Leading with Innovation
Serving with Compassion
ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

Cardiology

UNIVERSITY OF TORONTO

Special New Feature
Visit us at www.cardiologyupdate.ca for PowerPoint teaching slides on this topic

AN EDUCATIONAL PUBLICATION FROM THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

The Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) New Insights into the Prevention of Cardiovascular Events with the Newer versus the Older Antihypertensive Regimen

Originally presented by: Peter S. Sever, MD; Neil R. Poulter, MD; Björn Dahlöf, MD

An Educational Publication based on a Presentation at the Hotline Session of the European Society of Cardiology Annual Congress

September 3-7, 2005 Stockholm, Sweden

By GORDON W. MOE, M.D.

Although the benefits of antihypertensive drugs for the prevention of cardiovascular (CV) mortality and morbidity are well-established, there continues to be controversy about whether the "newer" antihypertensive agents (eg, calcium channel blockers [CCBs] and angiotensin-converting enzyme [ACE] inhibitors) are more effective than "older" therapies (based on diuretics or ß-blockers). The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) was the latest large-scale trial to report on the relative benefit of the "newer" versus the "older" antihypertensive agents. This issue of *Cardiology Scientific Update* discusses the late-breaking final results of the ASCOT-BPLA trial and their impact on the management of high-risk hypertensive patients.

The benefits of intensive blood pressure (BP) lowering in preventing CV mortality and morbidity in hypertension are well-documented.[1] However, the shortfall between the magnitude of coronary heart disease (CHD) prevention observed in meta-analyses of earlier hypertension trials and that predicted in long-term prospective observational studies[2] raises an important question: Did the older agents in the earlier trials – namely diuretics and ß-blockers – exert adverse effects that offset the benefit of BP lowering?[3] Newer agents (eg, CCBs and ACE inhibitors) may avoid some of these potential adverse metabolic effects and exert additional CV protective effects.[4-6] As a result, two large-scale trials, both with the same primary endpoint, were designed to compare the "newer" versus the "older" antihypertensive drugs:

1) the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the results of which were reported in 2002,[7] and in a previous issue of *Cardiology Scientific Update*

2) the recently reported Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial, the subject of this issue of *Cardiology Scientific Update*.

ASCOT-BPLA

ASCOT-BPLA was designed to provide further data on outcomes with newer agents over standard therapy with ß-blockers and diuretics and to provide some information on combinations of agents. Details of the rationale and methodology have been reported previously.[8,9] In brief, men and women aged 40 to 79 years were eligible if they were hypertensive (by the study definitions described below) and had at least 3 of the pre-specified CV risk factors listed in Table 1.

- Subjects not on antihypertensive medications had either systolic BP >160 mm Hg and/or diastolic BP >100 mm Hg at both the screening and randomization visits.
- Subjects already taking antihypertensive agents had either systolic BP >140 mm Hg and/or diastolic BP >90 mm Hg at randomization.

Eligible patients were randomized, using the PROBE design, to either amlodipine or atenolol, with added perindopril or bendroflumethiazide-K, respectively, to achieve target BP. The treatment protocols, including the"add-on therapy" of the 2 antihypertensive regimens are explained in Table 2.

The primary endpoint was:

- nonfatal myocardial infarction (MI) and fatal CHD

The secondary endpoints included:

- nonfatal MI (symptomatic only), fatal CHD
- all-cause mortality

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: Pre-specified cardiovascular risk factors for eligibility

• Smoking	• NIDDM
• LVH	• Peripheral vascular disease
• History of early CHD in first degree relative	• History of cerebrovascular event
• ECG abnormalities	• Male sex
• Age ≥55 years	• Plasma TC/HDL ratio ≥6
• Microalbuminuria/proteinuria	

CV = cardiovascular; NIDDM = non-insulin-dependent diabetes mellitus; LVH = left ventricular hypertrophy; ECG = electrocardiogram; CHD = coronary heart disease; HDL = high-density lipoprotein; TC = total cholesterol

- CV mortality
- fatal and nonfatal stroke
- fatal and nonfatal heart failure
- total coronary endpoints (fatal CHD, non-fatal MI [symptomatic and silent], chronic stable angina, unstable angina, fatal and non-fatal heart failure)
- total CV events and procedures (CV mortality, non-fatal MI [symptomatic and silent], unstable angina, chronic stable angina, life-threatening arrhythmias, silent non-fatal heart failure, non-fatal stroke, peripheral arterial disease, revascularization procedures, and retinal vascular thromboses)

The pre-specified tertiary endpoints are:

- silent MI
- unstable angina
- chronic stable angina
- peripheral arterial disease
- life-threatening arrhythmias
- development of diabetes mellitus
- development of renal impairment

The study assumed an annual rate of non-fatal MI and fatal CHD events of 2% among those allocated to ß-blocker-based therapy; after adjustment for withdrawals and crossovers, this estimate fell to 1.42% per year. If the CCB-based regimen reduced this risk by 20%, after estimating the adjustment for withdrawals and cumulative non-compliance (20% over 5 years), the intention-to-treat effect (ITT) was estimated to be a 15% reduction in risk. A sample size of 18,000 subjects was estimated to generate 1150 primary composite events, with an 80% power and two-sided significance of 5%. Randomization took place between February 1998 and May 2000; 19,257 hypertensive patients were randomized from 650 general practices in the United Kingdom, Ireland, Sweden, Finland, Denmark, Norway, and Iceland.

