METHODS AND DOSAGE FORMS FOR REDUCING HEART ATTACKS IN A HYPERTENSIVE INDIVIDUAL WITH A DIURETIC OR A DIURETIC AND AN ACE INHIBITOR COMBINATION

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/433,845, which was filed on December 16, 2002.

FIELD OF THE INVENTION

The present invention relates to methods and dosage forms for reducing and/or preventing the incidence of cardiovascular disease, including heart attacks, in individuals who are at risk, such as those individuals suffering from hypertension. The treatments and dosage forms of the present invention concern the administration of a diuretic, such as a thiazide diuretic like Thalitone®, either alone or in combination with an ACE-inhibitor, such as ramipril or ramiprilat like Altace®, to reduce and/or prevent the incidence of cardiovascular disease, namely, heart attacks or failure, in individuals who suffer from hypertension or are at risk.

SUMMARY OF THE INVENTION

It has now been discovered that the incidence of cardiovascular disease, including heart attacks, in individuals, especially those who are at risks for hypertension, can be reduced, if not eliminated by administering to such individuals and effective amount of a diuretic, such as a thiazide diuretic like chlorthalidone, either alone or in combination with an angiotensin-converting enzyme inhibitor ("ACE-Inhibitor"), such as ramipril or ramiprilat. When the diuretic is co-administered with the ACE-inhibitor, they may be administered in a single dosage form, such as a tablet, liquid, caplet or capsule, or in separate individual dosage forms. A preferred diuretic for use in accordance with the present invention is thalidone, such as Thalitone®, administered as a single daily dose in an amount of 15mg, 30mg, 45mg, 50mg, 60mg or more. A preferred ACE-inhibitor for use in accordance with the present invention is ramipril, such as Altace®, administered as a single daily dose in an amount of 1.25mg, 2.5mg, 5mg, 10mg or more.

Quite unexpectedly, it has now been discovered that the therapeutic effect of a diuretic in reducing or eliminating cardiovascular disease, including heart failure, in individuals at risk is much greater as compared to such individuals who are treated with a beta-adrenergic blocker, like propanolol and atenolol, a calcium-channel blocker, an ACE-inhibitor, such as Lisinopril, a vasodialator, such as hydralazine, a central agonists, such as oral clonidine or methyldopa, reserpine or an alpha$_1$-blocker, like prazosin and doxazosin. Even more unexpectedly, the therapeutic effect of the combination of a diuretic, such as a thizaide, like Thalitone®, and an ACE-inhibitor, such as Altace®, is far superior to the individual therapeutic effect achieved in such individuals when treated with only a diuretic or a beta-adrenergic blocker, like propanolol and atenolol, a calcium-channel blocker, an ACE-inhibitor, such as Lisinopril, a vasodialator, such as hydralazine, a central agonists, such as oral clonidine or methyldopa, reserpine or an alpha$_1$-blocker, like prazosin and doxazosin.

While the present invention has been described in the context of preferred embodiments and examples, it will be readily apparent to those skilled in the art that other modifications and variations can be made therein without departing from the spirit or scope of the present invention. Accordingly, it is not intended that the present invention be limited to the specifics of the foregoing description of the preferred embodiments and examples, but rather as being limited only by the scope of the invention as defined in the claims appended hereto.

I. Overview

This protocol describes a practice-based, randomized, clinical trial of antihypertensive pharmacologic treatment and, in a specific subset, cholesterol-lowering, in 40,000 high-risk hypertensive patients, including at least 55% African-Americans (self-described "black"). The purpose of the antihypertensive trial component is to determine whether the combined incidence of fatal coronary heart disease (CHD) and non-fatal myocardial infarction differs between diuretic (chlorthalidone) treatment and three alternative antihypertensive pharmacologic treatments -- a calcium antagonist (amlodipine), an ACE inhibitor (lisinopril), and an alpha adrenergic blocker (doxazosin)*. Because of the established benefit of antihypertensive treatment in reduction of stroke, total morbidity and mortality from cardiovascular diseases, and all-causes mortality, the antihypertensive trial component will not include a placebo or no-treatment control group. The purpose of the cholesterol-lowering trial component is to determine whether lowering serum cholesterol in moderately hypercholesterolemic men and women aged 55 years and older with the 3-hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor pravastatin will reduce all-cause mortality as compared to a control group receiving "usual care".

Secondary objectives of both trial components are to compare the effects of their respective treatment regimens on cardiovascular mortality, major morbidity, health costs, and health-related quality of life. Additional secondary objectives of the antihypertensive trial are to compare the effects of alternative treatments on all-cause mortality and on major hypertension-related morbidity such as incidence and regression of left ventricular hypertrophy and progressive renal dysfunction. Also the effect of the antihypertensive regimens on the aforementioned primary and secondary outcomes will be assess in key subgroups [over age 65, women, African-Americans, type II diabetics]. Also additional secondary objectives of the lipid-lowering trial are to assess the long-term safety of HMG CoA reductase inhibitors in men and women aged 55 years and above (particularly with regard to mortality from non-cardiovascular causes), the effect of lipid-lowering on cancer incidence and mortality, and the effect of lipid lowering on the combined incidence of fatal CHD and non-fatal myocardial infarction, especially in key subgroups [over age 65, women, African-Americans, type II diabetics]. Also, because this component of the trial will not be blinded, the incidence of myocardial infarction based on centrally coded changes in the biennial study ECG will be looked at as an end point. The mean duration of the trial is expected to be 6.0 years, ranging from 4.2 years (for the last patient entered) to 8 years (for the first patient entered).

To maximize statistical power for the primary hypotheses of the antihypertensive trial, i.e., the comparison of each alternative drug regimen to diuretic, 1.7 times as many patients will be assigned to its diuretic arm as to each of its other three arms (Table I.1). It is anticipated that half of ALLHAT participants will be randomized to both trial components and that half will be randomized only to the antihypertensive trial component.

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* On January 24, 2000, a recommendation to discontinue the doxazosin arm of the antihypertensive trial was accepted by NHLBI. Please refer to JAMA.2000;283:1967-1975.

Table I.1: Design of ALLHAT

Cholesterol-Lowering Trial (2 Arms)	Antihypertensive Trial (4 Arms)*				Total
	Chlorthalidone	Amlodipine	Lisinopril	Doxazosin*	
Pravastatin	3,655	2,115	2,115	2,115	10,000
Usual Care	3,655	2,115	2,115	2,115	10,000
Not Eligible	7,310	4,230	4,230	4,230	20,000
Total	14,620	8,460	8,460	8,460	40,000

Because of the prohibitive cost of incorporating so many participants in a traditional clinical trial structure employing independently funded clinics, this trial will adopt an organizational model using patients recruited through approximately 600 primary care and hypertension practices, clinics, and health centers, each contributing an average of 67 patients. Department of Veterans Affairs (VA) hypertension clinics are expected to comprise approximately 70 of these clinical sites and to contribute about 20% of the study patients. Forms will be kept to a minimum, and few clinical procedures not performed for routine patient care will be required.

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II. Background and Rationale

A. Antihypertensive Trial

1) Hypertension and Coronary Heart Disease (CHD)

An estimated 50 million people in the U.S. have elevated blood pressure (systolic blood pressure, SBP, ≥ 140 mmHg and/or diastolic blood pressure, DBP, ≥ 90 mmHg) or are taking antihypertensive medication. In 1983, 23 million people were taking antihypertensive drugs [1]. The ambulatory care cost of treating hypertension in the U.S. was estimated at $7.5 billion for 1986 [2]. These costs in large part are determined by the costs of the agents used, which, given the number of patients treated, have substantial economic implications. All other factors remaining constant, the incremental cost of treating 25 million patients with a drug costing $100 per patient-year of therapy compared to one costing $500 per patient-year is $10 billion.

Despite the known etiologic relationship of hypertension to CHD, large-scale randomized clinical trials in mild to moderate hypertension (DBP 90-114 mmHg) in largely middle-aged subjects failed to demonstrate conclusively that antihypertensive drug treatment reduces the occurrence of CHD death or non-fatal myocardial infarction. The pooled results of nine such trials, employing primarily thiazide-like diuretics and involving over 43,000 subjects, suggest a 9% benefit, with 95% confidence limits consistent with a 19% benefit or a 1% adverse outcome [3]. This observed treatment effect compares with a maximum predicted effect on CHD of approximately 23% for an equivalent BP difference, as derived from epidemiologic data. In contrast, the observed beneficial effect on stroke in these trials, 36%, is almost exactly that which would be predicted from epidemiologic data [4]. A more recent overview [5] of 14 trials in participants with all levels of hypertension estimated a somewhat larger effect (14% benefit, 95% confidence interval, 4-22%). While there is reason to suspect that this may be an over-estimate of the benefit, these overviews do not include the strongly positive results of recent trials in the elderly, especially the Systolic Hypertension in the Elderly Program (SHEP), in which diuretic-based treatment reduced stroke incidence by 36% and major CHD events by 27% (95% confidence interval, 4-43%)[6].

One explanation 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 [6,7]. The diuretic-induced increase in total cholesterol has been estimated to be approximately 4%, and in LDL cholesterol as much as 10% [7], though these effects may be attenuated with long-term treatment [5]. Such increases in blood lipids would be sufficient, if sustained, to offset a substantial portion of the CHD benefit from blood pressure reduction.

2) New Classes of Antihypertensive Agents

In the early 1980's two new classes of antihypertensive agents, the calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors, were developed and licensed for use in chronic antihypertensive therapy. These agents tend to cost more than older agents such as diuretics and beta-blockers, and evidence that might justify their use despite the increased cost (such as greater efficacy or fewer side effects) is limited [2]. The fourth Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) recommended beta-blockers, calcium antagonists, ACE-inhibitors and diuretics as equally acceptable first-line therapy [9]. All four classes of drugs have been found to control diastolic blood pressure as single agents in 50% or more of patients with mild hypertension. The fifth JNC report [10] reconsidered the choice of initial therapy and recommended diuretics and beta-blockers as preferred agents. In addition, JNC-V added the alpha adrenergic blockers, as well as drugs with combined alpha and beta blocking actions, as alternative first-line treatments.

Of these drug classes, only beta-blockers have been compared directly to diuretics in large-scale, long-term clinical trials in hypertension. Three such trials completed in Europe in 1985-86 showed approximate equivalence of effects on morbidity and mortality in diuretic- and beta-blocker-based regimens. Pooled analysis of these trials yields a 6% (95% confidence interval, -10% to +22%) lower CHD mortality from beta-blockers [11]. These data are in contrast to the recent Medical Research Council (MRC) Trial in the Elderly, in which patients treated with a thiazide diuretic had significantly lower rates of CHD compared to beta-blocker (atenolol) treatment or placebo, both by about 45%.

Other data have shown that calcium-blockers may inhibit development of atherosclerotic lesions in rabbit models, but trial data on morbidity and mortality are conflicting. One trial of diltiazem in post-MI patients was interpreted as showing benefit in patients without low ejection fraction, but an overview pooling all post-MI trials with calcium-blockers reported a 6% (-4% to +18%) increase in mortality [12]. An update of this overview including three additional trials in patients with angina pectoris or myocardial infarction suggests more favorable results with agents that slow the heart rate compared to dihydropyridine calcium blockers [13]. Other trials in hypertensives have shown a decrease in left ventricular mass with calcium-blocker treatment [14].

Among ACE-inhibitors, at least three of the seven licensed drugs in this class have been reported to reduce left ventricular hypertrophy [15]. ACE inhibitors reduce mortality in both severe and less severe heart failure [16], and reduce morbidity, including CHD, in asymptomatic left ventricular dysfunction [17]. With regard to effects on atherosclerosis, Chobanian and colleagues have reported prevention of coronary lesions in the Watanabe rabbit model [18], perhaps due to effects on cellular proliferation in the vessel wall.

Several alpha-blockers have been shown to have moderate favorable effects on the lipid profile, particularly on LDL cholesterol [19,20]. A few studies have also found improvements in insulin resistance, an observation that may be especially relevant to patients with type II diabetes mellitus [21,22]. There is also some evidence that these

agents may reduce left ventricular hypertrophy and platelet aggregability and stimulate tissue plasminogen activator [23-27].

Only two long-term randomized trials have compared representatives of all of these drug classes: the one-year trial conducted by the VA Cooperative Study Group on Antihypertensive Agents [28], and the 4.4-year Treatment of Mild Hypertension Study (TOMHS) [19]. While these trials have reported some differences in BP control, side effects, quality of life, biochemical effects, and target-organ changes, these differences did not present a pattern that consistently favored some drugs and not others.

Data from a large variety of studies in humans and animal models thus suggest that newer drugs may be superior, equivalent or inferior to standard drugs in the treatment of hypertension. A report from the British Hypertension Society stated: "We thus conclude that beta-blockers or diuretics are equally acceptable first-line treatments.... Unfortunately... large-scale trials have not used newer antihypertensives such as calcium antagonists and angiotensin-converting enzyme inhibitors. There are therefore no comparable data for these widely used drugs, and we urgently need large-scale comparative trials to assess the role of these agents [29]." U.S. investigators have arrived at similar conclusions [30-32].

3) Importance of Comparing Antihypertensive Agents in African-Americans

Hypertension is considerably more common among African-Americans than Caucasians, and its sequelae are more frequent and severe. Prevalence of hypertension in the second National Health and Nutrition Examination Survey (NHANES II) was 51% in African-Americans aged 25-74 years compared to 40% in Caucasians [33]. Incidence of end-stage renal disease secondary to hypertension is nearly eight-fold higher in African-American than Caucasian hypertensives [34]. Risks of left ventricular hypertrophy, stroke and stroke death have all been reported to be greater among African-American hypertensives. Suggested explanations for these differences have included higher prevalence of co-existing illnesses such as diabetes among African-Americans, and decreased access to medical care.

Given that treatment effectively reduces hypertension-related cardiovascular morbidity and mortality, populations with decreased access to care might be expected to suffer disproportionately high rates of these complications. In such groups, particularly those of lower socioeconomic status (SES), cost of drug therapy may become the overriding consideration in selection and maintenance of treatment. The current trend toward use of more expensive agents is thus more likely to become a barrier to treatment in lower SES persons, who are disproportionately represented by African-Americans and who also bear a greater burden of hypertension-related diseases. If cheaper drugs such as diuretics are equally effective in preventing the complications of hypertension as are other available agents, low SES African-Americans are those most likely to benefit from this information. If cheaper drugs are less effective, low SES African-Americans are those most likely to suffer the consequences, since they will tend to receive cheaper drugs or none at all. In either situation, and given the relative lack of clinical trials information in African-Americans, they should be heavily represented in the current trial

so that the results will be directly applicable to them. For these reasons, the population for this trial will be at least 55% African-American.

B. Cholesterol-Lowering Trial

1) Cholesterol and Coronary Heart Disease

Circulating levels of cholesterol, specifically cholesterol associated with the low-density lipoprotein (LDL) fraction, have been established by observational epidemiologic studies, by metabolic, pathologic, and genetic studies in humans and selected animal models, and by randomized clinical trials, to be a major etiologic factor in coronary heart disease (CHD) [35]. The clinical trials that have demonstrated a reduction in CHD incidence from lowering LDL-cholesterol levels have been conducted primarily in middle-aged men with hypercholesterolemia or established CHD [36-41]. Experimental evidence for the efficacy of cholesterol lowering in older men is confined to the analysis of small subgroups of clinical trials, and is lacking for women of any age. This paucity of clinical trial data led the National Cholesterol Education Program's (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults to allow considerable room for physician judgment regarding the elderly in their 1987 guidelines [42].

The uncertainty in application of the NCEP guidelines to older men and to women is a matter of considerable consequence to the public health. While myocardial infarctions in middle-age are responsible for tragic losses of life and productivity, more than 80% of all CHD deaths in the U.S. occur after age 65 [43]. Women comprise more than 60% of the population above age 65, and the majority of CHD events in this age group are in women. In 1989, CHD was responsible for nearly 400,000 deaths and $14.4 billion in direct health care costs annually in this age group. This annual toll can be expected to increase over the next four decades as the aging of the "baby boom" generation and gains in longevity shift the age distribution of the U.S. population upward.

While the evidence relating elevated cholesterol levels to CHD is strong and consistent, clinical trials [44,45] have not demonstrated that cholesterol-lowering reduces total mortality. Moreover, observational studies [46] show a U-shaped relationship of cholesterol and mortality, with higher mortality rates for persons with cholesterol levels less than 160 mg/dl and greater than 240 mg/dl compared to those in the range 160-240 mg/dl. Deaths from hemorrhagic stroke, some cancers, and respiratory and digestive diseases contribute to the excess mortality at the lowest cholesterol levels [46]. In addition, reductions in CHD mortality from moderate (drug-induced) cholesterol lowering in randomized primary prevention trials in hypercholesterolemic patients have been offset by increases in trauma-related mortality [44]. These trials were not designed with adequate statistical power to address total mortality within the planned treatment period, though some have observed favorable post-trial trends [45,47]. Larger and more powerful clinical trials are needed to address this issue.

2) Cholesterol in Older Persons and African-Americans

While observational studies suggest that clinical trial results may be applicable to men with lower cholesterol levels and to women, the prognostic power of cholesterol levels in these studies diminishes with advancing age [48-51]. Pooled analyses of 21 male and 13 female cohorts suggest that the decrease in CHD risk associated with lower blood cholesterol levels above age 65, though statistically significant at least in men, is perhaps 60% of that below age 65, with considerable variation among studies [50]. However, this apparent diminution in relative risk associated with aging may be more than offset by the concomitant increase in absolute incidence of CHD deaths and myocardial infarctions [51]. Thus, the potential public health value of cholesterol lowering in seniors cannot be ignored. The unanswered question is the extent to which these "attributable" CHD events are actually preventable when cholesterol-lowering treatment is initiated at a relatively advanced age.

Although LDL-cholesterol levels are slightly lower and HDL-cholesterol levels are slightly higher in African-Americans than non-minority populations, hypercholesterolemia is still a substantial problem among African-Americans, particularly in women with obesity and diabetes. Approximately 23% of African-American men and women aged 25-74 years had high-risk serum cholesterol levels in 1976-80 [33], in whom reduction of cholesterol levels would be expected to reduce CHD mortality and morbidity. Prior cholesterol-lowering trials have included only a handful of African-American subjects. The assumption that cholesterol lowering will produce similar reductions in CHD in African-Americans and Caucasians is unproven.

3) Use of HMG CoA Reductase Inhibitors in Older Men and Women

Many previous clinical trials of cholesterol-lowering in middle-aged men have been weakened by the limited efficacy and acceptability of the drugs employed. However, lovastatin, the first of the HMG CoA reductase inhibitors, has been used increasingly widely since its approval by the FDA in September, 1987, and has been efficacious and well-tolerated by patients of all ages [52-55]. Two small angiographic trials have demonstrated a beneficial effect of lovastatin on coronary atherosclerosis [56,57]. Two additional HMG CoA reductase inhibitors, pravastatin and simvastatin, were approved by the FDA in late 1991; both have been used for several years in other countries. The FDA is currently considering approval of a fourth HMG CoA reductase inhibitor, fluvastatin.

Few serious side effects of these drugs have been observed to date. The absence of adverse lenticular changes in the 1990 report of the EXCEL study of lovastatin [55] prompted the FDA to remove its requirement for annual slit lamp exams from the product label. Significant but reversible asymptomatic elevations in serum transaminase levels have been seen in 1-2% of patients who have received these drugs. Myositis, in rare cases progressing to rhabdomyolysis and renal failure, is the most serious reported side effect of the HMG CoA reductase inhibitors and is potentiated by concomitant use of other potentially myotoxic drugs (immunosuppressive drugs, fibrates, etc.) and by impaired renal function. However, the incidence of myositis is quite low in the absence of these factors and does not significantly exceed placebo rates at low doses. Although

HMG CoA reductase inhibitors may potentiate the effects of anticoagulants, clinically significant interactions with the antihypertensive agents to be used in ALLHAT have not been reported.

Overall, because of their efficacy, ease of administration, low toxicity, and compatibility with most other drugs, the HMG CoA reductase inhibitors appear to be well-suited for use in older men and women. They also offer the opportunity to extend our knowledge of the benefits and safety of cholesterol lowering to cholesterol levels and degrees of reduction not previously addressed by large clinical trials.

A two-year pilot study for a trial of cholesterol lowering in seniors (Cholesterol Reduction in Seniors Program, CRISP) was initiated in July, 1990, at five clinical centers. Although it used a conventional trials model, with funded clinical sites instead of the office-based recruitment model planned for the current trial, the pilot study demonstrated the feasibility of recruiting older persons into a trial of cholesterol lowering [58]. A total of 431 men and women aged 65 and above were recruited into the pilot, surpassing the goal of 400 subjects within ten months. The pilot study cohort, which is 72% female with 25% minorities, was followed through June, 1992, to compare the compliance, safety, and efficacy of two alternative dosage regimens (20 mg and 40 mg, daily) of lovastatin versus placebo. Both dosages were well-tolerated, with 85-90% compliance after one year of treatment. The mean LDL reduction (28%) obtained with the 40 mg dosage only slightly exceeded that obtained with the 20 mg dosage (24%). Small increases in HDL cholesterol (7% and 9%) and decreases in triglycerides (4% and 10%) were also observed (respectively) for the 20 mg and 40 mg dosages.

III. Hypotheses and Study Power

A. Antihypertensive Trial Component

The primary hypotheses of this trial component are that the combined incidence of fatal CHD and nonfatal myocardial infarction will be lower in hypertensive patients receiving (1) a calcium antagonist (amlodipine), (2) an ACE inhibitor (lisinopril), or (3) an alpha adrenergic blocker (doxazosin)* as first-line therapy than in those in whom a similar degree of blood pressure control is achieved using a thiazide-like diuretic (chlorthalidone) as first-line therapy. These hypotheses will be tested in a population of men and women aged 55 years and older, all with at least one additional CHD risk factor besides hypertension, of whom at least 55% will be African-American. The statistical power to test these hypotheses is approximately 82.5%, based on the following assumptions:

1) Sample size of 40,000 (approximately 22,000 men and 18,000 women), allocated among four treatment groups as shown in Table I.1.

2) Six-year incidence of CHD events of 7.8% in the diuretic group. This rate, 1.35% per year, is based on the experience of Framingham and HDFP (adjusted downward by 33-50% for temporal trends and by 25% for the healthy volunteer effect) and is similar to the rate observed more recently in SHEP.

3) A 20% reduction in CHD event rate (before adjustment for non-compliance and losses to follow-up, which combine to produce a 16.3% effective reduction) in each of the three non-diuretic treatment arms compared to the diuretic arm.

4) Using a time-dependent Markov model, rates of crossover between each of the other study drugs and chlorthalidone and/or non-study medication are assumed to be 2.75% in each of the first three years and 6% over the last three years of follow-up (based on TOMHS). The probability of crossing over at least once during the study is assumed to be approximately 24%. It is assumed (conservatively) that the CHD risk associated with the non-study drugs is the same as for chlorthalidone.

5) CHD status will be undeterminable at the end of the study for 16.8% of patients (8.6% of person-years) due to competing risks (non-CHD death) or loss to follow-up, based on data from Framingham and HDFP (see Appendix I).

6) A 25% reduction in CHD event rates (before adjustment for non-compliance and losses to follow-up) among the 10,000 patients randomized to the active treatment arm of the cholesterol-lowering trial component.

7) A type I error $\alpha = 0.05$ (two-sided). This corresponds to a critical Z-score of 2.37 after adjustment for multiple comparisons.

Power estimates ranged from 77 to 86% for more pessimistic or optimistic assumptions of crossover (#4) and loss (#5) rates. Additional details regarding these calculations may be found in Appendix I.

* On January 24, 2000, a recommendation to discontinue the doxazosin arm of the antihypertensive trial was accepted by NHLBI. Please refer to JAMA.2000;283:1967-1975.

Secondary hypotheses pertaining to the effect of the following end points in patients randomized to receive amlodipine, lisinopril, or doxazosin* (relative to those receiving chlorthalidone) will also be assessed: (1) all-cause mortality, (2) combined coronary heart disease (CHD + revascularization procedures + hospitalized angina), (3) stroke, (4) combined cardiovascular disease (CHD + stroke + revascularization procedures + angina [hospitalized or treated] + CHF [hospitalized or treated] + peripheral arterial disease [hospitalized or outpatient revascularization procedure]), (5) left ventricular hypertrophy by ECG, (6) renal disease including the reciprocal slope of serum creatinine and end-stage renal disease (dialysis or transplant), (7) health-related quality of life, (8) fatal and non-fatal cancer by type, and (9) gastrointestinal bleeding.

B. Cholesterol-Lowering Trial Component: (See Protocol Addendum 1)

The primary hypothesis of this trial component is that mortality from all causes will be lower in the subset of hypertensive patients described above 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 than in those randomized to receive usual care. The statistical power to test this hypothesis is approximately 80%, 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) Six-year total mortality of 13.2% (2.35% per year) in the usual care group (based on data from Framingham, HDFP and SHEP (see Appendix I). Based on mortality data in a high-risk subgroup of SHEP participants selected for comparability to ALLHAT patients, it is estimated that 40% of deaths will be due to CHD, 16% due to other cardiovascular causes, and 44% due to noncardiovascular causes.

