

# Results of the pilot study for the Hypertension in the Very Elderly Trial

Christopher J. Bulpitt<sup>a</sup>, Nigel S. Beckett<sup>a</sup>, Jonathan Cooke<sup>a</sup>, Dan L. Dumitrascu<sup>b</sup>, Blas Gil-Extremera<sup>c</sup>, Choudomir Nachev<sup>d</sup>, Maria Nunes<sup>a</sup>, Ruth Peters<sup>a</sup>, Jan A. Staessen<sup>e</sup> and Lut Thijs<sup>e</sup>, on behalf of the Hypertension in the Very Elderly Trial (HYVET) Working Group

**Background** The risks and benefits of treating hypertension in individuals older than 80 years are uncertain. A meta-analysis has suggested that a reduction in stroke events of 36% may have to be balanced against a 14% increase in total mortality.

**Objectives** To report the results of the pilot study of the Hypertension in the Very Elderly Trial (HYVET), which is in progress to address these issues.

**Methods** The HYVET-Pilot was a multicentre international open pilot trial. In 10 European countries, 1283 patients older than 80 years and with a sustained blood pressure of 160–219/90–109 mmHg were allocated randomly to one of three treatments: a diuretic-based regimen (usually bendroflumethiazide;  $n = 426$ ), an angiotensin-converting enzyme inhibitor regimen (usually lisinopril;  $n = 431$ ) or no treatment ( $n = 426$ ). The procedure permitted doses of the drug to be titrated and diltiazem slow-release to be added to active treatment. Target blood pressure was  $< 150/80$  mmHg and mean follow-up was 13 months.

**Results** In the combined actively treated groups, the reduction in stroke events relative hazard rate (RHR) was 0.47 [95% confidence interval (CI) 0.24 to 0.93] and the reduction in stroke mortality RHR was 0.57 (95% CI 0.25 to 1.32). However, the estimate of total mortality supported the possibility of excess deaths with active treatment (RHR 1.23, 95% CI 0.75 to 2.01).

## Introduction

The Hypertension in the Very Elderly Trial (HYVET) main trial is being conducted to determine the risks and benefits of the treatment of hypertension in individuals older than 80 years. As with other long-term treatments for the prevention of cardiovascular disease, the risks may change with age. For example, with anticoagulants there is concern that, in the very elderly, risks may outweigh benefits [1], and with low-dose aspirin the reverse may be the case [2].

The pilot trial was performed to test the trial administration, obtain a preliminary estimate of the rate of

**Conclusions** The preliminary results support the need for the continuing main HYVET trial. It is possible that treatment of 1000 patients for 1 year may reduce stroke events by 19 (nine non-fatal), but may be associated with 20 extra non-stroke deaths. *J Hypertens* 21:2409–2417 © 2003 Lippincott Williams & Wilkins.

*Journal of Hypertension* 2003, 21:2409–2417

**Keywords:** hypertension, very elderly, diuretics, angiotensin-converting enzyme inhibitors, stroke

<sup>a</sup>Faculty of Medicine, Imperial College London, UK, <sup>b</sup>University of Medicine and Pharmacy, Cluj, Romania, <sup>c</sup>Universidad de Granada, Granada, Spain, <sup>d</sup>St Anna Hospital, 1784 Sofia, Bulgaria and <sup>e</sup>Department of Molecular and Cardiovascular Research, Katholic University Leuven, Belgium.

Note: Previously presented at the Joint International Society of Hypertension–European Society of Hypertension meeting, Prague 2002.

Sponsorship: The HYVET Pilot Trial was supported by the British Heart Foundation. The main trial is supported by a programme grant from the British Heart Foundation and by the Institut de Recherches Internationales Servier.

Correspondence and requests for reprints to C.J. Bulpitt, Section of Care of the Elderly, Imperial College, Faculty of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK.  
Tel: +44 (0) 20 8383 3958; fax: +44 (0) 20 8743 0798;  
e-mail: c.bulpitt@ic.ac.uk

Received 20 January 2003 Revised 28 July 2003  
Accepted 6 August 2003

See editorial commentary page 2249

recruitment, test the techniques of measurement and recording, determine the safety of the active treatment and obtain a rough estimate of any treatment effects.

The pilot HYVET trial was an open design that worked well, but concerns were expressed that only the results of a double-blind trial conducted to Good Clinical Practice guidelines would be acceptable in the 21st century. After completion of the pilot trial, the main trial was started with an improved design [3]. Without knowledge of the results of the pilot trial, the Data Monitoring Committee decided that the results should be published and placed in the public domain. In the

event, the results closely support the rationale for the main trial, by starting to determine the risks and benefits of treating hypertension in this very elderly age group.

## Methods

In the pilot trial, patients older than 80 years and with hypertension were allocated randomly but equally to groups to receive a diuretic-based regimen, an angiotensin-converting enzyme (ACE)-based regimen or to no treatment. The drugs administered were bendroflumethiazide (bendrofluazide) and lisinopril; to these active treatments, diltiazem slow-release could be added to achieve target blood pressure. If one or more of these drugs was not available to a particular investigator, then a substitute was agreed. The antihypertensive medications were therefore prescribed according to local practice (usually the National Health System), and the pilot trial was started before the adoption of Good Clinical Practice guidelines by the European Union.

