ORIGINAL ARTICLE

Baseline characteristics of participants in the Hypertension in the Very Elderly Trial (HYVET)

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Abstract

The Hypertension in the Very Elderly Trial (HYVET) is a randomized double-blind trial of active antihypertensive treatment (indapamide 1.5 mg sustained release $\pm$ 2–4 mg perindopril) vs placebo in participants over the age of 80 years with a systolic blood pressure (SBP) of 160–199 mmHg during a placebo run-in period plus a diastolic blood pressure (DBP) of <110 mmHg. The trial has completed with 3845 subjects randomized and we report the baseline characteristics. The participants were a healthy group. The numbers smoking, drinking alcohol and having previous cardiovascular events were low, and their hypertensive status was not usually associated with the metabolic syndrome; 1.0% of the whole group had a total cholesterol over 8.0 mmol/l, 1.1% a blood sugar over 11.1 mmol/l (irrespective of anti-diabetic treatment) and 1.7% a serum urate over 460 μ mol/l (women) and 0.6% over 520 μ mol/l (men). A serum creatinine over 150 μ mol/l excluded participants from the trial. The gender differences and age comparisons were as expected but the women had higher average total and high-density-lipoprotein-cholesterol blood concentrations. Those with prior cardiovascular disease had an excess of the known cardiovascular risk factors. The baseline characteristics provide a basis for further understanding of the HYVET results, which have been published recently.

Key Words: Cholesterol, diabetes mellitus, hypertension, lifestyle characteristics, serum uric acid, very elderly

Introduction

The Hypertension in the Very Elderly Trial (HYVET) was performed to determine the risks and benefits of treating the very elderly (aged 80 and over) hypertensive with a low-dose diuretic, indapamide 1.5 mg Sustained Release (SR), to which may be added perindopril 2–4 mg with the aim of reaching a goal blood pressure (BP) of 150/80 mmHg or below. The trial was a randomized, double-blind, active treatment vs placebo study and conducted worldwide (1). The entry criteria included an average systolic BP

(SBP; after 2 months of taking placebo tablets) of 160–199 mmHg and a diastolic pressure (DBP) <110 mmHg. The active countries were China; Bulgaria, Romania and Russia in Eastern Europe; Finland, France and the UK in Western Europe; Tunisia and New Zealand. Since the trial participants differed according to gender, exact age (arbitrarily divided into 80–84.9, 85–89.9 and 90+ years), and whether they had previous cardiovascular disease (CVD), the baseline results for these different groups are presented in the article.

The characteristics of very elderly hypertensive subjects are generally not well known, since they represent "survivors" and may have relatively healthy lifestyles, and anthropometric and biochemical attributes contributing to their survival. These possibilities were explored and this publication indicates the characteristics of subjects to whom the HYVET results may be applied.

Participants and methods

The protocol for the HYVET trial has been published (1) together with protocols for side projects on cognitive function (2), ambulatory BP (3) and fracture incidence (4). Participants gave written informed consent, were instructed to stop all anti-hypertensive treatment and started on one placebo tablet daily for at least 2 months, with two further measurements of BP on placebo. BP was measured in the sitting position, twice after sitting for 5 min and, on the third visit and thereafter, the standing BP was taken twice after standing for 2 min. Appropriate ethics approval was obtained for all centres.

After at least 2 months, if the average of the four (two second and two third visit) SBPs was between 160 and 199 mmHg the participants were randomized within the HYVET trial, provided the other inclusion and exclusion criteria were met. At the start of the trial, the average sitting DBP had to be 90–109 mmHg but this criterion was later relaxed to <110 mmHg to allow for the recruitment of the numerous subjects with isolated systolic hypertension (ISH). Therefore, countries entering the trial later had a higher proportion of participants with ISH. The other inclusion criterion was age over 80 years (confirmed by national documentation). The exclusion criteria included accelerated hypertension; heart failure requiring treatment with anti-hypertensive medication; serum creatinine >150 µmol/l; a clinical diagnosis of dementia; gout; secondary hypertension; requirement for nursing care; serum potassium <3.5 mmol/l or >5.5 mmol/l; and haemorrhagic stroke in the last 6 months.

