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Relation between mortality and treated blood pressure in elderly patients with hypertension: report of the European Working Party on High Blood Pressure in the Elderly

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Abstract

***Objective*—To investigate the relation between mortality and treated systolic and diastolic blood pressures.**

***Design*—Randomised double blind placebo controlled trial. Mortality in the two treatment groups was examined in thirds of treated systolic and diastolic blood pressures.**

***Patients*—339 And 352 patients allocated to placebo and active treatment, respectively. The groups were similar at randomisation in sex ratio (70% women), mean age (71·5 years), blood pressure (182/101 mm Hg), and proportion of patients with cardiovascular complications (35%).**

***Measurements and main results*—In the placebo group total mortality rose with increasing systolic pressure whereas it had a U shaped relation with diastolic pressure, the total lowest mortality being in patients in the middle third of the distribution of diastolic pressure. In the group given active treatment total mortality showed a U shaped relation with systolic pressure and an inverse association with treated diastolic pressure. In both groups cardiovascular and non-cardiovascular mortality followed the same trends as total mortality. The increased mortality in the lowest thirds of pressure was not associated with an increased proportion of patients with cardiovascular complications at randomisation or with a fall in diastolic pressure exceeding the median fall in pressure in each group. In contrast, patients in the lowest thirds of pressure showed greater decreases in body weight and haemoglobin concentration than those in the middle and upper thirds of pressure.**

***Conclusions*—In patients taking active treatment total mortality was increased in the lowest thirds of treated systolic and diastolic blood pressures. This increased mortality is not necessarily explained by an exaggerated reduction in pressure induced by drugs as for diastolic pressure a U shaped relation also existed during treatment with placebo. In addition, patients in the lowest thirds of systolic and diastolic pressures were characterised by decreases in body weight and haemoglobin concentration, and the patients in the lowest thirds of diastolic pressure taking active treatment also by an increased non-cardiovascular mortality, suggesting some deterioration of general health.**

European Working Party on High Blood Pressure in the Elderly
Collaborating centres are listed at the end of this paper. Manuscript prepared by J Staessen and A E Fletcher

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Introduction

Several large studies of hypertension have recently been reviewed.[1,2] The observation in these studies of a J shaped relation between the risk of myocardial infarction and treated blood pressure[3-9] has led to the suggestion that a reduction of pressure induced by drugs might cause as well as prevent myocardial ischaemia.[1,10,11] None of the studies was placebo controlled, and other large hypertension-mortality intervention trials have either not confirmed[12-14] or not reported[15,16] this J shaped relation. In the international prospective primary prevention study in hypertension all patients received active drugs but patients with overt ischaemic heart disease were excluded[14]; there was no evidence for a J curve. In contrast, Coope and Warrender found that total mortality and deaths from myocardial infarction showed a J shaped relation with the diastolic pressure attained in elderly patients with

hypertension taking active treatment as well as in untreated controls.[17,18]

The present paper is based on the results of the trial conducted by the European Working Party on High Blood Pressure in the Elderly.[19-21] The trial comprised elderly patients with hypertension randomly allocated to placebo or active treatment. We studied the mortality in the patients, who were grouped in thirds of the distribution of treated blood pressure. In addition, the presence of cardiovascular complications at randomisation, the fall in diastolic pressure after randomisation, and some variables of general health, such as haemoglobin concentration and body weight, were examined as possible correlates of mortality.

Patients and methods

Study protocol—At entry to the trial all patients were aged ≥60 and had a sitting blood pressure when taking placebo during a run in period of 160-239/90-119 mm Hg. After stratification for sex, age, and the presence or absence of cardiovascular complications, 840 patients were randomised either to active treatment (hydrochlorothiazide and triamterene) or to matching placebo. If blood pressure remained high methyldopa was added to the active regimen and matching placebo in the control group. Full details of the protocol have been published.[19]

Statistical methods—Mortality was related to the blood pressure during randomised treatment (per-protocol analysis).[19] For reasons discussed below treated blood pressure was defined as the blood pressure at nine months of follow up. In the two treatment groups patients were subdivided into thirds by the 33rd and 66th centiles of their treated systolic and diastolic pressures. The centile boundaries are indicated by the term tertiles. Mortality in the thirds of treated pressure was adjusted for age and sex by the direct method[22] and compared in two tailed tests by calculating standard deviations. We used Student's *t* test to compare means.

