Amlodipine + perindopril rival standard therapy for hypertension

– Amitabh Prakash –

The combination of amlodipine plus perindopril is more effective than atenolol plus bendroflumethiazide in patients with hypertension who have a high risk for cardiovascular events, according to preliminary results of the ASCOT-BPLA trial presented at the 54th Annual Scientific Session of the American College of Cardiology (ACC) [*Orlando, Florida, US; March 2005*]. These data showed that a newer antihypertensive regimen, comprising amlodipine plus perindopril, was superior to a traditional regimen, comprising atenolol plus bendroflumethiazide, in preventing cardiovascular endpoints and new-onset diabetes mellitus in such patients. Both treatment regimens were equally well tolerated.

Contemporary issues in hypertension

Hypertension, a common cardiovascular disorder, is an established hard risk factor for coronary heart disease (CHD) and stroke. Traditional treatment regimens for hypertension involve drugs such as β-blockers and diuretics. The ASCOT-BPLA* trial, conducted in the UK, Ireland and Scandinavia, was designed to compare the effects of a newer antihypertensive regimen comprising a calcium channel antagonist plus an ACE inhibitor with those of a traditional regimen comprising a β-blocker plus a diuretic in hypertensive patients at high risk for cardiovascular events.

Co-chairman of the ASCOT-BPLA steering committee Professor Peter Sever, from the Imperial College, London, UK, commented that "*hypertension is the most common risk factor contributing to the global burden of disease, and with a projected 1.5 billion sufferers of hypertension by 2020 it is vital that we develop more effective treatments.*"

Presenting the ASCOT-BPLA trial, co-chairman Professor Björn Dahlöf, from the Sahlgrenska University Hospital, Östra, Sweden, added that "*traditional antihypertensive regimens provide inadequate CHD prevention and there are insufficient data evaluating the effect of newer antihypertensive agents, especially in specific combinations, on clinical outcomes.*"

Major study compares two regimens

Initiated in February 1998, ASCOT-BPLA was a large, investigator-led randomised controlled trial that included 19 257 patients aged 40–79 years who had hypertension, defined as a baseline BP of ≥ 160/100mm Hg untreated, or ≥ 140/90mm Hg following treatment with at least one drug.[1]** All patients had at least three risk factors for a future cardiovascular event, but none had a history of myocardial infarction or clinical signs or symptoms of CHD.

With the aim of lowering BP to a target of < 140/90mm Hg (< 130/80mm Hg in patients with diabetes), treatment was initiated with amlodipine 5 mg/day (titrated to 10 mg/day; n = 9639) or atenolol 50 mg/day (titrated to 100 mg/day; n = 9618). If required, perindopril 2–8 mg/day and bendroflumethiazide 1.25–2.5 mg/day were added to the amlodipine and atenolol arms, respectively. Patients not reaching target BP in either arm were then given add-on treatment with doxazosin GITS† 4–8 mg/day. Finally, patients in whom adequate BP had not been achieved were given additional drugs such as moxonidine or spironolactone.

The primary endpoint of the study was the combined incidence of nonfatal myocardial infarction and fatal coronary heart disease. Secondary objectives included all-cause mortality, cardiovascular mortality, fatal and nonfatal stroke, total cardiovascular events and procedures, and the combined incidence of the primary endpoint plus new-onset angina pectoris and fatal or nonfatal heart failure (total coronary endpoint). In addition, the study evaluated several tertiary endpoints, including the development of diabetes mellitus, the onset of renal impairment, and life-threatening arrhythmias.

Premature closure due to continued advantage

The last ASCOT-BPLA close out visit was expected in May 2005. However, in October 2004 the independent Drug Safety Monitoring Board (DSMB) recommended the closure of the BP-lowering arm "*because of concerns that those patients receiving atenolol/bendroflumethiazide would continue to be disadvantaged, particularly with regard to all-cause mortality, compared with the comparator group,*" said Professor Dahlöf.

The ASCOT-BPLA Steering Committee endorsed the recommendation of the DSMB, and trial closure began in December 2004 after a median follow-up period of 5.4 years.

Amlodipine/perindopril superior...

Compared with atenolol and bendroflumethiazide, treatment with amlodipine plus perindopril led to a significantly greater reduction in all-cause mortality, cardiovascular mortality and fatal and nonfatal stroke [*see table*].

Treatment with amlodipine and perindopril also led to a 10% reduction in the primary combined endpoint of nonfatal myocardial infarction plus CHD death, compared with atenolol and bendroflumethiazide; however, this difference did not reach statistical significance.

