

Was ASCOT won on fact, or publicity?

By Magnus Hird, a pharmacist practitioner from Blackpool

Many newspapers carried major stories and “Modern drugs ‘halve stroke risk’” proclaimed the BBC. They were reporting the publication of the blood pressure (BP) lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in *The Lancet*. These headlines were the culmination of nine months of publicity and speculation since the trial was stopped early due to “big advantages” for new drugs over an older treatment strategy. Experts were described as saying “prescribing practice should change immediately based on the ASCOT study’s conclusions”, but has the real message been lost in the hype?

Before looking at the BP results, the BBC headline deserves explanation. It relates to a misleading comparison between new drugs given with a statin and older drugs without a statin. In turn this derives from the fact that ASCOT had two parts: a lipid-lowering arm and a blood pressure arm. The lipid results were published in 2003 and reinforced what we already knew: using statins in high-risk hypertensive patients is a good idea. To combine the results in this way was entirely inappropriate.

In the BP study, 19,257 patients aged between 40 and 79 years who all had hypertension, plus at least three further risk factors (such as previous stroke, male sex or diabetes) were randomised to a treatment regimen based on amlodipine or atenolol. Patients who had previously had a heart attack or angina were excluded from the study. Treatments were intensified progressively in order to achieve a blood pressure target of 140/90mmHg (or 130/80mmHg in patients with diabetes). Initial doses of 5mg or 50mg were doubled then, and either 4mg of perindopril or 1.25mg of bendroflumethiazide were added to the respective arms. The doses of these add-on drugs could be doubled, followed by the use of doxazosin and other agents as needed. It is worth noting that using high doses of beta-blockers first line for hypertension is not an approach advocated by either the National Institute for Health and Clinical Excellence (NICE), the British Hypertension Society (BHS) or the major American guidelines.

The trial’s primary endpoint (the question it was designed to answer) was a composite of non-fatal myocardial infarction and cardiac death. Despite the headlines, at the end of the study there was no significant difference in the rate of this outcome. There were statistically significant reductions in the rates of

some of the other, important, outcomes such as stroke and total mortality, as well as two other measures added in during the analysis of the results. One of these was a composite of cardiovascular death, non-fatal stroke and myocardial infarction.

Although the quoted reductions in risk for these endpoints (23 per cent, 11 per cent and 16 per cent) sound impressive, they are of course relative. To put them in better context you would have to treat 100, 115 and 68 high-risk hypertensives, respectively, for five and a half years to prevent one of each of the above, something the authors admit are “fairly small absolute benefits”. The numbers would be even higher in the wider, generally lower-risk hypertensive population.

Despite the characteristics of the study population being balanced at the start, by the time the trial was stopped, the amlodipine group differed from the atenolol group. Among other things their average BP was 2.6mmHg lower, HDL cholesterol 0.1mmol/L higher and triglycerides 0.3mmol/L lower. These factors are potentially beneficial in terms of cardiovascular events.

In an editorial published alongside the study, Staessen and Birkenhager present predictions of the results they made before publication. Working on the basis that there would be a difference in BP between the two groups (something fairly obvious from the start given the dose schedule used in the atenolol arm) they used existing data on the effectiveness of antihypertensives to estimate what the reduction in events would be. Their predictions are pretty close and they conclude that the lower BP in the amlodipine arm entirely explains the results of ASCOT. The key message is that “in hypertensive patients it is the lowering of BP that produces most of the benefit”, not that new drugs are better than old ones. By the end of the study around a quarter of the patients in both groups had stopped taking the medicines due to adverse reactions: no difference overall, although there were small differences in the exact reasons for ceasing. This completely refutes the claims of one professor, whom the BBC quoted as saying “these modern drugs often cause less side effects than older ones”; clearly they do not.

The consequences of a raised risk of developing type 2 diabetes when taking high doses of beta-blockers with thiazide diuretics (an extra one patient for every 41 treated for five and a half years, which supports results seen in other trials) requires further debate. Clearly type 2 diabetes is important, but the

latest data from the Systolic Hypertension in the Elderly Program (SHEP) study suggest that those who do suffer this event on the medicines actually do better in the long-term than those on placebo.

Where we go from here rests with determining how the ASCOT findings integrate with the past 40 years of hypertension research and how best to resolve the paradox between treating a population and an individual. Those who suggest everything should change immediately risk throwing the baby out with the bathwater. ASCOT adds to what we know; it does not revoke or invalidate everything predating it. For example, the larger Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) provides a more appropriate analysis for today’s approach to hypertension. In this study none of the other treatments, including amlodipine, bettered the results obtained with a thiazide diuretic used first-line, the approach advocated by NICE. Previous meta-analyses of antihypertensive treatments have suggested that dihydropyridine calcium channel blockers (DCCBs) may be less effective than beta-blockers in preventing coronary events. By excluding patients at highest risk of coronary events (those with existing cardiovascular heart disease) ASCOT unfortunately avoided this question. Interestingly stroke patients were enrolled, a group for whom the meta-analyses suggested DCCBs may be better. Did these selection criteria bias the results of the study from the start?

What ASCOT does suggest is that using high doses of beta-blockers followed by thiazide diuretics may lower BP less than other potential combinations of drugs. Although one can question the relevance (as existing UK guidelines do not advocate this approach), this finding is important at a population level — 2–3mmHg differences in BP can translate to thousands of events avoided. Treatment guidelines need to look at these possibilities. However, at an individual level, such differences are unlikely to change outcomes and, ironically, poor proficiency in measuring BP, or the use of badly maintained equipment, is more likely to be relevant. Our challenge is to offer all patients with hypertension a regimen tailored to their situation that is likely to be taken and lower their BP to a level they are comfortable with. ASCOT provides us with no reasons not to continue starting with a thiazide in most patients, but adds to the reminders that treatment should be up-titrated as necessary rather than failing to respond to continuing raised BP.

The experts will continue to debate the nuances and minutiae but until new guidance is forthcoming we can reassure patients rather than add to their confusion and anxiety.

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