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Anglo-Scandinavian Cardiac Outcomes Trial: a brief history, rationale and outline protocol

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It is now more than a decade since discussions first took place on a new large scale cardiovascular morbidity/mortality trial in hypertension, in which newer classes of drugs such as the calcium channel blockers and the angiotensin converting enzyme inhibitors would be compared with traditional diuretic and/or β-blocker-based treatment.

ASCOT is a randomised controlled trial of the prevention of coronary heart disease (CHD) and other vascular events by blood pressure lowering, and uses a factorial design to assess the same endpoints by cholesterol lowering. It is the first trial designed to evaluate benefits of specific combinations of treatments of hypertension and one of only two major trials powered to detect differences in CHD outcome of two different treatment regimens.

The impetus for ASCOT was the lack of outcome data on newer types of blood pressure lowering agents, the absence of data on the evaluation of specific combination treatment regimens in hypertension, and the shortfall of CHD prevention using standard therapies based on diuretics and β-blockers. It was also felt that there was a need to evaluate multiple risk factor intervention in the prevention of CHD, as there were few data on the benefits of lipid lowering among hypertensive patients.

Pre-study discussions focused on two major issues. First, previous trials investigated the efficacy of diuretic and/or β-blocker-based treatment (together with older drugs, such as methyldopa and hydralazine) in reducing cardiovascular events in hypertensive patients. However, no outcome data were available with two classes of drugs readily accepted into common clinical practice, namely calcium channel blockers and ACE inhibitors.

The second issue focused on the observation from individual studies and subsequent meta-analyses that there was a shortfall in protection against CHD events in hypertensives treated primarily with β-blockers and diuretics. This was in contrast with the impressive evidence for protection against stroke.

It quickly became apparent that new trials were needed to compare two or more active treatments. These would require a very large number of patients to address whether CHD outcome depends on the type of drugs used to lower blood pressure. Discussions centred on the comparison of individual drugs as first-line treatments, with other drugs added to control blood pressure, or comparing specific treatment regimens using combination therapies. Similar discussions in the USA led to ALLHAT, a study which compares individual drugs with a variety of add-on drugs for the treatment of inadequate blood pressure control.

The other obvious need was for a trial to compare the standard treatment regimen of diuretic + β-blocker with a combination of newer agents. Following on from earlier discussions, the possibility of a factorial design trial was considered, in which additional hypotheses could be tested, such as the benefits of lipid lowering and anti-platelet agents in the hypertensive population.

These initial plans did not progress any further

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until 1991 when a British Hypertension Society Working Party was set up to re-visit the question of such a trial and to seek financial support for the study.

The Working Party readdressed the issues discussed previously and proposed a trial design to the annual meeting of the British Hypertension Society in September 1993. This was broadly similar to the earlier proposal for a comparison of individual drugs with a common add-on antihypertensive agent for those patients who failed to achieve adequate blood pressure control with first line therapies. They also ratified the earlier proposal for a factorial design study. At the same time on-going discussions were being held in Scandinavia along the same lines.

In 1995, following discussions between Peter Sever and Neil Poulter (London), and Bjorn Dahlöf and Hans Wedel (Gothenburg), a joint proposal for an outcome study was submitted to Pfizer, who agreed to support a study which later became known as ASCOT. The study outline was announced in 1996 and a Steering Committee was formed. After several meetings a working protocol was agreed and formed the basis of the study which started recruitment in 1998.

The primary objective of ASCOT is to assess and compare the long-term effects on non-fatal myocardial infarction and fatal coronary heart disease of a standard antihypertensive regimen of a β-blocker ± a diuretic with a more contemporary regimen of a calcium channel blocker ± an ACE inhibitor. The study also aims to compare the effects of a statin *vs* placebo among patients with a total cholesterol of $\leq$6.5 mmol/l on non-fatal myocardial infarction and fatal coronary heart disease. For those with higher cholesterol levels it was felt that contemporary clinical practice dictated the recommendation of lipid-lowering therapy, and it would be considered unethical to randomise such patients to placebo, even though in fact they were not receiving active lipid-lowering therapy.

The study has a large number of secondary and tertiary objectives including, in both the BP and lipid-lowering limbs of the trial, an evaluation of the effects of the different treatment regimens on stroke, all-cause mortality, heart failure, cardiovascular events and procedures. It will also study the development of diabetes and renal impairment and focus on major study end points in ethnic minority groups and other important subgroups.

ASCOT has a prospective randomised open blinded endpoint design (PROBE). A total of more than 19 000 patients have now been recruited into a 2 × 2 factorial trial of an antihypertensive first-line regimen of atenolol *vs* amlodipine to which a thiazide diuretic or the ACE inhibitor perindopril respectively may be added, with cholesterol lowering using atorvastatin *vs* placebo. It is predicted that 1150 primary events will occur over a 5-year follow-up period (an annual total CHD event rate of approximately 2%). In the hypertensive limb the study has >80% power at a significance level of 5%, to demonstrate a relative 20% additional benefit of the 'new' drug regimen over the older treatment. In the lipid-lowering limb, which includes more than 9000 patients, there is >90% power with a significance level of 1%, to detect a 30% relative risk reduction on coronary end points of statin *vs* placebo.

In order to achieve the desired event rate in the trial, hypertensive patients must have three additional risk factors for cardiovascular disease, such as smoking, non-insulin dependent diabetes, history of a cerebral vascular or a peripheral vascular disease and microalbuminuria. Therapeutic targets of the study are a blood pressure of <140/90 mm Hg in non-diabetics and <130/80 mm Hg in diabetics with no fixed target for the lipid-lowering limb.

The study is being co-ordinated for Scandinavia from the Göteborg University Clinical Research Institute in Göteborg and for the United Kingdom and Ireland from the Cardiovascular Studies Unit at Imperial College, London (St Mary's). These two groups have been responsible for the recruitment of at least 9000 patients each through approximately 900 primary health care centres in Scandinavia and 36 regional centres in the UK.

Trial recruitment began in February 1998 and was completed in May 2000. Follow up is for an average of 5 years with an anticipated presentation of results in the year 2004[1].

References

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