

## Montelukast (Singulair®) in asthma

- Montelukast can be prescribed under the Pharmaceutical Benefits Scheme, for children aged 2–14 years with frequent episodic or mild persistent asthma, from February 1, 2003
  - an Authority approval is required before prescribing
- Prescribing inhaled corticosteroids at the minimum effective dose remains the cornerstone of preventive therapy for persistent asthma in adults and children
- Montelukast might be used as an alternative to inhaled corticosteroids, sodium cromoglycate or nedocromil in children with frequent episodic asthma; it should not be used in conjunction with these drugs
- Montelukast should not be used to decrease the dose of inhaled corticosteroid
- Substitute low-dose inhaled corticosteroid therapy for montelukast if asthma control is not achieved after 2 weeks
- If control with inhaled corticosteroids is not achieved, adding a long-acting beta<sub>2</sub>-agonist is preferred to adding montelukast

Much of the evidence for montelukast comes from clinical trials mainly in adults, in patients with mild asthma, using placebo comparison groups, and of short duration (12 weeks or less).

**Recommendation:** Until further evidence of the efficacy and safety of montelukast is available, inhaled corticosteroids—at the lowest effective dose—should remain the cornerstone of preventive therapy for **persistent** asthma in both adults and children.

Montelukast may be an alternative to inhaled corticosteroids, sodium cromoglycate, or nedocromil in children with **frequent episodic** asthma. Large randomised controlled trials of longer duration comparing montelukast to alternative anti-asthmatic agents are needed to determine its place in asthma therapy.

### What is the place of montelukast in treating adult asthma?

A Cochrane review compared leukotriene-receptor antagonists (LTRAs) to inhaled corticosteroids in patients with mild-to-moderate asthma.<sup>1</sup> The review found a non-significant trend suggesting inhaled corticosteroids (in doses equivalent to beclomethasone 250–400 micrograms/day\*) are generally associated with greater improvements than using an LTRA.

Another systematic review noted that adding an LTRA to inhaled corticosteroid therapy was not more effective than doubling the corticosteroid dose in symptomatic patients.<sup>2</sup> This approach cannot be recommended until more evidence becomes available. In adults without adequately controlled asthma, adding a long-acting beta<sub>2</sub>-agonist to inhaled corticosteroid therapy is preferred to adding an LTRA.<sup>3</sup>

Montelukast might be trialled as an add-on to existing inhaled corticosteroid and long-acting beta<sub>2</sub>-agonist therapy in patients with severe asthma which remains uncontrolled, although there is no evidence that this is effective.

\* N.B. Beclomethasone doses quoted refer to CFC-containing formulations which are no longer available in Australia

## What is the place of montelukast in treating paediatric asthma?

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In children with **persistent** asthma, inhaled corticosteroids should be used initially as preventive therapy.

Studies in children to date have been of short duration, using surrogate measures of efficacy (e.g. symptom diaries, FEV<sub>1</sub>), and have not focused on asthma exacerbations as an outcome.<sup>4,5</sup> Unreliable results from lung function monitoring in children (particularly those aged less than 6 years) makes measuring drug efficacy in this group problematic.<sup>5,6</sup>

Head-to-head comparisons of LTRAs with standard therapy in children are needed to determine the optimal place of these agents in paediatric asthma management. For the moment, montelukast may be considered in children with **frequent episodic** asthma although low-dose inhaled corticosteroid, sodium cromoglycate or nedocromil are probably preferred on the basis of greater clinical experience.

The response to LTRAs in patients with asthma varies. The 2002 Asthma Management Handbook advises a change to low-dose inhaled corticosteroid if no response to montelukast is seen in children after 2 weeks.<sup>6</sup>

## Can montelukast be used as a sparing agent for the inhaled corticosteroid dose?

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No. There is no evidence that montelukast allows smaller doses of inhaled corticosteroid to be used *and* maintain adequate asthma control.

In adult patients with well-controlled mild-to-moderate asthma, there was no overall difference in the dose of inhaled corticosteroid that could be tapered following the addition of an LTRA compared to placebo.<sup>2</sup> In one trial, patients had their corticosteroid dose reduced by about one-third—without compromising asthma control—before the trial even began; this indicates that many patients receive higher doses of inhaled corticosteroids than clinically required.<sup>7</sup> Thus, in patients on medium-to-high inhaled corticosteroid doses, the size of the dose reduction possible by back-titrating the inhaled corticosteroid dose far outweighs that which can be achieved by adding an LTRA.<sup>2</sup>

The systematic review above did not find any trials investigating potential corticosteroid-sparing effects of LTRAs in children.

## What adverse effects or drug interactions are relevant?

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Montelukast is well tolerated. However, as with all new drugs, long-term safety has not been established. Churg–Strauss syndrome, an eosinophilic vasculitis, has been reported with LTRAs in individuals taking either oral or high, inhaled doses of corticosteroids. In many cases, the reaction followed reduction or withdrawal of corticosteroid therapy although not all cases coincided with such changes.

It is unclear whether Churg–Strauss syndrome is causally related to LTRAs or if the reduced corticosteroid use unmasks this allergic reaction. Patients prescribed montelukast should be monitored for any developing eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.<sup>8</sup>

The risk of clinically significant drug interactions with montelukast appears low.

## References

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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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## 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 Trial<sup>1</sup> (ALLHAT) and the Second Australian National Blood Pressure Study<sup>2</sup> (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

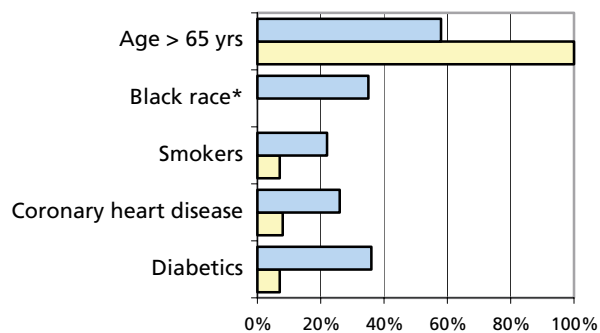
- Low-dose thiazide diuretics merit serious consideration by all clinicians as an initial and/or adjunctive treatment for hypertension.
- Treating elderly people with hypertension with thiazide diuretics can be expected to result in similar reductions in major cardiovascular outcomes, including mortality, 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'<sup>1</sup> 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
<b>No evidence of difference*</b>	<b>All cardiovascular events or death from any cause</b>	<b>Death from coronary heart disease or non-fatal myocardial infarction</b>	
	First cardiovascular event	Death from any cause; combined coronary heart disease†	
			Combined cardiovascular disease‡; stroke
<b>Some evidence of difference</b> (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.<sup>3</sup> However, the validity of heart failure diagnoses in ALLHAT has been questioned<sup>4,5</sup> 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

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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?

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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?

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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.<sup>6</sup> Neither study provides evidence about which combinations of medication should be used.

## Why do the study results appear to be conflicting?

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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.<sup>a</sup> 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.<sup>7</sup> Coupled with an increased population risk of stroke<sup>7</sup>, 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.

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<sup>a</sup> 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...

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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*".<sup>8</sup>

## 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).

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