Rationale and Design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)


Are newer types of antihypertensive agents, which are currently more costly to purchase on average, as good or better than diuretics in reducing coronary heart disease incidence and progression? Will lowering LDL cholesterol in moderately hypercholesterolemic older individuals reduce the incidence of cardiovascular disease and total mortality?

These important medical practice and public health questions are to be addressed by the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind trial in 40,000 high-risk hypertensive patients. ALLHAT is designed to determine whether the combined incidence of fatal coronary heart disease (CHD) and nonfatal myocardial infarction differs between persons randomized to diuretic (chlorthalidone) treatment and each of three alternative treatments—a calcium antagonist (amlodipine), an angiotensin converting enzyme inhibitor (lisinopril), and an α-adrenergic blocker (doxazosin). ALLHAT also contains a randomized, open-label, lipid-lowering trial designed to determine whether lowering LDL cholesterol in 20,000 moderately hypercholesterolemic patients (a subset of the 40,000) with a 3-hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor, pravastatin, will reduce all-cause mortality compared to a control group receiving “usual care.”

ALLHAT’s main eligibility criteria are: 1) age 55 or older; 2) systolic or diastolic hypertension; and 3) one or more additional risk factors for heart attack (e.g., evidence of atherosclerotic disease or type II diabetes). For the lipid-lowering trial, participants must have an LDL cholesterol of 120 to 189 mg/dL (100 to 129 mg/dL for those with known CHD) and a triglyceride level below 350 mg/dL. The mean duration of treatment and follow-up is planned to be 6 years. Further features of the rationale, design, objectives, treatment program, and study organization of ALLHAT are described in this article. Am J Hypertens 1996;9:342–360

KEY WORDS: Hypertension, hypercholesterolemia, pharmacologic therapy, clinical trial, ALLHAT trial, chlorthalidone, amlodipine, doxazosin, lisinopril, economics.
A n estimated 50 million people in the US have elevated blood pressure (systolic blood pressure \([SBP] \geq 140\) mm Hg or diastolic blood pressure \([DBP] \geq 90\) mm Hg) or are taking antihypertensive medication.\(^1,2\) Hypertension is considerably more common among blacks than among whites, and its sequelae are more frequent and severe in the former. Suggested explanations for these increased rates of complications among blacks have included a higher prevalence of coexisting illnesses, such as diabetes mellitus, and less effective treatment and control due in part to decreased access to medical care. The variation in cost of treating hypertension is, in large part, determined by the cost of the antihypertensive agents used.\(^3\) Given the number of patients treated (23 million in 1988–91), drug choice has substantial economic implications.\(^2,3\) All other factors remaining constant, the incremental yearly cost of treating 25 million patients with a drug costing $100 per patient compared to one costing $500 per patient is $10 billion.

Despite the known etiologic relationship of hypertension to coronary heart disease (CHD), results of large-scale randomized clinical trials in mild to moderate hypertension (\(DBP 90\) to 114 mm Hg) in largely middle-aged subjects have generally failed to demonstrate that antihypertensive drug treatment reduces the rate of CHD death or nonfatal myocardial infarction.\(^4\) Overviews of all hypertension trials have shown that antihypertensive treatment does lead to a reduction in CHD event rates.\(^5\) However, the reduction is less than expected based upon epidemiological data.\(^6\) Also, the cited overviews did not take into account the strongly positive results of the recent Systolic Hypertension in the Elderly Program (SHEP), in which diuretic-based treatment reduced major CHD events by 27% (95% confidence interval, 4 to 43%).\(^7\) Other trials in older persons with diastolic/systolic hypertension reported similar results.\(^8,9\) One possible explanation given for the failure of previous trials to demonstrate the expected degree of CHD reduction is that adverse effects of study drugs, particularly diuretics, may have offset the potential benefit of blood pressure reduction. These adverse effects include diuretic-induced hypokalemia, hypomagnesemia, hyperuricemia, hyperlipidemia, hyperglycemia, impaired insulin sensitivity, and probably increased ventricular ectopic activity.\(^1,10,11\) However, these side effects are minimal at currently recommended doses.

In the late 1970s and in the 1980s, new types of antihypertensive agents—calcium antagonists, angiotensin converting enzyme (ACE) inhibitors, and \(\alpha\)-adrenergic blockers—were developed and approved for use in chronic antihypertensive therapy. These agents are currently more costly to purchase on average. However, evidence that might justify their use in preference to the older classes of drugs is limited. Only two large long-term randomized trials have compared representatives of all of these drug classes: the 1-year trial conducted by the Department of Veterans' Affairs Cooperative Study Group on Antihypertensive Agents,\(^12\) and the 4.4-year Treatment of Mild Hypertension Study (TOMHS).\(^13\) While these trials have reported some differences in blood pressure control, side effects, quality of life, biochemical effects, and target-organ changes, these differences did not present a pattern that consistently favored one class of drugs over others. Also, these trials did not have clinical endpoints as the primary outcome for comparisons of drug classes.

