Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic

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

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group

Context Antihypertensive therapy is well established to reduce hypertension-related morbidity and mortality, but the optimal first-step therapy is unknown.

Objective To determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs treatment with a diuretic.

Design The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, active-controlled clinical trial conducted from February 1994 through March 2002.

Setting and Participants A total of 33 357 participants aged 55 years or older with hypertension and at least 1 other CHD risk factor from 623 North American centers.

Interventions Participants were randomly assigned to receive chlorthalidone, 12.5 to 25 mg/d (n=15 255); amlodipine, 2.5 to 10 mg/d (n=9048); or lisinopril, 10 to 40 mg/d (n=9054) for planned follow-up of approximately 4 to 8 years.

Main Outcome Measures The primary outcome was combined fatal CHD or nonfatal myocardial infarction, analyzed by intent-to-treat. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure [HF], and peripheral arterial disease).

Results Mean follow-up was 4.9 years. The primary outcome occurred in 2956 participants, with no difference between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% CI, 0.90-1.07) for amlodipine (6-year rate, 11.3%) and 0.99 (95% CI, 0.91-1.08) for lisinopril (6-year rate, 11.4%). Likewise, all-cause mortality did not differ between groups. Five-year systolic blood pressures were significantly higher in the amlodipine (0.8 mm Hg, $P=.03$) and lisinopril (2 mm Hg, $P<.001$) groups compared with chlorthalidone, and 5-year diastolic blood pressure was significantly lower with amlodipine (0.8 mm Hg, $P<.001$). For amlodipine vs chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% vs 7.7%; RR, 1.38; 95% CI, 1.25-1.52). For lisinopril vs chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% vs 30.9%; RR, 1.10; 95% CI, 1.05-1.16); stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 1.02-1.30); and HF (8.7% vs 7.7%; RR, 1.19; 95% CI, 1.07-1.31).

Conclusion Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.

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TREATMENT AND COMPLICATIONS among the 50 to 60 million people in the United States with hypertension are estimated to cost $37 billion annually, with antihypertensive drug costs alone accounting for an estimated $15.5 billion per year.[1] Antihypertensive drug therapy substantially reduces the risk of hypertension-related morbidity and mortality.[2-6] However, the optimal choice for initial pharmacotherapy of hypertension is uncertain.[7]

Earlier clinical trials documented the benefit of lowering blood pressure (BP) using primarily thiazide diuretics or β-blockers.[2,3,8] After these studies, several newer classes of antihypertensive agents (ie, angiotensin-converting enzyme [ACE] inhibitors, calcium channel blockers [CCBs], α-adrenergic blockers, and more recently angiotensin-receptor blockers) became available. Over the past decade, major placebo-controlled trials have documented that ACE inhibitors and CCBs reduce cardiovascular events in individuals with hypertension.[9-11] However, their relative value compared with older, less expensive agents remains unclear. There has been considerable uncertainty regarding effects of some classes of antihypertensive drugs on risk of

See also pp 2998 and 3039.

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coronary heart disease (CHD).[6,12-16] The relative benefit of various agents in high-risk hypertensive subgroups such as older patients, black patients, and patients with diabetes also needed to be established.[17]

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, multicenter clinical trial sponsored by the National Heart, Lung, and Blood Institute, was designed to determine whether the occurrence of fatal CHD or nonfatal myocardial infarction is lower for high-risk patients with hypertension treated with a CCB (represented by amlodipine), an ACE inhibitor (represented by lisinopril), or an α-blocker (represented by doxazosin), each compared with diuretic treatment (represented by chlorthalidone).[18] Chlorthalidone was found to be superior to doxazosin and was previously reported after early termination of the doxazosin arm of the trial.[19,20] Secondary outcomes included all-cause mortality, stroke, and other cardiovascular disease (CVD) events. A lipid-lowering subtrial was designed to determine whether lowering cholesterol with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (pravastatin) compared with usual care reduced all-cause mortality in a moderately hypercholesterolemic subset of ALLHAT participants.[18,21] To evaluate differences in CVD effects of the various first-step drugs, ALLHAT was designed with a large sample size (9000-15 000 participants/intervention arm) and long follow-up (4-8 years). This study presents results of the amlodipine and lisinopril vs chlorthalidone comparisons on major CVD outcomes.

METHODS

Study Design

The rationale and design of ALLHAT have been presented elsewhere.[18] Participants were men and women aged 55 years or older who had stage 1 or stage 2 hypertension with at least 1 additional risk factor for CHD events.[18,22] The risk factors included previous (>6 months) myocardial infarction or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, history of type 2 diabetes, current cigarette smoking, high-density lipoprotein cholesterol of less than 35 mg/dL (<0.91 mmol/L), or documentation of other atherosclerotic CVD. Individuals with a history of hospitalized or treated symptomatic heart failure (HF) and/or known left ventricular ejection fraction of less than 35% were excluded.