Amlodipine + perindopril rival standard therapy – *continued*

Risk reduction in outcomes with amlodipine + perindopril, compared with atenolol + bendroflumethiazide

	Risk reduction (%)	p-value
Primary endpoint:		
Nonfatal myocardial infarction + fatal coronary heart disease	–10	0.12
Secondary endpoints:		
Cardiovascular mortality	–24	0.0017
All-cause mortality	–14	0.005
Fatal and nonfatal stroke	–23	0.0007
Total cardiovascular events and procedures	–16	< 0.0001
Total coronary endpoint[a]	–14	0.0048
Tertiary endpoint:		
New-onset diabetes mellitus	–32	< 0.0001

[a] primary endpoint plus new onset angina and fatal or nonfatal heart failure

"*Premature closure of the trial (study was powered for 1150 patients with primary events but only 869 patients had a primary event when the study was terminated) and widespread use of statins reduced the number of primary endpoints and decreased the power of this trial to test the primary hypothesis,*" said Professor Sever.

There was a significant 23% reduction in the incidence of stroke with amlodipine and perindopril, compared with atenolol and bendroflumethiazide. Similarly, the incidences of other cardiovascular endpoints, including cardiovascular events and procedures and total coronary endpoint were also significantly reduced with amlodipine and perindopril compared with atenolol and bendroflumethiazide.

Consistent with results from earlier trials comparing newer antihypertensive regimens with β-blockers and thiazide diuretics, there was a significant 32% reduction in the incidence of new-onset diabetes mellitus with amlodipine and perindopril, compared with atenolol and bendroflumethiazide in the ASCOT-BPLA trial.

...in all subgroups

An analysis of total cardiovascular events and procedures revealed that amlodipine and perindopril was superior to atenolol and bendroflumethiazide across all subgroups of patients, including those with or without diabetes mellitus, smokers and nonsmokers, obese and non-obese patients, patients with or without left ventricular hypertrophy, men, women, patients aged ≤ 60 years and those aged > 60 years, patients with or without previous vascular disease, with or without renal dysfunction and with or without the metabolic syndrome.

Similar tolerability profiles

There was no difference between the two treatment regimens in the incidence of serious adverse events, and gastrointestinal disorders were the most common serious adverse events observed (5.2% of amlodipine/perindopril recipients and 5.3% of atenolol/bendroflumethiazide recipients).

Possible explanations for benefit

Professor Sever offered the following as possible explanations for the significant superiority of amlodipine and perindopril over atenolol and bendroflumethiazide: "*One of course is better BP lowering with amlodipine and perindopril but we don't think that's the whole story. We have reason to believe that there may well be an adverse interaction between atenolol and bendroflumethiazide and a statin, and also the potential for beneficial interaction between amlodipine and perindopril and a statin. Non-BP-lowering benefits of amlodipine and perindopril remain a possibility, as indeed are non-BP-related disadvantages of beta-blocker and thiazide combination.*"

Further answers sought

Discussing the results of the ASCOT BPLA trial, Dr Richard Devereux from the Cornell Medical Center, New York, US, commented that "*ASCOT BPLA was a randomized comparison of two treatment strategies in high-risk hypertensives, evaluating the effect of clinically applicable regimens on clinically relevant endpoints. However, it was not immediately clear if both treatment groups had similar BP control and similar use of other antihypertensive drugs, statins and aspirin.*" It is hoped that some of these questions will be answered when the final results of the ASCOT BPLA become available.

ASCOT-BPLA findings in perspective

Dr Devereux pointed out that benefits of the new treatment regimen using amlodipine and perindopril versus the older regimen included "*10 to 24% reduction in cardiovascular endpoints, one-third less new-onset diabetes mellitus, and better BP lowering (until attenuated by add-on therapy).*"

Dr Devereux felt that "*difference in outcomes could not be solely attributed to the initial drug in either treatment arm because the usage of beta-blocker and diuretics was nearly similar (73 vs 67%) in one arm, as was the usage of calcium channel antagonist and ACE inhibitor (78 vs 63%) in the other arm. Therefore, the ASCOT BPLA results highlighted the differences between regimens more than differences between specific classes of drugs.*"

He concluded by saying that "*these preliminary results were unlikely to change much with study close-out.*"

It is widely expected that hypertension guidelines will be reviewed after presentation and publication of the complete ASCOT BPLA results later in 2005.

* Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure-Lowering Agents

** This study was sponsored by Pfizer.

† Gastro-Intestinal Therapeutic System

1. Sever PS, et al. The Anglo-Scandinavian Cardiac Outcomes Trial: morbidity-mortality outcomes in the blood pressure-lowering arm of the trial. 54th Annual Scientific Session of the American College of Cardiology: Late Breakers : [36 pages] (plus oral presentation), 6 Mar 2005. Available from: URL: http://www.acc.org.

800999301