The inclusion criteria were: age more than 80 years, sitting systolic blood pressure (average of four readings) 160–219 mmHg, diastolic blood pressure 95–109 mmHg (later changed to 90–109 mmHg), standing systolic blood pressure > 140 mmHg (average of two readings) and provision of informed consent. The exclusion criteria were serum creatinine > 150 µmol/l, accelerated hypertension, congestive heart failure requiring treatment, inability to stand, cerebral or subarachnoid haemorrhage in past 6 months, need for blood pressure-decreasing treatment because of angina etc., the presence of gout, renal artery stenosis, dementia (abbreviated mental test score < 7/10 [4]) and a condition expected to limit survival severely.

The procedure has been published in full elsewhere [5]. The trial recruited individuals from both primary and secondary care and was of an open design. Two readings of sitting blood pressure were taken after the individual had rested for 5 min, in previously treated or untreated patients, provided treatment had been stopped for at least 1 week. One month later, the measurements were repeated again, with no treatment given during the intervening period. On this occasion the standing blood pressure was also taken on two occasions. The diastolic pressure was taken as phase V.

Patients were stratified into four groups on the basis of sex and age (80–89 years and > 90 years). The unit of randomization was the individual and the SAS Random Allocation of Treatments Balanced in Blocks Program was used to generate the schedule. Restricted random allocation to groups was used to ensure equal allocation per group within each centre and allocation to groups was performed centrally. There were three groups: no

treatment, diuretic-based treatment [usually bendroflumethiazide (bendrofluazide) 2.5 mg] and an ACE-inhibitor-based treatment (usually lisinopril 2.5 mg). To attain target blood pressure in the actively treated groups, the procedure allowed for the dose of diuretic or ACE inhibitor to be doubled (step 2), diltiazem slow-release 120 mg to be added (step 3) and diltiazem slow-release 240 mg to be added (step 4). The target blood pressures were a sitting systolic pressure less than 150 mmHg plus a sitting diastolic pressure less than 80 mmHg.

The main endpoints of the trial were stroke events, total mortality and cardiovascular, cardiac and stroke mortality. As this was an open study, the randomized treatment could be continued after a non-fatal event. Informed written consent was obtained before the individual was assigned to groups and Ethics Committee clearance was obtained for all centres.

The pilot trial was supported by the British Heart Foundation. It was not considered reasonable to ask the Foundation to bear the costs of treatment, double-blinding or monitoring of the study. However, although the pilot trial went smoothly and recruited in excess of the number of participants originally proposed (500 patients), it was decided that the main trial should be double-blind, with treatments provided by an industrial partner and monitoring to Good Clinical Practice. The pilot trial began in March 1994 and ended in June 1998. The main HYVET trial has now begun [3], with sponsorship from both the British Heart Foundation and the Institut de Recherches Internationales Servier.

## Statistical considerations

As the trial was a pilot trial with limited numbers and a short period of follow-up, interim analyses were not performed. Similarly, although power calculations are published [3,5], they are not relevant to the pilot trial. All analyses are presented on an intention-to-treat basis. Mortality from all causes, cardiovascular and non-cardiovascular causes, stroke, cardiac and other cardiovascular deaths were compared in the three trial groups, using both the log rank test [6] and the Cox proportional hazards model [7] to adjust for sex, age, previous myocardial infarction or previous stroke. The effect of treatment was also determined for fatal plus non-fatal stroke and the effects in the combined actively treated groups were also determined in comparison with no treatment. Database analysis was mostly carried out using SAS version 8.02.