Unless the drug regimen had to be tapered for safety reasons, individuals continued any prior antihypertensive medications until they received randomized study drug, at which point they stopped taking all previous medications. Treatment with the study drug was initiated the day after randomization. By telephone, participants were randomly assigned to chlorthalidone, amlodipine, or lisinopril in a ratio of 1.7:1:1. The concealed randomization scheme was generated by computer, implemented at the clinical trials center, stratified by center and blocked in random block sizes of 5 or 9 to maintain balance. Participants (n=33 357) were recruited at 623 centers in the United States, Canada, Puerto Rico, and the US Virgin Islands between February 1994 and January 1998. (The original reported number of 625 sites changed because 2 sites and their patients with poor documentation of informed consent were excluded.[20]) All participants gave written informed consent, and all centers obtained institutional review board approval. Follow-up visits were at 1 month; 3, 6, 9, and 12 months; and every 4 months thereafter. The range of possible follow-up was 3 years 8 months to 8 years 1 month. The closeout phase began on October 1, 2001, and ended on March 31, 2002.

Treatment

Trained observers using standardized techniques measured BPs during the trial.[20] Visit BP was the average of 2 seated measurements. Goal BP in each randomized group was less than 140/90 mm Hg achieved by titrating the assigned study drug (step 1) and adding open-label agents (step 2 or 3) when necessary. The choice of step 2 drugs (atenolol, clonidine, or reserpine) was at the physician's discretion. Nonpharmacologic approaches to treatment of hypertension were recommended according to national guidelines.[4,23] Step 1 drugs were encapsulated and identical in appearance so that the identity of each agent was double-masked at each dosage level. Dosages were 12.5, 12.5 (sham titration), and 25 mg/d for chlorthalidone; 2.5, 5, and 10 mg/d for amlodipine; and 10, 20, and 40 mg/d for lisinopril. Doses of study-supplied open-label step 2 drugs were 25 to 100 mg/d of atenolol; 0.05 to 0.2 mg/d of reserpine; or 0.1 to 0.3 mg twice a day of clonidine; step 3 was 25 to 100 mg twice a day of hydralazine. Other drugs, including low doses of open-label step 1 drug classes, were permitted if clinically indicated.[18,20]

Outcomes

The primary outcome was fatal CHD or nonfatal myocardial infarction combined.[18] Four major prespecified secondary outcomes were all-cause mortality, fatal and nonfatal stroke, combined CHD (the primary outcome, coronary revascularization, hospitalized angina), and combined CVD (combined CHD, stroke, other treated angina, HF [fatal, hospitalized, or treated nonhospitalized], and peripheral arterial disease). Coronary revascularization included coronary artery bypass graft, percutaneous angioplasty, insertion of stents, and atherectomy. Individual components of the combined outcomes were prespecified and examined, as were other secondary outcomes including cancer, incident electrocardiographic left ventricular hypertrophy, end-stage renal disease (ESRD) (dialysis, renal transplant, or death), and slope of the reciprocal of longitudinal serum creatinine measurements. Change in estimated glomerular filtration rate[24,25] was examined post hoc.

Study outcomes were assessed at follow-up visits and reported to the clinical trials center.[18] Hospitalized outcomes were primarily based on clinic investigator reports, and copies of death certificates and hospital discharge summaries were requested. Among all combined CVD events that resulted in deaths, hospitalizations, or both, the proportion with documentation (ie, a death certificate or a hospital discharge summary) was 99% in all 3 treatment groups. In addition, searches for outcomes were accomplished through the Center for Medicare and Medicaid Services, the Department of Veterans Affairs, the National Death Index, and the Social Security Administration databases. A death was ascertained by clinic report or by match with the aforementioned databases plus a confirmatory death certificate. A death pending confirmation is one found using databases but for which a confirmatory death certificate has not yet been obtained. Medical reviewers from the clinical trials center verified the physician-assigned diagnoses of outcomes using death certificates and hospital discharge summaries. More detailed information was collected on a random (10%) subset of CHD and stroke events to validate the procedure of using physician diagnoses.[18] When a large excess of HF became evident in the doxazosin arm, a 1-time sample of HF hospitalizations was reviewed by the ALLHAT Endpoints Subcommittee. Agreement rates between the subcommittee and clinic investigators were 90% (155/172) for the primary outcome, 85% (33/39) for HF hospitalizations,[26] and 84% (129/153) for stroke, and were similar in all treatment groups.

Two major safety outcomes, angioedema and hospitalization for gastrointestinal bleeding, were prespecified. Occurrence of gastrointestinal bleeding was ascertained from Center for Medicare and Medicaid Services and Department of Veterans Affairs hospitalization databases, representing 74% of ALLHAT participants (persons ≥65 years, Department of Veterans Affairs participants, or both).[27] Angioedema was ascertained using a solicited event question on a serious adverse event form.

