Resolving the differences between ACE inhibitors and diuretics – ALLHAT and ANBP2

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Summary

The protective effects of blood pressure reduction are clear. However, the choice of antihypertensive drug is less clear. Two trials comparing the effects of ACE inhibitors and diuretics have produced apparently conflicting conclusions. The US Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial reported that diuretic therapy was probably better, while the second Australian National Blood Pressure study suggested that ACE inhibitor-based regimens were superior. On balance, it appears that differences in the design and conduct of these two trials probably explain the differing results. Neither trial provides really compelling evidence for the preferential selection of one drug over the other. Achieving good blood pressure control is probably far more important than the drug with which that control is achieved.

Key words: antihypertensives, hypertension, cardiovascular disease.

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Introduction

The benefits of effective blood pressure reduction are well established, although the best means of achieving these benefits is less clear. Substantial data are now available from trials of diuretics, beta blockers, ACE inhibitors, calcium antagonists and angiotensin receptor blockers. However, if clinical trials report seemingly conflicting results, what do we believe? The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] and the second Australian National Blood Pressure study (ANBP2)[2] appear to have created exactly this dilemma.

ALLHAT and ANBP2

ALLHAT was a very large, North American trial in which around 42 000 people with hypertension were randomised to take either an ACE inhibitor, a diuretic, a calcium antagonist or an alpha adrenergic blocker. The alpha blocker arm of the study was terminated early after an interim analysis showed an excess of major cardiovascular events compared with the diuretic arm. This left around 33 000 people in the remaining three arms. About 24 000 were included in the ACE inhibitor versus diuretic comparison.

The ANBP2 study was a much smaller trial of around 6000 older hypertensive Australians. They were randomised to receive either ACE inhibitor- or diuretic-based treatment.

The main characteristics of each trial are shown in Table 1. In each trial, numbers of cardiovascular events in each treatment group were compared after a mean follow-up of 4–5 years. Both trials compared the outcomes of treatment with diuretics or ACE inhibitors.

Main findings (Table 2)

In ALLHAT, the primary outcome was coronary heart disease and the trial found no difference in the incidence of events between the ACE inhibitor group and the diuretic group. However, for the secondary outcomes, the risks of stroke (15% lower relative risk,

Table 1

Characteristics of ALLHAT and ANBP2 trials

Characteristics	ALLHAT	ANBP2
Study design	Randomised double-blind	PROBE
Number of participants	33 357	6083
Study population/ setting	North America ≥ 55 years Hypertension and one other CVD risk factor	Australia 65–84 years Hypertension only
Intervention	Diuretic v calcium antagonist v ACE-I	Diuretic v ACE-I
Median follow-up	4.9 years	4.1 years
Baseline characteristics		
Mean age	67 years	72 years
Women	47%	51%
Ethnicity	35% African-American	95% 'white'
Baseline BP	146/84	168/91
Diabetes	36%	7%
Coronary heart disease	25%	8%
Blood pressure goals	< 140/90	140/80

ACE-I ACE inhibitor
CVD cardiovascular disease
PROBE Prospective, Randomised Open with Blinded Endpoint assessment

Table 2

Main findings for ACE inhibitor versus diuretic in ALLHAT and ANBP2 [1,2]

	ALLHAT	ANBP2
Primary outcome	*Fatal CHD or non-fatal MI*	*CVD events or death from any cause*
ACE inhibitor	11.4 events/100 people/6 years	56.1/1000 people/year
Diuretic	11.5 events/100 people/6 years	59.8/1000 people/year
	No difference (Relative risk 0.99 CI 0.91–1.08)	No difference (Hazard ratio 0.89 CI 0.79–1.00)
Secondary outcomes	*Stroke*	*Stroke*
ACE inhibitor	6.3 events/100 people/6 years	9.2 events/1000 people/year
Diuretic	5.6 events/100 people/6 years	8.8 events/1000 people/year
	Higher risk with ACE inhibitor (Relative risk 1.15 CI 1.02–1.30)	No difference (Hazard ratio 1.02 CI 0.78–1.33)
	Heart failure	*Heart failure*
ACE inhibitor	8.7 events/100 people/6 years	5.6/1000 people/year
Diuretic	7.7 events/100 people/6 years	6.4/1000 people/year
	Higher risk with ACE inhibitors (Relative risk 1.19 CI 1.07–1.31)	No difference (Hazard ratio 0.9 CI 0.71–1.14)
	Combined CVD	*Combined CVD (first event)*
ACE inhibitor	33.3 events/100 people/6 years	33.7/1000 people/year
Diuretic	30.9 events/100 people/6 years	37.1/1000 people/year
	Higher risk with ACE inhibitor (Relative risk 1.10 CI 1.05–1.16)	Lower risk with ACE inhibitor (Hazard ratio 0.9 CI 0.77–1.01)
		Myocardial infarction (first event)
ACE inhibitor		4.7/1000 people/year
Diuretic		6.7/1000 people/year
		Lower risk with ACE inhibitor (Hazard ratio 0.68 CI 0.47–0.98)
Achieved blood pressure	2 mmHg higher systolic blood pressure with ACE inhibitor	No difference between treatments

