

Putting ALLHAT into Perspective

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Predictably, and with good reason, the outcomes of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (the ALLHAT study), reported in late 2002,¹ drew the interest of media journalists as well as the attention of the medical community and the health care industry. The nation's leading newspapers and television networks scrambled to provide coverage of the significant findings.

Although the abbreviated versions that made the headlines contained accurate information, the study outcomes and their implications were oversimplified and overinterpreted. Readers and viewers came away thinking that an inexpensive, 50-year-old drug, commonly known as a diuretic ("water pill"), worked for everyone as well as the newer, more expensive drugs for hypertension. Following this thread, some reporters and their interviewed subjects implicated the pharmaceutical industry as a villain for its role in developing and marketing the alternative drugs for the treatment of hypertension.

Now that experts in the field of hypertension have had time to evaluate the voluminous ALLHAT report, they have begun to question the strength of the study's design, the accuracy of the conclusions, and the flamboyant character of the researchers' announcement to the press.²⁻⁴ Adding to the confusion, a similar, large-population study reported contradictory findings⁵ in February 2003, casting doubt on the validity of claims made by the ALLHAT researchers.

This article does not seek to diminish the relevance or importance of ALLHAT but attempts to approach the findings in the context of the entire body of relevant hypertension research, current clinical practice, and existing national guidelines. The reality is that diuretics already top the list of recommended first-line pharmaceutical treatments for hypertension; for most patients, however, diuretics alone are ineffective in lowering and maintaining acceptable blood pressure levels over time. It often becomes necessary to add another type of antihypertensive drug or, in some cases, to switch to a different class of drug.

WHAT IS ALLHAT?

Initiated in 1994, ALLHAT was one of the first major comparative studies to include clinical outcomes.⁶ The following features were considered to be its strengths:

- sponsorship by the National Heart, Lung, and Blood Institute
- its broad scope (in comparing one drug from each of four major antihypertensive drug classes)

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- the selection of a low-dose diuretic as standard, or control, treatment
- its double-blind design, large sample size, and sufficient duration (more than 40,000 high-risk hypertensive patients were to be treated for four to eight years)
- the selection of trial outcomes (all major vascular complications of hypertension)⁷

ALLHAT sought to learn whether differences existed among the available antihypertensive agents in reducing the risk of cardiovascular disease. The study compared the effectiveness of a single, low-dose diuretic (*chlorthalidone*) with that of one drug from each of three newer drug classes: angiotensin-converting enzyme (ACE)-inhibitors, alpha blockers, and calcium-channel blockers.

WILL ALLHAT CHANGE THE TREATMENT OF HYPERTENSION?

The ALLHAT study validated current national hypertension treatment guidelines by demonstrating that using chlorthalidone as the initial treatment was as effective as using a drug from one of the alternative classes of antihypertensive agents known as ACE-inhibitors (*lisinopril*) and a calcium-channel blocker (*amlodipine*) in decreasing blood pressure and reducing the incidence of fatal coronary heart disease or non-fatal myocardial infarction (MI) and all-cause mortality. The study did not conclude that other classes of antihypertensive drugs are ineffective or unnecessary for treatment.

Some differences were observed; for instance, patients assigned to the diuretic group experienced a lower incidence of heart failure and stroke than patients assigned to the other groups. However, a cause-and-effect relationship cannot be firmly established without further study to account for the effects of variables such as the other drugs used in combination with the diuretic.

Physician guidelines for treating hypertension and reducing its complications have existed since the early 1900s; until recently, however, these recommendations were based solely on observations and expert opinions. The first validation by a controlled clinical trial did not occur until the late 1960s.⁸ Since then, the health care industry has increased its emphasis on research evidence as the basis for treatment decision guidelines. The National Institutes of Health (NIH) Guidelines (*JNC 7*)⁹ recommend diuretics, alone or in combination with other antihypertensive agents, for the initial pharmaceutical treatment of hypertension in the absence of "compelling reasons to the contrary."¹⁰

Many observational studies and clinical trials have shown that patients tolerate diuretics and beta blockers. These are the least costly antihypertensive medications and are as effective

