

## ALLHAT: Setting the Record Straight

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The findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have generated worldwide reaction from clinicians and researchers, including a recent commentary in this journal. Such response was expected for a trial of ALLHAT's size and scope, especially since its results challenged some widely held beliefs. This paper reviews key aspects of the ALLHAT design, analyses, findings, and conclusions to provide a perspective on the commentary about the trial's results and implications for clinical practice. Several of the most frequent comments regarding the study's results are addressed,

particularly with respect to heart failure and diabetes outcomes. Responses to these comments reinforce the investigators' original conclusion that thiazide-type diuretics should remain the preferred first-step drug class for treating hypertension and should generally be a part of any multidrug regimen.

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The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, multicenter clinical trial, was designed to determine whether the incidence of coronary heart disease (CHD) is reduced in high-risk patients with hypertension by a calcium-channel blocker (represented by amlodipine), an angiotensin-converting enzyme (ACE) inhibitor (represented by lisinopril), or an  $\alpha$ -blocker (represented by doxazosin), each compared with diuretic treatment (represented by chlorthalidone) (1). The overall findings of the trial, summarized in Table 1, showed that CHD risk was not improved for any of the 3 newer agents compared with chlorthalidone (2, 3) and that total mortality was similar for the 4 groups. However, diuretic-based therapy was superior to  $\alpha$ -blocker-based, ACE inhibitor-based, and calcium-channel blocker-based therapy in preventing 1 or more major forms of cardiovascular disease (CVD), including stroke and heart failure. Results were consistent for all outcomes by age, sex, diabetic status, and ethnicity, except for stroke and combined CVD. For these end points, we found significant heterogeneity in the lisinopril-chlorthalidone comparison by ethnicity: Black persons assigned to chlorthalidone had a greater reduction in risk for stroke and CVD, in keeping with larger blood pressure differences. On the basis of these findings, the ALLHAT investigators recommended that diuretics should be the drug of choice for initial hypertension therapy and, since most hypertensive patients require more than 1 drug, that diuretics should generally be part of any antihypertensive regimen.

Since the publication of the ALLHAT findings, there has been considerable reaction (favorable and unfavorable) from around the world, including a recent commentary in this journal (4-12). Such response was expected for a trial of ALLHAT's size and scope, especially since its results challenged some widely held beliefs. A review of certain aspects of the ALLHAT design, analyses, findings, and conclusions is warranted to provide a perspective on the trial's results and implications for clinical practice in the context of the commentaries. This article addresses several

of the most frequent comments regarding the ALLHAT results (Table 2).

### ISSUES REGARDING STUDY DESIGN

The hypertension community has been aware of ALLHAT for more than a decade. The concept was first presented to the National Heart, Lung, and Blood Institute Advisory Council in 1991. In 1993, the Institute's director approved the study protocol on the basis of recommendations from an external Protocol Review Committee. The design paper was published in 1996, and many presentations were subsequently given on the design of the trial (1, 13). Very few critical questions were raised before the results were reported (14).

#### Testing First-Step Therapy

ALLHAT was designed to address the issue of which class of drugs should be used for initial therapy for hypertension. An ideal trial would include all hypertensive patients, both low and high risk, and both untreated and treated patients (after an appropriate washout period). However, such a trial would have required even more patients, would have been more complex, and would have been unaffordable. ALLHAT was planned as a practice-based trial to mirror community treatment of hypertension, obtain sufficient patients, and capture the diversity of hypertensive patients (by age, sex, ethnicity, and diabetic status). It was conducted in high-risk patients to ensure that enough outcome events would occur over the course of the study to detect important treatment differences, if they existed. There was no washout period (except for selected drugs such as  $\beta$ -blockers) because many patients were taking multiple drugs and this would have complicated the conduct of what was intended to be a large, simple trial. However, the trial's findings (like many others) can and should be extrapolated beyond the exact sample in which it was conducted.