## Results

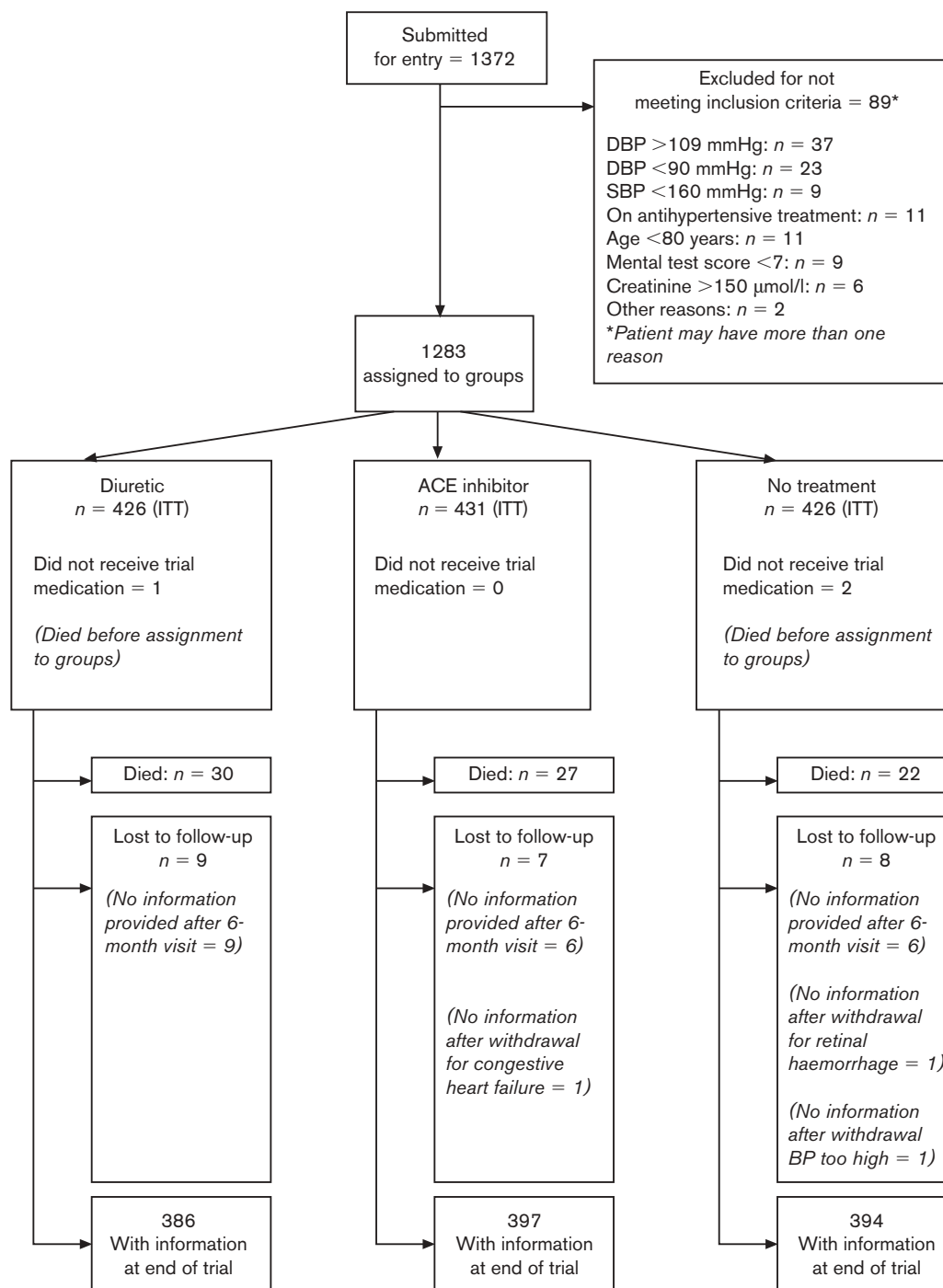
In this HYVET pilot trial, 1283 patients were allocated randomly to groups: 1130 (88%) in Bulgaria, 39 (3%) in Spain, 39 (3%) in Romania, 32 (2.5%) in the UK, 20

(1.5%) in Poland and smaller numbers in Finland, Lithuania, Ireland, Greece and Serbia.

Figure 1 presents the flow chart for the trial procedure. We do not have figures for the total number screened or followed in the trial run-in period, however, 89

individuals submitted entry forms but were not eligible for random allocation to groups. Of the 1283 patients who were assigned to groups, only 27 (2.1%) were lost to follow-up (had no end-of-trial information). The average duration of follow-up was 13 months. The numbers of patient-years of follow-up for those in the

Fig. 1



Flow chart for the HYVET-Pilot Trial. SBP, DBP, systolic and diastolic blood pressures; ACE, angiotensin-converting enzyme; ITT, intention-to-treat analysis; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

diuretic, ACE and no-treatment groups were 473, 493 and 466, respectively.

The average age of the patients was  $83.8 \pm 3.0$  (SD) years (range 79.5–96.1 years). Three patients were allocated randomly to groups in error, shortly before their 80th birthday, but their results are included in the analysis. Entry systolic blood pressure averaged  $181.5 \pm 11.3$  mmHg (range 160–217 mmHg) and entry diastolic pressure averaged  $99.6 \pm 3.4$  mmHg (range 90–114 mmHg). One patient with an average diastolic pressure of 113.8 mmHg was allocated randomly to groups in error. Average baseline concentration of creatinine was  $102.2 \pm 18.5$   $\mu$ mol/l and that of potassium  $4.32 \pm 0.48$  mmol/l. The three groups did not differ in baseline characteristics (Table 1). On average, the patients were not obese, with an average body mass index of 25 kg/m<sup>2</sup>; 48% had been previously treated, 3.0% had had a previous myocardial infarction, 4.5% a previous stroke, 4.2% were current smokers and 20.7% drank more than 1 unit of alcohol per day. Table 2 presents the blood pressures and treatments at the end of the trial. Of the 426 patients allocated randomly to a diuretic-based treatment, 385 (88.5%) were alive and provided information at the end of the trial. The corresponding numbers were 397 (89.8%) for ACE-based treatment and 394 (90.1%) for no treatment. The sitting blood pressure had decreased by an average of 30/16 mmHg (systolic/diastolic) with both diuretic- and ACE-based treatments, and by 7/5 mmHg with no treatment. The corresponding decreases in standing blood pressure were 26/15 mmHg, 27/16 mmHg and 3/

4 mmHg for diuretic-based, ACE-based and no treatment, respectively. In the diuretic-based treatment group, 97% were still taking a diuretic and 16% a calcium channel blocker. The diuretics were bendroflumethiazide (bendrofluazide; 51%), chlorthalidone (34%) and hydrochlorothiazide (13%). Thirteen percent of the patients received diltiazem in the ACE-based treatment group; 96% were still taking an ACE inhibitor, 54% lisinopril and 42% enalapril. In the 'no treatment' group only three individuals (0.8%) were receiving antihypertensive treatment.

