Hypertension and hyperlipidemia are potent cardiovascular risk factors. Treatment can lower blood pressure and reduce events, but the optimal drug for initial hypertension treatment and the benefits of long-term cholesterol reduction on clinical outcomes in understudied hypertensive subpopulations were unknown. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a long-term randomized, multicenter study undertaken to address these questions. In the hypertension component, 42,448 patients with mild-moderate hypertension and 1 or more other coronary risk factors were randomized to initial therapy with chlorthalidone, or to a newer antihypertensive agent—doxazosin (alpha blocker), amlodipine (calcium blocker), or lisinopril (angiotensin-converting enzyme inhibitor). The primary combined endpoint was coronary heart disease mortality or nonfatal myocardial infarction, with secondary endpoints including combinations of mortality, cardiac, and vascular complications. By interim analysis, doxazosin was shown inferior to diuretics in preventing secondary endpoints, resulting in early termination of this arm. There were no differences in primary endpoint frequency in chlorthalidone-amlodipine and chlorthalidone-lisinopril comparisons, but both amlodipine and lisinopril therapy resulted in more secondary events. In the lipid-lowering trial, 10,355 patients enrolled in the hypertensive trial with low-density-lipoprotein levels 100 to 189 mg/dL were randomized to pravastatin or usual care. There was no overall difference in the primary endpoint (total mortality) or most secondary endpoints, with statin therapy reducing stroke and coronary events modestly but nonsignificantly. Subgroup comparisons showed equivalent treatment effects in all groups except blacks, who had greater reduction in total coronary events but more strokes with pravastatin therapy and more strokes with lisinopril treatment.

**KEY WORDS:** cardiovascular events, hyperlipidemia/treatment, hypertension/treatment, review

Hypertension is a common health problem, especially among elders, requiring costly treatment of the primary disease and its frequent complications. Although pharmacologic treatment reduces the risk of hypertension-related morbidity and mortality, drug costs are a major contributor to the financial impact of this disease. Whether new, more expensive antihypertensive drugs offer additional...
benefit over less costly older agents had been unclear. Hyperlipidemia, frequently present concurrently, adds to the complexity, morbidity, and cost of the long-term management of hypertensive patients.

**ALLHAT Hypertension Study**

Early clinical trials demonstrated the ability of thiazide diuretics and beta blockers to lower blood pressure and reduce cardiovascular disease events. New classes of antihypertensive agents, including calcium-channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACE-i), and alpha-adrenergic blockers (AAB), became available for chronic hypertension management in the 1970s and 1980s. Placebo-controlled trials documented the ability of ACE-i and CCB to reduce cardiovascular events, but there was limited evidence of their performance compared with older, less expensive agents. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents and the Treatment of Mild Hypertension studies compared these drug classes, but did not have clinical outcomes as primary endpoints. Other trials examining effects of newer antihypertensives on secondary (surrogate) cardiovascular disease endpoints failed to clarify the relative value of these newer drug classes compared to diuretics in reducing the cardiovascular complications of hypertension. A large-scale comparative trial was needed to make this determination.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a long-term randomized, practice-based, multicenter clinical trial of older, high-risk hypertensive patients sponsored by the National Heart, Lung and Blood Institute. The antihypertensive study was a randomized, double-blind trial designed to determine whether the incidence of hard cardiovascular endpoints differs between diuretic (chlorthalidone) treated patients and those treated with a CCB (amlodipine), an ACE-i (lisinopril), or an AAB (doxazosin). The primary experimental hypothesis stated that the combined incidence of fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI) is lower in hypertensive patients treated with a CCB, ACE-i, or AAB as first line therapy than in those treated with a thiazide diuretic.