**Table 1. Major Findings and Limitations of ALLHAT\***

There were no treatment differences in the primary outcome of CHD or in total mortality.
Chlorthalidone was superior to doxazosin in preventing cardiovascular events, particularly heart failure and stroke. Mean average systolic blood pressure values were about 2–3 mm Hg higher in the doxazosin group; mean diastolic blood pressure values were equivalent.
Chlorthalidone was superior to lisinopril in preventing aggregate cardiovascular events, principally stroke (in black persons only), heart failure, angina, and coronary revascularization.
Mean systolic blood pressure averaged about 2 mm Hg higher in the lisinopril group than in the chlorthalidone group (4 mm Hg for black persons); mean diastolic blood pressure values were equivalent.
Although chlorthalidone did not differ from amlodipine in overall prevention of cardiovascular events, it was superior to amlodipine (by about one fourth) in preventing heart failure, overall and for hospitalized or fatal cases.
Mean systolic blood pressure averaged about 1 mm Hg higher, and mean diastolic blood pressure about 1 mm Hg lower, in the amlodipine group.
Serum potassium level was 0.3–0.4 mmol/L lower in the chlorthalidone group compared with the amlodipine and lisinopril groups. The occurrence of potassium levels <3.5 mmol/L was 6%–8% higher among those randomly assigned to receive chlorthalidone.
Fasting glucose level in the chlorthalidone group was 0.17 mmol/L (3 mg/dL) higher than in the amlodipine group and 0.28 mmol/L (5 mg/dL) higher than in the lisinopril group.
Among nondiabetic participants, incidence of fasting glucose level $\geq 7$ mmol/L ( $\geq 126$ mg/dL) in the chlorthalidone group was 1.8% higher than in the amlodipine group and 3.5% higher than in the lisinopril group.
Clinical outcome results were consistent for all outcomes by age, sex, diabetic status, and race (except for stroke and CVD, where there was significant heterogeneity in the lisinopril–chlorthalidone comparison by ethnicity; a greater reduction was seen with chlorthalidone in black persons, in keeping with larger blood pressure differences).
Agents available for step-up led to a somewhat artificial regimen (use of sympatholytics rather than diuretics and calcium-channel blockers) for step-up drugs in the ACE inhibitor group.
ALLHAT did not study the entire universe of all hypertensive patients, such as low-risk patients.
ALLHAT did not include a washout period for treated patients.

\* ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CHD = coronary heart disease; CVD = cardiovascular disease.

### Selection of First-Step and Step-up Therapy: Preclusion of Diuretics and Calcium-Channel Blockers as Second-Line Drugs

According to the study design, 4 agents representing 4 classes of antihypertensive drug therapy (diuretics, ACE inhibitors, calcium-channel blockers, and  $\alpha$ -receptor blockers) were to be given as first-step therapy in comparable doses to lower blood pressure. Second- and third-line agents were made available for patients whose blood pressure was not controlled by 1 drug.

Many have commented on ALLHAT's "odd design" in including  $\beta$ -blockers as a step-up agent for ACE inhibitors (4). However, so as not to dilute any differential effect of the 4 study drugs, the investigators discouraged step-up

use of a drug from the same class as a first-step agent unless there were compelling indications. Also, reserpine, clonidine, and hydralazine were provided as second- and third-line drugs in addition to atenolol for control of hypertension because they have different mechanisms of action than the first-step drugs (3 antiadrenergics and 1 vasodilator). The purpose of the step-up drugs was to increase the proportion of participants reaching the blood pressure goal. Of note, hypertension control (blood pressure < 140/90 mm Hg) with the ALLHAT treatment regimen was more than twice that achieved in ALLHAT participants before the start of the trial. Hypertension control with the ALLHAT regimen also exceeded that achieved in patients with hypertension who were surveyed in the Third U.S. National Health and Nutrition Examination Survey and reported taking antihypertensive medication (15, 16). Because blood pressure goals were achieved in so many patients, the first-step drugs could be compared largely independently of blood pressure differences.