Other relevant data come both from animal experiments and clinical trials in patients with heart disease. Calcium channel blockers inhibit development of atherosclerotic lesions in rabbit models, but clinical trial data on morbidity and mortality are conflicting. In a trial of diltiazem in post-myocardial infarction (MI) patients, post-hoc analyses suggested a detrimental effect in patients with a low ejection fraction, but benefit in patients without a low ejection fraction. An overview of all post-MI trials with calcium channel blockers reported a 6% (95% confidence interval, 4% to +18%) increase in mortality.\(^14\) An update of this overview that included three additional trials in patients with angina pectoris or myocardial infarction suggested unfavorable results, particularly with dihydropyridine calcium channel blockers.\(^15\) The increased mortality with the short-acting formulations of nifedipine and nicardipine occurred primarily in patients with a recent MI. This outcome might be different with a long-acting dihydropyridine, such as amlopidine.

Angiotensin converting enzyme (ACE) inhibitors reduce mortality in both severe and less severe heart failure,\(^16–18\) and reduce morbidity, including CHD, in asymptomatic left ventricular dysfunction.\(^19\) Improvements in insulin resistance have been reported with ACE inhibitors, an observation that may be especially...
relevant to patients with type II diabetes mellitus. Furthermore, Chobanian and colleagues have reported prevention of coronary lesions in the Watanabe rabbit model with captopril treatment, perhaps due to effects on cellular proliferation in the vessel wall. Antiatherosclerotic effects of ACE inhibitors have not been demonstrated in humans.

The α-blockers have been shown to have moderately favorable effects on lipid profile, particularly on HDL cholesterol, LDL cholesterol, and the LDL/HDL ratio. Improvements in insulin resistance also have been reported with α-blockers. There is some evidence that these agents may reduce platelet aggregability and stimulate tissue plasminogen activator.

These data from existing studies in humans and animal models do not permit a determination as to whether newer drugs are superior, equivalent, or inferior to older drugs in the treatment of hypertension and the prevention of its cardiovascular complications. Given the clinical and public health importance of this issue, results of large-scale comparative trials are urgently needed to assess the role of newer versus older antihypertensive agents in cardiovascular disease prevention.

Experimental evidence for the efficacy of cholesterol-lowering in reducing the incidence of CHD has been derived almost entirely from studies in white, middle-aged men, and is lacking for women, minorities, and the elderly. Observational epidemiological evidence further suggests that the relationship of cholesterol levels and CHD is less strong at older ages (although the attributable risk associated with cholesterol remains high in the elderly because of their high absolute event rates), and is less compelling for women and minorities than for men. Despite the reductions in CHD in metaanalyses of these trials, reductions in CHD mortality have been offset by increases in other causes of death. While the net change in total mortality tended to be favorable in high risk populations, such as men with prior myocardial infarction, it was not favorable in most primary prevention trials. However, the cholesterol-lowering trials published to date, with one exception, have not been designed with sufficient statistical power to address the impact on total mortality despite the reductions in CHD incidence. Also, the interpretation of these analyses has been clouded by the limited duration of treatment or degree of cholesterol-lowering in most of these trials, as well as the possible toxicity of some of the older cholesterol-lowering drugs. The advent of 3-hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors, which can lower LDL cholesterol levels by 25% or more with few apparent side effects, has facilitated the development of larger more powerful trials to address this issue. A recent 1-year pilot study, Cholesterol Reduction in Seniors Program (CRISP), demonstrated the feasibility of recruitment and retention of the elderly in a placebo-controlled trial of a reductase inhibitor.

The one exception noted above is the Scandinavian Simvastatin Survival Study (4S). This study randomized 4444 men and women from six Scandinavian countries with documented CHD and cholesterol levels between 212 and 309 mg/dL to treatment with simvastatin or placebo. The primary endpoint was total mortality with a median follow-up of 5.4 years. The results of the trial showed the following: 1) a reduction of 35% in the mean LDL cholesterol in the simvastatin group; 2) 30% fewer deaths in the simvastatin group compared to the placebo group; 3) a 42% decrease in CHD mortality without offsetting trends in other causes of death; 4) nonfatal CHD endpoints similarly and significantly reduced; 5) all-cause mortality reduced in older (60 to 70 years) and younger patients; and 6) CHD rate reductions for both men and women.

The 4S trial results were not yet reported when the present study was designed. When the results were announced, the Steering Committee considered the question of whether the cholesterol trial should continue. The decision to continue was based on two reasons. First, the 4S trial and Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) deal with very different study populations. Indeed, only 3% of the patients randomized to the ALLHAT cholesterol trial as of November 1994 would have satisfied the 4S trial entry criteria of prior CHD, age below 70 years, and total cholesterol greater than 212 mg/dL. Second, since the ALLHAT control group is assigned to receive "usual care" rather than a placebo, study physicians are not prevented from prescribing cholesterol-lowering drugs to any patient who is thought to need them. The only change made was to exclude patients with CHD and LDL above 129 mg/dL, the patients thought most likely to be advised to take cholesterol-lowering drugs. Previously, this upper limit had been 159 mg/dL. Although some physicians may also decide to prescribe these drugs for other ALLHAT "usual care" patients, the Steering Committee believed that the benefit of cholesterol lowering in primary prevention and in secondary prevention at LDL levels below 130 mg/dL was still uncertain, even after the 4S trial, and that most usual care patients in these categories would not receive such drugs.

