

How does the Australian (ANBP2) trial compare to the North American (ALLHAT)?

The ANBP2, a new study from Australia has found that patients on the ACEI, enalapril, did better than patients on the diuretic, hydrochlorothiazide. This would appear to challenge the conclusion of the recent ALLHAT trial. Thus, questions have arisen as to what we really know and whether the results from the two studies can be reconciled.

	ANBP2¹ ACEI –enalapril any dose vs Hydrochlorothiazide (HCT) any dose	ALLHAT² Chlorthalidone 12.5-25mg od vs Lisinopril 10-40mg od
Demographics	n=6,083 (ACEI=3,044; HCT=3,039) Age: 65-84yr; mean ≅ 72yr BP _{initial} : 168/91 Caucasian; relatively low CV risk Diabetes=7% Median Duration = 4.1yr	n=24,309 (Diuretic=15,255; ACEI=9,054) Age: 55-79yr; mean ≅ 67yr BP _{initial} : 146/84 Multiracial (35% black) Diabetes=36%; high CV risk ≥ 1 risk factor Median Duration = 4.9yr
Study Design	Prospective, randomized, open-label with blinded assessment of endpoints. The initial agent was recommended by phone, however choice of agent & dose was left to the family practitioner.	Prospective, randomized, double-blind. Larger trial; more absolute events for ALLHAT vs ANBP2 (CVD 6,455 vs 823, CHD 3,956 vs 368, Stroke 1,132 vs 219, Heart failure 1,482 vs 147). Well defined protocol for starting dose, increasing dose, and add-on agents.
Study EndPoints ANBP2: % over total study period mean 4.1yr ALLHAT % over total study period mean 4.9yr	1°: CV event or all-cause death ACEI 695 (22.8%) HCT 736 (24.2%) p=0.05 1°: 1st CV event or any-cause death ACEI 490 (16.1%) NS HCT 529 (17.4%) p=0.06 1°: All-cause death ACEI 195 (6.4%) NS HCT 210 (6.9%) p=0.27	1°: Fatal CHD & non-fatal MI Lisinopril 796 (8.8%) NS Chlorthalidone 1,362 (8.9%) p=0.81 2°: All Cause Death Lisinopril 1,314 (14.5%) NS Chlorthalidone 2,203 (14.4%) p=0.9
Subgroup Observations	♦ACEI benefit only in males; no difference and neutral trend in females	♦ACEI outcomes particularly poor in black subgroup.
Major Study Limitations	♦open-label design and lack of step up protocol allows bias in treatment approach ♦only 58% of ACEI group and 62% of diuretic group were receiving assigned treatment at end of study. ♦limited statistical power: smaller study, lower risk population	♦ACEI known to be less effective in blacks & also less well tolerated. ♦Add-on agents, especially atenolol, not ideal and not synergistic for ACEI group. (Limitations noted in RxFiles Hypertension Update – Feb/03)
Observations (observations limited by differences in groups studied)	♦decreased CV event and all cause death for ACEI vs diuretic seen in ANBP2; outcome differences not significant in the non-black subset of ALLHAT. ♦slightly greater systolic BP reduction in diuretic arm (early in ANBP2; overall in ALLHAT) ♦fatal stroke less in diuretic group in ANBP2; all-stroke less in ALLHAT. ♦the older subset (≥65yr) in ALLHAT also trended towards more benefit from diuretic vs ACEI, consistent with previous studies. In contrast the ANBP2 found more benefit from the ACEI (exclusively in elderly men).	
Possible explanations for differences: (apart from random chance or other factors unaccounted for)	♦much larger size and overall design of ALLHAT adds robustness to the results ♦limitations in trial design make results of ANBP2 difficult to assess. Physicians were unblinded to the drug used and had wide flexibility in adjusting the overall regimen. In the ANBP2 62% of the diuretic arm were on study drug at end of study, whereas in ALLHAT, >71% were receiving study diuretic at 5 years (>80% receiving same class). ♦different drugs used: it is unknown whether differences in individual agents may explain differences; however choice of diuretic, chlorthalidone in ALLHAT appears to have been partly due to a possible trend towards better outcomes than HCT in the MRFIT trial. ³ ♦differences in “add-on” drugs in regimen makes analysis of differences complex. ♦differences in BP lowering (diuretic had greater reduction in systolic BP in ALLHAT) ♦different populations studied; ALLHAT population at much higher risk	
Take home points	<ol style="list-style-type: none"> ACEIs have good outcome evidence in non-black hypertensive patients ALLHAT Low-dose thiazides have outcome advantages over ACEIs in black patients ALLHAT Low-dose thiazides have good outcome evidence in elderly patients with CV risk factors (including diabetes) ALLHAT; Low-dose thiazides good evidence in females ALLHAT, ANBP2 ACEIs have good outcome evidence in caucasian hypertensive male patients; low-dose thiazides also have good evidence ALLHAT & given limitations of ANBP2 trial design ACEIs and low-dose thiazides work synergistically & are a logical combination option in non-black patients CAUTION: very different study designs and population groups limit comparison 	

ACEI=angiotensin converting enzyme inhibitor BP=blood pressure CHD=coronary heart disease CV=cardiovascular HCT=hydrochlorothiazide NS=not statistically significant

References: 1) N Engl J Med 2003;348:583-92. 2) JAMA 2002;288:2981-2997. 3)Circulation 1990;82:1616-1628.