CME CREDIT

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ALLHAT says diuretics are better; ANBP2 says ACEs are better—Can we resolve the differences?

ABSTRACT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the second Australian National Blood Pressure Study (ANBP2) came to different conclusions about which class of drug to try first for treating high blood pressure: a diuretic or an angiotensin-converting enzyme (ACE) inhibitor. But when examined closely, the results may not be all that different after all.

SOME CLINICIANS may be feeling confused about which class of drugs is best for starting therapy for high blood pressure, after two major clinical trials reported apparently conflicting results.

On one hand, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) concluded that thiazide-type diuretics should be the initial treatment for most patients.[1]

But the Second Australian National Blood Pressure Study (ANBP2) suggested that initial therapy with angiotensin-converting enzyme (ACE) inhibitors leads to better outcomes than with diuretics, despite similar reductions of blood pressure.[2]

Which is right? Actually, if we carefully review the two trials, including their design and study populations, the results may be more compatible than the conclusions suggest. The bulk of the evidence still seems to favor the diuretics.

ALLHAT

ALLHAT ran from February 1994 through March 2002, and final results[1] were published in December 2002. This trial was discussed in earlier issues of the *Cleveland Clinic Journal of Medicine*.[3,4]

Patients. ALLHAT included 42,418 patients, all at high risk, all at least 55 years old. For admission, all had to have hypertension (treated or untreated, stage 1 or stage 2—systolic blood pressure 140–179 mm Hg and/or diastolic pressure 90–109 mm Hg) plus at least one other cardiovascular risk factor, eg, a remote myocardial infarction or stroke, type 2 diabetes mellitus, a high-density lipoprotein (HDL) cholesterol level lower than 35 mg/dL, left ventricular hypertrophy, or current cigarette smoking.

Treatment. Patients were randomized in a double-blind fashion to begin treatment with one of four agents:

- Amlodipine (Norvasc, a calcium antagonist)
- Chlorthalidone (Hygroton and other preparations, a thiazide-type diuretic)
- Doxazosin (Cardura, an alpha-adrenergic blocker)
- Lisinopril (Zestril, Prinivil, an ACE inhibitor).

Reserpine, clonidine, atenolol, and hydralazine could be added as needed to achieve and maintain a goal blood pressure lower than 140/90 mm Hg.

The primary outcome measured was the combined incidence of fatal coronary heart

The results may be more compatible than the conclusions suggest

disease or nonfatal myocardial infarction, which was analyzed by intention to treat.

Secondary outcomes were:

- All-cause mortality
- Stroke
- Combined coronary heart disease (fatal coronary heart disease, nonfatal myocardial infarction, coronary revascularization, or angina with hospitalization)
- Combined cardiovascular disease (combined coronary heart disease, stroke, treated angina without hospitalization, heart failure, and peripheral arterial disease).

Doxazosin arm stopped

In January 2000, at the recommendation of an independent safety review group, the doxazosin arm of the trial was stopped. While there was no significant difference in the primary outcome, the cumulative event rate for cardiovascular disease was 25% higher in the doxazosin group than in the chlorthalidone group ($P < .001$), and the risk of heart failure was more than twice as high in the doxazosin group than in the chlorthalidone group (relative risk 2.04; $P < .001$).

The ALLHAT doxazosin arm was stopped due to a higher incidence of heart failure

These findings were reported with the recommendation that alpha-blockers not be used as first-line therapy in hypertension.[3,4] It was pointed out that this assessment related only to alpha-blockers used as monotherapy; ALLHAT did not examine the use of an alpha-blocker as an add-on drug for treating hypertension.

Trial continued with lisinopril, amlodipine, chlorthalidone

ALLHAT continued to its conclusion for patients randomized to receive lisinopril, amlodipine, or chlorthalidone. A total of 33,357 participants were followed to the completion of the trial. The mean follow-up was 4.9 years.

At 5 years, 80.5% of the patients in the chlorthalidone group were still taking chlorthalidone or another diuretic, and 80.4% of those in the amlodipine group were still taking amlodipine or another calcium antagonist. Fewer patients in the lisinopril group (72.6%) were still taking lisinopril or another ACE inhibitor.

