New Results and Analyses Expand and Modify Key Interpretations of the ALLHAT Trial

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There can be little doubt that the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[1] has created controversy and criticism to equal that of any other reported hypertension trial.[2-5] ALLHAT generates particular interest in light of the nature of the debate. Beyond the design and results, observers have also voiced concern regarding the level of publicity and the politically and economically inspired interpretations that accompanied the release of the trial's initial results.[1] Concerned by what must have appeared a rather unenthusiastic response to their work, the authors of ALLHAT have embarked on a second generation of analyses.

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The recent meeting of the American Society of Hypertension (ASH), held in New York City in May 2004, provided an opportunity for presentation and discussion of 5 further aspects of the trial. The need for multi-drug regimens to control blood pressure in the high-risk cohort, the role of ethnicity in determining clinical outcomes, analyses of clinical endpoints in those patients who were treated with single-agent therapy during the trial (thus avoiding the confounding effects of added drugs), a further look at the controversy surrounding the trial's diagnosis of heart failure, and the pivotal issue of differing effects of antihypertensive agents on new-onset diabetes mellitus were all examined.

Background

In considering these interesting presentations, it is worth reviewing the highlights of the original ALLHAT report.[1] The clinical outcomes from 3 drug regimens, a diuretic (chlorthalidone), a calcium channel blocker (amlodipine), and an angiotensin converting enzyme (ACE) inhibitor (lisinopril), were compared in high-risk hypertensive patients. After almost 5 years of follow-up, during

Table 1
ALLHAT Details of Achieved Blood Pressure (BP)

	Chlorthalidone	Amlodipine	Lisinopril
Mean BP at study close (mm Hg)	134/76	135/75	136/76
BP below 140/90 mm Hg, %	68	66	61
Mean number of drugs used in combination	1.9	2.0	2.1
Patients controlled on 1 drug, %	28	24	24
Patients controlled on 2 drugs, %	24	26	18
Patients requiring ≥ 3 drugs for control, %	48	50	58

which the diuretic was significantly more efficacious than the other drugs in controlling blood pressure (due largely to the study's design characteristics, precluding the use of logical treatment combinations in the amlodipine and lisinopril groups), the chlorthalidone-treated patients appeared to have fewer major events. Although the primary study endpoint of fatal and non-fatal coronary events was virtually identical in the 3 treatment groups (despite the blood pressure inequality favoring chlorthalidone), chlorthalidone appeared to have an advantage over amlodipine in terms of preventing heart failure and an advantage over lisinopril in terms of preventing stroke. For this reason, chlorthalidone was proclaimed superior to the other drugs for the treatment of hypertension and accordingly was recommended as a preferred first-line treatment for the management of high blood pressure.

Despite a strong outcry concerning the study's design deficiencies and the misinterpretations that were believed to have led to these conclusions,[2-5] the implications of these claims found their way into subsequent published guidelines. In some ways, this was a foregone conclusion because the US guidelines—known as the Seventh Report of the Joint National Committee on the Prevention, Detection and Treatment of High Blood Pressure (JNC 7)[6]—are produced under the sponsorship of the same Federal government agency that was responsible for ALLHAT. For this reason, any further information regarding the ALLHAT trial might have additional clinical-practice implications, because it might directly influence how clinicians choose to manage their hypertensive patients.

The Challenge of Achieving Blood Pressure Control

Cushman and colleagues[7] presented their findings as part of a session at the ASH meeting devoted entirely to ALLHAT papers. In ALLHAT, after patients were randomized to treatment with chlorthalidone, amlodipine, or lisinopril, the treatment regimens were adjusted to achieve blood pressure control (< 140/90 mm Hg). At first, the initial drug doses could be increased and if control was still not achieved, it was possible to add second- or third-line drugs during subsequent visits. However, these additional drugs could not conflict with the initial study drugs. Therefore, diuretics, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers could not be used as add-ons. Most patients received a ß-blocker as their second-line drug, and clonidine and even reserpine were also fairly common choices.