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as the newer drugs in reducing morbidity and mortality.¹¹ The current guidelines also emphasize the value of combination therapy. The rationale is that most patients will require more than one agent to bring blood pressure to recommended goals (*JNC 7*).⁹

The NIH recommendations for treating hypertension define circumstances and indications for which the evidence favors certain classes of antihypertensive agents:

- beta blockers after a heart attack
- ACE-inhibitors for patients with heart failure and/or patients who have poor kidney function caused by diabetes
- calcium-channel blockers for patients prone to angina pain, bronchial spasms, or some types of irregular heartbeat⁹

As a class, calcium-channel blockers have had better patient acceptance because of their once-daily dosing, the absence of drowsiness or impotence (common with other antihypertensive medications, including diuretics), and a decrease in the frequency of office visits for monitoring. In addition to their effectiveness in lowering blood pressure, these drugs do not interact with other commonly prescribed medications for hypertension and do not cause metabolic changes requiring blood tests.¹²

The ALLHAT patients who received alpha blockers showed a highly significant (25%) excess risk of major cardiovascular events, causing researchers to terminate that part of the study early.¹ In light of this outcome, revised guidelines will probably recommend alpha blockers only if other agents (i.e., low-dose diuretics, beta blockers, and ACE-inhibitors) are ineffective in lowering blood pressure.

The ALLHAT data confirmed a tenet fostered by the current national hypertension guidelines: *most patients require a combination of drugs for adequate control of hypertension*. In fact, the researchers built step-up drug therapy into the study's protocol by permitting the addition of non-study classes of antihypertensive agents if the study drug alone was ineffective. ALLHAT statistics reported for the diuretic group, the ACE-inhibitor group, and the calcium-channel blocker group indicate that, of the patients remaining in the study by the end of the fifth year, 8.6% had been switched to a study drug other than the one initially assigned, and more than 70% of those still taking the initially assigned study drug were taking more than one drug to control their hypertension (Table 1).

At the end of five years, the mean number of drugs per patient across the three groups was 1.9 per patient. Given the variability resulting from the combined effects of added drugs, and given the high attrition rate among participants (only 59% of the original total remained in the study at the end of the fifth year), experts will probably remain cautious in making generalizations or in changing recommendations based solely on these findings.

WHAT DOES ALLHAT MEAN FOR PEOPLE WITH HYPERTENSION?

Hypertension is a complex disease with several root causes, an array of major risk factors, and a variety of complications, the most serious of which are organ (e.g., kidney, heart) damage, central nervous system injury, and heart disease. It is

important to understand that studies look at population averages and not at individual patients. When prescribing drugs for hypertension, physicians must consider each patient's unique medical history—metabolic state (evidence of diabetes or gout), kidney function, any heart muscle damage, and heart efficiency (cardiac output)—because each factor affects the choice of the initial and any subsequent therapy.

Perhaps the most unfortunate consequence of the publicity surrounding the announcement of the ALLHAT study is that it created undue public concern about antihypertensive drugs, when the real danger is that hypertension remains untreated or uncontrolled in near-epidemic numbers of Americans. The potential benefit to be gained from a subtle shift in treatment recommendations is relatively small, when compared with costs associated with the *underuse of all antihypertensive drugs nationwide*.

In 2002, the National Committee on Quality Assurance reported that of the more than 18 million workers with known and unknown hypertension in the U.S., "78 percent are not reaching established goals of adequate blood pressure control and therefore are at risk of a serious cardiovascular event."¹³

WHY CAN'T EVERYONE JUST TAKE A DIURETIC?

Metabolic Effects

Chlorthalidone represents one of three different types of diuretics. Each type works in a slightly different way, but all diuretics lower the amount of salt and water in the body, thereby helping to reduce blood pressure. Diuretic treatments are not benign, and not every patient can tolerate them. As a class of drugs, diuretics have been shown to contribute to heart enlargement, increase the risk of type-2 diabetes, and worsen blood lipid (cholesterol) profiles.