The percentage of patients in each group receiving the randomly allocated therapy as a single drug (monotherapy) is not available at this time, but will be addressed in a subsequent report. Approximately 40% of patients in all three treatment groups were receiving two or three antihypertensive drugs by the end of the trial.

ALLHAT results: Chlorthalidone group did well

Blood pressure. At 5 years, the mean systolic blood pressure was about 1 mm Hg higher in the amlodipine group than in the chlorthalidone group, and about 2 mm Hg higher in the lisinopril group than in the chlorthalidone group; the differences were statistically significant. The mean diastolic blood pressure was about 1 mm Hg lower in the amlodipine group than in the chlorthalidone group, but it was the same in the lisinopril and chlorthalidone groups.

Also at 5 years, 68.2% of patients in the chlorthalidone group were at their goal blood pressure, vs 66.3% in the amlodipine group ($P = .09$) and 61.2% in the lisinopril group ($P < .001$).

Biochemical data. Chlorthalidone had expected effects on laboratory values, and given the large sample size, almost all biochemical differences between treatment groups at 4 years were statistically significant. For example:

- The mean total cholesterol level was 1 to 2 mg/dL higher with chlorthalidone than with amlodipine or lisinopril.
- The mean serum potassium level was 0.3 to 0.4 mmol/L lower in the chlorthalidone group than in the other two treatment groups. Hypokalemia (a serum potassium level < 3.5 mmol/L) occurred in 8.5% of the chlorthalidone group, vs 1.9% of the amlodipine group and 0.8% of the lisinopril group.
- The mean fasting glucose level was 3 mg/dL higher in the chlorthalidone group than in the amlodipine group and 5 mg/dL higher than in the lisinopril group. Among nondiabetic participants, the incidence of fasting glucose levels higher than 126 mg/dL was higher with chlorthalidone than with amlodipine or lisinopril.
- The estimated glomerular filtration rate had decreased more at 4 years in the

chlorthalidone and lisinopril groups than in the amlodipine group.

Clinical outcomes. These metabolic differences did not translate into more adverse cardiovascular events or into a higher all-cause mortality rate with chlorthalidone. Findings:

- Chlorthalidone did not differ from amlodipine in overall cardiovascular event prevention, but was superior to amlodipine in preventing heart failure.
- Chlorthalidone was superior to lisinopril in preventing cardiovascular events, principally stroke, heart failure, angina, and coronary revascularization.
- Chlorthalidone was superior to doxazosin in preventing cardiovascular events, particularly heart failure and other cardiovascular disease.
- There were no differences for other secondary outcomes including peripheral arterial disease, end-stage renal disease, cancer incidence and mortality, or all-cause mortality.
- Results were consistent for all outcomes regardless of age, gender, and diabetic status, except for stroke and cardiovascular disease, for which there was significant heterogeneity by race. Among black participants the stroke rate was 40% higher in the lisinopril group than in the chlorthalidone group, the rate of combined cardiovascular disease was 19% higher, and the rate of congestive heart failure was 40% higher.

ALLHAT conclusions: Diuretics preferred

The ALLHAT investigators concluded that because a thiazide-type diuretic was superior in preventing one or more major forms of cardiovascular disease and because these drugs cost less, they should be the drugs of choice for first-step antihypertensive drug therapy in most patients, ie, those without a contraindication to a diuretic.

Moreover, since many participants needed more than one drug to control their blood pressure, the investigators concluded that "it is reasonable to infer that a diuretic be included in all multidrug regimens."

(Hypertension guidelines also list compelling indications for use of other classes of agents; see below.)

ANBP2 TRIAL

In February 2003, the ANBP2 Study Group reported a comparison of outcomes with an ACE inhibitor vs a diuretic for hypertension in the elderly.[2]

ANBP2 was a prospective, randomized, open-label study with blinded assessment of end points. Patients were followed for a median of 4.1 years, and the total numbers of cardiovascular events in the two treatment groups were compared using multivariate proportional-hazards models. The study was conducted at 1,594 family practices throughout Australia.

