Influence of Antihypertensive Drug Treatment on Morbidity and Mortality in Patients Over the Age of 60 Years. EWPHE Results: Sub-Group Analysis Based on Entry Stratification*

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The European Working Party on High blood pressure in the Elderly (EWPHE) trial was a double-blind randomized placebo-controlled trial of antihypertensive treatment in patients over the age of 60 years. Entry criteria included both a sitting diastolic blood pressure on placebo treatment in the range of 90–119 mmHg and a systolic blood pressure in the range of 160–239 mmHg. Eight-hundred and forty patients were randomly assigned either to active treatment (hydrochlorothiazide + triamterene) or a matching placebo. If blood pressure remained elevated methyldopa was added to the active regimen and matching placebo to the placebo regimen. Before randomization, the patients were stratified in eight strata according to sex, age groups between 60 and 69 years or 70 years and over, and the presence or absence of cardiovascular complications of hypertension.

Both the intention-to-treat and 'on randomized treatment' analyses suggested a benefit from active treatment in men and women. Formal statistical significance was achieved for male cardiovascular mortality (intention-to-treat analyses) and for cardiovascular events in females.

Although the event rates were greater for patients with previous cardiovascular events and patients over the age of 70 years, the percentage reduction in cardiovas-

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cular events was similar in these groups to those without complications and in patients between 60 and 69 years of age. However, little benefit from treatment could be demonstrated in patients over the age of 80 years. The presence or absence of smoking had no influence on response to treatment in these elderly patients.

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Introduction

Hypertension is one of the major risk factors for stroke and coronary heart disease in elderly subjects [1,2]. Such an association does not necessarily imply that morbidity and mortality are reduced when blood pressure is lowered by antihypertensive drugs. However, the recent trial of the EWPHE did show a decrease in cardiovascular mortality in the actively treated group as a whole [3], compared with the placebo group.

The present paper reports the results in eight strata defined according to age, sex and previous cardiovascular disease; these strata were defined before the start of the trial. In addition a *post hoc* analysis, where the patients are divided into smokers and non-smokers, will be presented in view of two recent reports [4,5] on the differences in treatment benefit between these two groups.

Patients and methods

Study protocol

The study protocol has been previously published in detail [6].

The inclusion criteria included: (1) age of 60 years or more at admission to the study; and (2) sitting blood pressure on placebo during the run-in period within certain limits, 160–239 mmHg for systolic and 90–119 mmHg for diastolic blood pressure.

All patients fulfilling the admission criteria were stratified according to sex, age (age range 60–69 years and 70 years and above) and previous cardiovascular complications. The latter included cerebrovascular accidents, cardiac findings such as left ventricular hypertrophy, angina pectoris, myocardial infarction and heart failure and renal involvement (albuminuria or renal insufficiency). The eight strata were:

(1) male patients between the ages of 60 and 69 years, without cardiovascular complications of hypertension;
(2) female patients between the ages of 60 and 69 years, without cardiovascular complications of hypertension;
(3) male patients aged 70 years or more without cardiovascular complications of hypertension;
(4) female patients aged 70 years or more without cardiovascular complications of hypertension;
(5) male patients between the ages of 60 and 69 years, with cardiovascular complications possibly related to hypertension;
(6) female patients between the ages of 60 and 69 years, with cardiovascular complications possibly related to hypertension;
(7) male patients aged 70 years or more, with cardiovascular complications possibly related to hypertension;
(8) female patients aged 70 years or more, with cardiovascular complications possibly related to hypertension.

The patients' stratification and treatment randomization were designed in such a fashion that in each of the participating centres a similar number of patients received active or placebo treatment.

After stratification the patients were randomly allocated to an active treatment or placebo treatment group. At first all patients received daily one diuretic capsule containing either 25 mg hydrochlorothiazide and 50 mg triamterene or a placebo. The dosage could be increased, after at least 2 weeks, to two capsules per day. If the blood pressure remained high after 1 month, methyldopa tablets (500 mg) could be added to the active treatment group and placebo tablets in the placebo group, starting with 1/2 tablet per day and increasing eventually to four tablets daily. Placebo capsules and tablets were identical in shape, taste and colour to the active-treatment group, and the trial was double-blind.

