

# The ASCOT trial: a closer look

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The results of the Anglo–Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) [1] are a major addition to our understanding of the appropriate way to provide antihypertensive drug therapy for hypertension.

Although it is true that, in all previously published trials, an admixture of additional drugs with the initial agent being studied has been invariable, sometimes reaching 80% of the enrollers [2], ASCOT-BPLA is the first published study purposely designed to compare combinations of ‘older’ drugs (i.e. a  $\beta$ -blocker followed by a diuretic) versus ‘newer’ drugs [i.e. a calcium channel blocker (CCB) followed by an angiotensin-converting enzyme inhibitor (ACEI)]. The data show a significantly greater protection against various cardiovascular diseases by the CCB followed by ACEI regimen than by the  $\beta$ -blocker followed by diuretic regimen.

In addition to the papers published in the *Lancet* [1,3], the authors have portrayed the rather tortured manner by which the trial was designed and the rather Herculean efforts expended to bring it to completion [4]. Beyond a good amount of such background information, all of the important findings are to be found in the papers published in the *Lancet* [1,3].

## A few relatively minor criticisms

No trial will ever be perfect but ASCOT-BPLA comes closer to perfection than most. The design started with either the CCB or the  $\beta$ -blocker and, if control was not achieved, the ACEI or diuretic was then added. By the end of the trial, 82.5% of those assigned to the CCB amlodipine were on that drug, whereas 58.5% of this group were on the ACEI perindopril. Similar figures are shown for those assigned to the  $\beta$ -blocker atenolol (79.4%) and the diuretic bendroflumethiazide (65.7%). Thus, in a strict sense, the trial was not truly a combination trial from the onset although the majority of patients did take a combination for most of the time.

Some critics might fault the decision to compare the newer drugs against a  $\beta$ -blocker, now clearly recognized

as inferior agents for primary prevention that ‘should not be used as reference drugs in *future* randomized controlled trials of hypertension’ (emphasis added) [5]. However, as noted by the ASCOT-BPLA investigations, ‘The most frequent combination of antihypertensive medications used worldwide when this trial was initiated was a  $\beta$ -blocker plus a diuretic and the most commonly used drugs within these classes were atenolol and thiazides, respectively’ [1].

Another possible criticism of ASCOT-BPLA is the inclusion of mostly older patients at high cardiovascular risk, such that the ‘results might therefore not be readily applicable to most hypertensive patients seen in daily practice’ [6]. However, this same recruitment policy has been used in most recent comparative trials to keep sample size within achievable limits. In earlier studies, when placebo arms were permissible, the outcomes were so markedly different between a placebo and the active drug that younger, healthier patients could be included and still provide significant differences.

It might be argued that the absence of a statistically significant difference between the two regimens on the primary end-point of non-fatal myocardial infarction and fatal coronary heart disease deflates the importance of the study. However, the decision by the Safety Monitoring Board to stop the trial to protect those on the  $\beta$ -blocker/diuretic regimen before the pre-determined number of events had occurred appears to be a reasonable explanation for the ASCOT-BPLA investigators to include coronary revascularizations in the primary outcome and to emphasize the differences in secondary end-points, including stroke.

I have one criticism, admittedly only over the use of one word but important nonetheless. In the first *Lancet* paper, the penultimate sentence states that the use of a CCB with an ACEI, ‘particularly when used in combination with effective lipid lowering, results in the *prevention* of most major cardiovascular events associated with hypertension’ (emphasis added) [1]. Clearly, the results are impressive but, as witnessed by the 796 cardiovascular events in the 9639 patients assigned to CCB + ACEI (compared to the 937 events in the 9618 assigned to  $\beta$ -blocker + diuretic), there was certainly no ‘prevention of most cardiovascular events associated with hypertension’ [1]. The ASCOT-BPLA investigators are now looking at further outcomes in those individuals in the blood pressure study who were previously shown to benefit from statin therapy in the ASCOT-LLA and

who were from the same population [7]. Therefore, more protection will likely be reported when the data on those individuals receiving both statin and CCB + ACEI ACEI are examined.

