

Who's right about thiazides - ALLHAT or ANBP2?

Previous evidence has supported the efficacy of both low-dose thiazides and ACE inhibitors in hypertension without directly comparing the drugs. The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial¹ (ALLHAT) and the Second Australian National Blood Pressure Study² (ANBP2) compared major cardiovascular outcomes for hypertension in patients treated with thiazide diuretics, ACE inhibitors, or calcium-channel blockers. Publication of these trials has generated much discussion about their apparently contradictory results and the implications for antihypertensive therapy. However, similarities in their primary outcomes may be more important than their other differences. This document is intended to help clinicians make prescribing decisions based on an informed understanding of these trials.

NPS Verdict

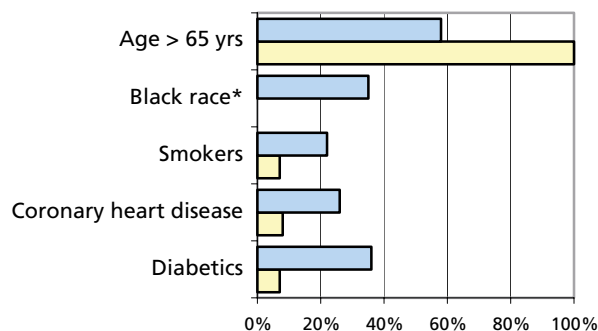
- Low-dose thiazide diuretics merit serious consideration by all clinicians as an initial and/or adjunctive treatment for hypertension.
- Treating elderly people with hypertension with thiazide diuretics can be expected to result in similar reductions in major cardiovascular outcomes, including mortality, as regimens which include an ACE inhibitor or a calcium-channel blocker.
- Previously suggested cardiovascular advantages of ACE inhibitors above and beyond their ability to control blood pressure were not seen in ALLHAT, nor were they demonstrated convincingly in ANBP2.

Practice points

- Low-dose thiazide diuretics are safe for use in people with diabetes, although some increase in blood glucose might occur.
- More than one agent is commonly needed to achieve blood pressure control, especially in high-risk groups, but significant reductions in blood pressure can be achieved in these people.
- Choice of drug should take into account compelling indications, associated morbidity, overall cardiovascular risk and of course individual response.

Were there important differences between the studies and populations?

Differences in study populations



ALLHAT: Compared an ACE inhibitor or a calcium-channel blocker with a thiazide diuretic in 33,357 people with hypertension (aged > 55 yrs), who included blacks, Hispanics and women; all of whom had at least one additional cardiovascular risk factor. ANBP2 population was 95% white; ethnic details of nonwhites

ANBP2: Compared ACE inhibitor-based regimen with diuretic-based regimen in a primary care setting, with 6083 elderly hypertensive patients who had few previous cardiovascular events.

*ALLHAT black subgroup included African-Americans and some black Hispanics. ANBP2 population was 95% white; ethnic details of non-whites not given.

The ALLHAT study population allows the findings to be applied to high-risk patients, such as diabetics, and to often under-represented groups such as African-Americans. These study populations may have also contributed to slight differences in outcome between the two studies.

Did thiazides perform better than ACE inhibitors?

Primary outcomes: Combined rates of major cardiovascular events including death were not markedly different between treatment groups in either study and, as such, claims of thiazide 'superiority'¹ overstate the results. Nonetheless findings of 'no difference' in the diverse, high-risk ALLHAT population, similar rates of adverse effects, favourable tolerability, good adherence over 5 years and efficacy in controlling blood pressure confirm that thiazides have an important role in therapy (Table 1).

Table 1. Primary and secondary outcomes in ALLHAT and ANBP2

	Thiazide vs ACE inhibitor		Thiazide vs calcium-channel blocker
	ANBP2	ALLHAT	ALLHAT
No evidence of difference*	All cardiovascular events or death from any cause	Death from coronary heart disease or non-fatal myocardial infarction	
	First cardiovascular event	Death from any cause; combined coronary heart disease†	
			Combined cardiovascular disease‡; stroke
Some evidence of difference (but see Secondary outcomes below)	ACE inhibitors showed some reduction in risk for: first myocardial infarction; and cardiovascular events or death in men only. ACE inhibitors increased the risk of fatal stroke, but not strokes overall. Note: Differences were mainly seen in men and this study was not powered to detect differences in results based on gender.	ACE inhibitors showed some increase in combined cardiovascular disease and stroke. Note: Increased risk was significantly related to black race.	Increased rates of heart failure for calcium-channel blockers.

Primary outcomes in **bold font**, secondary outcomes are in plain font.

* 'Difference' indicates a statistically significant result.

† Combined coronary heart disease (CHD) indicates CHD death, non-fatal myocardial infarction, coronary revascularisation procedures and hospitalised angina.

‡ Combined cardiovascular disease indicates CHD death, non-fatal myocardial infarction, stroke, coronary revascularisation procedures, hospitalised or treated angina, hospitalised or treated heart failure, and peripheral arterial disease.

Drugs used (ALLHAT/ANBP2): Thiazide (chlorthalidone/hydrochlorothiazide), ACE inhibitor (lisinopril/enalapril), calcium-channel blocker (amlodipine).

