

Antihypertensive treatment in the very elderly shows significant mortality benefit

A challenging trial of hypertension in the very elderly (HYVET), which took almost 10 years to complete, has provided proof that antihypertensive therapy in older patients saves lives. Therapy using low-dose indapamide (1.5 mg sustained release daily) with added perindopril in 73% of patients in the treated group resulted in significant reduction of rates of death from any cause, and nearly significant benefit for the risk of fatal or non-fatal stroke.



Dr N Beckett, clinical research fellow and honorary consultant physician, Department of Care of the Elderly, Imperial College, London

'HYVET provides unique evidence that hypertension treatment in the very elderly is beneficial and is associated with reduced risks of death from stroke, death from any cause, and heart failure.'

The intention-to-treat results showed a 21% reduction in total mortality rate, a 39% reduction in stroke mortality rate, which was significant, although the 30% reduction in all strokes did not quite reach statistical significance, a 64% reduction in fatal and non-fatal heart failure, and a 34% reduction in cardiovascular events.¹ The study was stopped early in July 2007 on the recommendation of an independent data-monitoring committee.

Announcing the results in the late-breaking clinical trial session at the ACC in Chicago, Dr Nigel Beckett, clinical research fellow and consultant physician in the Department of Care of the Elderly at Imperial College, London, empathetically described the physician's dilemma in treating the very elderly. 'We just did not know, prior to this study, whether there would be benefit in treating these very

elderly patients; in fact there was some evidence from meta-analyses that benefit might be offset by possible adverse effects.² Furthermore, most clinical trials in hypertension have not recruited patients in this age group', he pointed out.

HYVET was designed to resolve these persistent areas of clinical uncertainty. The design of the study took these complexities into account and built in additional safeguards so that patients with excessively high blood pressure in the placebo run-in phase or after randomisation were withdrawn from the trial. If a patient required additional antihypertensive medication above the placebo or the regimen of 1.5 mg indapamide (Natrlix SR) and 4 mg perindopril daily, these patients were withdrawn from the double-blind follow up and continued the study under open follow up. Data were analysed in terms of both intention-to-treat and per-protocol analysis.

Patients were included if they were 80 years or older and had persistent high blood pressure (defined as a sustained systolic blood pressure of 160 mmHg) after a placebo run-in period of at least two months with two blood pressure measurements during each of two visits, one month apart, after having been seated for five minutes. On the third visit and thereafter, the standing blood pressure was taken twice after the patient had been standing for two minutes. If the mean of the four systolic blood pressure measurements on the third and fourth visits was between 160 and 199 mmHg, patients were



Prof C Bulpitt, emeritus professor of Geriatric and Cardiovascular Medicine, Imperial College, London

'Blood pressure has to be taken in patients over the age of 80 and, if it is repeatedly high, the treatment has to be investigated. The question arises – what treatment? The treatment we used – indapamide SR 1.5 mg plus or minus perindopril – did the trick.'

randomised and entered into the study. At the start, the mean diastolic blood pressure while seated had to be 90–109 mmHg, but this was later relaxed to include patients with isolated systolic hypertension.

Table 1 describes data collected at study entry. Patients with known accelerated hypertension, congestive heart failure, previous stroke or dementia, or who were resident in a nursing home were excluded from the study.

'It should be noted that these were quite healthy elderly people – only 12% had had previous coronary vascular disease and 7% had diabetes. More than 90% of patients were known to be hypertensive, of whom approximately one-third had not previously been treated.'

The goal blood pressure was less than 150/80 mmHg; a systolic level which is the same as the Systolic Hypertension in Europe (Syst-Eur) trial³ but lower than the Systolic Hypertension in the Elderly Program (SHEP).⁴

A total of 4 761 participants entered the placebo run-in phase, and 3 845 were randomised. They were recruited from Europe, China, Australasia and Tunisia, and the two groups were well matched at baseline. Their mean age was 83.6 years, mean sitting blood pressure was 173.0/90.8 mmHg at baseline, 12% had a history of cardiovascular disease and 6.9% had diabetes. Mean follow-up was 2.1 years.

TABLE 1. DATA COLLECTED AT STUDY ENTRY IN HYVET

- Sitting blood pressure
- Standing blood pressure
- Sitting heart rate
- Weight and height
- Treatment, both current and discounted in the past six months
- Previous stroke, MI, skeletal fractures, major disease
- 12-lead ECG
- Smoking habits and alcohol consumption
- Type of accommodation
- Activities of daily living
- Orientation, memory, concentration test and mini mental state examination
- Biochemical screen: creatinine, potassium, sodium, urate, blood sugar, total and HDL cholesterol, dipstick-positive proteinuria

Blood pressure results

At two years, seated blood pressure had fallen by a mean of 14.5/6.8 mmHg in the placebo group ($n = 1\ 912$) and by 29.5/12.9 mmHg in the treatment group ($n = 1\ 933$). Therefore, a difference of 15.0/6.1 mmHg in the seated blood pressure was present between the two groups after two years. By two years, 19.9% of subjects in the placebo group had achieved the target blood pressure compared to 48.0% in the treatment group ($p < 0.001$).

Endpoints

In the intention-to-treat analysis, there was a 30% reduction in the primary endpoint of stroke, with 69 fatal and non-fatal strokes occurring in the placebo group compared to 51 in the treatment group (95% CI: 1–51%, $p = 0.06$). This equates to 11 strokes being prevented by treating 1 000 patients for two years. There was a 39% reduction in fatal stroke rate (95% CI: 1–62%, $p = 0.05$). Unexpectedly, there was a 21% reduction in all-cause mortality in the treatment group (95% CI: 4–35%, $p = 0.02$).

HYVET is the first blood pressure-

lowering study to show a mortality benefit in patients over the age of 80 years. Fatal and non-fatal heart failure events were reduced by 64% (95% CI: 42%, $p < 0.001$) and all cardiovascular events (cardiovascular mortality, stroke, myocardial infarction and heart failure) were reduced by 34% (95% CI: 18–47%, $p < 0.001$).

In the per-protocol analyses, all-cause mortality was decreased by 45% (95% CI: 7–67%, $p = 0.02$). The stroke rate was reduced by 34% with treatment (95% CI: 5–54%, $p = 0.03$), the heart failure rate by 72% (95% CI: 52–83%, $p < 0.001$) and the cardiovascular mortality rate by 27% (95% CI: 31–45%, $p = 0.03$).

In the patients followed up for at least two years, there were no significant differences between the two groups in changes in serum potassium, uric acid, glucose or creatinine levels. The number of reported serious adverse events was smaller in the treatment group than the placebo group (358 vs 448, $p = 0.001$).

Commenting on the study, Prof Bryan Williams, University of Leicester, UK, noted that HYVET is the most important trial in recent times with regard to its potential for impacting on blood pressure

guidelines. He pointed out that the increasing number of ageing people is having an important effect on the age structure of developed countries. 'Worldwide, the proportion of people aged 60-plus years is growing faster than any other age group. They are particularly vulnerable to cardiovascular disease and fear the debilitating effects of stroke, in particular.'

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2. Beckett NS, *et al.* Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**. Advance pub 10.1056/NejmMoa0801369.
3. Staessen JA, Fagard R, Thijs L, *et al.* Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension: the Systolic Hypertension in Europe (Syst-Eur) trial investigators. *Lancet* 1997; **350**: 757–764.
4. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *J Am Med Assoc* 1991; **265**: 3255–3264.