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# EXPERT OPINIONS.MR

CLINICAL IMPACT.

MEETING REPORT

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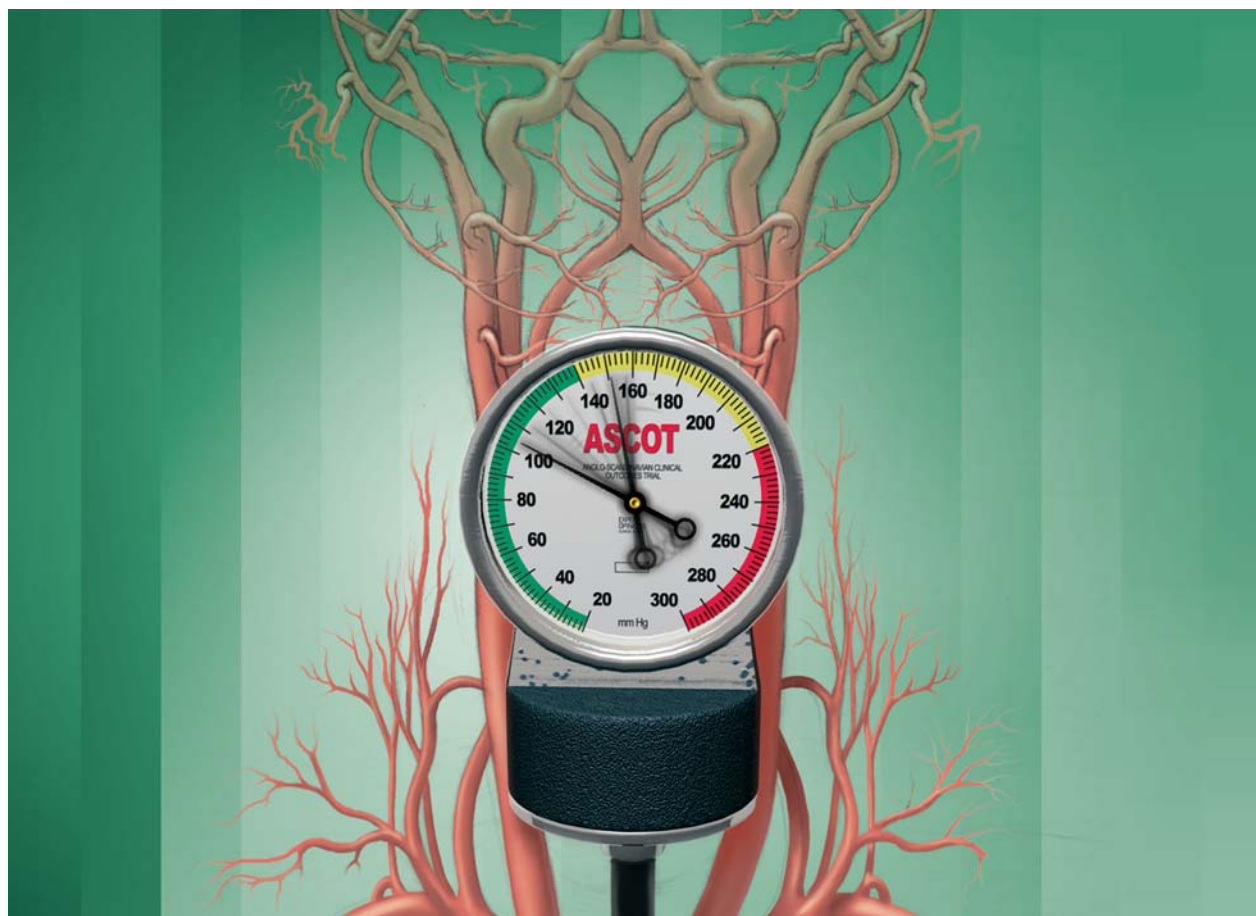
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## ASCOT-Blood Pressure Lowering Arm (BPLA):