Secondary outcomes: In both studies, differences tended to emerge in secondary outcomes of interest only. Because the patient numbers are smaller in these subgroups, the conclusions may be less robust, particularly where the observed result is different to that seen in the overall study population. In evaluating the importance of the differences in the table above, note that:

- higher rates of stroke in the ACE inhibitor group in ALLHAT were due to higher rates in the large black subgroup whose blood pressure was less well controlled; this finding was not seen in non-black subjects.
- lower rates of myocardial infarctions in the ACE inhibitor group in ANBP2 were mostly non-fatal and were observed only among men. As the study was not designed to test gender differences this result should be treated cautiously.
- higher risks of heart failure have previously been associated with calcium-channel blockers.³ However, the validity of heart failure diagnoses in ALLHAT has been questioned^{4,5} due to the apparent lack of a standard diagnostic protocol, and the possibility that heart failure symptoms (e.g. oedema) may have been masked in the diuretic group resulting in underdiagnosis.

Safety outcomes and adverse events

In ALLHAT, there were no significant differences in rates of hospitalised gastrointestinal bleeding, cancer or end-stage renal disease in the different treatment groups. Potassium and glucose increased in the thiazide group, but did not lead to a difference in clinical outcomes. Although there were slightly more discontinuations due to abnormal laboratory values for thiazides, discontinuations due to overall adverse effects were fewer for thiazides compared to ACE inhibitors. Adherence to medication over 5 years was also better in the thiazide group.

Adverse events were not reported in ANBP2.

What about people with diabetes?

Thiazides have sometimes been avoided in diabetes due to the metabolic effects seen at high doses. In ALLHAT, while there was a slight increase in the number of patients with fasting blood glucose > 7.0 mmol/L in the thiazide group compared to ACE inhibitors or calcium-channel blockers, importantly, cardiovascular outcomes were no different for those treated with thiazides in the large diabetic subgroup (n=12,063).

Is one drug enough to control hypertension?

Although study results are described according to the treatment initially assigned, additional medications were frequently required in both trials. In ANBP2, around one-third of those still taking the study drug were taking extra medications at the study's end. In ALLHAT, on average two antihypertensives were being taken after 5 years, and only 40% of those who achieved target blood pressure were on one agent.⁶ Neither study provides evidence about which combinations of medication should be used.

Why do the study results appear to be conflicting?

Modest benefits of ACE inhibitors in ANBP2 were not demonstrated in ALLHAT. The difference in results between the two studies may have been due to:

- **Poorer blood pressure control:** Fewer of those treated with ACE inhibitors in ALLHAT achieved the target blood pressure (61.2% vs diuretic 68.2%) and mean follow-up systolic blood pressure was 2 mmHg higher than the diuretic group. In ANBP2, blood pressure reductions were similar in both study arms.⁹ This variation alone may have affected outcomes and was possibly contributed to by:
 - **Artificial drug protocols** which added beta-blockers, clonidine and reserpine to the study drugs when extra drugs were needed. Adding beta-blockers + thiazides is a more conventional antihypertensive combination than ACE inhibitor + beta-blocker combinations. In ANBP2, GPs were aware of study drugs and were free to choose doses and additional medications—a scenario perhaps closer to real-life clinical practice.
 - **The high proportion of people of black race** may limit generalisability to non-black populations. Higher rates of stroke and cardiovascular disease in ACE inhibitor-treated African-Americans in ALLHAT were perhaps related to their known poorer response to drugs affecting the renin-angiotensin system.⁷ Coupled with an increased population risk of stroke⁷, the consequences of poorer blood pressure control in ALLHAT blacks generally may have been greater in this treatment group.

Even if the effects of ACE inhibitors were underestimated because of these factors, the evidence for thiazides on blood pressure control, major cardiovascular outcomes and safety remains strong. ANBP2 demonstrates that ACE inhibitors are effective in preventing major outcomes, but provides little evidence for a clear advantage over thiazides.

^a Target BP in ALLHAT was < 140/90 mmHg, in ANBP2 the target was to reduce systolic by 20 mmHg to < 160 mmHg then < 140 mmHg, and diastolic by at least 10 mmHg to < 90 mmHg and then < 80 mmHg if tolerated.

And finally...

Trial results should not be viewed in isolation but rather in the context of existing knowledge and individual patient needs. The editorial accompanying the ANBP2 study stated this well... "*In choosing between a diuretic and an ACE inhibitor, the physician can make a reasonable selection by reviewing the patient's history and course. We must remember that trials describe population averages for the purposes of developing guidelines, whereas physicians must focus on the individual patient's clinical responses*".⁸

References

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Hydrochlorothiazide availability in Australia

A new brand of hydrochlorothiazide (Dithiazide) has recently become available. The product has been available since March 2003, and first appeared in the printed Pharmaceutical Benefits Schedule in May 2003. Dithiazide is available in 25 mg tablets which can be split to provide a low-dose 12.5 mg formulation. Hydrochlorothiazide was previously available as Dichlotride but was withdrawn by the manufacturer in November 2002. The re-listing of hydrochlorothiazide from an alternative supplier means that there are now two thiazide diuretics in Australia that allow a very low dose, the other being chlorthalidone (Hygroton 25).

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the individual clinical circumstances of each point.

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