

## Introduction

Hypertension is one of the major risk factors for stroke and coronary heart disease in elderly subjects [1,2]. However, such an association does not necessarily imply that morbidity and mortality are reduced when blood pressure is lowered by antihypertensive drugs. Controlled trials with antihypertensive agents in elderly subjects have shown either no difference, or some possible, but not statistically significant, benefit [3-9].

In view of the uncertainties regarding treatment in elderly people, the EWPHE initiated a trial to assess the effects of antihypertensive drug therapy in patients above the age of 60 years. The double-blind multicentre trial started in 1972. The trial was brought to an end in the summer of 1984 when the Steering Committee reported that some present trial end-points had been reached. A full report on overall morbidity and mortality results in 840 randomized patients has recently been prepared [10]. The present paper is a summary and a discussion of the data concerning the study terminating events.

## Patients and methods

### Study protocol

The study protocol has been previously published in detail [11]. In brief, patients aged 60 years or more were admitted to the trial if their sitting blood pressure during the placebo run-in period was between 160 and 239 mmHg for systolic and between 90 and 119 mmHg for diastolic blood pressure and if they gave informed consent to participate in the trial.

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 half a 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 medication.

Patients remained in the double-blind part of the trial until the summer of 1984, unless one of the following events occurred: (1) being lost to follow-up; (2) interruption of all study treatment for more than 3 months or (3) one of the specific study-terminating events, including death, non-fatal cerebral or subarachnoid haemorrhage, development of hypertensive retinopathy grade III or IV, dissecting aneurysm, congestive heart failure not controllable without diuretics or antihypertensive drugs, hypertensive encephalopathy, severe increase in left ventricular hypertrophy and a rise in blood pressure exceeding the defined limits [11].

Data were sent to the co-ordinating office every 3 months using specially designed forms, and deaths and other terminating events were classified independently by two investigators into previously agreed categories [11]. These investigators were not aware of the treatment group to which the patients had been assigned. The surviving patients who left the double-blind part of the trial were followed up to July 1984, but only the date and the cause of death were recorded.

### 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 [11]. The latter was confined to mortality, owing to the difficulty of determining morbidity outside the period of double-blind follow-up. Life tables were computed using the BMDP IL survival program [12]. When a life table for one particular event was constructed, termination from another cause led to

The following centres collaborated in the EWPHE trial: University Hospital Haukeland, Bergen, Norway (P. Lund-Johansen, O.J. Ohm, P. Omvik); North Karelia Project, Helsinki, Finland (A. Alasoini, A. Koistinen, A. Nissinen, P. Puska, J. Tuomilehto, R. Varis); Zuiderziekenhuis, Rotterdam, The Netherlands (W. Birkenhäger, P. de Leeuw, P. Willemsse); Victoria Geriatric Unit, Glasgow, Scotland (K. Beard, J.L.C. Dall, the late J.P.R. MacFarlane, B.O. Williams); Aberdeen Royal Infirmary, Aberdeen, Scotland (T.A. Jeffers, J.C. Petrie, O.J. Robb, J. Webster); Royal College of Surgeons, Dublin, Ireland (M. Laher, P. McCormack, F. Meagher, E. O'Brien, W. O'Callaghan, K. O'Malley); Hammersmith Hospital, London, England (C.J. Bulpitt, P. Lewis, M. Murphy); St John's Hospital, London, England (R.C. Hamdy, N.H. Perera); St Charles Hospital, London, England (X. Chellappah, J. Morris, A.I. Suchett-Kaye); University Hospital, Cologne, West Germany (H. Feltkamp, A. Konrads, U. Laaser, K. Meurer); University Hospital Gasthuisberg, Leuven, Belgium (R. Fagard, the late J. Hellemans, P. Lijnen, W. Pelemans, J. Staessen, R. Van Hoof); University Hospital, Ghent, Belgium (M. Bogaert, D. Clement); Geriatric Hospital Le Valdor, Liège, Belgium (P. Brixko, A. Ernould, A. Mutters); University Hospital St Luc, Brussels, Belgium (J.F. De Plaen, Ch. van Ypersele); Medisch Centrum voor Huisartsen, Leuven, Belgium (M. Deruyttere); Hôpital Charles Foix, Ivry, France (P. Berthaux, F.