**OBJECTIVES AND DESIGN**

ALLHAT, sponsored by the National, Heart, Lung, and Blood Institute (NHLBI) in conjunction with the
Department of Veterans’ Affairs, is a practice-based, randomized, clinical trial in 40,000 high-risk hypertensive patients 55 years and older, of whom about 45% will be women and at least 55% will be black. ALLHAT has two components. The antihypertensive component is a randomized, double-blind trial designed to determine whether the combined incidence of fatal coronary heart disease (CHD) and nonfatal myocardial infarction differs between diuretic (chlorothalidone) treatment and three alternative antihypertensive pharmacologic treatments—a calcium antagonist (amlodipine), an ACE inhibitor (lisinopril), and an α-adrenergic blocker (doxazosin). The lipid-lowering component is a randomized, open-label trial designed to determine whether lowering serum cholesterol in 20,000 moderately hypercholesterolemic men and women aged 55 years and older (a subset of the 40,000 from the antihypertensive trial) with an HMG CoA reductase inhibitor (pravastatin) will reduce all-cause mortality as compared to a control group receiving “usual care.”

Hypostheses and Study Power The primary hypotheses of the antihypertensive trial component are that the combined incidence of fatal CHD and nonfatal myocardial infarction (first or recurrent) will be lower in hypertensive patients randomized to 1) a calcium antagonist (amlodipine), 2) an ACE inhibitor (lisinopril), or 3) an α-adrenergic blocker (doxazosin) as first-line therapy than in those randomized to a thiazide-like diuretic (chlorothalidone) as first-line therapy. Thus the statistical design must account for three primary comparisons.

To maximize statistical power for the antihypertensive trial, 1.7 times as many patients will be assigned to its diuretic arm as to each of its other three arms (Table 1). The rationale for the sample size is presented in the Appendix. One of the assumptions is that half of the ALLHAT participants will be randomized to both trial components and that half will be randomized to the antihypertensive trial component only. Secondary hypotheses for this component are listed in Table 2.

The primary hypothesis of the cholesterol-lowering trial component is that mortality from all causes will be lower in the subset of hypertensive patients with LDL cholesterol levels between 120 and 189 mg/dL (between 100 and 129 mg/dL for those with known CHD) who are randomized to receive pravastatin plus a cholesterol-lowering diet (National Cholesterol Education Program [NCEP] Step I diet) than in those randomized to receive diet plus usual care. The rationale for the sample size is presented in the Appendix. Secondary hypotheses for this component are listed in Table 2.

One of the main reasons for choosing all-cause mortality as the primary endpoint was that this trial is unblinded. Further, the assessment of myocardial infarction for this component will rely on the routine centrally coded electrocardiogram (ECG), rather than the potentially biased assessment of the study physicians. Although other secondary endpoints will be examined, these will be regarded as “soft data” that will at best confirm or supplement the primary endpoint.

While a blinded study would certainly have been preferable in many ways, other factors did not make it feasible within the overall context of ALLHAT. Compliance and cross-over rates will be monitored as the trial progresses, and the study will not be continued if the actual data indicate inadequate power.

<table>
<thead>
<tr>
<th>Table 1. Anticipated Sample Size of ALLHAT Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholesterol-Lowering Trial (2 Arms)</strong></td>
</tr>
<tr>
<td><strong>Chlorothalidone</strong></td>
</tr>
<tr>
<td>Pravastatin</td>
</tr>
<tr>
<td>Usual Care</td>
</tr>
<tr>
<td>Not Eligible</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

ENROLLMENT AND FOLLOW-UP PROCEDURES

Recruitment and Baseline Visits Recruitment for ALLHAT will rely on a variety of methods, particularly chart review within the participating clinical site to identify patients who are potentially eligible for the trial components. The visit schedule and procedures for ALLHAT participants are delineated in Table 3. Data needed to make the definitive determination of eligibility for the antihypertensive trial component will be obtained in two prerandomization visits, which will generally take place 1 day to 2 months apart. The objective of Visit 1 is to assess eligibility for and interest in ALLHAT and to begin withdrawing patients from β-blockers and central α-agonists if needed. It is anticipated that many treated hypertensive patients will have been identified by chart review, and that much of the pertinent information (eg, age, risk factor status, and...
### TABLE 2. SECONDARY HYPOTHESES FOR THE ALLHAT TRIAL COMPONENTS

**Antihypertensive Trial**—The following endpoints (or their incidence) will be reduced in patients randomized to receive amlodipine, lisinopril, or doxazosin relative to those receiving chlorthalidone:

1. All-cause mortality
2. Combined coronary heart disease (CHD or revascularization procedures or hospitalized angina)
3. Stroke
4. Combined cardiovascular disease (CHD or stroke or coronary revascularization procedures or angina [hospitalized or medically treated] or CHF [hospitalized or medically treated] or peripheral arterial disease [hospitalized or outpatient revascularization procedure]),
5. Left ventricular hypertrophy by ECG
6. Renal disease
   a. Slope and reciprocal of serum creatinine
   b. End-stage renal disease (initiation of chronic renal dialysis or kidney transplant)
7. Health-related quality of life
8. Major costs of medical care

**Lipid-Lowering Trial**—The following endpoints (or their incidence) will be reduced in patients randomized to receive pravastatin relative to those receiving usual care:

1. The combined incidence of CHD death and nonfatal myocardial infarction, especially in certain subgroups, eg, blacks, patients over age 65 (the original Cholesterol Reduction in Seniors Program [CRISP] hypothesis⁹), type II diabetics, and women
2. Changes in the biennial study ECG indicative of myocardial infarction
3. Cause-specific mortality (eg, cancer, trauma)
4. Total and site-specific cancer incidence
5. Health-related quality of life
6. Major costs of medical care

*CHD, coronary heart disease; CHF, congestive heart failure; ECG, electrocardiogram.*

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number of antihypertensive drugs) will already be known. Additional interim visits may be needed for patients on β-blockers or central α-agonists in order to step down the medication. Only patients who have been randomized to the antihypertensive trial component will be considered for randomization to the cholesterol-lowering trial component, and randomization to the latter will not take place before the first postrandomization visit for the antihypertensive trial, usually 4 weeks later.