In ridding the body of excess water through increased urinary excretion, diuretics can also deplete the body of some essential elements and cause imbalances in metabolism. They cause patients to excrete excessive amounts of potassium and bicarbonate, necessitating supplements to replace these essential elements. Conversely, they may cause excessive retention of calcium and uric acid, which can lead to gout. Patients taking diuretics require careful monitoring by physicians, along with the possible addition of drugs (e.g., potassium supplements and gout medications), and frequent blood tests to assess glucose tolerance and lipid profiles.

Variations in Effectiveness

Diuretics and the other classes of antihypertensive drugs vary in their efficacy, particularly among African-Americans, older adults, and diabetic patients.

African-Americans

Hypertension is more prevalent and is associated with worse outcomes in African-Americans patients.¹⁴ Although these patients respond well to diuretics, most require two or more antihypertension drugs to control their blood pressure by current standards.^{8,14,15} Longer-acting calcium-channel blockers are effective in reducing stroke and coronary artery disease in this population, and calcium-channel antagonists and ACE-inhibitors are effective in slowing the chronic progression of kidney disease in African-Americans with type-2 diabetic kidney disease.¹⁶

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Table 1 Changes in ALLHAT Group Participation and Medication Use over Five Years*

Measure	Medication		
	Diuretic	ACE-Inhibitor	Calcium-Channel Blocker
No. patients originally assigned to group	15,255	9,048	9,054
No. patients still in group at end of year five†	6,210	3,769	3,605
• No. patients still receiving study drug	4,623	2,826	2,307
• No. patients receiving study drug plus additional antihypertensive drugs	2,962	1,862	2,100
• No. patients switched to a different drug	583	270	320
Mean No. of antihypertensive drugs patients were receiving at end of year five	1.8	1.9	2.0

* For ALLHAT study outcomes, see *JAMA* 2002;288:2981–2997.¹
† By the end of year five, 41% of all patients originally assigned to one of the groups stopped their participation.
ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

Angiotensin-receptor blockers (ARBs) have been effective in type-2 diabetes for renoprotection. In its recent consensus statement, the International Society on Hypertension in Blacks (ISHIB) recommended initiating treatment with two drugs from different classes if blood pressure readings exceeded targets for control.¹⁴ The ISHIB considers ACE-inhibitors, calcium-channel blockers, and diuretics—as well as other classes of antihypertensive agents—to be appropriate in combination for treatment but suggests that diuretics coupled with calcium channel-blockers may be the most effective in this population.¹⁴

Older Patients (Aged 60 to 79)

Individual physical and medical differences increase as people age, making multiple treatment options necessary for safe and effective therapy. In addition to variations in action and side-effect patterns, different classes of medications—and different options within the same class—offer elderly patients choices among dosage forms and duration.

In the Systolic Hypertension in the Elderly Program (SHEP) trials, which used primarily diuretics and beta blockers, drug therapy decreased stroke risk by an average of 32% and cardiac events by 14%.¹⁷ More recently, a large-scale, prospective, randomized study has shown ACE-inhibitors to be superior to diuretics for treating hypertension and avoiding adverse events, such as heart disease and stroke, in older men.⁵ More trial results, including those from large numbers of subjects aged 80 and older, should become available in the next few years.

Patients with Diabetes

The incidence of type-2 diabetes, a chronic condition with life-threatening complications, increases with age, and aging populations are at risk for type-2 diabetes as well as hypertension. Because diuretics adversely affect glucose (sugar) tolerance and plasma lipids (cholesterol), other antihypertensive agents are recommended for the initial and ongoing hypertension treatment in patients with risk factors for diabetes. ACE-inhibitors are particularly valued for treating hypertension in patients with one of the complications of diabetes—diabetic renal disease.⁹

DO DRUG COMPANIES CREATE PROBLEMS OR FIND SOLUTIONS?

Which came first, the chicken or the egg? If diuretics had been a panacea for curing hypertension, it is unlikely that drug companies would have taken on the financial risk of developing alternative classes of antihypertensive drugs. As previously discussed, diuretics alone are often inadequate for controlling hypertension and are contraindicated for, or are not well tolerated by, some patients with certain conditions. Developing alternative classes of drugs to attack hypertension by different biochemical means was, and remains, a reasonable solution to a complex problem.

