Hypertension trials – the current evidence base and forthcoming trials

A review of the placebo-controlled trials in hypertension reveals many unanswered questions of clinical importance. Uncertainties remain about the optimal first-line agent, the optimal combination of antihypertensive agents and the optimal blood pressure targets, for example. This article discusses the evidence that we have and explains how studies such as ALLHAT and ASCOT may add to the evidence base.

Abstract

Recently reported and ongoing morbidity and mortality trials in hypertensive patients are addressing important unanswered questions in hypertension management. What is the optimal first-line treatment for hypertension, what is the ideal combination of antihypertensive drugs, how are these influenced in particular patient subgroups, and what are the treatment thresholds and blood pressure goals of treatment for optimal prevention of cardiovascular disease? Limitations of some recent trials are highlighted and emphasise the need for further prospective meta-analyses of studies to provide adequate power to address some of these important questions. Current ongoing large scale studies, including ALLHAT and ASCOT, will shortly be reporting results to the scientific community and are likely to influence management decisions across a wide range of patient subgroups.

Key words: Hypertension trials.

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Introduction

Since the introduction of antihypertensive therapies more than 50 years ago, a large number of placebo-controlled trials of antihypertensive drugs have demonstrated substantial reductions in cardiovascular morbidity and mortality. For reductions of systolic blood pressure of between 10 and 12 mmHg and reductions of diastolic blood pressure of between 6 and 7 mmHg, conclusions from a pooled analysis of the trial data suggested a reduction in stroke incidence of 38% and a reduction in the incidence of coronary heart disease events of around 16%.[1]

Compared with data from prospective observational studies, for a similar difference in blood pressure, the magnitude in stroke prevention was as expected, but there was a shortfall in protection against coronary heart disease events when comparing outcome trials with prospective observational data.

What was clear from these earlier studies, with treatment regimens largely based on diuretics and beta blockers, was that benefits were seen in patients with all grades of severity of hypertension, ranging from mild hypertension to moderate and severe hypertension.

There were several explanations put forward for the shortfall in protection of hypertensive subjects against coronary heart disease events. These included the possibility that the use of older drugs was associated with adverse metabolic sequelae that mitigated the potential benefits from blood pressure lowering.

A number of unanswered questions emerged from a review of the placebo-controlled trials in hypertension, including questions as to whether newer classes of drugs, such as calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, would confer greater advantages, particularly with respect to coronary heart disease prevention, than the older drugs; would there be advantages in lowering blood pressure to a greater extent than that which was observed in the earlier trials or could this cause harm?

Recently reported trials

A number of active comparator trials have reported over the past few years, including CAPPP, NORDIL, INSIGHT and STOP-2. Regrettably these trials were not sufficiently powered to address the question as to whether newer drugs would indeed be better than older drugs at preventing coronary heart disease. As a consequence, new meta-analyses have been prospectively planned to gain further insight into these important issues.

Additionally, trials have been conducted in particular high-risk subgroups of patients – examples of which will be briefly summarised here.

Systolic Hypertension in Europe (SYST-EUR) trial

This important trial followed on from the Systolic Hypertension in the Elderly Programme (SHEP) and evaluated potential benefits of treating isolated systolic hypertension (ISH). This placebo-controlled study was one of the first studies to evaluate a dihydropyridine calcium channel blocker, nitrendipine, in a hypertensive population, with cardiovascular morbidity and mortality assessments.

SYST-EUR was stopped early because of the magnitude of the benefit of treatment with the calcium chan-

nel blocker. Furthermore, this trial provided strong evidence against an earlier hypothesis that long-term therapy with some calcium channel blockers could increase the risk of coronary heart disease events – a highly questionable conclusion from some retrospective observational studies. Additionally, in SYST-EUR, the substantial cardiovascular benefits of effective control of isolated systolic hypertension in patients with non-insulin dependent diabetes mellitus (NIDDM) were demonstrated.[3]

Hypertension Optimal Treatment (HOT) study[4]

The HOT trial was designed to evaluate the optimum level to which blood pressure should be lowered and also to potentially address earlier concerns about a possible J-shaped effect.

