

Background

Outcome of treatment of hypertension

Over the past 25 years studies of the drug treatment of mild-moderate hypertension have demonstrated that reduction of blood pressure is associated with reduction in the risk of cardiovascular morbidity and mortality. In middle-aged subjects with hypertension, the risk of fatal and non-fatal stroke is reduced by approximately 40%, which is the benefit predicted from epidemiological studies. In contrast the risk of coronary heart disease is reduced by only 10-15% compared to the potential benefit of approximately 20-25% predicted from epidemiological studies. More recently, studies in older subjects (>65 years if age) have demonstrated that the benefit of blood pressure reduction in hypertensive individuals extends at least to the age of 84 years. In addition a similar beneficial outcome from blood pressure reduction has been shown in subjects 60 years of age and older with isolated systolic hypertension.

Drug treatments in hypertension outcome studies

The benefit of reducing blood pressure in all age groups has been shown particularly with drug regimens which are based on a diuretic as initial therapy. Since these studies were initiated or completed, there has been the introduction of newer classes of antihypertensive agents particularly the ACE inhibitors and calcium channel antagonists which have become widely accepted into practice.

At present there are no data to demonstrate whether therapy of hypertension based around these newer agents will achieve the same or different outcome in terms of improved morbidity and mortality for a similar degree of blood pressure reduction.

The experience with regimens based on beta-adrenoreceptor antagonists (bet-blockers) which provide tentative evidence that benefit may be less than with regimens based on a diuretic indicate that it is not possible to predict outcome using a particular class of drug despite a similar extent of blood pressure reduction.

As the newer antihypertensives have already become widely established in treatment regimens without any outcome data, determining any difference in outcome with treatment based around these agents compared with the accepted standard of diuretic based regimens is vital. Lack of such outcome data with the newer agents has led to inconsistencies in recommendations in various recent international and national guidelines for the management of hypertension.

The Aim of ANBP2

The primary aim of ANBP2 will be:

To determine in hypertensive subjects 65-84 years of age whether there is any difference in total cardiovascular events (fatal and non-fatal) over a five year treatment period between antihypertensive treatment with an ACE inhibitor-based regimen and treatment with a diuretic-based regimen.

In addition, differences between the treatment groups in a variety of other end-points including total mortality, cardiovascular mortality, non-cardiovascular mortality, fatal cardiovascular events, and non-fatal cardiovascular events will be included.

Important additional questions

Cost/benefit Analysis:

The cost of antihypertensive therapy is a major impact on community resources, eg approximately \$300M annually under the Australian Pharmaceutical Benefits Scheme, with a disproportionate contribution from the newer agents (40-50% total antihypertensive prescriptions) for which the costs are 3-15 times greater than with a diuretic or beta-blocker.

Quality of Life Analysis:

The newer types of agents have purported benefits to older treatment regimens in terms of improvement in quality of life and reduced side effects.

Impact of Left Ventricular Hypertrophy (LVH):

A sub-group of patients in ANBP2 will be involved in a study to determine the association of LVH to cardiovascular endpoints. In addition, regression of LVH with antihypertensive drug treatment will be assessed.

Genetic Involvement:

All subjects will have a blood sample to determine the association of the ACE gene and the angiotensinogen gene to cardiovascular outcomes.

Ambulatory Blood Pressure Monitoring:

The role of 24 hours ambulatory blood pressure monitoring will be assessed to determine whether it is a better predictor of cardiovascular events in comparison to casual blood pressure.

Current or planned comparative outcome studies in hypertension

At the present time one study examining outcome with newer agents has commenced in Sweden (STOP-Hypertension II) and another is proposed in the United Kingdom. In addition, an outcome study in systolic hypertension in the elderly (Syst-Eur) is in progress using the calcium channel antagonist nitrendipine as its primary drug therapy. STOP-Hypertension II is in subjects 70-84 years of age with moderate-severe hypertension - the entry criterion is a supine blood pressure 180/105 mmHg. The United Kingdom study is examining a different group, namely age 50 years or greater with a diastolic blood pressure > 95mmHg, with position in which blood pressure is measured currently unspecified and no systolic blood pressure entry criterion. In addition it must be noted that the results of the two previous MRC trials of the treatment of hypertension in the United Kingdom produced results somewhat at variance with those of other comparable studies. The third study, Syst-Eur, is aimed only at systolic hypertension in individuals over 60 years of age with sitting blood pressure 160-219 mmHg systolic and diastolic <95 mmHg; this study is comparing treatment based on a calcium channel antagonist to placebo.

Rationale for ANBP2 study

The ANBP2 study will be a comparative outcome trial over five years of treatment with a regimen based on a newer antihypertensive (ACE inhibitor) and of treatment based on an agent with an established beneficial outcome (diuretic).

As the incidence of cardiovascular events increases markedly with age and the likelihood of achieving a significant result with the planned sample size within the timeframe of the study depends on the number of observed events in each treatment group, the subjects for the study will be older antihypertensives aged 65-84 years. It has already been established that reduction of blood pressure in these older hypertensives with a diuretic-based regimen is associated with improved outcome. Subjects with both diastolic hypertension and isolated systolic hypertension will be included as outcome of treatment is similar in both groups - the entry blood pressure > 160mmHg systolic or > 90mmHg diastolic. The design of the ANBP2 study will reflect the real world of the treatment of mild-moderate hypertension in older subjects in Australia as it will be conducted during the routine management of subjects fulfilling Australian guidelines for treatment. The success of the previous Australian National Blood Pressure Study over a decade ago indicates that large outcome studies of this magnitude can be planned and executed in Australia. This study is aimed at producing a definitive result which will have a major influence on practice not only in Australia but worldwide, and as a result will refine protocols for the optimal management of hypertension. It will re-establish Australia as one of the major sites for the conduct of successful large outcome studies in hypertension. Having the study conducted in Australian general practices is also likely to produce a result which is much more influential to Australia practice than those from studies conducted in other countries.

GP Involvement

This study is being undertaken in general practice because that is where the majority of hypertension is seen and managed. Indeed, because of the number of patients required to give statistically significant results it is the only place research of this nature can take place. This also has the benefit of providing results directly related to general practice which is relevant to how general practitioners' patients are managed. Dealing with the elderly also necessitates them being seen in their usual practice under the supervision of their usual GP. Thus the general practitioner continues the management of the patient at all stages of the study, e.g. which patients are suitable to participate In the study, who may have their medication withdrawn and, with the exception of randomisation, patient management decisions.

Study Organisation

Management Committee

The study will be coordinated by a Management Committee appointed by the High Blood Pressure Research Council of Australia. This committee will provide overall policy for and direction of the project. It will be responsible for protocol generation and, where appropriate, modification, budgeting and all funding applications. The Management Committee consists of Professor LMH Wing (Chairman), Professor LJ Beilin, Associate Professor M Brown, Professor GJ Jennings, Professor CI Johnston, Dr J Marley, Professor JJ McNeil, Professor, TO Morgan, Professor J Shaw, Dr I Steven, Professor MJ West and Dr P Ryan. The overall Study Director, Dr Christopher Reid, is also a member of the Management Committee.

The Management Committee will meet regularly throughout the planning, execution and data analysis phases of the project, when it will consider reports from the Study Coordinator and the End-point Committee. The Management Committee will be responsible for all the publication and communications relating to the study.

Financial support for the study has been provided by Merck, Sharp & Dohme (Australia) Pty Limited and the Commonwealth Department of Health, Housing and Community Services.

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