Forette, J.F. Henry); Centro di Fisiologia Clinica e Ipertensione, Milan, Italy (G. Leonetti, X. Tammaro, L. Terzoli, A. Zanchetti); University Hospital Santa Maria, Lisbon, Portugal (F. de Padua, J. Forte, J.M. Pereira-Miguel).

The EWPHE trial was co-ordinated by A. Amery (Leuven) and A. De Schaepdryver (Ghent), Belgium.

The Steering Committee included A. Amery, A. De Schaepdryver, C. Dollery, J.V. Joossens and T. Strasser.

The advisors were E. Freis, the late F. Gross, M. Healy, S. Hoobler, P. Milliez and J. Willems.

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Requests for reprints to: Dr A. Amery, Inwendige Geneeskunde-Cardiologie, U.Z. Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

censoring the data at that point in time. Tests of significance were performed on the life table analysis during the Mantel-Cox estimate [13].

The percentage difference in deaths or events was calculated for the actively treated group, taking the rate in the placebo group as 100%. These rates were calculated per 1000 patient-years under observation. The confidence intervals (CI) for the percentage reduction in events in the active group were calculated as reported previously [10].

The difference in events between the placebo and active treatment group (events saved) were calculated using life table analysis over 7 years of observation as described elsewhere [11].

## Results

### Patients' characteristics at randomization and during the double-blind part of the trial

The patients ( $n = 840$ ) were randomized to placebo ( $n = 424$ ) and active treatment ( $n = 416$ ). As reported elsewhere the placebo and active treatment groups were similar in sex ratio, age ( $72 \pm 8$  years in both groups), sitting blood pressure at randomization (Table 1), weight, height and the percentage of patients with cardiovascular complications on admission to the trial. As shown in Table 1, throughout the double-blind part of the trial the blood pressure was lower ( $P < 0.001$ ) in the

actively treated patients compared with those on placebo (see Table 1).

### Intention-to-treat analysis (Table 2)

The duration of follow-up for the intention-to-treat analysis (all patients randomized, irrespective of subsequent dropout or changes in treatment) averaged 4.63 years in the placebo and 4.69 years in the active treatment group. The patient-years of observation were 1963 in the placebo and 1950 in the active treatment group. The small reduction in mortality rate from all causes was not significant ( $-9\%$ ,  $P = 0.41$ ), but the reduction in cardiac mortality ( $-38\%$ ,  $P = 0.036$ ) and all cardiovascular mortality ( $-27\%$ ,  $P = 0.037$ ) were both significant.

### Study-terminating events in the double-blind part of the trial

Further analyses were made on both fatal and non-fatal events that occurred while individual patients were still on randomized treatment. More patients in the placebo group reached a trial end-point, and the duration of follow-up in the double-blind part of the study was consequently shorter in this group (2.99 years) than in the actively treated group (3.36 years). The longest follow-up for a single patient was 11 years.

### Mortality (Table 3)

The total death rate was 70/1000 patient-years in the

**Table 1.** Experience during the double-blind part of the trial in active and placebo groups (Amery *et al.* [10], by courtesy of *Lancet*).

