.08 ± 0.03	4.05 ± 0.04

Another interesting observation concerns the doses of the hypotensive drugs used in the subgroup and in the whole population (table 9). Indeed the doses of hydrochlorothiazide, triamterene, and methyldopa used were very similar in both groups: this is against the generalized belief that solitary systolic hypertension is more sensitive to the antihypertensive therapy than systolic and diastolic hypertension.

Our study has shown that the association of diuretics and methyldopa is effective in significantly reducing systolic and systolic plus diastolic hypertension in elderly people, while causing mild elevation of serum creatinine, uric acid and blood glucose and preventing the natural slight rise of potassium observed in the placebo group (table 10). The accurate and constant follow-up of these patients must tell us if the balance between the blood pressure reduction and the biochemical changes positively or negatively influences the major causes of morbidity and mortality from cardiovascular diseases.

The following centres are collaborating in the EWPHE study:

University Hospital Haukeland, Bergen, Norway: P. Lund-Johansen, O.J. Ohm
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° The mean \pm standard error of the mean are given.

† Number of patients for whom this item is available.

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