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ASCOT – hold on to your horses!

Bryan Williams

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) reported the final results of its blood pressure lowering arm at the European Society of Cardiology (ESC) Annual meeting amidst much publicity (see news, pages 339–42). The claims ranged from those highlighting the fact that the primary end point of the study was non-significant and thus technically, the study outcome was neutral, to those suggesting that this study was going to transform the clinical management of hypertension across the world. So what was ASCOT and what does it tell us?

ASCOT was a multi-centre, prospective, randomised, controlled trial in 19,257 people with hypertension with a mean age of 63 years. The study had a factorial design that allowed two questions to be addressed. The first asked whether the addition of a statin (atorvastatin 10 mg once daily) would reduce cardiovascular events more effectively than placebo in a cohort of ASCOT patients who would not otherwise have been treated with a statin. The results of the lipid-lowering arm (ASCOT-LLA) were published two years ago and clearly demonstrated that the addition of a statin reduced the risk of coronary heart disease by 36% ($p<0.0005$) and stroke by 27% ($p<0.02$) when compared to placebo.[1]

The second question was addressed by the blood pressure lowering arm (ASCOT-BPLA), which compared conventional blood pressure lowering therapy (atenolol with the addition of bendroflumethiazide–K as required) with a more contemporary regimen of newer drugs (amlodipine with the addition of perindopril).[2] The patients were predominantly male (77%) with a mean age of 63 years and those with a history of myocardial infarction or treated angina were excluded. The median follow-up of patients in ASCOT-BPLA was 5.5 years, providing over 100,000 patient years of observation. ASCOT-BPLA was stopped earlier than anticipated after the data safety monitoring board recommended to the trial steering committee that the study should be stopped because of clear benefit of the amlodipine-based therapy on most cardiovascular end points and total mortality, even though the primary end point (fatal and non-fatal myocardial infarction) was non-significantly different.

Clinical trial purists would argue that since most of the power of a clinical trial is invested in its primary end point, if this is not significantly different, then subsequent analysis of secondary end points in ASCOT-BPLA should be treated with caution. Nevertheless, it is likely that the primary end point of ASCOT-BPLA would have been significant had the study completed its course. The only reason it did not complete the course was because of substantial, significant and important differences in key end points in favour of amlodipine-based treatment, such as stroke (reduced by 23%, $p<0.0003$), all-cause death (reduced by 11%, $p<0.025$), and all cardiovascular events and procedures (reduced by 16%, $p<0.0001$). There was also a significant reduction in new-onset diabetes (reduced by 30%, $p<0.0001$) in favour of amlodipine-based therapy.

Blood pressure control was better throughout the BPLA study with the amlodipine-based therapy and this is likely to have been the major driver of the differences in clinical outcome. This is not to belittle the findings – on the contrary, we recognise blood pressure control is key to improving clinical outcomes and in this regard, amlodipine-based therapy was clearly superior to conventional beta blocker/thiazide-based therapy. Moreover, these differences in blood pressure persisted throughout the study despite the fact that more add-on blood pressure lowering therapy was used in the atenolol-based arm of the study. Thus, message 1 is: *Choosing the correct drug to initiate therapy is important as it defines the subsequent quality of blood pressure control.*

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National guidelines

So will ASCOT-BPLA influence national guideline recommendations for blood pressure treatment? It is worth reflecting on the results in the context of current British Hypertension Society recommendations (BHS-IV).[3] The BHS advocates the use of the AB/CD algorithm which recommends that for the typical ASCOT-BPLA patient (majority over the age of 55 years), therapy should be initiated with C (a calcium channel blocker) or D (a thiazide diuretic), as either of these choices is likely to produce a better initial blood pressure lowering response than A (an angiotensin-converting enzyme [ACE] inhibitor or an angiotensin II receptor blocker) or B (a beta blocker). Thus the current BHS guidance would have advised against giving a beta blocker as initial therapy to the majority of patients studied in ASCOT-BPLA. So message 2 is: *The current BHS guidance on initiating therapy (AB/CD) in people aged ≥ 55 years is supported by the results of ASCOT-BPLA. Moreover, ASCOT and the recent VALUE study challenge the pre-eminence of D (thiazide) as the only initial therapy in this age group and support C (calcium channel blockers) as a suitable alternative – as suggested by the BHS-IV guideline.*