3) A 12.5% reduction in mortality in the pravastatin treatment arm. This estimate is based on the assumption that CHD mortality is reduced by 25%, that mortality from other cardiovascular diseases is reduced by 15%, and that other causes of mortality are unaffected. If it is assumed that full compliance to the drug regimen would reduce LDL cholesterol levels by 30% and that the mean LDL cholesterol level is 155 mg/dl at entry (Range: 120-189 mg/dl), a 25% reduction in CHD corresponds to a logistic regression coefficient of 0.0062. For comparison, the logistic coefficient relating total cholesterol to CHD mortality in 356,222 MRFIT (male) screenees was 0.0118 for the full age range (35-57 years) and 0.0086 for the 36,704 men in the oldest age group (55-57 years). Extrapolation from the MRFIT data suggests that the coefficient relating total cholesterol to CHD in ALLHAT might fall between 0.005 and 0.006.

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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. These rates are projected to yield 15.3% of pravastatin patients off treatment and 10.6% of usual care patients on treatment at the end of 6 years. Note that the power of the cholesterol-lowering trial, which (unlike the antihypertensive trial) focuses on the generic effects of cholesterol-lowering, rather than the effects of a specific drug or drug class, is not diminished by "crossovers" from pravastatin to other regimens that produce equivalent lipid changes.

5) No losses to follow-up.

6) A 10% reduction in mortality rate in each of the three non-diuretic treatment arms of the anti-hypertensive trial component.

7) A type I error $\alpha = 0.05$ (two-sided), corresponding to a critical Z-score of 1.96.

Power was also calculated for a range of annual mortality rates (2.2 to 2.5%) and for a somewhat more pessimistic set of assumptions regarding compliance (leading to 17.8% and 12.9% prevalence of drop-outs and drop-ins, respectively, at the end of six years). Statistical power estimates ranged from 75 to 82% under these assumptions (see Appendix I).

Secondary hypotheses pertaining to reduction of the following end points in patients randomized to receive pravastatin (relative to those receiving usual care) will also be assessed: (1) the combined incidence of CHD death and nonfatal myocardial infarction, especially in certain subgroups like African-Americans, patients over age 65 (the original CRISP hypothesis), type II diabetics, and women, (2) changes in the biennial study ECG indicative of myocardial infarction, (3) cause-specific mortality, (4) total and site-specific cancer incidence; and (5) health-related quality of life.

The power of this study to address the effect of pravastatin on the combined incidence of CHD death and nonfatal myocardial infarction is estimated to be 97% overall and close to 80% in any subgroup containing 10,000 patients with risk characteristics similar to the overall cohort (see Appendix 1). However, the objectivity of the clinical diagnosis of nonfatal myocardial infarction is potentially compromised by the fact that the treating physicians will not be blinded as to whether their patients have received pravastatin or usual care. To guard against bias, the incidence of nonfatal myocardial infarction will also be assessed by changes in the biennial study ECG, the evaluation of which will be performed by coders who are unaware of the patient's treatment assignment. A pravastatin-usual care difference in clinical events will be given credence only if confirmed by a qualitatively similar difference in the ECG end point.

IV. Eligibility and Exclusions

A. Antihypertensive Trial

1. Age/sex: Men and women aged 55 years and older.

2. Medical history: History of documented hypertension.

3. Seated blood pressure:

Eligibility is based on the patient's current treatment status and on the average of two seated blood pressure measurements at each of two visits (Table IV.1):

(a) Patients whose blood pressure has been controlled (the majority of blood pressure measurements ≤ 160/100 mmHg) with one or two antihypertensive drugs for at least two months are eligible. Patients who are taking three or more antihypertensive drugs at subtherapeutic doses or in ineffective combinations, and who are felt likely to be controllable on the ALLHAT protocol, can enter the trial at the discretion of the principal investigator or his/her designee.

(b) For untreated patients, a diagnosis of hypertension must first be established. (The JNC V criteria for diagnosing hypertension are included in the Manual of Operations.) Patients who are untreated or who have been treated for less than two months must meet the minimal as well as the maximal blood pressure criteria shown in Table IV.1. To qualify for entry, the lower SBP *or* DBP limit and *both* upper limits must be met on two occasions at least one day apart. Patients who do not meet the blood pressure entry criteria at Visit 1 or Visit 2 may be re-evaluated for blood pressure eligibility at a later time.

Table IV.1. Blood Pressure Eligibility Criteria

Status at Visit 1 and Visit 2		Lower Limit[1] (mmHg)		Upper Limit[2] (mmHg)	
		SBP	DBP	SBP	DBP
On 1-2 Drugs Used for Hypertension ≥ 2 Months	Visit 1	---	---	160	100
	Visit 2	---	---	180	110
On Drugs For < 2 Months or Currently Untreated	Visit 1 & Visit 2	140	90	180	110

[1] SBP *or* DBP lower limit must be met at Visit 1 and Visit 2
[2] SBP *and* DBP upper limit must be met at Visit 1 and Visit 2

4. At least one of the following:

a. One or more of the following manifestations of atherosclerotic cardiovascular disease:
   (i) Old or age-indeterminate myocardial infarction or stroke (>6 months),
   (ii) History of revascularization procedure (ever),
   (iii) Documented atherosclerotic cardiovascular disease. This includes, but is not limited to: coronary, peripheral vascular, aortic, or carotid stenosis as documented by angiography, Doppler studies, or diminished ankle-arm index; ischemic heart disease as documented by electrocardiography (e.g., ST-T wave changes), echocardiography, or radionuclide imaging; history of intermittent claudication; or history of transient ischemic attack. (A more complete list of manifestations of atherosclerotic cardiovascular disease is provided in the Manual of Operations.)

b. Type II diabetes mellitus [plasma glucose >140 mg/dl (fasting) or 200 mg/dl (non-fasting) and/or on insulin or oral hypoglycemic agent] (in the past 2 years),

c. HDL-cholesterol <35 mg/dl (on any 2 determinations *within past 5 years*)

d. Left ventricular hypertrophy (one of the following) on any ECG within the past 2 years:

• R amplitude in V_5 or V_6 > 26 mm. • R amplitude in V_5 or V_6 plus S amplitude in V_1 > 35 mm. • R amplitude in aVL > 12 mm. • R amplitude in Lead I > 15 mm. • R amplitude in Leads II or III, or aVF > 20 mm. • R amplitude in Lead I plus S amplitude in Lead III > 25 mm. • R amplitude in aVL plus S amplitude in V_3 > 28 mm for men or > 22 mm for women • Computerized ECG machine documented LVH
For visual LVH reading, QRS amplitudes are measured in the ***second to last complete normal beat*** of the lead.

e. Left ventricular hypertrophy on any echocardiogram (within the past 2 years) based on 25 mm or more combined wall (ventricular septum plus posterior wall) thickness.

f. Current cigarette smoking (any cigarettes smoked in past 30 days).

5. Exclusions:

a. Symptomatic MI or stroke within past six months.

b. Hospitalized or treated symptomatic congestive heart failure and/or ejection fraction < 35%, if known.

c. Angina pectoris within past 6 months. (This implies actual chest pain. If patient has history of angina and no chest pain, even if he/she is on antianginal drugs, then this exclusion ***does not*** apply. See exclusion 5e.)

d. Known renal insufficiency (serum creatinine $\geq$ 2 mg/dl).

e. Patients requiring diuretics, calcium antagonists, ACE inhibitors, or alpha adrenergic blockers for reasons other than hypertension. (If a patient is on a calcium-channel blocker for angina, he/she may be switched to a beta-blocker for this indication if it is deemed safe to do so. This exclusion criterion would not then be applicable.)

f. Patients requiring more than two antihypertensive drugs to achieve satisfactory blood pressure control (SBP $\leq$ 160 mmHg and DBP $\leq$ 100 mmHg). Patients who are taking three or more antihypertensive drugs at subtherapeutic doses or in ineffective combinations, and who are felt likely to be controllable on the ALLHAT protocol, can enter the trial at the discretion of the principal investigator or his/her designee. See IV A 3(a).

g. Sensitivity or contraindications to any of first-line study medications.

h. Factors suggesting a low likelihood of compliance with protocol; such as dementia, history of alcohol or drug abuse within past six months, plans to move or travel extensively, or history of unreliability in keeping appointments or taking prescribed drugs.

i. Diseases, such as non-curable malignancy, likely to lead to non-cardiovascular death over the course of the study.

j. Blood pressure over 180 mmHg systolic or over 110 mmHg diastolic on two separate readings during step-down of antihypertensive medications.

k. Current participation in another clinical trial

B. Cholesterol-Lowering Trial

1. Eligible and enrolled in antihypertensive trial.

2. Fasting LDL Cholesterol: 120 to 189 mg/dl (100 to 129 mg/dl for patients with known CHD). These cutpoints, which correspond roughly to the 30th and 90th percentiles in men and the 25th and 85th percentiles in women in the ALLHAT age range, are projected to include approximately 60% (24,000) of ALLHAT participants from whom 20,000 would remain after refusals and other exclusions.

3. Fasting triglyceride level below 350 mg/dl.

4. Additional Exclusions:

a. Current use of prescribed lipid-lowering agents or large doses ($\geq$ 500 mg/day) of non-prescription niacin . Eligible patients must be off lipid-lowering drugs at least two months and off probucol for more than one year at the time of Visit 2.

b. Contraindications to HMG CoA reductase inhibitors (e.g., significant liver disease, ongoing immunosuppressive therapy, known allergy or intolerance to the study drug).

c. Known untreated secondary cause of hyperlipidemia (e.g., hypothyroidism, nephrotic syndrome).

d. ALT > 2.0 x upper limit of normal.

V. Recruitment

Recruitment for ALLHAT will rely primarily on chart review to identify patients who are potentially eligible for the antihypertensive or both trial components. Data needed to make the definitive determination of eligibility for the antihypertensive trial component will be obtained in a series of pre-randomization visits, which will take place over a period generally not exceeding two months. The number and frequency of those visits will depend on the complexity of the patient's pre-study regimen, the blood pressure response to step-down from that regimen, and the patient's suitability for and interest in the cholesterol-lowering trial component. Because only patients who have been randomized to the antihypertensive trial component will be considered for randomization to the cholesterol-lowering trial component, randomization to the latter will not take place until the first post-randomization (4 week) visit for the antihypertensive trial. The steps leading from identification of these various categories of potential ALLHAT candidates to randomization in one or both study components are described below.

Chart Review:

At each clinical site, patients who might potentially be suitable for the antihypertensive component of ALLHAT and the subset of such patients who might also be eligible for the cholesterol-lowering component of ALLHAT will be identified by chart review. Information on blood pressure and antihypertensive treatment, LDL (or total if LDL is unavailable) cholesterol levels and cholesterol-lowering diet and/or drugs, other relevant medical history, and a sense of the patient's reliability and compliance with previously prescribed treatments should be reviewed for conformity with the study eligibility requirements (Chapter IV) before his/her initial study visit.

A. Antihypertensive Trial Component

Visit 1: Preliminary Determination of Eligibility and Interest

The objective of Visit 1 is to assess eligibility for and interest in ALLHAT and to begin withdrawing the patient from any existing antihypertensive medications. It is anticipated that the majority of treated hypertensives will have been identified by chart review, and that much of the pertinent information (age, risk factor status, number of antihypertensive drugs, etc.) will already be known. The investigator will be required to complete a one-page questionnaire to document that all the preliminary inclusion and exclusion criteria (Chapter IV) have been met. Any documentation not attainable by chart review or not available within the past two years (ECG to assess the presence of left ventricular hypertrophy, fasting glucose level for diabetes, total cholesterol (TC) level to assess lipid eligibility), or within the last five years for the two determinations of HDL, will be considered part of the patient's routine medical management and will not be specifically reimbursed by the study.

Visit 1 will consist primarily of obtaining the first entry blood pressure, answering the patient's questions about the study, and obtaining the patient's informed consent to begin the step-down if necessary from pre-study antihypertensive drugs. Recommendations for antihypertensive drug withdrawal are included below. If a patient's antihypertensive medications

can be safely switched without tapering, the participant may move directly to Visit 2. Visits 1 and 2 should be separated by at least one day, but need not be consecutive visits.

For untreated patients, a diagnosis of hypertension according to JNC V criteria needs to be established. Once this is done, those patients whose SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg and whose SBP and DBP do not exceed 180 and 110 mmHg, respectively (see Table IV.1), may also be considered for entry into ALLHAT. For new patients found to have elevated blood pressure at their initial visit to the clinical site, this initial visit may serve as ALLHAT Visit 1 provided that any additional evaluations needed to determine study eligibility are performed (at no cost to the study). The subsequent course of such patients is simplified by elimination of the need for a step-down from a pre-study drug regimen.

Step-down visits:

Not all patients on antihypertensive medications will require step-down visits. In general, the following categories of antihypertensive drugs can usually be stopped without tapering the dose:

1. Diuretics: The patient should be informed to contact the physician if he/she develops marked edema and/or significant increase in dyspnea (shortness of breath, either at night or on exertion).
2. Reserpine.
3. Angiotensin converting enzyme (ACE) inhibitors.
4. Calcium channel blockers.
5. Vasodilators (e.g., hydralazine).
6. $Alpha_1$-blockers (e.g., prazosin).

The following categories need to be tapered if the patient is taking more than the usual starting doses:

1. Central agonists (e.g., oral clonidine or methyldopa) - taper over 1-2 weeks
2. Beta-adrenergic blockers (e.g., propranolol or atenolol) - taper over 2 weeks

Post-myocardial infarction patients receiving beta-blockers for prophylaxis need not discontinue therapy. There may be occasional circumstances where, in the physician's judgment, closer monitoring or a longer period of withdrawal is preferred. Extra care should be taken in tapering antihypertensive drugs in those patients with cardiovascular disease.

Patients whose blood pressure exceeds 180 mmHg systolic or 110 mmHg diastolic should return within a few days for a repeat blood pressure measurement. If the blood pressure is still above 180/110, the patient should not be randomized into the antihypertensive trial.

Visit 2: Randomization:

Patients who have met all ALLHAT eligibility criteria and in the judgment of the investigator can safely discontinue all prior antihypertensive drugs and be randomized to one of the four ALLHAT treatment arms shall, after giving their informed consent, be entered into the study at Visit 2. This visit will generally take place between 1 day and 12 weeks after Visit 1, depending on the length of time required to step down from pre-study medications. 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 three 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 pre-study regimens may also be more difficult to maintain on a simple regimen during the trial.

The investigator will telephone the Clinical Trials Center regarding each patient who meets all eligibility requirements at Visit 2, including a signed consent form. The Clinical Trials Center will review the eligibility and exclusion criteria and will assign that patient a study identification number and a bottle number corresponding to (1) chlorthalidone, (2) amlodipine, (3) lisinopril, or (4) doxazosin*. The treatment assignment will be masked from both the practitioner and patient. A resting ECG, serum glucose, serum potassium and creatinine, fasting lipid profile and ALT should be obtained at this visit for all patients who are randomized. Each randomized patient will be issued an appropriate supply of his/her starting dose of the assigned study drug and will be instructed to return for the first dosage titration (Visit 3) four weeks later (see Section VI).

All randomized patients will be given appropriate hygienic advice (sodium and alcohol restriction, smoking cessation, exercise, caloric restriction if overweight) with reinforcement as needed during the trial.

B. Cholesterol-Lowering Trial Component

Visit 1: Preliminary Determination of Eligibility and Interest

Patients who have satisfied all Visit 1 eligibility requirements for the antihypertensive trial component (see above) and/or have consented to begin step-down from pre-study antihypertensive drugs should also be informed of the cholesterol-lowering trial component of ALLHAT. Those who indicate their possible interest in this component and have not been treated with lipid lowering drugs (including 500 mg or more per day of over-the counter niacin) during the two months preceding Visit 1 shall be considered as potential candidates for this trial. Patients who have taken probucol within one year preceding Visit 1 are also ineligible for this component of ALLHAT.

* On January 24, 2000, a recommendation to discontinue the doxazosin arm of the antihypertensive trial was accepted by NHLBI. Please refer to JAMA.2000;283:1967-1975.

Visit 2: Fasting LDL Determination (Randomization to Antihypertensive Trial Component)

A fasting lipid battery (total cholesterol, triglycerides, HDL-cholesterol, calculated LDL-cholesterol) and serum ALT will be obtained for patients who: are eligible and randomized into the antihypertensive trial component of ALLHAT. Patients who have not fasted at least 9 hours (12 hours optimum) should have their blood draw rescheduled within a week of Visit 2. If rescheduling for fasting lipids is required, this will be considered part of Visit 2.

Visit 3 or 4: Randomization

Patients with fasting LDL-C between 120 and 189 mg/dl (between 100 and 129 mg/dl for patients with known CHD) and fasting TG $\leq$ 350 mg/dl at Visit 2 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 sign the Informed Consent to participate in this ALLHAT component at Visit 3, the investigator will phone the Clinical Trials Center, review the eligibility and exclusion criteria for the lipid-lowering component, and receive a random assignment for the patient to either pravastatin or usual care. 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 will not be prescribed any lipid-lowering medication by ALLHAT. Patients assigned to usual care as well as those assigned to pravastatin will be advised to follow the NCEP Step I diet (<30% of calories from fat, <10% of calories from saturated fat, <300 mg cholesterol per day). A fasting lipoprotein profile will be obtained at this visit as a baseline for each randomized participant in this trial component.

Maintenance of Racial Composition of ALLHAT:

Before their practices are selected as clinical sites for ALLHAT, potential study investigators will be asked to indicate the approximate proportion of African-American patients they expect to recruit into the study. Clinical sites will be selected to produce an overall study population of at least 55% African-Americans and will be monitored by the Clinical Trials Center throughout the study to assure that their performance matches their expectations. If the overall proportion of African-Americans appears to be falling significantly short of 55%, the Steering Committee may implement remedial measures such as temporarily freezing recruitment of non-African-American patients at some or all existing clinical sites or adding new clinical sites to correct the shortfall.

Table V.1: Schematic Summary of Entry of Patients into Two ALLHAT Components:

Visit #	Months from Visit 2	Purpose	
		Antihypertensive Trial	Cholesterol-Lowering Trial
-	-6.0 to -0.2	Chart Review	
1*	-2.0 to -0.2	Assess Eligibility and Interest	
1a,b,c*	-1.5,-1.0,-0.5 (as needed)	Step down from pre-study antihypertensive drugs	
2	0	Randomization, diet/lifestyle counseling	Fasting LP profile**, ALT
3*	1	Routine data collection Dosage titration if needed	Randomization, Fasting LP Profile**, NCEP Step 1 diet
4	3	Routine data collection Dosage titration if needed	Dosage titration if needed ALT, TC
5,6,7	6,9,12 (more often if needed*)	Routine data collection Dosage titration if needed	Routine data collection Dosage titration if needed
8,9,10,..	Every 4 months	Routine data collection	Routine data collection

* Separate reimbursements are not provided for these visits. At Visit 3 (1 month), reimbursement is provided if the patient is randomized to the lipid-lowering component. For visits past 1 month, reimbursement is not provided for visits other than those at 3, 6, 9 and 12 months during the first year, and every 4 months thereafter.

**Total cholesterol, triglyceride, and HDL cholesterol levels. LDL calculated by Friedewald formula.

Post-randomization visits are shaded.

VI. Antihypertensive Intervention

The blood pressure goal in all four arms* will be <90 mmHg diastolic and <140 mmHg systolic.[1] 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. With rare exceptions, treatment should be intensified for patients with BP levels ≥ 160 mm Hg systolic and/or ≥ 100 mm Hg diastolic, even if low doses of drugs from the same classes as the blinded Step 1 drugs must be added.

The therapeutic goal is to achieve blood pressure control on the lowest possible dosage of the first-line drug. The addition of second-line (open label) drugs should be reserved for those in whom the maximal dosage level of the first-line drug is insufficient.

Each of the four* first-line drugs will be administered once daily in the morning. The following dosage levels will be available for each drug:

Table VI.1. First-Line (Blinded) Antihypertensive Drugs

Step 1 Agent	Initial Dose	Dose 1	Dose 2	Dose 3
Chlorthalidone	12.5	12.5	12.5	25
Amlodipine	2.5	2.5	5	10
Lisinopril	10	10	20	40
Doxazosin*	1	2	4	8

Sources of the four Step 1 agents are: chlorthalidone: Ogden Bioservices, Inc., Rockville, Maryland; amlodipine: Pfizer, Inc., New York, New York; and lisinopril: Zeneca Pharmaceuticals Group, Wilmington, Delaware; and doxazosin*: Pfizer, Inc., New York, New York.

The identity of the drug will be masked at each dosage level , but the identity of the dosage level will not be masked. The initial dosage level will be used only during the first week after randomization to minimize the potential side effects of doxazosin*. (For the other three drugs, the initial dose and Step 1 dosages are identical.) The Step 1 dosage level should be initiated at the end of the week. A clinic visit is not required.

All patients will be re-evaluated at least at 1 month for dose titration if needed (Visit 3) and at 3 months (Visit 4). Study medication will be initiated at the initial dose and patients should typically return at one-month intervals for any necessary increase in dosage until both the

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* On January 24, 2000, a recommendation to discontinue the doxazosin arm of the antihypertensive trial was accepted by NHLBI. Please refer to JAMA.2000;283:1967-1975.

[1]These goals follow the Fifth Joint National Committee recommendations [10]. The JNC set the systolic goal lower than that used in SHEP, which was between 140 and 159 mm Hg with a mean attained value of 142 mm Hg, because of the known strong epidemiologic relationship of systolic pressure with CVD mortality [59].

IX. Outcome Measurements

Occurrences of study endpoints will be documented by a checklist completed by the study physician at each follow-up visit and supplemented by interim reporting as needed. These diagnoses will be supported by copies of death certificates, discharge summaries and face sheets as described below. The following outcome measures will be obtained and tabulated over the course of the study:

A. Death (documented by death certificate).

The underlying cause of death will be classified by the physician-investigator at the clinical site as due to (1) Coronary Heart Disease, (2) Other Cardiovascular Disease, (3) Neoplastic Disease, (4) Other Medical Causes, or (5) Non-Medical Causes. 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 utilized for selected participants. Physicians will also be asked to report cause of death on the study endpoint form.

B. Cardiovascular End Points

1) Myocardial infarction (documented by hospital discharge summary or face sheet or by biennial study ECG), including suspected myocardial infarction with thrombolytic therapy.

2) Stroke (documented by hospital discharge summary or face sheet).

3) Congestive heart failure

   a) Hospitalized or procedure (documented by hospital discharge summary or face sheet)

   b) Not hospitalized but treated (documented by check box on end point questionnaire)

4) Angina pectoris

   a) Hospitalized or procedure (i) with or (ii) without a revascularization procedure (documented by hospital discharge summary or face sheet)

   b) Not hospitalized but treated (documented by check box on end point questionnaire)

5) Peripheral arterial disease

a) Hospitalized or procedure (i) with or (ii) without a revascularization procedure (documented by hospital discharge summary or face sheet) or outpatient revascularization procedure (documented by procedure sheet)

b) Treated medically as outpatient (documented by check box on end point questionnaire)

6) Left ventricular hypertrophy (documented by biennial study ECG)

The LVH inclusion criteria are based on specific ECG criteria as listed in IV.A.4.d and will be interpreted at the clinical site. ECGs will be re-read centrally to assign Minnesota Codes. The outcome criteria for LVH are based on the Minnesota Code. The Minnesota Coding Center will use Codes 3-1 or 3-3 to identify prevalent LVH. These amplitude criteria sets are generally considered "probable ECG-LVH", but when combined with any 4-3 or more severe 4-code, or 5-3 or more severe 5-code, it is considered "definite ECG-LVH".

Minnesota Code 3-1: R amplitude > 26 mm in either V_5 or V_6 or R amplitude > 20 in any of leads I, II, III, aVF, or R amplitude > 12 mm in lead aVL.

Minnesota Code 3-3: R amplitude in V_5 or V_6 plus S amplitude in V_1 > 35 mm or R amplitude > 15 mm but ≤ 20 mm in Lead I.

The Coding Center will also document incident ECG-LVH and progression/regression of ECG-LVH using serial ECG comparison.

C. Other End Points

1) Decreased renal function (documented by reciprocal slope of serum creatinine level versus time -- continuous measure)
2) End stage renal disease (initiation of chronic dialysis, kidney transplant)

a) Hospitalized or procedure (documented by hospital discharge summary or face sheet)

b) Treated as outpatient (documented by check box on end point questionnaire)

3) Cancer -- Site and Type

a) Hospitalized or procedure (documented by hospital discharge summary or face sheet)

b) Treated as outpatient (documented by check box on end point questionnaire)

4) Nonfatal accidents and attempted suicides

a) Hospitalized or procedure (documented by hospital discharge summary or face sheet)

b) Treated as outpatient (documented by check box on end point questionnaire)

5) Gastrointestinal bleeding

a) Assessed through data from the Health Care Finance Administration and the Department of Veterans Affairs

6) Quality of life -- A generic categorical measure of health status will be used to assess health related quality of life.

7) Medical care utilization-- Utilization data will be collected by interview. Costs will be assigned to each unit of utilization (hospitalization, office visits, procedures, etc.) based on its DRG. In addition, one question will be asked to ascertain quality of life on a continuous scale in order to determine quality-adjusted life years. For a 10% sample of patients over age 65, these interview data will be cross-checked versus Medicare records.

The study investigators will be required to complete and submit to the Clinical Trials Center a short end points questionnaire for each occurrence of a study endpoint identified at or between regular visits. For each end point involving a death or hospitalization, the investigator will also obtain and submit a copy of the death certificate or hospital discharge summary or face sheet upon which the diagnosis is based. For a random (10%) subset of hospitalized (fatal and nonfatal) myocardial infarctions and strokes, the Clinical Trials Center will request the more detailed information as described in Appendix I so that the in-hospital ECGs and enzyme levels (for myocardial infarctions), and neurologists' reports and CT and/or MRI reports (for strokes) can be evaluated by the study end points committee and the accuracy of the discharge diagnoses (versus the definitions in Appendix I) can be assessed.

