CME CREDIT

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Alpha-blockers and congestive heart failure: Early termination of an arm of the ALLHAT trial

ABSTRACT

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a large, randomized double-blind study comparing four antihypertensive agents (chlorthalidone, doxazosin, amlodipine, and lisinopril) in hypertensive patients older than 55 years. The doxazosin arm was terminated early, when the trial's safety and monitoring board noted a twofold higher incidence of congestive heart failure in patients receiving doxazosin than in those receiving chlorthalidone (8.13% vs 4.45% at 4 years, $P < .001$).

ALPHA-ADRENERGIC BLOCKING AGENTS (alpha-blockers) will likely be removed from the list of first-line antihypertensive drugs, in light of surprising findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT): an incidence of congestive heart failure twice as high among patients receiving the alpha-blocker doxazosin (Cardura) than among those receiving the thiazide diuretic chlorthalidone (Thalitone, Hygroton, and generic preparations).[1]

Confronted with these findings, the Director of the National Heart, Lung, and Blood Institute (NHLBI) stopped the doxazosin arm of the study, although the other arms comparing chlorthalidone with the angiotensin-converting enzyme inhibitor lisinopril (Prinivil, Zestril) and the calcium antagonist amlodipine (Norvasc) will continue for 2 more years.

Although these findings seem to argue against the use of doxazosin as a first-line antihypertensive, they do not address the drug's appropriateness in combination therapy. Further, the study did not examine the use of doxazosin as an adjunct in treating elevated cholesterol or benign prostatic hyperplasia.

ALLHAT should serve as a reminder that we should not measure the effectiveness of antihypertensive drugs only by their effects on surrogate markers such as blood pressure or serum cholesterol levels. Moreover, to assess the effect of therapy on the "hard" end points that really matter—morbidity and mortality—we will need to continue to conduct large-scale, long-term trials.

Current guidelines will need to be changed

WHAT IS THE BEST FIRST-LINE ANTIHYPERTENSIVE AGENT?

Hypertension significantly increases the risk of cardiovascular morbidity and mortality. A series of classic randomized clinical trials, culminating approximately 10 years ago, proved that diuretics and beta-blockers lower this risk (although fewer trials were conducted with beta-blockers than with diuretics).

Since those trials, several new classes of agents—calcium antagonists, angiotensin-

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converting enzyme (ACE) inhibitors, alpha-blockers, and angiotensin II antagonists—were approved and became popular. A trial using "hard" clinical end points found a calcium antagonist to be superior to placebo,[2] and other trials suggested that the other classes were equivalent to diuretics or beta-blockers in efficacy.[3–5]

Are the newer agents truly as good as the older ones? Many experts believed they would be even better. After all, diuretics and beta-blockers without intrinsic sympathomimetic activity raise serum cholesterol levels, whereas the new drugs do not—and alpha-blockers actually lower cholesterol. Diuretics lower serum potassium and magnesium levels and increase blood glucose levels; the new drugs do not—and the alpha-blockers actually improve insulin sensitivity. Diuretics lower blood pressure by volume depletion (at least in the short term), whereas the new drugs work by vasodilation, which is more physiologically correct. Some of the new drugs (such as ACE inhibitors) also have more of an effect on left ventricular hypertrophy. Thus, many of the new classes of antihypertensive drugs appear to have mechanisms of action and beneficial effects apart from blood pressure-lowering that would make them better than the older agents.

But trials were needed to find out, and one such trial was ALLHAT, which began enrollment in February 1994. Follow-up will continue until March 2002.

ALLHAT STUDY DESIGN

Sponsored by the NHLBI, the ALLHAT study is a randomized, double-blind, active-controlled comparison of four antihypertensive agents[6]:

- Chlorthalidone (a diuretic; 12.5 to 25 mg/day)
- Doxazosin (an alpha-blocker; 2 to 8 mg/day)
- Amlodipine (a calcium antagonist; 2.5 to 10 mg/day)
- Lisinopril (an ACE inhibitor; 10 to 40 mg/day).

In addition, approximately one fourth of the ALLHAT patients are also participating in a randomized, open-label trial to determine whether lowering serum low-density lipoprotein cholesterol levels with an HMG-CoA reductase inhibitor (pravastatin) reduces all-cause mortality compared with a control group receiving usual care.