Thirty patients (7.0%) died in the diuretic-based treatment group – a rate of 63.4/1000 patient-years; in the ACE-based treatment group 27 (6.3%) died – a rate of 54.8/1000 patient-years; in the no-treatment group, 22 (5.2%) died – a rate of 47.2/1000 patient-years.

The deaths were also classified into cardiovascular and non-cardiovascular deaths, with two deaths from an unknown cause arbitrarily included as non-cardiovascular deaths. There were 23, 22 and 19 cardiovascular deaths in the diuretic-, ACE- and no-treatment groups, respectively, and seven, five and three non-cardiovascular deaths in the corresponding three groups. The cardiovascular deaths were further subdivided into stroke (24 deaths), cardiac (29 deaths) and other cardiovascular (11 deaths). Two of the stroke deaths were haemorrhagic and the remainder were from infarction or unspecified. Fatal stroke occurred in six, seven and 11 patients in the diuretic-, ACE- and no-treatment groups; non-fatal strokes occurred in 0, five

**Table 1 Baseline characteristics of patients in the HYVET-Pilot trial**

	Diuretic-based treatment (n = 426)	ACE-based treatment (n = 431)	No treatment (n = 426)
Age (years)	83.8 $\pm$ 3.3 79.5–96.1	83.7 $\pm$ 3.0 79.8–93.0	83.8 $\pm$ 2.9 79.6–95.0
Women (%)	62.9	64.0	63.4
Entry BP (mmHg)			
Sitting SBP	181.5 $\pm$ 11.3	181.9 $\pm$ 11.3	181.0 $\pm$ 11.5
Sitting DBP	99.6 $\pm$ 3.4	99.6 $\pm$ 3.3	99.5 $\pm$ 3.6
Standing SBP	173.4 $\pm$ 12.6	173.6 $\pm$ 12.4	173.4 $\pm$ 12.3
Standing DBP	98.1 $\pm$ 6.1	98.3 $\pm$ 5.8	98.1 $\pm$ 5.7
Sitting heart rate (beats/min)	76.5 $\pm$ 9.5	76 $\pm$ 9.7	77.0 $\pm$ 9.9
Serum creatinine ( $\mu$ mol/l)	102.6 $\pm$ 18.0	102.4 $\pm$ 18.5	102.3 $\pm$ 18.4
Serum sodium (mmol/l)	141.6 $\pm$ 4.4	141.8 $\pm$ 4.5	142.0 $\pm$ 4.1
Serum potassium (mmol/l)	4.33 $\pm$ 0.50	4.32 $\pm$ 0.48	4.32 $\pm$ 0.47
Weight (kg)	67.8 $\pm$ 10.5	68.2 $\pm$ 11.4	67.9 $\pm$ 11.3
Height (cm)	163.8 $\pm$ 8.9	163.5 $\pm$ 8.7	163.3 $\pm$ 8.3
BMI (kg/m <sup>2</sup> )	25.3 $\pm$ 3.4	25.5 $\pm$ 3.4	25.4 $\pm$ 3.7
Previously treated (%)	46.8	48.3	48.5
Previous MI (%)	2.4	3.0	3.5
Previous stroke (%)	4.2	4.2	5.2
Smokers (%)			
Never	89.8	83.7	87.1
Past	7.3	11.2	8.3
Current	2.9	5.1	4.6
Alcohol > 1 unit/day (%)	21.3	22.5	18.4

Values are means  $\pm$  SD, ranges or percentages. ACE, angiotensin-converting enzyme; BP, blood pressure; SBP, DBP, systolic and diastolic blood pressures; BMI, body mass index; MI, myocardial infarction.

**Table 2 End of trial information (intention-to-treat analysis)**

	Diuretic-based treatment ( <i>n</i> = 386)	ACE-based treatment ( <i>n</i> = 397)	No treatment ( <i>n</i> = 394)
Blood pressure (mmHg)			
Sitting SBP	152 ± 13	151 ± 13	174 ± 11
Sitting DBP	84 ± 7	84 ± 7	95 ± 6
Standing SBP	148 ± 14	147 ± 13	170 ± 12
Standing DPB	83 ± 7	83 ± 7	94 ± 7
Any diuretic	376 (97.4)	3 (0.8)	1 (0.3)
Bendrofluzide			
2.5 mg	111 (28.8)	1 (0.3)	1 (0.3)
5.0 mg	81 (21.0)	1 (0.3)	0
> 5.0 mg	1 (0.3)	0	0
Hydrochlorothiazide			
12.5 mg	10 (2.6)	0	0
25 mg	21 (5.4)	0	0
50 mg	16 (4.1)	0	0
> 50 mg	4 (1.0)	0	0
Chlorthalidone			
25 mg	113 (29.3)	0	0
50 mg	17 (4.4)	0	0
Other diuretics	2 (0.5)	1 (0.3)	0
Any ACE inhibitor	1 (0.3)	381 (96.0)	2 (0.5)
Lisinopril			
2.5 mg	1 (0.3)	85 (21.4)	2 (0.5)
5.0 mg	0	126 (31.7)	0
> 5.0 mg	0	3 (0.8)	0
Enalapril			
2.5 mg	0	3 (0.8)	0
5.0 mg	0	12 (3.0)	0
10 mg	0	84 (21.2)	0
15 mg	0	8 (2.0)	0
20 mg	0	51 (12.8)	0
> 20 mg	0	7 (1.8)	0
Other ACE inhibitors	0	3 (0.8)	0
Calcium channel blockers			
Diltiazem			
60 mg	62 (16.1)	51 (12.8)	0
120 mg	9 (2.3)	6 (1.5)	0
180–240 mg*	39 (10.1)	32 (8.1)	0
14 (3.6)	13 (3.3)	0	
No antihypertensive	7 (1.8)	15 (3.8)	391 (99.2)

