

Commentary

Debate: Does it matter how you lower blood pressure?

Gordon T McInnes

University of Glasgow, Department of Medicine and Therapeutics, Western Infirmary, Glasgow, UK

Correspondence: Gordon T McInnes, University of Glasgow, Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT, UK. Tel: +44 (0)141 211 2319; fax: +44 (0)141 339 2526; e-mail: g.t.mcinnnes@clinmed.gla.ac.uk

Received: 23 January 2001

Accepted: 9 February 2001

Published: 1 March 2001

Curr Control Trials Cardiovasc Med 2001, **2**:63–66

© 2001 BioMed Central Ltd

(Print ISSN 1468-6708; Online 1468-6694)

Abstract

The evidence base for drug treatment of hypertension is strong. Early trials using thiazide diuretics suggested a shortfall in prevention of coronary heart disease. The superiority of newer drugs has been widely advocated but trial evidence does not support an advantage of beta-blockers, angiotensin converting enzyme inhibitors, calcium channel blockers or alpha-blockers for this outcome. Even meta-analyses have failed to clarify matters. If this issue is to be settled, bigger and better trials of longer duration in high-risk patients are needed. Meanwhile, the importance of rigorous blood pressure control using multiple drugs has been established. This should be the focus of our attention rather than agonising over differences in cause-specific outcomes that may not be generalisable to all patient populations.

Keywords: antihypertensive drugs, clinical trials, hypertension

Introduction

The evidence base in support of the drug treatment of hypertension is among the strongest in medicine. Prospective, randomised clinical trials in 50,000 individuals have demonstrated conclusively that pharmacological reduction of blood pressure reduces the risk of cardiovascular events and all-cause mortality [1].

The magnitude of reduction in stroke events in trials is exactly that predicted from long-term epidemiological studies for the differences in systolic and diastolic blood pressure achieved [1]. The reduction in the predominant complication of hypertension in Western populations (coronary heart disease events) is, while significant, rather less than that expected. Deleterious metabolic effects of diuretics that formed the basis of therapy in almost all the trials might explain the shortfall in coronary heart disease prevention. Other antihypertensive agents should avoid these unwanted actions and could have advantages in cardioprotection.

The suggestion that thiazide diuretics, at the low doses used currently, have a detrimental influence on coronary heart disease outcomes does not withstand careful scrutiny [2]. Because diuretics have no known beneficial effect on cardiovascular events independent of blood pressure reduction, these agents are the appropriate standard against which newer agents should be tested. Stroke events appear to be prevented to the extent predicted by blood pressure reduction, regardless of how this is achieved. The question of interest is whether newer drugs are superior to diuretics in prevention of coronary heart disease events for the same reduction in blood pressure; that is, having benefits beyond blood pressure control.

Beta-blockers

The first contenders were the beta-blockers. There were great expectations in the 1980s that these drugs would be superior to diuretics, particularly because beta-blockers reduce the risk of reinfarction or death in patients with

ACE = angiotensin converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CAPPP = Captopril Antihypertensive Prevention Project; CCB = calcium channel blockers; HOPE = Heart Outcomes Prevention Evaluation; STOP-2 = Swedish Trial in Old Patients with Hypertension-2.

coronary heart disease [3]. This hypothesis was tested in a series of large-scale controlled trials [4–8]. The results were inconclusive and, in some cases, deceptive [7,8].

Newer drugs

Selective alpha-blockers, angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCB), have potential advantages over diuretics and beta-blockers in prevention of coronary heart disease events, and advantages for surrogate endpoints have been claimed. Results of large outcome trials did not appear until 20 years after their introduction [9–14]. The wait was hardly worthwhile. Although no single trial detected a significant difference in coronary heart disease events between therapy based on newer drugs and that based on conventional agents, the precision of comparisons in individual trials was weak with wide 95% confidence intervals for differences. Since clinically useful differences between therapies in coronary heart disease events could not be excluded in any of the trials, individually the trials were not informative.

Individual trials had other shortcomings that cloud their interpretation. In the Captopril Antihypertensive Prevention Project (CAPPP), blood pressure at randomisation and persistently throughout the trial was higher in patients treated with captopril compared with those given conventional therapy [10]. It is almost certain that there was failure in the randomisation procedure [15], rendering the results unreliable. This extends to the findings in the subset with diabetes mellitus, where there appeared to be an advantage of ACE inhibition [10]. In the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) (ACE inhibitors or CCB versus beta-blockers or diuretics [9]) and the International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT) (CCB versus diuretics [12]), withdrawal rates from randomised therapy were unacceptably high (34–39 and 33–40%, respectively). This inevitably leads to underestimation of differences in treatment that would have been seen had there been full adherence to the randomised regimens. The apparent advantage of ACE inhibitor over CCB in STOP-2 [9] must be treated with caution since it arose from a subset analysis.