The main results of this report are shown in Table 1. On first analysis, the blood pressure results in ALLHAT appear impressive. Across treatment groups, blood pressure was reduced on average to approximately 135/75 mm Hg. It should be remembered, however, that patient recruitment into ALLHAT focused on individuals with relatively mild forms of hypertension, in the hope that monotherapy would often be successful and that the confounding effects of adding drugs would be minimized. Regardless, the relatively high control rates appear impressive. Chlorthalidone was the most efficacious drug, achieving blood pressure of less than 140/90 mm Hg in 68% of cases. Lisinopril was the least efficacious, achieving control in only 61%. Almost certainly, the difference between these drugs reflects the relatively modest blood pressure reductions achieved by ACE inhibitor therapy in the 35% of ALLHAT patients who were black. Overall, an average of 2 drugs was required in ALLHAT patients to achieve these blood pressure results.

It is noteworthy, however, that monotherapy was relatively ineffectual in achieving blood pressure control. Chlorthalidone was most successful, reaching this goal in 28% of patients; each of the other 2 drugs was successful in 24%. Adding a second drug appeared to be a useful strategy. The number of patients controlled on 2-drug regimens was as high as that of monotherapy. Even so, the data shown in Table 1 point out a remarkable fact: about 50% of patients randomized to chlorthalidone or amlodipine would require a third drug, if not more, to achieve control, whereas almost 60% of patients randomized to lisinopril would require a third drug or more.

In considering these data it is important to remember the artificiality of clinical trial design. For example,

most physicians would not select an ACE inhibitor as initial therapy in middle-aged or elderly African American patients. In addition, most 2-drug regimens selected by clinicians would almost certainly differ from the choices provided by the ALLHAT study design. One of the main conclusions of the ALLHAT investigators, not surprisingly, is that their data prove the inevitability of multiple-drug regimens in the treatment of most hypertensive patients. Even if this conclusion were driven to some extent by the illogical combinations prescribed by the ALLHAT protocol, most experts would still agree.

The low response rates to initial drug therapy, less than 30% in each of the 3 treatment arms, may again be somewhat misleading. Most clinicians, free to select the first agent most likely to correspond with the ethnic or other clinical features of their patients, would probably make more efficacious choices. It is also possible that some physicians, upon realizing that their first drug selection was totally ineffective in a particular patient, might discontinue and switch to a different drug. Overall, it might be possible to achieve blood pressure control in about 40% to 50% of patients through thoughtful selection of a single agent.[8]

The one conclusion of the ALLHAT investigators most likely to create an argument is the assertion that their findings support the recommendation of thiazide diuretics as the universally prescribed first-line therapy for hypertension.[6] Given the circumstances of the ALLHAT protocol design, the slight efficacy advantage seen with chlorthalidone hardly appears convincing. Of course, for an important segment of patients, diuretics may be considered a reasonable first choice, but evidence from other recent trials shows that alternatives to diuretics are at least as efficacious.[9] Despite such issues, these data from ALLHAT still represent a useful contribution to our knowledge of hypertension control.

Ethnicity Affects Outcomes

From the initial publication of ALLHAT, it became obvious that there were key differences in outcomes between white and black patients. One of the principal differences was in blood pressure response between these 2 groups within the lisinopril-treatment arms. Compared with those in the chlorthalidone group, black patients randomized to lisinopril had systolic blood pressure values that averaged 4 mm Hg higher. There was also a difference favoring diuretics among white patients, although it was less than in African Americans. The most dramatic expression of this difference was seen in stroke incidence. Among white patients, there was no difference between the diuretic and the ACE inhibitor, but there was a dramatic 40% excess stroke rate in black patients randomized to lisinopril. This finding should have surprised no one. It has been well known for some time that black patients do not achieve the same antihypertensive efficacy with ACE inhibitors (and other blockers of the renin-angiotensin system) as with classes such as diuretics or calcium channel blockers.

For this reason, observers believed the original published conclusion of ALLHAT,[1] that thiazides are superior to other drug classes, was driven, at least to a meaningful extent, by this ethnically dependent blood pressure artifact.[2-5] Some of the senior ALLHAT investigators apparently reached a similar conclusion. In March 2004, the chairman of the ALLHAT Steering Committee presented a new interpretation of these data at the annual meetings of the American College of Cardiology Scientific Session. The more recent ASH meeting provided an excellent opportunity to review these data more fully.