Statistical Methods

To maximize statistical power, 1.7 times as many participants were assigned to the diuretic group as to each of the other 3 groups.[18] Given the achieved sample size and expected event rate, treatment crossovers, and losses to follow-up, ALLHAT had 83% power to detect a 16% reduction in risk of the primary outcome between chlorthalidone and each other group at a 2-sided $\alpha = .0178$ ($z = 2.37$) to account for the 3 original comparisons.[28] Data were analyzed according to participants' randomized treatment assignments regardless of their subsequent medications (intent-to-treat analysis). Cumulative event rates were calculated using the Kaplan-Meier method. Although rates are presented only through 6 years, both the log-rank test and Cox proportional hazards regression model incorporated the participant's entire trial experience to evaluate differences between cumulative event curves and to obtain 2-sided *P* values. Only the Cox proportional hazard regression results are presented, because *P* values were essentially identical. Hazard ratios (relative risks [RRs]) and 95% confidence intervals (CIs) were obtained from the Cox proportional hazards regression model.[29] For consistency with $\alpha = .0178$, 95% CIs may be converted to 98.2% limits by multiplying the upper limit and dividing the lower limit by $RR^{(0.41/Z)}$, where Z is the value of the test statistic for the RR estimate. The Cox proportional hazards regression model assumption was examined by using log-log plots and testing a treatment × time (time-dependent) interaction term; if it was violated, the RR estimate from a 2-by-2 table was used.[29] Heterogeneity of effects in prespecified subgroups, (1) men and women, (2) participants less than 65 and 65 years or older, (3) black and nonblack participants, and (4) diabetic and nondiabetic participants, and the post hoc subgroups presence or absence of CHD at baseline, was examined by testing for treatment-covariate interaction with the Cox proportional hazards regression model by using $P < .05$. SAS version 8.0 (SAS Institute, Cary, NC) and STATA version 7 (Stata Corp, College Station, Tex) were used for statistical analyses.

A National Heart, Lung, and Blood Institute–appointed data and safety monitoring board met at least annually to review the accumulating data and to monitor for safety and efficacy. The Lan-DeMets version of the O'Brien-Fleming group sequential boundaries was used to assess treatment group differences, and conditional power was used to assess futility.[30,31]

RESULTS

Patient Characteristics

TABLE 1 presents baseline characteristics for the 33 357 participants in the chlorthalidone, amlodipine, and lisinopril treatment groups. The mean age was 67 years; 47% were women, 35% were black, 19% were Hispanic, and 36% were diabetic. There were nearly identical distributions of baseline factors in the 3 treatment groups.[22]

Visit and Medication Adherence

FIGURE 1 shows the number of participants randomized and followed up to the time of closeout. In all 3 treatment groups, the mean (SD) length of follow-up was 4.9 years (1.4 years), and 99% of expected person-years were observed. The maximum range of follow-up was 8.0, 7.9, and 8.1 years in the chlorthalidone, amlodipine, and lisinopril groups, respectively. At trial closeout, 419 (2.7%) of the chlorthalidone group, 258 (2.8%) of the amlodipine group, and 276 (3.0%) of the lisinopril group had unknown vital status. Among participants with unknown vital status, the distributions of most baseline factors were similar among the 3 treatment groups, but participants assigned to lisinopril were less likely to be black and more likely to be women, have untreated hypertension, evidence of CHD or atherosclerotic CVD, and a lower mean serum glucose.

Visit adherence decreased over time from about 92% at 1 year to 84% to 87% at 5 years in all 3 treatment groups (TABLE 2). Among participants in the chlorthalidone group who were contacted in the clinic or by telephone within 12 months of annual scheduled visits, 87.1% were taking chlorthalidone or another diuretic at 1 year, decreasing to 80.5% at 5 years; 67.5% (n=4387) were taking a diuretic without a CCB or an ACE inhibitor; and 13.2% were taking a diuretic with a CCB (5.8% [n=399]) or an ACE inhibitor (9.3% [n=641]). Only 9.0% were taking either a CCB (5.8% [n=399]) or an ACE inhibitor (5.6% [n=385]) without a diuretic at 5 years.

Among participants in the amlodipine group, 87.6% were taking amlodipine or another CCB at 1 year, decreasing to 80.4% at 5 years; and 63.8% (n=2502) were taking a CCB alone without a diuretic. Another 16.6% were taking a CCB with a diuretic, and only 6.9% were taking a diuretic without a CCB. Among participants in the lisinopril group, 82.4% were taking lisinopril or another ACE inhibitor at 1 year, decreasing to 72.6% at 5 years; 56.9% (n=2143) were taking an ACE inhibitor alone without a diuretic; and 15.7% were taking an ACE inhibitor with a diuretic at 5 years. About 8.5% were taking a diuretic without an ACE inhibitor.

