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THE ALLHAT TRIAL

Diuretics are still the preferred initial drugs for high blood pressure

ABSTRACT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared four antihypertensive agents in patients 55 years and older: chlorthalidone, doxazosin, amlodipine, and lisinopril. The doxazosin arm was terminated early because of an excess of congestive heart failure. Chlorthalidone was at least equivalent to amlodipine and lisinopril in all of the outcomes measured, and was better in some, notably heart failure.

KEY POINTS

Because of the superiority of thiazide-type diuretics in preventing one or more major cardiovascular events and their lower cost, a diuretic should be the initial antihypertensive agent.

Most patients ultimately need more than one drug in the regimen to control their blood pressure.

If a nondiuretic agent does not reduce a patient's blood pressure to below the goal of 140/90 mm Hg, a diuretic should be part of the antihypertensive regimen.

THIAZIDE-TYPE DIURETICS are still the preferred drugs for first-step antihypertensive therapy, since, compared with calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors, they are unsurpassed in lowering blood pressure, in reducing clinical events, and in tolerability, and they are less costly.

These are the conclusions of the massive Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).¹

Who would have believed it? The newer drugs were supposed to be better, for a variety of reasons.

The thiazide-type diuretics have metabolic side effects such as raising cholesterol and fasting glucose levels; in theory, this should make patients taking them more vulnerable to coronary artery disease.

ACE inhibitors have neurohormonal effects beyond lowering blood pressure and are of proven clinical benefit in patients with heart failure and after a myocardial infarction. In theory, these drugs should be more effective in preventing these conditions. They also slow the progression of diabetic kidney disease.

Calcium channel blockers were supposed to be better because they do not affect cholesterol or blood sugar levels and they lower blood pressure by vasodilation.

But there's nothing like a clear clinical fact to demolish an elegant theory.

ALLHAT STUDY DESIGN

ALLHAT, launched by the National Heart, Lung, and Blood Institute in 1994, compared four antihypertensive agents in a randomized, double-blind protocol²:

Do you have more questions about the ALLHAT trial?
E-mail them to us at ccjm@ccf.org

ALLHAT data: Chlorthalidone, amlodipine, and lisinopril are equivalent in preventing coronary heart disease

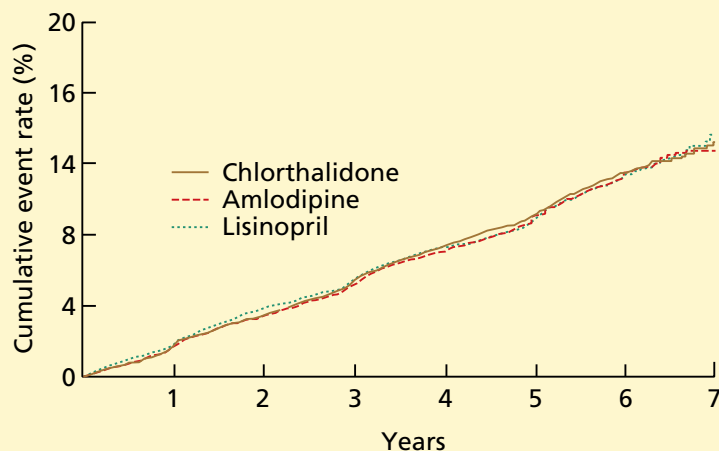


FIGURE 1. Cumulative event rates for the primary outcome (fatal coronary heart disease or nonfatal myocardial infarction) by treatment group.

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.

- **Chlorthalidone** (a thiazide-type diuretic sold as Hygroton, Thalitone, and generic preparations, 12.5 to 25 mg/day)
- **Doxazosin** (Cardura, an alpha-blocker, 2 to 8 mg/day). The doxazosin arm of the trial was stopped in 2000 owing to an excess in the 4-year rate of heart failure, 8.13% in the doxazosin group vs 4.45% in the chlorthalidone group.^{3,4}
- **Amlodipine** (Norvasc, a long-acting dihydropyridine calcium channel blocker, 2.5 to 10 mg/day).
- **Lisinopril** (Prinivil, Zestril, an ACE inhibitor, 10 to 40 mg/day).

ALLHAT did not include a beta-blocker arm, as this would have added another 10,000 patients to an already large and costly trial. Beta-blockers, like diuretics, are considered “traditional” antihypertensive agents and are of proven benefit.

If the study medication did not reduce the blood pressure to below the goal of 140/90 mm

Hg, the dose was titrated upward; if this did not achieve the goal then a second-step drug (atenolol, clonidine, or reserpine) was added. A third-step agent, hydralazine, was also available.

