

## ASCOT study highlights benefits of amlodipine in lowering central aortic systolic blood pressure

In the first application of an FDA-approved method for determining central aortic pressure within a major clinical trial, the amlodipine-based treatment (Norvasc<sup>®</sup>) was shown to achieve greater central aortic pressure lowering and improved haemodynamic indices.

The results<sup>1</sup> of this investigation showed in the selected subgroup of 2199 people from the 19257-person Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study<sup>2</sup> that, although brachial blood pressures were virtually the same, the central aortic systolic blood pressure was 4.3 mmHg lower and the central aortic pulse pressure was 3.0 mmHg lower in patients receiving amlodipine (Norvasc<sup>®</sup>) and the ACE inhibitor, perindopril (Coversyl<sup>®</sup>).

In ASCOT, the amlodipine/perindopril treatment was associated with significant reductions in major cardiovascular and renal outcomes and death compared to the atenolol/bendroflumethiazide treatment arm (Table I).

Speaking at the American Heart Association's annual meeting in Dallas on 13 November, Prof. Bryan Williams, professor of medicine in the Department of Cardiovascular Sciences at the University of Leicester in the UK, and principal investigator for the 'Differential-Impact-Principle Results of the Conduit Artery Function Evaluation' (CAFÉ) study in ASCOT noted that the results of this study are clear-cut, dramatic and potentially very important. They also may explain why certain types of hypertension treatment might be more effective than others.

In this study, researchers derived central aortic pressure by using the non-invasive Sphygmocor system approved by the US Food and Drug Administration (FDA) in 2001. The approach employs a computer program to estimate central aortic pressure by examining the shape of the pulse wave at the wrist. This information is then computed to generate a pulse wave and measurements of pressures in the large arteries of the body. 'The shape

of the pulse wave is influenced by the treatments we use to lower blood pressure. The CAFÉ study suggests that treatment based on amlodipine had more favourable effects on the shape of the pulse wave and pressures in the main arteries than treatment based on atenolol. This was true even though the blood pressure in the arm appeared similar. In effect, measuring blood pressure in the arm underestimated the benefit of amlodipine compared to atenolol'.<sup>2</sup>

'In this cohort, central pulse pressure was a significant determinant of total cardiovascular and renal events/procedures', Prof. Williams stated. 'This finding has major implications for interpreting the results of clinical trials. It also suggests a mechanism whereby certain categories of drug might be more effective than others at reducing blood pressure in the central arteries', Prof. Williams concluded.

**Comments from Prof. Lionel Opie, director of the Hatter Institute for Cardiovascular Research and the Cape Heart Centre, Cape Town**

**Q: How do these data fit into your understanding of calcium-channel blockers' favourable impact on the cardiovascular and renal outcomes in the ASCOT study?**

This new information confirms what is known, namely that calcium channel blockers and especially ACE inhibitors have direct, beneficial, protective effects on blood vessels, whereas beta-blockers do not. Previous evidence along these lines comes from the studies done by Ernesto Schiffrin from Montreal on isolated arteries taken from gluteal biopsies. The use of pulse-wave analysis to analyse vascular effects is chiefly promoted by Mike O'Rourke from Sydney and Jay Cohn from Minnesota. Dr O'Rourke

**Table I. Primary, secondary and selected tertiary end-points of the ASCOT-BPLA Trial.**

	Amlodipine-based regimen (n = 9 639) Rate per 1 000	Atenolol-based regimen (n = 9 618) Rate per 1 000	HR (unadjusted)	p-value
<i>Primary end-points</i>				
Non-fatal MI + fatal CHD	8.2	9.1	0.9	0.1052
<i>Secondary end-points</i>				
Non-fatal MI (excluding silent) + fatal CHD	7.4	8.5	0.87	0.0458
Total coronary end-point	14.6	16.8	0.87	0.007
Total CVS events and procedures	27.4	32.8	0.84	< 0.0001
All-cause mortality	13.9	15.5	0.89	0.0247
CVS mortality	4.9	6.5	0.76	0.001
Fatal and non-fatal stroke	6.2	8.1	0.77	0.0003
<i>Tertiary end-points</i>				
New-onset diabetes	11	15.9	0.7	< 0.0001
Development of renal impairment	7.7	9.1	0.85	0.0187

Reference: Prof. B. Rayner. Editorial. *Cardiovasc J South Afr* 2005. 16(5): 241-242.

has been particularly interested in pulse-wave patterns in hypertension,<sup>3</sup> and Dr Cohn in the pulse wave in heart failure. The CAFÉ sub-study of ASCOT shows that the beta-blocker/diuretic regime is less able to reduce the central aortic pressure than the CCB-ACE inhibitor regime. That is a logical explanation for the finding of Lindholm *et al.*<sup>4</sup> that beta-blocker therapy reduced stroke in hypertensive patients less well than predicted by the reduction of brachial artery blood pressure. It also explains why the CCB-ACE inhibitor regime reduced stroke more effectively than the beta-blocker-diuretic regime. As central blood pressure must also be relevant to the pressure exerted on coronary and renal arteries, reduced coronary events and delayed renal impairment are also explicable.

**Q: While the full data-set is not yet available, can you comment on the implications of this study, which as Poulter suggested in his editorial in the *Lancet*<sup>5</sup> ‘...the benefits of the amlodipine-based regimen might relate to differences such as blood pressure variability or central**

**blood pressure, or to other as yet undefined variables not related to blood pressure.’**

As discussed earlier, central blood pressure is one factor. Another is the better metabolic tolerance of the CCB-ACE inhibitor regime with less new diabetes and better blood lipid patterns.

**Q: Has this methodology of obtaining the pulse wave been adequately shown to be more correct than peripheral brachial measurement?**

These two measures give data on different physiological parameters. Brachial artery blood pressure is not the same as the predicted central blood pressure calculated from the pulse wave pattern. These measurements give different although complementary information. I agree with the comments made by Dr Joseph Izzo from the State University of New York, Albany, after the presentation at the American Heart meeting, namely that better blood pressure control can be achieved by measuring both parameters.

## References:

1. Dahlof B, *et al.* Prevention of cardiovascular events with an anti-hypertensive 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 randomized controlled trial. *Lancet* 2005 published online September 4, 2005. DOI: 10.1016/S0140-6736(05)67185-1.
2. e-News release. American Heart Association – [www.americanheart.org](http://www.americanheart.org). 11 Nov 2005.
3. O’Rourke MF, Adji A. An updated clinical primer on large artery mechanics: implications of pulse waveform analysis and arterial tonometry. *Curr Opin Cardiol.* 2005; **20**(4): 275-281.
4. Lindholm LH, *et al.* Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005; **366**(9496): 1545-1553.
5. Poulter NR, *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. Published online September 4, 2005. DOI:20.2016/S0140-6736(05)67186-3.

## Acknowledgement:

The electronic publication of this report has been sponsored by Pfizer.

[Norvasc® Product Information available here]