	Average blood pressure (mmHg, mean $\pm$ s.d.)				
	Placebo		Active		<i>P</i>
At randomization, SBP/DBP	182 $\pm$ 16/101 $\pm$ 7	( <i>n</i> = 424)	183 $\pm$ 17/101 $\pm$ 7	( <i>n</i> = 416)	0.65 (SBP); 0.98 (SBP)
After 1 year, SBP/DBP	172 $\pm$ 23/95 $\pm$ 12	( <i>n</i> = 287)	151 $\pm$ 17/88 $\pm$ 9	( <i>n</i> = 300)	< 0.001
After 3 years, SBP/DBP	172 $\pm$ 25/94 $\pm$ 11	( <i>n</i> = 171)	149 $\pm$ 16/85 $\pm$ 9	( <i>n</i> = 187)	< 0.001
After 5 years, SBP/DBP	171 $\pm$ 25/95 $\pm$ 9	( <i>n</i> = 93)	150 $\pm$ 20/85 $\pm$ 9	( <i>n</i> = 108)	< 0.001
After 7 years, SDP/DBP	167 $\pm$ 22/90 $\pm$ 9	( <i>n</i> = 27)	148 $\pm$ 18/85 $\pm$ 10	( <i>n</i> = 39)	< 0.001

SBP, sitting systolic blood pressure; DBP, sitting diastolic blood pressure; *n*, number of patients.

**Table 2.** Deaths in the intention-to-treat analysis (Amery *et al.* [10], by courtesy of *Lancet*).

Causes of deaths	Placebo group ( <i>n</i> = 424)		Active group ( <i>n</i> = 416)		Percentage change for active treatment <sup>†</sup>		
	Number of patients	Rate*	Number of patients	Rate*	Mean	95% confidence limits	<i>P</i> <sup>‡</sup>
All causes	149	76	135	69	-9	-28 to +15	0.41
Non-cardiovascular non-renal	54	28	61	31	+14	-21 to +64	0.48
All cardiovascular	93	47	67	34	-27	-46 to -1	0.037
Cerebrovascular	31	16	21	11	-32	-61 to +19	0.16
Cardiac	47	24	29	15	-38	-61 to -1	0.036
Other cardiovascular	15	8	17	9	-	-	-
Renal	1	-	4	2	-	-	-
Unknown cause of death	1	-	3	2	-	-	-

\*Rates are the number of patients having an event per 1000 patient-years of observation, and include all deaths up to 1 July 1984, whether the patients were still in the double-blind part of the trial or not. In 24 patients the life/death status was not known on 1 July 1984, but survival was known to an earlier date. Twelve of these people were in the actively treated group and 12 in the placebo group. <sup>†</sup>This mean and the 95% confidence limits were calculated for the actively treated group, placebo rate = 100%. <sup>‡</sup>*P* value comparing both treatment groups using Mantel-Cox statistics from life table analysis. -, Not calculated, since the rate in the placebo group was <10/1000 patient-years.

**Table 3.** Terminating fatal events on randomized treatment (Amery *et al.* [10], by courtesy of *Lancet*).

	Placebo group		Active group		Percentage change for active group <sup>†</sup>		
	Number of patients	Rate*	Number of patients	Rate*	Mean	95% confidence limit	P <sup>‡</sup>
All causes	89	70	73	52	-26	-45 to +1	0.077
Non-cardiovascular non-renal: total	28	22	30	21	-3	-42 to +62	0.96
Cardiovascular: total	61	48	42	30	-38	-58 to -8	0.023
Cerebrovascular	19	15	12	9	-43	-72 to +18	0.15
Cardiac	29	23	17	12	-47	-71 to -3	0.048
Myocardial infarction	16	13	7	5	-60	-84 to -4	0.043
Others (including sudden death)	13	10	10	7	-30	-69 to +59	0.44
Pulmonary embolism and/or infarction	7	6	8	6	-	-	-
Others	6	5	5	4	-	-	-
Renal	0	0	1	1	-	-	-

\*Rates are number of patients having an event per 1000 patient-years under observation. <sup>†</sup>Percentage change is calculated from the rates, placebo rate being 100%. <sup>‡</sup>P value comparing both treatment groups using Mantel-Cox statistics from life table analysis. -, Value not calculated, since the rate in the placebo group was <10/1000 patient-years.

placebo group and 52/1000 patient-years in the actively treated group while on their randomized treatment. This reduction did not achieve statistical significance (-26%,  $P = 0.077$ ).