About one fourth of the patients also participated in a trial of pravastatin (Pravachol) compared with usual care for elevated low-density lipoprotein (LDL) levels.⁵

Patients

The study included 33,357 patients (42,418 counting the discontinued doxazosin arm), all of whom were at least 55 years old (mean age 67) and had stage 1 or stage 2 hypertension (mean baseline blood pressure 146/84 mm Hg) plus at least one other risk factor, ie:

- Cigarette smoking: 22%
- Atherosclerotic cardiovascular disease: 52%
- Type 2 diabetes: 36%
- High-density lipoprotein cholesterol levels lower than 35 mg/dL: 12%
- Left ventricular hypertrophy detected by electrocardiography: 16%
- Left ventricular hypertrophy detected by echocardiography: 5% (echocardiography was not a required screening procedure).

This was not a study of middle-aged white men only: 47% of the patients were women, 35% were black, and 19% were Hispanic. They tended to be overweight bordering on obese, with a mean body mass index of nearly 30, and 36% were diabetic. Ninety percent were already taking antihypertensive drugs at baseline.

Results

After a mean follow-up of 4.9 years, neither the primary clinical outcome (fatal coronary heart disease or nonfatal myocardial infarction; **FIGURE 1**) nor the secondary outcomes of all-cause mortality, combined coronary heart disease, peripheral arterial disease, cancer, or end-stage renal disease had occurred more often in the chlorthalidone group than in the amlodipine or lisinopril groups.

Surprisingly, event rates were significantly lower in the chlorthalidone group than in one or both of the other groups for some of the other secondary outcomes (**TABLE 1**), ie:

- Stroke: 5.6% with chlorthalidone (6-year



rate) vs 6.3% with lisinopril ($P = .02$). The drugs were equivalent, however, in nonblack patients and nearly equivalent in diabetic patients.

- Combined cardiovascular disease (the combination of coronary heart disease death, nonfatal myocardial infarction, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease): 30.9% with chlorthalidone vs 33.3% with lisinopril ($P < .001$). The trend was greater in older patients and black patients than in younger patients and nonblack patients.
- Heart failure: 7.7% with chlorthalidone vs 10.2% with amlodipine ($P < .001$) and 8.7% with lisinopril ($P < .001$). The differences were significant for all subgroups.
- Hospitalization for heart failure or fatal heart failure: 6.5% with chlorthalidone vs 8.4% with amlodipine ($P < .001$).
- Angina: 12.1% with chlorthalidone vs 13.6% with lisinopril ($P = .01$).
- Coronary revascularizations: 9.2% with chlorthalidone vs 10.2% with lisinopril ($P = .05$).

All three drugs lowered blood pressure

All three drugs lowered blood pressure well, although systolic pressures were 1 to 2 mm Hg lower in the chlorthalidone group than in the other groups for most of the study. At 5 years, the mean blood pressure was 134/75 mm Hg in the chlorthalidone group, 135/75 in the amlodipine group, and 136/75 in the lisinopril group.

Also at 5 years, the percentage of patients who had achieved the goal blood pressure of less than 140/90 mm Hg was 68.2% in the chlorthalidone group, 66.3% in the amlodipine group, and 61.2% in the lisinopril group.

Adherence was good

All three regimens were well tolerated. At 5 years, the percentage of patients who were still receiving the study drug or another drug of the same class was:

- 80.5% in the chlorthalidone group (another 13.2% were taking a diuretic with a calcium channel blocker or an ACE inhibitor)
- 80.4% in the amlodipine group (another 16.6% were taking a calcium channel blocker with a diuretic)

TABLE 1

ALLHAT data: Chlorthalidone is at least as good as amlodipine or lisinopril

OUTCOME	6-YEAR INCIDENCE (%)		
	CHLORTHALIDONE	AMLODIPINE	LISINAPRIL
Primary outcome			
Coronary heart disease*	11.5	11.3	11.4
Secondary outcomes			
All-cause mortality	17.3	16.8	17.2
Combined coronary heart disease†	19.9	19.9	20.8
Stroke	5.6	5.4	6.3‡
Combined cardiovascular disease§	30.9	32.0	33.3‡
End-stage renal disease	1.8	2.1	2.0
Cancer	9.7	10.0	9.9
Heart failure	7.7	10.2‡	8.7‡
Angina	12.1	12.6	13.6‡
Coronary revascularization	9.2	10.0	10.2‡

*Fatal coronary heart disease or nonfatal myocardial infarction

†Coronary heart disease death, nonfatal myocardial infarction, coronary revascularization, and hospitalized angina

‡ $P \leq .05$

§Coronary heart disease death, nonfatal myocardial infarction, stroke, coronary revascularization, angina, heart failure, and peripheral arterial disease

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- 72.6% in the lisinopril group (another 15.7% were taking an ACE inhibitor with a diuretic).

