

RESEARCH PROJECTS

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) UK 30-year anniversary 1996-2026

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At the Royal Society of Medicine (London) on May 26th 2026, we held a symposium to commemorate the 30-year anniversary of ASCOT. Unfortunately, limited resources resulted in attendees being restricted to the UK/Ireland “half” of ASCOT. However, present and former colleagues who had participated in the original trial and its long-term follow-up in the UK and Ireland, together with a number of other guests, attended a meeting at which the history of the trial, the main results and the outcome of many sub-studies were presented. We were honoured to have the Presidents of the British and Irish Hypertension Society (Ian Wilkinson) and the International Society of Hypertension (George Stergiou) as co-chairmen of the meeting.

Peter Sever began the meeting with an account of the 10-year period preceding the trial from initial discussions at meetings of the European Blood Pressure Group in 1988 and 1989, to an agreement with Pfizer-NY in 1996, to support a trial based on a collaboration between UK investigators and the Gothenburg Trial Center led by Björn Dahlöf.

Neil Poulter presented the original factorial trial design which involved randomisation of almost 20,000 participants with hypertension and three associated cardiovascular risk factors into treatment with either amlodipine to which perindopril was added as necessary or atenolol to which a thiazide was added as necessary- the blood pressure-lowering arm (BPLA). In addition, those participants with a total cholesterol less than 6.5 mmol/L were randomised to atorvastatin or placebo- the lipid-lowering arm (LLA).

Both arms of the trial were terminated early- the LLA after 3.3 years due to highly significant benefits of the statin on myocardial infarction and other cardiovascular endpoints, and the BPLA after 5.5 years owing to the highly significant benefits of the amlodipine-based regimen compared with the atenolol-based regimen on stroke, and all-cause mortality.

In the UK, following closure of the trial, participants who were alive were tagged by NHS England and Public Health Scotland, which allowed electronic data on subsequent hospital admissions and mortality to be recorded- the ASCOT Legacy Programme, which eventually reported over 3,000 cardiovascular outcomes.

Over the ensuing 25 years ASCOT generated over 150 publications based on sub-studies and sub-analyses.

Alun Hughes and Jamil Mayet highlighted the results of several studies focussing on a more detailed phenotypic characterisation of a sub-study population of over 1,000 participants, including the application of pulse wave tissue doppler imaging of the heart as a powerful predictor of subsequent cardiovascular mortality and vascular studies providing further insight into the differential effects of the two antihypertensive treatment regimens on cardiovascular structure and function and their relation to disease outcomes.

Patsy Munroe and Helen Warren summarised the extensive utilisation of the ASCOT DNA resource to study genetic determinants of baseline phenotypic markers, determinants of blood pressure and lipid responses to treatment and determinants of cardiovascular endpoints. This genetic database has also contributed to wider international databases, which have provided unique information on blood pressure loci, new gene discoveries and gene variants associated with interindividual variation in treatment response.

Ajay Gupta presented the study on adverse effects of statins emphasising that during the blinded LLA of the trial there was no difference in reports of muscle related symptoms (and other side effects) between those assigned atorvastatin or placebo, but after the trial when all participants were offered statins and were aware of their statin treatment, there was a highly significant increase in muscle related adverse reactions in those taking atorvastatin compared with those who were not taking the drug. This important example of the nocebo response was probably exacerbated by widespread media reports of the harmful effects of statins, which many subsequent reviews have demonstrated have no scientific basis.

Ramzi Khamis reviewed the ASCOT biomarker programme involving studies with a wide range of biomarkers including the demonstration of the ongoing importance of inflammatory biomarkers such as CRP associated with cardiovascular outcomes.

