



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## The Answer: Thiazides First-line for Hypertension

### ALLHAT

The results from the largest hypertension trial ever conducted, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), have been published.<sup>1,2</sup> Over 30,000 patients with mild to moderate hypertension plus at least one cardiac risk factor were randomized to a first-line thiazide-like diuretic, an angiotensin converting enzyme inhibitor (ACEI), or a calcium channel blocker (CCB) and followed for 5 years. It did not include the alpha-blocker (doxazosin), which was stopped early because it caused more cardiovascular morbidity than the thiazide (**Therapeutics Letter #36**).

The strengths of the ALLHAT trial include its design (randomized, blinded), size (33,357 patients), and the diversity of the patient population (mean age, 67 yrs; 47% women; 59% white, 35% black; 36% diabetics; 25% with a history of heart disease; 22% smokers). Most patients (90%) had received other antihypertensive treatment. Step 1 therapy was a blinded once-daily dose titrated to a BP of <140/90 mmHg: chlorthalidone 12.5, 25 mg; lisinopril 10, 20, 40 mg; amlodipine 2.5, 5, 10 mg. Step 2 add-on therapy was non-blinded and chosen from atenolol 25-100 mg daily, clonidine 0.1-0.3 mg BID, or reserpine 0.05-0.2 mg daily. Step 3 add-on therapy was hydralazine 25-100 mg BID.

### ANBP2

The recently published Second Australian National Blood Pressure Study (ANBP2) compared first-line thiazides with ACEIs in 6083 hypertensive patients ranging in age from 65 to 84 years.<sup>3</sup> Patients and physicians were not blinded but individuals assessing the outcomes were. Hydrochlorothiazide (HCTZ) and enalapril were suggested initial therapy but the family practitioners were able to choose which thiazide or ACEI and the dose. For second and third-line therapy, beta-blockers, calcium channel blockers (CCBs) and alpha-blockers were recommended in both groups. Patients were elderly: mean age, 72 years; 51% women; 95% Caucasian; 7% diabetics; 8% with a history of heart disease; and 7% smokers.

### Which class was best at reducing mortality and morbidity?

The combined major outcomes from these 2 trials plus all other RCTs comparing first-line thiazides to CCBs<sup>4-7</sup> are shown in the Table. Total mortality, coronary heart disease and end-stage renal disease were not different for the different classes. The most convincing morbidity



difference was that **CCBs increased the incidence of heart failure** (events leading to death or hospitalization) over 5 years as compared to thiazides (ARI 1.7%, NNH = 61) or ACEIs (ARI 1.2%, NNH = 83). In addition, thiazides reduced the incidence of stroke as compared to ACEIs (ARR 0.5%, NNT = 200). Contrary to common opinion, in ALLHAT the thiazide was similar to the ACEI and CCB in preventing end-stage renal disease, and in a large subgroup of patients with diabetes (12,063) none of the pre-specified subgroup outcomes favored the ACEI or CCB as compared to the thiazide.<sup>1</sup>

### Which class was best tolerated?

Withdrawals due to adverse events (symptomatic or abnormal lab values) were higher with the ACEI, 3.3%, than the thiazide, 2.3%, (ARI 1.0%, NNH = 100) and than the CCB (2.2%, ARI, 1.1%, NNH = 91). This outcome was not reported in ANBP2.

### Which class lowered BP the best?

At one year, in ALLHAT, systolic BP with the thiazide was lower than the CCB by 1.6 mmHg and lower than the ACEI by 3.1 mmHg. Diastolic BP with the thiazide was higher than the CCB by 0.6 mmHg and lower than the ACEI by 0.6 mmHg. In ANBP2 thiazides also tended to lower BP more than ACEIs.

### Did thiazides cause metabolic effects?

In ALLHAT, the thiazide reduced potassium by 0.3 meq/L vs. CCBs and by 0.5 meq/L vs. ACEIs. The thiazide increased fasting glucose by 0.3 mmol/L vs. CCBs and by 0.4 mmol/L vs. ACEIs. It also increased cholesterol by 0.1 mmol/L vs. CCBs or ACEIs. Importantly, these differences in potassium, glucose and cholesterol did not lead to a difference in clinical outcomes.



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**What are the drug usage trends for hypertension in Canada?**

Based on a survey of hypertensive patients in Halifax comparing 1985 with 1995, the proportion of patients receiving thiazides as monotherapy decreased from 31% to 17%.<sup>8</sup> This was associated with an increase in CCB monotherapy (from 2% to 20%) and ACEI monotherapy (from 5% to 25%), while beta-blocker monotherapy remained unchanged at 22%.