The methods of randomization, data to be collected, end points for the trial, quality control, stopping rules for the trial and the trial committees have been published in detail (1). The treatment steps – indapamide sustained release (SR) 1.5 mg alone, indapamide +2 mg perindopril, and indapamide +4 mg perindopril (or corresponding matching placebos) – have been described, and the goal BP was a SBP <150 mmHg and a DBP <80 mmHg (1).

The baseline characteristics were collected during the placebo run-in period by the investigator, and included socio-demographic information, medical history, smoking and alcohol consumption, and biochemical results (measured in the centre's local approved laboratory).

The results were analysed by gender, three age groups and according to the presence or absence of previous CVD. Previous CVD was defined as previous stroke, myocardial infarction (MI) or congestive heart failure (CHF). Comparisons were made between the two sexes and between groups. Differences between baseline characteristics of men and women were adjusted for age group and vice versa. Similarly, the comparisons of those with previous CVD were adjusted for gender. The statistical methods included regression of continuous variables on age and chi-squared tests for trend when comparing the three age groups. Adjustments were achieved using generalized linear models.

Results

The average age of patients groups entered into the HYVET study was 83–84 years in both men and women; 70.3% were aged 80–84 years at randomization, 23.8% 85–89, 5.3% 90–95 and 0.6% over age 95. Three were over 100 years old and one was 105 years at randomization. Over 10% of women and 15% of men had had previous CVD disease. The excess in men was related to a higher prevalence of previous stroke (9% in men and 6% in women) and previous myocardial infarction (4% in men, 2% in women). Previous CHF was 3% in both men and women. Sixty-five per cent of women and 64% of men had been previously treated for hypertension. Tables I and II give the reported baseline characteristics and anthropometric, BP and biochemical measurements in men and women by age group.

Diabetes mellitus included reported prevalent cases, those receiving antidiabetic treatment and those identified from the measurements of blood sugar (>11.1 mmol/l irrespective of fasting or non-fasting). The prevalence amounted to 6–7% in both men and women, without consistent differences between the three age groups. The gender differences were as expected: men smoked more and drank more alcohol. Only 2% of the elderly women were current smokers and 13% of men. Thirty-five per cent of men drank alcohol and 7% of women. Those who drank consumed an average of 7 units/week (men) and 5 units/week (women).

Men were heavier and taller; women had higher average SBPs and a faster heart rate; men had higher serum creatinine, urea and uric acid average concentrations, and higher average haemoglobin and haematocrit measurements. Total cholesterol was higher in women than in men (5.4 vs 5.2 mmol/l, $p < 0.01$) as was high-density lipoprotein (HDL)-cholesterol (1.37 vs 1.32 mmol/l, $p < 0.01$).

Although women had an average SBP 2 mmHg higher than men, they also had a similar proportion of ISH (33%) as men (32%). DBPs were therefore almost identical in the two sexes.

Table I. Reported characteristics and anthropometric measurements in men and women, by age group, at baseline in the Hypertension in the Very Elderly Trial (HYVET) study.