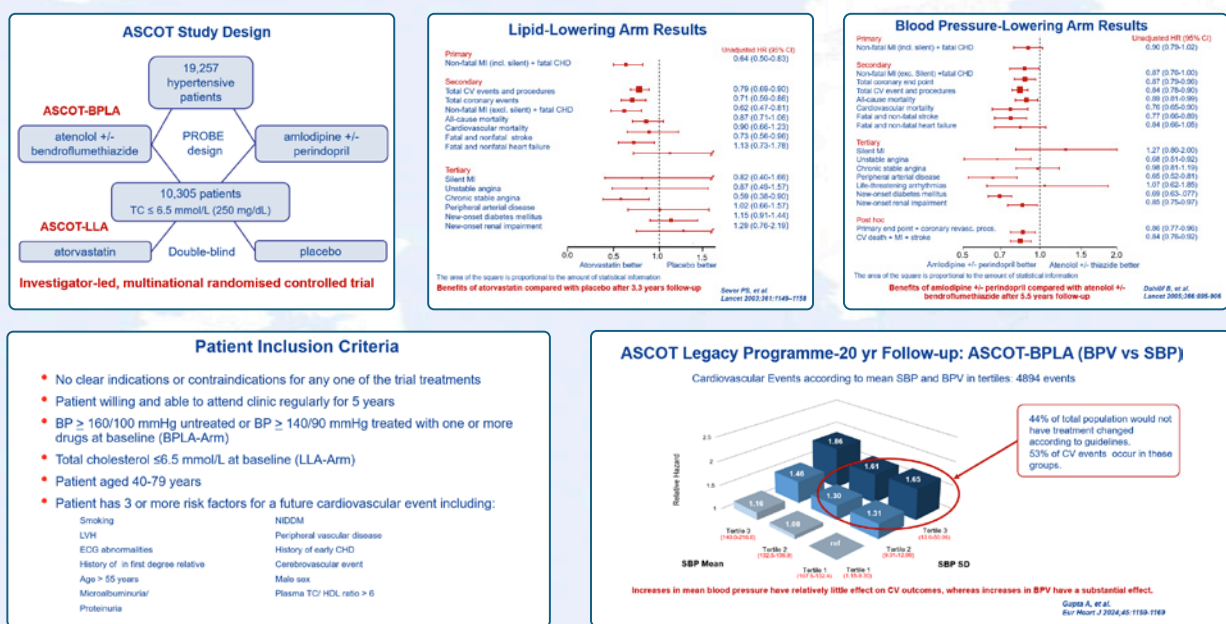
The ASCOT Legacy Programme produced a number of clinically important outcomes. Over the 20-year follow-up, those previously assigned the amlodipine-based regimen had significantly reduced strokes and cardiovascular events compared with the atenolol-based regimen, and those formerly assigned statins had significantly lower coronary events compared with placebo.

These findings, particularly for statins, have important implications for long-term management of lipid-lowering therapy to prevent cardiovascular disease.

One of the key findings in the main trial was that visit-to-visit (long-term) systolic blood pressure variability whilst on treatment was a far better predictor of cardiovascular outcomes than average blood pressures. Moreover, those assigned the amlodipine-based regimen had a greater reduction in long-term blood pressure variability than those assigned atenolol and this effect of amlodipine

ASCOT Trial Overview

A landmark cardiovascular outcomes trial that has transformed the prevention and management of cardiovascular disease through more than three decades of clinical research.



was shown to be the strongest explanator of the overall benefits of this regimen on cardiovascular outcomes. In the Legacy Study these effects of long-term systolic blood pressure variability were confirmed and critically it was demonstrated that even in those subjects with well controlled blood pressure, those with high blood pressure variability remained at high cardiovascular risk and accounted for approximately 50% of all cardiovascular events occurring during prolonged follow-up.

Neil Poulter summarised the key outcomes from ASCOT and their implications:

This was one of the first studies to show, in primary prevention, that statins conferred substantial protection against cardiovascular events and all-cause mortality. This protection conferred benefit over the ensuing 20 years - the legacy effect - and the routine use of statins is now recommended for most patients with hypertension largely on the basis of the ASCOT trial.

Amlodipine and perindopril were shown to be associated with highly significant benefits on cardiovascular outcomes compared with the traditional regimen of beta blocker and diuretic and has influenced the best combination of drugs recommended in guidelines since then.

Looking to the future, Amit Kaura presented some preliminary data and a fascinating insight into the potential for AI to explore the multiple ASCOT databases to provide new information on the phenotypic characterisation of individuals at high risk of developing cardiovascular events.

In summary, the chairmen Ian Wilkinson and George Stergiou emphasised the importance of ASCOT in the generation of national and international guidelines on hypertension and cardiovascular disease prevention.

The anniversary event concluded with drinks and a celebratory dinner.

The **ASCOT website** provides further details on sub-studies and publications.

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