Statistical methods

Both analyses on randomized treatment in the double-blind part of the trial (on-randomized-treatment or per-protocol analysis) and an overall intention-to-treat analysis were performed [6].

In addition to the previously published tests [6], the heterogeneity test between subgroups was performed using the method of relative risk [7].

Results

Patient characteristics at randomization in the strata

There were no significant differences at randomization

between the placebo and active treatment group within each of the different strata and for the total study population in age, body weight and height, sitting blood pressure, serum cholesterol and the percentage of smokers (Table 1).

Compared with the males, the females were older ($P = 0.001$); their average body weight and height were lower ($P < 0.001$), systolic blood pressure was higher ($P < 0.001$) but diastolic blood pressure was similar ($P = 0.46$); their serum cholesterol was higher ($P = 0.001$) and fewer of them smoked ($P < 0.001$).

Compared with the patients with uncomplicated hypertension, those patients with complications were older ($P < 0.0001$), their systolic blood pressure was higher ($P = 0.002$), but the diastolic blood pressure was similar ($P = 0.72$); there was no significant difference in body weight ($P = 0.13$), height ($P = 0.46$) and serum cholesterol ($P = 0.13$).

Compared with the patients below the age of 70 years, the patients in the older age group (70–97 years) had a lower body weight and height, their systolic blood pressure was higher, their serum cholesterol was lower, fewer smoked and their diastolic blood pressure was lower ($P < 0.01$ for all comparisons).

For the total study population the blood pressure at randomization was related to age, the systolic blood pressure increasing with age and the diastolic blood pressure being lower with advancing age [8].

Cardiovascular mortality in different strata according to the intention-to-treat analysis

The cardiovascular mortality in the intention-to-treat analysis (all randomized patients, irrespective of subsequent drop-outs or changes in therapy) is given in Table 2.

The test for heterogeneity between the eight strata did not indicate any statistical difference of the effect of treatment between the subgroups ($P = 0.83$). However, the small numbers in the strata prevent any assertion that the results were indeed similar. The lowest benefit was observed in females over the age of 70 years with and without cardiovascular complications at entry.

When the males were divided into smokers and non-smokers the average treatment effects were, respectively, −37% (95% confidence limits from −74 to +54%) and −53% (95% confidence limits from −79 to +5%).

Cardiovascular mortality in different strata during the double-blind study

The results were similar to those in the intention-to-treat analysis and are given in Table 3. Again, the heterogeneity test was negative ($P = 0.69$), indicating no definite difference in treatment efficacy in any strata.

When the males were divided in smokers and non-smokers the average treatment effects were, respectively −44% (95% confidence limits from −79 to +50%) and −52% (95% confidence limits from −82 to +31%).

Cardiovascular mortality and morbid study terminating events during the double-blind study in different strata

Non-fatal cardiovascular morbid study-terminating events included cerebral haemorrhage, papilloedema, retinal haemorrhages or exudates, and severe congestive heart failure not controlled by digitalis alone.

Cardiovascular study-terminating events (fatal and non-fatal morbid events combined) were reduced in the active treatment group (−44%, $P < 0.001$) when the total study population was considered.

In none of the strata (Table 4) was there an increase in the cardiovascular study-terminating events and the

Table 1. Characteristics of the patients at randomization in different strata.