### ISSUES REGARDING STUDY CONDUCT

#### Attrition

The mean length of follow-up in ALLHAT for the chlorthalidone, amlodipine, and lisinopril groups was 4.9 years, and 99% of expected person-years were observed. Trial closeout occurred from 1 October 2001 through 31 March 2002, and all but 953 participants, or 2.9% of the total, had known vital status during this time period. To ascertain the impact of losses to follow-up on the trial's findings, we performed several types of sensitivity analyses in addition to the intention-to-treat analyses. The original study analyses were regenerated on data sets that excluded losses to follow-up, excluded centers that had less than 99% follow-up, and included imputed times and events (using multiple imputation) (17). All analyses were consistent with the trial's published conclusions (18).

#### End Point Ascertainment and Secondary Outcomes

ALLHAT was designed as a large, simple trial. Because of its sheer size (with almost 11 000 CVD end points during follow-up), it was not feasible to systematically verify all end points (2). Because the trial was double-blind, there should have been no bias for or against a given treatment group when reporting and classifying end points. This strength is in contrast to the ALLHAT Lipid-Lowering Trial (ALLHAT-LLT), which was not double-blind and thus had potential bias for all nonfatal (secondary) outcomes. This led to our statement that secondary end points for the ALLHAT-LLT (but not the ALLHAT hypertension trial) would be regarded as "soft data" (1, 4).

Clinical outcomes were evaluated by investigators trained to follow specific end point definitions detailed in a manual of operations. Medical reviewers at the ALLHAT Clinical Trials Center verified the physician-assigned diagnoses using death certificates and hospital discharge summaries. More detailed information was collected on a ran-

dom (10%) subset of CHD and stroke events and was reviewed by the ALLHAT Endpoints Subcommittee to determine the validity of physician diagnoses. Agreement rates between the subcommittee and clinic investigators were 90% (155 of 172) for the primary outcome, 84% (129 of 153) for stroke, and 85% (33 of 39) in a smaller one-time sample of heart failure hospitalizations (2, 19). (The much larger Heart Failure Validation Substudy is described later.) Rates of agreement were similar in all treatment groups.

## ISSUES REGARDING CONCLUSIONS AND INTERPRETATIONS

### Primary versus Secondary Outcomes

Rates of ALLHAT's primary outcome—fatal CHD or nonfatal myocardial infarction—were essentially identical in the chlorthalidone, amlodipine, and lisinopril groups. With the small confidence intervals for the relative risks, this was an unequivocal null result, with no evidence of superiority for treatment with the newer antihypertensive agents compared with the diuretic. However, ALLHAT had several other important predefined clinical outcomes. Previous identification of a primary end point assures reasonable statistical power to test a question related to that end point, but it does not mean that the other outcomes are less important. From a public health viewpoint and from the perspective of patients, all major clinical outcomes in ALLHAT were worth examining. Clearly, total mortality (a secondary outcome) is an important outcome

**Table 2. Criticisms of and Confusions about ALLHAT\***

<b>Study design</b>
How could ALLHAT test first-step therapy, given the study's inclusion criteria and lack of a washout period?
Why were diuretics and calcium-channel blockers avoided as second-step drugs?
<b>Study conduct</b>
Doesn't the attrition rate necessarily bias the conclusions?
Wasn't the outcome ascertainment process flawed since end points were not systematically reviewed by a panel of experts? Aren't the secondary outcomes "soft end points"?
<b>Conclusions and interpretations</b>
Why do the authors emphasize the secondary outcome results?
Are the heart failure findings real? Can't all or most of the heart failure findings be explained by the use of antihypertensive medications, such as diuretics and calcium-channel blockers, before entry into ALLHAT?
Can't all or most of the outcome findings (especially the differential ethnicity subgroup findings for stroke) be explained by the observed blood pressure differences among the treatment groups?
Doesn't the increased incidence of new diabetes in the chlorthalidone group portend greater long-term cardiovascular risk for patients taking this drug?
Diuretics themselves may be cheaper, but does the cost of management with diuretics translate into less expensive therapy?
Can the findings be extrapolated to drugs within class?
Why do the findings from ALLHAT and the Second Australian National Blood Pressure Study seemingly conflict?

\* ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

**Table 3. Heart Failure Findings\***

<b>Validity</b>
Central review confirmed investigator-assigned heart failure diagnoses in 70%–84% of instances in each treatment group. The relative treatment group effects were, if anything, larger than previously published. <sup>†</sup>
<b>Early divergence</b>
Curve separation occurred early, but it also continued after the first year for doxazosin and amlodipine versus chlorthalidone. For lisinopril versus chlorthalidone, the curves also separated early but converged between 6 and 7 years. Previous diuretic use or edema due to ALLHAT calcium-channel blocker use have been ruled out as explanations.
<b>Translation into total mortality</b>
Small absolute difference in total heart failure did not translate into differences in total deaths, since such differences are unlikely to be detected during the trial because of random variation in rates of all other deaths. Planned post-trial mortality surveillance will examine whether a mortality difference emerges.

\* ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

<sup>†</sup> Based on reference 21.

in all trials of hypertension treatment. In ALLHAT, total mortality also did not differ among those assigned to first-step treatment with amlodipine, lisinopril, or chlorthalidone.

### Heart Failure Findings

Issues regarding the major heart failure findings are summarized in Table 3. Heart failure was a prespecified secondary outcome (1). The design paper listed it as a component of a major secondary outcome, combined CVD. It was listed separately on ALLHAT case-report forms, and a specified set of diagnostic criteria for heart failure (the same as those used in the Systolic Hypertension in the Elderly Program) were provided in the trial's manual of operations (Table 4) (20). Nevertheless, the Steering Committee and the Data and Safety Monitoring Board took additional precautions to examine the reliability of this diagnosis during the trial. As a result, the investigators conducted several validity studies (19, 21). The largest study included almost all heart failure hospitalizations and deaths (3031 in 2091 patients) in ALLHAT and all relevant material surrounding these events (hospitalizations, death certificates, radiography reports, left ventricular ejection fraction measurements). Specially trained cardiology fellows reviewed each presumed case of heart failure (2 independent reviews per case) according to both ALLHAT and Framingham criteria (Table 4), as well as the reviewers' global judgment. All reviewers were blinded to treatment assignment. This central review (different from the one-time sample described earlier) confirmed 70% to 84% of investigator-assigned heart failure diagnoses in each treatment group; relative treatment group effects were, if anything, larger than previously published (21).

Several authors have commented on the early divergence of the heart failure incidence curves in ALLHAT (4, 8, 9). Curve separation occurred early, but it also continued after the first year for doxazosin and amlodipine versus