Values are mean ± SD or number (%). ACE, angiotensin-converting enzyme; SBP, DBP, systolic and diastolic blood pressures. \*Only one patient received 180 mg.

and seven individuals in the three groups, respectively. The cardiac deaths were myocardial infarction (15), other ischaemic heart disease (eight), congestive heart failure (five) and sudden death (one). The other cardiovascular deaths were atherosclerosis (five), pulmonary embolism (four), hypertension (one) and aortic aneurysm (one). The non-cardiovascular deaths were pneumonia or respiratory disease (six), cancer (four), gastrointestinal haemorrhage (one), unknown (two) and trauma (two).

Table 3 gives the relative hazard rate (RHR) of having an event in an active treatment group compared with the no-treatment group adjusted for age, sex and, as appropriate, previous myocardial infarction and previous stroke. Most importantly, the 95% confidence limits are given and show, as expected for a pilot trial, that the treatment effects did not usually achieve statistical significance and that the confidence intervals (CI) were wide. The effect of being in the diuretic

group was non-significant, with RHRs of 1.31 (95% CI 0.75 to 2.27) for total deaths, 2.09 (95% CI 0.79 to 5.50) for cardiac deaths and 0.52 (95% CI 0.19 to 1.42) for stroke deaths. The corresponding results for being in the ACE group were 1.14 (95% CI 0.65 to 2.02) for total deaths, 1.40 (95% CI 0.50 to 3.92) for cardiac deaths and a similar 0.60 (95% CI 0.23 to 1.55) for stroke deaths. However, for the 'all stroke events' analysis, the RHR for fatal plus non-fatal strokes for both active treatment groups combined decreased to 0.47 (95% CI 0.24 to 0.91; *P* = 0.02). When results from the two active treatment groups were combined, total mortality with active treatment tended to be increased, with an RHR of 1.23 (95% CI 0.75 to 2.01), and cardiovascular mortality was 1.13 (95% CI 0.66 to 1.94), but stroke deaths tended to be reduced: RHR 0.56 (95% CI 0.25 to 1.26). Thus active treatment of 1000 patients for 1 year would save between five and 32 strokes, but tends to produce anything between a deficit of 12 or an excess of 48 deaths. The point

**Table 3 Relative hazard rates and 95% confidence intervals (CI) for mortality in the diuretic and angiotensin-converting enzyme (ACE) groups, adjusted for sex and age and, as appropriate, previous myocardial infarction (MI) and stroke**

Mortality	Number of deaths	Relative hazard rate (95% CI)					
		Diuretic group effect	ACE inhibitor group effect	Age(1 year)	Male sex	Previous MI	Previous stroke
Total	79	1.31 (0.75 to 2.27)	1.14 (0.65 to 2.02)	1.15 (1.08 to 1.22)	1.42 (0.89 to 2.25)	1.34 (0.47 to 3.83)	1.24 (0.49 to 3.12)
Cardiovascular	64	1.17 (0.63 to 2.14)	1.09 (0.58 to 2.03)	1.16 (1.09 to 1.24)	1.57 (0.95 to 2.61)	1.59 (0.55 to 4.61)	1.58 (0.62 to 3.99)
Stroke	24*	0.52 (0.19 to 1.42)	0.60 (0.23 to 1.55)	1.11 (1.00 to 1.24)	1.41 (0.62 to 3.24)	-	1.57 (0.37 to 6.89)
Cardiac	29*	2.09 (0.79 to 5.50)	1.40 (0.50 to 3.92)	1.14 (1.03 to 1.25)	1.53 (0.72 to 3.22)	4.16 (1.32 to 13.04)	-
Other CVD	11	1.97 (0.36 to 10.82)	2.64 (0.50 to 13.77)	1.26 (1.08 to 1.46)	2.29 (0.61 to 7.13)	-	-
Non-CVD	15	2.20 (0.57 to 8.51)	1.48 (0.35 to 6.20)	1.09 (0.95 to 1.26)	0.79 (0.25 to 2.53)	-	-
Fatal and non-fatal strokes	36	0.31 (0.12 to 0.79)	0.63 (0.30 to 1.31)	1.09 (1.00 to 1.19)	1.07 (0.54 to 2.14)	-	1.86 (0.56 to 6.17)

\*One patient was classified as having both a stroke and cardiac death. CVD, cardiovascular disease.

estimates suggest a saving of about 19 strokes (nine non-fatal) for a possible increase of 20 non-stroke deaths per 1000 patients treated for 1 year.