Patients. ANBP2 enrolled 6,083 patients, age 65 to 84. Few had had previous cardiovascular events. To enter, they had to have a systolic blood pressure of at least 160 mm Hg, or at least 140 mm Hg if the diastolic blood pressure was at least 90 mm Hg.

Treatment. Patients were randomized to receive an ACE inhibitor or a diuretic as initial therapy. Enalapril (Vasotec, others) was recommended as the ACE inhibitor and hydrochlorothiazide (HydroDiuril, others) was recommended as the diuretic, but the choice within each class was left to the family practitioner.

The goal of treatment was to achieve and maintain blood pressures below 140/80 mm Hg, if tolerated.

ALLHAT results were consistent across all subgroups

ANBP2 results: ACE inhibitors better, but only in men

Blood pressure. By the end of the study, blood pressure had decreased to a similar extent in both groups, by 26/12 mm Hg. At 5 years, the mean blood pressure was 141/79 mm Hg in the ACE inhibitor group and 142/79 in the diuretic group.

By the end of the trial, 35% of patients in the ACE inhibitor group and 33% of the diuretic group needed two or more agents for blood pressure control.

Clinical outcomes. Patients treated with ACE inhibitors achieved better outcomes than those treated with diuretic agents, despite similar reductions in blood pressure. Findings:

- All cardiovascular events or deaths from any cause: 695 (56.1/1,000 patient-years) in

TABLE 1

ALLHAT vs ANBP2: Baseline characteristics

	ALLHAT	ANBP2
No. in the ACE inhibitor group	9,061	3,044
No. in the diuretic group	15,255	3,039
Women, %	47	51
Black, %	35	5
Mean age, years	66.9	71.9
Baseline blood pressure, mm Hg	146/84	168/91
Previously treated for hypertension, %	90	62
Body mass index, kg/m^2	30	27
Current smokers, %	22	7
Patients with diabetes, %	36	7

ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ANBP2 = Second Australian National Blood Pressure Study

DATA FROM THE ALLHAT OFFICERS AND COORDINATORS FOR THE ALLHAT COLLABORATIVE RESEARCH GROUP. MAJOR OUTCOMES IN HIGH-RISK HYPERTENSIVE PATIENTS RANDOMIZED TO ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR CALCIUM CHANNEL BLOCKER VS DIURETIC: THE ANTIHYPERTENSIVE AND LIPID-LOWERING TREATMENT TO PREVENT HEART ATTACK TRIAL (ALLHAT). JAMA 2002; 288:2981–2997; AND WING LM, REID CM, RYAN P, ET AL. A COMPARISON OF OUTCOMES WITH ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND DIURETICS FOR HYPERTENSION IN THE ELDERLY. N ENGL J MED 2003; 348:583–592.

the ACE inhibitor group vs 736 (59.8/1,000 patient-years) in the diuretic group; hazard ratio 0.89, 95% confidence interval 0.79–1.00, P = .05.

- First cardiovascular events or deaths from any cause: 490 in the ACE inhibitor group vs 529 in the diuretic group, hazard ratio 0.89, P = .06.

Of particular interest, however, was that the benefits of ACE inhibitor therapy in both of these composite end points were limited to men, in whom the hazard ratio was 0.83 (P = .02). In women, the hazard ratio was 1.00 (P= .98), ie, the treatments were equivalent.

ANBP2 conclusions

- Starting antihypertensive treatment with ACE inhibitors in older subjects appears to lead to better outcomes than treatment with diuretics, despite similar reductions of blood pressure.
- These benefits were only demonstrated among male participants in the study.

RESOLVING THE DIFFERENCES

The results of these two apparently well-designed trials are certainly at odds with one another. I believe, however, that the divergent results become explainable when we think about the differences between the two trials and compare the numbers more closely.

Differences between the studies

Three very obvious differences are the designs of the trials, the numbers of patients involved, and the characteristics of the patients.