The findings of interest are shown in Table 2. Strictly speaking, these analyses are not new and could be derived from the information published in the original ALLHAT article. However, assembling the data in this new fashion gives rise to a conclusion that differs from that in the original report. It is evident that, when outcomes in the diuretic group are compared with those in the ACE inhibitor group, there are clear differences between black and white patients. In general, as might be expected from the blood pressure differences between the groups, black patients tended to do better on the diuretic when measured in terms of major outcomes. In white patients, where the blood pressure difference was less marked, outcomes were generally similar between the 2 treatment regimens.

According to the ALLHAT chairman, it is appropriate to amend the original study conclusion that thiazide diuretics are superior in providing cardiovascular protection in high-risk hypertensive patients. Instead, it would now be reasonable to state that whereas diuretics remain the preferred first-line drugs for black patients, ACE inhibitors and diuretics could be regarded as coequal recommendations for initiating therapy in whites. This reinterpretation does not get into such issues as patient compliance, drug tolerability, or cost, but for those who have followed the ALLHAT controversy from the beginning, there is considerable interest in this departure from the original study conclusion.

Missing from this analysis, however, is consideration of calcium channel blockers. Apart from the issue of heart failure—which became a major controversy unto itself and is dealt with later in this report—the calcium channel blocker amlodipine per-

Table 2
ALLHAT End Point Comparison (Lisinopril vs Chlorthalidone) in Blacks and Non-Blacks

End Point	Blacks, Relative Risk (95% CI)	Non-Blacks, Relative Risk (95% CI)
Nonfatal MI and CHD death	1.10 (0.94-1.28)	0.94 (0.85-1.05)
All-cause mortality	1.06 (0.95-1.18)	0.97 (0.89-1.06)
Combined CHD	1.15 (1.02-1.30)	1.01 (0.93-1.09)
Combined CVD	1.19 (1.09-1.30)	1.06 (1.00-1.13)
Stroke	1.40 (1.17-1.68)	1.00 (0.85-1.17)
Heart failure	1.32 (1.11-1.58)	1.15 (1.01-1.30)
End-stage renal disease	1.29 (0.94-1.75)	0.93 (0.67-1.30)

CHD, congestive heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

formed well in ALLHAT as far as major outcomes were concerned. The primary coronary end point was no different for amlodipine than for the other 2 drugs, and the other major end points of stroke and all-cause mortality actually trended slightly in its favor.[1] For many patients, the excellent antihypertensive efficacy and tolerability of calcium channel blockers continue to make them popular and appropriate choices. It will be interesting to see, as further data and analyses become available, whether more of ALLHAT's early conclusions will be modified.

Studies of Monotherapy in ALLHAT: The Use of On-Treatment Analyses

It is often difficult to interpret the results of clinical trials in hypertension because of the complexity of the treatment regimens used. Though investigators tend to compare results between treatment arms labeled with a particular drug, in reality patients within each cohort are typically receiving 2 or 3 drugs that could separately affect outcomes. For this reason, the ALLHAT investigators carried out and reported an analysis based solely on those patients who remained on monotherapy during the study.[10] It was decided to define monotherapy patients as those who, after 12 months of treatment, were still receiving single-agent therapy. The investigators reasoned that if a second drug had not been added by that stage of the study, it could be assumed that patients had responded adequately to their randomized drug. Appropriately, in performing the analysis of outcomes, only those events that occurred after the 12 month point of the study were included, hence the term "on-treatment analyses." In those cases where it became necessary after this newly created baseline to add a second drug in order to achieve blood pressure control, patients were withdrawn from further analysis. Thus, the results of this approach should also be labeled as "time-adjusted."

A relatively large number of patients were available for the monotherapy analysis starting at 12 months: for chlorthalidone there were 7701, for amlodipine 4485, and for lisinopril 3810. There were some modest differences between these treatment groups in their original baseline demographic and clinical characteristics, though according to the investigators these differences were small and not clinically meaningful. It should be noted, however, that whereas all patients included in these analyses were on monotherapy, there was still some small but potentially important blood pressure differences favoring chlorthalidone when compared with either amlodipine or lisinopril.