The effects of age on total mortality and cardiovascular mortality were highly statistically significant and the RHRs for 1 year of age ranged from 1.11 for stroke to 1.26 for other (non-stroke, non-cardiac) cardiovascular disease (Table 3). Male sex consistently (but not significantly) predicted cardiovascular disease, with RHRs between 1.41 (stroke) and 2.09 (other cardiac death). A previous myocardial infarction predicted a cardiac death (RHR 4.16, 95% CI 1.32 to 13.04), but a previous stroke did not conclusively predict a stroke death (RHR 1.57, 95% CI 0.36 to 6.89).

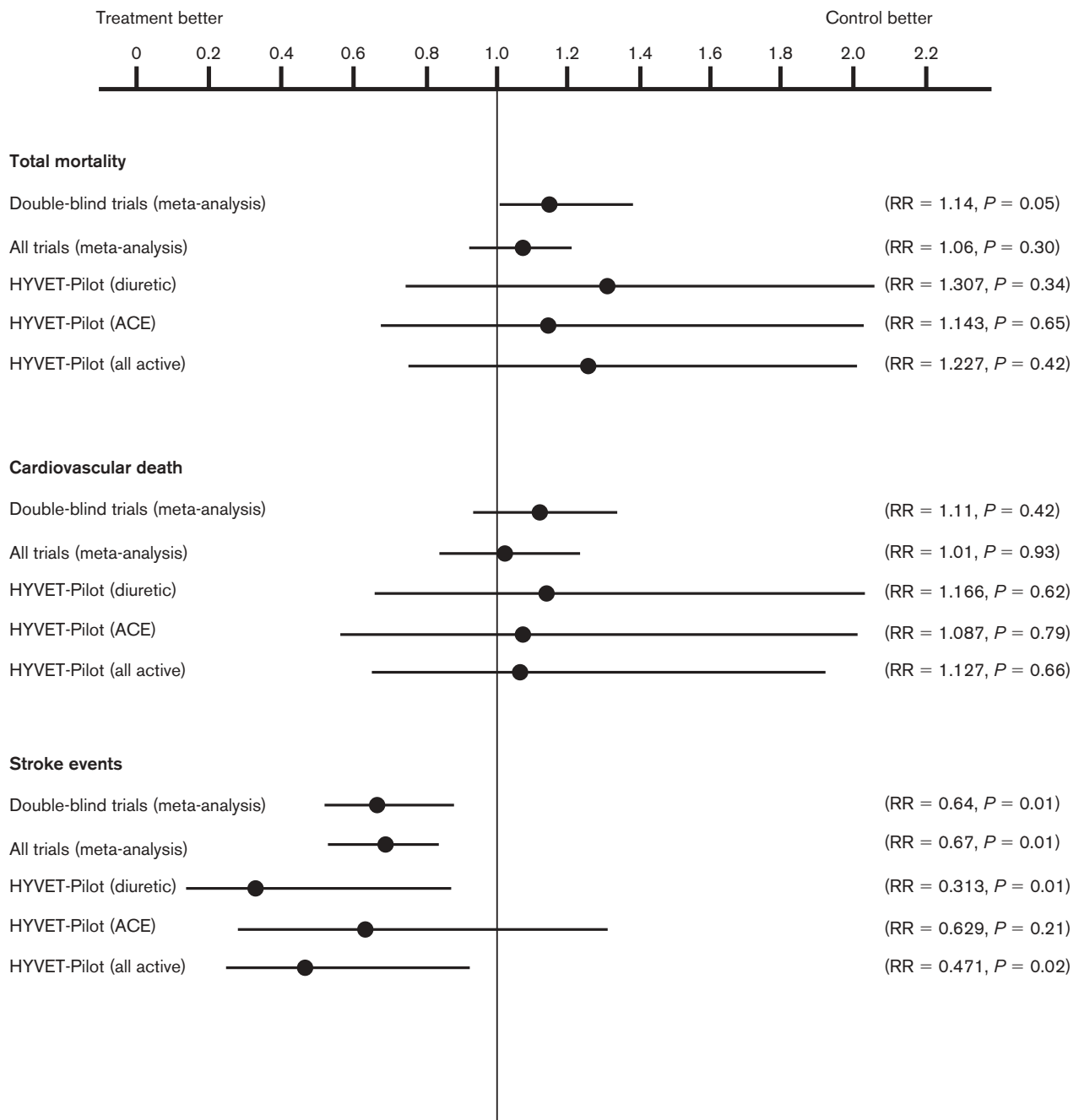
Baseline measurements for creatinine and potassium are given in Table 1. No patient was withdrawn from the trial because of renal problems during follow-up. Serum creatinine concentration was measured in 538 patients within 6 months of random allocation to groups and in 449 patients after 1 year of follow-up (85% of those who were available at that time). The mean  $\pm$  SD 'increase' in all patients at 6 months from baseline was  $-1 \pm 13$   $\mu$ mol/l for the diuretic group,  $+3 \pm 15$   $\mu$ mol/l for the ACE inhibitor group and  $+1 \pm 17$   $\mu$ mol/l for the no-treatment group [analysis of variance (ANOVA);  $P = 0.04$ ]. The corresponding mean increases at 12 months were  $+4 \pm 15$   $\mu$ mol/l,  $+4 \pm 16$   $\mu$ mol/l and  $+1 \pm 13$   $\mu$ mol/l (ANOVA;  $P = 0.14$ ). The mean changes in potassium from baseline to 6 months were  $-0.06 \pm 0.5$  mmol/l in the diuretic group,  $+0.01 \pm 0.04$  mmol/l in the ACE inhibitor group and  $-0.05 \pm 0.05$  mmol/l in the no-treatment group (ANOVA;  $P = 0.34$ ). The corresponding mean changes at 12 months were  $-0.1 \pm 0.04$  mmol/l,  $+0.01 \pm 0.05$  mmol/l and  $-0.01 \pm 0.4$  mmol/l (ANOVA;  $P = 0.001$ ). No significant differences changes were noted for uric acid at 6 or 12 months.