Blood pressure eligibility criteria for the antihypertensive trial, listed in Table 4, are based on the patient’s current treatment status and on the average of two seated blood pressure measurements at each of two visits. For untreated patients, the criteria used are the current JNC V definitions of diastolic and systolic hypertension (stage I-II).¹ For treated patients, the criteria are a reasonable degree of blood pressure control, ie, ≤ 160 mm Hg systolic and ≤ 100 mm Hg diastolic at visit 1, and ≤ 180 mm Hg systolic and ≤ 110 mm Hg diastolic at visit 2 (when medication may have been partially withdrawn). Additional inclusion and exclusion criteria for the antihypertensive and lipid-lowering trials are presented in Table 5.

**Randomization** Patients who meet the ALLHAT eligibility criteria, can safely discontinue prior antihypertensive drugs and be randomized to one of the four ALLHAT treatment arms, and give informed consent can enter the study at Visit 2. This visit will generally take place between 1 day and 8 weeks after Visit 1, depending on the length of time required to step down from prestudy medications or determine hypertension status. Patients initially taking no drugs or well-controlled on one drug may be randomized soon after Visit 1, while other patients may require a longer step down process (generally less than 2 months) before they can complete Visit 2. More prolonged step downs are discouraged (though not prohibited), since many patients who cannot quickly be withdrawn from their prestudy regimens may also be more difficult to maintain on a simple regimen during the trial. All randomized patients will be given appropriate hygienic advice (sodium and alcohol reduction, exercise, caloric restriction if overweight) with reinforcement as needed during the trial.

Patients who have satisfied all Visit 1 eligibility requirements for the antihypertensive trial component or have consented to begin a step down from prestudy antihypertensive drugs will also be informed of the cholesterol-lowering trial component of ALLHAT. Those who indicate interest and have not been treated with lipid-lowering drugs during the 2 months preceding Visit 1 are considered as potential candidates for this trial.

A fasting lipid battery (total cholesterol, triglycerides, HDL cholesterol, calculated LDL cholesterol¹⁴) and serum alanine transaminase (ALT, formerly SGPT) will be ob-
### TABLE 3. ALLHAT PATIENT VISIT SCHEDULE

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Months From Visit 2</th>
<th>Antihypertensive Trial</th>
<th>Cholesterol-Lowering Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>-6.0 to 1 day</td>
<td>Identify potential participant</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-2.0 to 1 day</td>
<td>Assess eligibility and interest</td>
<td></td>
</tr>
<tr>
<td>1a, b, c</td>
<td>As needed</td>
<td>Step down from prestudy antihypertensive drugs if on β-blockers or central α-agonists</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>Randomization, laboratory diet/lifestyle counselling</td>
<td>Fasting LP Profile*, ALT</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Routine data collection, dosage titration if needed†</td>
<td>Randomization, fasting LP profile, NCEP, step 1 diet</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Routine data collection, dosage titration if needed†</td>
<td>Dosage titration if needed, ALT, TC†</td>
</tr>
<tr>
<td>5, 6, 7</td>
<td>6, 9, 12 (more often if needed)†</td>
<td>Routine data collection, dosage titration if needed†</td>
<td>Routine data collection†</td>
</tr>
<tr>
<td>8, 9, 10, . . .</td>
<td>Every 4 months</td>
<td>Routine data collection†</td>
<td>Routine data collection†</td>
</tr>
</tbody>
</table>

* Total cholesterol, triglyceride, HDL, and LDL cholesterol levels. LDL calculated by the Friedewald formula.†
† Post-randomization visits.

ALT, Alanine aminotransferase; NCEP, National Cholesterol Education Program; TC, Total cholesterol.

Treated at Visit 2. Patients who indicated interest and who had an LDL cholesterol between 120 and 189 mg/dL (between 100 and 129 mg/dL for patients with known CHD) and fasting triglycerides ≤ 350 mg/dL at this visit will be informed by telephone of their eligibility for the cholesterol-lowering trial component and told to come in fasting for Visit 3. If they are eligible to participate in this ALLHAT component at Visit 3, the investigator will phone the Clinical Trials Center and receive a random assignment for the patient to either pravastatin or usual care. (Patients also can be randomized into this trial at Visit 4.) Each patient randomized to receive pravastatin will be issued an appropriate supply of 20 mg tablets and instructed to take two each evening. Patients assigned to usual care as well as those assigned to pravastatin will be advised to follow the NCEP Step 1 diet (≤30% of calories from fat, ≤10% of calories from saturated fat, ≤300 mg cholesterol/day). Study physicians retain the option to reduce the dosage in patients who cannot tolerate the full dose. Lipid profiles will be performed on all ALLHAT patients at Visit 2 and on all patients in the cholesterol trial at Visit 3. In the pravastatin group, cholesterol levels will also be measured at Visit 4 and all annual visits; full lipid profiles will be done in a randomly chosen 5% cohort. In the usual care group, cholesterol levels will be measured at the second, fourth, and sixth annual visits; full lipid profiles will be done in a randomly chosen 5% cohort.