Results

PATIENTS

Eighty five of the 424 patients randomised to placebo and 64 of the 416 patients randomised to active treatment left the study before the follow up visit at nine months; these patients were therefore not included in the present analyses. Of those excluded, 24 patients in the placebo group and 17 of those taking active treatment had died. Thus the analyses were of 339 patients randomised to placebo and 352 patients randomised to active treatment, and the number of patient years of observation were 1211 and 1351, respectively. The two groups analysed were similar at randomisation in sex ratio (nearly 70% women), mean age (71·5 years), systolic (182 mm Hg) and diastolic (101 mm Hg) blood pressures, and proportion of patients with cardiovascular complications (nearly 35%).

Tables I and II show the characteristics of the patients by thirds of treated systolic and diastolic blood pressures respectively. The ranges of blood pressure show that active treatment produced a shift in systolic and diastolic blood pressures. Indeed, blood pressure was similar in the lowest and middle thirds of the placebo and active treatment groups, respectively. Treated pressure was similar in the middle third of the group taking placebo and the highest third of the group taking active treatment.

TABLE I—*Characteristics of patients according to treatment and thirds of treated systolic pressure**

	Placebo group			Active treatment group		
	Lowest third (n=121)	Middle third (n=113)	Highest third (n=105)	Lowest third (n=120)	Middle third (n=126)	Highest third (n=106)
No of person years of follow up in double blind study	473	422	316	476	487	388
No (%) men at randomisation	42 (35)	37 (33)	21 (20)	38 (32)	37 (29)	31 (29)
No (%) with cardiovascular complications at randomisation	36 (30)	47 (42)	32 (30)	36 (30)	47 (37)	42 (40)
No (%) who smoked at randomisation	17 (14)	20 (18)	11 (10)	29 (24)	26 (21)	13 (12)
Mean (SD) age at randomisation (years)	72·3 (7·7)	70·2 (7·4)	72·5 (8·2)	71·6 (8·8)	71·0 (7·9)	71·7 (7·2)
Characteristics during follow up						
Extremes of treated systolic pressure* (mm Hg)	124-162	164-180	182-244	100-144	146-158	160-236
Treated systolic/diastolic pressure at middle of third (mm Hg)	151/88	172/97	201/104	134/84	152/88	172/92
Mean (SD) difference between treated pressure and pressure at randomisation (mm Hg):						
Systolic	−24 (15)	−7 (15)	9 (17)	−44 (18)	−29 (16)	−17 (19)
Diastolic	−11 (9)	−3 (9)	1 (11)	−16 (9)	−13 (8)	−9 (11)
Mean (SD) body weight at 9 months (kg)	65·2 (13·9)	68·6 (13·4)	66·6 (12·4)	64·5 (12·7)	65·8 (11·7)	66·9 (12·0)
Mean (SD) haemoglobin at 1 year (g/l)	140 (14)	142 (15)	146 (15)	139 (15)	141 (16)	142 (18)
No of patients in whom haemoglobin was measured	91	90	77	91	87	92

*Treated systolic pressure refers to sitting systolic pressure nine months after randomisation.