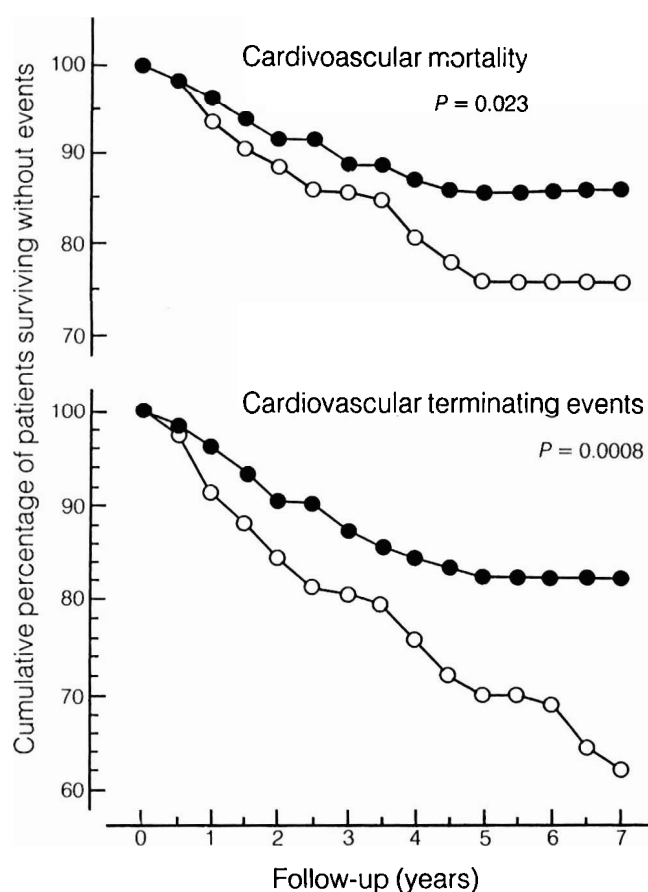
Total cardiovascular mortality rate was significantly reduced (-38%,  $P = 0.023$ , Fig. 1). The effect on overall cardiovascular mortality was due mainly to the fall in the cardiac mortality rate (-47%,  $P = 0.048$ , Fig. 2). The fall in cerebrovascular mortality was not significant (-43%,  $P = 0.15$ , Fig. 3). The actively treated group had 14 fewer cardiovascular deaths per 1000 patient-years.

There was no difference in non-cardiovascular, non-renal mortality rate (-3%,  $P = 0.96$ ). This mortality included deaths from neoplasms (10 in the placebo and eight in the active treatment group, respectively), deaths from infections (none versus two), deaths for pneumonia (10 versus seven), deaths from intestinal diseases (three versus three), a miscellaneous group (four versus four) and accidental deaths (one versus six). The latter group included four deaths after a fracture of the hip, all patients being on active treatment. Their age ranged from 71 to 90 years, three were women, all four were treated with a diuretic and two also received methyldopa. There was no clear indication of orthostatic hypotension. Their serum creatinine ranged from 1.1 to 1.5 mg% and their serum potassium from 3.2 to 4.5 mmol/l.