The most common reasons for not taking step 1 medication at 5 years in the chlorthalidone, amlodipine, and lisinopril groups were unspecified refusals (41.4% [n=775], 40.5% [n=443], and 37.9% [n=552], respectively) and symptomatic adverse effects (15.0% [n=282], 16.4% [n=180], and 18.1% [n=264], respectively). Elevated BP (4.5% [n=84], 3.5% [n=38], and 9.0% [n=131]) or other adverse effects such as abnormal laboratory values (3.8% [n=71], 1.6% [n=17], and 2.3% [n=34]) were other reasons given for discontinuation of step 1 medications. Among participants with available medication information at 1 year, 26.7%, 25.9%, and 32.6% of those assigned to chlorthalidone, amlodipine, and lisinopril, respectively, were taking a step 2 or step 3 drug. At 5 years, the corresponding percentages were 40.7%, 39.5%, and 43.0%, respectively. Usage patterns of specific step 2 drugs were similar among groups. Participants could be taking more than 1 step-up drug. At 1 year, 40.0% (n=4645), 44.0% (n=3017), and 43.8% (n=2764) of participants assigned to chlorthalidone, amlodipine, and lisinopril, respectively, still taking their

Table 1. Baseline Characteristics of the ALLHAT Participants*

Characteristic	No. of Participants (%)		
	Chlorthalidone (n = 15 255)	Amlodipine (n = 9048)	Lisinopril (n = 9054)
Age, mean (SD), y	66.9 (7.7)	66.9 (7.7)	66.9 (7.7)
Age range, y			
55-64	6471 (42.4)	3844 (42.5)	3869 (42.7)
≥65	8784 (57.6)	5204 (57.5)	5185 (57.3)
Ethnicity			
White, non-Hispanic	7202 (47.2)	4305 (47.6)	4262 (47.1)
Black, non-Hispanic	4871 (31.9)	2911 (32.2)	2920 (32.3)
White Hispanic	1912 (12.5)	1108 (12.2)	1136 (12.5)
Black Hispanic	498 (3.3)	302 (3.3)	290 (3.2)
Other	772 (5.1)	422 (4.7)	446 (4.9)
Women	7171 (47.0)	4280 (47.3)	4187 (46.2)
Education, mean (SD), y	11.0 (4.0)	11.0 (3.9)	11.0 (4.1)
Receiving antihypertensive treatment	13 754 (90.2)	8171 (90.3)	8164 (90.2)
Blood pressure, mean (SD), mm Hg	146 (16)/84 (10)	146 (16)/84 (10)	146 (16)/84 (10)
Treated at baseline	145 (16)/83 (10)	145 (16)/83 (10)	145 (16)/84 (10)
Untreated at baseline	156 (12)/89 (9)	157 (12)/90 (9)	156 (12)/89 (9)
Eligibility risk factors†			
Cigarette smoker	3342 (21.9)	1980 (21.9)	1981 (21.9)
Atherosclerotic CVD‡	7900 (51.8)	4614 (51.0)	4684 (51.7)
History of MI or stroke	3581 (23.5)	2098 (23.2)	2058 (22.7)
History of coronary revascularization	1986 (13.0)	1106 (12.2)	1218 (13.5)
Other atherosclerotic CVD	3604 (23.6)	2145 (23.7)	2152 (23.8)
Major ST depression or T-wave inversion	1572 (10.4)	908 (10.1)	940 (10.5)
Type 2 diabetes	5528 (36.2)	3323 (36.7)	3212 (35.5)
HDL-C <35 mg/dL	1798 (11.8)	1018 (11.3)	1061 (11.7)
LVH by electrocardiogram	2467 (16.2)	1533 (16.9)	1474 (16.3)
LVH by echocardiogram	695 (4.6)	411 (4.6)	402 (4.5)
History of CHD at baseline§	3943 (26.0)	2202 (24.5)	2270 (25.3)
Body mass index, mean (SD)	29.7 (6.2)	29.8 (6.3)	29.8 (6.2)
Current medication use			
Aspirin	5426 (35.6)	3268 (36.1)	3258 (36.0)
Estrogen supplementation (women only)	1273 (17.8)	752 (17.6)	727 (17.4)
Lipid trial participants	3755 (24.6)	2240 (24.8)	2167 (23.9)

*ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CVD, cardiovascular disease; MI, myocardial infarction; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; and CHD, coronary heart disease. Body mass index was calculated as weight in kilograms divided by the square of height in meters. To convert HDL-C to mmol/L, multiply by 0.0259.

†For trial eligibility, participants had to have at least 1 other risk factor in addition to hypertension. Thus, the indicated risk factors are not mutually exclusive or exhaustive and may not represent prevalence.

‡History of MI or stroke, history of coronary revascularization, major ST segment depression or T-wave inversion on any electrocardiogram in the past 2 years, other atherosclerotic CVD (history of angina pectoris; history of intermittent claudication, gangrene, or ischemic ulcers; history of transient ischemic attack; coronary, peripheral vascular, or carotid stenosis ≥50% documented by angiography or Doppler studies; ischemic heart disease documented by reversible or fixed ischemia on stress thalium or dipyridamole thalium, ST depression ≥1 mm for ≥1 minute on exercise testing or Holter monitoring; reversible wall motion abnormality on stress echocardiogram; ankle-arm index <0.9; abdominal aortic aneurysm detected by ultrasonography, computed tomography scan, or radiograph; carotid or femoral bruits).

§P = .03 for comparison of groups.

blinded medication were receiving the maximal study dose. At 5 years, the percentages were 56.9% (n=2629), 65.7% (n=1856), and 60.3% (n=1391), respectively.