X. Study Organization

Overview:

ALLHAT will employ an organizational structure that differs markedly from the usual NHLBI-supported clinical trial. The trial will be performed by a large number (600) of practicing physician-investigators who will be compensated on a per capita basis for each patient seen according to a fixed payment schedule. Approximately 20% of study patients are expected to be recruited by Department of Veterans Affairs (VA) 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, hiring regional coordinators to monitor recruitment and compliance, and for awarding and supervising subcontracts for a central laboratory and an ECG coding center. A Steering Committee will be selected for their expertise in the relevant subject areas. A detailed description of the nature and role of the study components is given below.

Program Office

The Program Office, located in the NHLBI, Division of Epidemiology and Clinical Applications (DECA) and Division of Heart and Vascular Diseases (DHVD), will award and monitor the contract that provides funding for the study, set up the agreements to fund the VA clinics, and hold the IND for the study. The Director, NHLBI, will appoint the Data and Safety Monitoring Board (DSMB) and the Chair and Vice-chair of the Steering Committee. With the concurrence of the Director, NHLBI, the Program Office will appoint the Steering Committee and any other committees deemed necessary to advise the NHLBI on issues pertaining to the progress or results of the study.

Clinical Trials Center:

The Clinical Trials Center will have primary responsibility for identifying suitable medical practices to participate in ALLHAT, paying them according to a fixed fee schedule for each patient randomized and study form completed, and for editing, storing, and analyzing data generated by the study. Its investigators and staff will have a central role in designing the data collection system and in monitoring data quality. Specific Clinical Trials Center responsibilities include:

1) Developing, preparing, and distributing the study protocol, data forms, and Manual of Operations and Procedures.

2) Appointing and paying practicing physicians to provide clinical sites for conduct of the study.

3) Appointing and paying regional coordinators (see below).

4) Obtaining Institutional Review Board (OPRR) approval for uncovered practices.

5) Maintaining files of annual financial disclosure statements for the Steering Committee members to identify potential conflicts of interest.

6) Subcontracting for a central laboratory and an ECG coding center to provide timely and standardized measurements needed by the study (see Chapter VIII).

7) Subcontracting for a Drug Distribution Center to receive, bottle, label, and distribute study medications to the clinic sites.

8) Monitoring the performance of study components and providing timely summary reports to the Program Office and to the Steering Committee.

9) During recruitment, monitoring the proportion of African-Americans at each clinical site and recommending appropriate corrective action if the overall proportion for the study as a whole appears to be falling significantly short of the 55% target.

10) Providing detailed and up-to-date statistical reports of study progress to the Data and Safety Monitoring Board (DSMB) at their semi-annual meetings (see below).

11) Maintaining a referral network for study participants who move to a new geographic region and are unable to continue to see their original study physician.

12) Providing logistical support (as needed) and minutes for study meetings.

13) Coordinating and supervising end point verification activities.

14) Initiating searches through the National Death Index to establish the vital status of patients who are lost to follow-up at intervals recommended by the DSMB and Steering Committee (see below).

15) Preparing study manuscripts in collaboration with the Steering Committee.

Clinical Sites:

These will consist of 600 separate medical practices, designated by the Clinical Trials Center to conduct the study. It is expected that some practices (particularly the VA clinics, HMOs, and large group practices) will provide larger numbers of patients and that some practices may contribute fewer than 100 patients. The proportion of African-Americans is also expected to vary among clinics, but will be monitored closely to ensure that the target of 55% overall is met (see Chapter V).

Each clinical site is expected to be under the supervision of a physician identified as responsible for the conduct of ALLHAT. However, study forms may be completed by a physician's assistant or nurse practitioner or other designated qualified personnel, consistent with the internal organization of that medical practice. At each site, one support staff member must be designated as chiefly responsible for protocol implementation; this person will participate in central training and annual meetings. Payment for each patient randomized to each ALLHAT component and for each study visit completed will be made by the Clinical Trials Center upon receipt of the relevant completed, correct and signed study form.

Regional Coordinators:

Regional coordinators will be physicians with expertise in hypertension and cholesterol lowering treatment, who will handle routine protocol questions for approximately 50 clinical sites apiece. Under direction of the Clinical Trials Center, they will assist in solving problems related to quality control, protocol adherence, recruitment and retention for the sites assigned to them. Physician coordinators will be supported by a nursing coordinator and may opt to participate as clinical sites as well. All participating VA hypertension clinics will be supervised by a single coordinator.

Drug Distribution Center

A Drug Distribution Center will be established by the Clinical Trials Center to (1) receive, package and distribute all pharmaceuticals required for the two ALLHAT components, (2) implement a system of masking so that the four first-line antihypertensive agents cannot be distinguished from each other by the study investigators or their patients (the second-line antihypertensive drugs will not be masked), and (3) provide appropriate supplies of all study medications to the clinical sites on a timely basis.

Steering Committee:

The Steering Committee will be appointed by the NHLBI to provide expert advice on the study protocol and on all subsequent decisions pertaining to the design and conduct of the study that do not require access to blinded data, and the eventual analysis and publication of the study results. Its voting members will be the NHLBI Project Officer, the principal investigator of the Clinical Trials Center, the Regional Coordinators, and 7-9 experts selected for their expertise and experience in the treatment of hypertension and/or hypercholesterolemia and in key clinical trials issues such as recruitment and adherence. Each Steering Committee member will be required to submit an annual financial disclosure statement to the Clinical Trials Center and to divest themselves of any stock holdings or retainer-type consultant positions in pharmaceutical and other companies that have a direct financial interest in the outcome of the study. The Steering Committee will meet once per year (more frequently during protocol development).

An Executive Committee will be instituted to oversee trial operations between Steering Committee meetings. Composition of the Executive Committee will include the Chair and Vice-Chair of the Steering Committee and representatives of the Program Office, the Clinical Trials Center, and the Department of Veterans Affairs. Reporting to the Executive Committee will be the following subcommittees: Eligibility and Medical Care, Operations, Publications and Ancillary Studies, Scientific and Educational Program, and Endpoints. Each of the subcommittees will have representation from the Program Office, Clinical Trials Center, and Steering Committee to oversee aspects of the trial that require frequent attention and/or special expertise, such as recruitment, adherence, quality control, blood pressure and lipid intervention, laboratory methods, endpoint verification, ancillary studies, publications, and the annual program for the investigators' meetings.

Protocol Review Committee:

The Protocol Review Committee will be responsible for advising the NHLBI regarding the initial approval of the study protocol. Its members and chair will be appointed by the Director, NHLBI, and will consist of at least seven experts who are not otherwise affiliated with the study. It will meet in Bethesda when the study protocol has been completed. The meeting will be attended by the principal investigator (and designated staff) of the Clinical Trials Center and the Chair and Vice-Chair of the Steering Committee who will make presentations and answer questions regarding the protocol, and by Program Office staff.

Data and Safety Monitoring Board (DSMB):

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 will be appointed by the Director, NHLBI, and will consist of at least seven experts who are not otherwise affiliated with the study. It is likely that the roster of the DSMB members may be largely or even entirely derived from the Protocol Review Committee, which will complete its mission as the DSMB is formed.

The DSMB will meet at least semi-annually. The principal investigator of the Clinical Trials Center and designated Clinical Trials Center staff will attend these meetings (but will not have a vote) and will be responsible for preparing and presenting up-to-date statistical reports on the progress of the study. These reports will include data on recruitment, randomization, adherence, blood pressure levels, plasma lipoproteins, adverse drug responses, and study end points, as well as statistical tests and special analyses requested by the DSMB. The Project Director (who will serve as the DSMB's Executive Secretary), Project Officer and designated NHLBI staff and the Chair and Vice-chair of the Steering Committee will also participate in these meetings in ex officio capacities.

During the active recruitment phase, the DSMB will monitor the progress of recruitment (particularly of African-American 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 DSMB will recommend when to end the active recruitment phase of the study. The approval of the DSMB will also be required for any significant changes in the protocol recommended by the Steering Committee during the course of the study. All votes will be decided by a simple majority.

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 study of an adverse effect of the study treatment(s) that is sufficient to override any potential benefit on CHD and preclude its further use in the target population;

2) compelling evidence from this or another study of a significant beneficial effect of the study treatment(s), such that its continued denial to the other study groups is ethically untenable;

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, etc.

The DSMB may convene an Executive Session at any time. DSMB members, the Project Director and the Project Officer will attend these sessions.

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

XI. Data Management

Report distribution

At least five types of reports will be generated:

1) Recruitment reports: These are expected to be generated at least weekly, by clinic and region and for the antihypertensive trial and the lipid-lowering trial. These will be distributed to the Project Office, Steering Committee and Regional Coordinators.

2) Other routine monitoring reports include data on visit and medication adherence, quality control and study endpoint documentation. These will be generated at least monthly by clinic and region, and will be distributed to the Project Office, Steering Committee and Regional Coordinators.

3) Reports for clinic use include randomization verification reports, visit schedules and reminders, endpoint documentation reports, and limited cross-forms edits. These will be generated no more often than monthly. Visit schedules are generated as participants are randomized and include all visit windows and expected special procedures for the duration of the study. Reports and appropriate listings will be sent to the clinics, and summary reports will be sent to the Project Office, Steering Committee and Regional Coordinators.

4) Steering Committee reports will be generated for annual meetings and will be similar to routine recruitment and monitoring reports.

5) Data and Safety Monitoring Board reports will include recruitment and monitoring data by treatment group for both the antihypertensive trial and the lipid-lowering trial. They will also include summary reports of data from the central laboratory and biennial and event ECG data, as well as study endpoints by treatment group.

Quality Control

All clinical sites will be required to attend one of three regional training sessions. These training sessions will include orientation to the study protocol, blood pressure measurement training and certification, orientation to the ECG procedures, and training in completion and transfer of study forms.

Periodic refresher training will be held in conjunction with regularly scheduled Steering Committee 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.

All forms will be reviewed for completeness and accuracy at the Clinical Trials Center prior to data entry. Any problems identified will be resolved by telephone or facsimile transmission with the clinical site. Study forms will then be double data entered. Limited cross-forms edits will be performed to identify missing forms and procedures.

Unblinding

In some special circumstances (e.g., a medical emergency), a patient's assigned treatment group may be revealed. The Regional Coordinators will be the first line of advice in the decision of whether to break the blind or not. If the Regional Coordinator cannot be reached, the investigator should try to contact any of the other Regional Coordinators, or Dr. Davis or Dr. Goff at the Clinical Trials Center, or Dr. Payne or Dr. Cutler at NHLBI to discuss the relevant medical issues. If medically appropriate, an effort will be made to maintain the blinding of the patient and the clinical center investigator. If the regional coordinator agrees, or if the investigator is insistent, the investigator should contact the Clinical Trials Center to determine the unblinded treatment assignment. If there is an emergency and the Clinical Trials Center cannot be contacted, the investigator will reveal the unblinded treatment assignment by contacting a central unblinding facility.

When breaking the blind is determined to be necessary, the circumstances will be documented on a 1-page form by the clinic investigator. The form will be forwarded to the Clinical Trials Center and data entered onto the masterfile as a permanent part of the patient's study record.

Stopping Study Medications

If an investigator believes it is necessary to withdraw a patient from study treatment because of an adverse effect, other symptoms, of physician's judgment, it may not be necessary to break the blind on the patient. The Regional Coordinators will be the first line of advice in the decision of whether to withdraw the patient from study treatment. If the Regional Coordinator agrees, or if the investigator is insistent, the investigator should contact the Clinical Trials Center to inform them that this action is being taken and the reasons for it.

Reimbursements

The clinical sites will be reimbursed on a capitation basis for each randomization to the antihypertensive trial, randomization to the lipid-lowering trial, each protocol-required follow-up visit, and each completed study endpoint. These payments will be made monthly from the Clinical Trials Center. In order for a reimbursement to be authorized, a study form must be received at the Clinical Trials Center, all questions regarding that form must be resolved, and the form must be entered onto the study database. In the case of study endpoints, reimbursements will be in several parts made separately for the study form itself, the death certificate or discharge summary, and for additional documentation for the 10% sample for verification.

Data Analysis

The primary endpoint of the antihypertensive component of ALLHAT is fatal plus nonfatal CHD. The primary response variable is time from randomization to development of this event. The log rank test [60] will be used to compare each of the non-diuretic treatment groups to the diuretic one. For the secondary endpoints of all-cause mortality, stroke, combined coronary (CHD + revascularization procedures + hospitalized angina) and cardiovascular (CHD + stroke + revascularization procedures + angina [hospitalized or treated] + CHF [hospitalized or treated] + peripheral arterial disease [hospitalized or outpatient revascularization procedure]) outcomes, and end-stage renal disease, the log rank test will also be used. The log rank test will also be used to test if there are treatment differences in the following subgroups for the outcome of fatal and non-fatal CHD -- 1) men and women, 2) $\geq$ 65 years and < 65 years, 3) African Americans, and 4) diabetics and non-diabetics. For the outcomes of 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 inverse of the slope of creatinine will be calculated for each participant. The weighted average of the participants' inverses in each treatment group will be calculated and these averages will be compared across groups using the longitudinal models of Laird and Ware [61].

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 lipid-lowering therapy to the group assigned to no treatment. For the secondary endpoints of fatal and nonfatal CHD, fatal and nonfatal cancer and cause-specific mortality, the log rank test will also be used. The log rank test will also be used to test if there are treatment differences in the following subgroups for the outcome of fatal and non-fatal CHD - 1) men and women, 2) $\geq$ 65 years and < 65 years, 3) African Americans, and 4) diabetics and non-diabetics. 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 and Analysis (See Protocol Addendum 2)

Interim monitoring will focus on patient intake - overall and within clinical center, center adherence to protocol, baseline comparability of treatment groups, sample size assumptions with regard to event rates, crossover rates, competing risk and lost to follow-up, adverse effects data, and effect of treatment on the primary and secondary study outcomes. Interim analyses will coincide with the meetings of the Data and Safety Monitoring Board (DSMB).

We recommend the DSMB use stochastic curtailment for monitoring treatment differences in both the hypertension and the lipid-lowering studies [62,63]. By this method, termination in favor of the alternative hypothesis (H_a) may be considered if the conditional probability of rejecting the null hypothesis (H_o) at the scheduled end of the study given the current data and assuming H_o is true, is greater than or equal to some pre-specified value γ_o. Alternatively, termination in favor of the null hypothesis would be considered if the conditional probability of rejecting H_o under the design specified alternative hypothesis is less than some pre-specified value γ_a. With this procedure, the type I error is inflated slightly above α (depending on the number of looks at the data, the timing of the looks, and the value of γ_o) and the type II error is slightly inflated above β (again, depending on the number of looks at the data,

the timing of the looks, and the value of γ_a). The choice of the γ's will be determined by the DSMB.

These monitoring procedures are suggested as guides for the complex and subjective decisions the DSMB must make when considering to continue or to terminate randomization and/or follow-up at each of its meetings.

Hypertension Trial

In this trial, we have three* comparisons of interest -- diuretic compared to angiotensin converting enzyme inhibitor, diuretic compared to calcium channel blocker, and diuretic compared to alpha blocker*. Each comparison would have its own monitoring guideline under the Dunnett procedure with α=0.019. Figure 1 shows the 80% stochastic curtailment boundaries for each of the comparisons. The looks will depend on the information time (the number of recorded CHD events divided by the expected number of CHD events) at the calendar time of the Data and Safety Monitoring Board meetings.

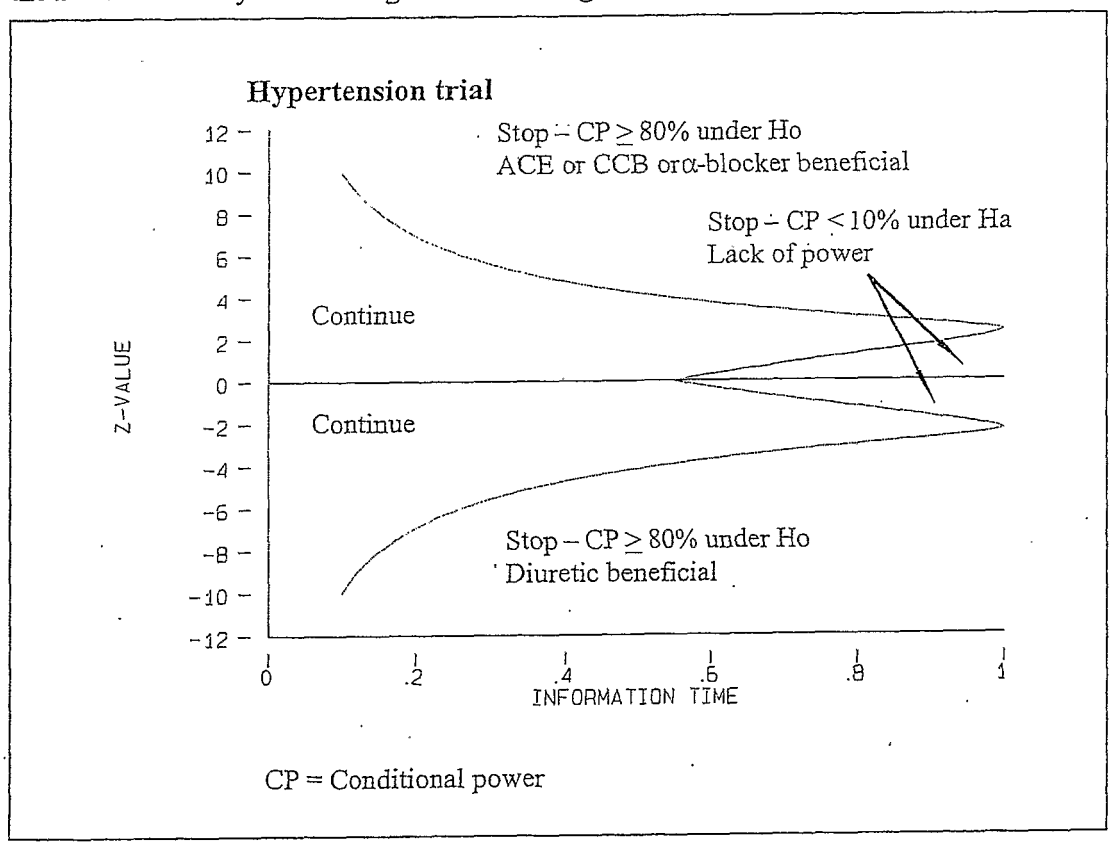


Figure 1. Monitoring boundaries for the hypertension trial - ACE (or CCB or alpha-blocker*) vs. diuretic

* On January 24, 2000, a recommendation to discontinue the doxazosin arm of the antihypertensive trial was accepted by NHLBI. Please refer to JAMA.2000;283:1967-1975.

We would also wish to use a rule for stopping because of lack of power to show an effect. Here we also propose to use stochastic curtailment or conditional power. We would consider stopping if the conditional power under the proposed alternative hypothesis is less than 10%. Figure 1 also displays this conditional power boundary.

Total mortality will also be monitored in the hypertension trial.

Lipid Lowering Trial

For this trial we would propose similar procedures as to that of the hypertension trial with the exception that there is only one comparison (all-cause mortality) with an α=0.05. Figure 2 depicts the monitoring boundaries.

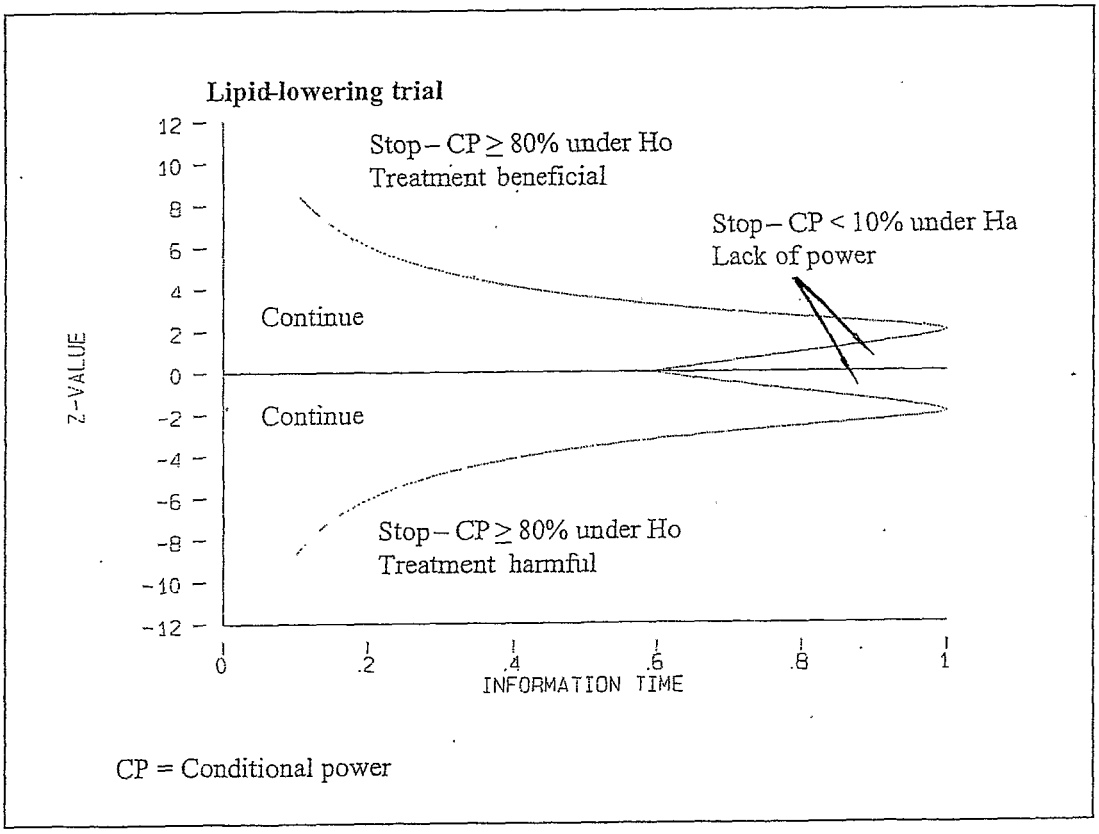


Figure 2. Monitoring boundaries for the lipid-lowering trial.

XII. Vanguard Phase

The initial six months of the study will comprise a vanguard phase for the full-scale trial. Twenty practices will be selected to carry out this vanguard phase with the goal of randomizing six hundred (of the full complement of 40,000) patients. Objectives of the vanguard phase include:

1. To determine the feasibility of recruitment and follow-up of out-patient hypertensive subjects in office-based practices and hypertension clinics;

2. To determine the proportion of antihypertensive trial subjects eligible and willing to participate in the cholesterol-lowering trial;

3. To optimize strategies for recruitment of at least 55% African-American participants;

4. To develop methods for maximizing adherence to antihypertensive and cholesterol-lowering medication regimens in out-patient hypertensive subjects;

5. To optimize strategies for retention of out-patient hypertensive subjects in office-based practices;

6. To develop methods for standardized endpoint ascertainment in office-based practices and hypertension clinics; and

7. To assess and optimize the effectiveness of various operational strategies, such as drug distribution, Institutional Review Board approval, training, and activities involving the Regional Coordinators.

If the vanguard phase establishes the basic feasibility of this protocol, any necessary modifications will be made and additional practices will be recruited as needed to meet the recruitment goals of the study.

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Appendix I: Sample Size Calculations

Power calculations for ALLHAT were done separately for the antihypertensive (AH) and lipid lowering (LL) components. For the AH component power was based on two-tailed comparisons of the diuretic arm to each of the other arms using an overall Type I error rate of .05. This was accomplished using a Dunnett type adjustment for multiple comparisons. For the LL component there was only one comparison, hence no adjustment was needed.

To estimate power for ALLHAT, we had to specify expected event rates, treatment effects, and rates of crossovers and losses to follow-up from competing risks or other reasons.

Antihypertensive Component

We conservatively estimated the CHD rate in the diuretic arm to be about 1.35% a year (a 6 year rate of approximately 7.8%). This was based on exponential regression models applied to data from Framingham 12, Framingham 16, and HDFP. We included from the Framingham data all hypertensives aged 45-75, excluding those with recent MI (within 2 years). The variables included in the model were age, sex, and whether or not the patient was at high risk (defined as meeting ALLHAT entry criteria). Rates were adjusted to a mean age of *67* and a 55% prevalence of males. A similar analysis was done on the HDFP data, which included those 50 years old and older. The stepped and referred care cohorts of HDFP were analyzed separately. The following reductions were applied for secular trends and the healthy volunteer effect.

Table 1: Adjustment Factors

Trial	Secular Trend Reduction	Volunteer Reduction
Framingham 12	1/2	1/4
Framingham 16	1/3	1/4
HDFP	1/2	1/4

For example, the estimated yearly event rate from the exponential regression of Framingham 12 was multiplied by (1-1/2)(1-1/4)=3/8. The estimated event rates based on the exponential regressions adjusted for secular trends and the healthy volunteer effect were as follows:

Table 2: Estimated Yearly CHD Rates From Framingham and HDFP

Trial	Estimated Event Rates Per Year
Framingham 12	1.32%
Framingham 16	1.42%
HDFP Referred Care	1.76%
HDFP Stepped Care	0.92%

We felt that a 1.35% yearly CHD rate was reasonable. SHEP rates were somewhat higher. SHEP rates automatically incorporate a healthy volunteer effect, and since it was a recent trial, its rates would need less of a secular trend adjustment. We decided to consider a range of event rates from 1.05% a year to 1.65% a year.