TABLE II—*Characteristics of patients according to treatment and thirds of treated diastolic pressure**

	Placebo group			Active treatment group		
	Lowest third (n=119)	Middle third (n=92)	Highest third (n=128)	Lowest third (n=132)	Middle third (n=110)	Highest third (n=109)
No of person years of follow up in double blind study	441	353	417	481	427	443
No (%) of men at randomisation	29 (24)	35 (38)	37 (29)	29 (22)	39 (35)	40 (37)
No (%) with cardiovascular complications at randomisation	43 (36)	28 (30)	44 (34)	48 (36)	40 (36)	36 (33)
No (%) who smoked at randomisation	17 (14)	13 (14)	18 (14)	28 (21)	21 (19)	19 (17)
Mean (%) age at randomisation (years)	74·5 (8·7)	71·2 (6·7)	69·3 (6·8)	74·1 (9·2)	70·8 (6·3)	68·2 (6·3)
Characteristics during follow up						
Extremes of treated diastolic pressure* (mm Hg)	60-90	92-98	100-138	56-84	86-90	92-126
Treated systolic/diastolic pressure at middle of third (mm Hg)	160/85	173/95	186/108	147/78	151/88	159/98
Mean (SD) difference between treated pressure and pressure at randomisation (mm Hg):						
Systolic	−22 (19)	−8 (16)	4 (17)	−38 (21)	−30 (18)	−22 (19)
Diastolic	−14 (8)	−4 (6)	4 (9)	−20 (8)	−12 (6)	−5 (8)
Mean (SD) body weight at 9 months (kg)	62·5 (12·9)	67·2 (11·8)	70·5 (13·8)	62·8 (12·3)	65·2 (11·9)	69·8 (11·2)
Mean (SD) haemoglobin at 1 year (g/l)	137 (15)	144 (12)	146 (16)	135 (18)	141 (13)	146 (15)
No of patients in whom haemoglobin was measured	96	66	96	100	87	83

*Treated diastolic pressure refers to sitting diastolic pressure nine months after randomisation.

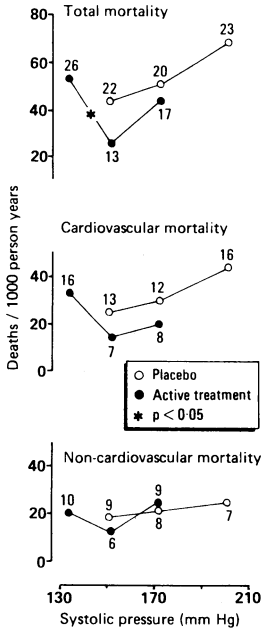

FIG 1—*Total, cardiovascular, and non-cardiovascular mortalities adjusted for age and sex in thirds of treated systolic pressure in patients randomised to placebo or active treatment. Figures are numbers of deaths in each third*

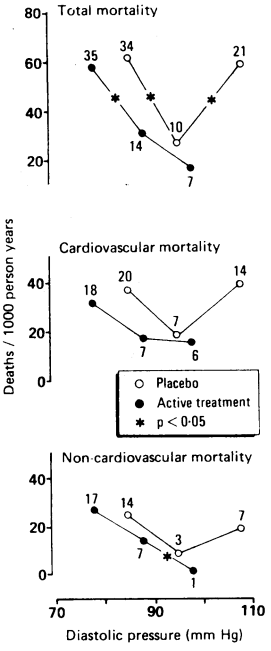

FIG 2—*Total, cardiovascular, and non-cardiovascular mortalities adjusted for age and sex in thirds of treated diastolic pressure in patients randomised to placebo or active treatment. Figures are numbers of deaths in each third*

Mortality after nine months

From the visit at nine months until the end of the double blind study 65 patients in the placebo group and 56 in the group taking active treatment died. As the age and sex distributions varied in the thirds of blood pressure (tables I and II) only adjusted rates are presented. The conclusions, however, were not different when the calculations were based on crude rates (number of deaths per person years at risk). For a similar achieved systolic (fig 1) or diastolic (fig 2) blood pressure mortality was lower in those taking active treatment than in those taking placebo.