Table 4. Heart Failure Criteria\*

<p><b>ALLHAT criteria for evaluation of heart failure (must have one from each category)†</b></p> <p><b>Category A</b></p> <ul style="list-style-type: none"> <li>Paroxysmal nocturnal dyspnea</li> <li>Dyspnea at rest</li> <li>NYHA classification III</li> <li>Orthopnea</li> </ul> <p><b>Category B</b></p> <ul style="list-style-type: none"> <li>Rales</li> <li>Ankle edema</li> <li>Tachycardia</li> <li>Cardiomegaly on chest radiography</li> <li>Chest radiograph characteristic of CHF</li> <li>S<sub>3</sub> gallop</li> <li>Jugular venous distention</li> </ul> <p><b>Original Framingham heart failure criteria (2 major or 1 major plus 2 minor criteria)</b></p> <p><b>Major</b></p> <ul style="list-style-type: none"> <li>Paroxysmal nocturnal dyspnea</li> <li>Jugular venous distention</li> <li>Rales</li> <li>Cardiomegaly on chest radiography</li> <li>Acute pulmonary edema</li> <li>S<sub>3</sub> gallop</li> <li>Central venous pressure</li> <li>Circulation time <math>\geq 25</math> s</li> <li>Hepatojugular reflux</li> <li>Pulmonary edema, congestion, or cardiomegaly on autopsy</li> </ul> <p><b>Minor</b></p> <ul style="list-style-type: none"> <li>Bilateral ankle edema</li> <li>Nocturnal cough</li> <li>Dyspnea on exertion</li> <li>Hepatomegaly</li> <li>Pleural effusion</li> <li>Decreased vital capacity one third from maximum</li> <li>Tachycardia with heart rate <math>\geq 120</math> beats/min</li> </ul> <p><b>Major or minor</b></p> <ul style="list-style-type: none"> <li>Weight loss <math>\geq 4.5</math> kg in 5 d in response to treatment of heart failure</li> </ul>
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\* ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CHF = congestive heart failure; NYHA = New York Heart Association.

† Based on the ALLHAT manual of operations, version 5.3.4, and the Systolic Hypertension in the Elderly Program (20).

chlorthalidone. For lisinopril versus chlorthalidone, the curves also separated early but converged between years 6 and 7. Suggested reasons for the early separation were the precipitation of edema with amlodipine and the unmasking of edema when diuretics were withdrawn from those who had been taking them before the trial. One of the central review algorithms used criteria that did not allow peripheral edema to be used in the heart failure diagnosis. This had little impact, reducing the heart failure confirmation percentage from 71% to 70% and not altering the treatment group differences.

During the recruitment period for ALLHAT (1994–1998), IMS data indicate that the percentage of treated U.S. hypertensive patients taking diuretics decreased from approximately 30% to just over 20% (22). In addition, within ALLHAT, information about previous medication use was collected on the hospitalized and fatal cases of heart failure as a follow-up to the central review study. When case-only design theory was used to assess interac-

tions (23), the analyses did not support an effect of pre-entry diuretic use on the observed heart failure differences (data to be published).

The addition of second- and third-line drugs probably contributed to the lessening of the divergence starting at 6 to 12 months after randomization. The excess risk for heart failure with doxazosin as monotherapy was reduced but not eliminated when participants began taking diuretics,  $\beta$ -blockers, or ACE inhibitors. In that previous analysis of doxazosin versus chlorthalidone, the greatest divergence occurred during the first year but continued thereafter. Paradoxically, the greatest differential benefit of chlorthalidone versus doxazosin after the first year occurred in the subgroup with well-controlled blood pressure ( $<140/90$  mm Hg), indicating that this difference was not explained by the blood pressure differential (24). The ALLHAT results are consistent with the well-known protective effect of ACE inhibitors in the prevention and treatment of heart failure. However, in a head-to-head comparison, diuretics were better. This was true in subgroups of black and non-black persons, by 32% and 15%, respectively. These heart failure differences within each ethnic group were not significantly different from each other (that is, there was no heterogeneity).

It has been speculated that the differences in heart failure incidence should have been reflected in differences in total mortality. The lisinopril–chlorthalidone difference in patients with hospitalized heart failure over 6 years was 0.4%. The excess of such cases in the lisinopril group ( $0.004 \times 9054$ ) equals 36 patients. The case-fatality rate among patients with hospitalized heart failure over an average follow-up of 2.5 years was approximately 25%. Thus, 9 excess cases of fatal heart failure would have been expected in patients assigned to lisinopril, less than 1% of all deaths in this group ( $n = 1303$ ). Similar calculations for the amlodipine group yield 154 excess cases of hospitalized heart failure. The estimated number of fatal heart failure cases is 39, which is approximately 3% of the total number of deaths in this group ( $n = 1237$ ). Such differences in deaths are unlikely to be detected because of random variation in rates of all other deaths. Planned post-trial mortality surveillance will examine whether a mortality difference emerges.