Crossover rates were estimated from TOMHS. We fit a time-dependent Markov model to the data. A model assuming a 2.75% chance of crossing over to another medication during each of the first three years, and 6% for each of the last three years appears to fit well (see Figure 1). Under this model, about 24% of all patients will cross over to another medication at least once in 6 years, and about 21% of all patients will be crossed over to another medication at the end of 6 years. A patient in the diuretic arm who crosses over to another active antihypertensive medication is assumed to have a reduced event rate even though some of the other antihypertensives may confer no benefit. A patient in an active antihypertensive arm who crosses over to another antihypertensive medication is assumed to have an increased event rate consistent with the diuretic arm even though that patient may have crossed over to another antihypertensive medication that is as beneficial as that to which he/she was assigned. A patient may cross over and then cross back. We assume that because the physician will have leeway to select among a wide variety of second line antihypertensive medication, there will be a negligible percentage of patients who are taking no medication whatsoever. This assumption is somewhat anti-conservative, but we feel that it is offset by the conservative assumptions alluded to above. We also considered two other rates with 22% and 26% probability of crossing over at least once, respectively. These correspond to approximately 20% and 22.5% of patients on another medication at the end of 6 years, respectively (see Figures 2 and 3). The latter rate appears to be quite conservative. The three rates of 22%, 24%, and 26% for at least one crossover will henceforth be referred to as crossover rates 1, 2, and 3, respectively.

Loss from competing risks was estimated to be approximately 8% over 6 years. This was composed of other cardiovascular mortality (2.6% over 6 years) and non-cardiovascular mortality (5.4% over 6 years). These rates were calculated in a manner similar to the way we computed event rates for the primary endpoint. The same healthy volunteer and secular trend adjustments were applied. We added about 1.5% per year for losses to follow-up, yielding a total loss rate of approximately 16.8% over 6 years. We considered two other loss rates of

16.8%±5%. The three loss rates of 11.8%, 16.8%, and 21.8% will henceforth be referred to as loss rates 1, 2, and 3, respectively.

To compute power for the AH component we also had to consider the LL component. It appears from HDFP and Framingham that the patients who qualify for the LL component are at approximately the same risk as those who do not. We therefore made this assumption. Before considering the benefit of antihypertensive medication, we reduced the event rate in the LL active arm by 25% to account for beneficial effects of cholesterol lowering. Note that this is conservative in that it assumes that all of the LL active patients will stay on the drug and receive its full benefit. We assumed that 20,000 of the 40,000 ALLHAT patients would be in the LL component.

We assumed a 20% reduction in event rate in an active antihypertensive arm. We then computed power based on:

1) The optimal allocation of patients to the diuretic and treatment arms, namely the ratio of the number of patients in the diuretic arm to the number in each other AH arm should be:

$$(\text{total \# arms} - 1)^{1/2} = \sqrt{3} \quad \text{(see Table 3).}$$

2) An adjustment for comparisons of each treatment to the diuretic (adjusted critical value of approximately c=2.37).

Table 3: Approximate Allocation of Patients

Cholesterol-lowering trial	Antihypertensive Trial			
	Diuretic	Calcium Channel Blocker	ACE Inhibitor	Alpha Blocker*
LL Placebo	3.7k	2.1k	2.1k	2.1k
LL Active	3.7k	2.1k	2.1k	2.1k
Not in LL Component	7.3k	4.2k	4.2k	4.2k

We used a computer program which estimates trial event rates based on yearly rates of events, crossovers, and losses. We ran this program separately for patients in the LL active and LL placebo arms. Based on these values and the allocation of patients specified in Table 3, we obtained trial event rates for the diuretic arm and the other AH arms. For example, using a

* On January 24, 2000, a recommendation to discontinue the doxazosin arm of the antihypertensive trial was accepted by NHLBI. Please refer to JAMA.2000;283:1967-1975.

yearly event rate of approximately .0135, crossover rate 2, and loss 2, we estimate that the trial event rates would be as follows:

Table 4: Estimated 6 Year CHD Rates

LL category	Diuretic Arm	Other AH Arm
LL Placebo	.0710	.0595
LL Active	.0537	.0449
Non LL	.0710	.0595

We estimate the overall event rate in the diuretic arm and another AH arm to be:

$$p_0=(.0710)(.75)+(.0537)(.25)=.0667,$$
$$p_1=(.0595)(.75)+(.0449)(.25)=.0559.$$

An arcsin transformation was used for the test statistic.

$$Z=\frac{\arcsin\left(\sqrt{\hat{p}_0}\right)\arcsin\left(\sqrt{\hat{p}_1}\right)}{\sqrt{(1/4)(1/n_0+1/n_1)}}. \quad (1)$$

In Formula (1), n_0 and n_1 are the sample sizes in the diuretic and another AH arm, respectively, and p_0 and p_1 are the observed proportion of events in those arms. For the optimal allocation of patients, $n_0 = 40{,}000\left[\sqrt{3}/\left(3+\sqrt{3}\right)\right] = 14{,}641$ and $n_1 = 40{,}000\left[1/\left(3+\sqrt{3}\right)\right] = 8{,}453$. We will reject if the Z statistic exceeds the adjusted critical value c=2.37. If we denote the cumulative normal distribution function by $\Phi(x)$, power can be shown to be:

$$\Phi\left(\frac{\arcsin\left(\sqrt{p_0}\right)\arcsin\left(\sqrt{p_1}\right)}{\sqrt{(1/4)(1/n_0+1/n_1)}}-c\right). \quad (2)$$

Recall that for our example using a yearly event rate of .0135, crossover rate 2, and loss 2, we found that p_0=.0667 and p_1=.0559. Substituting these values and n_0=14,641 and n_1=8,453 into Formula (2), we get power =.824.

Lipid Lowering Component

The primary endpoint for the lipid lowering component is total mortality. We assume that the vital status of all participants can be ascertained from the National Death Index, hence there will be no loss to follow-up.

Based on previous experience with HMG CoA reductase inhibitors, we feel that compliance will be quite good, with the bulk of noncompliance occurring early in the trial. We also estimate that given the cost of LL agents and the relatively modest lipid levels of the patients, there will not be many LL placebo patients taking active LL medication. We assume that each year about 2% of all LL placebo patients will take active LL medication with a benefit similar to that of Pravastatin (2% *dropin* per year). This means that about 11.4% of all LL placebo patients will take active medication at least once in 6 years. We further assume that 5% of the LL active patients will stop taking their medication at some point in the first year, and that in each of the remaining years about 2.5% of LL active patients will stop taking their medication (*dropout* rate of 5% in the first year and 2.5% each year thereafter). This corresponds to approximately 16.3% of LL active patients stopping their medication at least once in 6 years. Under the above assumptions, approximately 10.6% of all LL placebo patients will be taking active medication at the end of 6 years, and about 15.3% of the LL active patients will be off their medication at the end of 6 years. We also considered a more pessimistic set of assumptions, namely a yearly dropin rate of 2.5% and a dropout rate of 6% during the first year and 3% a year thereafter. The first set of assumptions will be referred to as dropin/dropout 1, and the more pessimistic set of assumptions will be referred to as dropin/dropout 2.

We estimated the mortality rate to be approximately 2.35% per year. This estimate was based on separate incidence rates for CHD mortality (between 4.5% and 5% over 6 years), other cardiovascular mortality (about 2.6% over 6 years), and non-cardiovascular mortality (about 5.4% over 6 years). These separate rates were estimated using the parametric regression methods we used for the primary endpoint.. The same secular trend and healthy volunteer adjustments were made as were made for the AH component. This gave an estimated mortality rate between 2.25% and 2.30% per year. We increased this to 2.35%/year based on a somewhat higher mortality rate observed in SHEP. We considered a range of yearly mortality rates between 2.20% and 2.50%.

It is difficult to estimate a reasonable percent reduction in mortality from LL medication. A 14% reduction would occur if there were a 30% reduction in CHD death, a 15% reduction in other cardiovascular mortality, and no reduction in non-cardiovascular mortality. This seems a little optimistic. We felt that a 12.5% reduction was reasonable, so we considered three different percent reductions, 11%, 12.5%, and 14%.

We reduced the mortality rate in the three AH arms other than the diuretic by 10%.

Six year mortality rates were computed for the LL placebo and LL active arms in a manner similar to the calculations for the AH component. Separate rates were computed for the diuretic arm and other AH arms, and a combined rate was obtained using the allocations shown in Table 3. The 6 year rates in the LL component of ALLHAT are shown in Table 5 below.

Table 5: Estimated 6 Year Mortality Rates

LL category	Diuretic Arm	Each Other AH Arm
LL Placebo	.13253	.11998
LL Active	.11903	.10769

The 6 year rates in the LL placebo and active arms are therefore:

$$p_0 = \left[\sqrt{3}/\left(3+\sqrt{3}\right)\right](.13253) + \left[3/\left(3+\sqrt{3}\right)\right](.11998) = .12457$$

$$p_1 = \left[\sqrt{3}/\left(3+\sqrt{3}\right)\right](.11903) + \left[3/\left(3+\sqrt{3}\right)\right](.10769) = .11184$$

Power was again computed using the arcsin transformation. The only differences between this calculation and the AH calculation are that the sample sizes n_0 and n_1 in the LL placebo and active arms are equal, and there is no adjustment for multiple comparisons. Thus we can use Formula 2 with $n_0=n_1=10,000$ and $c=1.96$.

Results

Power for the AH component under different assumptions is depicted in Figures 4-6. There is not a great difference in power under the different assumptions. Looking at crossover rate 2 and loss 2, we see that the power under the anticipated diuretic rate of 1.35% per year is 82.4%, as we calculated above.

Power for the LL total mortality component is depicted in Figure 7. We see that the power is almost exactly 80% under dropin/dropout rate 1 and a 12.5% reduction in mortality from LL treatment. It drops to 68.6% if there is only an 11% reduction in mortality (other assumptions as before). On the other hand, the power will be 88.1% if there is a 14% reduction in mortality from LL treatment (other assumptions as before). Under the more pessimistic dropin/dropout rate 2, the power is 76.9% under a 2.35%/yr mortality rate and a 12.5% reduction in mortality from LL treatment (not shown in the graph).

Appendix II: Detailed Definitions of Coronary Death, Nonfatal Acute Myocardial Infarction and Stroke

Coronary Death:

Death consistent with coronary heart disease (CHD) as underlying cause on death certificate, plus any one of the following:

1) Pre-terminal hospitalization with myocardial infarction,
2) Previous angina or myocardial infarction and no known potentially lethal non-coronary disease process
3) Death within 24 hours of symptoms of CHD or death within 24 hours without symptoms but with no known potentially lethal non-coronary disease process (includes instantaneous death and unwitnessed death)
4) Death resulting from a procedure related to coronary artery disease such as coronary bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

Note: Deaths due to a non-coronary underlying cause in which the terminal event was an MI shall be ascribed to the underlying cause -- not to CHD.

Coronary death will be subclassified as:

1) Definite fatal MI: no known non-atherosclerotic cause and definite MI within 4 weeks of death,
2) Definite fatal CHD: no known non-atherosclerotic cause and one or both of the following: chest pain within 72 hours of death or a history of chronic ischemic heart disease in the absence of valvular heart disease or non-ischemic cardiomyopathy, or
3) Possible fatal CHD: no known non-atherosclerotic cause, and death certificate consistent with underlying cause.

   In patients without a known potentially lethal non-coronary disease process, coronary death will also be classified as rapid or non-rapid, based on whether death did or did not occur within 24 hours after the onset of symptoms (or the time at which the patient was last seen without symptoms).

Nonfatal Acute Myocardial Infarction

The identification and coding of definite clinical acute myocardial infarction (MI) should be based on meeting at least two of the following three generally accepted criteria, consistent with the World Health Organization criteria:

1. Symptoms (such as chest pain) compatible with an acute MI of at least 20 minutes duration.

2. ECG changes compatible with an acute MI, such as new persistent ST segment elevation of

≥ 0.1 mV or new pathologic Q waves (QRS>0.04 sec), each in two contiguous leads.

3. A serum biochemical marker compatible with an acute MI, such as:
   - ✓ Total CK at least twice the upper limits of normal with an MB fraction of >5% of total CK, or
   - ✓ Troponin >2 times the upper limit of normal, or
   - ✓ LDH1/LDH2 ratio ≥1.

Stroke

Rapid onset of persistent neurological deficit attributable to an obstruction or rupture of the arterial system, including stroke occurring during surgery, that is not known to be secondary to brain trauma, tumor, infection, or other non-ischemic cause. The deficit must last more than 24 hours unless death supervenes or there is a demonstrable lesion compatible with acute stroke on CT or MRI scan.

A. Non-fatal stroke (either of the following):

1) Unequivocal objective findings of a localizing neurological deficit (with or without recent onset of severe headache or loss of consciousness), AND duration longer than 24 hours AND absence of other disease process causing neurological deficit such as neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder, and/or

2) Diagnosis of stroke based on abnormality demonstrated by CT or MRI consistent with current neurological symptoms or signs, or positive lumbar puncture (for subarachnoid hemorrhage).

B. Fatal stroke: Death certificate listing stroke as consistent with, underlying, or immediate cause of death, plus any one or more of the following:

1) Preterminal hospitalization with stroke as defined above,

2) Previous stroke and no known potentially lethal non-cerebrovascular disease process, and/or

3) Stroke diagnosed as cause of death at post-mortem examination.

Appendix III: Electrocardiographic Criteria for Silent Myocardial Infarction, Ischemia, Left Ventricular Hypertrophy, and Bundle Branch Block

The ALLHAT study records electrocardiographic information from baseline and biennial clinic visits and from a sample of acute hospitalizations that are designated as quality control events. Clinic ECGs are evaluated for prevalent and interim events including "silent" myocardial infarction.

Prevalent and Interim ECG Findings at Clinic Visits

A determination that an ALLHAT participant has prevalent MI, ischemia, LVH or bundle branch block can be made using Minnesota Code criteria. Interim MI, ischemia, LVH or bundle branch block can be made using the criteria shown for simultaneous comparison of ECGs.

Prevalent Baseline ECG Findings

1. Prevalent MI
   Baseline ECG coded:
   a) any 1 -1 -x code
   OR
   b) any 1-2-x PLUS 4-1-x, or 4-2, or 5-1, or 5-2

2. Prevalent Ischemia
   Baseline ECG coded:
   a) any 4-2 through 4-1-x
   b) any 5-2 through 5-1

3 Prevalent LVH
   Baseline ECG coded:
   a) 3-1 or 3-3 (soft LVH)
   b) 3-1 or 3-3 PLUS any 4-3 through 4-1-x, or 5-3 through 5-1 (hard LVH)

4. Prevalent bundle branch block
   Baseline ECG coded:
   a) 7-1-1
   b) 7-2-1
   c) 7-4

Interim ECG Events

An evolving ECG pattern between the baseline visit and an ECG from a later visit confirmed by simultaneous ECG comparison documents the interim event.

a. Interim MI

Any ED1 through ED7

b. Interim ischemic event
Any EV1 -EV9 pattern

c. Interim LVH or progression / regression of LVH
E-LVH 1 through E-LVH 4

d. Interim bundle branch block
EBBB 1 through EBBB 3

Attachment 1
Simultaneous Comparison of ECGs

Simultaneous ECG Comparison Explanations:

- A code 1-2-6 is considered no Q-code for the purposes of serial comparison.
- An Equivocal Q-code is a 1-2-8 or any 1-3-x code.
- A Diagnostic Q-code is any 1-1-x or any 1-2-x except 1-2-6 or 1-2-8.
- The designation of "ED" means evolving diagnostic Q-code pattern.
- All ED patterns are confirmed as significant increase by serial comparison.
- An ED1 through ED7 cannot be assigned if a 7-1-1 code is present.
- An ED2 through ED7 cannot be assigned if a 7-2-1 or 7-4 code is present.
- The designation "EV" means evolving ST-T wave pattern.
- All EV patterns are confirmed as significant increases or decreases by serial comparison.
- An EV1 through EV9 cannot be assigned if a 7-1-1, 7-2-1, or 7-4 code is present.

Significant Serial Change Patterns

Definite Q-wave MI (evolving diagnostic pattern)

ED1. No Q-code (or a 1-2-6) in baseline ECG followed by a record with a Diagnostic Q-code (Minnesota Code 1-1-1 through 1-2-5 or 1-2-7), confirmed as a significant increase.

OR

A 1-2-8 or any 1-3-X code in baseline ECG followed by a record with any 1-1-X code, confirmed as a significant increase.

ED2a. An Equivocal Q-code (1-2-8 or any 1-3-x code) and no major ST depression in baseline ECG followed by a record with a Diagnostic Q-code (1-1 -1 to 1 -2-5 or 1-2-7) PLUS a major ST depression (4-1-X or 4-2), confirmed as a significant increase.

ED2b. An Equivocal Q-code (1-2-8 or any 1-3-x code) with pre-existing major ST depression (4 1-X or 4-2) in baseline ECG followed by a record with a Diagnostic Q-code (1-1 - 1 to 1-2-5 or 1-2-7) PLUS more severe ST depression (4-1-X), confirmed by a significant increase.

ED3a. An Equivocal Q-code (1-2-8 or any 1-3-x code) and no major T-wave inversion in baseline ECG followed by a record with a Diagnostic Q-code (1-1-1 to 1-2-5 or 1-2-7) PLUS a major T-wave inversion (5-1 or 5-2), confirmed as a significant increase.

ED3b. An Equivocal Q-code (1-2-8 or any 1-3-x code) with pre-existing major T-wave inversion (5-1 or 5-2) in baseline ECG followed by a record with a Diagnostic Q-code (1-1 - 1 to 1 -2-5 or 1 -2-7) PLUS more severe T-wave inversion (5-1 or 5-2), confirmed as a significant increase.

ED4a. An Equivocal Q-code (1-2-8 or any 1-3-x code) and no ST elevation in baseline ECG followed by a record with a Diagnostic Q-code (1-1 -1 to 1 -2-5 or 1 -2-7) PLUS an ST segment elevation (9-2), confirmed as a significant increase.

ED4b. An Equivocal Q-code (1-2-8 or any 1-3-x code) with pre-existing ST elevation (9-2) in the baseline ECG followed by a record with a Diagnostic Q-code (1-1 -1 to 1 -2-5 or 1 -2-7) PLUS more severe ST elevation (9-2), confirmed as a significant increase.

ED5. No Q-code (or a 1-2-6) and neither 4-1-X nor 4-2 in baseline ECG followed by a record with an Equivocal Q-code (1-2-8 or any 1-3-x code) PLUS 4-1-X or 4-2, confirmed as a significant increase.

ED5b. No Q-code (or a 1 -2-6) with pre-existing major ST depression (4-1 -x to 4-2) in baseline ECG followed by a record with an Equivocal Q-code (1-2-8 or any 1-3-x code) PLUS more severe ST depression (4- 1-X), confirmed as a significant increase.

ED6a. No Q-code (or a 1 -2-6) and neither 5-1 nor 5-2 in baseline ECG followed by a record with an Equivocal Q-code (1-2-8 or any 1 -3-x code) PLUS a 5-1 or 5-2, confirmed as a significant increase.

ED6b. No Q-code (or a 1 -2-6) with pre-existing major T-wave inversion (5-1 or 5-2) in baseline ECG followed by a record with an Equivocal Q-code (1-2-8 or any 1-3-x code) PLUS more severe T-wave inversion (5-1 or 5-2), confirmed as a significant increase.

ED7a. No Q-code (or a 1 -2-6) and no 9-2 in baseline ECG followed by a record with an Equivocal Q-code (1-2-8 or any 1-3-x code) PLUS a 9-2, confirmed as a significant increase.

ED7b. No Q-code (or a 1 -2-6) with pre-existing ST elevation (9-2) in the baseline ECG followed by a record with an Equivocal Q-code (1-2-8 or any 1-3-x code) PLUS more severe ST elevation (9-2), confirmed as a significant increase.

Diagnostic ECG:

D1. An ECG record with a Diagnostic Q-code (1-1-1 to 1-2-5 or 1-2-7).

D2. An ECG record with ST segment elevation (9-2) PLUS T wave inversion (5-1 or 5-2).

Evolving ST-T Pattern:

This diagnosis cannot be assigned if a 7-1-1, 7-2-1, or 7-4 is present. For hospitalized participants, the EV patterns can occur from either increases or decreases in the severity of the code.

EV1. Either 4-0 (no 4-code), 4-4 or 4-3 in baseline ECG followed by a record with 4-1-1, 4-1-2, or 4-2, confirmed as a significant increase; OR for hospital ECGs only, 4-1-1, 4-1-2, or 4-2 in the earliest hospital ECG followed by an event record with a 4-0, 4-4, or 4-3, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no significant increase in Q codes found.

EV2. Either 4-2 or 4-1-2 in baseline ECG followed by a record with 4-1 -1, confirmed as a significant increase, or a 4-2 in baseline followed by a record with 4-1-2, confirmed as a significant increase; OR for hospital ECGs only, 4-1-1 in the earliest hospital ECG followed by an event record with a 4-1-2 or 4-2, confirmed as a significant decrease, OR 4-1-2 in the baseline ECG followed by a 4-2 in the follow-up ECG, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no ignificant increase in Q codes found.

EV3. Either 5-0, 5-4 or 5-3 in baseline ECG followed by a record with 5-2 or 5-1, confirmed as a significant increase; OR for hospital ECGs only, 5-1 or 5-2 in the earliest hospital ECG followed by an event record with a 5-0, 5-4 or 5-3, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no significant increase in Q codes found.

EV4. Code 5-2 in baseline ECG followed by a record with 5-1, confirmed as a significant increase; OR for hospital ECGs only, 5-1 in the earliest hospital ECG followed by an event record with a 5-2, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no significant increase in Q codes found.

EV5. Code 9-0 in baseline ECG followed by a record with 9-2, confirmed as a significant increase; OR for hospital ECGs only, 9-2 in the earliest hospital ECG followed by an event record with a 9-0, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no significant increase in Q codes found.

EV6. Code 4-1-1 in baseline ECG followed by a record with 4-1-1, confirmed as a significant increase; OR for hospital ECGs only, 4-1-1 in the earliest hospital ECG followed by an event record with a 4-1-1, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no significant increase in Q codes found.

EV7. Code 5-1 in baseline ECG followed by a record with 5-1, confirmed as a significant increase; OR for hospital ECGs only, 5-1 in the earliest hospital ECG followed by an event record with a 5-1, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no significant increase in Q codes found.

EV8. Code 5-2 in baseline ECG followed by a record with 5-2, confirmed as a significant increase; OR for hospital ECGs only, 5-2 in the earliest hospital ECG followed by an event record with a 5-2, confirmed as a significant decrease.

Plus

Either no Q-code in both the baseline ECG and the follow-up ECG OR Q-code(s) present in baseline ECG or follow-up ECG but no significant increase in Q codes found.

EV9a. No Q-code (or a 1-2-6) and pre-existing major ST depression, T wave inversion, or ST elevation (4-2 / 4-1-x, 5-2 / 5-1, or 9-2) in baseline ECG followed by an Equivocal Q-code (1-2-8 or any 1-3-x code) and less severe or absent ST depression, T wave inversion, or ST elevation (4-0 /4-4 / 4-3 / 4-2 / 4-1-x, 5-0 / 5-3 / 5-2 / 5-1, or 9-0 / 9-2), with Q-code confirmed as a significant increase, and ST or T wave changes confirmed as a significant decrease.

EV9b. An Equivocal Q-code (1-2-8 or any 1-3-x code) and pre-existing major ST depression, T wave inversion, or ST elevation (4-2 / 4-1-x, 5-2 / 5-1, or 9-2) in baseline ECG followed by a Diagnostic Q-code (1-1-1 to 1-2-5 or 1-2-7) and less severe or absent ST depression, T wave inversion, or ST elevation (4-0 / 4-4 /4-3 / 4-2 / 4-1-x, 5-0 / 5-3 / 5-2 / 5-1, or 9-0 / 9-2), with Q-code confirmed as a significant increase, and ST or T wave changes confirmed as a significant decrease.

Evolving Bundle Branch Block

E-BBB 1. No 7-1-1 in reference followed by an ECG with 7-1-1 with the QRS duration increased by ≥ 0.02 sec., confirmed as a significant increase.

E-BBB 2. No 7-2-1 in reference followed by an ECG with 7-2-1 with the QRS duration increased by ≥ 0.02 sec., confirmed as significant increase.

E-BBB 3. No 7-4 in reference followed by an ECG with 7-4 with the QRS duration increased by ≥ 0.02 sec., confirmed as a significant increase.

Evolving LVH

E-LVH 1. No 3-1 in the reference ECG followed by an ECG with a 3-1, confirmed as a sigificant increase.

E-LVH 2. No 3-3 in the reference ECG followed by an ECG with a 3-3, confirmed as a significant increase.

E-LVH 3. 3-1 in the reference ECG followed by an ECG with 3-1 or no 3 code confirmed as a significant decrease.

E-LVH 4. 3-3 in the reference ECG followed by an ECG with 3-3 or no 3 code confirmed as a significant decrease.

Equivocal ECG Pattern:

EI. An ECG record with a 1-2-8; or an ECG record with a 1-3-x in the absence of 7-2-1 or 7-4.