These hypertensive patients were randomised to three groups with targets of ≤90, ≤85 and ≤80 mmHg diastolic blood pressure, but the groups eventually differed by only 4 mmHg, dramatically reducing the power of the study to detect differences between the three blood pressure target categories. In addition, the cardiovascular event rate was lower than expected in the trial. However, the results of an on-treatment analysis, as opposed to an intention-to-treat analysis, identified optimal levels of goal blood pressures, circa 140/85 mmHg – treatment goals that have subsequently been incorporated into many guidelines. HOT also attempted to evaluate the possible benefits of the addition of aspirin to antihypertensive therapy. While there was a reduction of 15% in cardiovascular events in the active treatment group, the cardiovascular benefit was offset by an excess incidence of gastrointestinal bleeds.[5]

'The recent meta-analysis of the Blood Pressure Lowering Trialists' Collaboration suggested no major differences between 'older' and 'newer' classes of agents'

United Kingdom Prospective Diabetes Study (UKPDS)[6]

This large study included a blood pressure lowering arm which evaluated the effects of different degrees of hypertension control on micro- and macro-vascular end points in a type 2 diabetic population. The benefits of tight blood pressure control were clearly demonstrated. Stroke was reduced by 44%, coronary heart disease (CHD) by 31% and any diabetes-related end point by 34% in the group achieving tight control.

International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT)[7]

INSIGHT compared the dihydropyridine CCB – nifedipine GITS – with the diuretic combination of thiazide/amiloride. Atenolol was add-on therapy in both arms. There was no significant difference between the two groups in cardiovascular outcome, but a non-significant trend in favour of the diuretic-based treatment regimen on coronary heart disease events.

Heart Outcomes Prevention Evaluation (HOPE) trial[8]

This was not, in the strict sense, a blood pressure lowering trial, although the antihypertensive drug – the ACE inhibitor, ramipril – was administered in a placebo-controlled study in high cardiovascular risk patients. The substantial benefits observed in this trial for many cardiovascular end points were originally attributed to non-blood pressure lowering effects of the drug. However, in a small ambulatory blood pressure monitoring substudy of HOPE, substantial blood pressure differences were observed in the ramipril limb, where blood pressures fell by an average 10/4 mmHg over the 24-hour assessment period: this would be sufficient to explain the cardiovascular benefits from ramipril in the study.[9]

Recent meta-analysis – the Blood Pressure Lowering Treatment Trialists' Collaboration[10]

This more recent meta-analysis included 75,000 patients from 15 trials which met pre-specified criteria.[11] It suggested that there were no major differences between 'older' and 'newer' classes of agents but the data were too few to allow definitive conclusions to be made. Certain trends were suggested, however. For example, stroke events were somewhat lower, and coronary heart disease events, including heart failure, were somewhat higher with calcium channel blocker regimens than with standard drugs (diuretics and beta blockers). In the case of ACE inhibitors, no significant differences were observed compared with diuretic or beta-blocker based regimens, except for the expected trend in favour of ACE inhibitors in the case of heart failure. There were, however, design problems with at least one of the studies included in this analysis (the CAPPP study) – further data are required before making any definitive conclusions on this class of drugs in general, although their role in specific high-risk subgroups is not questioned.

By 2003, data from about 270,000 patients will be available from this analysis, with more than a million patient-years of follow-up. This will provide more valuable guidance on the optimal use of antihypertensive therapies.

Trials in high-risk groups

Several studies have been published of high-risk groups, often with newer classes of agents, such as the angiotensin II receptor antagonists.

Three of these studies – The study of effects of Irbesartan on Microalbuminuria in Hypertensive Patients with Type 2 Diabetes (IRMA2);[12] Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL);[13] and Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT)[14] – demonstrated renoprotective effects and reduced renal morbidity, independent of blood pressure

reduction, in type 2 diabetic patients treated with these blockers of the renin angiotensin system.

In 1996, the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[15] was commenced to study the effects of blood pressure lowering with a regimen including the ACE inhibitor, perindopril, and indapamide in patients with a previous stroke or transient ischaemia. Active treatment reduced blood pressure by 9/4 mmHg and recurrent stroke by 28%, irrespective of baseline blood pressure. While demonstrating the benefits of antihypertensive therapy in these patients, it left questions about optimal target blood pressures unanswered.

