

Backgrounder

## **Background to the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)**

### ***What was the ASCOT study?***

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was the largest study of patients with hypertension (high blood pressure) ever conducted in Europe. It compared the effectiveness of a combination of antihypertensive (blood pressure lowering) drugs – a calcium antagonist, amlodipine ± an angiotensin converting enzyme (ACE) inhibitor (perindopril) – with the widely used combination of a beta-blocker, atenolol ± a diuretic (bendroflumethiazide).

In addition to the Blood Pressure Lowering Arm (BPLA),<sup>1</sup> a large group of patients in the Lipid Lowering Arm (LLA) were also randomised to atorvastatin, a cholesterol-lowering drug, or placebo.<sup>2</sup>

Both the BPLA and LLA arms of the ASCOT study were stopped early – the BPLA due to the significant mortality benefits achieved in the amlodipine ± perindopril arm (versus the beta-blocker ± diuretic combination), and the LLA due to significant benefits on fatal coronary heart disease (CHD) and non-fatal myocardial infarction (MI), or heart attack, in the atorvastatin-treated arm (versus placebo).

### ***What was the rationale for ASCOT-BPLA?***

Earlier outcome studies have provided insufficient data on combinations of newer types of blood pressure lowering drugs versus older but widely used combinations. This is critically important as patients often require more than one antihypertensive drug to achieve treatment goals.

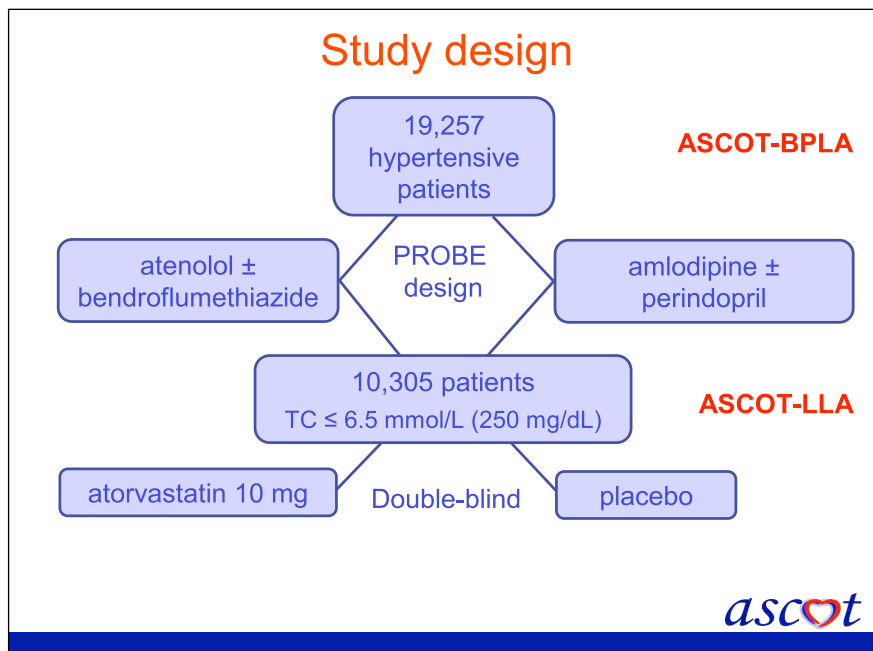
Additionally, earlier studies have shown a less than expected benefit in the prevention of CHD when standard drugs with adverse metabolic effects have been used.

**What were the primary and secondary objectives of ASCOT-BPLA?**

ASCOT compared the effect on non-fatal MI and fatal CHD of the widely used regimen of beta-blocker ± diuretic with the more contemporary regimen of a calcium channel blocker ± ACE inhibitor. Secondary endpoints included stroke, all coronary events, total cardiovascular events and procedures, cardiovascular mortality, all cause mortality and heart failure. Development of diabetes during treatment was also studied.

**What was the study design?**

More than 19,000 patients in the UK, Ireland and the Scandinavian countries (Sweden, Norway, Finland, Denmark and Iceland) were randomised.