Mortality in thirds of systolic pressure—In patients taking placebo total, cardiovascular, and non-cardiovascular mortality (fig 1) tended to increase from the lower to the upper third. In patients taking active treatment fewer patients died in the middle than the lowest third ($p<0·05$). When the three thirds of systolic blood pressure were compared a U shaped relation was apparent between treated systolic pressure and total mortality (fig 1). A similar trend was also observed for cardiovascular and non-cardiovascular mortality.

Mortality in thirds of diastolic pressure—In patients treated with placebo mortality from all causes was lower ($p<0·05$) in the middle than the two other thirds (fig 2). Cardiovascular and non-cardiovascular mortality showed a similar U shaped tendency. In patients taking active treatment both total ($p<0·004$) and non-cardiovascular ($p<0·007$) mortality were higher in the lowest than the highest third of blood pressure, and a similar trend was also present for cardiovascular mortality (fig 2).

DETERMINANTS OF MORTALITY

Cardiovascular complications at randomisation—In general, total and cardiovascular mortality were higher in patients with than in those without cardiovascular complications at randomisation. Cardiovascular complications at randomisation were not more prevalent in the lower thirds of pressure in either treatment group (tables I and II). The trends shown for total and cardiovascular mortality in figures 1 and 2 were similar in patients with and without cardiovascular complications at randomisation.

Fall in diastolic blood pressure—The median fall in diastolic blood pressure from randomisation to nine months later was 4% in patients taking placebo and 13% in those taking active treatment. The high total mortality in the lowest thirds of treated diastolic blood pressure (figure 2) was not associated with a greater than median fall in diastolic blood pressure. Indeed, in the lowest third of diastolic blood pressure in patients taking placebo the risk ratio for patients with a greater than median fall in pressure compared with patients with a smaller fall was 1·04 (95% confidence interval 0·25 to 4·36). Similarly, in the active treatment group the risk ratio was 1·41 (0·54 to 3·62).

Changes in body weight and haemoglobin concentration—Table III shows the changes in body weight at nine months with double blind treatment and in haemoglobin concentration at one year (haemoglobin concentration was not measured at nine months) as the percentage change in these measurements between these follow up visits and randomisation. The most pronounced decreases in body weight and haemoglobin concentration tended to occur in the patients in the lowest thirds of systolic and diastolic blood pressure during treatment.

Discussion

In contrast to many,[3-9] though not all,[17 18] previous studies that have reported a J shaped relation between treated blood pressure and mortality the present analysis was of patients taking placebo as well as of those taking active treatment. We defined treated blood pressure as the pressure nine months after randomisation because in both our treatment groups the average blood pressure decreased until this time, after which no further fall was observed.[23] Results based on the average of all blood pressure readings were not materially different but were not presented as they may have been biased by non-fatal events such as myocardial infarction and malignant disease developing during treatment. Indeed, these conditions often cause a fall in pressure and are related to subsequent mortality, thereby possibly giving rise to a spuriously high association between a low pressure and a fatal outcome.[24]

In the elderly patients treated with placebo and admitted into the European trial total mortality tended to rise with higher systolic pressure at nine months. In contrast, in the same treatment group the relation between total mortality and diastolic pressure was U shaped with a nadir at around 95 mm Hg. In the Framingham study a similar pattern—that is, a linear increase in risk with higher systolic pressure and a J shaped relation between cardiovascular risk and diastolic pressure with a nadir at around 90 mm Hg—was shown, at least when the effects of logistic smoothing were removed.[25 26] Coope *et al* who screened 10732 patients aged 60 to 79, observed a U or J shaped relation of total cardiovascular and coronary mortality with casual systolic and diastolic blood pressures, the lowest incidence being at a systolic pressure of 160-179 mm Hg and a diastolic pressure of 80-89 mm Hg.[27] In a population based study in Sweden there was a U shaped relation between total mortality and both systolic and diastolic pressures in