The only information on the relative value of alpha-blockade in coronary heart disease prevention comes from the prematurely discontinued arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [14]. The primary reason was an apparent excess risk of heart failure in doxazosin-treated patients compared with those randomised to chlorthalidone. However, several factors make interpretation difficult. The diagnostic criteria for heart failure were unconvincing, on-treatment systolic blood pressure was higher in doxazosin-treated subjects, and the discontinuation rate was almost twice as high in patients randomised to alpha-blockers. The other reason for early discontinuation was futility: even

if continued, the chance of detecting an advantage of doxazosin over chlorthalidone-based therapy for coronary heart disease outcomes was less than 1%. We are left, probably for ever, with the unsatisfactory finding that alpha-blocker therapy might be 10% better or 17% worse than diuretic therapy for this outcome. ALLHAT has thus also been uninformative. ALLHAT is the only study with sufficient statistical power to assess the impact on coronary heart disease separately but, if the rest of the trial is conducted similarly to the doxazosin arm, ALLHAT may end up as a monumental waste of effort and resources.

The Heart Outcomes Prevention Evaluation (HOPE) study [11] merits particular mention. Although not a comparison of a new drug against conventional therapy in hypertensive patients, it has been interpreted as showing an advantage of ACE inhibition beyond blood pressure control. That active therapy (ramipril) was better than inactive therapy (placebo) in reducing heart attacks is hardly surprising, but the magnitude of the reduction was greater than that predicted from epidemiological data for the small difference in blood pressure observed. The reduction in cardiovascular events per mmHg difference in blood pressure was, however, no greater than that seen in other high-risk populations, such as diabetics, treated with other forms of antihypertensive therapy [16]. In the absence of a positive control group, treated with another agent providing equivalent blood pressure control, no definitive conclusions can be reached. A better acronym for HOPE might be 'HYPE'.

Meta-analyses

In the face of uncertainty from individual trials, it has become fashionable to resort to meta-analysis. The Blood Pressure Lowering Treatment Trialists' Collaboration, collecting data from over 30 trials, should provide adequate power to more reliably compare different antihypertensive regimens with respect to particular events. A recently published preliminary analysis [17], however, has not taken the matter of differential protection against coronary heart disease much further forward.

Differences in cause-specific effects between active therapies were of borderline significance. No differences were detected in comparisons of ACE inhibitors and conventional therapy, but this analysis was heavily dependent on the unreliable CAPPP [10] and STOP-2 [9]. Compared with conventional therapy, CCB-based therapy was associated with a 13% reduction in strokes and an increase of similar magnitude (12%) in coronary heart disease events, with no difference between CCB types. For both outcomes, 95% confidence intervals were wide and the sizes of any true differences could not be determined reliably. Direct comparison of ACE inhibitor and CCB-based therapies depended on only these two trials, between which there was significant heterogeneity and over 90% of events were reported from STOP-2 [9]; this does not

provide reliable evidence of a difference between ACE inhibitor and CCB-based regimens.

Pahor *et al* [18] simultaneously published a meta-analysis that suggested a highly significant 26% excess risk of coronary heart disease events with CCB-based therapy compared with other treatments. This retrospective analysis used data on 27,743 patients from nine trials, while the Trialists' review [17] was based on 23,454 patients from six of these trials. The analysis of Pahor *et al* [18] had fewer coronary heart disease events and more strokes than that of the Trialists [17] (ratio, 0.86 versus 1.09), emphasising differences in the populations included. Nevertheless, there was no real difference between the meta-analyses – the clinically relevant message is that there remains uncertainty.

Both meta-analyses [17,18] had limited statistical power to detect differences in cause-specific outcomes. There are insufficient data to suggest that ACE inhibitors are superior to diuretics and beta-blockers, and insufficient power to provide a definitive comparison of the efficacy of CCBs against that of diuretics, beta-blockers and ACE inhibitors for coronary heart disease events. The quality of a meta-analysis depends on the quality of the studies included; in both of these examples, the studies included had major shortcomings.

The pattern of events in recent trials (a relatively low proportion of cardiovascular deaths and a high rate of stroke events) is not anticipated from epidemiological data or from trials comparing active therapy against placebo where cardiovascular deaths and coronary heart disease predominate [1]. The ratio of coronary heart disease to stroke events was 3:2 in early trials [1], while in the recent trials [9,10,12,13] the ratio was 1:1. The newer drugs therefore appear to have been tested in an environment very different from that where the older drugs were evaluated, and the hypothesis of a shortfall in coronary heart disease prevention was generated.

The short duration of trials might have contributed to the failure to detect differential effects on coronary heart disease events. It is conceivable that blood pressure lowering *per se* may have a particularly important role in preventing stroke that is manifested rapidly while the influence of drug therapy on coronary heart disease may take longer to appear. Clinical trials provide short-term answers to long-term problems and are, in effect, surrogates for real life where treatment is often given for a lifetime.