# Results of a Landmark Clinical Trial

## Introduction

Early clinical trials in hypertension validated the use of diuretics and beta-blockers (BB) in the prevention of cardiovascular events, such as stroke and myocardial infarction. An intriguing observation in these studies was that blood pressure lowering seemed to have a more profound effect on preventing stroke rather than MI. Although other drugs were commonly used for the treatment of hypertension in the 1960s and 1970s, such as direct vasodilators and centrally-acting agents, similar evidence with these drug classes was lacking. Therefore, diuretics and BB soon became entrenched as cornerstones of therapy in the management of hypertension, and were routinely recommended as first-line monotherapy in major guidelines. With the introduction of calcium channel blockers (CCB) and angiotensin-converting enzyme inhibitors (ACEI) in the 1980s, clinicians were given a wider array of effective antihypertensive agents from which to choose. In the last decade, the addition of angiotensin receptor blockers (ARB) has further broadened the choice of drugs for the management of hypertension.

Head-to-head studies with agents from different classes have largely shown similar efficacy at lowering blood pressure, with no single class of drugs clearly being superior in this regard. Important differences between drug classes have been noted with respect to dosing intervals, 24-hour efficacy, drug interactions, metabolic effects, and tolerability. Importantly, many of the newer agents remain much more expensive than the older, traditional diuretics and beta blockers. In an era of constrained resources in healthcare, the issue of cost-effectiveness of newer agents versus older agents has appropriately been raised. As a result, there have been numerous clinical trials comparing drug classes in their efficacy at preventing the cardiovascular complications of chronic hypertension. The findings from such studies have led the Canadian Hypertension Education Program to recommend five different classes of drugs as initial monotherapy in uncomplicated hypertension (diuretics, BB, CCB, ACEI and ARB).<sup>1</sup>

There has been considerable debate in recent years as to whether or not newer antihypertensive agents are truly more cardioprotective than older agents. Although several studies have suggested broader benefits of newer agents, no convincing superiority in the prevention of major CV events has been demonstrable. The recently reported ASCOT blood pressure lowering study (ASCOT-BPLA), however, may influence the management of hypertension in the future.

## ASCOT Study Design and Methods

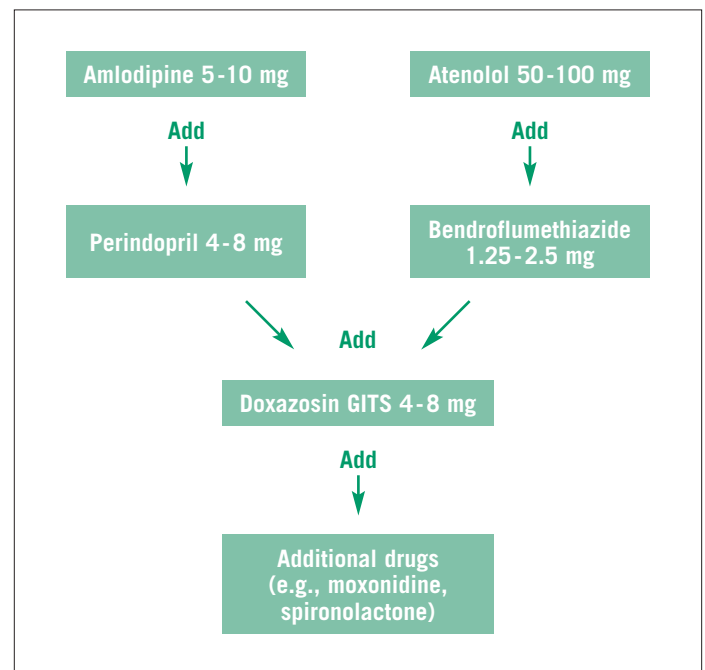
The preliminary findings from the Anglo-Scandinavian Cardiac Outcomes Trial were reported at the Scientific Sessions of the American College of Cardiology in March, 2005 in Orlando, Florida.<sup>2</sup> The final study results were recently published in the September 10<sup>th</sup> edition of The Lancet.<sup>3</sup>

The ASCOT study was a randomized, controlled trial of the prevention of CHD and other vascular events by BP and cholesterol lowering in a factorial study design. Recognizing from past studies and clinical experience that most patients with hypertension require multiple agents to control BP, the ASCOT investigators employed a strategy of comparing different drug combinations rather than individual agents. The ASCOT study, therefore, was not designed to compare specific drugs, but rather to compare blood pressure-lowering strategies using newer versus older agents.