Design: Double-blind vs open-label. ALLHAT was a randomized, double-blind, active-control clinical trial, whereas ANBP2 was a prospective, randomized, open-label design with a blinded end point. The open design of ANBP2 left it open to potential bias in reporting events on the part of site investigators or the treating physicians, especially for events that might have been expected to be less common in the ACE inhibitor treatment group, such as myocardial infarction or congestive heart failure. The primary end point in ANBP2 also included "soft" events such as transient ischemic attacks.

ALLHAT was bigger. Even counting only the patients in the ACE inhibitor and diuretic groups of ALLHAT, far more patients were available for comparison in ALLHAT than in ANBP2 (24,309 vs 6,083).

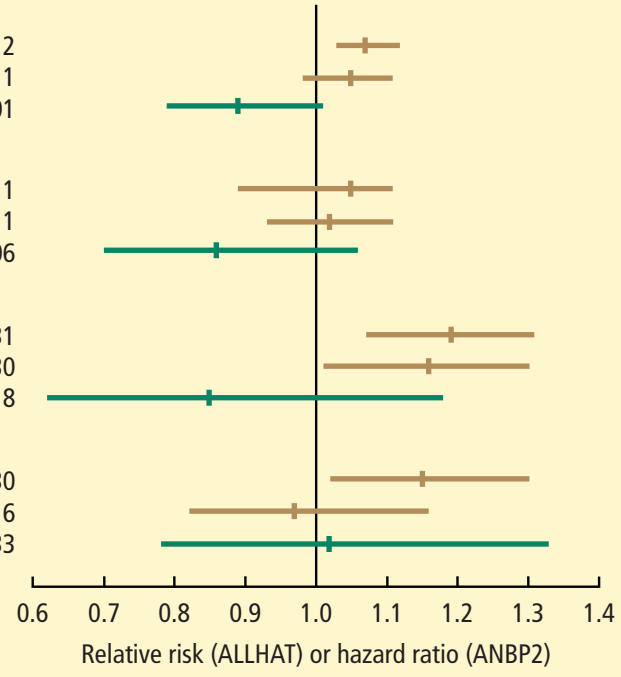
Far more events also occurred in ALLHAT than in ANBP2: cardiovascular disease 6,455 vs 823; coronary heart disease 3,956 vs 368; stroke 1,132 vs 219; and heart failure events 1,482 vs 147.

ANBP2 patients were older, but at lower risk. ALLHAT focused on hypertensive patients at increased cardiovascular risk, since the study required one or more additional risk factors for entry. In ANBP2, while the mean age at entry was higher, few patients had previous cardiovascular events, many fewer smoked, and the prevalence of diabetes mellitus was one fifth that in ALLHAT (TABLE 1). In ALLHAT, 35% were black vs 5% in ANBP2.

Other differences. In ALLHAT, treatment differences were consistent across gender subgroups, whereas in ANBP2, differences were noted only among men. In both trials, systolic blood pressure was slightly

ALLHAT and ANBP2 outcomes: Maybe not so different after all

OUTCOME	RR (ALLHAT) HR (ANBP2)	95% CI
First cardiovascular event and total mortality		
ALLHAT (total cohort)	1.07	1.03-1.12
ALLHAT (white, non-Hispanic)	1.05	0.98-1.11
ANBP2	0.89	0.79-1.01
First coronary heart disease event		
ALLHAT (total cohort)	1.05	0.89-1.11
ALLHAT (white, non-Hispanic)	1.02	0.93-1.11
ANBP2	0.86	0.70-1.06
Heart failure		
ALLHAT (total cohort)	1.19	1.07-1.31
ALLHAT (white, non-Hispanic)	1.16	1.01-1.30
ANBP2	0.85	0.62-1.18
Stroke		
ALLHAT (total cohort)	1.15	1.02-1.30
ALLHAT (white, non-Hispanic)	1.97	0.82-1.16
ANBP2	1.02	0.78-1.33



ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ANBP2 = Second Australian National Blood Pressure Study, RR = relative risk, HR = hazard ratio, CI = 95% confidence interval

DATA COURTESY OF THE ALLHAT STUDY GROUP

FIGURE 1

lower with diuretic therapy than with ACE inhibitors.

Comparing the numbers

The ALLHAT study group recently reviewed these two trials and suggested that results can be fairly well reconciled by examining the 95% confidence intervals for the hazard ratios of selected end points in ANBP2 and the relative risks in ALLHAT (FIGURE 1).

