

C o m m e n t a r y

The ASCOT Trial

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Results of the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) trial have finally been published.¹ The results of this trial had been repeatedly highlighted in the media and at numerous medical meetings before publication. The headlines proclaimed that “newer antihypertensive drugs” were more effective in reducing coronary heart disease (CHD) events than standard therapy, i.e., a calcium channel blocker (CCB)-based treatment program with an angiotensin-converting enzyme inhibitor (ACEI) added was more effective in preventing cardiovascular (CV) disease than a β -blocker-based regimen with a diuretic added if necessary. Beta blockers and diuretics were considered together as examples of older drugs.

The primary end point in the ASCOT study was nonfatal myocardial infarction, including silent infarcts and fatal CHD. Analysis of this nonblinded study was appropriately based on intention to treat (see page 751 in this issue of *The Journal of Clinical Hypertension* for details and results). The study, contrary to what many had been led to believe, failed to show a statistically significant difference in the primary end point between the two regimens. This may have been a result of the study’s having been stopped early because of secondary outcomes. Analyses of secondary outcomes, which included fatal and nonfatal stroke, total CV events, and all-cause mortality, revealed that the CCB/ACEI regimen was more effective in reducing events than the β blocker/diuretic regimen.

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Only a few investigators have come forward to highlight some of the problems with the ASCOT study report, i.e., the choice of the initial comparator medication or the use of secondary outcomes as an indication for specific treatment recommendations. Contrast this to what happened with the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),² when the use of secondary outcomes to define differences in outcomes was severely criticized (the ALLHAT study was not referenced in the *Lancet* article on ASCOT). In ALLHAT the primary end point of CHD events was similar, with a diuretic-based treatment program compared with an ACEI- or CCB-based regimen. Benefit from one specific regimen could not be established for the primary outcome. Secondary end points were considered, however, and then factored into the benefit equation. The number of heart failure events was fewer in the diuretic group than in the CCB or ACEI groups. Stroke events were less frequent with diuretics than with ACEIs. ALLHAT was a blinded, non-industry-sponsored trial. Critics of ALLHAT were quick to comment on and criticize the use of secondary outcomes as criteria of benefit; many have never accepted the ALLHAT results. Blood pressure (BP) differences between groups, especially between black and white subjects, and not specific actions of specific medications, were invoked to explain the difference in benefit.

In ASCOT, BPs, especially during the first 6 months, were lowered to a greater degree in the group who received the CCB, amlodipine, compared with the group who primarily received the β blocker, atenolol, during the initial titration period. The BP differences were not surprising; once-a-day atenolol is not expected to be as effective as a long-acting CCB in lowering BP. Statistical manipulations were presented to demonstrate that,



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although there was a BP difference during this period, it was *not* the BP difference that accounted for the benefit; there must have been some specific effect of specific drugs. When the authors of the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial of Cardiovascular Events in Hypertension³ used a similar type of statistical correlation in an attempt to prove that the BP differences were the reason for a better outcome for myocardial infarction with a CCB-based compared with an angiotensin receptor blocker (ARB)-based regimen, they were severely criticized.

It is not inappropriate to consider secondary end points as indicators of outcome and as guides to treatment, especially when they appear to affect mortality, as they did in ASCOT—but too often, when primary end point results do not turn out as anticipated, statisticians forget some of their basic principles.

The Swedish Trial in Old Patients with Hypertension-2 (STOP-2)⁴ in patients over 60 years of age, carried out in a population with demographics similar to the ASCOT population (although the protocol differed from that in ASCOT), reported a somewhat different result. STOP-2 failed to show an *overall* difference in CV outcome between a CCB/ACEI and diuretic/ β blocker regimen with similar degrees of BP lowering STOP-2 also was not referenced in the ASCOT report.

The ASCOT study used the wrong “standard” drug as initial therapy and comparator. What would the results have been if a diuretic had been the first drug of choice, with upward titration and a β blocker added? Early BP changes would have compared a CCB to a diuretic. There might not have been early differences in BPs between the two groups, and perhaps no difference in secondary outcome. It is well known, based on previous studies, especially in the elderly, that a diuretic is more effective in lowering BP and reducing the occurrence of CHD events than a β blocker.⁵ The impression given by the authors of ASCOT is that the *older drugs considered together* are not as effective as newer agents; this conclusion includes diuretics as one of the “older drugs.” Many of the differences in outcome in ASCOT probably resulted from the use of a β blocker as initial therapy.

The authors should certainly have commented on the Systolic Hypertension in the Elderly Program (SHEP),⁶ a double-blind, placebo trial that demonstrated statistically significant decreases in both CHD and cerebrovascular events in diuretic-treated patients (with other drugs added as necessary) before reaching conclusions regarding the lack of benefit of these agents in CHD.

This is important in view of the initial assumptions of the ASCOT investigators that diuretics/ β blocker-based treatment trials had reported a shortfall in CHD event reduction, an assumption that has been disproved.^{7–10} The SHEP trial also was not referenced in the ASCOT report.