CHD coronary heart disease
CVD cardiovascular disease
MI myocardial infarction
CI 95% confidence interval

95% CI* 2–30%), heart failure (19% CI 7–31%) and combined cardiovascular events (10% CI 5–16%) were all lower in those taking diuretics. In other words, aside from myocardial infarction for which there was no apparent difference, diuretics seemed to be superior to ACE inhibitors.

The ANBP2 trial reported an 11% (0–21%) reduction in the risk of its primary outcome (any cardiovascular event or death from any cause) in favour of the ACE inhibitor group compared to the diuretic group. In terms of the secondary outcomes, there was a 32% (1–53%) greater reduction in the risk of non-fatal myocardial infarction with ACE inhibitor therapy compared to diuretic therapy. There were corresponding trends towards greater reductions in the ACE inhibitor group for heart failure and other cardiovascular events. Overall therefore, ACE inhibitors seemed to be superior to diuretics, however, for both primary and secondary outcomes, differences between treatment groups in cause-specific fatal and nonfatal events were only seen in men.

Findings with respect to diabetes

The risk of developing type 2 diabetes in the ALLHAT trial was 40% higher with diuretic therapy than with ACE inhibitor therapy. However, the longer-term clinical relevance of this observation is not known. In the diabetic sub-group of ALLHAT, there was no difference between ACE inhibitors and diuretics for any of the cardiovascular outcomes, except for heart failure. There was a 20% reduction in the risk of heart failure with diuretic therapy compared with ACE inhibitors, irrespective of

* CI confidence interval

whether the patients had diabetes or not. ANBP2 has not yet reported findings with respect to diabetes.

Why do the study results appear to be in conflict?

At first glance, the two studies appear to reach opposite conclusions, that is, the ALLHAT findings favour diuretics whereas the ANBP2 findings favour ACE inhibitors. However, when comparing the studies, one needs to consider the ways in which systematic differences between the trials and random variation about the estimates of effect might affect the validity of this conclusion. Two particular differences between ALLHAT and ANBP2 were the blood pressure reductions that were achieved in the randomised groups and the ethnicity of the study populations.

Target blood pressure

In both trials, doctors aimed to achieve similar target blood pressures by first using the drugs under investigation and then adding other antihypertensives as required. In ANBP2 the blood pressure reductions were almost identical in each group. However, in ALLHAT, the systolic blood pressure at follow-up was 2 mmHg higher in the ACE inhibitor group compared with the diuretic group. While small, a 2 mmHg lower systolic blood pressure would, on the basis of epidemiology, be expected to result in an approximately 10% lower stroke risk and a 7% lower coronary risk.[3] The smaller benefits of ACE inhibitors observed in ALLHAT might therefore be attributable to the less effective blood pressure control achieved in this group.

Ethnicity

ALLHAT included a large proportion (over one-third) of African-Americans, while most patients in ANBP2 were white. Subsidiary analyses suggested that the increased risk in those receiving an ACE inhibitor in ALLHAT might have been partly attributable to less effective blood pressure control with ACE inhibitors (4 mmHg higher at follow-up) among black patients. This is an observation which has been reported elsewhere.[4]

Design

The two trials differed in study design. In ANBP2, the PROBE (Prospective, Randomised Open with Blinded Endpoint assessment) design meant that general practitioners were aware of the assignment of study drugs and were free to choose the most appropriate second-line drug to achieve blood pressure control.

In ALLHAT, not only were physicians blind to treatment assignment, but they were also restricted, by protocol, to using potentially less favourable combinations of drugs. Sub-optimal combinations are a further possible explanation for the follow-up differences in blood pressure in the two randomised groups.