	n		Age* (in years)		Body weight* (kg)		Height* (cm)		Sitting blood pressure* (mmHg) Systolic		Sitting blood pressure* (mmHg) Diastolic		Serum cholesterol* (mg%)		Smokers (%)	
Stratum	Plac.	Act.	Plac.	Act.	Plac.	Act.	Plac.	Act.	Plac.	Act.	Plac.	Act.	Plac.	Act.	Plac.	Act.
1. M < 70 non-compl.	48	47	65	65	74	74	170	168	176	175	102	102	250	240	40	38
2. F < 70 non-compl.	93	92	65	65	67	68	157	157	178	180	101	101	258	260	9	14
3. M ≥ 70 non-compl.	25	27	75	76	71	70	167	168	184	177	101	97	233	243	48	26
4. F ≥ 70 non-compl.	107	101	78	78	63	64	154	154	187	185	100	100	244	240	4	7
5. M < 70 compl.	25	33	65	66	78	69	168	166	172	176	101	102	246	229	28	46
6. F < 70 compl.	29	31	66	65	74	66	158	157	181	184	101	102	266	273	14	16
7. M ≥ 70 compl.	27	22	75	76	70	69	168	163	184	188	100	101	220	204	37	32
8. F ≥ 70 compl.	70	63	79	79	60	59	154	155	188	193	100	100	249	236	4	6
All males	125	129	69	69	73	71	168	167	179	178	101	101	239	232	38	36
All females	299	287	73	73	65	64	155	156	184	185	100	101	252	249	6	10
All non-compl.	273	267	71	71	67	68	159	159	182	181	101	100	249	247	16	17
All compl.	151	149	74	73	68	64	159	159	184	187	100	101	246	238	16	21
Age 60–69 years	191	197	65	65	71	69	162	161	178	179	101	101	255	252	19	25
Age 70–97 years	233	219	78	78	64	64	157	157	186	187	100	100	242	237	13	12
All smokers	67	76	69	69	69	66	165	161	178	177	99	102	244	241	100	100
All non-smokers	357	340	72	72	67	67	158	159	183	184	101	100	249	244	0	0
All patients	424	416	72	72	67	66	159	159	182	183	101	101	248	244	16	18

*The mean is reported for each subgroup. Compl., hypertension with cardiovascular complication; Plac., placebo group; Act., active-treatment group; M, males; F, females, < 70, etc., less than 70-years old, etc.

Table 2. Cardiovascular mortality in different strata according to intention-to-treat analysis.

Stratum	Placebo group		Active group		Percentage change for active treatment†		
	Number of events	Rate*	Number of events	Rate*	Mean	95% confidence limits	*P*-value‡
1. M < 70 non-compl.	7	27	5	20	−27	−77 to +129	0.55
2. F < 70 non-compl.	8	16	4	8	−52	−86 to +59	0.22
3. M ≥ 70 non-compl.	8	110	3	26	−76	−94 to −9	0.022
4. F ≥ 70 non-compl.	26	54	24	56	+3	−41 to +80	0.89
5. M < 70 compl.	3	NR	3	NR	NR	NR	NR
6. F < 70 compl.	4	NR	3	NR	NR	NR	NR
7. M ≥ 70 compl.	12	127	6	83	−35	−75 to +74	0.22
8. F ≥ 70 compl.	25	100	19	89	−11	−51 to +62	0.70
All males	30	52	17	28	−47	−70 to −3	0.029
All females	63	45	50	37	−18	−43 to +19	0.28
All non-compl.	49	37	36	27	−27	−52 to +12	0.15
All compl.	44	68	31	50	−27	−54 to +15	0.14
Age 60–69 years	20	19	13	12	−38	−69 to +25	0.17
Age 70–97 years	73	80	54	63	−21	−44 to +13	0.17
All smokers	15	54	10	27	−50	−78 to +10	0.084
All non-smokers	78	46	57	36	−22	−44 to +11	0.13
All patients	93	47	67	34	−27	−47 to −1	0.037

*Rate = number of events per 1000 patient years of observation. †This mean and the 95% confidence limits were calculated for the active-treatment group taking the rate in the placebo group as 100%. ‡Comparison between both treatment groups with Mantle-Cox statistics from life-table analysis. NR, not reported, since the number of events in the placebo group was less than five; Compl., hypertension with cardiovascular complication before randomization; M, males; F, females; <70, etc., less than 70 years old, etc.

Table 3. Cardiovascular mortality in different strata during the double-blind study.

