

## Drug treatment of hypertension

*Most patients will need a treatment cocktail—including a thiazide diuretic*

**H**ypertension is one of the most important preventable causes of premature death worldwide,<sup>1</sup> and the benefits of antihypertensive drugs have been confirmed by the largest evidence base from clinical trials in medicine. Many classes of drugs are available for treatment, and debate has raged about whether the benefits of treatment are purely a function of the quality of blood pressure control or whether the type of drug used might also be a powerful determinant of outcome. This is a key question because the difference in cost between “older” drugs (thiazides or  $\beta$  blockers) and “newer” drugs (such as angiotensin converting enzyme (ACE) inhibitors or calcium channel blockers) is substantial. A meta-analysis of trials of treatment for hypertension with the newer drugs found that ACE inhibitors and calcium channel blockers were likely to reduce cardiovascular morbidity and mortality by the same order of magnitude as  $\beta$  blockers or thiazides,<sup>2</sup> but such analyses have insufficient statistical power to detect cause specific outcomes with regard to specific drugs.

Recently, the “antihypertensive and lipid lowering to prevent heart attack trial” (ALLHAT)—the largest ever randomised trial of antihypertensive treatment—reported its results.<sup>3</sup> It was designed to determine whether the choice of first line treatment for hypertension influenced cardiovascular outcome. Importantly, the trial was sufficiently large to examine cause specific outcomes and was the first hypertension study to have sufficient power to examine the combined incidence of fatal coronary heart disease and non-fatal myocardial infarction as the primary end point.

ALLHAT was a randomised double blind controlled clinical trial conducted in 623 centres in North America. The trial randomised 42 418 patients with mild to moderate hypertension aged 55 years or older (mean age 67 years) with one additional cardiovascular risk factor to one of four antihypertensive treatments: the diuretic chlorthalidone (12.5-25 mg daily), the ACE inhibitor lisinopril (10-40 mg daily), the calcium channel blocker amlodipine (2.5-10 mg daily), or the  $\alpha$  blocker doxazosin (1-8 mg daily). The doxazosin arm was stopped prematurely in 2000 after a reported excess of cardiovascular events (principally congestive heart failure) compared with the reference drug, chlorthalidone.<sup>4</sup> This left 33 357 patients who completed the trial for a mean follow up of 4.9 years.

The design of the trial ensured the inclusion of large numbers of patients’ groups, previously under-represented in trials of blood pressure—notably

women (15 658, 47%), black Americans (10 702, 35%), Hispanics (5246, 19%), and people with diabetes mellitus (12 063, 36%). The primary outcome occurred in 2956 participants, and no differences were found between the rates with the reference drug chlorthalidone (11.5%), and amlodipine (11.3%) and lisinopril (11.4%). Moreover, this conclusion is valid irrespective of the patient’s sex, ethnicity, or the presence or absence of diabetes. Four major secondary end points were prespecified—all cause mortality, fatal and non-fatal stroke, combined coronary heart disease, and combined cardiovascular disease. No difference was found between chlorthalidone and amlodipine for any of these major secondary end points. No difference was found between lisinopril and chlorthalidone for two of the secondary end points (all cause mortality or combined coronary heart disease). However, lisinopril was significantly less effective than the diuretic at reducing the other two secondary end points—stroke and combined cardiovascular disease.

Heart failure was diagnosed significantly more often over six years in patients randomised to either amlodipine (more by 38%) or lisinopril (19%) compared with chlorthalidone. This finding must be viewed with caution. It should be emphasised that this was not a primary or major secondary end point of the study and it was not well validated. It is not surprising that patients randomised to diuretic got less oedema than those randomised to ACE inhibitor or calcium channel blocker. Moreover, from a clinical perspective it is not a major finding in that patients with hypertension similar to those randomised in this trial (aged  $\geq 55$  years, mean age 67 years) would receive a diuretic as part of their treatment.