### TREATMENT PROGRAM

**Antihypertensive Intervention** The blood pressure goal in all four arms is <90 mm Hg diastolic and <140 mm Hg systolic. The therapeutic goal is to achieve blood pressure control on the lowest possible dosage of the first-line drug. The number and dose of study drugs prescribed in pursuit of these goals will be influenced by patient tolerance and clinical judgment, particularly in use of greater than two-drug regimens.

The dosage levels available for each drug are listed in Table 6.

The identity of the drug will be masked at each dosage level. The initial dosage level will be used only during the first week after randomization to minimize potential first dose hypotension with doxazosin. For the other three drugs, the initial dose and Step 1 dosages are identical. Also, in order to allow three dose levels for the other agents with maintenance of the blind, doses 1 and 2 of chlorthalidone are both 12.5 mg. Patients will typically return at 1-month intervals for any necessary increase in dosage until both the
TABLE 4. ALLHAT BLOOD PRESSURE ELIGIBILITY CRITERIA

<table>
<thead>
<tr>
<th>Status at Visit 1 and Visit 2</th>
<th>Lower Limit* (mm Hg)</th>
<th>Upper Limit† (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP</td>
<td>DBP</td>
</tr>
<tr>
<td>Taking 1–2 drugs for hypertension for at least 2 months</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Taking drugs for &lt; 2 months or currently untreated</td>
<td>140</td>
<td>90</td>
</tr>
</tbody>
</table>

* SBP or DBP lower limit must be met at Visit 1 and Visit 2.
† SBP and DBP upper limit must be met at visit 1 and Visit 2.
‡ Visit 1 only.
§ Visit 2 only.

systolic and diastolic goal pressures are reached. If the initial dose of the blinded drug is not tolerated, it will be discontinued. A rechallenge with the medication can be attempted later, but patients will be treated with open-label drugs as needed to provide adequate blood pressure control and will continue to be followed in the study.

For patients in any of the four treatment arms who are unable to attain satisfactory blood pressure control on the maximum tolerable dosage of their first-line drug, a choice of second- and third-line drugs are provided in open-label form for use in addition to (not substitution for) the first-line drug (Table 6), unless the first-line drug is not tolerated. The choice of second-line drug(s) is at the discretion of the treating study investigator. Since the study investigators are blinded to the identity of the first-line drug to which each patient is assigned, it is likely that the frequency of use of each of the second-line drugs will be similar among the four treatment arms. Although in special cases, investigators may choose to prescribe second-line antihypertensive drugs other than those provided by the study, thiazide diuretics, calcium antagonists, ACE inhibitors, and α-adrenergic blockers are avoided unless maximum tolerated doses of a three-drug regimen have been tried and are unsuccessful in controlling blood pressure.

Cholesterol-Lowering Intervention The cholesterol-lowering component of ALLHAT will employ a randomized comparison of an HMG CoA reductase inhibitor (pravastatin) plus diet versus usual care plus diet in a subset of patients participating in the antihypertensive component of the study. The dosage of pravastatin will be 40 mg, taken in the evening. All participants in this ALLHAT component will receive instruction in the Step I diet recommended by the National Cholesterol Education Program43 upon randomization into the study. Randomization into this trial component will take place at least 4 weeks and up to 90 days after randomization into the antihypertensive component of ALLHAT.

DETERMINATION OF OUTCOMES

Endpoint Ascertainment Occurrences of study endpoints will be documented by a checklist completed at each follow-up visit and supplemented by interim reporting as needed. These diagnoses will be supported by copies of death certificates and hospital discharge summaries. The outcomes that will be obtained and tabulated over the course of the study are listed in Table 7. The underlying cause of death will be classified by the physician-investigator at the clinical site. A National Death Index (NDI) search will be performed near the end of the study to identify and document deaths that may have occurred among patients who are lost to follow-up. Because of the time lag inherent in the NDI, a private tracing service will also be used for selected participants.

The study investigators will be required to complete and submit to the Clinical Trials Center a short endpoints questionnaire for each occurrence of a study endpoint identified at or between regular visits. For each endpoint involving a death or hospitalization, the investigator will also obtain and submit a copy of the death certificate or hospital discharge summary upon which the diagnosis was based. For a random (10%) subset of hospitalized (fatal and nonfatal) myocardial infarctions and strokes, the Clinical Trials Center will request more detailed information. For this subset, inhospital ECGs and enzyme levels (for myocardial infarctions), and neurologists' reports and computed tomography (CT) or magnetic resonance imaging (MRI) reports (for strokes) will be evaluated by the study Endpoints Committee and the accuracy of the discharge diagnoses assessed.

Data Analyses The primary endpoint of the antihypertensive component of ALLHAT is combined fatal
TABLE 5. MAJOR ALLHAT INCLUSION AND EXCLUSION CRITERIA

**Antihypertensive Trial**

1. Inclusion
   a) One or more manifestations of atherosclerotic cardiovascular disease: 1) old (>6 months) or age-indeterminate myocardial infarction or stroke; 2) history of revascularization procedure; or 3) documented atherosclerotic cardiovascular disease.
   b) Type II diabetes mellitus [plasma glucose >140 mg/dL (fasting) or 200 mg/dL (nonfasting) or on insulin or oral hypoglycemics]
   c) HDL cholesterol <35 mg/dL (at ≥2 determinations within past 5 years)
   d) Left ventricular hypertrophy on electrocardiogram or echocardiogram
   e) ST-T wave electrocardiogram changes indicative of ischemia
   f) Current cigarette smoking