Table 2: Two antihypertensive treatment regimens that were compared

	Calcium channel blocker-based regimen	ß-blocker-based regimen
Step 1	Amlodipine 5 mg	Atenolol 50 mg
Step 2	Amlodipine 10 mg	Atenolol 100 mg
Step 3	Amlodipine 10 mg Perindopril 4 mg	Atenolol 100 mg BFZ 1.25 mg + K^+
Step 4	Amlodipine 10 mg Perindopril 8 mg (2x4 mg)	Atenolol 100 mg BFZ 2.5 mg + K^+
Step 5	Amlodipine 10 mg Perindopril 8 mg (2x4 mg) Doxazosin GITS 4 mg	Atenolol 100 mg BFZ 2.5 mg + K^+Doxazosin GITS 4 mg
Step 6	Amlodipine 10 mg Perindopril 8 mg (2x4 mg) Doxazosin GITS 8 mg	Atenolol 100 mg BFZ 2.5 mg + K^+Doxazosin GITS 8 mg

BFZ = bendroflumethiazide; GITS = gastrointestinal transport system

Table 3: Baseline characteristics

	Amlodipine-based regimen (n=9639)	Atenolol-based regimen (n=9618)
Demographic and clinical characteristics		
Sex		
Male	7381 (77%)	7361 (77%)
Female	2258 (23%)	2257 (23%)
Age (years)	63.0 (8.5)	63.0 (8.5)
<60	3558 (37%)	3534 (37%)
>60	6081 (63%)	6084 (63%)
White	9187 (95%)	9170 (95%)
Current smoker	3168 (33%)	3109 (32%)
Alcohol consumption (units/week)	8.0 (11.6)	7.9 (11.7)
Systolic blood pressure (mm Hg)	164.1 (18.1)	163.9 (18.0)
Diastolic blood pressure (mm Hg)	94.8 (10.4)	94.5 (10.4)
Heart rate (bpm)	71.9 (12.7)	71.8 (12.6)
Body-mass index (BMI) (kg/m^2)	28.7 (4.6)	28.7 (4.5)
Bodyweight (kg)	84.6 (15.7)	84.6 (15.3)
Total cholesterol (mmol/L)	5.9 (1.1)	5.9 (1.1)
LDL cholesterol (mmol/L)	3.8 (1.0)	3.8 (1.0)
HDL cholesterol (mmol/L)	1.3 (0.4)	1.3 (0.4)
Triglycerides (mmol/L)	1.8 (1.0)	1.9 (1.0)
Glucose (mmol/L)	6.2 (2.1)	6.2 (2.1)
Creatinine (µmol/L)	98.7 (16.6)	98.7 (17.0)
Medical history		
Previous stroke or TIA	1050 (11%)	1063 (11%)
Diabetes*	2567 (27%)	2578 (27%)
Left-ventricular hypertrophy*	2091 (22%)	2076 (22%)
Atrial fibrillation	117 (1%)	113 (1%)
ECG abnormalities other than LVH*	2206 (23%)	2249 (23%)
Peripheral vascular disease	586 (6%)	613 (6%)
Other relevant cardiovascular disease	533 (6%)	486 (5%)
Drug therapy		
Previous antihypertensive treatments		
None	1841 (19%)	1825 (19%)
1	4280 (44%)	4283 (45%)
≥2	3518 (36%)	3510 (36%)
Lipid-lowering therapy	1046 (11%)	1004 (10%)
Aspirin use	1851 (19%)	1837 (19%)

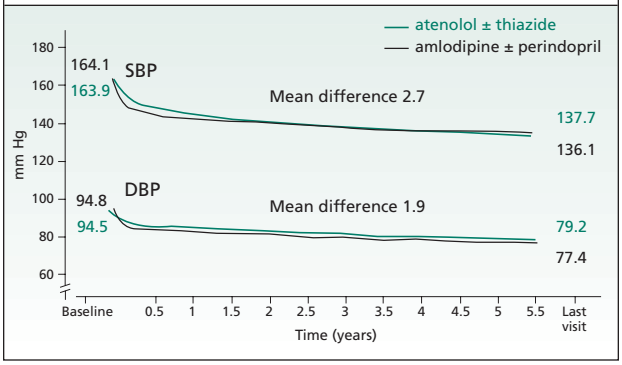
Data are mean (SD) or number (%); TIA = transient ischemic attack

* Based on information from Investigator, electrocardiogram (ECG) and glucose concentrations.