Most patients needed more than one drug to control their blood pressure. At 5 years, the mean number of medications per patient was 1.8 in the chlorthalidone group, 1.9 in the amlodipine group, and 2.0 in the lisinopril group. Those requiring a step 2 or step 3 drug at 5 years were 40% with chlorthalidone, 39.5% with amlodipine, and 43% with lisinopril.

Higher cholesterol, lower potassium, more diabetes with chlorthalidone

As expected, patients in the chlorthalidone group developed higher cholesterol levels, lower serum potassium levels, and higher fasting blood glucose levels than those in the other groups.

The mean cholesterol level was 216 mg/dL at baseline, falling at 4 years to 197 mg/dL in the chlorthalidone group, to 196 mg/dL in the amlodipine group ($P = .009$ vs chlorthalidone), and to 195 mg/dL in the lisinopril group ($P < .001$ vs chlorthalidone).

Also at 4 years, 8.5% of the patients in the chlorthalidone group had developed hypokalemia (serum potassium < 3.5 mEq/L), compared with 1.9% in the amlodipine group ($P < .001$) and 0.8% in the lisinopril group ($P < .001$). Similarly, the incidence of new-onset diabetes (fasting blood glucose ≥ 126 mg/dL) was 11.6% in the chlorthalidone group, compared with 9.8% in the amlodipine group ($P = .04$) and 8.1% in the lisinopril group ($P < .001$).

Nevertheless, these biochemical changes did not translate into more cardiovascular events or deaths in the chlorthalidone group.

Results of the pravastatin substudy

In the pravastatin substudy, at 4.8 years total cholesterol levels were reduced by 17% in the pravastatin group vs 8% with usual care.⁵ However, the rates of all-cause mortality and coronary heart disease were similar for the two groups; the reason is that 32% of the usual-care patients with coronary heart disease and 29% of those without coronary heart disease were also taking lipid-lowering drugs by the end of the study.

■ PUBLIC HEALTH IMPACT

The initial choice of antihypertensive treatment has important consequences from the public health point of view. More than 40 million Americans have hypertension. If any class of drug is superior to another in preventing the consequences of hypertension, many people might benefit.

Moreover, the ALLHAT findings should aid patients who struggle to pay for prescription drugs: The 2002 *Drug Topics Red Book* indicates that generic chlorthalidone 25 mg costs \$15.95 for 100 tablets, compared with \$97.96 for Prinivil 10 mg, \$102.76 for Zestril 10 mg, and \$145.13 for Norvasc 5 mg. Using the cheaper drugs could save billions of dollars.

While these potential savings may be observed in patients whose blood pressure is controlled with monotherapy, potential sav-

ings will be less across the population since so many patients will require two or more drugs for control of blood pressure.

■ HOW WILL ALLHAT AFFECT RECOMMENDATIONS?

Clearly, the next report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII), expected in May 2003, will rely heavily on the results of the ALLHAT study.

The ALLHAT results provide compelling evidence that thiazide-type diuretics should be the initial drugs of choice for patients with hypertension. If implemented by practicing physicians, we should see an eventual shift in prescription patterns, which could result in very significant cost savings in medications.

This is not a new recommendation, since the last JNC report (JNC VI)⁶ also recommended that diuretics should be considered for initial therapy, with drugs of other classes added as necessary to achieve a goal blood pressure of 140/90 mm Hg or less.

We now have the weight of evidence-based data showing that the occurrence of coronary heart disease, death, and nonfatal myocardial infarction is identical with amlodipine, lisinopril, and chlorthalidone treatment, and that chlorthalidone proved superior for selected secondary cardiovascular outcomes.

If blood pressure is not controlled with an initial agent other than a diuretic, the addition of a diuretic is strongly recommended, as it was in the JNC VI report. JNC VII will certainly place even greater emphasis on the importance of treating blood pressures to recommended goals and on the fact that a majority of hypertensive patients will require two or more agents in combination to achieve those blood pressure goals.

Patients with comorbid conditions

Diabetes. For selected comorbidities such as type 1 diabetes mellitus with proteinuria or congestive heart failure, the JNC VI report recommended ACE inhibitors and lower goal blood pressures than for patients with uncomplicated hypertension. Most patients with

Biochemical changes did not translate into cardiovascular events or deaths with chlorthalidone



type 1 diabetes mellitus and nephropathy are receiving diuretics as part of their ongoing care.