2. Exclusion
   a) Symptomatic myocardial infarction or stroke within the past 6 months
   b) Symptomatic congestive heart failure or ejection fraction <35%, if known
   c) Angina pectoris within the past 6 months
   d) Serum creatinine ≥2 mg/dL
   e) Requirement for thiazide-like diuretics, calcium antagonists, angiotensin converting enzyme inhibitors, or α-blockers for reasons other than hypertension
   f) Requirement for more than two antihypertensive drugs to achieve satisfactory blood pressure control
   g) Sensitivity or contraindications to any of the first-line study medications
   h) Factors suggesting a low likelihood of compliance with the protocol, eg, plans to move or travel extensively
   i) Diseases likely to lead to noncardiovascular death over the course of the study
   j) Blood pressure >180 mm Hg systolic or >110 mm Hg diastolic on two separate readings during screening or step-down

**Lipid-Lowering Trial**

1. Inclusion
   a) Enrollment in the antihypertensive trial
   b) An LDL cholesterol of 120–189 mg/dL (100–129 mg/dL for patients with known congestive heart disease) with a triglyceride level ≤350 mg/dL

2. Exclusion
   a) Current use of prescribed lipid-lowering agents or large doses (≥500 mg/day) of nonprescription niacin
   b) Contraindications to hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors (eg, significant liver disease, ongoing immunosuppressive therapy, known allergy or intolerance to the study drug)
   c) Known untreated secondary cause of hyperlipidemia (eg, hypothyroidism, nephrotic syndrome)
   d) Alanine aminotransferase (ALT) >2.0 × upper limit of normal

CHD and nonfatal MI. The primary response variable is time from randomization to development of this event. The log-rank test will be used to compare each of the nondiuretic treatment groups to the diuretic group. For the secondary endpoints of all-cause mortality, stroke, combined coronary and cardiovascular outcomes, and end-stage renal disease, the log-rank test will also be used. For the outcomes of left ventricular hypertrophy (LVH) by ECG and health-related quality of life, comparison of proportions will be used to see if there are differences in the treatment groups. For the outcome of renal disease, the reciprocal of a participant’s creatinine values at baseline, 3 months, and years 2, 4, and 6 will be obtained. Using treatment group as a fixed effect and time as a random effect, a treatment by time interaction effect will be estimated using the longitudinal models of Laird and Ware.

The primary endpoint of the lipid-lowering component of ALLHAT is all-cause mortality. The primary response variable is time from randomization to death. The log-rank test will be used to compare the group assigned to pravastatin plus diet to the group assigned to usual care plus diet. For the secondary endpoints of combined fatal CHD and nonfatal MI, fatal and nonfatal cancer, and cause-specific mortality, the log-rank test will also be used. In addition, the log-rank test will be used to compare treatments within each of the following subgroups for the outcome of combined fatal CHD and nonfatal MI: men, women, ≥ 65 years, < 65 years, blacks, nonblacks, diabetics, and nondiabetics. For the outcomes of MI by ECG and health-related quality of life, comparison of proportions will be used to see if there are differences in the treatment groups.

Interim monitoring will focus on patient intake.
TABLE 6. ALLHAT FIRST- (BLINDED), SECOND-, AND THIRD-LINE (OPEN LABEL) ANTIHYPERTENSIVE DRUGS*  

<table>
<thead>
<tr>
<th>Step 1 Agent</th>
<th>Initial Dose†</th>
<th>Dose 1‡</th>
<th>Dose 2‡</th>
<th>Dose 3‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorothalidone</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>25</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>2.5</td>
<td>2.5</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>40</td>
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<tr>
<td>Doxazosin</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Step 2 and Step 3 Agents</td>
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<tr>
<td>Reserpine</td>
<td>0.05 daily or</td>
<td>0.1 daily</td>
<td>0.2 daily</td>
<td></td>
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<tr>
<td></td>
<td>0.1 every 2</td>
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<tr>
<td></td>
<td>days</td>
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<tr>
<td>Clonidine (oral)</td>
<td>0.1 twice daily</td>
<td>0.2 twice daily</td>
<td>0.3 twice daily</td>
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</tr>
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<td>Atenolol</td>
<td>25 daily</td>
<td>50 daily</td>
<td>100 daily</td>
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<tr>
<td>Hydralazine (third-line)</td>
<td>25 twice daily</td>
<td>50 twice daily</td>
<td>100 twice daily</td>
<td></td>
</tr>
</tbody>
</table>

† All doses in milligrams.

does and inclusive each clinical center; center adherence to protocol; baseline comparability of treatment groups; sample size assumptions with regard to event rates, cross-over rates, competing risk, and loss to follow-up; adverse effects data; and effects of treatment on the primary and secondary study outcomes. Interim analyses will coincide with the meetings of the Data and Safety Monitoring Board (DSMB). Stochastic curtailment will be used for monitoring treatment differences in both the antihypertensive and the lipid-lowering studies.45,46