TABLE III—*Mean (SD) percentage changes in body weight and haemoglobin concentration during follow up in patients randomised to placebo and active treatment grouped according to thirds of treated systolic and diastolic blood pressures*

	Placebo group			Active treatment group		
	Lowest third	Middle third	Highest third	Lowest third	Middle third	Highest third
	Systolic blood pressure					
Body weight:						
No of patients	121	113	105	120	126	106
Change	−2·8 (0·8)***	−1·2 (0·6)	0·9 (0·5)	−2·4 (0·5)***	−0·6 (0·7)	−0·9 (0·5)
Haemoglobin concentration:						
No of patients	91	90	77	91	87	92
Change	−0·6 (1·0)	−0·7 (0·8)	2·2 (1·4)	−2·2 (0·9)**	−1·8 (0·9)*	−0·5 (1·0)
	Diastolic blood pressure					
Body weight:						
No of patients	119	92	128	132	110	109
Change	−3·0 (0·9)**	−1·2 (0·6)*	0·6 (0·4)	−2·1 (0·5)***	−1·1 (0·5)*	−0·5 (0·8)
Haemoglobin concentration:						
No of patients	96	66	96	100	87	83
Change	−0·2 (1·3)	−0·5 (0·8)	1·1 (0·4)	−3·2 (1·0)***	−0·8 (0·8)	−0·1 (0·9)

*p<0·05. **p<0·01. ***p<0·001.

subjects aged 40 to 69, while in those aged 70 and over a U shaped curve was seen only for diastolic pressure.[28 29] The relation between diastolic pressure and mortality is certainly more complex than a linear increase with rising pressure.[25-30]

In the actively treated patients in this trial the relation between total mortality and the treated systolic pressure was U shaped with a nadir at around 150 mm Hg, whereas total mortality increased gradually with decreasing diastolic pressure. Previous studies, which were mostly retrospective and not placebo controlled, focused attention on the possible deleterious effects of an exaggerated reduction in blood pressure induced by drugs, especially on the incidence of coronary events.[3-7] In some studies these conclusions were based on the average of all pressure readings throughout follow up[5-7] or on small differences with wide confidence intervals in the number of deaths between subgroups of treated pressure.[5 6]

Although an exaggerated reduction in blood pressure may be harmful, perhaps by impeding the coronary or cerebral circulation,[1 10 11 31] the present findings suggest that an excessive drug induced reduction in blood pressure is not the only mechanism underlying the J curve.[3-9] Indeed, in the present study (fig 2) and in earlier reports by Coope and Warrender[17 18] an increased mortality was also noticed in patients with a low diastolic blood pressure taking placebo. An exaggerated drug induced reduction in blood pressure is likely to be most harmful in patients with cardiovascular complications, in whom the coronary and cerebral circulations are already compromised. In the present study, however, cardiovascular complications at entry did not alter the relation between mortality and treated pressure. This finding is at variance with the reports of Cruickshank *et al*, who showed that the J shaped relation was confined to hypertensive patients with complications of atherosclerosis.[5 6]

Among the patients in the lowest thirds of treated diastolic pressure mortality was similar regardless of whether the fall in diastolic pressure after randomisation exceeded the median fall. Furthermore, not only cardiovascular mortality, which is likely to be adversely affected by an excessive reduction in blood pressure, but also non-cardiovascular mortality followed a pattern similar to that of total mortality (figs 1 and 2). Finally, patients with the lowest pressure during randomised treatment also experienced the greatest falls in body weight and haemoglobin concentration during the first year of follow up (table III). This could be related to some deterioration of general health.

In conclusion, the present analysis showed that in elderly patients with hypertension given active treatment total mortality had a U shaped relation with treated systolic pressure and an inverse association with treated diastolic pressure. The U curve between mortality and diastolic pressure in the patients taking placebo indicates that the increased mortality in the lower thirds of the actively treated patients may not be drug induced. This increased mortality could also be the expression of some deterioration in general health, as suggested by the decreases in body weight and haemoglobin concentration.