Primary study results

The trial was stopped prematurely in November 2004 after 5.5 years of follow-up because of a difference between the two groups in all-cause mortality. The final results of ASCOT-BPLA were recently presented at the European Society of Cardiology Congress and also published.[10,11] The key baseline characteristics are shown in Table 3. Patients were well-matched between the groups; >80% were on previous antihypertensive treatment and

Figure 1: Effects on blood pressure



SBP = systolic blood pressure; DBP = diastolic blood pressure

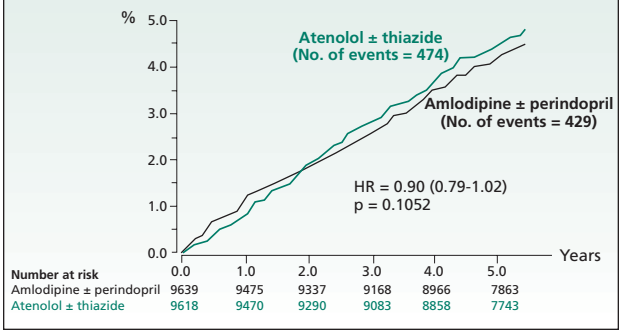
most were White males, with a mean age of 63 years. The effects of BP are shown in Figure 1. Both groups had significant declines in BP. When compared to patients assigned to the atenolol-based regimen, BP values were lower in patients assigned to the amlodipine-based regimen throughout the trial, These differences were greatest at 3 months and the mean difference throughout the trial was 2.7/1.9 mm Hg. The percentage of time on medication by treatment group (amlodipine, perindopril, or amlodipine + perindopril, or atenolol, bendroflumethiazide, or atenolol + bendroflumethiazide), during the first year of follow-up and for the entire study is shown in Table 4. Throughout the study, an average 50% of patients were taking the combination of amlodipine + perindopril as allocated, with or without other antihypertensive drugs. On the other hand, an average 55% were taking the combination of atenolol+ bendroflumethiazide as allocated, with or without other antihypertensive drugs.

Results of the primary endpoint are shown in Figure 2. The primary endpoint of non-fatal MI (including silent MI) plus fatal CHD decreased by 10% in those allocated to the amlodipine-based regimen compared with those allocated to the atenolol-based regimen. This difference, however, did not reach statistical significance. All results of the primary, secondary, and tertiary endpoints, as well as post-hoc endpoints, are shown in Figure 3. There were significant reductions in all of the secondary endpoints (except for fatal and nonfatal heart failure), as well as some of the tertiary endpoints, including new-onset diabetes and renal impairment, among those allocated to the amlodipine-based regimen.

Table 4: Mean proportion of time (%) on antihypertensive medication by treatment group

	Year 1	All study
Amlodipine-based group		
Amlodipine	88.2	82.5
Perindopril	46.2	58.5
Amlodipine + perindopril	39.1	49.5
Atenolol-based group		
Atenolol	87.4	79.4
Bendroflumethiazide	56.6	65.7
Atenolol + bendroflumethiazide	49.1	54.9

Figure 2: ASCOT-BPLA primary endpoint: Non-fatal MI, fatal CHD



The retrospectively-defined combined endpoint of CV mortality, MI, and stroke was significantly reduced by 16%, while the primary endpoint and coronary revascularization was also significantly reduced.

About one-quarter of the patients stopped therapy because of an adverse event, with no significant difference between the allocated treatment groups. There was a significant difference in favour of the amlodipine-based regimen in the proportion of patients who stopped trial therapy because of serious adverse events (Table 5).

Discussion and clinical implications

In this large-scale study on moderately high-risk hypertensive patients, the "newer" amlodipine-based regimen reduced most of major CV endpoints, including non-fatal non-silent MI and fatal CHD, CV mortality, fatal and nonfatal stroke, and all-cause mortality, as well as new-onset diabetes when compared to the "older" atenolol-based regimen. There was also a reduction of about 10% in the primary endpoint of nonfatal MI or fatal CHD, but this did not reach statistical significance. The ASCOT-BPLA investigators suggested that the power calculation for this endpoint was based on 1150 events and, when the study was stopped prematurely,