TABLE 7. ALLHAT OUTCOMES

1. Death
   a. Definite myocardial infarction
   b. Definite coronary heart disease
   c. Possible coronary heart disease
   d. Stroke
   e. Congestive heart failure
   f. Other cardiovascular disease
   g. Cancer
   h. Accident, suicide, or homicide
   i. Other noncardiovascular cause
   j. Unknown cause
2. Myocardial infarction
3. Stroke
4. Angina (hospitalized or treated)
5. Congestive heart failure (hospitalized or treated)
6. Peripheral arterial disease (hospitalized or treated)
7. New cancer diagnosis (hospitalized or treated)
8. Accident or attempted suicide (hospitalized or treated)
9. Left ventricular hypertrophy (biennial study, electrocardiogram)
10. Renal function
    a. Slope of the reciprocal of serum creatinine level versus time
    b. End-stage renal disease (initiation of chronic renal dialysis or kidney transplant)
11. Quality of life
12. Medical care use

ORGANIZATIONAL STRUCTURE

ALLHAT has an organizational structure that differs markedly from the usual NHLBI-supported clinical trial. This so-called ‘large, simple trial’ model, implemented previously in the International Study of Infarct Survival (ISIS) trials coordinated by Oxford University investigators56 and first used by NHLBI in the Digitalis Investigative Group trial,31 is appropriate when the following conditions apply: 1) a very large sample size is needed, 2) a streamlined protocol is possible, 3) the targeted conditions are commonly encountered in clinical practice, and 4) there is widespread interest in the study question among clinicians.

The trial will be performed by a large number (400 to 500) of practicing physician-investigators who will be compensated on a per capita basis for each patient seen according to a fixed payment schedule. Approximately 15% to 20% of study patients are expected to be recruited by Department of Veterans’ Affairs (DVA) hypertension clinics. The Clinical Trials Center, in addition to its conventional data handling and monitoring responsibilities, will be responsible for identifying and paying these physician-investigators, for enlisting regional physician and nurse study coordinators to monitor recruitment and compliance, and for
awarding and supervising subcontracts for a drug distribution center, a central laboratory, and an ECG coding center. A Steering Committee of experts in the relevant subject areas has also been appointed by NHLBI.

Practitioners will be reimbursed a fixed fee for each patient randomized to each component of the trial and for each subsequent study visit completed. This fee is expected to cover the costs of the data collection (step down and titration visits, questionnaires, blood drawing, ECG recording) specified above. The fee does not include the cost of required laboratory work and ECG coding, which will be performed by central facilities and paid for directly by the Clinical Trials Center, or the costs of documenting study endpoints, for which there will be separate reimbursement.

The Clinical Trials Center will have overall responsibility for training and quality control. All clinical sites will be required to attend a training session. The training session will include orientation to the study protocol, blood pressure measurement training and certification, orientation to ECG and laboratory procedures, and training in recruitment and retention of participants, as well as completion and transfer of study forms. Periodic refresher training will be held in conjunction with regularly scheduled Study Investigators' meetings. These refresher sessions may include a review of correct blood pressure measurement procedures or any problem that may be identified through review of routine monitoring activities.

The Clinical Trials Center's responsibilities with regard to quality control include: 1) reviewing all forms for completeness and accuracy prior to data entry; 2) resolving problems by telephone or facsimile transmission with clinical sites; 3) providing double data entry of forms; 4) cross-forms editing to identify missing forms and procedures; 5) monitoring the performance of study components and providing timely summary reports to the Program Office and to the Steering Committee; and 6) providing detailed and up-to-date statistical reports of study progress to the DSMB at their meetings.

The DSMB will be responsible for monitoring all aspects of the study, including those that require access to blinded data. The DSMB and its chair were appointed by the Director of NHLBI; they are experts who are not otherwise affiliated with the study. During the active recruitment phase, the DSMB will monitor the progress of recruitment (particularly of black patients) and the random allocation of participants to the various treatment arms and may recommend modifications in (or termination of) one or both study components if the study design goals are not being met. The approval of the DSMB will also be required for any other significant changes in the protocol recommended by the Steering Committee during the course of the study.

At any time during the study, the DSMB may recommend discontinuation of any of the treatment arms of either study component on any of the following grounds:

1) Compelling evidence from this or another trial of a significant adverse effect of the study treatment(s) that is sufficient to override any potential benefit regarding CHD and preclude its further use in the target population;
2) Compelling evidence from this or another trial of a significant beneficial effect of a study treatment, such that its continued denial to the other study groups is ethically untenable; or
3) A very low probability of successfully addressing the study hypotheses within a feasible time frame, because of inadequate recruitment, compliance, drug response, event rate, or other key performance criteria.

The Director of the NHLBI will make the final decision on whether or not to accept the DSMB's recommendation to discontinue any component of the study.

CONCLUSIONS

Hypertension is a frequent health problem in Americans, especially among older individuals and blacks. It is associated with a significantly increased risk of morbidity and mortality. Only diuretics and β-blockers have been shown to reduce this risk in long-term clinical trials among hypertensive individuals. Whether newer more costly antihypertensive agents confer increased benefit or not in terms of reduced incidence of cardiovascular disease is unknown.

Also unknown is the potential benefit of treating moderately hypercholesterolemic older men and women with an HMG CoA-reductase inhibitor in terms of reduced incidence of not only coronary heart disease but also total mortality. The results of ALLHAT are expected to be available by the year 2002, and should help resolve these issues of major importance to medical practice and public health.

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phases of ALLHAT of Dr. Teri Manolio, former NHLBI project officer.

