

Treating hypertension in older people: revisiting the evidence

Hypertension is a major modifiable risk factor for cardiovascular disease. The current treatment strategy for treating hypertension in older adults has evolved through a series of randomised control trials over the past three decades. Beneficial effects of treating hypertension up to the age of 80 years has been unequivocally established while the benefits of treating it beyond that age need to be weighed against the risks involved in this vulnerable group of adults.

Dr Prabhath Fernando Specialist Registrar in Geriatrics and G(D)M, New Cross Hospital, Wolverhampton, WV10 0QP, UK

**Dr Amit Arora MD Consultant Physician, University Hospital of North Staffordshire, Stoke-on-Trent, ST4 6QG, UK
email prabhathfernando@gmail.com**

Hypertension is a major modifiable risk factor for cardiac, cerebral and renal vascular diseases. The prevalence of hypertension in the UK is 46% amongst people over 65 years of age.¹ It is defined as blood pressure greater than 140/90mmHg.² But the 2006 NICE guidance for the management of hypertension, published in collaboration with the British Hypertension Society, only recommend pharmacotherapy (in addition to lifestyle modifications) for persistently elevated blood pressure greater than 160/100mmHg or greater than 140/90mmHg in patients at raised cardiovascular risk.² This article will review the evidence for the treatment of hypertension in older people.

Data for older people

Several intervention studies have reviewed the effects of treating hypertension in older people.

In 1985, the European Working Party on High Blood Pressure in the Elderly (EWPHE) study demonstrated a clear benefit of treating hypertension in older adults.³ This double-blind controlled trial involved 840 patients who were aged over 60 years, had an average systolic blood pressure of 160–239mmHg, and had an average diastolic blood pressure of 90–119mmHg. They were randomised to receive a combination of hydrochlorothiazide and triamterene or matching placebo. If the predetermined blood-pressure target was not achieved, methyldopa was added to the treatment group while a matching placebo was added to the controls. The mean follow up period was

4-6 years. At the end of the study, the mean blood pressure was significantly lower in the active treatment group, with a mean difference of 19/5mmHg. A significant reduction in cardiovascular and cardiac mortality, by 21% and 38% respectively, and a non-significant reduction in stroke by 32% was also observed in the treatment arm.

Another study (published in 1986),⁴ of elderly patients aged 60–70 years, showed a consistent difference of 18/11mmHg between patients taking active treatment (atenolol with/without bendroflumethiazide) and patients taking placebo throughout the study period (4-4 years) with the lower pressures being observed in the active treatment group. Patients receiving active treatment were associated with a 42% reduction in stroke and a 22% reduction in cardiovascular deaths compared with those receiving placebo.

The 1991 Swedish Trial in Old Patients with Hypertension (STOP-Hypertension),⁵ also highlighted the benefits of treating older hypertensive adults. In the study, patients were randomly assigned to receive a β -blocker or a thiazide diuretic, or placebo. At the end of the study, blood pressure in the intervention groups was significantly lower (by a mean of 19.5/8.1mmHg) compared with that in the placebo group. The combined primary endpoint of fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, and other cardiovascular deaths was significantly reduced by 40% in the treatment groups. Additionally, a significant reduction of all-cause death by 43% was also noted.

The Systolic Hypertension in Elderly Program (SHEP) was a landmark study of isolated systolic hypertension. It enrolled 4736 patients aged 60 years or older with a systolic

blood pressure of >160mmHg and diastolic blood pressure of <90mmHg. The investigators randomised patients to receive chlorthalidone, which was combined with atenolol and reserpine (which is no longer available) to achieve a target systolic blood pressure of <160mmHg or to reduce systolic blood pressure by >20mmHg. Patients in the active treatment group saw a greater reduction in blood pressure than those in the placebo arm, and the mean difference in blood pressure between the two groups was 11/3mmHg. Active treatment also lowered the incidence of stroke by 36%, the incidence of cardiovascular endpoints by 32%, and the incidence of coronary endpoints by 23%.⁶

Treatment of hypertension and isolated systolic hypertension is clearly beneficial in older people between the ages of 60 and 80 years in terms of reducing the risk of strokes, coronary heart disease and cardiovascular mortality. A meta-analysis that reviewed 16,564 hypertensive patients who were aged older than 60 years found that 43 patients need to be treated for five years to prevent one cerebrovascular event. Furthermore, it found that 63 patients need to be treated to prevent one cardiovascular event and only 18 need to be treated to prevent one cardiovascular (cardiac or cerebrovascular) event.⁷ The authors concluded that the trial participants were healthier in terms of cardiovascular disease and risk factors and competing comorbidities compared with older hypertensive people living in the community.

