Editorial Commentary

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Practical Implications

Suzanne Oparil

Rationale

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), sponsored by the National Heart, Lung, and Blood Institute (NHLBI), is the largest outcome trial of antihypertensive treatment ever carried out and the only large blood pressure (BP) trial to be carried out in a US population in the past decade.1 The rationale for ALLHAT, which was designed in the early 1990s, was the urgent need to determine which of the several classes of antihypertensive drugs that had been developed and released for clinical use was most effective in preventing coronary heart disease (CHD), defined as fatal CHD and nonfatal myocardial infarction.2

The only randomized trials that had previously compared representatives of the antihypertensive drug classes, the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents3 and the Treatment of Mild Hypertension Study (TOMHS),4 showed BP reductions with all classes but were not powered to evaluate CHD outcomes. Further, prior outcome trials had shown that the reduction in CHD event rates with antihypertensive treatment was less than expected based on epidemiologic data.5 Adverse effects of study drugs, particularly diuretics, including hypokalemia, hypomagnesemia, hyperuricemia, hyperlipidemia, insulin resistance, and ventricular ectopic activity, had been adduced to account for the disappointing outcomes of earlier trials by offsetting the beneficial effects of BP reduction.6,7 To further complicate the picture, benefits beyond BP reduction had been attributed to some antihypertensive drug classes, ie, improved survival and reduced morbidity in persons with heart failure or left ventricular dysfunction treated with angiotensin-converting enzyme (ACE) inhibitors8–10 and improved insulin sensitivity and lipid profiles with α-blocker treatment.11 In contrast, another antihypertensive drug class, the dihydropyridine calcium channel blockers (CCBs), had been associated with unfavorable outcomes in patients with acute myocardial infarction or unstable angina.12 There were no data comparing the effectiveness of different classes of antihypertensive drugs in preventing cardiovascular disease (CVD) outcomes and no outcome data at all on the effectiveness of antihypertensive treatment in high-risk populations, including blacks and persons with type 2 diabetes. A final issue was the rapidly rising cost of treating hypertension in the US, a cost that was driven, in part, by increased acquisition prices of the newer classes of drugs compared with the older diuretics, the only class that had been shown to reduce CVD outcomes.

Design and Baseline Data

In response to these needs, ALLHAT was designed to test the primary hypothesis that the combined incidence of fatal CHD and nonfatal myocardial infarction would be lower in hypertensive persons randomized to representatives of the newer antihypertensive drug classes—the CCB amlodipine, the ACE inhibitor lisinopril, or the α-blocker doxazosin—than in those randomized to the thiazide-like diuretic chlorthalidone as first-line therapy. Secondary hypotheses were that participants randomized to the newer drugs would have a reduced incidence of all-cause mortality and of other CVD endpoints, including combined CHD (CHD, coronary revascularization procedures, or hospitalized angina), stroke, combined CVD (CHD, stroke, coronary revascularization procedures, angina, heart failure, or peripheral arterial disease), left ventricular hypertrophy (LVH) by electrocardiogram (ECG), renal disease, improved health-related quality of life, and reduced major costs of medical care.

Hypertensives at high risk of CVD events because of age (≥55 years) and the coexistence of other risk factors (HDL cholesterol <35 mg/dL, current cigarette smoking), preexisting CVD, or type 2 diabetes were eligible for the trial. ALLHAT was planned to include 55% blacks and 45% women because of the paucity of outcomes data for these subgroups of hypertensive persons.

Because of the large number of statistical comparisons needed to test the primary hypothesis, a large sample size was needed, and 42 418 participants were recruited into the trial at 623 clinical practice sites in the US, Canada, Puerto Rico, and the US Virgin Islands. Many of these sites had no prior research experience. The mean age of participants at the time of enrollment was 67 years; 35% were black, 19% Hispanic; 36% had type 2 diabetes; 47% had existing CVD; 47% were women; 90% were receiving medications for treatment of their hypertension.13 Thus, ALLHAT participants mirrored
the high risk US hypertensive population, a profile not seen in previous outcome trials.

