Impact of ASCOT on hypertension treatment and guidelines in older adults

Hypertension remains the most prevalent and preventable cause of cardiovascular (CHD) and cerebrovascular (CVD) disease, and there is good evidence that antihypertensive drugs are effective [1]. Interest in the condition remains high, with a number of recent large studies and published guidelines by both the BHS (British Hypertension Society) and the National Institute of Clinical Excellence (NICE) [2, 3]. The main questions at present are:

1. Does it matter which drug is used?
2. Are the benefits of antihypertensive agents purely related to their blood pressure (BP)-lowering effects or do some agents have additional beneficial effects whilst others have adverse metabolic effects?
3. Are newer agents more effective than the widely used thiazides and β-blockers in prevention of CHD and CVD? More than 2 million people in the UK are still prescribed β-blockers (mainly for hypertension) [4].

The recently published ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial - Blood Pressure Lowering Arm ASCOT-BPLA) [5] trial provides important data that partly answer these questions and are likely to change clinical practice further. We have restricted discussion to the BP-lowering arm of the study although there was also a lipid-lowering arm [6], which showed significant benefits with atorvastatin over placebo in CHD and CVD outcomes.

The ASCOT trial [5] is a large British and Scandinavian randomised control trial (RCT) involving >19,000 patients and comparing two different drug regimes—either a calcium channel blocker (amlodipine) adding in an angiotensin-converting enzyme inhibitor (ACE-I) (perindopril) as needed, or a β-blocker (atenolol) adding in a thiazide diuretic (bendroflumethiazide) as needed. Patients were moderate risk untreated (>160/100 mmHg) or treated hypertensives who had failed to reach target (>140/90 mmHg), and who had at least three of a number of cardiovascular risk factors (including left ventricular hypertrophy, type 2 diabetes, peripheral vascular disease, microalbuminuria, prior stroke or transient ischaemic attack and a number of other factors). The majority were white (95%) and male (77%), mean age was 63 years (range 40–79), and 81% were already on at least one antihypertensive agent. Patients were followed-up regularly for >5 years and drugs titrated on an open design aiming for target <140/90 mmHg or <130/80 mmHg for diabetics.

The results showed a mean difference in BP-lowering effect (2.7/1.9 mmHg) between the groups in favour of the calcium channel blocker±ACE-I group that is both statistically and clinically meaningful. The main finding was that the calcium channel blocker±ACE-I combination was superior compared with a β-blocker±thiazide in preventing fatal and non-fatal strokes (reduced by 23%), total cardiovascular events and procedures (16%), all-cause mortality (11%), plus an lower incidence of developing diabetes (30%) and renal impairment (15%). Other important results were that by the end of the trial, most patients were taking at least two drugs, with only 15% on amlodipine and 9% on atenolol monotherapy. Adverse effects of drugs remain an important barrier to effective therapy, with 25% of both groups discontinuing treatment because of this. Notably, 23% of the amlodipine group developed leg oedema and 16% on atenolol complained of fatigue.

The main drawback in interpreting the results was that the study was stopped prematurely and so the main primary end-point (non-fatal myocardial infarction and fatal coronary heart disease) did not reach significance. The trial was stopped early because of a significant overall reduction in all-cause mortality in the amlodipine±perindopril arm. The authors argue convincingly that clinical practice changed during the study period with a more aggressive approach to vascular interventions and that if the primary end-point was combined with coronary revascularisations then significant results were obtained.

How generalisable are the results to the populations we treat? The study population was predominantly white, male, with mean age 63 years, and did not recruit many older patients, having an upper age limit of <80 years for inclusion. Apart from the criticisms of studies focusing on white, younger males, the study included the sort of patients we see
in practice, with patients recruited from both primary care (in the Nordic countries) and secondary care (UK and Ireland). There were relatively few exclusion criteria. The patients were a moderate risk group having both hypertension plus at least three other risk factors. The study selection criteria increased the proportion of type 2 diabetics (27%), possibly biasing the results in favour of an ACE-I. Other studies in diabetic patients have shown favourable outcomes with an ACE-I [7].