The Losartan Intervention for Endpoint reduction (LIFE) trial investigated the effects of losartan versus atenolol in hypertensive patients with left ventricular hypertrophy (LVH) determined by ECG.[16] Hydrochlorothiazide was used as the add-on therapy to both the angiotensin receptor blocker (ARB) and the beta blocker.

This was the first trial to show a significant difference in major cardiovascular events between two drug classes for an equivalent reduction in blood pressure, although some suggestion of the disadvantages of beta blockers was demonstrated in the Medical Research Council trials of mild hypertension and of treatment of the elderly, in which beta blockers did less well than diuretics in terms of cardiovascular outcomes. In LIFE, inference has been drawn that differences in treatment in favour of losartan may be independent of blood pressure reduction. The overriding question raised is whether the difference would have been comparable if the comparison had been conducted with a diuretic. Nevertheless, it seems reasonable pro tem to include an angiotensin receptor blocker in the therapeutic regimen for patients with left ventricular hypertrophy on ECG.

Unanswered questions

So, despite these trials which have reported in recent years, many of the important clinical questions remain (table 1). They include:

- What is the optimal first-line agent to prevent coronary disease and cardiovascular events?
- What are the optimal drugs to combine when monotherapy does not adequately control blood pressure?
- What are the optimal targets and thresholds for initiating treatment?
- What are the advantages of combining antihypertensive therapy with concomitant medications, e.g. statins?
- Do the answers to all these questions differ for different subgroups of patients?

Two large studies which will report in the next two to three years will hopefully help us to answer some of these questions.

Figure 1. Schematic of protocol of ALLHAT

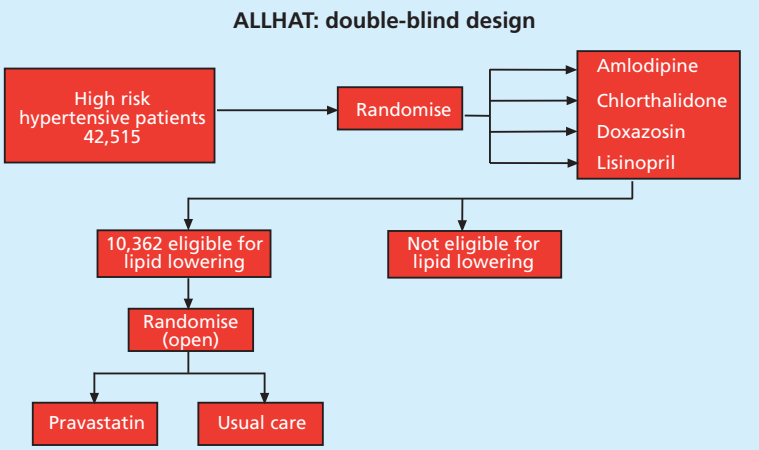


Table 1. Outstanding issues in the management of hypertension

- Definitive information on the optimal first-line agent in different subgroups of patients
- Which combination(s) of antihypertensive agents should be preferred over other combinations?
- At what level of blood pressure or cardiovascular risk should antihypertensive therapy be initiated?
- What should be the target blood pressure?
- What is the magnitude of additional benefits provided by concomitant use of statins in hypertensive patients?
- The evaluation of additional end points including heart failure and dementia

What is the optimal first-line agent?

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was developed to address this question, with head-to-head comparisons of a CCB (amlodipine); an ACE inhibitor (lisinopril); and a selective alpha-1 inhibitor (doxazosin) versus chlorthalidone in 40,000 high-risk hypertensive patients (see figure 1).[17] The doxazosin arm was withdrawn due largely to a reported increase in a secondary end point (heart failure),[18] despite no differences in the primary end point of fatal CHD and non-fatal myocardial infarction. The interpretation of this outcome has been much debated.[19]

ALLHAT has been powered to compare fatal and non-fatal CHD events in the treatment arms and to provide meaningful analyses of subgroups of patients – for example, diabetics, African-Americans and women.

However, ALLHAT has a significant disadvantage. It proved impossible to

find a single common add-on agent that would be equally effective for all four limbs of therapy. Therefore, a number of outmoded and rarely used agents, such as reserpine, have been used. Also, the differences in blood pressure lowering effects of the primary drugs in the age groups studied may confound attempts to explain potential differences in cardiovascular outcomes.