As far as the primary endpoint of fatal and non-fatal coronary events was concerned, there were no differences among the 3 treatment groups. The hazard ratio for amlodipine compared with chlorthalidone was 1.13, and for lisinopril it was 0.94. Neither of these values was statistically significant.

The investigators also reported the combined cardiovascular end points, which were a composite of coronary heart disease, heart failure, coronary revascularization, angina, and other related end points. For this analysis, there was now an advantage for chlorthalidone compared with amlodipine (the event rate was 11% higher), but the results were similar for chlorthalidone and lisinopril. The investigators pointed out, though, that the relative advantage to chlorthalidone for the composite end point, as compared with the primary coronary end point, was driven primarily by heart failure findings. In fact, the heart failure hazard ratio for amlodipine compared with chlorthalidone was 1.41, whereas that for lisinopril was 1.14.

The ALLHAT investigators claim that this analysis, considering monotherapy patients only, is similar to that observed with the complete, originally reported cohort, and therefore confirms the original conclusions. Unfortunately, their argument rests with the fact that the advantages to diuretic therapy depend almost entirely on 1 end point, the highly debated diagnostic issue of heart failure.[2-4]

In fairness, putting the contentious issue of heart failure diagnosis aside, the investigators of ALLHAT are to be praised for undertaking and publishing this type of secondary analysis. By utilizing a logically defined cohort of patients, and starting their end point analysis with a baseline translocated to the 12-month point of the study, they have shown a willingness to explore their data in a more innovative fashion.

Revisiting the Heart Failure Controversy

Heart failure was perhaps the most controversial of the end points reported in the original ALLHAT paper. Unfortunately, the ASH meeting presentation regarding this issue was given as a faculty lecture and was not accompanied by an abstract or other published materials.

Dr. Barry Davis, one of the senior officials of ALLHAT, gave this presentation, focusing on how heart failure diagnoses were verified in the trial, and gave some interesting background information about those patients who developed heart failure during the study. Dr. Davis discussed criticisms that had been leveled at the completeness of the heart failure diagnosis during the study, including the assertion that if patients in the amlodipine treatment arm had as great an excess of this diagnosis (compared with the diuretic) as claimed, and considering the very poor prognosis associated with this condition, this finding should have resulted in an increased mortality rate in the amlodipine group.[2-4] In fact, mortality was slightly lower in this group than in the diuretic group, casting doubt on the validity of the heart failure findings. Dr. Davis argued, however, that given the actual number of heart failure events, and the relatively short duration of their follow-up, a discernible effect on mortality might not have been expected during the trial.

It is almost certain, though, that this issue will never be adequately addressed. When diuretics are given as treatment in hypertension, particularly when used in relatively full doses, they can potentially mask the clinical findings of congestion. This effect confounds findings in 2 ways. First, when prior therapy includes diuretics and patients are switched at study entry to nondiuretic treatment, there is a good possibility that previously masked signs of congestion will become clinically apparent and be falsely attributed to the recently administered study drug. Second, those patients in the trial randomized to diuretic therapy, bearing in mind that diuretics were not allowed in the other treatment arms, are less likely to manifest clinical signs of congestion than those in the comparison groups. Therefore they are less likely to be fully evaluated for the possibility of heart failure. There is no question that patients with clinical evidence of heart failure appropriately confirmed in the hospital setting should count as such in the study population. The problem lies in those patients with left ventricular dysfunction who, because of the suppression of their symptoms, were not fully evaluated. This difficulty of heart failure diagnosis is intrinsic to any hypertension trial utilizing the design of ALLHAT. This is not a criticism of the trial, per se, but rather a diagnostic dilemma with no ready solution. As discussed earlier, it is unfortunate that the key study findings in ALLHAT were largely driven by highly uncertain heart failure data.