#### Non-fatal study-terminating events (Table 4)

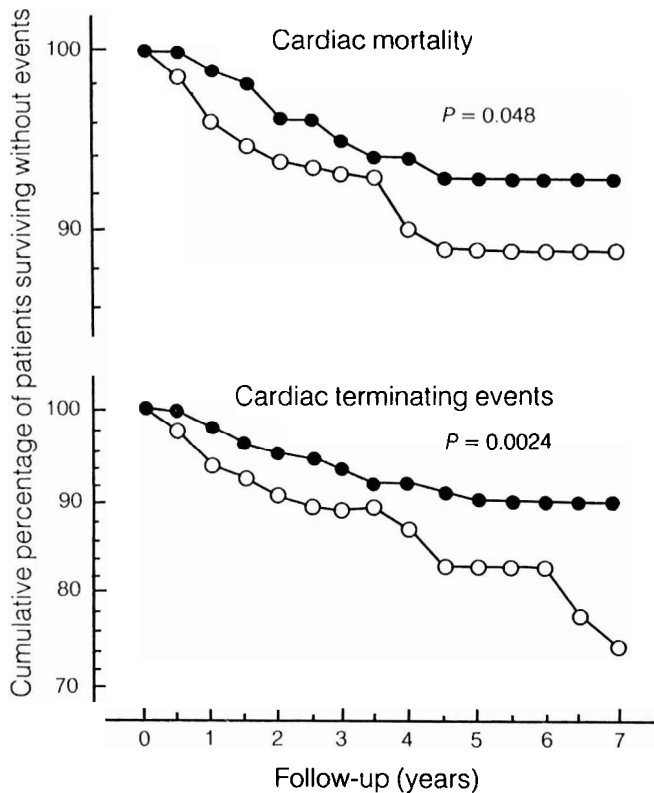
Non-fatal morbid cardiovascular study-terminating events (Table 4) occurred at a rate of 20/1000 patient-years in the placebo group and 8/1000 patient-years in the actively treated group. This reduction (-60%,  $P = 0.0064$ ) was mainly accounted for by a 63% reduction in severe congestive heart failure, not controlled by digitalis alone. There were 21 fewer study-terminating non-fatal morbid cardiovascular events per 1000 patient-years in the actively treated patients.

Cardiovascular study-terminating events (fatal and non-fatal morbid events combined) were reduced in the active treatment group (-44%,  $P = 0.0008$ , Fig. 1), both for cardiac events (-53%,  $P = 0.0024$ , Fig. 2) and for cerebrovascular events (-46%,  $P = 0.058$ , Fig. 3).



**Fig. 1.** The cumulative percentage of survivors without events calculated for the patients on randomized treatment (● active, ○ placebo) using the life table method [12]. Cardiovascular study-terminating events include deaths and study-terminating morbid events (group A of Table 4). (From Amery *et al.* [10], with modifications; by courtesy of *Lancet*).

Non-fatal non-morbid cardiovascular study-terminating events are also included in Table 4. The non-morbid cardiovascular study-terminating event rate was reduced (-70%,  $P = 0.0006$ ), but these events were not



**Fig. 2.** The cumulative percentage of survivors without cardiac study-terminating events calculated for the patients on randomized treatment (● active, ○ placebo) using the life table method [12]. Cardiac study-terminating events include cardiac deaths and severe congestive heart failure (see group A of Table 4).

employed in calculating the total cardiovascular event rate since they constituted either less-hard data or were not true morbid events (e.g. rise in blood pressure).

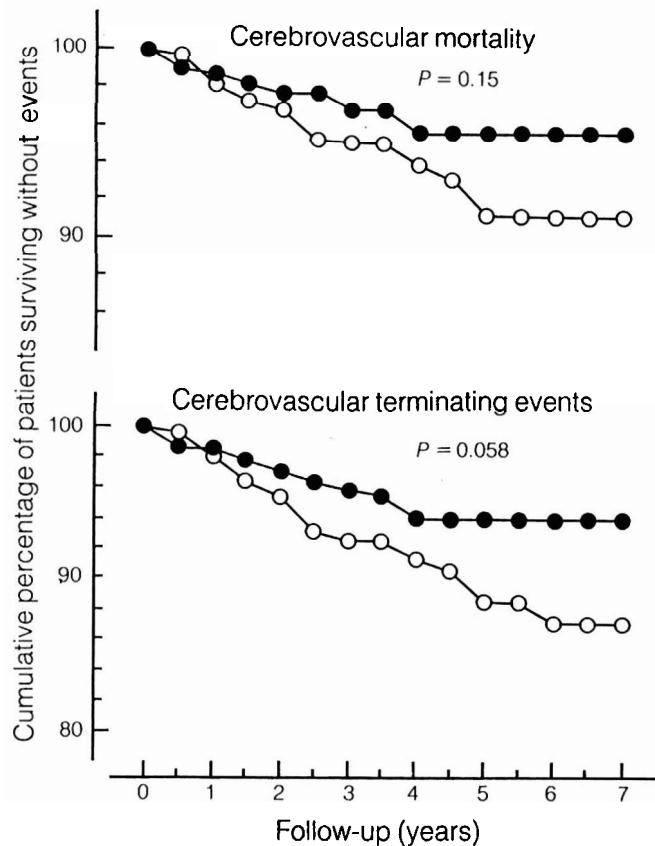
#### Other reasons for stopping randomized treatment (Table 5)