The ALLHAT data do not clearly support a recommendation for the use of an ACE inhibitor as initial therapy in diabetic patients without renal disease. However, there are limited data from other clinical trials to support the use of an ACE inhibitor as initial therapy, particularly in patients with diabetes without nephropathy.

The use of chlorthalidone was associated with a higher incidence of new-onset diabetes during the trial. There is evidence from other clinical trials to suggest that an ACE inhibitor may delay the new onset of type 2 diabetes mellitus.^{7,8} Future clinical trials will be required to determine if delaying the new onset of diabetes mellitus in older patients will reduce mortality or diabetic vascular complications.

Given the rise in serum glucose and cholesterol with chlorthalidone, the current ALLHAT data do not clarify the role for early treatment with a diuretic in an important population subgroup, ie, patients with the metabolic syndrome (obesity, hypertension, dyslipidemia, and insulin resistance). It is hoped that later subgroup analysis of this important patient population will further clarify this issue.

It is encouraging to note that there were no differences in this study for the primary outcomes and most secondary outcomes, despite the presence of hypertension, a significant percentage of diabetic patients, an HDL cholesterol level less than 35 mg/dL in 11% to 12%, and a baseline body mass index of 29 to 30.

Heart failure and myocardial infarction. Virtually all patients with congestive heart failure are already receiving a thiazide diuretic as part of standard therapy by the time an ACE inhibitor is added. Beta-adrenergic blockers have now assumed a role in the long-term management of congestive heart failure when added to a standard regimen that includes both a diuretic and an ACE inhibitor.

Beta-blockers without intrinsic sympathomimetic activity (ie, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol,

timolol) are recommended for secondary cardioprotection following recovery from a myocardial infarction. They are also widely prescribed to patients with evidence of ischemic heart disease and following interventional therapy in patients with coronary disease. It is unlikely that JNC VII will recommend substituting a diuretic for a beta-blocker in these situations, but certainly the addition of a diuretic to a beta-blocker when blood pressure is not optimally controlled will be very appropriate.

While ALLHAT did not include a beta-blocker treatment arm, there are extensive clinical data on the use of diuretics and beta-blockers as first-line agents. A meta-analysis of these early trials suggested that benefits appear to be greater with diuretics than with beta-blockers.⁹

What about angiotensin-receptor blockers?

The ALLHAT study did not include a treatment group with an angiotensin-receptor blocker (ARB), as there was little clinical experience available with this class of agents when the ALLHAT study was started. Data do support therapy with an ARB in patients with type 2 diabetic nephropathy, in patients with heart failure, and in patients with high blood pressure and left ventricular hypertrophy, with or without diabetes.

For many patients, 140/90 is not low enough

Current recommendations call for a blood pressure target of 130/80 mm Hg or less, and preferably less than 125/75 mm Hg, in patients with diabetic or nondiabetic renal disease and proteinuria greater than 1 g/24 hours. A blood pressure target of 130/80 may also be preferred for patients with a prior history of a cardiovascular event, stroke or transient ischemic attacks, or other evidence of target organ damage, including microalbuminuria.

It is likely that JNC VII will continue to emphasize these lower blood pressure goals for selected comorbidities. In view of recent information, the goal blood pressure of less than 125/75 mm Hg, which is extremely difficult to achieve, may be tempered to a more realistic goal of 130/80 mm Hg.

Patients on nondiuretics for hypertension with comorbid conditions need not necessarily change

If the first drug does not control pressure, do not keep trying different single agents

If the first antihypertensive agent used fails to control blood pressure at the recommended goal of $\leq 140/90$ mm Hg or lower in patients with selected comorbidities, physicians must increase the dosage or add another drug from another class. Certainly, if the initial drug was not a diuretic, then a diuretic should be added as a step 2 agent.

This point must be emphasized, and physicians must be discouraged from sequentially trying single drugs from other classes at random in an attempt to achieve optimal control with a single drug. Most patients ultimately require more than one drug, and a diuretic should be part of nearly every multidrug regimen.

■ A PERSONAL VIEW

The large number of participants and the prolonged follow-up clearly make the ALLHAT trial extremely relevant to clinical practice.

The primary outcomes in the trial were fatal coronary heart disease or nonfatal myocardial infarction—all very hard end points. In contrast, many other clinical trials used surrogate outcomes to suggest broad conclusions and recommendations.