Conclusions

Over the years, since new drugs were introduced, expectations appear to have waned. Whereas in the beginning the new drugs were promoted as being superior to older drugs, the objective now seems to be to suggest equivalence

with diuretics and beta-blockers. In the absence of any clear overall advantage, diuretics and beta-blockers should remain the first-step drug therapies, with newer agents added as necessary for blood pressure control.

Uncertainties remain about the application of experience based upon relative reduction in risk in individual populations with varying absolute risk for cause-specific outcomes. The generalisation of results is only appropriate if the population to be treated is similar to that studied. Data from populations in which stroke outcomes are as common as coronary heart disease events may not be readily extrapolated to Western societies where coronary heart disease predominates. For this outcome, there appears to be little to choose between therapies.

Recent trials [16,17] have demonstrated the critical importance of rigorous control of blood pressure in reducing the risk of cardiovascular disease. Tight control reduces coronary heart disease by 19% [17] compared with less intensive control, and under-reporting of events in the largest individual trial [16] may have led to an underestimate of the benefit. In the majority of patients, rigorous blood pressure control necessitates the use of two or more antihypertensive agents in combination. The beneficial effects of additional blood pressure lowering far outweigh any postulated differential effect between drugs. The time has come to stop worrying about which drug to prescribe and to instead devote our energies to lowering blood pressure using all available therapies.

References

- Collins R, MacMahon S: **Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease.** *Br Med Bull* 1994, **50**:272–298.
- McInnes GT, Yeo WW, Ramsay LE, Moser M: **Cardiotoxicity of diuretics: much speculation – little substance.** *J Hypertension* 1992, **10**:317–335.
- Yusuf S, Peto R, Lewis J, Collins R, Sleight P: **Beta-blockade during and after myocardial infarction: an overview of the randomized trials.** *Progr Cardiovasc Dis* 1985, **27**:335–371.
- Medical Research Council Working Party: **MRC trial of treatment of mild hypertension: principal results.** *Br Med J* 1985, **291**: 97–104.
- MRC Working Party: **Medical Research Council Trial on treatment of hypertension in older adults: principal results.** *Br Med J* 1992, **304**:405–412.
- IPPPSH Collaborative Group: **Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the International Prospective Primary Prevention Study in Hypertension (IPPPSH).** *J Hypertens* 1985, **3**: 379–392.
- Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G: **Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study.** *JAMA* 1988, **259**:1976–1982.
- Wilhelmsen L, Berglund G, Elmfeldt D, Fitzsimons T, Holzgreve H, Hosie J, Hornkvist P-E, Pennert K, Tuomilehto J, Wedel H: **Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY Trial.** *J Hypertens* 1987, **5**:561–572.
- Hansson L, Lindholm LH, Ekblom T, Dahlöf B, Lanke J, Schersten B, Wester PO, Hedner T, de Faire U: **Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity. The Swedish Trial in Old Patients with Hypertension-2 Study.** *Lancet* 1999, **354**:1751–1756.

10. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, Luomanmäki K, Dahlöf B, de Faire U, Mörlin C, Karlberg BE, Wester PO, Björck J-E, for the Captopril Prevention Project (CAPP) study group: **Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPP) randomized trial.** *Lancet* 1999, **353**:611–616.
11. HOPE (Heart Outcomes Prevention Evaluation) Study Investigators: **Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients.** *N Engl J Med* 2000, **342**:145–153.
12. Brown M, Palmer C, Castaigne A, de Leeuw PW, Mancina G, Rosenthal T, Ruilope LM: **Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT).** *Lancet* 2000, **356**:366–377.
13. Hansson L, Hedner T, Lund-Johannsen P, Kjeldsen SE, Lindholm L, Syvertsen JO, Lanke J, de Faire H, Dahlöf B, Karlberg BE, for the NORDIL Study Group: **Randomised trial of efforts of calcium antagonists compared with diuretics and β -blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) Study.** *Lancet* 2000, **356**:359–365.
14. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: **Major cardiovascular events on hypertensive patients randomized to doxazosin vs chlorthalidone. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).** *JAMA* 2000, **283**:1967–1975.
15. Peto R: **Failure of randomisation by 'sealed' envelope.** *Lancet* 1999, **354**:73.
16. Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S, for the HOT Study Group: **Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.** *Lancet* 1998, **351**:1755–1762.
17. Blood Pressure Lowering Treatment Trialists' Collaboration: **Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials.** *Lancet* 2000, **355**:1955–1964.
18. Pahor M, Psaty BM, Alderman MH, Applegate WS, Williamson JD, Cavazzini C, Furberg CD: **Health outcomes associated with calcium antagonists compared with the first-line antihypertensive therapies: a meta-analysis of randomised controlled trials.** *Lancet* 2000, **352**:1949–1954.