A total of 19,257 patients from Scandinavia and the UK were recruited into the study between February 1998 and May 2000. Inclusion criteria included a screening baseline BP of  $\geq 160/100$  mm Hg untreated, or BP  $\geq 140/90$  mm Hg despite treatment with at least one drug. Patients were aged 40-79 with no previous MI or current clinical CHD. Apart from hypertension, three or more additional CHD risk factors were required. The primary endpoint of the study, which was event-driven, was the composite of non-fatal MI (including silent) and fatal CHD death. Assuming 1,150 primary events over the course of follow-up, the study had at least 80% power to detect a 16% relative risk reduction with one treatment strategy versus the other. Secondary endpoints included all-cause mortality, stroke, and heart failure. In a factorial design, 10,305 ASCOT patients were also randomized to lipid-lowering therapy with

atorvastatin 10 mg daily or placebo. The results of the lipid-lowering arm of ASCOT, which was terminated prematurely for efficacy, have been published and showed a statistically significant reduction in non-fatal MI and CHD death with lipid-lowering in this population.<sup>4</sup>

Upon entry into ASCOT-BPLA, patients were randomized to receive standard antihypertensive therapy, or more contemporary management, to a target BP of  $<140/90$  mm Hg, or  $<130/80$  mm Hg in the presence of diabetes (see Figure 1). The study was conducted with a PROBE design (prospective, randomized, open-label, blinded endpoint). In the standard therapy arm, patients were started on atenolol, and the long-acting diuretic bendroflumethiazide was added to achieve BP targets. Patients randomized to contemporary treatment were started on the CCB amlodipine, with the ACEI perindopril added, as needed, to reach target. In both arms, patients who did not reach target BP levels with combination therapy were additionally prescribed the alpha-blocker doxazosin. If more than three drugs were necessary, physicians could then choose from several additional agents, including spironolactone and moxonidine. Obviously, drugs from one randomization scheme were excluded from the other.



**Figure 1. Treatment algorithm to BP targets  $<140/90$  mm Hg or  $<130/80$  mm Hg in patients with diabetes**

## ASCOT Study Results<sup>3</sup>

Baseline characteristics were well matched for all important variables (see Table 1). Patients were, on average, 63 years old, one-quarter female, one-third current smokers, with an average blood pressure of 164/95 mm Hg. Patients had 3.7 additional CHD risk factors, the most common being age  $\geq 55$ , male gender, presence of microalbuminuria, and smoking. Blood pressure was reduced by an average of 26.6/16.6 mm Hg in both groups, to 136.1/77.4 mm Hg in the contemporary group and 137.7/79.2 mm Hg in the standard care group. An early difference in blood pressure was noted between treatment groups, with lower BP in the contemporary treatment arm. This early difference, however, waned over the course of the study, such that the mean average difference in blood pressure was 2.7/1.9 mm Hg, in favour of the contemporary treatment group. The majority of patients in both treatment groups required combination antihypertensive therapy, with 78% requiring at least two antihypertensive agents. Total and LDL-cholesterol levels were similar between groups. However, HDL-cholesterol levels were 0.1 mmol/L higher ( $p < 0.0001$ ), and triglycerides were 0.3 mmol/L lower ( $p < 0.0001$ ), in the contemporary treatment arm.