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Prevalence and diagnosis of chronic respiratory symptoms in adults

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Abstract

***Objective*—To investigate the prevalence and diagnosis of chronic respiratory disease in adults.**

***Design*—Screening questionnaire was sent to all patients aged 40-70 on the register of a group general practice; those responding positively were sent a detailed questionnaire and invited for assessment of respiratory function by forced expiratory volume in one second, forced vital capacity, peak flow rate, and reversibility studies with a β adrenergic inhaler.**

***Setting*—Group general practice in south west London.**

***Results*—Of 2387 patients aged 40-70, 1444 completed a screening questionnaire. Of the 509 patients who reported cough, phlegm, wheeze, or shortness of breath, 324 responded to a detailed questionnaire, 256 of whom had simple respiratory function assessed. Chronic bronchitis affected 106 (17%) men and 58 (7%) women, and wheeze occurring at least once a week affected 60 (9%) men and 20 (3%) women. Only a half to a third of patients had received a diagnostic label of chronic bronchitis or asthma for their symptoms. There was considerable clinical and physiological similarity (including reversibility of the airways) between patients labelled as having asthma and having chronic bronchitis. A label of asthma was used more often for patients of social classes I and II.**

***Conclusions*—Comparison with prevalence surveys carried out in the 1950s showed that respiratory symptoms are as common now as then, but the risk of disabling chronic bronchitis has fallen, more among men than women, probably because of their reduced smoking. Changes in diagnostic fashion, together with increased detection, may have contributed to the upward trend in reported morbidity from asthma over the past 30 years.**

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Introduction

Trends in mortality and morbidity from asthma and chronic bronchitis show important differences. For asthma there has been an increase in admissions to hospital, attendances at general practitioners, and, possibly, deaths.[1-4] For chronic bronchitis and emphysema there has been a decline in all these indicators.[5,6] These contrasting trends have been attributed to changes in aetiological factors, which have affected prevalence and severity, as well as to changes in medical care, including changes in diagnosis, management, and presentation of patients.[7]

As asthma and chronic bronchitis in adults share some important symptomatic and pathophysiological features, diagnostic transfer may also contribute to these trends. It has been reported in studies from America,[8,9] but its extent and implications have not been examined in the general population in the United Kingdom. We investigated the prevalence of chronic respiratory symptoms and their associated diagnostic labels and medical care in a general adult population and examined the extent to which illnesses labelled as asthma or chronic bronchitis differed in their clinical and physiological features and what other factors were associated with the acquisition of these labels. We also compared their prevalences with those found in similar studies that were carried out in the 1950s.[10-14]

Methods

The age-sex register of a group general practice in south west London was used to identify men and women aged 40-70. They were sent a previously validated screening questionnaire that inquired about coughing on winter mornings, phlegm on winter mornings, wheezing or whistling in the chest, shortness of breath on washing and dressing, and distance walked on the level before becoming short of breath.[15] Up to two reminders were sent. Patients who responded positively to at least one question were sent a detailed respiratory questionnaire that included questions on chronic bronchitis from the Medical Research Council's respiratory questionnaire.[16] Questions were also asked about the frequency and duration of symptoms over the past year; walking capability on the level, on hills, and on stairs; and the effect of the respiratory illness on everyday life and activities. Subjects were asked to record what they considered to be the diagnosis of their condition. The diagnosis recorded in the general practitioner's case notes was also obtained.

All subjects who completed the detailed questionnaire were invited to the surgery for tests of respiratory function. Forced expiratory volume in one second, forced vital capacity, and peak expiratory flow rate were measured with a McDermott spirometer, which was calibrated daily; the best of five attempts was recorded. Height was measured to the nearest centimetre. Reversibility with a β adrenergic inhaler was assessed 10 minutes after inhalation of 1 mg of terbutaline (four puffs) from a Nebuhaler (Astra