In covering the ALLHAT outcomes, the media made generalizations based on reported price differentials among the specific study drugs and concluded that diuretics as a class of drugs were considerably less expensive than the other classes. In reality, the price differential is not very great. There are less expensive ACE-inhibitors and calcium-channel blockers than those chosen for the study.¹⁴

People interpret data in various ways. Since the publication of the ALLHAT outcomes, some journalists have used national prescription-utilization data to show a *decrease in diuretic prescriptions as a percentage of total prescriptions* for hypertension. They characterize this as a negative trend, and they blame drug companies.^{18,19} Examining the same national prescription data for the same two-decade time period, we can see that the *number of diuretic prescriptions increased by 10 million* (from 109 million to 119 million). Actually, both of these observations would be expected, given that most patients require more than one drug class for optimal blood pressure control.

Much of the research on new drugs is done under the auspices, and at the expense of, drug companies. This research consists of clinical trials that compare each new drug with a placebo to test the effectiveness of the drug, to ensure its safety, and to secure approval of the Food and Drug Administration (FDA). Industry and health policy leaders agree that it is unreasonable to expect pharmaceutical companies to conduct large-scale, high-cost drug comparison trials such as ALLHAT. This is not to say that the government should bear the entire burden; in fact, several pharmaceutical manufacturers made substantial financial contributions toward the NIH's \$125

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million budget for ALLHAT. It has been reported that Pfizer contributed a total of \$50 million and that AstaZeneca and Bristol-Myers Squibb joined Pfizer in contributing drugs for the study.²⁰

WHICH QUESTIONS REMAIN UNANSWERED?

As with all research, regardless of the scope or size, ALLHAT doesn't just *answer* questions; it *raises more* questions. For example, patients receiving chlorthalidone had fewer strokes than patients receiving one of the two other drugs, but what are the implications for diuretics as a class of drugs? Would a different diuretic drug perform as well or better? Similarly, there are ACE-inhibitors that provide better blood pressure control over the duration of each dose than lisinopril, the study drug. Would an ACE-inhibitor with better 24-hour control have shown better results?

Answers to these and other questions are beginning to appear in the literature. In another recent study, researchers compared a different ACE-inhibitor with hydrochlorothiazide, a diuretic commonly prescribed by American physicians. They concluded that antihypertension treatment consisting of ACE-inhibitors in older patients, particularly in men, seemed to produce better primary and secondary outcomes than diuretic treatment, despite similar reductions in blood pressure.⁵ These findings appear to contradict those of the ALLHAT reports.

SUMMARY

Although diet and other lifestyle modifications remain the frontline methods of attack on hypertension, the ALLHAT study reinforces current medical practice and national guidelines that recommend diuretics as a first-line drug in hypertension therapy. In all likelihood, national guidelines will continue to recommend, and physicians will continue to prescribe, diuretics (alone or in combination with another antihypertensive agent) as initial therapy because of their proven benefits; however, treatment must always be tailored to each patient's unique physiology, metabolism, and temperament. Not everyone with hypertension responds effectively to diuretics; indeed, earlier and subsequent studies have shown that most patients need a combination of drugs to maintain an acceptable blood pressure.

The message to the public should be as follows:

- If you are told that you have hypertension, ask your doctor about starting out with a diuretic. Especially in the initial stages of the condition, this drug may be effective in lowering your blood pressure to a safe level without significant side effects.
- Because hypertension is complex, your physician should monitor your condition closely. At any time during the course of the disease, it may become necessary to switch to another medication or to add a drug to your treatment to maintain control of your blood pressure.
- If you are already taking one or more medications to control blood pressure, keep taking them as prescribed, and ask your doctor about the potential benefits of changing medications.

We in the medical community and the health care industry hail ALLHAT for its significant contribution to the literature

and to our understanding of the effectiveness of specific drugs in treating hypertension and in reducing the risks for primary and secondary adverse outcomes, but we caution against overinterpreting the findings and generalizing about treatments that must remain individualized.

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