Figure 3: All endpoints

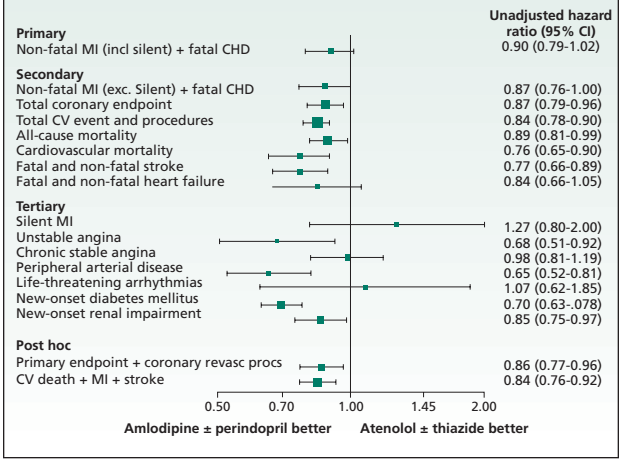


Table 5: Adverse events leading to study drugs discontinuation

Adverse event	Amlodipine ± perindopril (%)	Atenolol ± thiazide (%)
Total	2358 (24.5)	2402 (25.0)
Serious	162 (1.7)	254 (2.6)*

* $p<0.0001$

they had reached only 905 events; therefore, the study was underpowered for the primary endpoint.

One of the issues raised in this trial,[12] as well as in several of the recent large comparative trials, is the BP differences observed between groups. Like the differences in BP observed in the VALUE and ALLHAT studies,[7,13] there were also differences from the outset in BP control between groups in ASCOT-BPLA. Although BP was virtually identical by the end of the trial, the mean difference was 2.7/1.9 mm Hg. To address this issue, the ASCOT-BPLA investigators reported additional analyses that compared differences in accumulated mean BP levels at sequential times with sequential differences in coronary and stroke events.[11] Serial mean matching for differences in systolic BP was used to adjust hazard ratios for differences in these events. Both techniques were employed previously in the VALUE trial.[13,14] In addition, a Cox-regression model was used to assess the effects of differences in accumulated mean levels of various measures of BP, serum HDL-cholesterol, triglycerides, and potassium, fasting blood glucose, heart rate, and body weight on differences in event rates. In contrast to the VALUE trial,[14] there were no temporal links between the size of the differences in BP and different event rates. Serial mean matching for differences in systolic BP attenuated hazard ratios for coronary and stroke events to a similar degree. However, there are limitations to these types of analyses and, as the authors admit, the multivariate adjustments procedures are likely incomplete and underestimate the true effects of the variables in question, including BP.

Conclusion

The results of ASCOT-BPLA are relevant to clinical practice for two reasons:

- First, ASCOT-BPLA is the first trial that formally compares 2 antihypertensive "combinations;" this is important because many patients with hypertension require combination therapy in order to achieve target BP control.[15-17]
- Second, until recently, ß-blockers and diuretics have been the most commonly used combination in many parts of the world, in part because these agents – alone or in combinations – have been shown to reduce CV events and because they are relatively inexpensive.[1,18]

However, the combined use of a CCB and an ACE inhibitor offers biologically-plausible advantages that include superior lowering of BP and a reduction in CV endpoints and new-onset diabetes. The main results of ASCOT-BPLA lend further support to these observations. Clinicians should take these results into consideration when deciding on an antihypertensive treatment strategy in high-risk hypertensive patients.

References

1. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003;362:1527-35.
2. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990;335:765-74.
3. Grimm RH, Jr., Leon AS, Hunninghake DB, Lenz K, Hannan P, Blackburn H. Effects of thiazide diuretics on plasma lipids and lipoproteins in mildly hypertensive patients: a double-blind controlled trial. *Ann Intern Med* 1981;94:7-11.
4. Nayler WG. Review of preclinical data of calcium channel blockers and atherosclerosis. *J Cardiovasc Pharmacol* 1999;33 Suppl 2:S7-11.
5. Staessen JA, Wang JG, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001;358:1305-15.
6. Lopez-Sendon J, Swedberg K, McMurray J, et al. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. *Eur Heart J* 2004;25:1454-70.
7. 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). *JAMA* 2002;288:2981-97.
8. Sever PS, Dahlof B, Poulter NR, et al. Anglo-Scandinavian Cardiac Outcomes Trial: a brief history, rationale and outline protocol. *J Hum Hypertens* 2001;15 Suppl 1:S11-S12.
9. Sever PS, Dahlof B, Poulter NR, et al. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens* 2001;19:1139-47.
10. Dahlof B, Sever PS, Poulter NR, et al. 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.
11. Poulter NR, Wedel H, Dahlof B, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA). *Lancet* 2005;366: 907-13.
12. Staessen JA, Birkenhager WH. Evidence that new antihypertensives are superior to older drugs. *Lancet* 2005;366:869-71.
13. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;363:2022-31.
14. Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet* 2004;363:2049-51.
15. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; 21:1011-53.
16. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
17. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998;351:1755-62.
18. 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). SHEP Cooperative Research Group. *JAMA* 1991; 265:3255-64.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Pfizer Canada to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.