The study design was pragmatic, with an open treatment and blinded end-point design. We still need better data on women, frail and older age groups (hopefully the ongoing HYVET trial will answer this), and other ethnic groups.

Prior to publication, clinical practice was changing to follow either the BHS [2] or NICE [3] guidelines. The BHS AB/CD rule would in older patients allow either a calcium channel blocker or diuretic monotherapy as first-line and an ACE-I or β-blocker as second-line agent. If ASCOT’s results were implemented, then calcium channel blockers would be first line and ACE-I second line, with most patients requiring a combination. So do the results justify such a change? The study does not provide any evidence that calcium channel blockers are superior to ACE-Is. Comparison of other trials has also failed to show any overall difference between them [1]. Calcium channel blockers from this trial are certainly effective and this builds on previous evidence such as the Syst-Eur trial in older patients with isolated systolic hypertension [8]. Can diuretics still be used first line? The study design does not provide sufficient evidence against diuretics as they were used as second-line agent to β-blockers. ALLHAT [9] provided good evidence that diuretics were as good as and possibly superior in some respects (see below) to ACE-Is and calcium channel blockers. The ALLHAT [9] trial was a large North American study that showed that diuretics (chloothalidone), calcium channel blockers and ACE-Is were essentially as good as each other in preventing major coronary events, and possibly some advantage with diuretics in preventing heart failure. The (ANBP2) Second Australian National Blood Pressure Study Group [10], however, showed evidence that ACE-Is were superior to diuretics in older males. The differences might be partly due to ethnicity, with ALLHAT (30% black) and ANBP2 (95% white patients) likely to have a different response to ACE-Is, with an expected lesser response in black patients. The main difficulties in comparing ASCOT and ALLHAT results are that the ALLHAT study included 30% black patients who do not respond as well to ACE-Is, and the non-inclusion of β-blockers. ASCOT does not tell us if calcium channel blockers or ACE-Is are superior to each other as only 15% initiated on amlodipine remained on it as monotherapy, and ALLHAT results suggest they are probably equivalent. Given the additional costs of calcium channel blockers, it would seem reasonable to continue using diuretics first line and either an ACE-I or calcium channel blocker second line until there is more evidence. The BHS and NICE are in the process of reviewing whether any amendments to current guidelines are needed as a consequence of ASCOT.

So where does this leave β-blockers? The trial provides sufficient evidence that atenolol should not be used in preference to the other three classes of agents. There is reasonable evidence that we should not expect atenolol to have as great an effect on hypertension outcomes as although it lowers brachial pressures that we routinely measure and use as a marker of systemic hypertension, atenolol does not have as great an effect on central blood pressure in the aorta [4]. β-Blockers also have adverse metabolic effects, especially when used in combination with diuretics, that may limit their benefits [11]. The MRC trial of treatment of hypertension in older adults (aged 65–74) [12] back in 1992 had already shown that whilst diuretics significantly reduced the risk of stroke (31%) and coronary events (44%) compared with placebo, there was no significant reduction in these end-points for atenolol. A recent important meta-analysis of β-blockers in primary hypertension showed that the relative risk for stroke was 16% higher with β-blockers than with other drugs [4]. There are sufficient differences between β-blockers to not dismiss the whole class; for instance, nebivolol (a selective β1-receptor blocker) lowers central pressures and has effects on nitric oxide [13] that influence arterial compliance and may have beneficial effects. β-Blockers remain cheap and effective drugs for angina, post-myocardial infarction and increasingly in heart failure. The relative benefits of the amlodipine±perindopril approach have to be taken in context as between 220 and 650 patients would need to be on this regime rather than the older regimes for 1 year to prevent one cardiovascular event or one death, respectively [14]. As most patients will have their hypertension treated for many years, these numbers would translate with time into a more meaningful benefit. Despite the efficacy of this trial, only 32% of diabetics and 60% of non-diabetics reached target BP control.