Power

The differences in the size of the trials and the numbers of events observed produced markedly different levels of precision about the estimates of effect obtained in each study. No previous trial of antihypertensive therapy has approached the size of ALLHAT which recorded nearly 5000 deaths, 3000 coronary events and more than 1500 strokes. The large study size increased the power to detect differences between the treatments as evidenced by the tight confidence limits around the estimates of effect.

Relative to ALLHAT, ANBP2 was small, and had greatly reduced power to reliably detect the differences between the treatments and to examine the effects on cause-specific outcomes or in patient sub-groups. For every outcome reported in ANBP2 the confidence intervals were considerably wider than those for ALLHAT. In almost every case the confidence intervals in ANBP2 substantially overlapped the estimates of effect identified in ALLHAT.

How different are the results?

Overall, the findings of ALLHAT and ANBP2 are probably not as divergent as they might at first seem. The differences are likely to be explained by the systematic differences between the studies and uncertainty about the point estimates of effect. Certainly, for coronary heart disease, the evidence for superiority of one drug over the other is very weak. For stroke and heart failure, there is some evidence from ALLHAT that a greater benefit was achieved with diuretic therapy. However, this is probably explained by the greater reduction in blood pressure seen in patients taking diuretics.

Conclusion

The ANBP2 versus ALLHAT debate highlights the need for clinicians to consider the most reliable evidence for the relative benefits of different blood pressure lowering regimens. Overviews or meta-analyses that combine results of individual studies can serve exactly this purpose. A collaboration comprising the investigators of large trials of blood pressure lowering drugs (the Blood Pressure Lowering Treatment Trialists' Collaboration) has conducted such overviews.

The first cycle of results from these overviews showed that treatment with any of the commonly used antihypertensive drugs reduced the overall risk of major cardiovascular events and that all regimens were broadly comparable.[5] The second cycle of results from the collaboration, based on data from more than 160 000 patients, provides more definitive evidence about the effects on individual outcomes such as stroke, ischaemic heart disease and heart failure.[6]

On the basis of the evidence available to date, good blood pressure control appears to be far more important than whether or not it is achieved with an ACE inhibitor or a diuretic.

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 105)

7. Thiazide diuretics are as effective as ACE inhibitors in reducing overall mortality in patients with hypertension.
8. Treatment with thiazide diuretics is associated with significantly more strokes than treatment with ACE inhibitors.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Adalimumab

Humira (Abbott Australia)

vials/pre-filled syringes containing 40 mg solution

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2.1

Modern treatment for rheumatoid arthritis aims to modify the disease process with drugs such as methotrexate.[1] In some patients treatment with disease-modifying drugs is unsuccessful and biological agents such as the inhibitors of tumour necrosis factor alpha (TNF-α) may be needed.[2]

Adalimumab is a genetically engineered antibody. It is a 'humanised' antibody as its gene sequence is not derived from animals. Adalimumab binds to TNF-α preventing it from acting on receptors on the surface of cells. This blocks the inflammatory process and results in a rapid fall in the erythrocyte sedimentation rate and concentrations of C-reactive protein.

Although adalimumab only needs to be administered once every two weeks, it has to be injected. After subcutaneous injection it takes five days to reach the peak serum concentration. These concentrations are higher than the concentration in synovial fluid. Serum concentrations are increased if the patient is also taking methotrexate.

Significantly more patients respond to adalimumab than to placebo. After 26 weeks 46% of patients will have had a 20% improvement compared to 19% of those given a placebo. A study of 36 patients who took adalimumab for two years found that there was no radiological progression of the arthritis in 15.[3]

Adalimumab has also been studied in combination with methotrexate. After 24 weeks there was a 20% improvement in 45 of the 67 patients taking methotrexate and adalimumab 40 mg. Only nine of the 62 patients who took methotrexate and a placebo had a similar response.[4]

As adalimumab has an immunosuppressant effect there is a risk of serious infection. Patients should be checked for latent tuberculosis before they start treatment. Caution is also needed if the patient has a demyelinating disease. Antibodies to adalimumab can develop during treatment and this tends to reduce the therapeutic response. Some patients experience hypersensitivity reactions.

During clinical trials 6.6% of patients discontinued treatment with adalimumab because of adverse effects. Common adverse effects include injection site reactions, dizziness and infections.