During randomized treatment, 128 patients defaulted from follow-up and 52 refused to continue their randomized treatment for various reasons but continued to attend. Relative data are detailed in Table 5. Only withdrawal because of serious intercurrent illnesses (mainly neoplasms) was less frequent in the actively treated group ( $P = 0.022$ ). There were 291 patients still in the double-blind part of the trial when it was stopped in the summer of 1984.

## Discussion

There are many patients over the age of 60 years with high blood pressure, but until now little scientific evidence has been produced to justify antihypertensive drug treatment. The present trial, conducted by the EWPHE was a double-blind, placebo-controlled trial that concentrated on elderly hypertensive patients.

The trial was initiated 13 years ago and the range of blood pressure accepted was wide: 160-239/90-119 mmHg. However, relatively few patients with pressures



**Fig. 3.** The cumulative percentage of survivors without cerebrovascular study-terminating events calculated for the patients on randomized treatment (● active, ○ placebo) using the life table method [12]. Cerebrovascular study-terminating events include cerebrovascular deaths, cerebral haemorrhage and retinal haemorrhages, exudates or papilloedema (see group A of Table 4).

in the upper part of this range [11] were selected, and the mean  $\pm$  s.d. of blood pressure at randomization was  $183 \pm 17/101 \pm 7$ . Thus, the blood pressure levels are rather typical of those that might be considered for treatment today. The trial was stopped in the summer of 1984, when previously agreed stopping rules were applicable.

As reported elsewhere [10], only 35% of the 840 randomized patients were still in the double-blind part when it was terminated; 19% of the patients had died, 4% had a terminating morbid cardiovascular event, 5% had a study-terminating non-morbid event and 36% left the double-blind part prematurely for other reasons. Those who left the double-blind part discontinued their randomized treatment. A proportion of those on active treatment will have stopped antihypertensive treatment and a proportion in the placebo group will have been started on active treatment. For this reason the intention-to-treat analysis would be expected to give a lower level of statistical significance than an analysis confined to those patients who continued their randomized treatment. For ethical reasons, the stopping rules for the trial were based on the more-sensitive on-randomized-treatment analysis. In the event, cardiovascular deaths were reduced by 38% in the on-randomized-treatment analysis and by 27% in the

**Table 4.** Terminating non-fatal cardiovascular and renal events on randomized treatment (Amery *et al.* [10], by courtesy of *Lancet*).

	Placebo group		Active group		Percentage change for active group <sup>†</sup>			
	Number of patients	Rate*	Number of patients	Rate*	Mean	95% confidence limits	P <sup>‡</sup>	
Non-fatal, morbid cardiovascular terminating events:								
Total	25	20	11	8	-60	-88 to -19	0.0064	
Cerebral haemorrhage	3	2	4	3	-	-	-	
Papilloedema, retinal haemorrhages or exudates	5	4	0	0	-	-	-	
Severe congestive heart failure (not controlled by digitalis alone)	17	13	7	5	-63	-85 to -10	0.014	
Non-fatal, non-morbid cardiovascular terminating events:								
Total	30	24	10	7	-70	-85 to -38	0.0006	
Severe increase in blood pressure	19	15	2	1	-90	-98 to -59	0.0001	
Therapy required:								
β-blocker	10	8	6	4	-	-	-	
Calcium antagonist	0	0	1	1	-	-	-	
Diuretics	0	0	1	1	-	-	-	
Severe left ventricular hypertrophy or dilatation	1	1	0	0	-	-	-	
Renal: severe increase in serum	1	1	4	3	-	-	-	