A total of 42,448 patients were initially randomized into the hypertensive trial; following early termination of the doxazosin arm (see below), 33,357 patients remained in the final antihypertensive comparison. Subjects consisted of men and women aged 55 years and older with mild to moderate hypertension and at least one additional risk factor for CHD (previous MI or stroke, left ventricular hypertrophy on echocardiogram or electrocardiogram, type 2 diabetes, smoking, high-density lipoprotein less than 35 mg/dL, or established atherosclerotic cardiovascular disease) from 623 clinical centers in the United States, Puerto Rico, the US Virgin Islands, and Canada. In addition to lifestyle modification recommendations, participants were randomly assigned to receive chlorthalidone 12.5 to 25 mg, amlodipine 2.5 to 10 mg, or lisinopril 10 to 40 mg, each once daily in titrated doses on the basis of response. The blood pressure goal (based on an average of 2 seated measurements) was a diastolic blood pressure (DBP) <90 mm Hg and systolic blood pressure (SBP) <140 mm Hg. For participants unable to achieve target BP control with the maximum tolerated dosage of the assigned blinded treatment, open label second line (atenolol 25–100 mg daily, clonidine 0.1–0.3 mg twice daily, or reserpine 0.05–0.2 mg daily) and third line (hydralazine 25–100 mg twice daily) agents were added at the discretion of the investigator. Low doses of the assigned study therapy, administered in an open label fashion, were permitted if clinically indicated. Follow-up visits were at 1, 3, 6, 9, and 12 months following randomization, and every 4 months thereafter. Total follow-up averaged 4.9 (range 3.7–8.1) years.

The primary combined endpoint was fatal CHD or nonfatal MI. Prespecified secondary outcomes were all-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome, coronary revascularization [bypass surgery, angioplasty, stents, atherectomy], and hospitalized angina), and combined cardiovascular disease (combined CHD, stroke, other treated angina, heart failure [HF–fatal, hospitalized or treated nonhospitalized], and peripheral arterial disease). Individual components of the combined outcomes, as well as cancer, left ventricular hypertrophy on ECG, end-stage renal disease, and other parameters of renal function were also examined. Determination of event occurrences took place at follow-up visits and reports of study outcomes were confirmed by hospital discharge summaries and copies of death certificates. Searches of selected government databases were conducted to capture and/or verify study events. Additional outcome data were also collected on a subset of CHD and stroke events. Following the termination of the doxazosin arm (see below), a sample of HF admissions was also reviewed. Angioedema and hospitalization for gastrointestinal bleeding were the 2 major prespecified safety outcomes for examination. Data were analyzed using the intention-to-treat principle and standard statistical methods. An independent Data Safety Monitoring Board (DSMB) met at least annually to perform prespecified interim
analyses, monitoring for treatment safety and efficacy.\textsuperscript{3}

**Antihypertensive Results**

In January 2000, after an average patient follow-up period of 3.3 years, the DSMB terminated the doxazosin treatment arm (9067 patients) after identifying higher relative risks (RR) vs chlorthalidone of stroke (RR 1.19), combined cardiovascular disease (RR 1.25), angina (RR 1.16), and HF (RR 2.04)\textsuperscript{4}; these patients were excluded from further analyses. At study conclusion, vital status was known for over 97% of randomized patients in the 3 remaining treatment arms. Baseline subject characteristics were similar across all treatment groups. Although visit adherence was comparable (84%–87%) in all 3 cohorts, medication adherence was similar for the chlorthalidone and amlodipine groups (80.5%; 80.4%) but lower (72.6%) in the lisinopril group at 5 years. All groups required similar adjunctive therapy, and usage patterns for second and third line therapy were similar among treatment cohorts. Details of the crossover therapy are described elsewhere.\textsuperscript{3}

At 5 years of follow-up, nearly two thirds of patients had achieved a goal BP <140/90 mm Hg (chlorthalidone 68.2%, amlodipine 66.3%, lisinopril 61.2%). Average SBP was 133.9, 134.7, and 135.9 mm Hg, and average DBP was 75.4, 74.6, and 75.4 mm Hg, respectively.\textsuperscript{5} The mean number of drugs prescribed was 2 ± 1, with 63% of patients receiving at least 2 drugs.\textsuperscript{5}

Serum cholesterol fell progressively in all 3 treatment groups, and at 4 years more than a third of all participants reported taking lipid-lowering therapy. Mean serum potassium levels at 4 years had fallen 0.2 mEq/L for chlorthalidone patients, while increasing 0.1 mEq/L for both amlodipine and lisinopril patients compared to baseline values ($p < .001$). The incidence of new diabetes (fasting serum glucose ≥126 mg/dL) at 4 years was greatest in the chlorthalidone group (11.6%), but only 9.8% and 8.1% in the amlodipine and lisinopril groups respectively. Although glomerular filtration rate (78 mL/min/1.73 m$^2$) was similar at baseline and diminished over time in all 3 groups, the decline was less in the amlodipine group (to 75.1 mL/min/1.73 m$^2$, $p < .001$) but equal in the chlorthalidone and lisinopril arms (to 70.0 and 70.7 mL/min/1.73 m$^2$, respectively, $p = .03$).\textsuperscript{3}