Intermediate Outcomes

Given the large sample size in ALLHAT, almost all differences in follow-up BP and biochemical measurements were statistically significant (TABLE 3 and TABLE 4). Mean seated BP at randomization was about 146/84 mm Hg in all 3 groups, with 90% of participants reporting current antihypertensive drug treatment (Table 1). Follow-up BPs in all 3 groups are shown in Table 3 and FIGURE 2.

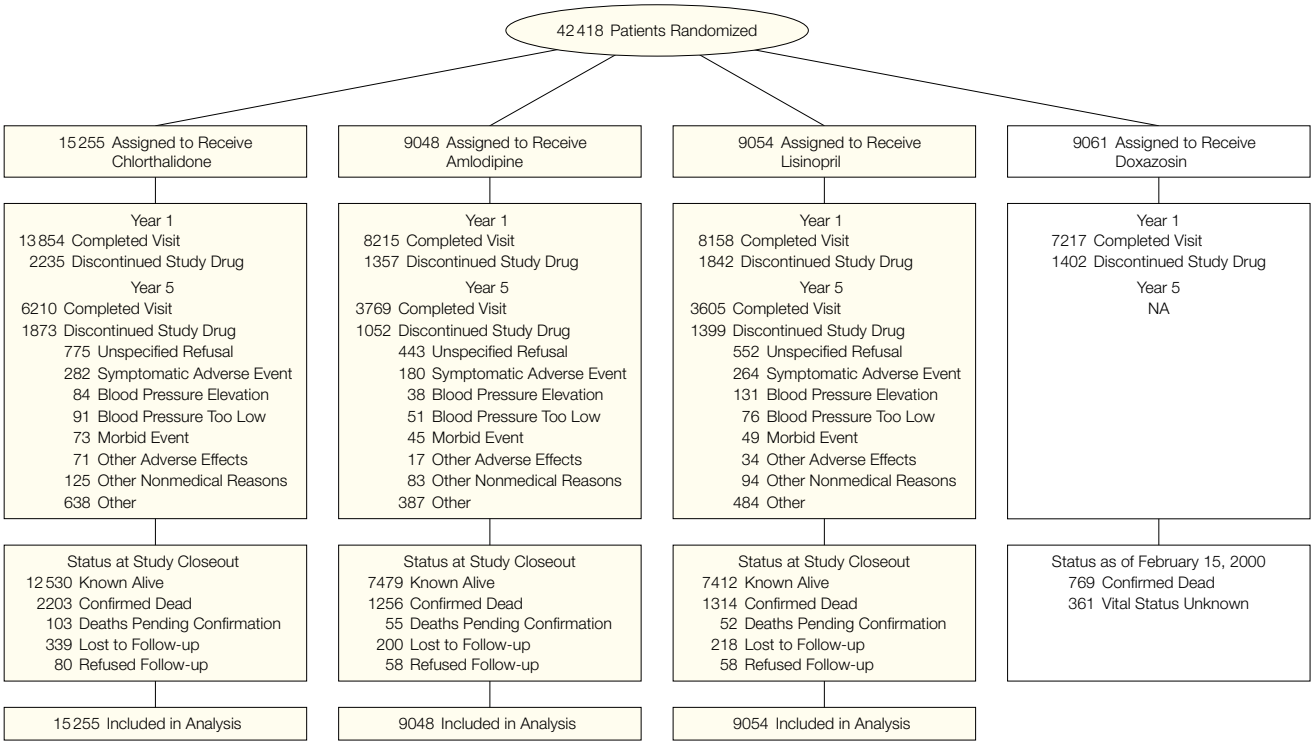
Mean total serum cholesterol levels at baseline and 4 years follow-up are shown in Table 4. At 4 years, about 35% to 36% of participants in all 3 groups reported taking lipid-lowering drugs, largely statins, some as a result of participation in the ALLHAT lipid trial. Mean serum potassium levels at baseline and follow-up are also shown; about 8% of the chlorthalidone group were receiving potassium supplementation at 5 years compared with 4% in the amlodipine group and 2% in the lisinopril group. Among individuals classified as nondiabetic at baseline, with baseline fasting serum glucose less than 126 mg/dL (7.0 mmol/L), incidence of diabetes (fasting serum glucose, ≥126 mg/dL [7.0 mmol/L]) at 4 years was 11.6%, 9.8%, and 8.1%, respectively.

Mean estimated glomerular filtration rate at baseline was about 78 mL/min per 1.73 m^2 in all groups. At 4 years, it was 70.0, 75.1, and 70.7 mL/min per 1.73 m^2 in the chlorthalidone, amlodipine, and lisinopril groups, respectively. The slopes of the reciprocal of serum creatinine over time were virtually identical in the chlorthalidone and lisinopril groups (–0.018 and –0.019 dL/mg per year), whereas the decline in the amlodipine slope (–0.012 dL/mg per year) was less than that of the chlorthalidone slope ($P<.001$).