In October 2004, the data safety monitoring board recommended that the ASCOT blood pressure lowering study be terminated early for efficacy reasons. This recommendation was accepted by

**Table 1. Baseline characteristics of ASCOT-BPLA patients<sup>2,3</sup>**

	<b>Amlodipine/perindopril</b> (n=9,639)	<b>Atenolol/thiazide</b> (n=9,618)
<b>Demographics and clinical characteristics</b>		
Women	2,258 (23%)	2,257 (23%)
White	9,187 (95%)	9,170 (95%)
Current smoker	3,168 (33%)	3,109 (32%)
Age (years)	63.0 (8.5%)	63.0 (8.5%)
SBP (mm Hg)	164.1 (18.1%)	163.9 (18.0%)
DBP (mm Hg)	94.8 (10.4%)	94.5 (10.4%)
Heart rate (bpm)	71.9 (12.7%)	71.8 (12.6%)
BMI (kg/m <sup>2</sup> )	28.7 (4.6%)	28.7 (4.5%)
Risk factors	3.7 (0.9%)	3.7 (0.9%)
<b>Drug therapy</b>		
Previous antihypertensive treatments		
0	1,841 (19%)	1,825 (19%)
1	4,280 (44%)	4,283 (45%)
≥ 2	3,518 (36%)	3,510 (36%)
Lipid-lowering therapy	1,046 (11%)	1,004 (10%)
Aspirin	1,851 (19%)	1,837 (19%)

**The ASCOT study, for the first time, convincingly shows that a treatment strategy employing amlodipine and perindopril prevents more deaths than a strategy employing atenolol and a thiazide diuretic.**

the steering committee, and the trial was terminated in December 2004, with a mean follow-up duration of 5.5 years. During this time, 903 primary events had occurred (compared to the required 1,150 set out in the original protocol).

Contemporary antihypertensive therapy with a CCB and ACEI resulted in a highly significant 11% reduction in all-cause mortality, compared with standard therapy with a BB and diuretic ( $p=0.02$ ) (see Table 2). Although all-cause mortality was a secondary endpoint, these findings certainly supported the decision to prematurely terminate the study, even though a statistically significant effect on the primary endpoint could not be demonstrated due to lack of power (10% reduction in non-fatal MI and CHD death,  $p=0.1052$ ). However, significant reductions in all of the secondary endpoints (with the exception of fatal and non-fatal heart failure) were seen with the contemporary regimen. These endpoints were: non-fatal MI and fatal CHD (excluding silent MI) (13%,  $p=0.0458$ ), total

coronary events (13%,  $p=0.0070$ ), total CV events and procedures (16%,  $p<0.0001$ ), cardiovascular mortality (24%,  $p=0.0010$ ), and fatal and non-fatal stroke (23%,  $p=0.0003$ ). Significant reductions were also observed for unstable angina (32%,  $p=0.0115$ ), peripheral arterial disease (35%,  $p=0.0001$ ), development of diabetes (30%,  $p<0.0001$ ) and development of renal impairment (15%,  $p=0.0187$ ).

Pre-specified subgroup analyses did not identify any subgroup that experienced significantly greater or lesser benefit from contemporary therapy. A time-dependent analysis for all cardiovascular events and procedures shows clear consistency in risk reduction throughout the whole trial period, despite the fact that blood pressures were particularly divergent during the first 6 months, and then almost identical for the duration of the trial. Treatment combinations were well tolerated, with few differences in serious adverse events. It was also mentioned during the presentation that, since the majority of patients in each arm required combination therapy, the benefits ▶

**Table 2. Major endpoints for amlodipine and perindopril versus atenolol and bendroflumethiazide<sup>3</sup>**

<b>Endpoint</b>	<b>Hazard ratio</b>	<b>95% CI</b>	<b>P value</b>
Fatal CHD/non-fatal MI	0.90	0.79-1.02	0.1052
All-cause mortality	0.89	0.81-0.99	0.0247
Total coronary endpoint: fatal CHD/non-fatal MI/new-onset angina/heart failure	0.87	0.79-0.96	0.0070
Fatal and non-fatal stroke	0.77	0.66-0.89	0.0003
Total CV events and procedures	0.84	0.78-0.90	<0.0001
CV mortality	0.76	0.65-0.90	0.0010
New diabetes mellitus	0.70	0.63-0.78	<0.0001

seen in the amlodipine/perindopril arm could not be attributed to any one drug alone, but rather were attributable to the combination strategy.