No significant differences were observed between the amlodipine and chlorthalidone arms, or between lisinopril and chlorthalidone arms, for the primary outcome (Figs 1 and 2). The amlodipine group did have a 38% higher risk of HF ($p < .001$), but no

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**FIGURE 1.** Relative risks and 95% confidence intervals for lisinopril-chlorthalidone comparisons in prespecified groups. Scales are shown in natural logarithm. Reproduced with permission from JAMA.\textsuperscript{3} Copyright 2002, American Medical Association.
significant differences in the amlodipine-chlorthalidone comparison for other secondary outcomes were demonstrated. Similarly, secondary outcomes of all-cause and cause-specific mortality, combined CHD, peripheral vascular disease, cancer, or end-stage renal disease were equivalent in the lisinopril-chlorthalidone comparison. However, the lisinopril group had a 15% higher risk of stroke (p = .02) (40% higher in blacks) and a 10% higher risk of combined cardiovascular disease (p < .001), when compared to the chlorthalidone cohort. Lisinopril-treated patients had a 19% higher risk of HF (p < .001), 11% higher risk of hospitalized/treated angina (p = .01), and 10% higher risk of coronary revascularization (p = .05) than chlorthalidone-treated subjects.

For the primary safety outcomes, there were no significant differences noted in hospitalizations for gastrointestinal bleeding. Angioedema occurred in all 3 groups, with significantly greater frequency in the lisinopril-treated (0.4%) than in chlorthalidone-treated (0.1%) patients.

**ALLHAT Lipid-Lowering Trial**

Investigative evidence has confirmed the etiologic role of elevated levels of low-density-lipoprotein (LDL) cholesterol in CHD. Recent clinical trials have also demonstrated that LDL-lowering therapy reduces the risk for CHD and related events. However, these studies were often too small to assess total mortality or other clinical outcomes in specific subgroups.

The ALLHAT Lipid Lowering Trial was a randomized, nonblinded study of 10,355 participants, conducted concurrently with the antihypertensive study, at 513 ALLHAT clinical sites. Site participation was based on the ability to successfully enroll and randomize eligible participants. The primary hypothesis of the Lipid Lowering Trial was that total mortality is lower in hypertensive participants with baseline LDL values of 120 to 189 mg/dL (100–129 mg/dL for those with known CHD) who are randomized to pravastatin plus a cholesterol-lowering diet than in those assigned to receive diet plus usual care (defined as any cholesterol-lowering regimen felt to be indicated by the patient’s health care provider). Site participation was based on the ability to successfully enroll and randomize eligible participants. The primary hypothesis of the Lipid Lowering Trial was that total mortality is lower in hypertensive participants with baseline LDL values of 120 to 189 mg/dL (100–129 mg/dL for those with known CHD) who are randomized to pravastatin plus a cholesterol-lowering diet than in those assigned to receive diet plus usual care (defined as any cholesterol-lowering regimen felt to be indicated by the patient’s health care provider). Site participation was based on the ability to successfully enroll and randomize eligible participants. The primary hypothesis of the Lipid Lowering Trial was that total mortality is lower in hypertensive participants with baseline LDL values of 120 to 189 mg/dL (100–129 mg/dL for those with known CHD) who are randomized to pravastatin plus a cholesterol-lowering diet than in those assigned to receive diet plus usual care (defined as any cholesterol-lowering regimen felt to be indicated by the patient’s health care provider). Site participation was based on the ability to successfully enroll and randomize eligible participants. The primary hypothesis of the Lipid Lowering Trial was that total mortality is lower in hypertensive participants with baseline LDL values of 120 to 189 mg/dL (100–129 mg/dL for those with known CHD) who are randomized to pravastatin plus a cholesterol-lowering diet than in those assigned to receive diet plus usual care (defined as any cholesterol-lowering regimen felt to be indicated by the patient’s health care provider). Site participation was based on the ability to successfully enroll and randomize eligible participants. The primary hypothesis of the Lipid Lowering Trial was that total mortality is lower in hypertensive participants with baseline LDL values of 120 to 189 mg/dL (100–129 mg/dL for those with known CHD) who are randomized to pravastatin plus a cholesterol-lowering diet than in those assigned to receive diet plus usual care (defined as any cholesterol-lowering regimen felt to be indicated by the patient’s health care provider). Site participation was based on the ability to successfully enroll and randomize eligible participants. The primary hypothesis of the Lipid Lowering Trial was that total mortality is lower in hypertensive participants with baseline LDL values of 120 to 189 mg/dL (100–129 mg/dL for those with known CHD) who are randomized to pravastatin plus a cholesterol-lowering diet than in those assigned to receive diet plus usual care (defined as any cholesterol-lowering regimen felt to be indicated by the patient’s health care provider). Site participation was based on the ability to successfully enroll and randomize eligible participants. The primary hypothesis of the Lipid Lowering Trial was that total mortality is lower in hypertensive participants with baseline LDL values of 120 to 189 mg/dL (100–129 mg/dL for those with known CHD) who are randomized to pravastatin plus a cholesterol-lowering diet than in those assigned to receive diet plus usual care (defined as any cholesterol-lowering regimen felt to be indicated by the patient’s health care provider).
life, and medical care costs. Study endpoints were ascertained at the follow-up visits and documented by means similar to those described for the antihypertensive trial.