## Discussion

Figure 2 presents a comparison of the possible increases in total mortality from active treatment in the present pilot trial with the results of the meta-analysis of the result of controlled trials in individuals older than 80 years reported by Gueyffier *et al.* [8]. Similarly, the possible increase in cardiovascular mortality is compared with the results of the meta-analysis, together with the reduction in fatal plus non-fatal strokes. The results of the pilot trial agree very well with those of the meta-analysis. Thus the problem of assessing the risks and benefits from treatment of mild-to-moderate hypertension in individuals older than 80 years remains. The main HYVET trial is designed to provide definitive answers to this problem, and by 7 July 2003 had already enrolled 1469 patients.

It is of interest that cross-sectional epidemiological

Fig. 2



Comparison of HYVET-Pilot results with those of the meta-analysis by Gueyffier *et al.* [7]. Point estimates of the relative hazard rates are given, together with the 95% confidence intervals. RR, relative risk; ACE, angiotensin-converting enzyme.

studies do not reveal an excess total mortality in hypertensive elderly individuals [9], and a longitudinal study of blood pressure changes between ages 70 and 90 years has shown that individuals alive at the age of 93 years had higher blood pressures at age 90 years than those who had died. In addition, those with a greater individual systolic blood pressure at age 79 years than

at age 70 or 75 years also tended to survive to the age of 90 years [10].

The number of deaths in the pilot trial were insufficient to suggest any mechanism that could underlie the increase in mortality. The main trial, if confirming this problem, is expected to identify the mechanism,

although a previous large trial in the elderly failed to reach any conclusion. The UK Medical Research Council trial in the elderly aged 65–74 years [11] reported both a non-significant decrease in total mortality and a 26% reduction in cardiovascular deaths in 1081 patients given a diuretic, but non-significant increases in total mortality of 7% and in cardiovascular mortality of 6% in 1102 patients given a  $\beta$ -blocker. A partial explanation appeared to be that men given atenolol had a general increase in cancer rate, but women given atenolol had the lowest cancer rate and the men tended to have a slight increase in cardiovascular mortality. The increase in cancer mortality has not been confirmed [12].

The main weaknesses of the pilot trial were that it was an open study and also was not conducted to the standards of Good Clinical Practice. The problem with the use of an open design is that both patient and investigator know the treatment given. This can lead to bias in several different ways. Investigator bias may affect what is written on a death certificate: for example, if the patient has both a myocardial infarction and a stroke before death, the investigator may tend to record a stroke as the underlying cause of death if the patient is receiving no treatment and blood pressure is high. The problem was addressed, to some extent, by coding endpoints without knowledge of the treatment. However, it is difficult to correct for the initial bias.

Both the investigators' and the patients' knowledge of treatment may affect the withdrawal rates, for example favouring the removal from the trial of a patient who is receiving no treatment but has high blood pressure that approaches but does not exceed a terminating outcome. In a placebo-controlled, double-blind trial, there is always doubt as to the nature of the treatment, and the pressure to withdraw because of an adverse event is less. Similarly, the investigators' and the patients' knowledge will affect the reporting of adverse drug events. In a double-blind trial, 'adverse drug events' are also reported in those receiving placebo, and thus an accurate estimate of true drug effects may be obtained by comparing the active and placebo groups. In an open trial, adverse events are not reported for the placebo group. Similarly, an individual's quality of life is improved by their entering a trial, and it is probable that one component of this effect is receiving treatment. It is likely that, in an open study, measures of quality of life when the individual is receiving no treatment will not improve, and the benefits of treatment may be over-emphasized. Lastly, it is possible that knowledge of the treatment will affect the blood pressure that is recorded, with high measurements being repeated in those receiving active treatment, but not in the control patients. In actively treated patients, the second reading is likely to be lower, exaggerating the effect of treatment.