Another interesting aspect of drug combinations is that ASCOT-BPLA used the combination of a calcium channel blocker with an ACE inhibitor. This combination is considered appropriate by the AB/CD algorithm and helps validate the algorithm. However, it is not a combination used as commonly as others and few examples of fixed dose combinations of C+A exist. In my view, this is likely to change as a consequence of ASCOT-BPLA and the C+A combination will become much more popular. Furthermore, the use of beta blocker/thiazide combinations is likely to decline. Existing guidance from BHS-IV and the National Institute for Clinical Excellence (NICE) hypertension guideline[4] already cautions against the use of a beta blocker/thiazide combination because of the increased risk of developing diabetes in patients exposed to this drug combination – a recommendation supported by ASCOT-BPLA, which also showed a 30% increase in the risk of developing diabetes in patients allocated to this combination. Message 3 is: *Reflecting on the AB/CD algorithm, an important consequence of the ASCOT study is that if D (thiazide) is used as initial therapy in people aged ≥ 55 years, then if further blood pressure lowering is required, then the use of an A drug rather than a beta blocker is preferred.*

Whether beta blockers should remain a suitable choice for younger patients (< 55 years of age) has not been adequately addressed by ASCOT-BPLA, or for that matter, any other trial. The fact remains that we have too little information on the appropriate treatment of younger patients with hypertension. Nevertheless, the clear evidence that beta blockers, especially in combination with diuretics, will increase the risk of developing diabetes and also induce other metabolic disturbances (notably increased triglycerides and reduced high-density lipoprotein cholesterol), all of which could potentially negate the benefits of blood pressure lowering over time, suggest that beta-blocker-based treatment appears less suitable than alternatives for the routine treatment of hypertension in younger patients, and initiation with an A drug might be preferred, with subsequent addition of a C or D drug as required.

Lessons learnt

ASCOT-BPLA has thus reinforced the evidence base for many of the existing recommendations in the current BHS-IV guideline. In particular, it has supported the recommendation that beta-blocker-based treatment is not an optimal initial treatment for older patients with hypertension. It has also raised concern about the use of beta blockers for the routine treatment of hypertension in any patient, in the absence of any compelling indication for beta blockade, e.g. the treatment of symptomatic angina. Perhaps the most significant data from ASCOT came from ASCOT-LLA,[1] which suggested that patients with hypertension and at higher risk of cardiovascular disease, should also receive a statin, irrespective of their baseline cholesterol level, to optimise their cardiovascular disease risk reduction. This important recommendation has already been incorporated into existing guidance in BHS-IV.

In conclusion, ASCOT has helped to clarify and confirm many aspects of existing guidance for the treatment of hypertension. NICE working in collaboration with the BHS has established an expert group to look at the results of ASCOT in the context of existing data and guidance. This is an important development that will be applauded by many doctors. The remit of this group is to advise NICE as to whether any amendments to existing national guidance for the treatment of hypertension is necessary. Until this process has been completed, the most appropriate advice for doctors and their patients is to follow existing guidance and endeavour to obtain the most effective blood pressure control possible, and to actively consider the use of statin therapy in hypertensive patients at higher risk of cardiovascular disease.

Conflict of interest

BW was an ASCOT investigator and Regional Coordinator. He is a Past-President of the British Hypertension Society and was Chairman of the writing committee for the current BHS guidelines (BHS-IV) and a member of the NICE hypertension guideline development group. He is also a Trustee of the Blood Pressure Association.

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