E2. An ECG record with ST-segment depression (4-1-x, 4-2, or 4-3).

E3. An ECG record with T-wave inversion (5-1, 5-2, or 5-3).

E4. An ECG record with ST-segment elevation code 9-2.

Other ECG Pattern:

All other ECG findings, including normal.

Uncodable ECG Pattern:

UI. Technical errors coded 9-8-1 by Minnesota Code.

a. Three or more missing leads.

b. Muscle tremor artifact that produces possible false initial R's.

c. Other technical errors making Q-wave measurement impossible, such as extreme lack of centering, or marked clipping.

d. Other conditions defined as "uncodable" by the Minnesota Code.

Absent ECG:

A. No ECG available for coding.

Appendix IV: Quality Control Evaluation of Hospitalized Myocardial Infarctions (MI)

The following definitions for acute hospitalized MI are not intended for the classification on the AL04 by site investigators, but rather for quality control assessment review by the Endpoints Subcommittee.

The criteria presented are based on the CCSP Pilot Study, the Minnesota Heart Survey, and other surveillance studies as incorporated into the ARIC study. The combinations of pain, ECG and enzyme categories required for each diagnosis below are approximately the same as those contained in the above-mentioned documents.

Definite Hospitalized MI

Must meet one or more of the following criteria:

1. Evolving diagnostic ECG pattern (ED1 - ED7) (Appendix III, Attachment 1)

OR

2. Diagnostic ECG pattern (D1 or D2) and abnormal enzymes (Appendix III, Attachment 1)

OR

3. Cardiac pain (defined below) and abnormal enzymes

AND

   a. Evolving ST-T pattern EV1-EV9 (Appendix III, Attachment 1)

OR

   b. Equivocal ECG pattern E1 through E4 (Appendix III, Attachment 1)

Probable in-hospital MI

Must meet one or more of the following criteria in the absence of sufficient evidence for Definite Hospitalized MI:

1. Cardiac pain and abnormal enzymes

   or

2. Cardiac pain and equivocal enzymes and

   a. Evolving ST-T pattern

   or

b. Diagnostic ECG pattern

or

3. a. Abnormal enzymes and

b. Evolving ST-T pattern

Suspect in-hospital MI

Must meet one or more of the following criteria in the absence of sufficient evidence for Definite or Probable in-Hospital MI.

1. Abnormal enzymes

or

2. Cardiac pain and incomplete enzymes and

a. Diagnostic ECG pattern

or

b. Evolving ST-T pattern

or

3. Cardiac pain and equivocal enzymes

or

4. Equivocal enzymes and

a. Diagnostic ECG pattern

or

b. Evolving ST-T pattern

or

c. Equivocal ST-T pattern

The definitions of specific elements of chest pain, enzymes and ECGs which contribute to the final diagnosis of definite, probable, suspect, or no MI are provided below.

Definition of Cardiac Pain

Pain having both of the following characteristics:

1. It occurs anywhere in the anterior chest, left arm, or jaw.

and

2. Absence of a definite non-cardiac cause of pain.

Abnormal Cardiac Enzymes

Enzymes are classed as abnormal if any enzyme values recorded meet any of the following criteria:

1.a. CK-MB is "present": (if laboratory uses the criterion of "present" or "absent" without reporting a more specific value) or the CK-MB is greater than or equal to 10% of the total CK value,

and

b. There is no known non-ischemic cause (cardiac surgery, severe muscle trauma, rhabdomyolysis) for the elevated enzyme value.

or

2.a. The ratio $LDH_1 : LDH_2 \geq 1$.

and

b. There is no evidence of hemolytic disease.

or

3.a. Total CK and LDH are both at least twice the upper limits of normal. (These increases do not have to occur on the same day).

and

b. There is no known non-ischemic cause (cardiac surgery, severe muscle trauma, rhabdomolysis) for the elevated enzyme value and no evidence of hemolytic disease.

Equivocal Cardiac Enzymes

Enzymes are classed as "equivocal" if the criteria for abnormal enzymes are not met and if:

1. Either total CK or total LDH are at least twice the upper limits of normal.

or

2. Both total CK and total LDH are between the upper limits of normal and twice the upper limits of normal. (These increases do not have to occur on the same day.)

or

3. CK-MB - 5-9% of total CK or is "weakly present."

A summary of the enzyme diagnostic criteria, as related to total CK and LDH is given in the following algorithm, Table 1.

Table 1. Algorithm for Total CK and LDH Enzyme Diagnostic Criteria

		Total CK		
		Upper Limit of Normal		Twice Upper Limit of Normal
TOTAL LDH	Twice Upper Limit of Normal	Equivocal	Equivocal	Abnormal
	Upper Limit of Normal	Normal	Equivocal	Equivocal
		Normal	Normal	Equivocal

Table 2
Proposed ALLHAT Diagnostic Criteria for In-Hospital MI

Cardiac Pain	ECG Findings	Enzymes	Diagnosis
Present	Evolving Diagnostic Pattern (ED1-ED7)	Abnormal	Definite MI
		Equivocal	Definite MI
		Incomplete	Definite MI
		Normal	Definite MI
	Diag. ECG Pattern	Abnormal	Definite MI
		Equivocal	Probable MI
		Incomplete	Suspect MI
		Normal	No MI
	Evolving ST-T (EV1 - EV9)	Abnormal	Definite MI
		Equivocal	Probable MI
		Incomplete	Suspect MI
		Normal	No MI
	Equivocal ECG Pattern	Abnormal	Definite MI
	Equivocal	Probable MI	
		Incomplete	No MI
		Normal	No MI
	Absent, Uncodable, or other	Abnormal	Probable MI
		Equivocal	Suspect MI
		Incomplete	No MI
		Normal	No MI
Not Present, Unknown or Missing	Evolving Diagnostic Pattern (ED1-ED7)	Abnormal	Definite MI
		Equivocal	Definite MI
		Incomplete	Definite MI
		Normal	Definite MI
	Diag. ECG Pattern	Abnormal	Definite MI
		Equivocal	Suspect MI
		Incomplete	No MI
		Normal	No MI

Evolving ST-T Pattern (EV1-EV9)	Equivocal	Abnormal	Probable MI
		Equivocal	Suspect MI
		Incomplete	No MI
		Normal	No MI
Equivocal ECG Pattern	Equivocal	Abnormal	Suspect MI
		Equivocal	Suspect MI
		Incomplete	No MI
		Normal	No MI
Absent, Uncodable or other		Abnormal	Suspect MI
		Equivocal	No MI
		Incomplete	No MI
		Normal	No MI

PROTOCOL ADDENDUM 1

Revised Power for Lipid-Lowering Portion of ALLHAT

Power for the lipid-lowering portion of ALLHAT was revised based on a total sample size of 10,000 and subgroups of size 4,000. The dropout rate was taken as the more pessimistic of the two scenarios in the protocol-6% in the first year and 3% per year thereafter. The dropin was also taken as the more pessimistic of the two protocol scenarios, namely 2.5% per year. The loss for total mortality was taken to be 0, while for the CHD it was as specified in the protocol for the antihypertensive component (slightly over 3% per year). The event rates shown are after accounting for benefits of antihypertensive therapy. The power results are shown in Tables 1 and 2. A more pessimistic loss of 5% per year was also considered. This reduced power by about 2 percentage points.

Table 1: Power for total mortality
Loss assumed to be 0, dropout=6% in first year, 3% per year thereafter, dropin=2.5% per year.

Treatment Reduction	Control Rate/year	N = 4,000	N = 10,000
	.01		
	.015		
10% reduction	.020		
	.025		
	.030	19%	41%
	.01	13%	25%
	.015	17%	35%
12.5% reduction	.02	21%	44%
	.025	24%	52%
	.030	28%	59%
	.01	16%	34%
	.015	22%	47%
15% reduction	.02	28%	58%
	.025	33%	68%
	.030	39%	75%
	.01	26%	55%
	.015	37%	72%
20% reduction	.02	46%	84%
	.025	54%	91%
	.030	62%	95%
	.01	39%	76%
	.015	54%	90%
25% reduction	.02	65%	96%
	.025	75%	99%
	.030	82%	99%+
	.01	53%	90%
	.015	70%	98%
30% reduction	.02	82%	99%
	.025	89%	99%+
	.030	94%	99%+

Table 2: Power for CHD

Same dropout and dropin as above. Power assuming the loss rate in the protocol is given.

Treatment Reduction	Control Rate/year	N = 4,000	N = 10,000
	.008	21%	44%
	.010	25%	52%
20% reduction	.012	29%	60%
	.014	33%	66%
	.016	36%	72%
	.008	31%	63%
	.010	37%	73%
25% reduction	.012	43%	80%
	.014	48%	86%
	.016	53%	90%
	.008	42%	80%
	.010	50%	88%
30% reduction	.012	58%	93%
	.014	64%	96%
	.016	70%	98%
	.008	55%	91%
	.010	65%	96%
35% reduction	.012	72%	98%
	.014	79%	99%
	.016	84%	99%+

PROTOCOL ADDENDUM 2
Monitoring Boundaries

When data are examined repeatedly in a trial, the type 1 error rate can be increased dramatically if no account is taken of these multiple "looks" (Armitage, Mc.Pherson and Rowe, 1969; Proschan, Follmann, and Waclawiw, 1992). Boundaries have been constructed in two-armed trials that either eliminate or greatly ameliorate this type 1 error rate inflation. These are called group-sequential rather than sequential boundaries because interim analyses are conducted after groups of data accrue rather than after every new observation. The most popular of these require extremely strong evidence to declare significance very early in the trial, and roughly the same degree of evidence at the end of the trial that would be required had there been no interim looks. This was not the case for the first group-sequential procedure proposed (Pocock, 1977). For this reason, Pocock himself recommends against using his procedure (personal communication).

The O'Brien-Fleming (1979) boundary has the above properties. The drawback is that it requires the number of looks to be specified in advance, and these looks must occur after equal increments of information. In the context of this trial, *information time* t is estimated by the ratio of the number of events observed thus far to the number expected by the end of the trial. Thus t=0 is the beginning and t=1 is the end of the study. Suppose we planned eight looks at the data after equal increments of information (numbers of events). The boundary is given in Figure 1 for the comparison of a given arm with the diuretic. A multiple comparison adjustment has been made for the three comparisons with the diuretic.

Lan and DeMets (1983) proposed a "spending function" approach which allows the data to be examined after different amounts of information, and does not require the number of looks to be specified in advance. The spending function $\alpha^*(t)$ represents the cumulative amount of type 1 error probability that is spent by information time t, with $\alpha^*(1)=\alpha$. The amount of type 1 error probability spent is inextricably linked to information time. This contrasts with the method of Slud and Wei (1982), which spends a fixed amount of type 1 error probability at each look at the data, regardless of the information time. Serious inflation of the type 1 error rate can occur with the Slud and Wei procedure, but not with the Lan-DeMets procedure (Proschan, Follmann, and Waclawiw, 1992). One of the spending functions suggested by Lan and DeMets (see the equation in the Appendix) has boundaries very similar to the O'Brien-Fleming boundary if the looks happen to occur after equal increments of information (see Figure 1). The advantage of the Lan-DeMets approach is that it can be used even when the looks are not equally spaced. In this case the boundaries would change somewhat.

Another extremely useful monitoring tool is conditional power (Lan, Simon, and Halperin, 1982 or Lan and Wittes, 1988). The conditional probability of obtaining a statistically significant result at the end of the trial is computed under different hypothesized treatment effects. Unlike the O'Brien-Fleming or Lan-DeMets boundaries, conditional power is usually used to justify terminating a trial which has no realistic chance of producing a statistically significant result. The trial is stopped if the conditional power is very low even assuming a large treatment benefit for the remainder of the trial. Stochastic curtailment refers to stopping a trial because the conditional power crosses a pre-specified threshold value. For example, one could agree to stop the trial if the conditional power assuming the pre-specified alternative hypothesis is less than or equal to .10. If one uses such a rule, the chance of a type 2 error (accepting the null hypothesis when it is false) is greater than it would be without stochastic curtailment. This is because one could accept the null hypothesis at the end of the study or at an interim point.

The degree of type 2 error rate inflation is quite small. Lan, Simon, and Halperin (1982) showed that it is fairly small even if one monitors the trial continuously. Davis and Hardy (1990) showed that in the more realistic situation in which a trial is monitored 5 to 10 times, the inflation is much smaller.

An important issue that comes up in group sequential monitoring is that of information time. We mentioned above that information time is estimated using the number of events observed thus far divided by the number expected by the end of the trial. But the number in what arms? In two armed monitoring one could either use the total number of events in both arms or the number of events in the control arm. The advantage of using both arms is that it provides a larger sample size to estimate information time. A disadvantage is that in order to estimate the number of events to expect by the end of the trial, one has to project not only a control group event rate, but a treatment effect as well. We have four antihypertensive arms in ALLHAT, hence three treatment effects to specify. It is recommended that we use the diuretic arm events to determine information time.

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APPENDIX

Recommended Spending Function

$$\alpha^*(t) = 2[1\Phi(z_{\alpha/4}/\sqrt{t})],$$

The Lan-DeMets spending function we recommend is where α is the two-sided type 1 error rate for a given comparison with diuretic, Φ is the standard normal distribution function, and $z_{\alpha/4}$ is its $100(1-\alpha/4)$th percentile. When we adjust for multiple comparisons with the diuretic, the value of $z_{\alpha/4}$ becomes approximately 2.64.

PROPOSED STOPPING RULES

1) Use Lan-DeMets version of O'Brien-Fleming for harm/benefit.
2) The boundaries will be symmetric.
3) Information time will be calculated as proportion of expected events in diuretic arm.
4) Take first look at about 10% of information time and then annually at DSMB meetings.
5) Pay special attention at beginning to results that cross the Haybittle-Peto boundary of Z=4.0 for the antihypertensive component, Z=3.0 for the lipid-lowering component.
6) Use conditional power under the protocol specified alternative hypothesis for futility.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (1994-2002)

The University of Texas School of Public Health
Coordinating Center for Clinical Trials

ALLHAT Home Page

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a practice-based clinical trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The trial is being conducted in approximately 600 office-based practices and general medical and specialty clinics throughout the U.S.A., Puerto Rico, the Virgin Islands, and in Canada.

A total of 42,418 patients were enrolled between February 14, 1994 and January 31, 1998, a large percentage of whom are African-American. A vanguard phase was conducted in the first half of 1994; the full-scale trial began in the fall of 1994 and will continue for eight years, until March 31, 2002.

The study has two components:

- An antihypertensive component, to determine whether newer antihypertensive agents, such as ACE inhibitors, calcium blockers, and alpha blockers, reduce incidence of coronary heart disease (CHD) in high-risk hypertensives when compared to diuretics.

- A lipid-lowering component, to determine whether reduction of serum cholesterol with pravastatin, an HMG-CoA reductase inhibitor, reduces total mortality in moderately hypercholesterolemic older hypertensives.

Because the efficacy of lipid-lowering can be tested in a subset of patients targeted for study in the antihypertensive component of ALLHAT, the two trials have been combined for approximately the cost of conducting either one alone.

Because African-Americans suffer disproportionately from hypertension and its sequelae, a large percentage of participants will be African-American.

Background

Antihypertensive Component

In the early 1980's, three new classes of antihypertensive agents, the calcium antagonists, angiotensin-converting enzyme (ACE) inhibitors, and alpha-adrenergic blockers, were developed and licensed for use in chronic antihypertensive therapy. Some of these agents can cost up to 30 times as much as older therapies such as diuretics and beta blockers. They are also believed to have fewer side effects and may have ancillary properties (in addition to their blood-pressure lowering effects) that could reduce morbidity and mortality from coronary heart disease (CHD).

Comparison of these agents in such studies as the TOMHS (*Arch Intern Med* 1991; 151:1413-1423) and the VA Monotherapy Trial (*N Engl J Med* 1993; 328:914-921), however, has failed to show major differences in side effects or blood pressure lowering. Efficacy of newer agents in preventing CHD has not been evaluated in large-scale clinical trials. Yet, despite their increased cost and lack of proven superiority over older agents, their use (particularly use of calcium antagonists and ACE inhibitors) has increased

dramatically in the past five to ten years.

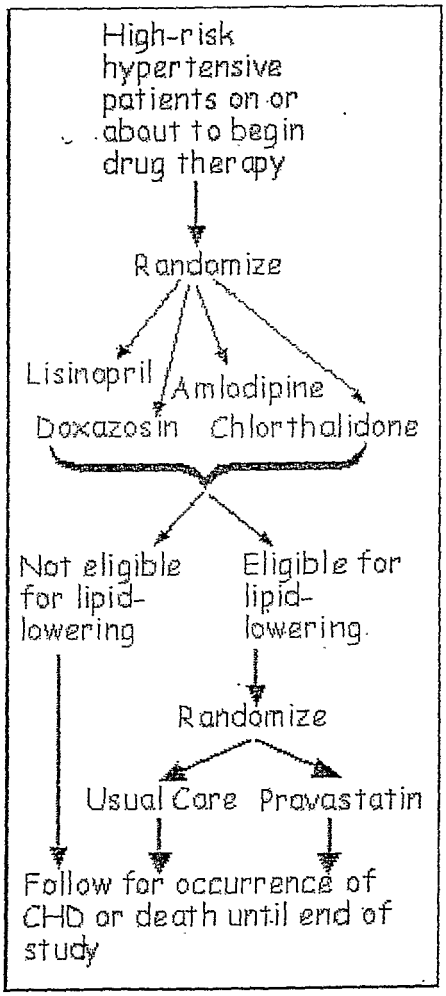
Lipid-Lowering Component

Elevated cholesterol is known to be a major CHD risk factor, but trials demonstrating a reduction in CHD from cholesterol lowering have not demonstrated a net reduction in all-cause mortality. Since these trials have been conducted primarily in middle-aged men, the extrapolation of their findings to older men and women has also been questioned. The introduction of HMG-CoA reductase inhibitors in the late 1980's provided a powerful new lipid-lowering therapy that is well-tolerated and has few adverse effects. A recent NHLBI study conclusively demonstrated the feasibility and efficacy of lowering cholesterol with lovastatin in older adults (*Arch Int Med* 1994; 154:529-539).

ALLHAT Study Design

The rationale and design for ALLHAT has been published (*Am J Hypertension* 1996; 9:342-360). In ALLHAT, hypertensive patients are randomly assigned to receive one of four drugs in a double-blind design. No patient receives placebo, and a limited choice of second step agents are provided for patients not controlled on first-line medication. Patients are followed every 3 months for the first year and every 4 months thereafter for an average of 6 years of follow-up.

Approximately 10,000 of the patients in the antihypertensive component were also randomized to diet plus lipid-lowering or diet plus usual care in an unblinded design. After randomization, frequency and content of follow-up visits for the two trial components are identical.



ALLHAT Study Candidates

- Antihypertensive Component
  - Age 55 years or older
  - Known hypertensive with BP less than or equal 160/100 mmHg on treatment, or BP greater than or equal 140/90 mmHg and less than or equal 180/110 without treatment
  - At least one of the following:
    1. Left ventricular hypertrophy on ECG or echocardiogram
    2. Known atherosclerotic CVD
    3. Type II diabetes mellitus
    4. HDL cholesterol <35 mg/dl
    5. Current cigarette smoker
- Major Exclusions:
  - Recent MI or stroke
  - Known congestive heart failure or angina pectoris
  - Need for any study drug for reasons other than hypertension
  - Need for more than two antihypertensive drugs to control BP
  - Serious systemic disease
  - Elevated serum creatinine (2 mg/dl or greater)

- Lipid-Lowering Component
  - Eligible and randomized in antihypertensive component
  - LDL cholesterol 120-189 mg/dl (100-129 for patients with CHD)
- Major Exclusions:
  - Current use of lipid-lowering medications
  - Contraindications to HMG-CoA reductase inhibitors
  - Known untreated secondary cause of hyperlipidemia
  - ALT > 2 times upper limit of normal



Revised February 20, 2002

ALLHAT News Article

THE UNIVERSITY OF TEXAS-HOU
HEALTH SCIENCE CENTER
Monday Morning
Monday, April 17, 2000

Study Shows Blood Pressure Drug Lowers Risk of Cardiovascular Disease

By Jackie Preston

Office of Public Affairs

Chlorthalidone, a common diuretic used to treat people with high blood pressure, dramatically decreases the risk of cardiovascular disease compared to doxazosin, an alpha-blocker, say researchers at UT-Houston.

The findings were reported by School of Public Health researchers as part of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which is an eight-year, multi-center study funded by the National Heart, Lung and Blood Institute (NHLBI). The study results will be published in the April 19 issue of the Journal of the American Medical Association.

"We showed that study participants who took chlorthalidone cut their risk of heart failure in half, compared to those who took doxazosin," said Barry R. Davis, M.D., Ph.D., professor of biometry at the School of Public Health and deputy director of the school's Coordinating Center for Clinical Trials.

ALLHAT researchers want to know if cheaper drugs, such as diuretics, are better in combating high blood pressure and its adverse side effects, including heart attack and stroke.

The study followed 24,335 patients age 55 and older with high blood pressure and at least one of several cardiovascular disease risk factors, such as diabetes and a history of stroke. The patients were randomly assigned to receive one of four high blood pressure drugs, including chlorthalidone and doxazosin.

"The doxazosin group had a 25 percent increased risk for cardiovascular disease and a doubled risk for heart failure compared with the chlorthalidone group," Davis said.

The NHLBI halted the doxazosin part of the study early based on the findings.

Davis said the study may lead to better therapies for older patients with high blood pressure.

"Our study results proved that at present, chlorthalidone should be the first line of defense in treating older adults with high blood pressure at risk for heart disease," Davis said.

The School of Public Health was awarded a $103.2 million contract from the NHLBI to coordinate ALLHAT in 1993, making it the largest contract ever awarded to UT-Houston.

More than 4.6 million Americans suffer from heart failure, a leading cause of disability and death in the U.S. and the most common hospital discharge diagnosis among people age 65 and older.

More than 50 million Americans have high blood pressure, or hypertension. The disease is 50 percent more prevalent in African-Americans than in whites.

April 20, 2000

Relationship of Antihypertensive Treatment Regimens and Change Blood Pressure to Risk for Heart Failure in Hypertensive Patients Randomly Assigned to Doxazosin or Chlorthalidone: Further Analyses from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial

Barry R. Davis, MD, PhD; Jeffrey A. Cutler, MD; Curt D. Furberg, MD, PhD; Jackson T. Wright Jr., MD, PhD; Michael A. Farber, MD; James V. Felicetta, MD; and John D. Stokes, MD, for the ALLHAT Collaborative Research Group*

Background: The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial reported that treatment initiated with doxazosin compared with chlorthalidone doubled the risk for heart failure in high-risk hypertensive patients (relative risk, 2.04 [95% CI, 1.79 to 2.32]). Patients assigned to doxazosin therapy had a mean in-trial systolic/diastolic blood pressure 3/0 mm Hg higher than that in patients assigned to chlorthalidone. Sixty-eight percent (6167 of 9061) of the former patients and 59% (9081 of 15 256) of the latter patients were given additional medications to achieve a target blood pressure of less than 140/90 mm Hg.

Objective: To ascertain the influence of open-label antihypertensive drugs and subsequent blood pressure on relative risk for heart failure.

Design: Randomized, double-blind, active-controlled clinical trial.

Setting: 623 sites in the United States and Canada.

Patients: Hypertensive patients 55 years of age or older with at least one additional risk factor for cardiovascular disease.

Intervention: Chlorthalidone (12.5 to 25 mg/d) or doxazosin (2 to 8 mg/d) for a planned follow-up of 4 to 8 years.

Measurements: Data on blood pressure, medication, and incident heart failure (treated outside hospital, hospitalized, or fatal) from February 1994 through December 1999.

Results: After the treatment groups were categorized as having no exposure to open-label medications (monotherapy) or exposure to open-label therapy, the relative risk for heart failure with doxazosin versus chlorthalidone was 3.10 (CI, 2.51 to 3.82) and 1.42 (CI, 1.20 to 1.69), respectively. After adjustment for follow-up systolic/diastolic blood pressure, the overall relative risk was 2.00 (CI, 1.72 to 2.32).

Conclusion: In high-risk patients with hypertension, the higher risk for heart failure while taking doxazosin compared with chlorthalidone is attenuated but not eliminated by adding other antihypertensive drugs. The small observed difference in systolic blood pressure does not explain this increased risk.

Ann Intern Med. 2002;137:313-320. www.annals.org

For author affiliations, see end of text.

*For a complete list of members of the ALLHAT Collaborative Research Group, see JAMA. 2000;283:1973-5.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, multicenter clinical trial including 42 418 participants at 623 clinical sites, is designed to determine whether treatment begun with a calcium-channel blocker (amlodipine), an angiotensin-converting enzyme inhibitor (lisinopril), or an α-adrenergic blocker (doxazosin) compared to treatment with a diuretic (chlorthalidone) reduces the incidence of fatal coronary heart disease or nonfatal myocardial infarction in high-risk patients with hypertension (1). Secondary end points are all-cause mortality, stroke, and other cardiovascular events. A lipid-lowering trial in a subset of 10 356 participants is designed to determine whether decreasing cholesterol levels with a hydroxymethyl glutamyl coenzyme A reductase inhibitor (pravastatin) compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic patients.