Stratum	Placebo group		Active group		Percentage change for active treatment†		
	Number of events	Rate*	Number of events	Rate*	Mean	95% confidence limits	*P*-value‡
1. M < 70 non-compl.	5	33	3	18	−45	−87 to+131	0.41
2. F < 70 non-compl.	5	13	1	3	−80	−98 to+73	0.11
3. M ≥ 70 non-compl.	5	93	3	34	−63	−91 to+55	0.21
4. F ≥ 70 non-compl.	14	51	14	43	−14	−59 to+79	0.64
5. M < 70 compl.	1	NR	3	NR	NR	NR	NR
6. F < 70 compl.	3	NR	1	NR	NR	NR	NR
7. M ≥ 70 compl.	9	145	4	78	−46	−84 to+74	0.26
8. F ≥ 70 compl.	19	113	13	81	−28	−65 to+45	0.29
All males	20	58	13	31	−47	−73 to+7	0.10
All females	41	44	29	30	−33	−59 to+7	0.087
All non-compl.	29	34	21	22	−34	−63 to+15	0.16
All compl.	32	79	21	47	−41	−66 to+3	0.057
Age 60–69 years	12	18	6	8	−55	−83 to+20	0.11
Age 70–97 years	49	84	36	56	−33	−56 to+3	0.078
All smokers	9	57	8	29	−48	−80 to+34	0.26
All non-smokers	52	47	34	30	−36	−58 to−1	0.049
All patients	61	48	42	30	−38	−58 to−8	0.023

For explanations of symbols, see Table 2.

tendency to decrease ranged from −26% to −80%. No stratum could be defined where the treatment was statistically more effective when applying the heterogeneity test for the eight strata ($P = 0.38$), between sexes ($P = 0.84$), between patients with uncomplicated and complicated hypertension at randomization ($P = 0.72$) or between smokers and non-smokers ($P = 0.66$). When the males were divided into smokers and non-smokers the average treatment effect was, respectively, −35% (95% confidence limits from −74 to +59%) and −53% (95% confidence limits from −80 to +12%).

The effectiveness of treatment was established at the 5% level of significance (ignoring the fact of multiple comparisons) in the following strata (Table 4): females aged 60–69 years without cardiovascular complications (−80%), total female group (−44%), patients group without cardiovascular complications (−49%), group with complications (−39%), group aged 60–69 years (−53%), the group aged over 70 years (−41%) and the non-smokers (−43%).

Table 4. Cardiovascular study-terminating events (fatal + morbid) in different strata during the double-blind part of the study.

Stratum	Placebo group		Active group		Percentage change for active treatment†		
	Number of events	Rate*	Number of events	Rate*	Mean	95% confidence limits	*P*-value‡
1. M < 70 non-compl.	6	40	4	24	−39	−83 to +117	0.41
2. F < 70 non-compl.	10	26	2	5	−80	−96 to −8	0.024
3. M ≥ 70 non-compl.	6	112	3	34	−69	−92 to +23	0.11
4. F ≥ 70 non-compl.	21	76	15	46	−39	−69 to +19	0.13
5. M < 70 compl.	1	NR	5	NR	NR	NR	NR
6. F < 70 compl.	6	61	2	16	−73	−95 to +34	0.093
7. M ≥ 70 compl.	12	194	5	97	−50	−82 to +42	0.32
8. F ≥ 70 compl.	24	143	17	106	−26	−60 to +38	0.31
All males	25	72	17	40	−44	−70 to +4	0.062
All females	61	66	36	37	−44	−63 to −16	0.0044
All non-compl.	43	50	24	25	−49	−69 to −17	0.008
All compl.	43	106	29	64	−39	−62 to −2	0.025
Age 60–69 years	21	31	11	14	−53	−77 to −3	0.038
Age 70–97 years	65	111	42	66	−41	−60 to −13	0.0075
All smokers	12	76	10	37	−51	−79 to +12	0.075
All non-smokers	74	67	43	38	−43	−61 to −17	0.0037
All patients	86	68	53	38	−44	−60 to −21	<0.001

For explanations of symbols, see Table 2.