**What are the cost implications?**

In our previous Letters #7, 8 and 28 we outlined the differences in costs of the available antihypertensives and these have been updated on our website. To appreciate the implications of these cost differences, the maximum dose of the first-line agents used in ALLHAT have been used to calculate the cost to one individual of 10 years therapy (drug cost not including dispensing fees): **generic chlorthalidone 25 mg = \$37, generic lisinopril 40 mg = \$7,139, and brand-name amlodipine 10 mg = \$7,420.**

**Do these results alter hypertension treatment?**

If you presently use a thiazide as your first choice in all patients with hypertension, the ALLHAT results confirm your practice, and most of your treated hypertensive patients receive a thiazide alone or as a part of combination therapy. The rare exception would be a patient with recurrent gout associated with thiazide use, or a patient with a concurrent symptomatic condition that could be managed with one drug (eg. beta-blocker for angina pectoris). If not, you now have the

opportunity to increase the use of thiazides, decrease costs, and modestly improve outcomes for your patients.

**How do you increase thiazide use?**

To start a new patient on a thiazide, begin with HCTZ or chlorthalidone 12.5 mg daily, and if there is an inadequate BP response after 1-2 months increase to a maximum dose of 25 mg daily. To switch patients from another class of antihypertensive, either stop the drug or reduce the dose to half and add 12.5 mg of a thiazide. Within 2 to 3 visits over a 3-month period, it is easy to complete the switch and establish whether the same BP control is achieved.

**What is the role for other classes of antihypertensive drugs?**

Other classes of drugs are needed in many patients as second or third-line therapy, and can be substituted for first-line thiazide when it is ineffective or not tolerated.

**Conclusions:**

- Total mortality, coronary heart disease and end-stage renal disease are similar for first-line thiazides, CCBs and ACEIs.
- **Heart failure is increased with first-line CCBs as compared to thiazides or ACEIs.**
- Stroke is reduced with first-line thiazides as compared to ACEIs.
- BP control and tolerability are better with first-line thiazides as compared to ACEIs.
- Cost is substantially less for thiazides as compared to beta-blockers, ACEIs, CCBs, alpha blockers, and angiotensin receptor blockers.

This Letter contains an assessment and synthesis of publications up to March 2003. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 45 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

**Table: Major outcomes from all first line head-to-head trials for elevated BP.**

Outcome	Trial	Thiazide %	ACEI %	CCB %	RR (95% CI) Thiazide vs ACEI	RR (95% CI) Thiazide vs CCB
Mortality	ALLHAT	14.4	14.5	13.9	1.00 (0.93-1.06)	1.04 (0.98-1.11)
	ANBP2	6.9	6.4		1.08 (0.89-1.30)	
	Other <sup>+</sup>					0.97 (0.80-1.18)
	Combined <sup>^</sup>				1.00 (0.95-1.07)	1.03 (0.97-1.10)
Coronary heart disease	ALLHAT	8.9	8.8	8.8	1.02 (0.93-1.10)	1.01 (0.93-1.10)
	ANBP2	2.7	1.9		1.39 (1.00-1.94)	
	Other <sup>+</sup>					0.93 (0.71-1.21)
	Combined <sup>^</sup>				1.04 (0.96-1.12)	1.00 (0.93-1.09)
Stroke	ALLHAT	4.4	5.0	4.2	0.88 (0.78-0.98)*	1.06 (0.94-1.20)
	ANBP2	3.6	3.9		0.91 (0.71-1.17)	
	Other <sup>+</sup>					1.03 (0.77-1.39)
	Combined <sup>^</sup>				0.88 (0.79-0.98)*	1.06 (0.94-1.18)
Heart failure	ALLHAT	4.7	5.2	6.4	0.91 (0.81-1.02)	<b>0.74 (0.67-0.83)**</b>
	ANBP2	2.8	2.3		1.22 (0.89-1.66)	
	Other <sup>+</sup>					<b>0.52 (0.29-0.95)*</b>
	Combined <sup>^</sup>				0.94 (0.85-1.05)	<b>0.73 (0.66-0.81)**</b>
End-stage renal disease	ALLHAT	1.3	1.4	1.4	0.91 (0.73-1.14)	0.89 (0.71-1.11)

<sup>^</sup> calculated using Review Manager, Cochrane Collaboration. \*p < 0.05, \*\*p < 0.0001.

+ combined data from 4 other trials comparing thiazides with CCBs<sup>4-7</sup>

Heart failure – events leading to death or hospitalization.

End-stage renal disease – kidney disease death, kidney transplant or start of chronic renal dialysis.

RR – risk ratio.

**References**

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