In January 2000, the doxazosin arm of the trial was discontinued (2) because major cardiovascular disease (relative risk, 1.25 [95% CI, 1.17 to 1.33]; $P < 0.001$), especially heart failure (relative risk, 2.04 [95% CI, 1.79 to 2.32]; $P < 0.001$), was significantly increased compared with the chlorthalidone arm. Equally important, a low probability existed that doxazosin would show benefit over chlorthalidone for the primary end point by the scheduled study end, given the lack of difference (relative risk, 1.02 [95% CI, 0.90 to 1.17]; $P > 0.2$] at that time. These intention-to-treat analyses compared patients assigned to chlorthalidone with patients assigned to doxazosin.

In this article, we analyze how treatment changes may have affected the comparison of doxazosin with chlorthalidone in terms of heart failure. Our major objectives are to ascertain to what extent the relative risk with doxazosin versus chlorthalidone depends on 1) whether the assigned drugs were used as monotherapy or in combination with other agents and 2) the difference in decreases in systolic and diastolic blood pressure.

Methods

Study Design

The rationale and design of ALLHAT are described in detail elsewhere (1). In brief, eligible participants were men

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Context

Previously published results of this randomized, double-blind trial showed that hypertensive patients treated with doxazosin rather than chlorthalidone more often developed heart failure. Did differences in blood pressure control or treatment with other drugs explain these findings?

Contribution

This analysis shows that the slightly worse blood pressure control achieved with doxazosin did not explain higher risks for heart failure. Risks with doxazosin versus chlorthalidone were highest among patients who received monotherapy (relative risk, 3.10) and lowest among patients who received stepped care with additional drugs (relative risk, 1.42).

Implications

Increased risks for heart failure with doxazosin versus chlorthalidone are attenuated but not eliminated when additional antihypertensive drugs are used.

—The Editors

and women 55 years of age or older who had systolic or diastolic hypertension (≥140/90 mm Hg or hypertension controlled with medication) plus at least one additional risk factor for coronary heart disease events. The risk factors included previous (>6 months) myocardial infarction or stroke, left ventricular hypertrophy on electrocardiography or echocardiography, history of type 2 diabetes, current cigarette smoking, and a low high-density lipoprotein cholesterol level. Persons with a history of hospitalized or treated symptomatic heart failure or a known ejection fraction less than 0.35 were excluded.

Unless the drug regimen required tapering for safety, participants who had been taking antihypertensive medications continued to do so until the day of randomization, at which point they stopped taking all previous medications. On the day after randomization, treatment with the study drug was initiated.

Enrollment occurred from February 1994 through January 1998. The original reported number of 42 448 participants and 625 sites changed because 30 patients with poor documentation of informed consent were excluded (2). Participants were assigned by a computer-generated randomization schedule in a ratio of 1.7:1 to receive chlorthalidone or doxazosin. Randomization was stratified by center and blocked over time to maintain the ratio. All participants gave written informed consent, and all centers obtained institutional review board approval.

Ascertainment of Outcomes

At each clinic visit, occurrence of study end points was assessed by the clinical investigator. A hospital discharge summary was required for each hospitalized study outcome, and a death certificate was required for each death. ALLHAT defined symptomatic heart failure as clear-cut signs or symptoms of left or right ventricular dysfunction that cannot be attributed to other causes. A patient had to have at least one symptom (paroxysmal nocturnal dyspnea, dyspnea at rest, New York Heart Association class III dyspnea or other symptoms [on less than ordinary exertion], or orthopnea) and one sign (rales, ankle edema, tachycardia, cardiomegaly or characteristic pulmonary pattern on chest radiography, S_3 gallop, or jugular venous distention) (3). Symptoms and signs were determined by the clinic investigator through patient history, chart review, or consultation with the treating physician, but such data were not collected centrally.

A one-time sample of 24 hospitalized or fatal heart failure events was reviewed in a blinded manner by the ALLHAT Endpoints Subcommittee; 20 of 24 (83%) were deemed to have complete data for a definitive diagnosis. Of the 20 cases, the agreement rate between the subcommittee and the clinic investigators was 90% (18 of 20) and similar in both treatment groups. Details on the validity of diagnosis of heart failure will be provided in a future report.

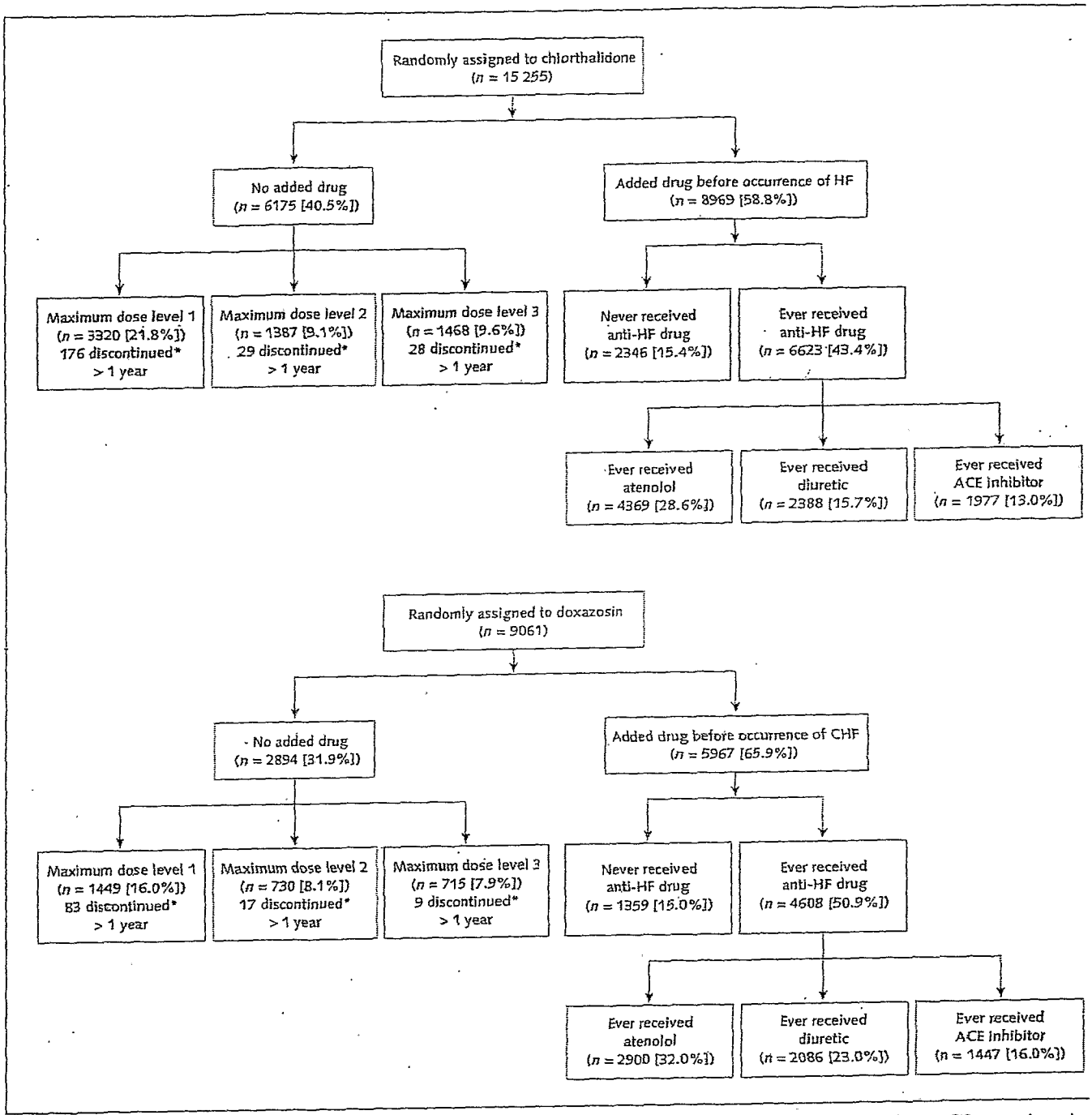
Measurement and Treatment of Blood Pressure

The ALLHAT protocol specified a stepped-care treatment program for hypertension. Trained observers using standardized techniques measured blood pressures during the trial (1, 2). All blood pressures were calculated as the average of two measurements obtained with a 30-second interval between them. The blood pressure goal in all four study arms was less than 140/90 mm Hg. This level was to be achieved with the lowest possible dose of blinded first-line drug, with addition of second- and third-line open-label therapy as needed after reaching the maximal dose of first-line drug.

Chlorthalidone and doxazosin were to be taken once daily in the morning. By design, doses were selected to achieve equivalent blood pressure control in the treatment groups. The first, second, and third dosage levels were 12.5 mg/d, 12.5 mg/d (sham titration), and 25 mg/d, respectively, for chlorthalidone and 2 mg/d, 4 mg/d, and 8 mg/d for doxazosin. Double-blinded 1-mg and 12.5-mg doses of doxazosin and chlorthalidone, respectively, were used for the first week to minimize the frequency of postural hypotension associated with doxazosin. The identity of drugs was masked at each dosage level, but dosage level was not.

After randomization, patients were seen for dose titration as needed at 1 and 3 months per the protocol, but they could return more often until target blood pressure was reached. Subsequently, required visits occurred at 3-month intervals during the first year and at 4-month intervals thereafter. Open-label second-step drugs were added as needed and tolerated. These agents were reserpine (0.05 to 0.2 mg/d), clonidine (0.1 to 0.3 mg twice daily), and atenolol (25 to 100 mg/d). The choice of second-step drug was at the discretion of the treating clinician-investigator. The third-step agent was hydralazine (25 to 100 mg

Figure. Participants who underwent randomization and were followed in the monotherapy and open-label therapy analyses, by study treatment group.



Values in parentheses are percentages of total participants. *Patients discontinued from therapy with randomly assigned drug. ACE = angiotensin-converting enzyme; HF = heart failure.

twice daily). Details of these therapies are provided elsewhere (1).

Investigators could choose to prescribe open-label antihypertensive drugs other than those provided by the study. However, use of the drug classes under study—thiazide diuretics, calcium antagonists, angiotensin-converting enzyme inhibitors, and α-adrenergic blockers—was strongly discouraged to avoid dilution of treatment comparisons. When clinical conditions other than uncontrolled hypertension (for example, angina or heart failure) were present, drugs from any study class could be used. If a step 1 drug was specifically required for blood pressure control while blinded drug treatment was continued, the step 1 drug could be added as open-label therapy but the dose

Table 1. Baseline Characteristics of Participants

Characteristic	No Exposure to Open-Label Drugs (Monotherapy)		Exposure to Open-Label Therapy	
	Chlorthalidone Group	Doxazosin Group	Chlorthalidone Group	Doxazosin Group
Participants, *n*	6175	2894	8969	5967
Age, *y**	66.8 ± 7.9	66.8 ± 8.0	67.0 ± 7.5	66.8 ± 7.6
Ethnicity, %				
White, non-Hispanic	37.5	37.8	53.8	50.5
Black, non-Hispanic	33.4	28.3	30.9	35.1
White Hispanic	18.8	22.5	8.3	7.9
Black Hispanic	5.1	6.0	2.0	2.2
Other	3.9	5.5	4.9	4.3
Women, %	51.3	50.7	44.1	44.4
Level of education, *y*	10.50 ± 4.1	10.4 ± 4.5	11.3 ± 4.0	11.3 ± 3.7
Current cigarette smoking, %	24.5	23.4	20.2	20.9
Receiving antihypertensive treatment before study entry, %	85.5	84.9	93.3	92.8
Atherosclerotic cardiovascular disease, %	39.9	42.1	48.8	47.3
ST-T wave, %	9.9	8.5	10.2	10.5
Type 2 diabetes, %	35.4	35.0	36.2	35.1
Low high-density lipoprotein cholesterol level, %	11.9	11.5	12.7	12.2
Left ventricular hypertrophy, %				
On electrocardiography	15.0	14.3	16.4	16.7
On echocardiography	3.5	3.2	4.6	4.6
Blood pressure, *mm Hg**				
Systolic	143.9 ± 15.3	144.4 ± 15.4	147.8 ± 15.7	147.2 ± 15.8
Diastolic	83.8 ± 9.8	83.9 ± 9.9	84.1 ± 10.3	83.9 ± 10.1
Serum potassium level, *mmol/L**	4.4 ± 0.7	4.4 ± 0.8	4.3 ± 0.7	4.3 ± 0.6
Fasting serum glucose level, *mmol/L (mg/dL)**	6.9 ± 3.4 (124 ± 61)	6.8 ± 3.3 (126 ± 59)	6.9 ± 3.1 (124 ± 56)	6.8 ± 3.0 (126 ± 54)
Serum creatinine concentration, *μmol/L (mg/dL)**	77.8 ± 23.3 (0.8 ± 0.3)	77.8 ± 23.3 (0.8 ± 0.3)	77.8 ± 23.6 (0.8 ± 0.3)	77.8 ± 22.9 (0.8 ± 0.3)
Serum cholesterol level, *mmol/L (mg/dL)**				
Total cholesterol	5.6 ± 1.1 (216 ± 42)	5.6 ± 1.1 (216 ± 42)	5.6 ± 1.1 (216 ± 42)	5.6 ± 1.1 (216 ± 42)
Low-density lipoprotein cholesterol	3.5 ± 1.0 (135 ± 37)	3.5 ± 1.0 (135 ± 37)	3.5 ± 1.0 (135 ± 37)	3.5 ± 0.9 (135 ± 35)
High-density lipoprotein cholesterol	1.2 ± 0.4 (46 ± 15)	1.2 ± 0.4 (46 ± 15)	1.2 ± 0.4 (46 ± 15)	1.2 ± 0.4 (46 ± 15)
Fasting triglycerides	2.0 ± 1.5 (177 ± 133)	1.9 ± 1.9 (168 ± 168)	2.0 ± 1.5 (177 ± 133)	1.9 ± 1.3 (168 ± 115)

* Values with the plus/minus sign are the mean ± SD.

could not exceed one half the maximum recommended by the Fifth Joint National Committee (4). In most such cases, unblinding the patient or the investigator to treatment assignment was not necessary. (Overall, <1% of drug identities were provided to either participant or investigator.) Any of nine possible open-label drug types—diuretic, calcium-channel blocker, angiotensin-converting enzyme inhibitor, α-adrenergic blocker, atenolol, reserpine, clonidine, hydralazine, and other antihypertensive drug (which could include nonatenolol β-blockers, although drug name was not logged)—could be recorded at each visit. Because diuretics, angiotensin-converting enzyme inhibitors, and β-blockers are beneficial in preventing or treating heart failure, we call these *antihypertensive heart failure drugs*. Data on antihypertensive drug use before study enrollment were collected, but not by drug class.

Statistical Analysis

Data were analyzed for use of additional drugs according to participants' randomized treatment assignments and regardless of continuation of blinded study treatment. The outcomes "all heart failure" (treated outside hospital, hospitalized, or fatal) and "hospitalized or fatal heart failure" were examined by treatment group for the entire cohort. The time to event for the previously published "as-randomized" analyses was the interval from randomization to first diagnosis of heart failure for patients who had an outcome, or from randomization to study end or loss to follow-up for those without an outcome. In this study, outcome rates were compared by treatment group for participants with no exposure to open-label medication, and results of this comparison were contrasted with rates in the respective treatment groups with such exposure. Similar comparisons were done for patients with exposure and those with no exposure to antihypertensive heart failure medications. Dose–exposure analyses were done to compare the influence of the two doses of chlorthalidone with that of the three doses of doxazosin (six possible comparisons) on the observed relative risk.

Cumulative event rates were calculated by using the Kaplan–Meier procedure (5). Relative risks (hazard ratios) with 95% CIs and two-sided *P* values were calculated by using a proportional hazards model (5). The drug-exposure and no-drug-exposure analyses were also performed by using Cox regression with a time-dependent covariate representing exposure and an interaction term representing the product of this term and drug assignment. Cox regression analyses limited to the duration of receipt of the various doses of doxazosin and chlorthalidone were also per-

formed. Because these time-dependent analyses are subject to statistical and epidemiologic biases, the *P* values, relative risks, and confidence intervals for them should be interpreted with caution (6).

To account for differences in systolic blood pressure between the randomized treatment groups as previously reported, two types of analyses were performed. First, participants were stratified by their blood pressure at 9 to 12 months after randomization into categories of systolic blood pressure (≥140 mm Hg or <140 mm Hg), diastolic blood pressure (≥90 mm Hg or <90 mm Hg), and combinations of these blood pressures (eight groupings). Mean differences in systolic and diastolic blood pressure between the treatment groups at this time and event rates, relative risks, and 95% CIs beyond 1 year were calculated. Second, Cox regression analyses of the entire cohort that included fixed covariates of baseline systolic and diastolic blood pressure and time-dependent covariates of follow-up systolic and diastolic blood pressure were performed.

Follow-up blood pressures were obtained at clinic visits. Missed visits resulted in missing blood pressures. Reasons for missing visits were recorded and included loss to follow-up, refusal to return, and intercurrent illness. Analyses were done by using all available information (which decreased sample sizes owing to missing values) and by assigning follow-up blood pressures for the missing observations (a measurement not captured in the last 6 months) according to time period and treatment group by using the method of multiple imputation (7, 8).

Role of the Funding Source

The National Heart, Lung, and Blood Institute sponsored the study and was involved in all aspects other than direct operations of the study centers. This included collection, analysis, and interpretation of the data plus the decision to submit the manuscript for publication.

RESULTS

The results presented here are restricted to the same data set as the previously published analysis (1). The median duration of follow-up for all participants was 3.3 years. Five hundred (3.3%) patients in the chlorthalidone group and 338 (3.7%) patients in the doxazosin group were lost to follow-up. During the trial, about 59% of patients in the chlorthalidone group and 68% of patients in the doxazosin group were stepped up to additional drugs.

The Figure shows the number of patients who were randomly assigned and followed to the time of each analysis. It also shows the number of participants who reached the maximal dose level of blinded step 1 drug and those who were stepped up to any open-label drug or any antihypertensive heart failure open-label drug before heart failure occurred. The relative risk for receiving additional medications before reported onset of heart failure (doxazosin versus chlorthalidone) was 1.31 (95% CI, 1.27 to 1.35) ($P < 0.001$). Of patients who never started taking antihypertensive heart failure medication, about one fourth started therapy with a calcium antagonist; these patients had few heart failure events (7 and 2 in the chlorthalidone and doxazosin groups, respectively).

Table 1 shows baseline characteristics of the chlorthalidone and doxazosin groups, stratified by no exposure to open-label medication and exposure to such drugs. In each stratum, the distribution of characteristics by treatment group was very similar, with a few exceptions. In the

Table 2. Event Rates and Relative Risks for All Heart Failure and Hospitalized or Fatal Heart Failure

Heart Failure and Medication Category	Events per 100 Persons at 4 Years*		Patients with Outcomes		Relative Risk (95% CI)	*P* Value
	Chlorthalidone Group	Doxazosin Group	Chlorthalidone Group	Doxazosin Group		
	←		*n*	→		
All heart failure						
As randomly assigned	4.46 ± 0.26	8.14 ± 0.43	420	491	2.04 (1.79–2.32)	<0.001
No exposure to open-label therapy	2.64 ± 0.31	6.63 ± 0.79	144	227	3.10 (2.51–3.82)	<0.001
Exposure to open-label therapy	6.93 ± 0.59	8.75 ± 0.72	276	264	1.42 (1.20–1.69)	<0.001
Exposure to antihypertensive heart failure open-label therapy	6.90 ± 0.69	9.81 ± 0.95	207	214	1.45 (1.20–1.76)	<0.001
No exposure to antihypertensive heart failure open-label therapy	6.10 ± 1.22	7.43 ± 1.62	69	50	1.25 (0.87–1.80)	>0.2
Hospitalized or fatal heart failure						
As randomly assigned	3.53 ± 0.23	5.77 ± 0.37	327	346	1.83 (1.58–2.13)	<0.001
No exposure to open-label therapy	2.03 ± 0.28	3.69 ± 0.57	109	139	2.52 (1.96–3.24)	<0.001
Exposure to open-label therapy	5.64 ± 0.54	6.77 ± 0.62	218	207	1.39 (1.15–1.68)	<0.001
Exposure to antihypertensive heart failure open-label therapy	5.86 ± 0.64	7.83 ± 0.87	172	172	1.38 (1.12–1.71)	<0.001
No exposure to antihypertensive heart failure open-label therapy	4.01 ± 0.90	4.61 ± 1.22	46	35	1.31 (0.85–2.04)	>0.2

* Data are presented as the mean ± SE.

Table 3. Relative Risk for Heart Failure, by Dose of Doxazosin Compared with Chlorthalidone, in Participants Not Exposed to Open-Label Therapy

Doxazosin Dosage vs. Chlorthalidone Dosage	All Heart Failure		Hospitalized or Fatal Heart Failure	
	Relative Risk (95% CI)	*P* Value	Relative Risk (95% CI)	*P* Value
2 mg/d vs. 12.5 mg/d	2.81 (2.24–3.53)	<0.001	2.27 (1.73–2.98)	<0.001
4 mg/d vs. 12.5 mg/d	3.51 (2.78–4.43)	<0.001	2.84 (2.15–3.76)	<0.001
8 mg/d vs. 12.5 mg/d	3.25 (2.28–4.64)	<0.001	2.81 (1.84–4.30)	<0.001
2 mg/d vs. 25 mg/d	2.43 (1.73–3.42)	<0.001	1.84 (1.22–2.77)	0.004
4 mg/d vs. 25 mg/d	3.04 (2.10–4.39)	<0.001	2.30 (1.48–3.58)	<0.001
8 mg/d vs. 25 mg/d	2.81 (2.24–3.53)	<0.001	2.27 (1.73–2.98)	0.043

monotherapy stratum, the doxazosin arm included more black patients than white patients compared with the chlorthalidone arm, whereas in the open-label therapy stratum, the chlorthalidone arm included more black patients than white patients. In addition, in the monotherapy stratum, the doxazosin arm included more Hispanic patients and more persons with atherosclerotic cardiovascular disease but fewer persons with ST-T wave abnormalities. About 30% of participants who had been taking antihypertensive therapy before study entry had a blood pressure less than 140/90 mm Hg. Overall, the mean blood pressures for persons receiving previous therapy (90.2%) and those not receiving previous therapy were 145/83 mm Hg and 156/89 mm Hg, respectively.

Table 2 shows results of Cox regression analyses comparing the treatment groups with respect to heart failure outcomes for all patients as randomly assigned, those with no exposure to open-label medication, and those with exposure to such medication. The 4-year event rates are higher among participants exposed to open-label medication than in those not exposed. For both outcomes, the risk with doxazosin treatment compared with chlorthalidone treatment is substantial, in patients without and with exposure to open-label drugs. The risk ratios in the monotherapy groups (3.1 for all cases of heart failure and 2.5 for hospitalized or fatal heart failure) are greater than those in the as-randomized groups. The risk ratios for participants with exposure to open-label medication are smaller (about 1.4) but still statistically significant ($P < 0.001$).

Cox regression with a time-dependent covariate representing exposure to open-label therapy (or antihypertensive heart failure open-label therapy) plus the interaction term of exposure and treatment assignment yielded nearly identical results. When race, Hispanic ethnicity, presence of atherosclerotic cardiovascular disease, and presence of ST-T wave abnormalities were added as covariates, the findings were essentially unchanged.

Table 3 shows the relative risk for all heart failure and hospitalized or fatal heart failure in the treatment groups, according to dose levels of doxazosin and chlorthalidone. This analysis is limited to duration of follow-up with no exposure to open-label therapy. The increased risk was apparent at all dose levels of doxazosin. At a fixed dose of chlorthalidone, an increase in relative risk was noted when the dose of doxazosin was increased from 2 mg to 4 mg but not when it was increased from 4 mg to 8 mg. For a fixed dose of doxazosin, relative risks were decreased when the dose of chlorthalidone was increased from 12.5 to 25 mg. However, all relative risks were substantial and consistent with the overall results.

The results of the two outcome comparisons for the entire cohort shown in Table 2 are not controlled for follow-up blood pressure. Throughout the trial, systolic blood pressure was 2 to 3 mm Hg higher in the doxazosin group than the chlorthalidone group, but diastolic blood pressure did not differ substantially between the groups (2). The proportions of missing blood pressure measurements were 7% at 1 month, 16% at 6 months, 16% at 1 year, 20% at 3 years, and 16% at 5 years.

Table 4 shows event rates and relative risks of the treatment groups for heart failure outcomes beyond 1 year, with stratification to control for blood pressure at 1 year. The stratum with the lower systolic or diastolic blood pressure had a higher relative risk and a smaller difference in mean systolic blood pressure for doxazosin versus chlorthalidone. In the combination groupings, the stratum with the best control (blood pressure < 140/90 mm Hg) had the greatest relative risk and only a small difference in mean systolic blood pressure. After adjustment for baseline and follow-up blood pressures, the results were essentially unchanged for all heart failure (relative risk, 2.04 [CI, 1.79 to 2.32] vs. 2.00 [CI, 1.76 to 2.28]; $P < 0.001$) and hospitalized or fatal heart failure (relative risk, 1.83 [CI, 1.58 to 2.13] vs. 1.80 [CI, 1.54 to 2.09]; $P < 0.001$).

DISCUSSION

We found that doxazosin is less effective than chlorthalidone in preventing major cardiovascular events, especially heart failure. Because this was an active control trial, we cannot determine whether chlorthalidone was beneficial, doxazosin was harmful, or both. Chlorthalidone has been shown to prevent and treat heart failure (9), whereas doxazosin has not been shown to do either. In the Systolic Hypertension in the Elderly Program, risk for heart failure was reduced by 50% with use of chlorthalidone compared with placebo (9).