	Men				Women				Gender difference, p^a	Change with age, p^a
	All	80–84	85–89	90+	All	80–84	85–89	90+		
Number	1519	1141	322	56	2326	1666	540	120		
ISH patients (%)	31.8	33.0	28.9	23.2	32.9	33.7	31.1	29.2	0.48	0.07
Current smokers (%)	13.0	14.0	9.3	14.3	2.2	2.1	3.0	0.9	<0.001	0.08
Drink alcohol (%)	34.5	34.2	36.0	32.1	6.8	6.4	8.5	3.3	<0.001	0.49
Previous MI (%)	4.2	3.9	5.0	5.4	2.5	2.3	2.2	6.7	0.004	0.05
Previous CHF (%)	2.6	2.5	2.5	7.1	3.1	2.9	3.0	5.8	0.45	0.06
Previous hypertension (%)	90.0	89.0	92.9	92.9	89.8	89.6	90.6	89.2	0.82	0.14
Previous anti-hypertensive treatment (%)	64.3	66.2	59.9	50.0	64.9	66.5	62.4	55.0	0.67	<0.001
Previous stroke (%)	8.9	9.6	6.5	7.1	5.4	5.9	4.4	3.3	<0.001	0.01
Previous CVD (%)	14.6	14.9	12.7	17.9	9.9	10.1	8.5	13.3	<0.001	0.74
Diabetes (%)	6.9	7.4	5.9	1.8	6.8	7.2	5.4	8.3	0.99	0.13
Weight (kg)	70.4	70.6	70.0	70.0	61.3	61.9	60.2	59.0	<0.0001	<0.0001
Height (cm)	169	169	169	169	157	157	157	156	<0.0001	0.07
BMI (kg/m ²)	24.7	24.7	24.6	24.4	24.7	24.9	24.2	24.1	0.59	<0.0001

^aGender p -values adjusted for age and vice versa. ISH, Isolated systolic hypertension; MI, Myocardial infarction; CHF, Congestive heart failure; CVD, Cardiovascular disease; BMI, Body mass index.

Average BPs differed little between the three age groups. Blood glucose and fasting blood glucose tended to decrease with age, whereas average serum creatinine and potassium increased and haemoglobin decreased. A history of stroke decreased with advancing age, as did the proportion of participants who were previously treated.

The biochemical measurements at baseline were available for more than 99%, with the exception of HDL-cholesterol, only available in 95% and urea only available in 97%; 1.0% of the whole group had total cholesterol over 8.0 mmol/l, 1.1% blood sugar over 11.1 mmol/l (irrespective of anti-diabetic treatment or fasting) and 1.7% a serum urate over 460 μ mol/l (women) and 0.6% over 520 μ mol/l (men).

Table III gives the baseline characteristics of the participants according to gender and presence or otherwise of previous CVD. Those who had prior CVD were more likely to have cardiovascular risk factors such as diabetes mellitus, a higher average body mass index (BMI), total cholesterol, blood sugar, creatinine, a marked 9% increase in serum uric acid and a modest increase in serum potassium. Participants with previous CVD were also more likely to have been previously treated for hypertension.

Discussion

It is important to report the baseline characteristics of trial participants in order fully to understand the

Table II. Blood pressure and biochemical measurements in men and women, by age group, at baseline in the Hypertension in the Very Elderly Trial (HYVET) study.

	Men				Women				Gender difference, p^a	Change with age, p^a
	All	80–84	85–89	90+	All	80–84	85–89	90+		
Sitting SBP (mmHg)	172	172	172	173	174	173	174	174	<0.0001	0.07
Sitting DBP (mmHg)	90.9	90.8	91.0	91.5	90.7	90.7	90.6	90.6	0.53	0.47
Standing SBP (mmHg)	167	167	167	166	169	169	169	168	<0.0001	0.91
Standing DBP (mmHg)	88.7	88.8	88.5	88.8	88.6	88.7	88.4	88.7	0.82	0.32
Pulse rate (1 min)	74.0	74.2	73.6	72.6	74.8	74.9	74.5	75	<0.01	0.23
Total cholesterol (mmol/l)	5.15	5.11	5.21	5.51	5.39	5.39	5.37	5.39	<0.001	0.17
HDL-cholesterol (mmol/l)	1.32	1.33	1.30	1.28	1.37	1.37	1.35	1.38	0.0006	0.24
Glucose (mmol/l)	5.46	5.49	5.39	5.21	5.39	5.43	5.33	5.22	0.24	0.013
Fasting glucose (mmol/l)	5.47	5.51	5.37	5.20	5.37	5.40	5.35	5.17	0.092	0.038
Urea (mmol/l)	6.47	6.41	6.69	6.46	6.20	6.19	6.20	6.39	<0.0001	0.11
Creatinine (μ mol/l)	93.5	92.7	96.0	96.8	85.9	84.9	88.2	89.4	<0.0001	0.0001
Uric acid (μ mol/l)	299	298	300	305	267	266	271	266	<0.0001	0.64
Potassium (mmol/l)	4.36	4.35	4.38	4.44	4.33	4.33	4.34	4.34	0.058	0.0037
Sodium (mmol/l)	142	142	142	142	141	141	142	142	0.47	0.011
Haemoglobin (g/dl)	13.8	13.8	13.7	13.3	12.7	12.8	12.7	12.6	<0.0001	0.0145
Haematocrit (%)	41.4	41.5	41.3	39.9	38.9	38.8	39.1	39.2	<0.0001	0.26