**Preliminary Findings**

The α-blocker arm of ALLHAT was terminated early (January 2000) because of an increased incidence of major CVD events, particularly heart failure, and for futility (a very low likelihood of observing a significant treatment-related difference for the primary outcome by the scheduled end of the trial).14,15 The primary CHD outcome did not differ between the α-blocker and diuretic treatment arms, however.

**Blood Pressure Control**

Follow-up of participants in the remaining 3 arms of ALLHAT was completed in March 2002, after a mean of 4.9 years. Overall, BP control (goal BP ≤140/90 mm Hg) was greatly improved from only 27% at enrollment to 66% at the conclusion of the study.16 Systolic BP was <140 mm Hg in 67% of participants; diastolic BP was <90 mm Hg in 92%, confirming that systolic BP is more difficult to control than diastolic BP in older populations. Almost two thirds of participants were on 2 or more antihypertensive drugs by the end of the trial, and among those who were controlled, only 40% were on a single drug; 35% required 2 drugs, and 23% 3+ drugs. These observations indicate that BP control in usual practice settings can be greatly improved with careful follow-up and monitoring and with aggressive use of currently available antihypertensive medications.

Interestingly, BP was less well controlled in women and in participants who were older, diabetic, obese, had LVH or higher baseline systolic BP, and in blacks. Blacks were 31% less likely to be controlled than nonblacks and were less likely to be treated with multiple drugs. Available data do not explain the poorer BP control in black ALLHAT participants—whether this relates to physiological or lifestyle differences, differences in practice patterns of the ALLHAT investigators, or poorer medication adherence by the black participants is not yet clear. Cost of medications was not an issue, as all of the antihypertensive medications prescribed by the ALLHAT protocol were provided to the participants without cost.

**Final Results**

In the analysis of ALLHAT final results, all treatments were compared with the diuretic. BP control by treatment assignment showed interesting differences: systolic BPs were significantly higher in the CCB (0.8 mm Hg, P=0.03) and ACE inhibitor (2 mm Hg, P<0.001) groups than in the diuretic group, and the ACE inhibitor–diuretic disparity was even greater (4 mm Hg) in blacks.1 Diastolic BP was lower in the CCB (0.8 mm Hg, P<0.001) than in the diuretic group.

There was no difference between treatments in the primary outcome (nonfatal myocardial infarction and fatal CHD) or in all-cause mortality. Secondary outcomes did show interesting differences, however. For the CCB-diuretic comparison, all secondary outcomes were similar except for a 38% excess risk of developing heart failure and a 35% higher risk of being hospitalized for heart failure. The ACE inhibitor–diuretic comparison showed many more differences: participants assigned to the ACE inhibitor experienced 10% more combined CVD events (19% more in blacks), including 15% more strokes (40% more in blacks), 19% more heart failure (32% more in blacks), 11% more angina (hospitalized or treated), and 10% more coronary revascularizations than those assigned to the diuretic. Treatment effects were consistent across 3 of the 4 predefined subgroups (age, sex, diabetic status) for both treatment comparisons. In the black subgroup, however, the relative risks of stroke, heart failure, combined CVD, and combined CHD among those randomized to the ACE inhibitor compared with the diuretic were significantly higher than in nonblacks. These differences could not be attributed to differences in BP control, because adjustment for follow-up BPs as time-dependent covariates in a Cox-proportional hazards regression model reduced the relative risks for stroke and heart failure only slightly in the black subgroup.

Primary safety outcomes included hospitalization for gastrointestinal bleeding, which did not differ among treatment groups, and angioedema, which was significantly more common in the ACE inhibitor group, especially among blacks.

**Comments**

ALLHAT fulfilled its promise in that it clearly refuted its own primary hypothesis, that the newer classes of antihypertensive drugs would be superior to a thiazide-type diuretic in preventing fatal and nonfatal CHD when given as a first-line therapy. There was no difference between treatment groups (even the discontinued α-blocker group) with respect to this primary endpoint. There were, however, major differences, some of them surprising, among treatment groups with respect to major secondary endpoints.

