Hypertension in the older patient

In the UK, hypertension affects around 20% of the adult population and is particularly prevalent in the elderly population. With new clinical guidance from NICE due to be published this year, this article looks at the landmark HYVET trial that found that the use of antihypertensive treatment in people over 80 years of age reduced mortality for all causes by 21%. This study, along with the joint guidelines from NICE and the British Society of Hypertension, indicate that different classes of antihypertensive drugs have differing effects depending on the age of the patient.

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In any treatment we must consider benefit versus risk, and society as a whole needs to take into account the cost. This is especially true in preventative medicines and particularly true in the management of hypertension. Risk increases with age and most of the evidence we have in hypertension has been accumulated in the highest risk population, those aged over 50 years. This article will concentrate on two publications that have looked specifically at the question of treatment in different age groups. The joint NICE and British Society of Hypertension guidelines published in 2006 will first be reviewed. The second part of the article will look at the results of the Hypertension in the Very Elderly Trial (HYVET).

Joint guidelines

The first NICE hypertension guideline, published in 2004, attracted some criticism for the somewhat complicated treatment algorithm that recommended thiazide diuretics as first-line treatment and β-blockers as second line for all but those at risk of diabetes. The diabetics would receive ACE inhibitors or angiotensin receptor blockers (ARBs) as second-line treatment. Calcium channel blockers (CCB) were third-line treatment. In light of new evidence, which emerged following the publication of the guidance, it was decided that a partial revision of the pharmacological aspects of the guideline should be undertaken. This venture was conducted jointly with the British Hypertension Society, and the Primary Care Cardiovascular Society was asked to nominate a GP and primary care nurse to join the new Guideline Development Group. The evidence base used for this update included four new trials, of which the largest were ASCOT and VALUE. Sixteen other trials were also analysed, of which the largest was the ALLHAT study.

NICE has very specific rules regarding the quality of evidence it examines and in any review, it looks at clinical benefit initially and then performs health economic modelling. In this review, it examined the evidence in age cohorts of fewer than 55, 65, 75 and 85 years. The least evidence available was for the under 55 years age group. There was insufficient clinical outcome data for the younger age group, and NICE therefore needed to rely on the surrogate endpoint of blood pressure lowering. In this respect, it found that ACE inhibitors were superior in the younger, more renin active, population.

The health economics modelling uses incremental cost effective ratios (ICER) that are based on a calculation of the cost of each quality adjusted life year (QALY) gained. NICE also considered the effect of the different drug groups in terms of the risk of cardiovascular events, heart failure and diabetes. The inclusion of diabetes risk will not have favoured thiazide diuretics or β-blockers, which both lead to earlier onset of diabetes. The modelling was of course based on 2006 prices, at a time when most CCBs, ACE inhibitors and ARBs were branded drugs and relatively expensive compared with today. Despite this, the winners in the over 55 years age category, and even more so in the over 65 years age group, were the CCBs and thiazide diuretics.

The guideline committee assumed a class effect for each group of drugs. It did, however, point out that there was no specific evidence available for the UK’s most popular thiazide diuretic, bendroflumethiazide. In most head-to-head trials, the β-blockers were
inferior to the other drug classes and therefore they were declared fourth-line choices. Again there was a class effect assumption even though most of the trials used atenolol.

Black patients were excluded from the under 55 years recommendation to use ACE inhibitors or ARBs. This was because in ALLHAT, there were more events in the lisinopril arm compared with the chlortalidone arm among black patients. In addition, in the LIFE study there were more strokes among black patients in the losartan arm compared with the atenolol arm. The other fourth line drugs, which were recommended are α-blockers and diuretics. In the full version of the guideline they further explain that by diuretics they mean higher doses of diuretics or the addition of spironolactone or amiloride. Spironolactone is especially effective if patients have hypoaldosteronism and even in small doses such as 12.5 mg or 25 mg, will be very effective. A clue to hypoaldosteronism is the presence of hypokalaemia. The guideline warns that the use of these potassium sparing diuretics requires more frequent monitoring of renal function and electrolytes. If the use of four agents fails to control blood pressure, then referral to a specialist is recommended. All these recommendations are summarised in the very useful NICE/BHS algorithm, which has been well accepted and certainly very popular in primary care.