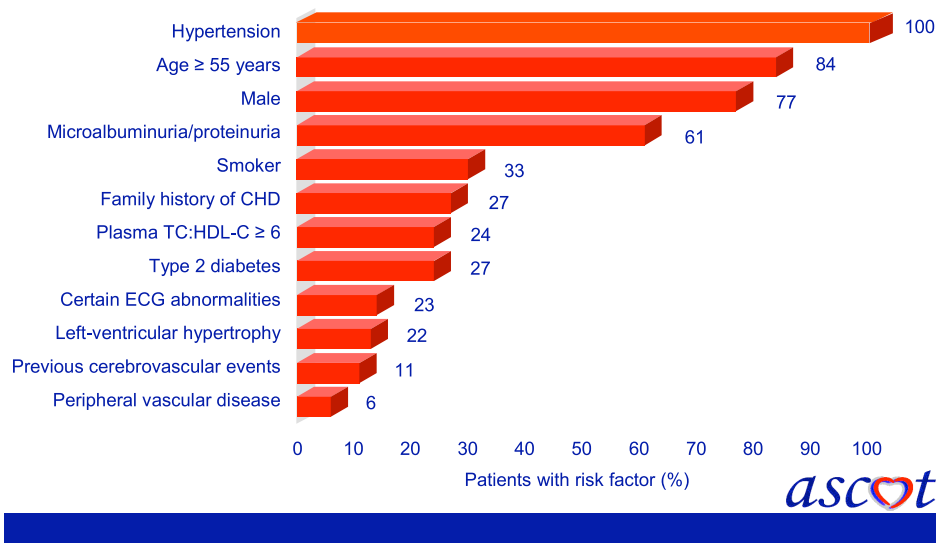


**What was the treatment population?**

Patients treated in ASCOT are typical of those generally seen in daily practice. They had hypertension ( $\geq 160/100$  mmHg untreated or  $\geq 140/90$  mmHg following treatment with  $\geq 1$  drug); were men and women ages 40-79 years with no previous MI or current clinical CHD; and  $\geq 3$  other CHD risk factors. These risk factors are those commonly seen in hypertensive populations.

**ASCOT patient population risk factor profile**

All patients in ASCOT have hypertension plus  $\geq 3$  risk factors for CHD



**How does the ASCOT population compare with earlier studies?**

The predicted level of risk in these patients is below that of most other well-known studies of hypertension – e.g., Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) and Valsartan Antihypertensive Long-term Use Evaluation (VALUE) – both of which, in contrast to ASCOT, included patients with established CHD.

***Why did the Data and Safety Monitoring Board recommend halting ASCOT-BPLA?***

Having recommended premature termination of ASCOT-LLA in 2002, the independent Data and Safety Monitoring Board recommended stopping BPLA because the group receiving the beta-blocker  $\pm$  diuretic were suffering more fatal events compared with those treated with amlodipine  $\pm$  perindopril. Therefore, trial closure began in December 2004 and ended in June 2005.

***What is the importance of ASCOT?***

The results from ASCOT have had a major impact on recent guidelines and will continue to have an influence on groups responsible for recommending the appropriate treatment of patients with hypertension. (For example, the outcomes of ASCOT-BPLA have resulted in changes to the recent NICE/British Hypertension Society (BHS) guidelines.)<sup>3</sup>

Additionally, the combined reduction in risk achieved by lowering blood pressure with a combination of agents – amlodipine  $\pm$  perindopril – and effectively lowering cholesterol demonstrated in ASCOT-LLA has been recognised in the NICE/BHS<sup>3</sup> and European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines.<sup>4</sup>

ASCOT-LLA also demonstrated that hypertensive patients with additional risk factors benefited from treatment with atorvastatin irrespective of their cholesterol level at the beginning of treatment with resulting changes to ESH/ESC<sup>4</sup> and BHS IV guidelines.<sup>5</sup>

Twenty-five percent of patients (4,760 of 19,257) stopped therapy because of an adverse event, with no significant difference between the allocated treatment groups. However, 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 (2 percent [162 of 9,639] vs. 3 percent [254 of 9,618],  $p < 0.0001$ ).

The most commonly seen adverse events on the amlodipine-based regimen were peripheral oedema and cough (23 percent and 19 percent, respectively, vs. 6 percent and 8 percent on the atenolol-based regimen). The most commonly seen adverse events on the atenolol-based regimen were dizziness and fatigue (16 percent and 16 percent, respectively, vs. 12 percent and 8 percent on the amlodipine-based regimen).<sup>6</sup>

### ***Where can you find more information about ASCOT?***

The ASCOT Web site ([www.ascotstudy.org](http://www.ascotstudy.org)) features a wide range of resources and background information for journalists, health care professionals and the general public.

The site includes:

- Slide kits summarising key study results
- Webcasts conducted by the Executive Committee of ASCOT
- News releases discussing the implications of ASCOT for the future management of patients with high blood pressure
- Links to key papers
- Contact details for spokespeople in different countries

### **References**

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  5. Williams B, Poulter NR, Brown MJ *et al*. BHS IV guidelines for hypertension management. *BMJ* 2004;**328**:634-40.
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