What about other drugs? Despite using modern drugs such as calcium channel blockers and ACE-Is, ASCOT still shows a high incidence of adverse drug side effects, which are barriers to compliance and effective therapy, particularly in the elderly. ARBs (angiotensin receptor blockers) have a growing evidence base, with losartan plus thiazide superior to atenolol plus thiazide in the LIFE trial [15] (another piece of evidence against atenolol as an antihypertensive agent). In the LIFE trial, <15% in the ARB arm discontinued therapy because of any adverse effect, compared with 25% of patients in both arms of ASCOT. It is still not completely clear if ACE-Is and ARBs offer additional protection above their BP-lowering effect or whether the adverse metabolic effects seen with β-blockers and diuretics explain some differences in outcomes seen. For instance, in LIFE, the 1.1 mmHg difference in systolic BP in favour of ARB over atenolol seems unlikely to explain fully the 25% relative risk reduction in stroke, the 25% lower incidence of new-onset diabetes or the 33% reduction in the rate of new-onset atrial fibrillation [16]. In ASCOT, there was a 30% reduction in new-onset diabetes in the calcium channel blocker±ACE-I group compared with β-blocker±thiazide. The exact role of ARBs in hypertension guidelines remains uncertain although they are an obvious alternative if ACE-I-induced cough develops. Questions remain of whether the ARBs should be viewed as an alternative or add-on agent in combination with an ACE-I.
ASCOT confirms that for most patients combination therapy is required, and the cost–benefits of monotherapy are less important than the costs of combination therapy, and this will continue to be important in devising national guidelines.

**Conclusion**

Diuretics remain a first-line option along with calcium channel blockers in older adults unless there is a risk of developing diabetes when ACE-Is are preferred. ACE-Is for older adults are second-line agents in combination with either of these. Atenolol should no longer be used as a first-, second- or third-line antihypertensive agent, but β-blockers continue to have an important role in angina and heart failure, and other β-blockers may still have a beneficial role in hypertension. ASCOT reinforces that most patients do not reach target line agents without any sense of failure is important. Whilst doctors are rightly concerned with fixed drug combinations into a single tablet, particularly in trying to sort out which agent might be responsible for adverse events, once patients are shown to respond to agents with no side effects, then fixed drug combinations may improve compliance and should be introduced at an early stage if the cost–benefits are favourable (more expensive agents versus better compliance and thus better outcome prevention). Above all, the results of ASCOT remind us that hypertension can be treated and serious complications reduced.

**Key points**

ASCOT
- β-Blockers are no longer first-, second- or third-line antihypertensives.
- The calcium channel blocker±ACE-I combination is superior to a β-blocker±diuretic.
- Most patients require two or more antihypertensives.
- There was a lower incidence of new-onset diabetes in the calcium channel blocker±ACE-I group.
- There are still relatively high adverse drug effects with the current main classes of antihypertensives.

ALLHAT
- Lowering the BP is more important than the agent used.
- There was some evidence that diuretics may be better than calcium channel blockers or ACE-Is.

ANBPS
- ACE-Is are superior to diuretics in older males.
- LIFE
- An ARB±diuretic is superior to a β-blocker±diuretic.
- ARBs lower the incidence of diabetes and atrial fibrillation.
- Overall
- Calcium channel blockers, ACE-Is and diuretics are all effective antihypertensive agents.
- Atenolol should no longer be used in preference to the other agents as an antihypertensive.

- Guidelines for older adults will need updating.
- As most patients require at least two drugs, arguments over which drug is best as monotherapy or first line are probably not that relevant.
- Which drug combinations are most beneficial, cost-effective and best tolerated with least adverse events remains uncertain.
- Updated guidelines should also address the role of ARBs.

**References**

10. Wing LM, Reid CM, Ryan P et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics...