The excess risk of heart failure with the CCB and the α-blocker was predictable from previous studies.17–19 However, the absence of excess CHD, cancer, gastrointestinal bleeding, and all-cause mortality with the CCB does not support previous reports based on observational data and clinical trials of short-acting CCBs.18,20 Further, there was no significant difference in the incidence of end stage renal disease between the CCB and diuretic groups, and comparison of the reciprocal creatinine slopes actually suggested a slower decline in renal function in the CCB group, although interpretation of the latter finding is open to question. Preservation of renal function with CCB treatment is consistent with findings of the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial, which was carried out in a European population without baseline renal disease,21 but contrasts with findings of studies carried out in persons with baseline diabetic or nondiabetic renal insufficiency and associated proteinuria.22,23 In the latter trials, amlodipine treatment appeared to accelerate the development of renal insufficiency. Importantly, ALLHAT enrolled a low renal risk population (mean baseline serum creatinine = 1.0 mg/dL; serum creatinine >2 mg/dL, was an exclusion criterion), and end stage renal disease was not a primary endpoint of the trial. Taken together, the ALLHAT results give assurance that long-acting CCBs are safe and effective alternatives to diuretics as first-line antihypertensive treatment.
Another surprising result of ALLHAT was the superiority of diuretic-based treatment to ACE inhibitor–based treatment in preventing stroke, heart failure, angina, and coronary revascularization. These findings are counterintuitive, considering the proven efficacy of ACE inhibitors in delaying the transition from left ventricular dysfunction to heart failure, as well as in the treatment of established heart failure.10-12 These differences between ACE inhibitor and diuretic treatment were present in all 4 prespecified subgroups, even diabetics, in whom ACE inhibitor treatment would be expected to be superior, and were even greater in blacks. The latter observation is consistent with reports of poorer BP responses to ACE inhibitors23 and lesser effects of ACE inhibitors in secondary prevention of heart failure in blacks.24,25 Importantly, although the differential responses for disease outcomes and BP responses were in parallel, the differences in outcomes were not substantially reduced by statistically adjusting for systolic BP. Further, ACE inhibitor–based therapy was no better than diuretic-based treatment in preserving renal function, contrary to published findings in high renal-risk populations.22

Adverse metabolic effects of diuretic treatment were common in ALLHAT. Hypokalemia (serum K+ <3.5 mEq/L) occurred in nearly 13% at year 2 of the trial, and 8% were receiving K+ supplements at 5 years; fasting glucose was elevated (>126 mg/dL) in nearly 12% of previously nondiabetic participants at 2 years, and total cholesterol was significantly higher in the other treatment groups. Despite these abnormalities in surrogate endpoints, no excess of CVD events or mortality was associated with diuretic treatment.

Limitations of ALLHAT, acknowledged by the authors and discussed in the accompanying editorial,27 include the following: (1) the failure to achieve identical BPs in all treatment groups, a particular problem in the black subgroup; (2) a trial design that resulted in a somewhat artificial regimen of step-up drugs (no diuretics or CCBs allowed) in the ACE inhibitor group; (3) uncertainty about whether the results can be extrapolated from the specific drugs tested to other drugs in the ACE inhibitor group; (4) omission of newer agents, released since ALLHAT was designed, such as angiotensin receptor blockers and selective aldosterone receptor antagonists, and of β-blockers, which are often used to treat hypertension in high risk persons. Finally, the comments on the cost differential between diuretic-based and newer drug-based regimens in the ALLHAT results paper are limited to considerations of drug acquisition costs, which may not accurately reflect the whole picture. A formal cost-benefit analysis based on the results of ALLHAT is forthcoming.

Despite these limitations, some of which are inherent in any randomized, controlled trial, the results of ALLHAT provide convincing evidence that thiazide-type diuretics are the best initial therapy for hypertension in a high risk US population. It is likely that these findings will be given substantial weight in the deliberations of the 7th Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure, which will soon be announced.

References


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