In ALLHAT, not all participants continued to take

their assigned treatment, and reasons for stepping up to open-label medication might have differed between the randomized groups. These reasons may have had a differential effect on subsequent risk for heart failure. A major finding of the current study is that higher risk for heart failure with doxazosin compared with chlorthalidone was attenuated but not eliminated by the addition of other antihypertensive drugs.

The current analyses are subject to indication and diagnostic bias (10). Indication bias happens when the investigator gives additional medication on the basis of signs and symptoms, for example, to control blood pressure or reduce perceived side effects. Diagnostic bias can occur when the investigator or patient is influenced by knowledge about treatment. Participants in the doxazosin group were significantly more likely (relative risk, 1.31) than those in the chlorthalidone group to receive other drugs, and administration of other drugs tended to occur earlier in the doxazosin group. Since time to heart failure was shorter in the doxazosin group than the chlorthalidone group, a greater proportion (46%) of all heart failure events occurred before use of open-label therapy in the doxazosin group compared with the chlorthalidone group (34%), resulting in an exaggeration of the relative risk. Diagnostic bias should not have occurred because open-label therapy had not yet been given. Indication bias is possible because blood pressures and side effects may have influenced why certain participants were stepped up to additional medication but others were not.

On the basis of this reasoning, participants with exposure to open-label medication should have had an attenuated relative risk. This effect was seen for all cases of heart failure and hospitalized or fatal heart failure. In addition, the presence of other drugs could have further influenced the differences because of blood-pressure–related and unrelated effects. Diagnostic and indication bias could have played some role, since participants and investigators knew which open-label drugs were being taken and why. The postexposure results indicate that open-label therapy, including antihypertensive heart failure therapy, diminished but did not eliminate the relative risks of both outcomes in the two treatment groups. The incidence of these outcomes in each treatment group was higher after exposure to other drugs than before such exposure. Perhaps participants with hypertension that was harder to control were at greater risk for heart failure.

Analyses by dose that were restricted to participants taking monotherapy are subject to the same potential biases described above. For a fixed dose of chlorthalidone, the relative risk tended to increase with increasing doses of doxazosin, whereas for a fixed dose of doxazosin, the relative risk decreased with the increased dose of chlorthalidone. Increasing doses of doxazosin relative to increasing doses of chlorthalidone were associated with shorter duration of treatment with the medication. If doxazosin had no effect on prevention of heart failure, comparison of patients taking a fixed dose of chlorthalidone with patients taking increasing doses of doxazosin might include an increasing proportion of persons at greater risk for heart failure owing to harder-to-control blood pressure. This effect would tend to increase the relative risk.

Finally, the mean systolic blood pressure was 2 to 3 mm Hg lower in the chlorthalidone group than the doxazosin group throughout the trial. However, the relative risks changed little after adjustment for differences in blood pressure throughout the trial. On the basis of results from the Framingham Heart Study (11), this observed difference in systolic blood pressure would be associated with at most a 2% reduction in relative risk, a finding consistent with ours (relative risk, 2.00 after adjustment [reduced from 2.04]). In addition, stratification of participants by blood pressure at 1 year showed that lower blood pressures were associated with greater relative increases in risk. It appears that in ALLHAT, the degree of difference in blood pressure does not explain the increased risk for heart failure in the doxazosin group compared with the chlorthalidone group. Possible limitations of our analyses include measurement error in blood pressure and possible loss of bal-

Table 4. Event Rates and Relative Risk for Heart Failure after 1 Year of Therapy with Doxazosin or Chlorthalidone, and Differences in Blood Pressure 9 to 12 Months after Randomization

Blood Pressure	Rate of Heart Failure		Relative Risk with Use of Doxazosin vs. Chlorthalidone (95% CI)	Difference in Systolic/Diastolic Blood Pressure between Doxazosin Group and Chlorthalidone Group
	Chlorthalidone Group	Doxazosin Group		
mm Hg	←——— *events/100 person-years* ———→			*mm Hg*
Systolic				
≥140	1.48	1.93	1.30 (1.05–1.60)	1.6/0.0
<140	0.96	1.51	1.58 (1.18–2.13)	0.4/−1.2
Diastolic				
≥90	1.54	1.79	1.17 (0.88–1.53)	4.3/0.3
<90	1.09	1.76	1.61 (1.29–2.00)	2.4/−0.6
Systolic/diastolic				
≥140/≥90	1.53	1.79	1.17 (0.88–1.55)	2.3/0.0
≥140/<90	1.41	2.10	1.49 (1.08–2.05)	1.2/−0.3
<140/≥90	1.61	1.79	1.11 (0.25–3.98)	0.2/−0.1
<140/<90	0.92	1.50	1.63 (1.20–2.05)	0.5/−1.1

ance of known and unknown characteristics, since we used posttrandomization variables.

In patients at very low risk for heart failure, such as young persons with uncomplicated hypertension or those without other risk factors for cardiovascular disease, the findings of ALLHAT neither support nor refute a strategy of initial therapy with α-adrenergic blockers, allowing addition to or replacement of other antihypertensive drug classes if blood pressure is not well controlled. In older men with benign prostatic hypertrophy in whom an α-adrenergic blocker seems like the best treatment for the uropathy, coexisting hypertension should be treated with another antihypertensive drug as well. However, our analyses provide no guidance as to selection of a second drug class.

In summary, doxazosin recipients were more likely than chlorthalidone recipients to be given additional drugs. A disproportionately higher rate of heart failure occurred in the doxazosin group than the chlorthalidone group before exposure to additional medication. The data suggest a dose–response relationship for doxazosin compared with chlorthalidone. Stepping up to any drug, even a heart failure prevention drug, decreased but did not eliminate the relative risk for heart failure events. Differences in blood pressure during receipt of study treatment appeared to account for very little of the observed results. The principal finding remains that treatment with doxazosin compared with chlorthalidone carries an excess risk for heart failure in high-risk patients with hypertension, regardless of the dose used or addition of other drugs.

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Baseline Characteristics of Participants in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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Abstract—Diuretics and β-blockers have been shown to reduce the risk of cardiovascular morbidity and mortality in people with hypertension in long-term clinical trials. No study has compared newer more costly antihypertensive agents (calcium antagonists, ACE inhibitors, and α-adrenergic blockers) with diuretics for reducing the incidence of cardiovascular disease in an ethnically diverse group of middle-aged and elderly hypertensive patients. The study is a randomized, double-blind, active-controlled clinical trial designed to determine whether the incidence of the primary outcome, fatal coronary heart disease or nonfatal myocardial infarction, differs between treatment initiation with a diuretic versus each of 3 other antihypertensive drugs. Men and women aged ≥55 years with at least 1 other cardiovascular disease risk factor were randomly assigned to chlorthalidone (12.5 to 25 mg/d), amlodipine (2.5 to 10 mg/d), lisinopril (10 to 40 mg/d), or doxazosin (2 to 8 mg/d) for planned follow-up of 4 to 8 years. This report describes the baseline characteristics of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) participants. A total of 42 448 participants were randomized from 625 sites in the United States, Canada, Puerto Rico, and the US Virgin Islands. The mean age was 67 years, with 35% aged ≥70 years. Among those randomized, 36% were black, 19% were Hispanic, and 47% were women. The sample includes a high proportion of people with diabetes (36%), patients with existing cardiovascular disease (47%), and smokers (22%). There were no important differences between the randomized treatment groups at baseline. ALLHAT will add greatly to our understanding of the management of hypertension by providing an answer to the following question: are newer antihypertensive agents similar, superior, or inferior to traditional treatment with diuretics? (*Hypertension.* 2001;37:19-27.)

Key Words: hypertension, essential ■ antihypertensive agents ■ diuretics ■ clinical trials ■ lipids

Over 40 million people in the United States have elevated blood pressure (BP), ie, systolic BP (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥90 mm Hg, or they are taking antihypertensive medication.[1] Hypertension affects half of white American men and women aged 60 to 74 years and over two thirds of black men and women in this age group. Large-scale randomized clinical trials conducted in the 1970s and 1980s in largely middle-aged subjects with stage 1 and 2 hypertension (DBP 90 to 114 mm Hg) demonstrated that antihypertensive drug treatment reduced the rate of stroke by 40%. However, in contrast to the findings for stroke, the reduction for coronary heart disease (CHD) events was 10% to 15%, which was less than expected on the basis of epidemiological data.[2]

Subsequently, in the Systolic Hypertension in the Elderly Program (SHEP) trial, low-dose thiazide diuretic treatment was shown to reduce CHD death and nonfatal myocardial infarction (MI) by 27% (95% CI 6% to 43%).[3] Other trials in older persons with diastolic and systolic hypertension reported similar results.[4,5] One possible explanation for the failure of earlier trials to demonstrate the expected degree of CHD reduction is that adverse effects of study drugs, partic-

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ularly high-dose thiazide diuretics, may have offset the potential benefit of BP reduction. These adverse effects include diuretic-induced hypokalemia, hypomagnesemia, hyperuricemia, hyperlipidemia, hyperglycemia, impaired insulin sensitivity, and, possibly, increased ventricular ectopic activity.[5–8] However, these side effects are minimal at currently recommended doses (eg, 12.5 to 25 mg chlorthalidone), and a recent meta-analysis underlined the particular CHD benefit for regimens based on low-dose diuretics.[9]

In the late 1970s and the 1980s, newer and costlier antihypertensive agents, such as calcium antagonists, ACE inhibitors, and α-adrenergic blockers, were introduced for use as antihypertensive agents. However, evidence that might justify their use in preference to the older classes of drugs is limited and conflicting. Only a few studies have examined different antihypertensive agents in parallel group trials. The ACE inhibitor captopril has been compared with diuretics and/or β-blockers in 2 large trials, the Captopril Prevention Project (CAPPP)[10] and the UK Prospective Diabetes Study (UKDPS).[11] Neither study showed an overall advantage for captopril in the prevention of the primary cardiovascular end point. The results of some observational studies and clinical trials have raised questions about the efficacy of calcium antagonists, particularly the short-acting dihydropyridines, for preventing cardiovascular events in hypertensive patients with heart disease or diabetes[12–15]; however, other data suggest that the commonly prescribed calcium antagonists are safe and effective for preventing cardiovascular morbidity in these groups of patients.[16–19]

Four randomized trials have compared representatives of ≥3 drug classes. The 1-year trial conducted by the Department of Veterans' Affairs Cooperative Study Group on Antihypertensive Agents,[20] the 4-year HANE study,[21] and the 4.4-year Treatment of Mild Hypertension Study (TOMHS)[22] reported some differences in BP control, side effects, quality of life, biochemical effects, and target-organ changes. However, these differences did not present a pattern that consistently favored one class of drugs over others. These trials did not have cardiovascular end points as the primary outcome for comparisons of drug classes. The recently completed Swedish Trial in Old Patients with Hypertension (STOP-2)[23] compared ACE inhibitors, calcium antagonists, and diuretics and/or β-blockers in 6614 older patients with hypertension. In that study, BP reduction and fatal and nonfatal cardiovascular events were similar among the 3 groups. However, STOP-2 did not include blacks, persons with stage 1 hypertension, or anyone aged <70 years. Furthermore, the results of this trial need confirmation in a larger trial with a broader population of hypertensive persons.

Thus, more data are needed to permit an assessment of whether the newer classes of drugs are superior, equivalent, or inferior to diuretics for lowering the rates of hypertensive cardiovascular complications. In particular, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study was designed to determine whether the combined incidence of fatal CHD and nonfatal MI differs between diuretic treatment and 3 alternative antihypertensive pharmacological treatments. To generalize the results of ALLHAT to a broad population of people with hypertension, the study was designed to recruit high proportions of groups heavily burdened by hypertension-related morbidity: the elderly, women, African Americans, and people with type 2 diabetes. In addition to the antihypertensive trial, the trial also randomized a subset of participants to a lipid-lowering trial designed to compare total mortality in patients with mild to moderate hypercholesterolemia randomized to pravastatin versus usual care. The baseline characteristics of this group will be described in a separate report. The present report describes in detail the baseline characteristics of the participants in the antihypertensive component of ALLHAT.

Methods

The double-blind, randomized, active-controlled design of ALLHAT has been described in detail previously.[24] The participants in ALLHAT are high-risk hypertensive patients recruited at 625 clinical sites in the United States, Canada, Puerto Rico, and the US Virgin Islands. Recruitment took place between February 14, 1994, and January 31, 1998. The trial is scheduled to end in March 2002, after a mean follow-up of 6 years. However, in February 2000, the doxazosin arm of the trial was discontinued because of the 4-year cumulative congestive heart failure rate of doxazosin compared with chlorthalidone (8.1% versus 4.5%, respectively). Additionally, there was a 25% higher risk of combined cardiovascular disease outcomes in the doxazosin group (relative risk 1.25, 95% CI 1.17 to 1.33).[25]

BP eligibility criteria were based on the patient's current antihypertensive treatment status and on the average of 2 seated BP measurements at each of 2 visits. For untreated patients (or those treated for <2 months), the BP inclusion criteria at both visits were SBP of at least 140 mm Hg or DBP of at least 90 mm Hg. At both visits, SBP ≤180 mm Hg and DBP ≤110 mm Hg were required. For those who had been on treatment with 1 to 2 drugs for ≥2 months, the criteria at visit 1 were SBP ≤160 mm Hg and DBP ≤100 mm Hg, and the criteria at visit 2 were SBP ≤180 mm Hg and DBP ≤110 mm Hg. The higher readings at visit 2 allowed for partial withdrawal of antihypertensive medication. Patients who were taking therapeutic doses of >2 antihypertensive drugs were not eligible. In addition to meeting the BP eligibility criteria, patients had to be at least 55 years old and have at least 1 additional risk factor for cardiovascular morbidity. These additional inclusion criteria are listed in Table 1, along with the exclusion criteria for the trial. The initial design included recruitment goals of 45% women and 55% black participants.

After giving their informed consent, participants were randomly assigned to receive 1 of 4 double-blinded step 1 treatments given once daily: chlorthalidone (12.5 mg for the first and second titration and 25 mg for the third), amlodipine (2.5, 5, or 10 mg), lisinopril (10, 20, or 40 mg), or doxazosin (2, 4, or 8 mg). Each of the study medications is identical in appearance at all dosages. Randomization was blocked and stratified by clinical center. Allocation of participants into each arm was in the ratio of 1.7:1:1:1, with the largest number assigned to chlorthalidone to maximize statistical power for the comparison of the diuretic arm to each of the 3 nondiuretic arms.

The initial doxazosin dose was 1 mg for 1 week, followed by 2 mg for 1 month and monthly titrations thereafter to achieve a BP goal of SBP <140 and DBP <90 mm Hg. Chlorthalidone, amlodipine, and lisinopril were titrated similarly, beginning with the lowest dose, except that there was no dosage change after 1 week. Additionally, open-label medications were provided to treat participants who did not attain satisfactory BP control on the maximum tolerated dose of blinded step 1 medication. Three open-label medications were available in step 2, and 1 was available in step 3. The step 2 medications provided include reserpine (0.05 to 0.2 mg daily), clonidine (0.1 to 0.3 mg twice daily), and atenolol (25 to 100 mg once daily). The step 3 medication is hydralazine (25 to 100 mg twice daily). All participants were given standard advice on lifestyle factors (sodium, alcohol, physical activity, and caloric intake), with reinforcement as needed during the study.

TABLE 1. Additional Inclusion and Exclusion Criteria

- Additional inclusion criteria (any 1 of those listed)
  - Old (>6 mo) or age-indeterminate MI or stroke documented by
    - Hospital diagnosis
    - Q waves on ECG
    - Akinesis or dyskinesis on echocardiogram or ventriculogram
    - Brain infarct on CT or MRI
  - History of revascularization procedure including
    - Angioplasty (coronary or peripheral vascular)
    - Bypass surgery (coronary, peripheral vascular, carotid, vertebrobasilar)
    - Aortic aneurysm repair
    - Other revascularization (atherectomy, stent placement)
  - Other documented atherosclerotic cardiovascular disease, including
    - History of angina pectoris
    - History of intermittent claudication, gangrene, or ischemic ulcers
    - History of transient ischemic attack
    - Coronary, peripheral vascular, or carotid stenosis of ≥50% documented by angiography or Doppler studies
    - Ischemic heart disease documented by
      - Stress thallium (reversible or fixed ischemia)
      - Dipyridamole thallium (reversible or fixed ischemia)
      - Exercise testing (ST depression ≥1 mm for ≥1 min)
      - Stress echocardiogram (reversible wall motion abnormality)
      - Holter monitoring (ST depression ≥1 mm for ≥1 min)
    - Ankle-arm index <0.9
    - Abdominal aortic aneurysm detected by ultrasonography, CT, or x-ray
    - Carotid or femoral bruits
  - Major ST depression or T-wave inversion on ECG within past 2 y
    - J-point depression at 0.5 mm and following ST segment flat or downsloping in any of leads I, II, aVL, or V_1–V_6
    - T-wave inverted at least 1 mm in any of leads I, II, aVL, aVF, or V_2–V_6
  - Type 2 diabetes mellitus
    - Fasting plasma glucose ≥7.8 mmol/L within past 2 y
    - Nonfasting plasma glucose ≥11.1 mmol/L within past 2 y
    - Taking insulin or oral hypoglycemic agent
  - Current cigarette smoking
  - HDL cholesterol <0.90 mmol/L on 2 occasions within past 5 y
  - Left ventricular hypertrophy on ECG or echocardiogram within past 2 y
    - R amplitude in V_5 or V_6 >26 mm
    - R amplitude in V_5 or V_6 plus S amplitude in V_1 >35 mm
    - R amplitude in aVL >12 mm
    - R amplitude in lead I >15 mm
    - R amplitude in leads II or III or a VF >20 mm; R amplitude in lead I plus S amplitude in lead III >25 mm
    - R amplitude in aVL plus S amplitude in V_3 >28 mm for men or >22 mm for women
    - Computerized ECG machine documented left ventricular hypertrophy
    - Combined wall thickness of ≥25 mm on echocardiogram
- Exclusion criteria
  - Symptomatic MI or stroke within past 6 mo
  - Symptomatic congestive heart failure
  - Left ventricular ejection fraction <35%, if known
  - Symptomatic angina pectoris within the past 6 mo
  - Known renal insufficiency (serum creatinine ≥180 μmol/L)
  - Requirement for thiazide-like diuretics, ACE inhibitors, calcium antagonists, or α-adrenergic blockers for reasons other than high BP
  - Sensitivity or contraindication to any of step 1 medications
  - Requirement for >2 antihypertensive drugs to achieve satisfactory BP ≤160/100 mm Hg or BP >180/110 mm Hg
  - Low likelihood of compliance with protocol (eg, dementia, substance abuse)
  - Diseases likely to lead to noncardiovascular death during course of study
  - Current participation in another clinical trial

TABLE 2. Frequency Distribution of ALLHAT Participants by Race, Ethnicity, Gender, Age at Trial Entry, History of Diabetes at Trial Entry, and Preexisting ASCVD

			Gender		Age					
Race	Total	Hispanic	Male*	Female*	55–59 y	60–69 y	70–79 y	80+ y	Diabetes	ASCVD
White, n	25 292 (59.6)	5314	14 698	10 592	4321	11 445	7 790	1736	8 476	13 278
Black, n	15 094 (35.6)	1406	6 852	8 241	3298	7 008	3 817	971	6 023	5 790
Asian/Pacific Islander, n	481 (1.1)	11	275	206	97	242	130	12	173	243
American Indian/ Alaskan native, n	78 (0.2)	5	57	21	21	37	20	0	32	39
Other, n	1 503 (3.5)	1364	698	805	352	723	376	52	593	555
Total, n	42 448	8100	22 580	19 865	8089	19 455	12 133	2771	15 297	19 905
Total, %	100.0	19.1	53.2	46.8	19.1	45.8	28.6	6.5	36.0	46.9

Values in parentheses are percentages.

*Cell may not sum to total because of missing gender data on 2 white participants and 1 black participant.

At baseline, participants had blood drawn for the measurement of serum potassium, fasting glucose, creatinine, total cholesterol, HDL cholesterol, triglycerides, and alanine aminotransferase. LDL cholesterol was estimated by the Friedewald formula. When possible, participants who had consumed food or beverages within the past 8 hours were asked to return later for a fasting blood draw. An ECG was performed if there was no existing ECG within the past year. All ECGs were then centrally read with the use of Minnesota Code criteria. At baseline, the clinical center study coordinator was instructed to complete a questionnaire listing the inclusion criteria (Table 1), checking all conditions that were known and documented to apply to the participant. In addition, the questionnaire included items about race, ethnicity, gender, years of education, current estrogen use, current regular aspirin use, cigarette smoking (past or current), and the presence of CHD. The presence of CHD was defined as a history of MI (including silent MI), primary cardiac arrest, coronary revascularization, angina, angiographically defined coronary stenosis >50%, or reversible coronary perfusion defect on noninvasive cardiac testing. Height and weight were measured at baseline.

For the baseline data in the present study, a participant was considered to have diabetes if type 2 diabetes mellitus was checked on the list of inclusion criteria (Table 1). The criteria for the diagnosis of diabetes were the criteria of the American Diabetes Association at the inception of the study, and these were not changed when the American Diabetes Association lowered the fasting glucose criterion in 1997.[26] A participant was considered to have atherosclerotic cardiovascular disease (ASCVD) according to the following definition: if CHD as defined above was listed as present on the baseline questionnaire, or if the inclusion criteria checklist noted the presence of old or age-indeterminate MI or stroke, history of revascularization procedure, or other ASCVD (see Table 1 for definitions).

Follow-up procedures, study end points, and ascertainment of events have been described previously.[24,25] The primary study end point is the combined incidence of fatal CHD and nonfatal MI. The study sample size was calculated to have 80% power to detect a 16% difference in the primary end point between the diuretic and each of the other 3 drug groups, after accounting for treatment crossovers, losses to follow-up, and multiple comparisons.

Results

Table 2 provides the frequency distribution of ALLHAT randomized participants by race, ethnicity, gender, age at entry, history of diabetes, and preexisting ASCVD. Of the 42 448 participants randomized in ALLHAT, 25 292 (59.6%) were white, and 15 094 (35.6%) were black. Asians and American Indians made up 1.1% and 0.2%, respectively. Participants classifying themselves as "other" were the third largest group, with 1503 (or 3.5%) of the total randomized, most of whom also described themselves as being of Hispanic origin. There were 8100 (19.1%) Hispanic participants; of these, 65.6% designated themselves as "white Hispanic"; 17.4%, as "black Hispanic"; 0.2%, as either "Asian Hispanic" or "American Indian Hispanic"; and 16.8%, as "other Hispanic." Men constituted 53.2% of the ALLHAT participants. The largest age category for participants was aged 60 to 69 years (45.8%). The second largest age subgroup was aged 70 to 79 years (28.6%), and there were 19.1% aged 55 to 59 years and 6.5% aged ≥80 years. At baseline, a large proportion of ALLHAT participants had diabetes mellitus (36.0%) and/or evidence of ASCVD (46.9%).

Table 3 shows baseline characteristics by randomized treatment group. By design, the chlorthalidone group was the largest, with 15 268 participants (36.0%), and each of the 3 other drug groups had just over 9000 participants (21.3%). In this table, and all subsequent tables, the non-Hispanic white category excludes the 5314 (12.5%) participants who described themselves as "white Hispanics." The participants have been combined with the "other" category. The black category includes both Hispanic and non-Hispanic blacks. The characteristics of Hispanic ALLHAT participants will be described in more detail in a separate publication. Three significant, but small, differences ($P<0.05$) in the randomized treatment groups were noted. There was a small difference in serum potassium between the lisinopril and chlorthalidone groups, which is likely due to the drawing of fasting blood after randomization in some participants. Compared with the chlorthalidone group, the participants randomized to amlodipine were slightly less likely to have a history of CHD and had a slightly lower creatinine level.