### Implications

Previous studies comparing standard antihypertensive therapy to newer agents have mostly demonstrated similar efficacy on the prevention of cardiovascular events.<sup>5-8</sup> The ALLHAT study, the largest hypertension trial conducted to date, initially revealed a higher incidence of heart failure with an alpha-blocker, and subsequently continued comparison in over 30,000 patients with chlorthalidone, amlodipine, and lisinopril.<sup>9</sup> The primary CV endpoint was similar in all three groups, although an unexpected excess of heart failure was noted in the ACEI group, admittedly a secondary endpoint. These findings led to experts recommending

**Thus, beyond blood pressure, additional vascular protective properties of amlodipine and perindopril likely account for part of clinical benefit noted in the ASCOT study.**

diuretics once again as first-line therapy and dismissing any additional cardioprotective effects of ACEI in patients with uncomplicated hypertension. Subsequently, the ANBP-2 study demonstrated a significant advantage of enalapril over a diuretic in preventing cardiovascular events, leading to further confusion as to the relative benefits of one drug class over another.<sup>10</sup>

The ASCOT study, for the first time, convincingly shows that a treatment strategy employing amlodipine and perindopril prevents more deaths than a strategy employing atenolol and a thiazide diuretic. Consistent benefits on all cardiovascular endpoints were noted, along with additional effects on renal function and prevention of diabetes. These findings are certainly in line with other studies evaluating the metabolic effects of a CCB and an ACEI. Importantly, the ASCOT study also showed that BP is reduced more quickly with the newer treatment strategy. The importance of rapid and sustained blood pressure reduction was also demonstrated in the VALUE trial, in which amlodipine lowered BP more effectively than the ARB valsartan, resulting in earlier benefit on clinical events.<sup>11</sup>

Although BP was slightly lower with contemporary treatment in ASCOT, this BP differential likely accounts for only a small proportion of the noted benefit on all-cause mortality and CV events. This is supported by the time-dependent analysis within ASCOT, as well as by the fact that the observed benefits in ASCOT greatly outweighed the benefits expected with such a small BP differential. Although it is possible that certain adverse metabolic and/or vascular effects of BB/thiazide may have heightened the event rate in this arm, this once again is unlikely to explain the entire benefit noted. Thus, beyond blood pressure, additional vascular protective properties of amlodipine and perindopril likely account for part of the clinical benefit noted in the ASCOT study.

Now published, the ASCOT study should indeed lead to a re-evaluation of hypertension treatment recommendations. The ASCOT results may impact the Canadian Hypertension Education Program (CHEP) recommendations for a number of reasons. Firstly, enhanced emphasis on achieving target blood pressure should be incorporated, and perhaps the identification of specific drug combinations to quickly and effectively achieve target BP will also be provided. The ASCOT results certainly demonstrate that the combination of amlodipine and perindopril is a powerful choice in this respect, and that beta-blockers may no longer warrant the recommendation of first-line drugs. Secondly, the reduction in new-onset diabetes was significant with the CCB-ACEI combination, which again may warrant mention within the recommendations. Thirdly, the benefit of the use of statins in all hypertensive patients with additional CV risk factors cannot be overlooked and should be re-emphasized.

In the interim, it would seem prudent to apply the ASCOT results to middle-aged and older subjects with hypertension, additional CHD risk factors, and the absence of compelling indications for specific drugs. In such patients, prompt and sustained BP control with a CCB/ACEI-based strategy (such as the amlodipine/perindopril strategy used in ASCOT) seems to offer optimal blood pressure effect and prevention of all-cause mortality and cardiovascular events. ■

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