Eligibility criteria included concurrent enrollment in the antihypertensive component, triglycerides ≤ 350 mg/dL and fasting LDL of 120 to 189 mg/dL for those with no known CHD or 100 to 129 mg/dL for those with CHD. This latter upper LDL limit was lowered from 159 mg/dL in April 1994 following the release of another clinical trial demonstrating benefit from more aggressive therapy for secondary prevention. Eligible lipid values were based on the average of 2 fasting LDL measurements taken at the ALLHAT antihypertensive baseline and 1-month follow-up visits.

Participants were instructed to follow the National Cholesterol Education Program (NCEP) Step I diet. Patients assigned to pravastatin initially received 20 mg daily, with dosage increased to 40 mg as needed to achieve a 25% reduction in LDL. After 1000 participants had been enrolled, a uniform dosage of 40 mg daily was adopted for all participants in the pravastatin group. Dietary and/or pharmacologic lipid-lowering interventions in the usual care group were implemented at the discretion of the participants’ primary care providers. However, aggressive therapy for this group was discouraged unless dictated by a change in clinical status. Follow-up visits for the Lipid Lowering Trial study coincided with those for the antihypertensive trial.

**Lipid-Lowering Results**

Baseline characteristics were similar between the 2 treatment cohorts. Average follow-up was 4.8 years. Higher mean total cholesterol and LDL values were found in participants without known CHD compared to those with CHD (226.6 vs 205.2 mg/dL and 148.1 vs 129.3 mg/dL, respectively), reflecting the differences in the eligibility criteria for these populations. Although slightly lower in the usual care group, visit adherence exceeded 85% for both groups throughout the trial. Compliance with pravastatin therapy steadily declined from year 2 (87%) to year 6 (77%). Crossovers to statin therapy in the usual care group increased from 8% (year 2) to 17% (year 4). Nearly one third of all participants started lipid-lowering therapy during the trial (32% with CHD; 29% without CHD) regardless of their CHD status at baseline. At year 4, the reduction in total cholesterol was greatest for the pravastatin group (17.2% vs 7.6% for usual care) and the final total cholesterol difference between the 2 treatment groups was 9.6%. Similarly, year 4 LDL levels in the pravastatin arm also showed a greater decline (27.7%) than that in the usual care group (11%). HDL increased by 3.3% in the pravastatin group and 3.4% in the usual care group.

There was no significant difference in all-cause or cause-specific mortality between the 2 treatment arms. Strokes, CHD events, HF, and cancer incidences were similar in both pravastatin and usual care groups.

No significant differences between treatment groups were demonstrable for any outcomes when patients were stratified by age, gender, or history of type 2 diabetes. However, pravastatin therapy did provide a more favorable effect on CHD events in blacks than in non-blacks, while parallel analyses for stroke showed less benefit from pravastatin treatment, and no differences in combined cardiovascular outcomes.