Primary and Secondary Outcomes

Amlodipine vs Chlorthalidone. No significant difference was observed between amlodipine and chlorthalidone for the primary outcome (RR, 0.98; 95% CI, 0.90-1.07) or for the secondary outcomes of all-cause mortality, combined CHD, stroke, combined CVD, angina, coronary revascularization, peripheral arterial disease, cancer, or ESRD (TABLE 5, FIGURE 3, and FIGURE 4). The amlodipine group had a 38% higher risk of HF ($P<.001$) with

Figure 1. Randomization and Follow-up of Participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial



NA indicates not applicable. Eligibility data were not collected for nonrandomized screenees. All randomized participants were included in the analyses. A patient may have more than 1 reason for discontinuing study drug; therefore, numbers do not sum to total. On January 24, 2000, the National Heart, Lung, and Blood Institute decided to discontinue the doxazosin group and report results.[18] Study closeout for chlorthalidone, amlodipine, and lisinopril groups was from October 1, 2001, through March 31, 2002. Collection of last events for the doxazosin group had a closeout interval from October 15, 1999, through February 15, 2000, which captures more information than that reported previously.[24]

a 6-year absolute risk difference of 2.5% and a 35% higher risk of hospitalized/fatal HF ($P<.001$). The treatment effects for all outcomes were consistent across the predefined subgroups (FIGURE 5) and by absence or presence of CHD at baseline. Cause-specific mortality rates (except for unintentional injuries/suicides/homicides in amlodipine compared with chlorthalidone, not a prespecified hypothesis) were similar for the 2 groups (TABLE 6).

Lisinopril vs Chlorthalidone. No significant difference was observed between lisinopril and chlorthalidone for the primary outcome (RR, 0.99; 95% CI, 0.91-1.08) or for the secondary outcomes of all-cause mortality, combined CHD, peripheral arterial disease, cancer, or ESRD (Table 5, Figures 3 and 4). Cause-specific mortality rates were also similar in the 2 groups (Table 6). The lisinopril group had a 15% higher risk for stroke ($P=.02$) and a 10% higher risk of combined CVD ($P<.001$), with a 6-year absolute risk difference for combined CVD of 2.4%. Included in this analysis was a 19% higher risk of HF ($P<.001$), a 10% higher risk of hospitalized/fatal HF ($P=.11$), an 11% higher risk of hospitalized/treated angina ($P=.01$), and a 10% higher risk of coronary revascularization ($P=.05$). The treatment effects for all outcomes were consistent across subgroups by sex, diabetic status (FIGURE 6), and baseline CHD status. For combined CHD, there was a significant differential effect by age ($P=.01$ for interaction) with RRs (lisinopril vs chlorthalidone) of 0.94 for those less than 65 years vs 1.11 in those 65 years or older. However, when age was modeled as a continuous variable, there was no significant interaction. For stroke and combined CVD, there was a significant differential effect by race ($P=.01$ and $P=.04$ for interaction, respectively). The RRs (lisinopril vs chlorthalidone) were 1.40 (95% CI, 1.17-1.68) and 1.00 (95% CI, 0.85-1.17) for stroke and 1.19 (95%

Table 2. Visits Expected and Completed and Antihypertensive Medication Use at Annual Visits

	Years, No. (%)				
	1	2	3	4	5
Chlorthalidone					
Expected visits	15 067 (98.8)	14 711 (96.4)	14 272 (93.6)	12 380 (81.2)	7243 (47.5)
Completed visits	13 854 (91.9)	12 988 (88.3)	12 335 (86.4)	10 618 (85.8)	6210 (85.7)
Receiving blinded study drug	11 618 (83.9)	10 367 (79.8)	9372 (76.0)	8149 (72.9)	4623 (71.2)
Receiving blinded study drug or same class	12 063 (87.1)	11 001 (84.7)	10 202 (82.7)	9034 (80.8)	5247 (80.5)
Full crossovers*	707 (5.1)	865 (6.7)	944 (7.7)	921 (8.2)	583 (9.0)
Partial crossovers†	469 (3.4)	770 (5.9)	1054 (8.5)	1223 (10.9)	860 (13.2)
Receiving step 2 or 3‡	3703 (26.7)	4185 (32.2)	4395 (35.6)	4244 (38.0)	2642 (40.7)
Other antihypertensive medication	594 (4.3)	586 (4.5)	618 (5.0)	609 (5.5)	320 (4.9)
No. of antihypertensive medications, mean (SD)	1.4 (0.7)	1.5 (0.8)	1.6 (0.9)	1.7 (1.0)	1.8 (1.0)
Amlodipine					
Expected visits	8937 (98.8)	8733 (96.5)	8510 (94.0)	7411 (81.9)	4343 (48.0)
Completed visits	8215 (91.9)	7672 (87.9)	7355 (86.4)	6341 (85.6)	3769 (86.8)
Receiving blinded study drug	6858 (83.5)	6106 (79.6)	5630 (76.6)	4886 (73.3)	2826 (72.1)
Receiving blinded study drug or same class	7192 (87.6)	6532 (85.2)	6116 (83.2)	5367 (80.5)	3151 (80.4)
Full crossovers*	232 (2.8)	342 (4.5)	369 (5.0)	401 (6.0)	270 (6.9)
Partial crossovers†	548 (6.7)	666 (8.7)	818 (11.1)	881 (13.2)	649 (16.6)
Receiving step 2 or 3‡	2124 (25.9)	2456 (32.0)	2590 (35.2)	2457 (36.9)	1548 (39.5)
Other antihypertensive medication	478 (5.8)	499 (6.5)	546 (7.4)	568 (8.5)	314 (8.0)
No. of antihypertensive medications, mean (SD)	1.4 (0.7)	1.5 (0.8)	1.7 (0.9)	1.7 (1.0)	1.9 (1.0)
Lisinopril					
Expected visits	8942 (98.8)	8725 (96.4)	8458 (93.4)	7356 (81.2)	4315 (47.7)
Completed visits	8158 (91.2)	7574 (86.8)	7185 (84.9)	6142 (83.5)	3605 (83.5)
Receiving blinded study drug	6316 (77.4)	5418 (71.5)	4897 (68.2)	4155 (64.4)	2307 (61.2)
Receiving blinded study drug or same class	6721 (82.4)	5944 (78.4)	5536 (77.1)	4824 (74.8)	2736 (72.6)
Full crossovers*	285 (3.5)	387 (5.1)	430 (6.0)	455 (7.0)	320 (8.5)
Partial crossovers†	475 (5.8)	662 (8.7)	797 (11.1)	857 (13.3)	593 (15.7)
Receiving step 2 or 3‡	2661 (32.6)	2747 (36.3)	2788 (38.8)	2625 (40.7)	1620 (43.0)
Other antihypertensive medication	836 (10.2)	869 (11.5)	858 (12.0)	822 (12.7)	480 (12.7)
No. of antihypertensive medications, mean (SD)	1.5 (0.8)	1.7 (1.0)	1.8 (1.0)	1.9 (1.1)	2.0 (1.2)