Obviously, this was a relative short study that was prematurely stopped. Much more protection would likely have been seen with a much longer trial but 'prevention' is really too much to claim.

Perhaps the most serious criticism of ASCOT-BPLA is the persistent differences in blood pressure between the two regimens, a problem almost universally seen in large randomized controlled trials. The end-study differences in ASCOT-BPLA were 2.7/1.9 mmHg. The ASCOT-BPLA investigators estimated that these lower blood pressures with the CCB + ACEI regimen could be responsible for a 4–8% reduction in coronary events and an 11–14% reduction in strokes. However, in an editorial accompanying the ASCOT-BPLA papers, Staessen and Birkenhäger [6] provide evidence that these blood pressure differences would reduce 15% of coronary events and 21% of strokes, and conclude that 'the 2.7 mmHg systolic gradient is sufficient to explain the cardiovascular benefit of amlodipine with or without perindopril' [6].

An even greater difference in blood pressures (5.9/2.4 mmHg) between the two regimens was noted during the first 6 months of ASCOT-BPLA. Such an early difference was used to explain most of the greater benefit of a CCB-based regimen versus an ARB-based regimen in the VALUE trial [8]. Furthermore, the ASCOT-BPLA investigators concluded that 'blood pressure was the biggest single contributor to stroke events, but differences in high-density lipoprotein cholesterol were most important for coronary event' [3]. These later differences could obviously be attributed to the  $\beta$ -blocker.

### Major confirmations

ASCOT-BPLA strongly reconfirms two major points reported in previously published trial data. First, the typical need for two or more drugs to adequately control most hypertensives and, even then, the inability to adequately control a good number, particularly those with diabetes [9]. Second, the propensity of  $\beta$ -blocker plus diuretic therapy to uncover much more new-onset diabetes than observed with drugs that inhibit the renin-angiotensin system [10].

The potentiation of diabetes by  $\beta$ -blockers appears certain [11]. However, in a prospective study by Gress *et al.* [11], diuretic therapy (with no knowledge of dosage) was not associated with onset of diabetes over a 6-year follow-up whereas  $\beta$ -blocker use was associated with a 28% increase. High doses of diuretic [i.e. 50–100 mg of hydrochlorothiazide (HCT)], reduce insulin sensitivity

as much as  $\beta$ -blockers [12] but there are inadequate data on the diabetogenic potential of low-dose diuretic (i.e. 12.5–25 mg of HCT).

The diuretic used in ASCOT-BPLA was bendroflumethiazide (1.25 mg and then 2.5 mg per day). There are no comparative trials of HCT versus bendroflumethiazide but the latter diuretic is longer acting [13] and, similar to the chlorthalidone used in the ALLHAT trial [9], may be more potent than HCT.

The threat of diabetes is worrisome. One non-randomized study based on a small number of patients who started with higher blood pressure and blood glucose, and who then received an admixture of diuretics, found an increase in cardiovascular events over a 3.1-year follow-up compared to patients who did not take a diuretic [14]. However, no increase in cardiovascular events was observed in those individuals who developed diabetes during either the 5–7-year follow-up in the ALLHAT study [9] or the 14.3-year follow-up of the Systolic Hypertension in the Elderly Program [15].

### The need for diuretics

This concern about provoking diabetes is one reason for arguing against the use of diuretics, certainly as an initial therapy as advocated by ALLHAT, or even as an add-on therapy in those individuals not controlled by the initial choice. Nonetheless, diuretics are effective in themselves [16] and additive to the efficacy of all other classes of agents. Perhaps the most striking example of the advantage of concomitant diuretic is provided by the PROGRESS trial [17], where an ACEI alone had little effect on either blood pressure or stroke recurrence, whereas excellent reductions in both blood pressure and stroke recurrence were seen when a diuretic was added to the ACEI.

Although the design of ASCOT-BPLA precluded the addition of a diuretic to those in the CCB + ACEI arm, a diuretic is usually needed to adequately control hypertension. Not only do they enhance the efficacy of other drugs, but also they counter the tendency for reactive sodium retention by the kidneys because the blood pressure is reduced by non-diuretic drugs. With currently recommended low doses, a diuretic should always be considered.