\*Rates are number of patients having an event per 1000 patient-years under observation. <sup>†</sup>Percentage change is calculated from the rates, placebo rate being 100%. <sup>‡</sup>*P* value comparing both treatment groups using Mantel-Cox statistics from life table analysis. -, Value not calculated, since the rate in the placebo group was <10/1000 patient-years.

**Table 5.** Other reasons for stopping randomized treatment. (Amery *et al.* [10], by courtesy of *Lancet*).

	Placebo group		Active group		Percentage change for active treatment <sup>†</sup>		
	Number of patients	Rate*	Number of patients	Rate*	Mean	95% confidence limits	P <sup>‡</sup>
Premature stopping: total	157	124	149	107	-14	-31 to +8	0.18
Lost to follow-up	69	54	59	42	-23	-45 to +10	0.18
Stopping of trial medication (>3 months)	22	17	30	21	+23	-29 to +114	0.39
Non-fatal intercurrent disease	25	20	13	9	-53	-76 to -8	0.022
Centre stopped the trial	11	9	10	7	-	-	-
Patients stopped after 5 years in the study	11	9	18	13	-	-	-
Moderate increase in blood pressure	11	9	0	0	-	-	-
Low blood pressure off randomized treatment	2	2	15	11	-	-	-
Breaking treatment code required	3	2	3	2	-	-	-
Failure of drug supply	2	2	0	0	-	-	-
Stopping for unknown reason	1	1	1	1	-	-	-
Termination of the trial in summer 1984	122		169				

\*Rates are number of patients having an event per 1000 patient-years under observation. <sup>†</sup>Percentage change is calculated from the rates, placebo rate being 100%. <sup>‡</sup>*P* value comparing both treatment groups using Mantel-Cox statistics from life table analysis. -, Value not calculated, since the rate in the placebo group was <10/1000 patient-years.

intention-to-treat analysis. Morbidity was not reported outside the double-blind part of the study, as such data may have been subjected to considerable bias.

During the double-blind part of the present trial a 44% reduction of cardiovascular study-terminating events (fatal + non-fatal morbid events combined) was observed. This result is similar to those in patients aged more than 60 years, both in the Veterans Administration Co-operative Study Group Trial [9] and the Australian Therapeutic Trial in Mild Hypertension [6,14] (-59% and -39%, respectively).

In the Hypertension Detection and Follow-up Program [15] the 5-year death rate from all causes in the age group from 60 to 69 years was 16% lower in the stepped care

than in the referred care group. In the present study the age range was wider; mortality from all causes was 26% lower in the actively treated than in the placebo group on randomized treatment, and 9% lower in the intention-to-treat analysis.

Previous trials of antihypertensive therapy [7-9,14,15] have demonstrated a reduction of the incidence of stroke. In the present trial, cerebrovascular mortality was reduced, although this difference did not attain statistical significance.

Some methodological aspects of the trial must be discussed. In such a long-term trial the steering committee must have 'repeated-looks' at the data for ethical reasons. Because of these 'repeated-looks' (seven

were actually done out of 10 allowed in the trial design), the level of statistical significance required to stop the trial was increased to 1% on any one occasion. Such a level of significance is equivalent to an overall level of approximately 5% [16]. The intention-to-treat analysis was not performed at each of these occasions.