However, although all of these studies are useful, they leave several important questions unanswered. For example, optimum treatment targets to aim for, which agents to use first, and whether the data can be extrapolated to the oldest old.

Treatment targets

The Hypertension Optimal Treatment (HOT) trial reviewed optimum blood-pressure targets as one of its two objectives.⁸ Participants were aged 50–80 years, with a mean age of 61 years, and were randomly assigned to one of three diastolic blood pressure target groups: ≤90mmHg, ≤85mmHg, or ≤80mmHg. The average duration of follow up was 3.8 years. Antihypertensive therapy, with felodipine at a dose of 5mg once a day, was given to all patients. Additional therapy and dose increments were used to reach the specified target blood pressure. Angiotensin-converting-enzyme (ACE) inhibitors or β-blockers were added at the second step and the dose of felodipine was increased to 10mg a day as the third step. Doubling the dose of either the ACE inhibitor or the β-blocker was the fourth step with a diuretic at step

five. Diastolic blood pressure was reduced by 20.3mmHg, 22.3mmHg, and 24.3mmHg in the ≤90mmHg, ≤85mmHg, and ≤80mmHg target groups, respectively. The lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6mmHg with a mean systolic blood pressure of 138.5mmHg; the lowest risk of cardiovascular mortality occurred at 86.5mmHg with a mean systolic blood pressure of 138.8mmHg. In patients with diabetes, there was a 51% reduction in major cardiovascular events in the target group ≤80mmHg compared with the target group ≤90mmHg. However the adverse event reporting of this trial with regard to antihypertensive medications was not satisfactory. Further, a non-significant increase in cardiovascular deaths was noted at the lowest level of blood pressure. This was not due to an increase in fatal myocardial infarctions or fatal strokes. Whether this reflected other comorbidities, such as dementia or cancer, associated with lower blood pressure was unclear.

Treatment options

While some studies have focused on age groups or treatment targets, others have reviewed treatment options. For example, a 1995 population-based cohort study demonstrated that short-acting dihydropyridine calcium-channel blockers are associated with a 60% increase in adjusted risk of myocardial infarction compared with β-blockers when used for controlling hypertension.⁹ A subsequent meta-analysis concluded that moderate-to-high doses of short-acting nifedipine increases the risk of mortality in a dose-dependent manner in patients with a history of coronary heart disease.¹⁰

The Heart Outcomes Prevention Evaluation (HOPE) Study examined the benefits of ACE inhibitors in patients with diabetes. It found that ramipril, compared with placebo, reduced the risk of the combined primary endpoint of myocardial infarction, stroke or death due to cardiovascular causes by 22%. But, the reduction in risk was only partly attributable to the reduction in blood pressure because the majority of patients did not have conventional hypertension (eg, ≥160/100mmHg) at baseline and the mean reduction in blood pressure was extremely small (3/2mmHg). The results support NICE's current recommendations that patients with diabetes require a lower treatment threshold for hypertension.²

In the Lipid Lowering Treatment (ALLHAT) trial,¹¹ hypertensive participants, who had a mean age of 67 years and all of whom had at least one other risk factor

for cardiovascular disease, were randomised to receive chlorthalidone, amlodipine, or lisinopril. The mean follow-up was 4.9 years. Compared with the chlorthalidone group, the amlodipine group had a 38% higher risk of heart failure, and the lisinopril group had a 15% higher risk of stroke, a 10% higher risk of combined cerebrovascular disease, and a 19% higher risk of heart failure. Five-year systolic blood pressure was significantly higher in the amlodipine and lisinopril groups compared with the chlorthalidone group. Similarly, diastolic blood pressure was significantly lower in the amlodipine group compared with the chlorthalidone group. The results concluded that thiazide-type diuretics should be used as a first line treatment for hypertension.

The Intervention For End-point reduction in hypertension (LIFE) study showed that the angiotensin-receptor blocker (ARB) losartan reduced the relative risk of the primary composite endpoint of cardiovascular morbidity and mortality by 13% compared with the β -blocker atenolol for a similar degree of blood pressure reduction.¹² Similarly, fatal and non-fatal strokes were reduced by 25% in patients treated with losartan.