More Information on New-Onset Diabetes

The original ALLHAT publication included information comparing the relative incidence of new-onset diabetes among the 3 main treatment groups, but the ASH meeting provided investigators an opportunity to present interesting updated information.[11] As the authors pointed out, earlier hypertension trials demonstrated that ACE inhibitors or angiotensin-receptor blockers were effective in significantly preventing new-onset diabetes when compared with either placebo or ß-blockers. On the other hand, there was no definitive information comparing these agents with diuretics or calcium channel blockers. Nor, according to the presenters, was there any information regarding the further cardiovascular prognosis of patients who become diabetic during the course of antihypertensive therapy. Interestingly, however, just a few weeks before the ASH meetings, and certainly after the ALLHAT authors had submitted their abstract, an authoritative paper appeared in the literature documenting the long-term effects of new-onset diabetes on subsequent clinical events.[12]

Instead of considering all non-diabetic patients (at the start of the ALLHAT trial) as the population at risk for developing diabetes, the authors further analyzed data based on 2 groups: those who were clearly normoglycemic (with fasting glucose levels < 110 mg/dL) and those defined as having impaired fasting glucose (between 110 and 125 mg/dL).

The effect of the 3 treatment regimens on fasting glucose and incident diabetes for each of these patient groups is shown in Table 3. For normoglycemic patients, the average fasting glucose value was 91 mg/dL. Their average age was 67 and 30% were African Americans. Their results are similar to those previously reported in the original paper. Incidence levels of new-onset diabetes were significantly higher in the diuretic-

Table 3
ALLHAT Treatment Effect on Fasting Glucose (FG) Levels in Non-Diabetics

	Chlorthalidone	Amlodipine	Lisinopril
	Normal FG at Baseline (< 110 mg/dL)		
FG at 4 years (mg/dL)	102.0*	99.8	98.8
Incident diabetes, %	11.5*	8.3	7.6
	Impaired FG at Baseline (110-125 mg/dL)		
FG at 4 years (mg/dL)	138.8†	135.0	122.9
Incident diabetes, %	52.5	45.5	36.8

*$P < .006$ versus other 2 drugs
†$P < .001$ versus lisinopril
Reproduced with permission from Barzilay et al.[11]

treated group than for the other 2 treatment groups, indicating that calcium channel blockers and, to an even greater extent, ACE inhibitors might have advantages in protecting hypertensive patients from developing diabetes.

The findings in patients with impaired fasting glucose, though, were particularly interesting. As shown in Table 3, mean fasting glucose levels in these patients rose clearly above the threshold (126 mg/dL) for the diagnosis of diabetes and a remarkably high proportion of these individuals finished the trial with a diagnosis of diabetes. Again, a higher proportion of those being treated with the diuretic achieved this diagnosis than did those treated with the other drugs, but for all 3 treatment groups, a startlingly high number of patients became diabetic. It is likely, though, that the study did not run for a sufficient duration after the disease manifested to allow its adverse cardiovascular effects to become evident. Concomitant treatment with ß-blockers, which are also potentially diabetogenic, might have added to these numbers.

The patients with impaired fasting glucose, although not fully defined in terms of other clinical characteristics, almost certainly represented those whom we now refer to as having the metabolic syndrome. Typically, these people have abdominal obesity, abnormal levels of high-density lipoprotein cholesterol and triglycerides, increased blood pressure and, obviously, impaired glucose tolerance. ALLHAT draws sharp attention to the fact that such patients are particularly vulnerable to progression to diabetes. Although they are clearly at greatest risk for this adverse development if treated with a thiazide diuretic, the relatively high incidence rates with the other therapies indicate that such patients must be managed with great care to prevent progression to diabetes.

This important report from the ALLHAT group concluded, as in the original published paper,[1] by stating that patients developing diabetes during the course of the study did not appear to have a higher incidence of cardiovascular events than those who did not become diabetic. It is possible that the blood pressure differences favoring chlorthalidone among the treatment groups in ALLHAT might partly explain why the new diabetics in the diuretic group did not appear to have an increased number of events. However, other investigators following a cohort of treated hypertensive patients for up to 15 years have reported that the incidence rates of major cardiovascular or renal events in new-onset diabetics is about 3-fold of that observed in non-diabetic patients, similar to that in patients known to have been diabetic prior to the administration of any antihypertensive therapy.[12] Most important, these new results from ALLHAT should have the effect of focusing even greater attention on the management of hypertensive patients with metabolic abnormalities. ■

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