Most of the patients in the present trial were recruited from clinics, rather than by screening a population. Caution must be exercised when extrapolating the results to elderly people in general with elevated blood pressures. Indeed, the patients were not recruited by screening of the population at large; therefore the patients studied do not constitute a random sample. In most centres a patient log was not kept; where this was available 53% of the patients originally considered did enter the trial. Many patients were not eligible because of the selection criteria. Also, a specific drug regimen was used, and extrapolation to other drug regimens is not necessarily valid. However, the patients were drawn from a wide variety of sources: community, general medical and geriatric services in different European countries [11], and the data should therefore have a wider application than data generated from a single country, as has been the case in previous trials of antihypertensive therapy. The main benefits identified were a reduction in fatal myocardial infarction, severe congestive heart failure and stroke. Non-cardiovascular mortality was not affected by active treatment. Minor adverse effects included a decrease in glucose tolerance [17] and an elevation of serum uric acid [18] and creatinine [19] in patients treated with diuretics. Overall, the balance sheet favoured active treatment in the patients who were included in the EWPHE trial.

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The trial was carried out in consultation with WHO and was supported by the Belgian National Research Foundation (NFWO) and the Belgian Hypertension Committee. Merck Sharp and Dohme, and Smith, Kline and French prepared tablets of methyl dopa (500 mg) and matching placebos and diuretic capsules (25 mg hydrochlorothiazide and 50 mg triamterene) and matching placebos. The drugs were processed under the supervision of A. De Maesschalck, pharmacist, with the advice of G. Van Herpe. J. Vanhollenbeke from Boehringer Pharma, Belgium, collaborated in quality control.

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# **Influence of Hypotensive Drug Treatment in Elderly Hypertensives: Study Terminating Events in the Trial of the European Working Party on High Blood Pressure in the Elderly**

A. Amery, W. Birkenhäger, P. Brixko, C. Bulpitt, D. Clement, P. de Leeuw, J.F. De Plaen, M. Deruyttere, A. De Schaepdryver, C. Dollery, R. Fagard, H. Feltkamp, F. Forette, J. Forte, R. Hamdy, J.F. Henry, J.V. Joossens, A. Koistinen, G. Leonetti, P. Lund-Johansen, J. Morris, A. Nissinen, E. O'Brien, K. O'Malley, W. Pelemans, T. Strasser, J. Tuomilehto, J. Webster, B. Williams and A. Zanchetti

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 90-119 mmHg and a systolic blood pressure in the range of 160-239 mmHg. The patients ( $n = 840$ ) were randomized either to active treatment (hydrochlorothiazide + triamterene) or matching placebo. If the blood pressure remained elevated, methyldopa was added to the active regimen and matching placebo in the placebo group.

An overall intention-to-treat analysis, combining the double-blind part of the trial and all subsequent follow-up, revealed a non-significant change in total mortality rate ( $-9\%$ ,  $P = 0.41$ ) but a significant reduction of cardiovascular mortality rate ( $-27\%$ ,  $P = 0.037$ ). The latter was due to a reduction of cardiac mortality ( $-38\%$ ,  $P = 0.036$ ) and to a non-significant decrease of cerebrovascular mortality ( $-32\%$ ,  $P = 0.16$ ).

In the double-blind part of the trial, total mortality rate was not significantly reduced ( $-26\%$ ,  $P = 0.077$ ). Cardiovascular mortality was reduced in the actively treated group ( $-38\%$ ,  $P = 0.023$ ), due to a reduction of cardiac deaths ( $-47\%$ ,  $P = 0.048$ ) and to a non-significant decrease of cerebrovascular mortality ( $-43\%$ ,  $P = 0.15$ ). Deaths from myocardial infarction were reduced ( $-60\%$ ,  $P = 0.043$ ).

Study-terminating morbid cardiovascular events were significantly reduced by active treatment ( $-60\%$ ,  $P = 0.0064$ ).

In the patients randomized to active treatment there were 14 fewer cardiovascular deaths per 1000 patient-years during the double-blind part of the trial.

Version 3

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