However, other studies have indicated that older patients or black patients may benefit from a different combination of antihypertensives. The landmark Anglo-Scandinavian Cardiac Outcomes Trial¹³ (ASCOT) enrolled patients aged 40–79 years. Patients were assigned either amlodipine with perindopril added as required or to atenolol with bendroflumethiazide and potassium supplements added as required to achieve a target blood pressure of <140/90 mmHg. For patients with diabetes, the target blood pressure was <130/80mmHg.

The study was stopped prematurely because of the benefits in favour of amlodipine +/- perindopril versus atenolol +/- bendroflumethiazide. The primary endpoint of fatal and non-fatal myocardial infarction was non-significantly reduced in the amlodipine-based group by 10%. But, amlodipine (+/- perindopril) did significantly reduce the risk of non-fatal and fatal stroke by 23%, the risk of total coronary events by 13%, the risk of total cardiovascular events and procedures by 16%, the risk of all-cause mortality by 11%, the risk of cardiovascular mortality by 24%, and the incidence of diabetes by 30%. These results, along with other studies, clearly indicated that β -blockers should not be used as first-line treatment for hypertension. After the results of ASCOT were published, NICE amended its guidance for the management of hypertension. β -blockers should now only be used as a fourth-line treatment.

Treating the oldest old

Treatment of hypertension in people 80 years of age or older has been an area of uncertainty. Epidemiological studies have been

consistent in suggesting that blood pressure and the risk of death are inversely related among people in this age group. A meta-analysis¹⁴ found that treatment of hypertension in people aged 80 years or older reduced the incidence of stroke by 34%, the incidence of heart failure by 39%, and cardiovascular events by 22%. No benefit for cardiovascular death was observed, but an increased relative risk of death from all causes by 6% with treatment was found and it was not significant.

The HYVET trial

HYVET¹⁵ (Hypertension in the Very Elderly Trial) was a double-blind, randomised, placebo-controlled trial that enrolled 3845 hypertensive patients aged 80–105 years. The mean age was 83.6 years, 73% of study participants were aged 80–84 years, and 4.6% were aged ≥ 90 years. The mean blood pressure at baseline was 173/90.8 mmHg and patients were assigned to indapamide, with perindopril added on if required, to achieve a target blood pressure of 150/80 mmHg or to matching placebo. The mean duration of follow up was 1.8 years. At termination of the trial, the mean blood pressure was 15/6.1 mmHg lower in the active treatment group compared with the placebo group. The primary endpoint of fatal and non-fatal strokes was reduced by 30% in the treatment group.

After a premature termination of the trial, the authors concluded that reduction in the risk of death from stroke with active treatment was significant in both intention-to-treat and per-protocol analyses, and the incidence of heart failure was significantly lower in the treated population. It was also concluded that HYVET was one of the few individual studies of hypertension showing benefits of blood pressure reduction on mortality. However, there are significant caveats that affect the applicability of the results of this trial to clinical practice. For example, the vast majority of patients in the study were of Eastern European or Chinese origin. Therefore, given that these populations have an increased risk of fatal stroke compared with the Western population, the benefits observed in HYVET may not extrapolate into other populations. Furthermore, because of the way adverse events were reported in the study, it is difficult to weight the risk and benefits of long-term pharmacological therapy for the oldest old.

The latest evidence for the oldest old

A recent (2010) Cochrane review on pharmacotherapy for hypertension in the elderly analysed data for older people older than 80 years.¹⁶ It included data from EWPHE, HEP,

SHEP-PS, STOP-Hypertension, SHEP, Syst-Eur, HYVET-P and HYVET trials.

According to the Cochrane analysis, antihypertensive treatment does not appear to reduce the risk of death in people aged 80 years or older but does appear to reduce stroke. Therefore, the benefit of therapy should be carefully weighed against the risks in each individual. Perhaps, we should remember the NICE guidance for the management of hypertension with respect to those aged 80 years or over. It states that those who reach 80 years of age while on treatment should remain on therapy, especially if they have target organ damage.² For those aged 80 years or over at the time of diagnosis, it concedes no clear guidance can be given. In any case, it should be remembered that there is no benefit demonstrated in reducing blood pressure below 150/80 mmHg at present in this group of patients.

Conclusion

Benefits of treating hypertension in older people between ages 65 and 80 years have been unequivocally established by clinical trials. But, the benefits of such treatment in hypertensive adults beyond the age of 80 years seem to be less pronounced and particularly the quality of available evidence is less satisfactory. Therefore, it is imperative that clinicians should weigh between pros and cons of antihypertensive therapy before committing older adults for or continuing such treatment in this vulnerable group of people.

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