

# DRUG UPDATE

No. 24

May 2003

## THIAZIDES FOR HYPERTENSION

The largest randomised comparative clinical trial of antihypertensive therapy, ALLHAT, has recently shown no significant difference between 3 classes of anti-hypertensive agents, when used first line, in the incidence of fatal and non-fatal myocardial infarction. The thiazide-related diuretic, chlorthalidone was superior to lisinopril in reducing the risk of stroke and cardiovascular disease and associated with less heart failure than amlodipine. No difference in efficacy was found within patient subgroups including those with diabetes. ALLHAT underscores the current guidance that low-dose thiazide diuretics are the antihypertensive agents of first choice in the absence of contraindications or specific indications for an alternative.

### *What are they?*

Thiazide and related diuretics inhibit sodium reabsorption at the proximal end of the distal convoluted tubule although the exact mechanism for reducing blood pressure is unclear. The most commonly known and used drug in this class is bendrofluazide. Chlorthalidone is chemically different to bendrofluazide but pharmacologically indistinguishable. Other thiazides do not offer any advantages over these two agents and metolazone is more expensive and only appropriate in special patient groups. Guidelines such as the British Hypertension Society Guidelines (1999)<sup>1</sup> suggest that thiazide diuretics should be used as first line agents particularly in the elderly. There has been debate as to whether or not they are as effective as newer agents in preventing cardiovascular events. Although studies have shown a reduction in blood pressure is associated with a reduced risk of stroke, the reduced risk of coronary heart disease has been less than expected.<sup>2,3</sup>

### *What new evidence is available?*

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)<sup>4</sup> was designed to determine whether the occurrence of clinically relevant cardiovascular events is lower for patients with hypertension treated with different agents.

It was a randomised double-blind comparison of a diuretic (chlorthalidone), ACE inhibitor (lisinopril), calcium channel blocker (amlodipine) or alpha blocker (doxazosin) as initial therapy for moderate hypertension. The patients were at least 55 years old and had at least one additional risk factor for coronary heart disease (CHD).<sup>4</sup> 42,418 patients were randomised to chlorthalidone (12.5 – 25 mg/day), amlodipine (2.5 – 10 mg/day), lisinopril (10 – 40 mg/day) or doxazosin (2 – 8 mg/day). A subgroup of 10,355 patients with moderate hyperlipidaemia were also randomised to pravastatin 40 mg/day or usual care (not discussed here).<sup>5</sup>

Second and third-line agents, prescribed at the discretion of investigators, were atenolol, clonidine, reserpine and hydralazine. The proportion of patients who were taking a second or third-line drug after 5 years were similar in each

group (approximately 40%).

An interim review after 3.3 years found that doxazosin was associated with significantly greater risks of cardiovascular disease (CVD), stroke and heart failure than chlorthalidone and this arm was discontinued.<sup>6</sup> The remaining 33,357 patients (mean age 67) were followed up for approximately 5 years; 90% were taking antihypertensive medication at randomisation and the mean blood pressure at baseline was 146/84 mmHg.

### *What were the results?*

The proportion of patients in which target blood pressure (140/90 mmHg) was achieved after 5 years was 68% with chlorthalidone, 66% with amlodipine and 61% with lisinopril. Blood pressure control with lisinopril was worse in African Americans than in other patients.

There was no difference in the primary endpoint of combined incidence of fatal CHD and non-fatal myocardial infarction and when comparing initial treatment with chlorthalidone, amlodipine and lisinopril. Compared with chlorthalidone, amlodipine was associated with a 38% greater risk of heart failure (diagnosed clinically and not a predefined endpoint) and lisinopril was associated with a significantly greater risk of stroke (15%) and combined CVD (10%). Although final blood pressure was 2 mmHg greater with lisinopril than chlorthalidone the differences in risk remained statistically significant after adjustment.