Baseline characteristics by gender and race are provided in Table 4. The mean age of the participants was 67 years, and both male and female white participants were older than the black participants. This difference resulted primarily from a larger proportion of blacks compared with whites in the 55 to 59 age category (29.1% versus 15.8%, respectively) and a larger proportion of whites compared with blacks in the 70 to 79 age category (32.0% versus 25.9%, respectively). A

TABLE 3. Baseline Characteristics by Antihypertensive Treatment Group

	Antihypertensive Agent				
Baseline Characteristics	Chlorthalidone	Amlodipine	Lisinopril	Doxazosin	All
Sample size	15 268	9053	9060	9067	42 448
Female, %	47.0	47.3	46.3	46.4	46.8
Race, %					
White, non-Hispanic	47.2	47.6	47.0	46.4	47.1
Black	35.2	35.5	35.5	36.3	35.6
Other*	17.6	16.9	17.5	17.2	17.4
On BP treatment, %	90.2	90.3	90.2	90.2	90.2
Smoking status, %					
Current	21.9	21.9	21.9	21.7	21.8
Past	40.5	40.0	40.3	40.1	40.3
History of diabetes, %	36.3	36.8	35.5	35.5	36.0
History of CHD, %	26.0	24.5‡	25.2	26.2	25.7
Aspirin use, %	36.0	36.5	36.4	36.5	36.3
LVH on ECG,† %	5.2	5.2	5.4	5.0	5.2
Age, y	66.9±7.7	66.9±7.7	66.9±7.7	66.8±7.7	66.9±7.7
Education,† y	11.0±4.0	11.0±3.9	11.0±4.1	11.0±4.0	11.0±4.0
Visit 1 BP					
SBP, mm Hg	144.8±13.8	144.8±14.0	145.0±14.1	144.8±13.9	144.8±14.0
DBP, mm Hg	83.3±9.9	83.2±10.0	83.4±9.9	83.5±9.7	83.4±9.9
Pulse, bpm	73.7±10.7	73.6±10.7	73.5±10.8	73.5±10.7	73.6±10.7
BMI, kg/m^2	29.7±6.1	29.8±6.1	29.8±6.1	29.7±5.9	29.8±6.1
Potassium,† mmol/L	4.34±0.69	4.35±0.70	4.37±0.72‡	4.36±0.70	4.35±0.70
Fasting glucose,† mmol/L	6.85±3.24	6.83±3.16	6.82±3.11	6.80±3.12	6.83±3.17
Creatinine, μmol/L	77.83±23.65	77.06±22.13§	77.83±22.89	77.83±21.36	77.83±22.89
Total cholesterol, mmol/L	5.60±1.13	5.61±1.14	5.58±1.10	5.57±1.10	5.59±1.12
cLDL cholesterol,† mmol/L	3.52±0.97	3.51±0.97	3.52±0.95	3.51±0.94	3.52±0.96
HDL cholesterol,† mmol/L	1.21±0.38	1.22±0.38	1.21±0.38	1.21±0.37	1.21±0.38
Fasting triglycerides, mmol/L	1.95±1.48	1.95±1.53	1.95±1.58	1.92±1.53	1.95±1.52

Values are mean±SD, unless indicated otherwise. LVH indicates left ventricular hypertrophy; BMI, body mass index; and cLDL, calculated LDL.

*Other races include 5314 nonblack Hispanics, 78 American Indians/Alaskan natives, and 481 Asians/Pacific Islanders. Black Hispanics were included in black category.

†ECGs were available for only 38 955 participants; education was provided by 39 538 participants; serum potassium, creatinine, and cholesterol levels were available for 40 126 participants; fasting glucose was available for 31 255 participants; cLDL cholesterol was available for 37 498 participants; HDL cholesterol was measured in 40 099 participants; triglycerides were measured in 31 304 participants.

‡$P<0.01$; §$P<0.05$ (for each characteristic, 2-proportion or 2-sample mean difference tests were performed comparing each of the 3 nondiuretic groups with chlorthalidone, respectively).

smaller proportion of female participants compared with male participants was white (38.5% versus 54.6%, respectively), and a larger proportion was black (41.5% versus 30.4%, respectively).

Most of the participants (90.2%) were receiving antihypertensive treatment at baseline. Compared with other groups, blacks who had received antihypertensive treatment for ≥2 months had slightly higher baseline DBP and also had a lower BP control rate (SBP <140 and DBP <90 mm Hg) at baseline compared with whites (26.9% versus 29.8%, respectively). The best BP control was observed in white males (30.9%). BP control levels were 28.1% in white females, 27.6% in black males, and 26.3% in black females. Black males were more likely to be current smokers, and blacks, in general, were more likely to have a history of diabetes, had a higher resting pulse, and had a higher glucose level. Black women had higher body mass index, and blacks, overall, compared with whites were much more likely to have central laboratory readings of left ventricular hypertrophy on ECG (8.6% versus 3.3%, respectively). Whites were more likely than blacks to use aspirin (48% versus 25%, respectively) and estrogen (28.4% versus 11.4%, respectively, among women). Furthermore, whites were almost twice as likely as blacks to have a history of CHD (33% versus 17%, respectively). Baseline lipoprotein levels differed by race and gender subgroup. Blacks had higher total cholesterol, LDL choles-

TABLE 4. Baseline Characteristics of ALLHAT Participants Stratified by Gender and Race

	All			Male			Female		
Characteristic	All	White (NH)	Black	All	White (NH)*	Black*	All	White (NH)*	Black*
Sample size, n (%)	42 448±100.0	19 978±47.1	15 094±35.6	22 580±53.2	12 337±54.6	6,852 ±30.3	19 865±46.8	7,639±38.5	8,241±41.5
Age, y	66.9±7.7	67.5±7.5	66.3±7.8	66.7±7.3	67.1±7.0	66.1±7.4	67.1±8.2	68.0±8.1	66.4±8.2
55–59, %	19.1	15.8	21.8	18.0	15.3	20.8	20.3	16.7	22.8
60–69, %	45.8	45.9	46.4	47.9	48.3	48.3	43.5	42.2	44.9
70–79, %	28.6	31.9	25.3	29.2	32.0	25.9	27.9	31.7	24.8
≥80, %	6.5	6.3	6.4	4.9	4.4	5.1	8.4	9.5	7.6
Education, y	11.0±4.0	12.3±3.2	10.1±3.8	11.5±4.0	12.6±3.4	10.1±4.0	10.4±3.9	11.9±2.8	10.1±3.6
Entry treatment status									
On medications ≥2 mo, %	86.8	87.2	86.9	86.0	86.9	85.4	87.8	87.6	88.1
SBP, mm Hg	143±13	143±13	143±13	142±13	142±13	142±13	143±13	143±13	143±13
DBP, mm Hg	82±10	81±9	83±10	82±9	81±9	84±9	82±10	80±10	83±10
On medications <2 mo, %	3.4	2.8	4.0	3.5	2.8	4.4	32.	2.7	3.7
SBP, mm Hg	158±13	158±13	160±13	158±13	159±13	160±13	158±14	158±13	160±13
DBP, mm Hg	89±10	88±9	91±10	90±10	88±9	93±10	89±10	87±10	90±10
Untreated, %	9.8	10.0	9.1	10.4	10.2	10.2	9.1	9.7	8.2
SBP, mm Hg	159±12	158±11	159±13	158±12	158±11	158±13	160±12	159±12	160±13
DBP, mm Hg	91±9	89±9	92±9	91±9	89±9	93±9	90±9	89±9	92±9
SBP/DBP <140/90, %	27.4	29.8	26.9	28.6	30.9	27.6	26.1	28.1	26.3
Cigarette smoker, %	21.8	21.0	25.1	24.0	20.8	31.7	19.3	21.5	19.7
Exsmoker, %	40.3	47.4	34.5	52.5	58.0	44.7	26.4	30.2	26.0
Never smoked, %	37.9	31.6	40.4	23.5	21.3	23.6	54.3	48.3	54.3
History of diabetes, %	36.0	31.5	39.9	34.0	31.2	36.1	38.4	32.1	43.1
History of CHD, %	25.6	33.1	17.4	31.1	38.7	20.7	19.3	24.3	14.7
Treatment with aspirin, %	36.3	48.0	25.3	43.5	54.1	30.2	28.2	38.2	21.3
Treatment with estrogen, %	...	...	...	...	...	...	18.0	28.4	11.4
ECG LVH, %	5.2	3.3	8.6	5.0	3.1	9.0	5.4	3.6	8.2
Pulse, bpm	73.6±10.7	72.9±11.0	74.7±10.5	72.5±11.1	71.8±11.2	73.8±10.9	74.8±10.1	74.5±10.4	75.4±10.1
Weight, kg	83.1±18.1	85.2±18.1	84.5±18.2	87.8±16.7	90.2±16.4	87.6±17.3	77.7±18.0	77.2±17.9	81.8±18.6
BMI, kg/m^2	29.8±6.1	29.6±5.8	30.5±6.7	29.1±5.2	29.3±5.0	28.9±5.4	30.4±6.9	30.0±6.8	31.6±7.1
Serum analytes									
Potassium, mmol/L	4.4±0.7	4.4±0.6	4.3±0.8	4.4±0.7	4.4±0.6	4.3±0.7	4.3±0.7	4.3±0.6	4.2±0.8
Fasting glucose, mmol/L	6.83±3.17	6.58±2.77	7.04±3.53	6.82±3.11	6.60±2.72	6.78±3.31	6.95±3.36	6.56±2.85	7.29±3.71
Creatinine, μmol/L	77.83±22.89	77.06±19.84	82.40±25.94	82.40±22.89	83.17±19.08	91.56±26.71	69.43±19.84	67.91±17.55	73.25±21.36
Total cholesterol, mmol/L	5.59±1.12	5.58±1.10	5.63±1.16	5.40±1.05	5.35±1.01	5.37±1.08	5.86±1.15	5.94±1.14	5.85±1.18
cLDL cholesterol, mmol/L	3.52±0.96	3.48±0.91	3.60±1.03	3.41±0.90	3.38±0.87	3.45±0.96	3.65±1.00	3.64±0.96	3.71±1.07
HDL cholesterol, mmol/L	1.21±0.38	1.13±0.35	1.35±0.41	1.12±0.33	1.03±0.29	1.23±0.37	1.34±0.39	1.29±0.39	1.43±0.41
Fasting triglycerides, mmol/L	1.95±1.52	2.20±1.70	1.46±1.02	1.98±1.53	2.16±1.66	1.49±1.07	1.94±1.52	2.28±1.76	1.50±1.03

Values are mean±SD, unless indicated otherwise. NH indicates non-Hispanic. Black Hispanics were included in black category.
*Cell may not sum to total because of missing gender data on 2 white participants and 1 black participant.

TABLE 5. Entrance Criteria by Gender and Race

	All			Male			Female		
Characteristic	All	White (NH)	Black	All*	White (NH)*	Black*	All*	White (NH)*	Black*
Sample size, n	42 448	19 978	15 094	22 580	12 337	6 852	19 865	7 639	8 241
History of MI/stroke, %	23.1	27.8	19.6	27.8	31.7	23.9	17.9	21.5	16.2
Revascularization procedure, %	12.9	20.8	5.4	17.8	25.9	7.2	7.4	12.6	4.0
Other ASCVD, %	24.0	27.5	19.7	23.2	26.7	18.3	24.9	28.7	21.0
Ischemic ST-T wave changes, %	10.4	9.2	13.1	9.8	8.7	12.9	11.1	10.1	13.2
Type 2 diabetes mellitus, %	36.0	31.5	39.9	34.0	31.2	36.1	38.4	32.1	43.1
Current smoking, %	19.9	19.1	22.3	21.4	18.3	27.5	18.2	20.2	18.0
HDL cholesterol <35 mg/dL, %	11.7	16.4	6.6	15.2	20.1	8.5	7.7	10.5	4.9
LVH by echocardiogram, %	4.1	4.1	4.1	3.8	3.5	3.7	4.5	5.2	4.4
LVH on ECG, %	16.5	9.8	24.2	16.8	9.8	27.6	16.2	9.8	21.3

Black Hispanics were included in black category.
*Cell may not sum to total because of missing gender data on 2 white participants and 1 black participant.

terol, HDL cholesterol, and markedly lower triglyceride levels than did whites. Women had higher total cholesterol, LDL cholesterol, and HDL cholesterol, whereas men had higher triglycerides.

Table 5 lists the proportion of participants with each of the risk factor criteria that qualified participants for entry in the trial. Compared with black participants, white participants were more likely to be entered into the study on the basis of history of MI and/or stroke, revascularization procedures, or other ASCVD. Blacks more often qualified for the study for ischemic ECG changes, diabetes, smoking, and left ventricular hypertrophy on ECG. Men were more likely to be entered into the study because of previous MI, stroke, or revascularization, whereas women were more likely to be entered on the basis of a history of diabetes. Low HDL cholesterol, defined as <35 mg/dL, was a frequent inclusion criterion for white men (20.2%) but much less so in blacks and white women.

Baseline characteristics for high-risk subgroups are given in Table 6. People with diabetes mellitus made up 15 294 (36.0%) of the ALLHAT participants. As expected, diabetic participants were more overweight compared with other groups, with a mean body mass index of 31.1 kg/m^2. Diabetics also had higher fasting glucose (9.51 mmol/L), higher triglycerides (191.1 mg/dL), and lower HDL cholesterol (44.9 mg/dL) compared with other subgroups. There was a lower proportion of diabetes among participants with baseline cardiovascular disease and vice versa. In some cases, after eligibility was established, the documentation of additional entry criteria may have been incomplete. The group aged >70 years had somewhat higher baseline systolic and lower diastolic pressures compared with the other high-risk groups, and this group was more likely to have left ventricular hypertrophy. In both the >70-year-old and diabetic groups, women made up half of the group. Approximately 60% of the ASCVD and currently smoking subgroups were men.

Discussion

ALLHAT is the largest randomized double-blind trial ever conducted in patients with hypertension. Over a period of 4 years, 625 centers in the United States, Canada, Puerto Rico, and the US Virgin Islands enrolled 42 448 high-risk patients. High risk was determined on the basis of the presence of hypertension, age ≥55 years, and at least 1 additional cardiovascular risk factor.

Patients in ALLHAT were randomly assigned to 1 of 4 treatment groups: chlorthalidone, amlodipine, lisinopril, or doxazosin. The treatment groups were balanced at baseline, with no clinically important differences in any of the recorded variables. The study by design included a high percentage of African Americans (35.6%) and nearly equal proportions by gender (46.8% women). It also included a large cohort of Hispanic participants (19.1%). At entry, 35.1% of the patients were aged >70 years, 36% had diabetes, 46.9% had a history of ASCVD (over half of whom had CHD), and 22% were current smokers. Because of the large number of patients enrolled in ALLHAT, it will be possible to examine the effect of the ALLHAT treatments in these subgroups.

Blacks and Hispanics have been underrepresented in most previous trials. In hypertension trials that measured cardiovascular events, blacks have represented a significant subgroup only in trials with diuretic-based active therapy arms. Blacks are known to have more frequent and more severe hypertension that develops at an earlier age.[1] This finding is reflected in the ALLHAT group at baseline: the black participants are younger and have higher DBP. Blacks also suffer more cardiovascular complications and have higher risk for end-stage renal disease.[6,27] At baseline in the present study, compared with whites, blacks were less likely to be enrolled on the basis of a history of previous MI or stroke, revascularization procedures, or ASCVD, and blacks were more likely to be enrolled on the basis of diabetes, smoking, or left ventricular hypertrophy on ECG. ALLHAT will provide an excellent opportunity to study and evaluate the effect the type of therapy and BP control on cardiovascular events in blacks.

ALLHAT also may be able to address some questions raised from other trials. In CAPPP, patients with hypertension were randomized in an open-label fashion to either conventional therapy (diuretics or β-blockers) or captopril.[10] Al-

TABLE 6. Characteristics of Cardiovascular Risk Factor Subgroups

	Risk Factor Subgroups				
Baseline Characteristics	Diabetes	ASCVD	Smokers	≥70 y	All
Sample size, n (%)	15 297±36.0	19 905±46.9	9272±21.8	14 904±35.1	42 448
Female, %	49.9	42.4	41.5	49.1	46.8
Race, %					
White, non-Hispanic	41.2	55.5	45.3	51.3	47.1
Black	39.4	29.1	40.9	32.1	35.6
Other*	19.4	15.4	13.8	16.6	17.4
History of diabetes, %	100.0	24.5	20.0	34.1	36.0
History of CHD, %	18.8	54.4	17.4	30.1	25.6
ASCVD, %	31.9±0.4	100.0	33.4±0.5	56.7±0.4	6.9±0.2
Current smoking, %	12.1	15.6	100.0	13.2	21.8
LVH on ECG,† %	8.9	11.4	13.0	17.9	16.5
Age, y	66.5±7.4	68.2±7.8	64.1±6.8	75.5±4.7	66.9±7.7
Visit 1 BP					
SBP, mm Hg	144.7±13.5	144.4±14.0	145.2±14.6	145.9±13.7	144.8±14.0
DBP, mm Hg	82.1±9.9	82.5±10.0	84.7±10.0	80.9±10.0	83.4±9.9
BMI, kg/m^2	31.1±6.2	29.2±5.8	28.3±5.9	28.3±5.4	29.8±6.1
Potassium,† mmol/L	4.4±0.7	4.4±0.7	4.4±0.7	4.4±0.7	4.4±0.7
Fasting glucose,† mmol/L	9.39±3.87	6.33±2.73	6.12±2.68	6.53±2.81	6.83±3.17
Creatinine, μmol/L	76.3±24.42	80.12±22.13	77.83±22.89	81.64±23.65	77.83±22.89
Total cholesterol, mmol/L	5.57±1.18	5.59±1.12	5.56±1.12	5.53±1.09	5.59±1.12
cLDL cholesterol,† mmol/L	3.47±0.98	3.52±0.95	3.49±0.96	3.48±0.94	3.52±0.96
HDL cholesterol,† mmol/L	1.16±0.35	1.2±0.37	1.23±0.40	1.24±0.39	1.21±0.38
Fasting triglycerides, mmol/L	2.16±1.85	1.94±1.44	1.90±1.58	1.79±1.22	1.95±1.52

Values are mean±SD, unless indicated otherwise.

*Other races include 5314 nonblack Hispanics, 78 American Indians/Alaskan natives, and 481 Asians/Pacific Islanders. Black Hispanics were included in black category.

†ECGs were available for only 38 955 participants; serum potassium, creatinine, and cholesterol levels were available for 40 126 participants; fasting glucose was available for 31 255 participants; cLDL cholesterol was available for 37 498 participants; HDL cholesterol was measured in 40 099 participants; and triglycerides were measured in 31 304 participants.

though there was no difference in cardiovascular mortality or fatal and nonfatal MI between the 2 groups, fatal and nonfatal strokes were more frequent in the group treated with captopril. This finding was partially attributed to the fact that the captopril group had higher baseline SBP and baseline DBP, which remained slightly higher than values in the conventional therapy group throughout the study. No such baseline BP differences exist in ALLHAT.

The recently completed Heart Outcomes Prevention Evaluation (HOPE) study compared the effect of the ACE inhibitor ramipril with placebo in older high-risk patients with preserved left ventricular function.[28] That study demonstrated that compared with placebo, ramipril significantly reduced the rates of death, MI, stroke, revascularization procedures, heart failure, and other cardiovascular complications. Less than half the patients in HOPE had hypertension. In hypertensive participants, study medication was added to their existing hypertensive therapy, resulting in lower SBP and DBP in ramipril-treated patients. Although this small amount of BP lowering (2 to 3 mm Hg) would be expected to account for well under half of the benefit of ramipril, the HOPE study design leaves many questions unanswered. Thus, ALLHAT still remains uniquely positioned to provide an answer to the primary question: are newer antihypertensive agents superior, similar, or inferior to traditional therapy with diuretics?

ALLHAT is an ongoing study examining the highest priority hypertension treatment question at the turn of the century. The results of ALLHAT will significantly add to our understanding of the management of hypertension and will also contribute to the formulation of future management guidelines.

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

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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 (eg, 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.

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An estimated 50 million people in the US have elevated blood pressure (systolic blood pressure [SBP] ≥ 140 mm Hg or diastolic blood pressure [DBP] ≥ 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 α-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 amlodipine.

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

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relevant to patients with type II diabetes mellitus.[20,21] Furthermore, Chobanian and colleagues have reported prevention of coronary lesions in the Watanabe rabbit model with captopril treatment,[22] 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.[13,23] Improvements in insulin resistance also have been reported with α-blockers.[24] There is some evidence that these agents may reduce platelet aggregability and stimulate tissue plasminogen activator.[25–27]

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),[28] and is less compelling for women and minorities than for men.[29] Despite the reductions in CHD in metaanalyses of these trials, reductions in CHD mortality have been offset by increases in other causes of death.[30–40] While the net change in total mortality tended to be favorable in high risk populations,[34,40] such as men with prior myocardial infarction,[30,32] it was not favorable in most primary prevention trials.[31] However, the cholesterol-lowering trials published to date, with one exception,[41] 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.[30,35–40] 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.[42]

The one exception noted above is the Scandinavian Simvastatin Survival Study (4S).[41] 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 (chlorthalidone) 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."

Hypotheses 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 (chlorthalidone) 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).[43] 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[44]) 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.

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 1. ANTICIPATED SAMPLE SIZE OF ALLHAT TREATMENT GROUPS

Cholesterol-Lowering Trial (2 Arms)	Antihypertensive Trial (4 Arms)				Total
	Chlorthalidone	Amlodipine	Lisinopril	Doxazosin	
Pravastatin	3,655	2,115	2,115	2,115	10,000
Usual Care	3,655	2,115	2,115	2,115	10,000
Not Eligible	7,310	4,230	4,230	4,230	20,000
Total	14,620	8,460	8,460	8,460	40,000

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] hypothesis[38]), 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.

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, $\leq$ 160 mm Hg systolic and $\leq$ 100 mm Hg diastolic at visit 1, and $\leq$ 180 mm Hg systolic and $\leq$ 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 cholesterol[44]) and serum alanine transaminase (ALT, formerly SGPT) will be ob-

TABLE 3. ALLHAT PATIENT VISIT SCHEDULE

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

** Total cholesterol, triglyceride, HDL, and LDL cholesterol levels. LDL calculated by the Friedewald formula.[45]*

† Postrandomization visits.

ALT, Alanine aminotransferase; NCEP, National Cholesterol Education Program[44]; TC, Total cholesterol.

tained 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 I 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 10% cohort. In the usual care group, cholesterol levels will 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

Status at Visit 1 and Visit 2	Lower Limit* (mm Hg)		Upper Limit† (mm Hg)	
	SBP	DBP	SBP	DBP
Taking 1–2 drugs for hypertension for at least 2 months	—	—	160‡ 180§	100‡ 110§
Taking drugs for < 2 months or currently untreated	140	90	180	110

* *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 Program[43] 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, in-hospital 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[46] 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.[47]

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*

	Initial Dose†	Dose 1†	Dose 2†	Dose 3†
Step 1 Agent				
Chlorthalidone	12.5	12.5	12.5	25
Amlodipine	2.5	2.5	5	10
Lisinopril	10	10	20	40
Doxazosin	1	2	4	8
Step 2 and Step 3 Agents				
Reserpine		0.05 daily or 0.1 every 2 days	0.1 daily	0.2 daily
Clonidine (oral)		0.1 twice daily	0.2 twice daily	0.3 twice daily
Atenolol		25 daily	50 daily	100 daily
Hydralazine (third-line)		25 twice daily	50 twice daily	100 twice daily

** Sources of the four first-line agents are: chlorthalidone: Ogden Bioservices, Inc., Rockville, Maryland; amlodipine: Pfizer, Inc., New York, New York; lisinopril: Zeneca Pharmaceuticals Group, Wilmington, Delaware; and doxazosin: Pfizer, Inc., New York, New York.*

† All doses in milligrams.

overall and within 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.[48,49]

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 investigators[50] and first used by NHLBI in the Digitalis Investigative Group trial,[51] 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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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 chlorthalidone 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.[43]

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) II[52] data for ages 65 to 74 years, in which the LDL cholesterol cutpoints 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 drop-outs 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 2.35% / 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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Having described the invention, what is claimed is:

(1) A method of reducing cardiovascular disease in an individual at risk comprising

administering to the individual on a daily basis an effective amount of a diuretic, wherein the therapeutic effect of the diuretic to reduce cardiovascular disease in such an individual is greater than such therapeutic effect in such an individual treated with only a beta-adrenergic blocker.

(2) A method of reducing cardiovascular disease in an individual at risk comprising

administering to the individual on a daily basis an effective amount of a diuretic, wherein the therapeutic effect of the diuretic to reduce cardiovascular disease in such an individual is greater than such therapeutic effect in such an individual treated with only a calcium-channel blocker.

(3) A method of reducing cardiovascular disease in an individual at risk comprising

administering to the individual on a daily basis an effective amount of a diuretic, wherein the therapeutic effect of the diuretic to reduce cardiovascular disease in such an individual is greater than such therapeutic effect in such an individual treated with only a vasodialator.

(4) A method of reducing cardiovascular disease in an individual at risk comprising

administering to the individual on a daily basis an effective amount of a diuretic, wherein the therapeutic effect of the diuretic to reduce cardiovascular disease in such an individual is greater than such therapeutic effect in such an individual treated with only a central agonist.

(5) A method of reducing cardiovascular disease in an individual at risk comprising

administering to the individual on a daily basis an effective amount of a diuretic, wherein the therapeutic effect of the diuretic to reduce cardiovascular disease in such an individual is greater than such therapeutic effect in such an individual treated with only reserpine.

(6) A method of reducing cardiovascular disease in an individual at risk comprising

administering to the individual on a daily basis an effective amount of a diuretic and an ACE-inhibitor, wherein the therapeutic effect of the diuretic and ACE-inhibitor to reduce cardiovascular disease in such an individual is greater than such therapeutic effect in such an individual treated with only such diuretic.

(7) A method of reducing cardiovascular disease in an individual at risk comprising

administering to the individual on a daily basis an effective amount of a diuretic and an ACE-inhibitor, wherein the therapeutic effect of the diuretic and ACE-inhibitor to reduce cardiovascular disease in such an individual is greater than such therapeutic effect in such an individual treated with only a vasodialator, a central agonist, a calcium-channel blocker, an $alpha_1$-blocker, a beta-adrenergic blocker, reserpine.

(8) A method of claim 1, 2, 3, 4, 5, 6 or 7, wherein the diuretic is chlortahlidone.

(9) A method of claim 6 or 7, wherein the diuretic is chlortahlidone.

(10) A method of claim 6 or 7, wherein the ACE-inhibitor is ramipril.

(11) A method of claim 6 or 7, wherein the ACE-inhibitor is ramiprilat.

(12) A method of claim 6 or 7, wherein the diuretic is chlortahlidone and the ACE-inhibitor is ramipril.

(13) A method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, wherein the cardiovascular disease is heart failure.

(14) A method of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13, wherein the individuals is a hypertensive individual.