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**APPENDIX**

**Considerations for Sample Size**

The statistical power to test the primary hypothesis of the antihypertensive trial is approximately 82.5%, based on the following assumptions: 1) sample size of 40,000 (approximately 22,000 men and 18,000 women); 2) 6 year incidence of CHD events of 7.8% in the diuretic group (derived from the Framingham Study, the Hypertension Detection and Follow-up Program [HDFP], and the Systolic Hypertension in the Elderly Program [SHEP] [personal communication]); 3) a 16.3% reduction in the CHD event rate after adjustment for noncompliance and losses to follow-up in each of the three nondiuretic treatment arms compared to the diuretic arm; 4) rates of cross-over between each of the other study drugs and chlorothalidone and nonstudy medication of 2.75% in each of the first 3 years and 6% over the last 3 years of follow-up (rates derived from the TOMHS [personal communication])—yielding a cumulative 24% rate of patients crossing over to another medication at least once in 6 years; 5) CHD status undeterminable at the end of the study for 16.8% of patients due to competing risks (non-CHD death) or loss to follow-up; 6) a 25% reduction in CHD event rates (before adjustment for noncompliance and losses to follow-up) among the 10,000 patients randomized to the active treatment arm of the cholesterol-lowering trial component; and 7) a type I error of 0.05 (two-sided), corresponding to a critical Z-score of 2.37 after adjustment for multiple comparisons using the Dunnett procedure.

The original ALLHAT protocol used an age criterion of 60 or greater and did not include current cigarette smoking as a risk factor. Lowering the entry age de-
creased the CHD event rate, but the addition of the smoking risk factor resulted in the CHD event rate estimate remaining at 1.35% / year. More pessimistic or optimistic assumptions were also considered. These include event rates of 1.05% / year to 1.65% / year and cross-over rates of 22% to 26% with loss rates of 11.8% to 21.8%. Power estimates ranged from 77% to 86% under these assumptions.

Based on National Health and Nutrition Examination Survey (NHANES II32 data for ages 65 to 74 years, in which the LDL cholesterol cutoffs for ALLHAT patients without CHD corresponded to the 25th and 86th percentile (men) and to the 14th and 76th percentile (women), just over 60% of patients in the ALLHAT study will be LDL-eligible for the cholesterol-lowering trial. It was assumed that about 80% of LDL-eligible patients (or 50% of all ALLHAT patients) would participate in the cholesterol-lowering trial. Slightly lower estimates (slightly under 60%) were later obtained in the more recent (1988–91) NHANES III data (National Center for Health Statistics, personal communication), reflecting a general downward temporal trend in LDL cholesterol levels as well as the incorporation of more data from blacks and from persons aged 75 to 84 years.

The statistical power to test the primary hypothesis of the cholesterol-lowering trial is approximately 85.5%, based on the following assumptions: 1) sample size of 20,000 (approximately 11,000 men and 9,000 women) allocated equally between pravastatin and usual care groups; 2) 6 year total mortality of 12.2% (2.15% / year) in the usual care group (derived from Framingham, HDFP and SHEP [personal communication]); 3) a 14% reduction in mortality in the pravastatin treatment arm before adjustment for dropouts and drop-ins; 4) a “dropout” rate (from pravastatin treatment to no treatment) of 5% in year 1, and 2.5% in all subsequent years, and a “drop-in” rate (from no treatment to pravastatin or a similar drug) of 2% per year—cumulative rate of 15.3% of pravastatin patients off treatment and 10.6% of usual care patients on treatment at the end of 6 years; 5) no losses to mortality follow-up; 6) a 10% reduction in mortality rate in each of the three nondiuretic treatment arms of the antihypertensive trial component; and 7) a type I error $\alpha = 0.05$ (two-sided), corresponding to a critical Z-score of 1.96.

The drop-in and drop-out rates were derived from several assumptions. 1) Based on previous experience with HMG CoA reductase inhibitors, compliance was expected to be quite good, with the bulk of noncompliance occurring early in the trial. 2) In most cases the study physician is the patient’s primary care physician and thus, there is less concern about outside physicians changing patients’ medicines than in a more conventional university-based trial. 3) The patients being considered for the cholesterol-lowering trial have lower LDL cholesterol levels than are typically treated in ordinary practice. Many patients in the US who clearly need cholesterol-lowering drugs are not being treated despite far higher LDL levels. Given the cost of lipid-lowering agents and the relatively modest lipid levels of the patients, not many patients assigned to no medication are expected to be taking active lipid-lowering medication. 4) ALLHAT physicians are advised not to randomize patients who are already receiving cholesterol-lowering drugs or who in their opinion should receive these drugs as part of their “usual care.” Thus, potential cross-overs to active treatment are for the most part not being randomized in the first place. 5) Following the publication of the 4S trial results, the protocol was amended to exclude patients with established CHD and LDL cholesterol above 130 mg / dl from the cholesterol-lowering trial. Also, the 4S study had a drop-in rate of 13% and a drop-out rate of 10% over the course of 5.4 years.

In the original ALLHAT protocol with an age criterion of 60 years or greater and not including current cigarette smoking as a risk factor, we estimated a 2.5% / year mortality rate and an unadjusted treatment difference of 12.5%. With the protocol modifications and with the results of the 4S trial study (adjusted 30% treatment difference), the new assumptions were felt to be reasonable.

More pessimistic or optimistic assumptions were also considered. These include 1) mortality rates of 2.15% / year to 2.50% / year; 2) drop-out rate of 17.8% and drop-in rate of 12.9%; and 3) reductions in mortality of 12.5% to 14%. Power estimates ranged from 76 to 90% under these assumptions.

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