What does this new information tell us about the drug treatment of hypertension? This trial reaffirms current recommendations that a thiazide diuretic is at least as effective as a first line treatment as more expensive alternatives in an older population with hypertension.<sup>5</sup> Importantly, this also applies to people with diabetes mellitus in whom doctors have been reluctant to prescribe thiazide diuretics, a reluctance that is no longer justified. The new information also dismisses previous concerns about the safety and efficacy of calcium channel blockers for the treatment of hypertension.<sup>6</sup> This sends out an important and powerful message to those who generate and publish unsound conclusions from small studies, post hoc analyses, and observational data. Such observations are usually sensational, often wrong, and they have the

potential to do much harm to patients—there is no substitute for a large randomised clinical trial for the formulation of healthcare policy.

The halo of ACE inhibition has been dented by this trial. There was no evidence of the much touted benefits of ACE inhibition “independent of blood pressure” in terms of protection against cardiovascular disease and stroke. It is well recognised that older people and black people respond less well to ACE inhibition with regard to reduction of blood pressure than younger people and white people because their renin-angiotensin systems are more suppressed. Blood pressure was less well controlled in patients randomised to lisinopril throughout the trial, especially in black patients. Small differences in blood pressure (2-4 mm Hg) in large clinical studies can have a major impact on outcome and are the most likely explanation for the reduced protection against stroke and cardiovascular disease with ACE inhibition in this trial. But this is a double edged sword, and the same argument must also apply to explain the benefit when similarly small blood pressure differences occurred in favour of ACE inhibition compared with placebo in studies such as HOPE.<sup>7,8</sup> Such small blood pressure differences can no longer be dismissed as unimportant or irrelevant to clinical outcomes.<sup>9</sup>

When ALLHAT was designed in the early 1990s much debate arose about the need to define first line treatment for hypertension. This has become less relevant in clinical practice as trials continue to confirm that most patients require more than one drug to control blood pressure. This was also confirmed in this trial, which showed that 63% of patients required two or more drugs to control blood pressure to less than 140/90 mm Hg. Moreover, blood pressure control was more difficult in patients at highest risk—older patients, patients with highest systolic blood pressure at baseline, black patients, or diabetic patients—who generally require more than two drugs.<sup>10</sup> ALLHAT does not give information about the ideal combination of drugs required to achieve optimal blood pressure targets. One cannot conclude that the combination of a diuretic with a newer drug would not be more effective than a diuretic and  $\beta$  blocker combination at reducing blood pressure, morbidity, and mortality.

The key message from this trial is that what matters most is getting blood pressure controlled, and that this

is overwhelmingly more important than the means. Combinations of several drugs will be required for most patients, and such an antihypertensive treatment cocktail should include a thiazide diuretic. ALLHAT perhaps heralds the end of an era of initial treatment comparisons for hypertension and points to a new need for “real world research.” In managing hypertension we have a range of effective and safe drugs and a robust evidence base for treatment. But if patients are to benefit from this trial, and all before it, we now need to define the best way of implementing the evidence in clinical practice.

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Competing interests: BW has received travel bursaries and honorariums for presentations at medical and scientific conferences and has served as a consultant to numerous pharmaceutical companies concerning the treatment of hypertension. He is also the president of the British Hypertension Society and a trustee of the Blood Pressure Association.

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## Intimate examinations and other ethical challenges in medical education

*Medical schools should develop effective guidelines and implement them*

In this issue, Coldicott et al report an exploratory survey that shows, among other findings, that up to a quarter of intimate examinations in anaesthetised or sedated patients seem not to have had adequate consent from patients (p 97).<sup>1</sup> This paper will generate a firestorm of controversy, wide media interest, and perhaps even calls for a public inquiry. Through the controversy, let us keep one point uppermost in mind: identifying the problem is only half the battle—the other half is coming up with an effective solution.

The fact that this report has been published at all represents a triumph of academic freedom. In particular, Coldicott, a medical student, deserves high praise for seeing this controversial study through to publication. The medical school examined in the study is probably not the only medical school in the world with similar practices, and the authors and their institution have done patients and the medical community a service by highlighting this problem.

*Education and debate*  
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