There is little doubt that the use of an ACEI or ARB-based treatment regimen (and in some instances a CCB) will result in fewer cases of new-onset diabetes (NOD) than a program based primarily on a β blocker or a diuretic, but the significance of this finding has not been settled.¹¹ A β blocker, the initial drug used in ASCOT, has been shown to increase the incidence of NOD to a greater degree than other drugs, including a diuretic.¹²

The long-term significance of NOD remains to be clarified. The follow-up results of SHEP appeared to indicate that NOD did not carry the same prognosis as pretreatment diabetes,¹³ in contrast to a study with a small number of events which indicated similar outcomes between NOD and pretreatment diabetes.¹⁴

Although one cannot question the fact that therapy with a CCB-based regimen is effective and appropriate therapy for many hypertensive patients and may provide a better outcome than a β -blocker-based regimen, the ASCOT statements regarding optimal management and choice of medications do not reflect all of the available data. Conclusions about the results being “generalizable” and that they should lead to a reevaluation of guidelines do not appear to be justified.

THE ISSUE OF COST

The authors of ALLHAT were accused of reaching conclusions based on the economics of care, i.e., diuretics are less expensive and therefore should be used as initial therapy. Critics ignore the fact that good science was employed in ALLHAT to reach that conclusion—that these agents were as or possibly more effective in some subsets of patients than other medications. While cost should not be a factor in the choice of therapy for any disease if one therapy is clearly superior to another, ASCOT does not establish this fact. There are too many conflicting data from other studies to conclude that one drug is better than another or one combination superior to another in the management of hypertension *if BP lowering is equivalent*. We continue to believe that, while there are certain subsets of patients who may benefit from therapy with specific agents, for example, ACEIs or ARBs in combination with a diuretic in diabetic nephropathy, the major benefit in terms of

reducing CV events is achieved by the lowering of BP. This can be done effectively with many different combinations. As ASCOT and numerous trials have reported, a majority of patients, especially those with grade II hypertension or comorbidities, will require more than one medication to achieve goal BPs. The two medications used in one arm of the ASCOT trial, a CCB and an ACEI, are effective and can be used as definitive therapy for many hypertensive patients. There is little evidence, however, that these agents reduce CV events more than other combinations, including a diuretic as initial therapy with a β blocker added or an ACEI, ARB, or CCB/diuretic combination.

Media coverage and dissemination before publication are indicated if the results of a study are truly of major clinical importance, but ASCOT-BPLA was not a critical study. It has confirmed that a β -blocker-based regimen may not be as effective as other treatments. Results, however, should not change the way physicians initially treat hypertension or the recommendation of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)¹⁵ that thiazide diuretics be used as initial therapy in most patients. The ASCOT results *suggest and confirm* what previous JNC reports¹⁶ had recommended—that β blockers may not be first-choice therapy in elderly patients unless there is a specific indication for their use, i.e., post-myocardial infarction or congestive heart failure.

REFERENCES

- Dahlof B, Sever PS, Poulter NR, et al, for the ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895–906.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2981–2997.
- Mann J, Julius S. The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial of cardiovascular events in hypertension. Rationale and design. *Blood Press*. 1998;7:176–183.
- Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity in the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354:1751–1756.
- Medical Research Council Working Party. Medical Research Council trial of treatment of hypertension in older adults: principal results. *BMJ*. 1992;304:405–412.
- SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255–3264.
- Moser M, Hebert PR, Hennekens CH. An overview of the meta-analyses of the hypertension treatment trials. *Arch Intern Med*. 1991;151:1277–1279.
- Hebert PR, Moser M, Mayer J, et al. Recent evidence on drug therapy of mild to moderate hypertension and decreased risk of coronary heart disease. *Arch Intern Med*. 1993;153:578–581.
- Hypertension Detection and Follow-up Program Cooperative Group. Persistence of reduction in blood pressure and mortality of participants in the Hypertension Detection and Follow-up Program. *JAMA*. 1988;259:2113–2122.
- The Multiple Risk Factor Intervention Trial Research Group. Mortality rates after 10.5 years for participants in the Multiple Risk Factor Intervention trial. *JAMA*. 1990;263:1795–1801.
- Moser M. New-onset diabetes in the hypertension treatment trials: a point of view [published correction appears in *J Clin Hypertens (Greenwich)*. 2005;7:194]. *J Clin Hypertens (Greenwich)*. 2004;6:610–613.
- Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *N Engl J Med*. 2000;342:905–912.
- Kostis JB, Wilson AC, Freudenberger RS, et al, for the SHEP Collaborative Research Group. Long-term effect of diuretic-based therapy on fatal outcomes in subjects with isolated systolic hypertension with and without diabetes. *Am J Cardiol*. 2005;95:29–35.
- Verdecchia P, Reboldi G, Angeli F, et al. Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension*. 2004;43:963–969.
- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
- The sixth report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure [published correction appears in *Arch Intern Med*. 1998;158:573]. *Arch Intern Med*. 1997;157:2413–2446.