### Is the polypill the solution

In ASCOT-BPLA, it took an average 2.2 pills to control hypertension to below 140/90 mmHg for nondiabetics and to below 130/80 mmHg for diabetics. The average reduction in blood pressure was from 164/95 mmHg to 137/78 mmHg (a 27/17 mmHg decrease). Nonetheless, at the end of the trial, only 60% of those without diabetes and only 32% of those with diabetes had reached the systolic and diastolic goals.

These results are similar to those seen in most large antihypertensive trials. Two issues are obvious: (i) why were the other 40% of the ASCOT-BPLA patients not controlled and (ii) is 140/90 (and 130/80 for diabetics) the appropriate goal of therapy. With respect to the first issue, adverse events caused 25% of ASCOT-BPLA patients to stop therapy. Many of these adverse events, including dizziness, fatigue, lethargy, peripheral coldness and erectile dysfunction, suggest a too great or too fast reduction in blood pressure. Unfortunately, blood pressure measurements were not taken out of the clinics, and the relationships between blood pressure and symptoms could not be determined.

Adverse effects of even the 'newer' drugs are a reason for some patients to stop therapy but, either by trial design or by physician inertia [18], many patients do not reach the study goal because they are not prescribed adequate therapy. The results of a tightly controlled, vigorously conducted trial such as ASCOT-BPLA must certainly be better than can be achieved in usual practice.

For this and other reasons, the potential of the prevention of hypertension has become even more desirable. Because lifestyle modifications are usually not adequate, two approaches using drugs have been advocated. One, the gradualist approach, is to give antihypertensive drugs to those individuals who are not yet hypertensive [19]. The other, more broad approach, is to give everyone over the age of 55 years, or who have any existing cardiovascular disease, a polypill containing three blood pressure-lowering drugs at half standard dose: a statin, folic acid and 75 mg of aspirin [20]. This strategy was claimed to be capable of reducing cardiovascular disease by more than 80%. Obviously, a good deal of the putative benefit would come from the prevention not only of hypertension, but also dyslipidemia and thrombosis.

Many authors initially doubted the use of such a polypill. However, ASCOT-BPLA again showed that even more than two antihypertensives in full doses may not be enough to control established hypertension. ASCOT-LLA also showed the benefit of administering a statin, regardless of the level of serum cholesterol. Moreover, fixed dose combination pills improve adherence to therapy [21].

For these and other reasons, the use of combination tablets is receiving additional support [22]. The members of this group [22] and others question the wisdom of the six choices included by Wald and Law [20]. As for the three antihypertensive choices, a  $\beta$ -blocker now appears to be a poor one [5], likely more rationally substituted by a CCB on the basis of the ASCOT-BPLA data [1]. A statin clearly is important, whereas the evidence for folic acid is uncertain [22]. Interestingly, a low dose of aspirin

may be the component most likely to cause a serious adverse effect (i.e. gastrointestinal bleeding) [23].

The second major issue is the appropriate goal of therapy. Recent expert committee guidelines have recommended 140/90 mmHg for most patients and 130/80 mmHg for those with concomitant diabetes or renal disease. As reviewed elsewhere [13], the evidence in favour of the lower goal for patients with diabetes or renal disease is by no means conclusive. On the other hand, treatment of hypertensives to below 140/90 mmHg has never been demonstrated to lower the risk of heart attack and stroke down to the level experienced by never-hypertensive people. Obviously, we have enough trouble getting patients to achieve the current goals. However, they may not be the appropriate goals.

## Conclusion

Despite the expenditure of a great amount of effort and money, the control of hypertension has been only partially effective in protecting people from cardiovascular events. In a recent survey of the reasons behind the decrease in coronary mortality in England and Wales from 1981 to 2000, the 7.7% mean population fall in blood pressure was found to provide only approximately 10% of the benefit [24].

The ASCOT-BPLA data provide evidence for a way to improve on past experience. However, as much as they promise, a great deal more will need to be done to control cardiovascular and renal diseases. Whether or not this will require a broad approach using a polypill for everyone, as I now believe, the application of the ASCOT-BPLA data to clinical practice will surely help.

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