**Discussion**

The antihypertensive component of ALLHAT compared the ability of the older thiazide diuretic chlorthalidone to that of the AAB doxazosin, the CCB amlодipine, and the ACE-i lisinopril to lower the incidence of major complications of hypertension. Doxazosin was determined to be inferior to diuretic in preventing stroke, angina, HF, and combined cardiovascular disease risk, and this study arm was terminated early. The incidence of fatal CHD and nonfatal MI did not differ significantly among the 3 remaining treatment groups. Chlorthalidone, however, was superior in reducing several secondary adverse outcomes. Diuretic was superior to amlodipine in preventing HF, and superior to lisinopril in tolerability, antihypertensive efficacy, and preventing combined cardiovascular disease events (stroke, HF, angina, and coronary revascularization). The primary and secondary outcome results for the amloidipine-chlorthalidone comparisons were similar for all subgroups. In the lisinopril-chlorthalidone comparison, results were similar by age, gender, and diabetic status. This consistency of findings across subgroups suggests a consistent application of these results to treatment of most high-risk hypertensive elders. The 10% higher rate of combined cardiovascular disease seen in the lisinopril (vs chlorthalidone) cohort contrasts with the benefits of ACE-i reported in some cardiovascular and renal event reduction studies. The increased rate of combined cardiovascular disease and stroke was greater in black than non-black subjects, who also suffered more HF and poorer BP response when treated with lisinopril. Similar findings have been reported in other studies of ACE-i therapy in blacks.

The ALLHAT antihypertensive results apply only to the individual drugs studied. However,
when combined with other trial evidence, these data may allow for some generalizations about the representative drug classes. Available evidence now suggests that thiazide-type diuretics should be considered the drugs of choice for initial therapy in uncomplicated hypertension, particularly in patients with additional cardiovascular disease risk factors. Generically available diuretics can provide a considerably less expensive alternative to newer, patent-protected antihypertensive agents. For patients who cannot take diuretics, CCB or ACE-i therapy may be acceptable alternatives. As most hypertensive patients will require more than one agent to achieve and maintain BP control, it appears reasonable to include a diuretic in any multidrug antihypertensive regimen.

It is important to realize the limitations of the antihypertensive study design when extrapolating the results to clinical care. Patients with significant preexisting HF were excluded from enrollment; thus, despite lisinopril’s inferior performance in ALLHAT hypertensive patients, this study in no way suggests that hypertensive patients with left ventricular dysfunction should receive thiazides in lieu of ACE-i. Although progression to end-stage renal disease and decline in renal function were secondary outcomes, ALLHAT results do not suggest that diuretics should be prescribed preferentially over ACE-i to hypertensive diabetic patients at risk of nephropathy. Hypertensive patients who may have required amlodipine for control of symptomatic angina were also excluded, as patients were required to be symptom free off study drugs prior to enrollment. Finally, none of the agents studied (including doxazosin) were added as second or third line agents as part of a multidrug regimen. Hence, neither safety nor efficacy (nor lack thereof) of any of the study drugs in these, and other, alternate populations/settings can be inferred from the ALLHAT results.

The ALLHAT Lipid Lowering Trial provided information on the value of cholesterol lowering in specific subgroups underrepresented in earlier lipid-lowering trials. Both ALLHAT Lipid Lowering Trial study groups demonstrated substantial cholesterol reductions, yielding only a modest difference at study conclusion. Pravastatin conferred only a small, nonsignificant decrease in CHD, and no mortality reduction. However, ALLHAT Lipid Lowering Trial should not be interpreted as a negative trial but rather as an inconclusive trial. The modest elevations in total cholesterol and LDL in the study population likely reduced the potential for event reduction in the treatment group. Also, diet, lifestyle modification, and frequent prescribing of statins in the usual care group resulted in less difference in the mean plasma lipid values at the end of the study than initially expected. In the context of a modest cholesterol difference, these results are not inconsistent with findings from other large lipid intervention trials, supporting vigorous LDL lowering as necessary to achieve a substantial reduction in cardiovascular risk. Likewise, these findings do not give cause to alter current cholesterol treatment recommendations, but support the continued pursuit and attainment of adequate cholesterol and LDL reductions as important goals when lipid-lowering therapy is indicated, and reaffirm current knowledge of the safety and efficacy of statin therapy in the treatment of cardiovascular disease.

The ALLHAT hypertension trial was a landmark clinical investigation supporting the importance of BP control in reducing major cardiovascular disease events while providing a head-to-head comparison of newer and older antihypertensive agents. It strengthens the evidence for the effectiveness of less expensive diuretics in reducing cardiovascular morbidity and mortality, when compared to the newer but more expensive lisinopril and amlodipine. The ALLHAT Lipid Lowering Trial failed to show benefit in most cardiovascular outcomes from statin therapy, yet lower total and LDL cholesterol levels in the usual care group, and frequent statin use in this cohort, may explain the disparity between this and other lipid-lowering interventional studies.

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