As many patients with hypertension require combinations of antihypertensive agents to achieve their treatment goal, these issues could significantly reduce the usefulness of ALLHAT in daily practice.

What is the optimal combination of antihypertensive agents?

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[20] has been specifically developed to address the need to establish an optimal combination of antihypertensive therapies. ASCOT compares amlodipine (5-10 mg) ± perindopril (4/8 mg) with a standard regimen of atenolol (50/100 mg) ± bendrofluazide (1.25/2.5 mg). Therefore, ASCOT allows clear comparisons of 'old' and 'modern' combinations (figure 2).

The availability of meaningful subgroups, e.g. hypertensive diabetics, will also ensure that conclusions can be drawn on these high-risk groups.

What is the optimal target for blood pressure control?

While data from the HOT study are not definitive, they have been used to establish the diastolic blood pressure targets in guidelines.[5,21] The data for establishing systolic blood pressure targets are even less robust.

Therefore, new studies are urgently needed which will address this question. The authors of this paper have designed a vitally needed study directed at ascertaining optimal systolic blood pressure targets and funding is urgently required.

What is the benefit of adding concomitant medications to antihypertensive therapy?

Most patients with hypertension suffer concomitant disorders which require additional treatments, including statins. To date, the only completed study to investigate the value of additive therapy has been the HOT study, which combined aspirin with antihypertensive therapy. Its results emphasised the need to limit aspirin to specific high-risk groups if benefits are to outweigh harm.[4]

The combination of antihypertensive therapy with a statin is clearly one of the most important clinical questions we face. Both ALLHAT[17] and ASCOT[20] are addressing this issue, although the two trials differ as ALLHAT includes patients with a history of CHD whereas ASCOT does not.

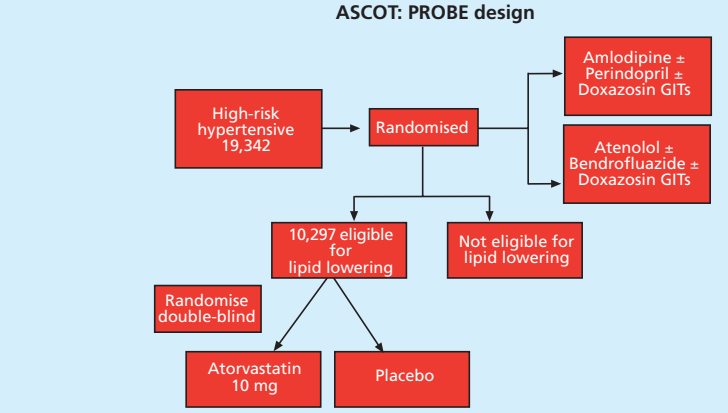
In ALLHAT, patients with a history of CHD and LDL cholesterol of 2.59-3.33 mmol/L mg/dL, or those without CHD and LDL cholesterol of 2.59-4.91 mmol/L, are randomised to receive pravastatin or usual care.

In the ASCOT trial, patients without established CHD with a total cholesterol of ≤6.5 mmol/L were randomised to atorvastatin 10 mg or placebo. This arm of the study was stopped prematurely on 1 October 2002, on the recommendation of the trial's independent Data and Safety Monitoring Committee, in the light of highly significant benefits associated with the use of atorvastatin. The full results of this arm of ASCOT will be published in 2003.

Future clinical trials in hypertension

While the benefit of effective control of blood pressure has been consistently

Figure 2. Schematic of protocol of ASCOT



Key messages

- On-treatment analysis of HOT study data identified optimal levels of goal blood pressures, circa 140/85 mmHg
- Three recent studies have shown renoprotective effects in type 2 diabetes patients treated with angiotensin II receptor antagonists
- The ASCOT trial has been designed to find the optimal combination of antihypertensive agents
- The combination of antihypertensive therapy with a statin is one of the most important clinical questions that we face

demonstrated in prospective clinical trials, important questions remain unanswered. These are often critical clinical questions for daily practice, e.g. the optimal combination of antihypertensive drugs.

Studies such as ASCOT and, with some reservations, ALLHAT, are expected to provide some of the answers in the near future.

However, further new trials are required to address other critical questions, notably the optimal threshold for treatment in lower risk patients and optimal targets, particularly for systolic blood pressure.

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