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL, High-density lipoprotein.

^aGender p -values adjusted for age and vice versa.

Table III. Baseline characteristics of Hypertension in the Very Elderly Trial (HYVET) participants according to gender and previous cardiovascular disease (CVD).

	Previous CVD				CVD effect <i>p</i> ^a
	Women		Men		
	Yes	No	Yes	No	
Number	231	2095	221	1298	
ISH patients (%)	38.1	33.3	33.0	31.6	0.13
Current smokers (%)	3.5	2.1	11.3	13.3	0.46
Drink alcohol (%)	5.6	6.9	28.5	35.5	0.59
Previous anti-hypertensive treatment (%)	74.9	63.8	75.1	62.4	<0.001
Diabetes (%)	13.0	6.2	12.7	5.9	<0.001
Weight (kg)	62.2	61.3	71.5	70.3	0.052
Height (cm)	157	157	168	169	0.12
BMI (kg/cm ²)	25.3	24.6	25.2	24.6	0.001
Blood Pressure					
Sitting SBP (mmHg)	172	174	171	172	0.0001
Sitting DBP (mmHg)	89.7	90.8	90.4	91.0	0.047
Standing SBP (mmHg)	167	169	164	167	<0.0001
Standing DBP (mmHg)	87.7	88.8	88.1	88.8	0.050
Pulse rate (1 min)	76.1	74.7	74.0	74.0	0.10
Total cholesterol (mmol/l)	5.58	5.36	5.25	5.13	0.0025
HDL-cholesterol (mmol/l)	1.36	1.37	1.30	1.33	0.45
Glucose (mmol/l)	5.65	5.37	5.48	5.45	0.026
Fasting Glucose (mmol/l)	5.64	5.34	5.47	5.47	0.037
Urea (mmol/l)	6.2	6.2	6.8	6.4	0.021
Creatinine (μmol/l)	86.4	85.9	95.8	93.1	0.12
Uric acid (μmol/l)	287	265	322	295	<0.0001
Potassium (mmol/l)	4.3	4.3	4.3	4.4	0.037
Sodium (mmol/l)	141	141	141	142	0.058
Haemoglobin (g/dl)	12.9	12.7	13.8	13.8	0.07
Haematocrit (%)	39.0	38.9	41.3	41.4	0.96

Abbreviations as in Tables I and II.

^aEffects of CVD adjusted for gender differences.

results of any trial. Nevertheless, any gender or age difference or finding related to previous CVD must be interpreted with caution. The data are not population based and form a group with above average health for their age. For example, only 6–7% reported diabetes mellitus against an expected prevalence of at least 14% at age 75–79 years (5,6) and few subjects smoked (7,8) or consumed an excess of alcohol (9–12). In addition, they were all hypertensive and may be expected to have a higher prevalence of the components of the metabolic syndrome, although, surprisingly, there was little evidence for this except those with prior CVD disease. Nevertheless, most of the gender differences have been previously recognized and it would appear reasonable to report them in this article. We shall discuss how our participants' characteristics differ from the population at this and younger ages, and shall also discuss age group differences and compare the participants with previous CVD with those without. The major countries contributing to the trial were Bulgaria, China, Romania and Russia.