Patients

Patients are men and women age 55 and older with hypertension (systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg, or currently taking antihypertensive medication) plus at least one additional risk factor for coronary heart disease, including previous myocardial infarction or (MI) stroke, left ventricular hypertrophy by electrocardiogram or echocardiogram, type 2 diabetes mellitus, current cigarette smoking, or a low level of high-density lipoprotein cholesterol.

A total of 42,448 patients were recruited and randomized, 15,268 to receive chlorthalidone, 9,067 to receive doxazosin, and the rest to receive the other drugs.

The baseline characteristics in the chlorthalidone and doxazosin groups (which were well matched) were as follows:

- Mean age: 67 years
- Women: 47%
- Black: 35%
- Mean blood pressure: 145/83 mm Hg
- Being treated for hypertension: 90%
- Atherosclerotic vascular disease: 45%
- Type 2 diabetes: 36%
- Smokers: 22%
- Mean serum creatinine level: 1.0 mg/dL
- Mean serum cholesterol level: 216 mg/dL.

Outcomes measured

Predefined outcomes measured were the incidences of:

- Coronary heart disease (the primary outcome, including both coronary death and nonfatal MI)
- All-cause mortality
- Stroke
- "Combined coronary heart disease" (coronary death, nonfatal MI, revascularization procedure, and hospitalization for angina)
- "Combined cardiovascular disease" (coronary death, nonfatal MI, stroke, revascularization, angina, congestive heart failure, and peripheral arterial disease).

TABLE 1

4-Year outcomes from ALLHAT: Chlorthalidone vs doxazosin

OUTCOME	4-YEAR RATE (%)		RELATIVE RISK IN DOXAZOSIN GROUP	95% CONFIDENCE INTERVAL	*P* VALUE
	CHLORTHALIDONE GROUP (N=15,268)	DOXAZOSIN GROUP (N=9,067)			
Coronary heart disease*	6.30	6.26	1.03	0.90–1.17	.71
All-cause mortality	9.08	9.62	1.03	0.90–1.15	.56
Combined coronary heart disease†	11.97	13.06	1.10	1.00–1.12	.05
Stroke	3.61	4.23	1.19	1.01–1.40	.04
Combined cardiovascular disease‡	21.76	25.45	1.25	1.17–1.33	< .001
Congestive heart failure	4.45	8.13	2.04	1.79–2.32	<.001
Coronary revascularization	5.20	6.21	1.15	1.00–1.32	.05
Angina	10.19	11.54	1.16	1.05–1.27	<.001
Peripheral artery disease	2.87	2.89	1.07	0.88–1.30	.50

*Fatal coronary heart disease and nonfatal myocardial infarction
†Fatal coronary heart disease, nonfatal MI, revascularization procedure, and hospitalization for angina
‡Coronary heart disease death, nonfatal MI, stroke, coronary revascularization procedure, angina (treated in hospital or as outpatient) congestive heart failure (treated in hospital or as outpatient), and peripheral arterial disease (in-hospital or outpatient revascularization)

ADAPTED FROM THE ANTIHYPERTENSIVE AND LIPID-LOWERING TREATMENT TO PREVENT HEART ATTACK TRIAL (ALLHAT). MAJOR CARDIOVASCULAR EVENTS IN HYPERTENSIVE PATIENTS RANDOMIZED TO DOXAZOSIN VS CHLORTHALIDONE. JAMA 2000; 283:1967–1975.

ALLHAT STUDY RESULTS: DOXAZOSIN STUDY STOPPED

As in all major clinical trials, an advisory committee periodically reviews the safety of the ALLHAT. Following independent data reviews on January 6 and January 21, 2000, the director of the NHLBI accepted a recommendation to stop the doxazosin treatment arm. The median follow-up was 3.3 years at that point.

The finding that prompted this decision? Compared with patients in the chlorthalidone group, patients in the doxazosin group had:

- A 25% higher incidence of "combined cardiovascular disease" ($P < .001$)
- Twice the incidence of congestive heart failure ($P < .001$).

These higher incidences were approximately the same in all subgroups studied: patients both older and younger than 65 years, black and nonblack, men and women, Hispanic and non-Hispanic, and with or without diabetes mellitus.

On the other hand, there were essentially no differences in the rates of fatal coronary heart disease or nonfatal MI (the primary outcome) or all-cause mortality between the two treatment groups (TABLE 1),[1] and there were only small trends toward more events in the doxazosin group for the other outcomes.