Discussion

The EWPHE trial was designed to permit analysis into eight strata in accordance with sex, age (<70 and >70 years) and the presence or absence of cardiovascular complications at entry. Smoking history was not defined in advance as a criterion for analysis, but was included subsequently because of the results of the MRC [4] and IPPPSH [5] trials. The main problem with subgroup analysis in the EWPHE trial lay in the relatively small number of morbid events in each subgroup.

The only one of the eight specified strata in which cardiovascular mortality was reduced significantly in the intention-to-treat analysis was in men >70 years old without cardiovascular complications (95% confidence limits −94% to −9%, $P = 0.022$). Substantial reductions in morbid events were seen in several other strata, but none reached statistical significance. There was a statistically significant reduction in the intention-to-treat analysis in all men, but not in all women. It is of interest that the cardiovascular event rate was almost identical in placebo and actively treated women of 70 years and older with or without pre-existing complications (Table 2).

Other clinical trials have suggested that the benefit of treatment may be less or even negative in women patients [9]. In the white female group in the HDFP [10] the mortality from all causes was slightly higher in the stepped-care group than the referred care group, but also the blood pressure was somewhat higher in the former. In the Australian National Hypertension Study [11,12] there was no significant benefit of treatment in female subgroups in mortality or in all cardiovascular events combined. The recent MRC trial [4] report showed a significant difference ($P = 0.05$) in mortality experience between the sexes in an interaction analysis. There were more deaths in the actively treated than in the placebo-treated women, and in men the situation was reversed.

The Veterans Administration Cooperative Study Group on Antihypertensive Agents [13–15] (VA) has shown that the effectiveness of hypotensive drugs in decreasing the incidence of morbid events was similar in patients below 50 years (55%), between 50 and 59 years (68%) and patients above 60 years of age (54%). The HDFP [10] showed a percentage reduction in mortality in the stepped-care group of 6% in the patients between 30 and 49 years, 25% in the patients of the sixth decade and 16% in the patients of the seventh decade. In the ANHS [12] the reduction of trial end-points was similar in the patients aged between 60 and 69 years (−39%) and in the total population (−30%).

In a previous report [16] the relationship was calculated between outcome and treatment, age, sex, presence or absence of cardiovascular complications at randomization, and systolic and diastolic blood pressure at randomization, using the Cox proportional hazard regression model in the BMDP 2L Survival Program. Interactions between treatment and these other five variables were also examined. This analysis of the EWPHE data showed a significant effect of treatment, age, sex and systolic (but not diastolic) blood pressure. When the model was expanded to examine whether the effect of treatment differed with age, an age–treatment interaction term was demonstrated ($P = 0.048$) for the intention-to-treat analysis. This may be related to a decrease in treatment effect with advancing age, especially in the 155 patients over the age of 80 years, the great majority of whom (n = 140) were women. The benefits of treatment were not related to the level of systolic or diastolic blood pressure at randomization. The only exception to this statement was the group of patients (n = 172) with diastolic pressures between 90 and 94 mmHg in whom the benefit of treatment is not established.

The small number of smokers in the EWPHE trial makes it impossible to make a definitive statement about differential benefits such as were seen in the MRC [4] and the IPPPSH [5] trial. In male EWPHE patients the benefits

of treatment were similar in smokers (−37%) and non-smokers (−53%) in the intention-to-treat analysis.

One-third of patients who entered the EWPHE trial had a previous history of cardiovascular complications. These patients had a much higher rate of study-terminating events than patients without such a history at entry, but the percentage reduction in the event rate by treatment was similar in both groups.

The proportional reduction in event rate was similar in most of the subgroups defined by the entry strata (men and women above and below 70 years, with and without complications at entry).

However, *post hoc* analysis using a Cox model [16] has suggested that the patients over 80 years of age, 90% of whom were women, may not derive benefit.

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