Nevertheless, it is difficult to see how investigator or patient bias could affect both the results of the pilot trial and the meta-analysis – namely a reduction in stroke events balanced by an increase in total mortality. However, the main trial is double-blind and conducted to Good Clinical Practice standards, and it is expected to report in 2005. Meanwhile, it is possible that treatment of 1000 patients for 1 year may reduce fatal plus non-fatal strokes by 19 but be associated with an excess of 20 non-stroke deaths.

## References

- 1 Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation: a multicenter, prospective, randomized trial. Japanese Nonvalvular Atrial Fibrillation – Embolism Secondary Prevention Cooperation Study Group. *Stroke* 2000; **31**:817–821.
- 2 Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989; **321**:129–135.
- 3 Bulpitt CJ, Fletcher A, Beckett NS, Coope J, Gil-Extremera B, Forette F, et al. Hypertension in the Very Elderly Trial (HYVET) protocol for the main trial. *Drugs Aging* 2001; **18**:151–164.
- 4 Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. *Age Ageing* 1972; **1**:233–238.
- 5 Bulpitt CJ, Fletcher AE, Amery A, Coope J, Evans JG, Lightowler S, et al. The Hypertension in the Very Elderly Trial (Hyvet): rationale, methodology and comparison with previous trials. *Drugs Aging* 1994; **5**: 171–183.
- 6 Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966; **50**:163–170.
- 7 Cox DR. Regression models and life tables. *J R Statist Soc* 1972; **34**:187–220.
- 8 Gueyffier F, Bulpitt C, Boissel J-P, Schron E, Ekblom T, Fagard R, et al. Antihypertensive drugs in very old people: a subgroup meta-analysis of randomised controlled trials. *Lancet* 1999; **353**:793–796.
- 9 Bulpitt CJ, Fletcher AE. Prognostic significance of blood pressure in the very old. *Drugs Aging* 1994; **5**:184–191.
- 10 Lernfelt B, Svanborg A. Change in blood pressure in the age interval 70–90. Late blood pressure peak related to longer survival. *Blood Press* 2002; **11**:206–212.
- 11 MRC Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ* 1992; **304**:405–412.
- 12 Fletcher AE, Beevers DG, Bulpitt CJ, Coles EC, Dollery CT, Ledingham JG, et al. Cancer mortality and atenolol treatment. *BMJ* 1993; **306**: 622–623.

## Appendix

### Hypertension in the Very Elderly Trial (HYVET) working group

*Lead Investigator:* Christopher Bulpitt.

*Co-Investigator:* Astrid Fletcher.

*Writing Committee:* Christopher Bulpitt, Maria Nunes, Jonathan Cooke, Ruth Peters, Nigel Beckett.

### Steering Committee

John Coope, Blas Gil-Extremera, Francoise Forette, Choudomir Nachev, Kevin O'Malley, John Potter, Peter Sever, Jan Staessen, Cameron Swift, Jaakko Tuomilhto.

### Data Monitoring Committee

Jan Staessen (Chairman), Astrid Fletcher, Lut Thijs, Jonathan Cooke (ex officio).



**Co-ordinating Centre Staff**

Nigel Beckett and Maria Nunes (trial co-ordinators), Ruth Peters and Sarah Mirza (quality control), Jonathan Cooke (statistician).

nen (Finland), F. Forette (France), J. Duggan (Ireland), G. Gensini (Italy), T. Grodzicki (Poland), G. Clara (Portugal), D.L. Dumitrascu (Romania), Y. Nikitin (Russia), B. Gil-Extremera (Spain), B. Williams (UK).

**Researchers involved in the HYVET-Pilot trial****UK**

S. Bailey (Chadderton), H. Bethel (Alton), N. Coni (Cambridge), J. Coope (Macclesfield), N. Gainsborough (Brighton), G. Greveson (Newcastle), P. McCaffrey (Lurgan), P. Murdoch (Falkirk), N.D. Pandita-Gunawardena and C. Rajkumar (London), J. Potter (Leicester), S. Soloman (Oldham), B. Williams (Glasgow).

**Bulgaria**

S. Belova (Vidin), R. Kermova (Pleven), S. Mantov (Stara Zagora), E. Mantova, C. Nachev, D. Popov, D. Smilkova and V. Stoyanovsky (Sophia), V. Sirakova (Varna), P. Solakov (Plovdiv), T. Vasileva (Dobrich), D. Yankulova (Bankya).

**Finland**

R. Antikainen (Oulu).

**Romania**

S. Babeanu (Bucharest), D. Dumitrascu (Cluj).

**Spain**

B. Gil-Extremera, M.L. Arjona-García (Granada).

**Lithuania**

J. Arlauskas (Trakuraj).

**Ireland**

J. Duggan (Dublin).

**Poland**

Z. Chodorowski (Gdansk), T. Grodzicki (Krakow).

**Greece**

A. Efstratopoulos (Athens).

**Serbia**

M. Davidovic (Belgrade).

**Extra committees in the main HYVET trial****Ethics committee**

John Grimley-Evans, Robert Fagard (Chairman), Brian Williams.

**Endpoint Committee**

Christopher Davidson (Chairman), Joe Duggan, Nicki Gainsborough, M.C. De Vernejoul.

**National Co-ordinators**

R. Warne and I. Puddey (Australia), H. Celis (Belgium), C. Nachev (Bulgaria), L. Lisheng (China), R. Antikai-