### Blood Pressure Differences

ALLHAT was designed to compare the incidence of cardiovascular outcomes in high-risk hypertensive persons initially treated with 1 of 4 active antihypertensive agents. The goal was to achieve equivalent blood pressure control in all 4 groups, although mean decrease in blood pressure was not a declared outcome of the trial. Nonetheless, blood pressure results are of interest to the clinician as the main proximal target of treatment and to epidemiologists for explaining the results. The chlorthalidone-based regimen happened to be the most effective in reducing clinical outcomes and, to a small degree, in lowering blood pressure. If

a given agent (for example, an ACE inhibitor) is less effective in reducing clinical events unless it is used with an agent like chlorthalidone to effectively lower blood pressure, it is not clear why treatment would be started with anything other than the diuretic.

Do differences in achieved systolic blood pressure explain treatment differences in the cardiovascular findings? Meta-regressions of effects of blood pressure differences on trial results (25) suggest that they might to some extent, except for heart failure. In ALLHAT, the small differences in achieved mean systolic blood pressure and diastolic blood pressure— $\pm 1$  mm Hg—between the amlodipine and chlorthalidone groups and the lisinopril and chlorthalidone groups in nonblack persons should have had no or a negligible effect on cardiovascular event rates. In these comparisons, the observed rates of heart failure were higher with amlodipine (38%) and lisinopril (15%) than with chlorthalidone. The differences were larger in black persons than in nonblack persons, especially for stroke and combined cardiovascular events. Because of this, the 4 mm Hg higher mean systolic blood pressure in the lisinopril group appears to explain less than half of the observed higher risk for stroke (40%) and congestive heart failure (32%) compared with chlorthalidone, based on the blood pressure-related effect predicted from observational data (26).

### Diabetes Incidence

Incident diabetes (unlike heart failure) was not a pre-specified secondary outcome. Nevertheless, the ALLHAT investigators thought it was important enough to include it in the primary paper. The results are consistent with other literature showing that thiazide diuretics are associated with a small increase in serum glucose level (approximately 0.17 to 0.22 mmol/L [3 to 4 mg/dL]), at least in the short term (27–30). For comparison of lisinopril (or amlodipine) and chlorthalidone, the results of the primary and major secondary clinical outcomes were consistent by baseline diabetic status (2). Thus, for diabetic patients, lisinopril was observed to have no special advantage (and amlodipine no particular detrimental effect) for CVD outcomes and end-stage renal disease compared with chlorthalidone. In fact, chlorthalidone was superior to lisinopril for several CVD outcomes and superior to amlodipine for heart failure in both diabetic and nondiabetic participants. Overall, the treatment-related differences in serum glucose level seen in ALLHAT did not translate into more cardiovascular events or higher all-cause mortality in the chlorthalidone group compared with the other 2 groups during the trial. In fact, patients taking doxazosin had a far lower mean level of glucose compared with those taking chlorthalidone, but this failed to translate into better reduction in CVD outcomes for the former group (3). Finally, thiazide-associated diabetes can probably be prevented or reversed with maintenance of potassium balance and, to a lesser extent, with adequate weight control, increased physical activity, or caution when using  $\beta$ -blockers in combination therapy (31, 32).

While ALLHAT had one of the longest follow-ups of any trial of its type (average, 4.9 years), outcomes cannot be predicted beyond the trial's duration. This caveat applies to any clinical trial. Furthermore, lack of evidence that a trial's results will hold up decades after the trial ends do not prove that a different outcome will result. Whether thiazide-associated diabetes carries the same prognosis as naturally occurring diabetes needs to be assessed in observational studies (33, 34). Further follow-up from ALLHAT itself will be valuable. The fact that avoidance or restoration of a potassium deficit has been repeatedly shown to avoid or correct abnormalities in glucose tolerance suggests a benign prognosis.