The HYVET study

HYVET was published in 2008 and therefore arrived too late for the NICE guideline revision in 2006. The evidence for treating high blood pressure in people over the age of 80 years was very sparse and all of it came from sub-analysis of trials with predominantly younger patients. It was designed to confirm the hypothesis generated by Gueyffier’s meta-analysis that treating patients of this age would only reduce the incident of stroke (36% relative risk reduction) and would in fact increase mortality by 14%. This meta-analysis result appeared to be confirmed by the HYVET pilot trial. Patients were included if they had an untreated systolic blood pressure between 160 and 199 mmHg and a diastolic blood pressure of less than 110 mmHg. They were excluded if their standing blood pressure was less than 140 mmHg, an important safety concern being the possible over treatment of people with postural hypotension. The target systolic blood pressure was only 150 mmHg. 4761 patients were recruited worldwide with many coming from Eastern Europe and China. 1912 completed the placebo arm and 1933 received active treatment with indapamide plus or minus perindopril. Approximately 80% of patients had both drugs. The trial took about seven years to complete but in fact, finished one year early on ethical grounds because the second planned interim analysis showed a positive reduction in not only stroke but also the secondary endpoint of all-cause mortality. This was an unexpected result.

The final results using an intention to treat analysis revealed an all stroke reduction of 30%, total mortality reduction of 21% and fatal stroke reduction of 39%. A very impressive finding was the reduction of new onset heart failure of 64%. Heart failure was an exclusion from the study but clearly in this age group, we would expect many new cases to emerge. Heart failure diagnosis confirmation was robust and all cases were thoroughly reviewed by the endpoints committee. The per protocol analysis results were even more impressive with an all stroke reduction of 34%, total mortality reduction of 28%, fatal stroke reduction of 45% and new onset heart failure of 72%. The blood pressure separation was 15/6 mmHg.
Safety was a very important consideration in this age group. There were no significant differences between the two arms in terms of biochemistry outcomes. The serious adverse events numbered 448 in the placebo group and 358 in the active group. The overall conclusion was that in relatively fit and healthy 80 year olds, there was a significant benefit in treating blood pressure. This was achieved safely but with care to avoid over treating postural hypotension and using a modest target of systolic blood pressure 150 mmHg. As a result of this trial, all guidelines throughout the world will need to change to reflect the need to treat blood pressure in our very elderly populations.

Summary

Evidence is available to indicate that different classes of antihypertensive drugs have differing effects depending on the age of the patient. We therefore need to reflect this in our initial choices of treatment. In particular, CCBs and diuretics are most effective in patients over the age of 55 years. As the prices of drugs vary, the economic modelling will indicate different preferences also. Until the publication of HYVET we had very little evidence that people over 80 years benefitted from treatment of hypertension. We now know that they can be safely and effectively treated assuming they are reasonably fit and excessive blood pressure lowering targets are avoided.

Specifically we should treat patients aged over 80 years if their systolic blood pressure is above 160 mmHg. The target blood pressure is less than 150 mmHg systolic, and the drugs used in this age group should be a thiazide-like diuretic plus an ACE inhibitor. There have been very few trials conducted in the very elderly and no other publications other than the many HYVET sub-analyses since 2008. There is need for more trials looking not only at lower targets and different drug combinations in the very elderly but also the question of whether or not cholesterol lowering is beneficial in this age group. We need a Cholesterol in the Very Elderly Trial.

Conflict of interest: Dr McCormack was an investigator and steering committee member for HYVET, in 2006 he was the Chairman of the Primary Care Cardiovascular Society and is currently a member of the NICE Hypertension Guidelines Development Group. Within the previous year he has not received any honoraria from pharmaceutical companies in relation to drugs used for the treatment of hypertension.

References

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