*Full crossovers: (1) assigned to chlorthalidone, not on step 1, no open-label diuretic, but on open-label calcium channel blocker (CCB) or angiotensin-converting enzyme (ACE) inhibitor; (2) assigned to lisinopril, not on step 1, no open-label ACE inhibitor, but on open-label diuretic; (3) assigned to amlodipine, not on step 1, no open-label CCB, but on open-label diuretic.
†Partial crossovers: (1) assigned to chlorthalidone, on step 1 or open-label diuretic and on open-label CCB or ACE inhibitor; (2) assigned to lisinopril, on step 1 or open-label ACE inhibitor and on open-label diuretic; (3) assigned to amlodipine, on step 1 or open-label CCB and on open-label diuretic.
‡Step 2: atenolol, clonidine, or reserpine; step 3: hydralazine.

CI, 1.09-1.30) and 1.06 (95% CI, 1.00-1.13) for combined CVD in blacks and nonblacks, respectively.

The mean follow-up systolic BP for all participants was 2 mm Hg higher in the lisinopril group than the chlorthalidone group, 4 mm Hg higher in blacks, and 3 mm Hg higher in those 65 years or older. Adjustment for follow-up BP as time-dependent covariates in a Cox proportional hazards regression model slightly reduced the RRs for stroke (1.15 to 1.12) and HF (1.20 to 1.17) overall and in the black subgroup (stroke, 1.40 to 1.35; and HF, 1.32 to 1.26), but the results remained statistically significant.

Primary Safety Outcomes

Six-year rates of hospitalization for gastrointestinal bleeding, available only in Medicare and Department of Veterans Affairs participants, occurred in 8.8%, 8.0%, and 9.6% participants in the chlorthalidone, amlodipine, and lisinopril treatment groups, respectively, with no significant differences (Table 5). Angioedema occurred in 8 of 15 255 (0.1%), 3 of 9048 (<0.1%), and 38 of 9054 (0.4%) persons in the chlorthalidone, amlodipine, and lisinopril treatment groups, respectively. Significant differences were seen for the lisinopril vs chlorthalidone comparison overall ($P<.001$), in blacks (2 of 5369 [<0.1%] for chlorthalidone, 23 of 3210 [0.7%] for lisinopril; $P<.001$), and in nonblacks (6 of 9886 [0.1%] for chlorthalidone, 15 of 5844 for lisinopril [0.3%]; $P=.002$). The only death from angioedema was in the lisinopril group.

COMMENT

Neither amlodipine (representing CCBs, particularly dihydropyridine [DHP]–CCBs) nor lisinopril (representing ACE inhibitors) was superior to chlorthalidone (representing thiazide-type diuretics) in preventing major coronary events or in increasing survival. Chlorthalidone was superior to amlodipine (by about 25%) in preventing HF, overall, and for hospitalized or fatal cases, although it did not differ from amlodipine in overall CVD prevention. Chlorthalidone was superior to lisinopril in lowering BP and in preventing aggregate cardiovascular events, principally stroke, HF, angina, and coronary revascularization. ALLHAT previously reported that chlorthalidone was superior to doxazosin (representing α-blockers) in reducing BP and preventing cardiovascular events, particularly HF.[19,20]