### Cost of Antihypertensive Management

Although subordinate to safety and efficacy, cost of drugs and medical care for the individual and society should be considered in the selection of antihypertensive agents. One of the stated objectives of ALLHAT was to answer the question, "Are newer types of antihypertensive agents, which are currently more costly, as good as or better than diuretics in reducing CHD incidence and progression?" Consideration of drug cost could have a major impact on health care expenditures in the United States. Previous data showed that diuretic use declined from 56% to 27% of antihypertensive prescriptions between 1982 and 1992. On the basis of this, the health care system would have saved \$3.1 billion in estimated costs of antihypertensive drugs if the pattern of prescriptions for treatment of hypertension had remained at the 1982 level. Further economic analyses based on the results of ALLHAT are under way. Information to date suggests that drug acquisition costs drive these comparisons. Although the risk for hypokalemia and hyperglycemia mandates some laboratory monitoring when diuretics are used, such monitoring is not proven to be greater than that required during administration of ACE inhibitors or in the routine care of patients with risk factors.

### Extrapolating Findings to Drugs within a Class

Another issue commonly raised is whether the ALLHAT results can be extrapolated from the specific drug tested to other drugs of the same class. For  $\alpha$ -blockers, ACE inhibitors, and dihydropyridine calcium-channel blockers, such extrapolation seems reasonable (8).

Do the results for chlorthalidone apply to thiazide diuretics in general and especially to hydrochlorothiazide, the most widely prescribed diuretic in the United States? The Multiple Risk Factor Intervention Trial (35), which examined special intervention and usual care groups, demonstrated that mortality trends were less favorable at clinics where special intervention clinicians favored hydrochlorothiazide over chlorthalidone. This led to a protocol change: It was recommended that all patients switch from hydrochlorothiazide to chlorthalidone, and the maximum dose was reduced from 100 mg to 50 mg.

There are several reasons why the conclusions from

this experience are not robust. First, it was based on a post hoc subgroup analysis. Second, it was based on a group identifier (clinic) rather than individual patient treatments, and analyses based on individual patients did not offer much support for a drug difference. Finally, if the change in the treatment regimen (for most but not all hypertensive participants) played a role in the results being more favorable for the special intervention group after the protocol change (continuing into the post-trial period), it was impossible to distinguish changes in drug (hydrochlorothiazide to chlorthalidone) from reductions in dose. Apart from the results of the Multiple Risk Factor Intervention Trial, data from studies using various thiazide-type diuretics (chlorthalidone, hydrochlorothiazide, indapamide, and bendrofluzide) suggest similar benefits among all thiazide-type diuretics tested in CVD prevention trials against placebo, usual care, or another drug class (27, 36–43; Psaty B. Personal communication).

### Results from the Second Australian National Blood Pressure Study versus the ALLHAT Results

The Second Australian National Blood Pressure Study (ANBP2), a practice-based open-label trial, was the only other large trial besides ALLHAT to compare diuretic-based (hydrochlorothiazide recommended) with ACE inhibitor-based (enalapril recommended) antihypertensive treatment. A total of 6083 participants, 65 to 84 years of age, were treated and followed for a mean of 4.1 years (43). The primary end point was a composite of all cardiovascular events (initial and recurrent) plus all-cause mortality. Cardiovascular events included major coronary events, stroke and transient ischemic attacks, heart failure (not otherwise defined), acute occlusion of any other major artery, and dissecting or ruptured aortic aneurysm. The results for the primary end point marginally favored the ACE inhibitor group (relative risk, 0.89 [95% CI, 0.79 to 1.00];  $P = 0.05$ ). The corresponding results using first cardiovascular event or death from any cause or first cardiovascular event had essentially the same relative risks, with  $P$  values of 0.06 and 0.07, respectively. The relative risks were 0.83 in men ( $P = 0.02$ ) and 1.00 in women ( $P > 0.2$ ); however, the treatment effect by sex interaction was nonsignificant ( $P = 0.15$ ).