Symptomatic adverse effects accounted for 15% of patients discontinuing chlorthalidone, 17% discontinuing amlodipine and 18% discontinuing lisinopril. Among patients not diabetic at baseline, the incidence of diabetes (defined as fasting blood glucose > 7.0 mmol/L) at 4 years was 11.6% with chlorthalidone, 9.8% with amlodipine and 8.1% with lisinopril (statistical significance not reported). Total cholesterol levels decreased in all patients but after 4 years significantly more patients taking chlorthalidone had levels greater than 6.2 mmol/l (14.4%) than either amlodipine (13.4%) or lisinopril (12.8%). Renal function was similar with chlorthalidone and lisinopril but declined significantly more slowly with amlodipine.

### Remaining controversy?

Further evidence will continue to emerge fuelling debate as to which antihypertensive therapy is better as first line, including the recent Second Australian National Blood Pressure Study (ANBP2). This was a randomized open-label study with blinded assessment of outcomes comparing the initial use of an ACE inhibitor to diuretic.<sup>7</sup> The initial recommendation was to prescribe enalapril or hydrochlorothiazide the subsequent choice of agent and dose being made by the family practitioner. This study was much smaller than the ALLHAT study with 6083 subjects. The results suggest that there was a significant reduction in cardiovascular events in subgroup analysis of male patients receiving an ACE inhibitor (hazard ratio 0.83 with 95% CI, 0.71-0.97; p=0.02). However the results overall were, hazard ratio 0.89 with 95% CI, 0.79-1.00; p=0.05 and there was no apparent difference between the agents in women, hazard ratio 1.00 with 95% CI, 0.83-1.21; p=0.98.

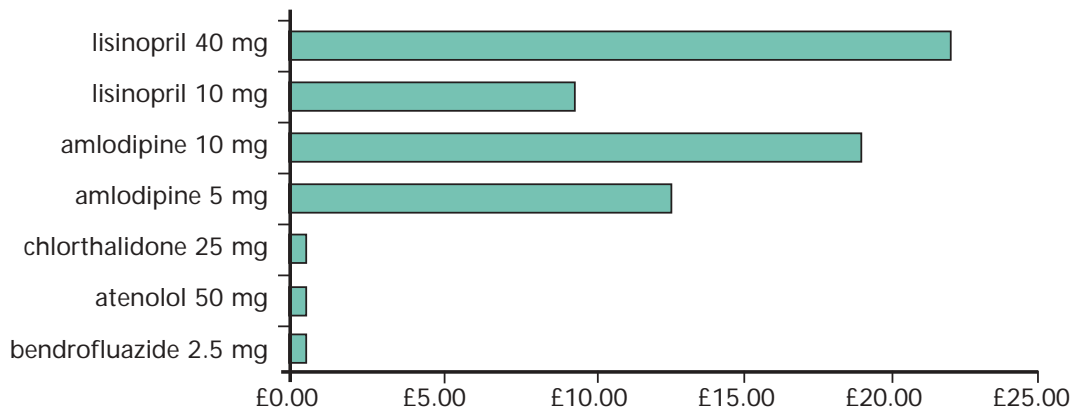
### What are the implications for treating hypertension?

As a first-line treatment for hypertension, chlorthalidone appears at least as effective as amlodipine or lisinopril in reducing morbidity and mortality in patients at increased risk, irrespective of age (at least in those greater than 55 years); sex; ethnicity; and diabetes status. These findings can probably be generalised to all thiazide diuretics, dihydropyridine calcium channel blockers and ACE inhibitors.<sup>8</sup>

Although some controversy remains such as that raised by the subgroup analysis of the ANBP2 study the much larger ALLHAT study confirms current guidance that, in the absence of contraindications, and unless an alternative is positively indicated, a low-dose thiazide diuretic is the first-line antihypertensive of choice for most patients. They have the advantage of being considerably less expensive although many patients will require additional treatment to achieve blood pressure targets.

### How much do they cost?

Cost for 28 days treatment (prices from MIMS April 2003)



NB. Doses shown are for general comparison only and do not imply therapeutic equivalence

### REFERENCES

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial, CC-case control study, C-cohort study, L-letter

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