Another reason for stopping the doxazosin arm of the study: At that point, about 61% of the coronary heart disease events that had been expected to occur in the chlorthalidone group had already occurred. The investigators calculated that there was only a 1% chance that doxazosin would eventually prove to be more beneficial than chlorthalidone by the end of the trial, based on the protocol-specified alternative hypothesis of a 16% reduction in coronary heart disease events.

TRIAL RAISES QUESTIONS

The ALLHAT findings raise a number of questions to which, at present, we have no answers.

Blood pressure lowering is only a surrogate endpoint

Do alpha-blockers cause heart failure, or just prevent it less?

Unfortunately, it is not possible to determine whether the incidence of congestive heart failure with doxazosin observed in ALLHAT is the same as, less than, or more than would be expected without antihypertensive treatment.

What caused the differences?

There are several theories but no definitive answer.

Doxazosin lowered systolic blood pressure less. At 1 year, the mean blood pressure was 140/79 mm Hg in the doxazosin group and 137/79 mm Hg in the chlorthalidone group. At 4 years, the numbers were 137/76 vs 135/76 mm Hg.

But could a difference of 2 to 3 mm Hg in systolic blood pressure explain the differences in end points? Several recent trials in older patients[2,5,7] suggest that 3 mm Hg could explain a 10% to 20% increase in congestive heart failure, but not the doubling of risk observed in ALLHAT. Similar calculations for stroke and angina from earlier trials[8,9] (using diuretics and beta-blockers) suggest that 3 mm Hg could explain most of the differences in stroke or angina events observed in ALLHAT.

The study did not address the use of doxazosin to treat BPH

Also of interest: more people stopped taking doxazosin than chlorthalidone. At 4 years, 86% of patients assigned to chlorthalidone were still taking a diuretic, while 75% of those assigned to doxazosin were still taking an alpha-blocker. With both drugs, symptomatic side effects were the number-one reason for stopping, followed by "unspecified refusal."

Alpha-blockers may affect left ventricular hypertrophy less. Left ventricular hypertrophy (LVH) is a common precursor of heart failure. As yet we have no data on the effect of the different agents on LVH in ALLHAT, but previous studies[10–12] suggested that alpha-blockers may affect LVH less than do diuretics.

Alpha-blockers may have adverse biochemical effects, increasing plasma volume[13] and possibly increasing plasma norepinephrine levels.[14] The significance of these effects is unknown.

RECOMMENDATIONS

On the basis of the ALLHAT observations, it would seem appropriate to recommend that doxazosin not be used as monotherapy in managing stage 1 or 2 hypertension (ie, 140–179/90–109 mm Hg).

This means changing the guidelines. For example, the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[15] recommends diuretics and beta-blockers for initial monotherapy of uncomplicated hypertension, but also recommends other classes of agents, including alpha-blockers, if there are specific indications for them—benign prostatic hyperplasia or dyslipidemia in the case of alpha-blockers. Treatment guidelines from several other countries include similar recommendations.

ALLHAT did not address the many patients who receive doxazosin as part of combination therapy for hypertension. It may be appropriate to continue using doxazosin for patients who are also receiving a diuretic and possibly other classes of antihypertensive agents concurrently. Patients who are taking an alpha-blocker as part of combination therapy may wish to discuss the issue of continuing this therapy with their physicians.

Similarly, this study did not address the use of doxazosin (or other alpha-blockers) as an adjunct to treat elevated cholesterol or benign prostatic hyperplasia in normotensive patients. Continued use of these agents in these conditions appears appropriate, except perhaps in the early stages of heart failure, ie, in patients with mildly or moderately decreased systolic function. Given that other classes of drugs are available to treat hypertension, elevated cholesterol, and benign prostatic hyperplasia, it may be reasonable to avoid alpha-blockers in this situation, although we have no data.

CONTINUED NEED FOR LARGE TRIALS

Antihypertensive agents are traditionally approved on the basis of how well they lower blood pressure. It is assumed that lowering blood pressure will reduce morbidity and mortality regardless of the agent used, and clinical

trials have supported this notion. As a consequence, blood pressure has long been used as a surrogate end point to predict the rate of cardiovascular outcomes such as MI, stroke, and all-cause mortality.

ALLHAT suggests some modification in this notion. Different antihypertensive agents can have different physiologic effects—which we may not even be aware of—that can add up to differences in morbidity and mortality. And the only way to find out about these effects is to conduct large studies to assess morbidity and mortality.

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