Frohlich (44) weighed the supposedly conflicting results of ANBP2 and ALLHAT, suggesting possible explanations such as the samples studied and the specific drugs used. Additional substantial differences should be noted. There were almost twice as many cardiovascular events in ALLHAT as participants enrolled in ANBP2, and ALLHAT was a double-blind study. ANBP2 used a randomized, open-label, blinded end point design, increasing the potential for bias in the reporting of events (the rates of some outcomes might have been “expected” to be lower with the ACE inhibitor). Even given the possible biases, however, the results of ANBP2 are consistent with those of ALLHAT if the upper confidence limit for the relative risks

in ANBP2 is compared with the estimates of relative risk in ALLHAT (45).

### LIMITATIONS AND EXPECTATIONS

Some limitations are obvious. Several new antihypertensive drugs that were not evaluated in ALLHAT have been or may soon be released (for example, angiotensin-receptor blockers and selective aldosterone antagonists). Although participants, their physicians, and the ALLHAT research staff were blinded to the study medication, and the study participants’ treatment teams were urged to achieve recommended blood pressure goals, equivalent blood pressure reduction was not fully achieved in the treatment groups, as summarized earlier. Furthermore, as we previously noted, the agents available for step-up led to a somewhat artificial regimen of step-up drugs in the ACE inhibitor group (sympatholytics rather than diuretics and calcium-channel blockers). This may have contributed to the higher achieved blood pressure in the ACE inhibitor group, especially in black persons. However, mean blood pressure during follow-up was well below 140/90 mm Hg in all treatment groups. As has also been previously noted, like other primary prevention outcome trials, ALLHAT did not study the entire universe of hypertensive patients, such as low-risk individuals and treated patients who had a washout period. Last, we did not routinely collect information on type of previous use of antihypertensive medication, which might have provided additional insight.

Some of our responses to criticisms and confusions present limited details in part because they are derived from papers in progress that will more fully address the issues raised in this paper, especially those related to heart failure and diabetes. We believe that these pending papers, available in the near future, will shed additional light on these and other areas.

All drugs may have both known and unknown beneficial and adverse effects. Knowledge of the benefits and risks of a medication allows physicians to select the best possible treatment for patients. The simple question ALLHAT was designed to address has been answered. As first-step agents, the newer drugs (ACE inhibitors, calcium-channel blockers, and  $\alpha$ -blockers) add no value over and above diuretics in preventing CHD or any of the other major forms of CVD. They are less effective in preventing heart failure and are more expensive than diuretics.

Many researchers and clinicians seemed to have been surprised by the following ALLHAT results: 1) Angiotensin-converting enzyme inhibitors were not the best form of first-step antihypertensive drug therapy in preventing cardiovascular events, and 2) calcium-channel blockers were not the worst agents in terms of CHD and deaths. Some of these expectations were derived from preclinical studies, extrapolation from surrogate outcomes, and case-control and other observational studies, all of which had limitations (10). This is why results from randomized, double-

blind, clinical end point trials are needed whenever possible to provide the optimal basis for therapeutic decisions. Individual trials and meta-analyses of trials support or are consistent with ALLHAT results (6, 25, 42, 43, 45, 46).

What about the future? ALLHAT has raised many interesting questions that may stimulate new research. For example, if we posit that a diuretic should be the first choice for antihypertensive therapy, then what class of drugs should be used next in a stepped-care treatment program? Should treatment begin with 2 drugs? If so, which?

## CONCLUSIONS

Lowering high blood pressure is of fundamental importance in reducing CVD risk. How it is lowered does matter. Antihypertensive drugs vary in their efficacy to lower blood pressure and can have blood pressure-independent effects, as seen with regard to preventing heart failure. Diuretics should remain the preferred first-step drugs for treatment of hypertension and should be a cornerstone in the arsenal for care of hypertensive patients.

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