For patients with newly diagnosed, uncomplicated hypertension, I fully agree with the primary conclusion of the study recommending that thiazide-type diuretics should be the drugs of choice for initial therapy. Diuretics are of proven benefit in lowering blood pressure, and in this trial a diuretic proved at least as effective as a calcium antagonist or ACE inhibitor in lowering the incidence of combined fatal coronary heart disease or nonfatal myocardial infarction, and proved superior for selected secondary end points. They have a proven safety record, are well tolerated, and provide a cost-effective alternative for initiating therapy.

One might raise the question whether other thiazide diuretics are comparable to chlorthalidone. Early studies comparing chlorthalidone and hydrochlorothiazide did demonstrate comparable effects and in fact suggested that chlorthalidone 12.5 mg was comparable to 25 mg of hydrochlorothiazide and was very well tolerated in doses up to 25 mg daily.

While beta-blockers were included in many of the early diuretic-based trials, they were not compared in the ALLHAT study. In four previous randomized trials in which initial treatment with a diuretic was compared with a beta-blocker, cardiovascular disease outcomes were not different between the treatments. However, the trial with results most favorable to diuretics involved patients over the age of 60, similar to those who would be enrolled in ALLHAT.

For patients who cannot take a diuretic, initial therapy with other classes of agents would be quite appropriate. However, only a small group of patients should be unable to take a thiazide-type diuretic.

For patients whose blood pressures are not controlled on monotherapy with another agent, a diuretic should certainly be added to the regimen as a second-step agent. Diuretics, when added to an agent of any other class, including the calcium antagonists, confer an additive effect on lowering both systolic and diastolic blood pressure.

We already have multiple fixed combinations available with diuretics, which can serve to reduce the number of pills in the regimen and also offer a potential cost savings. In patients with stage 2 hypertension or higher, the clinician may wish to consider initiating therapy with one of these fixed combinations.

For patients whose blood pressures are well controlled on monotherapy with another agent, the decision to switch to a diuretic will be more difficult for many clinicians. For many years, we have discouraged physicians from altering effective therapy in their hypertensive patients, and most physicians who initiate therapy with an agent other than a diuretic have a reason for doing so, even if that reason is not supported by evidence-based guidelines.

Do black patients fare worse on ACE inhibitors?

Of particular interest is the apparent benefit of chlorthalidone over lisinopril for the prevention of stroke among black as opposed to non-black participants and the apparent benefit of chlorthalidone vs lisinopril among all subgroups for congestive heart failure.

A diuretic should be part of nearly every multidrug regimen



The mean systolic blood pressure was 2 mm Hg higher in the lisinopril group than in the chlorthalidone group, which was statistically significant because of the large number of participants in the study.

The black subgroup actually had a blood pressure 4 mm Hg higher in the lisinopril group, suggesting that a blood pressure difference could have played a significant role. Poorer blood pressure response with ACE inhibitors in black patients has also been evidenced in prior trials, as has been a lesser effect of ACE inhibitors in secondary prevention of heart failure in this population.

As noted earlier, the choice of initial agent may be more difficult in other selected subgroups such as patients with stage 1 hypertension and evidence of the metabolic syndrome or the new-onset diabetics with no evidence of nephropathy. Physicians have been increasingly encouraged to start ACE inhibitors early in these conditions despite the absence of hard data.

Do calcium antagonists preserve renal function?

The calcium antagonist amlodipine fared very well in comparison to the diuretic with the exception of a secondary end point, congestive heart failure, for which the diuretic was clearly superior.

Moreover, despite identical estimated glomerular filtration rates (GFR) at baseline, the amlodipine-treated patients had a signifi-

cantly higher estimated GFR than both chlorthalidone and lisinopril-treated patients at 4 years of follow-up.

This is contrary to data from the recently published African American Study in Kidney Disease (AASK),¹⁰ in which amlodipine-treated patients had a more rapid decline in renal function following an initial rise in GFR compared with patients receiving an ACE inhibitor.

These data might provide some reassurance to clinicians from the standpoint of using calcium antagonists in patients with hypertension and renal disease. Nevertheless, there were no substantial differences in the incidence of end-stage renal disease in ALLHAT, and further subgroup analysis is needed, particularly for the black subgroup in ALLHAT, compared with the patients in the AASK trial.

Does ALLHAT apply to younger patients, other subgroups?

The ALLHAT population represents a high-risk group of patients over age 55 and may not be generalizable to younger patients with uncomplicated hypertension.

There will undoubtedly be other examples of patients in whom the decision process will be clouded by issues of age, race, hypertension complications, or other comorbidities. Hopefully, further subgroup analysis of the extensive data base provided by the ALLHAT study will help to further clarify future recommendations.



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