The characteristics of the over 80-year-old hypertensives recruited to HYVET

Subjects who reach the age of 80 in the countries in the HYVET trial are survivors who have exceeded

the expected average lifespan of someone born before 1927. This, plus the fact that they have survived despite having a high BP leads us to expect that they have a lifestyle conducive to long survival, or biochemical and anthropometric characteristics associated with long life. Additionally they were often treated prior to entering the trial and/or may have had hypertension for only a short period. Thirteen per cent of all men were still currently smoking cigarettes and 2% of women. This contrasted with 49% of adult men in Bulgaria, 32% in Romania, 63% in the Russian Federation (7) and 67% of men in the Minhang District of China (8). Women are known to smoke very little compared with men [10–24% in Eastern Europe (7) and 2% in the Minhang District of China (8)]. These rates are generally higher than the average 2% observed in the HYVET. Similarly alcohol consumption in adults in Europe is high (9,10) and is increasing markedly in China (11). However, male subjects entering the HYVET study consumed only about 1.5 l pure alcohol/year and women 0.2 l/year. This compares with a population estimate of 9–12 l/person/year in Europe.

The vast majority of patients were already known to be hypertensive and 64% had previously been on antihypertensive treatment. They had very low rates of previous myocardial infarction but 9% of men and 6% of women had previously suffered a stroke.

Despite the fact that the subjects had hypertension, there was no evidence that these elderly subjects often had extreme results for variables that could contribute to the metabolic syndrome, with the important exception of those with previous CVD.

Gender differences

The greater proportion of men who smoked, drank alcohol or had previous MI or stroke is well recognized as is the greater height and weight of men. More importantly, there was no excess of ISH, or participants with diabetes or CHF, in either gender. Average BMI was identical in the two sexes.

The higher average SBP (2mmHg) and pulse rate in women (0.8beats/min) were probably not clinically important, but total and HDL-cholesterol concentrations tended to be higher in women. In men average urea, creatinine and uric acid were, as expected, higher. Despite a long time lapse from menopause, women still had lower average haemoglobin and haematocrit values. Average blood glucose did not differ between the sexes, nor did serum sodium.

Differences between three age groups

The oldest age group (over 90 years) tended to report more MI and previous CHF but less stroke than the younger groups. Fewer in this over-90 group had been previously treated for hypertension and their weight was lower together with their BMI. Their average creatinine concentration was higher, as was serum sodium. None of these biochemical differences appeared of immediate clinical importance.

Differences between those with and without previous CVD

The participants with previous CVD had higher BMI levels, blood sugar and total cholesterol concentrations. They also had a more frequent history of diabetes mellitus. They tended to have received more anti-hypertensive treatment in the past and had higher average serum uric acid, and potassium concentrations. These findings mainly reflect the risk factors for CVD (glucose, diabetes, cholesterol, uric acid), possibly the effects of previous anti hypertensive treatment (uric acid) and perhaps the effect of CVD itself (blood urea). The slightly lower SBP was presumably a reflection of the greater perceived need for treatment in a hypertensive participant who had prior CVD disease. The increase in serum uric acid did not reflect the fact that the prior CVD group had more frequently been treated with anti-hypertensive medication.

The strength of this report is the large number of participants involved. As the participants were

randomized equally to active or placebo treatment, gender, age and previous CVD should be equal in the two randomized groups. Nevertheless, the baseline information is of great importance when assessing the final results (13). One weakness is that the trial participants do not necessarily represent the population from which they were recruited. In fact, we present information to suggest that they tended to be healthy survivors although those with previous CVD had many cardiovascular risk factors in excess.

As subjects with dementia, severe postural hypotension and those requiring nursing care were excluded, a "healthy" group of participants was to be expected.

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Appendix

The committee members and investigators for HYVET were as follows:

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