(Hazard ratio is synonymous with relative risk—here, the incidence of an event in the ACE inhibitor group divided by the incidence in the diuretic group. However, in both ALLHAT and ANBP2, this simple quotient underwent further adjustment and may not have been calculated the same way. Strictly speaking, the numbers cannot be compared head-to-head; we do so here only to suggest as a hypothesis that the findings of the two studies are not incompatible.)

For example, for first coronary events, the upper limit of the confidence interval of 1.06 in ANBP2 is compatible with the ALLHAT relative risk of 1.05. Similarly, for stroke the upper limit of 1.33 in ANBP2 is compatible with ALLHAT's relative risk of 1.15, and the upper limit for heart failure of 1.18 in ANBP2 is comparable to ALLHAT's relative risk of 1.19. Also, the hazard ratios in ANBP2 cited here did not achieve statistical significance, since the 95% confidence intervals included 1.0.

These total comparisons are still limited by the large differences in the racial makeup of the patient populations. In an effort to better mirror the population in ANBP2, only

those ALLHAT patients who were white and non-Hispanic were also compared. Some 11,414 patients were available for this comparison. Again, the relative risks for this subgroup of the ALLHAT population compare reasonably well with the confidence intervals noted in ANBP2 (FIGURE 1).

A PERSONAL VIEW

Compared with ALLHAT, ANBP2 had one fourth the participants, five to 10 times fewer end points, and an open-label design. Despite these differences, the upper 95% confidence intervals of ANBP2 are compatible with ALLHAT's estimates of relative risk for coronary events, stroke, and heart failure. In ALLHAT, no ACE inhibitor advantage was observed for any outcomes in either white men or women, and heart failure outcomes were worse compared with the diuretic.

While the aggregate analysis will have to await those planned by the Blood Pressure Lowering Treatment Trialists collaboration, the totality of evidence from ALLHAT and other studies still seems to favor diuretics.

In my view, the data support the recommendation that many (but not necessarily most) new hypertensive patients should have therapy initiated with an oral diuretic. For those with new-onset, uncomplicated hypertension, initiation of treatment with an oral diuretic would appear to be most appropriate, and highly indicated in African Americans.

In type 2 diabetes or metabolic syndrome, an angiotensin antagonist may suppress proteinuria

Indications for specific classes of agents

Latest guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[5] emphasize indications for initial therapy with specific classes of agents.

Type 2 diabetes. We are dealing with an epidemic of type 2 diabetes and associated obesity in the United States, which may warrant alternate considerations for initial therapy. I would initiate therapy in a type 2 diabetic patient with new-onset hypertension and microalbuminuria with an angiotensin II antagonist, such as an ACE inhibitor or possibly an angiotensin receptor blocker, which conforms to JNC 7 recommendations for diabetic patients.

Metabolic syndrome. Similarly, the growing population of patients with early metabolic syndrome, manifested by hypertension, obesity, hyperlipidemia, and insulin resistance or frank diabetes, without other cardiovascular risk factors, may also warrant initial treatment with an angiotensin II antagonist.

In these populations, an angiotensin II antagonist will suppress urinary protein excretion, may delay the onset of diabetic nephropathy, and from preclinical observations, may also improve insulin sensitivity and prevent the new onset of type 2 diabetes mellitus. Diuretics, on the other hand, do not suppress urinary protein excretion and may enhance the new onset of type 2 diabetes mellitus.

Systolic hypertension. The calcium antagonist amlodipine received less attention in the ALLHAT study, but we have evidence that calcium antagonists are also very effective in both reducing blood pressure and reducing cardiovascular morbidity and mortality in middle-aged and older patients, particularly those with systolic hypertension.

Use a diuretic for add-on therapy

For patients who are started on an agent other than a diuretic, a diuretic remains the most appropriate add-on agent should monotherapy not be effective in achieving and maintaining goal blood pressure. Most hypertensive patients will not be controlled with monotherapy but will require two or more drugs in combination to achieve recommended blood pressure goals.

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