It is not surprising that no significant differences in CHD and stroke rates were found between chlorthalidone and

Table 3. Number of Participants, Mean Blood Pressure, Achieved Blood Pressure Goal, and Blood Pressure Difference at Baseline and Annual Visits

				P Value	
	Chlorthalidone	Amlodipine	Lisinopril	Amlodipine vs Chlorthalidone	Lisinopril vs Chlorthalidone
No. of Participants (%)					
Baseline	15 255 (100)	9048 (100)	9054 (100)		
1 Year	12 862 (84.3)	7609 (84.1)	7521 (83.1)		
2 Years	11 740 (77.0)	6883 (76.1)	6700 (74.0)		
3 Years	10 698 (70.1)	6381 (70.5)	6076 (67.1)		
4 Years	9379 (61.5)	5637 (62.3)	5325 (58.8)		
5 Years	5301 (34.7)	3195 (35.3)	2963 (32.7)		
Systolic Blood Pressure, Mean (SD), mm Hg					
Baseline	146.2 (15.7)	146.2 (15.7)	146.4 (15.7)	.98	.39
1 Year	136.9 (15.8)	138.5 (14.9)	140.0 (18.5)	<.001	<.001
2 Years	135.9 (15.9)	137.1 (15.0)	138.4 (17.9)	<.001	<.001
3 Years	134.8 (15.4)	135.6 (15.2)	136.7 (17.3)	.001	<.001
4 Years	133.9 (15.7)	134.8 (15.0)	135.5 (17.2)	.002	<.001
5 Years	133.9 (15.2)	134.7 (14.9)	135.9 (17.9)	.03	<.001
Diastolic Blood Pressure, Mean (SD), mm Hg					
Baseline	84.0 (10.1)	83.9 (10.2)	84.1 (10.0)	.52	.49
1 Year	79.3 (9.9)	78.7 (9.5)	79.9 (10.5)	<.001	<.001
2 Years	78.3 (9.6)	77.7 (9.6)	78.6 (10.3)	<.001	.03
3 Years	77.2 (9.5)	76.4 (9.6)	77.3 (10.3)	<.001	.42
4 Years	76.5 (9.7)	75.7 (9.6)	76.6 (10.4)	<.001	.48
5 Years	75.4 (9.8)	74.6 (9.9)	75.4 (10.7)	<.001	.94
Achieved Blood Pressure Goal of <140/90 mm Hg, No. (%)					
Baseline	4149 (27.2)	2497 (27.6)	2381 (26.3)	.56	.12
1 Year	7434 (57.8)	4200 (55.2)	3806 (50.6)	<.001	<.001
2 Years	7161 (61.0)	3951 (57.4)	3625 (54.1)	<.001	<.001
3 Years	6836 (63.9)	4046 (63.4)	3597 (59.2)	.54	<.001
4 Years	6293 (67.1)	3709 (65.8)	3360 (63.1)	.15	<.001
5 Years	3615 (68.2)	2118 (66.3)	1813 (61.2)	.09	<.001
Systolic Blood Pressure, Δ mm Hg*					
Baseline		0	0.2		
1 Year		1.6	3.1		
2 Years		1.2	2.5		
3 Years		0.8	1.9		
4 Years		0.9	1.6		
5 Years		0.8	2.0		
Diastolic Blood Pressure, Δ mm Hg*					
Baseline		−0.1	0.1		
1 Year		−0.6	0.6		
2 Years		−0.6	0.3		
3 Years		−0.8	0.1		
4 Years		−0.8	0.1		
5 Years		−0.8	0		

*Compared with chlorthalidone group.

Table 4. Biochemical Changes by Treatment Group*

				P Value	
	Chlorthalidone	Amlodipine	Lisinopril	Amlodipine vs Chlorthalidone	Lisinopril vs Chlorthalidone
Cholesterol, mg/dL					
No. of participants (%)					
Baseline	14 483 (94.9)	8586 (94.9)	8573 (94.7)		
2 Years	10 206 (66.9)	6025 (66.6)	5739 (63.4)		
4 Years	8495 (55.7)	5025 (55.5)	4711 (52.0)		
Mean (SD)					
Baseline	216.1 (43.8)	216.5 (44.1)	215.6 (42.4)	.47	.38
2 Years	205.3 (42.1)	202.5 (42.2)	202.0 (42.8)	<.001	<.001
4 Years	197.2 (42.1)	195.6 (41.0)	195.0 (40.6)	.009	<.001
≥240 mg/dL, No. (%)					
Baseline	3838 (26.5)	2284 (26.6)	2178 (25.4)	.89	.06
2 Years	1898 (18.6)	1018 (16.9)	976 (17.0)	.005	.03
4 Years	1223 (14.4)	673 (13.4)	603 (12.8)	.13	.005
Potassium, mEq/L					
No. of participants (%)					
Baseline	14 487 (95.0)	8586 (94.9)	8573 (94.7)		
2 Years	9877 (64.7)	5794 (64.0)	5516 (60.9)		
4 Years	8315 (54.5)	4919 (54.4)	4616 (51.0)		
Mean (SD)					
Baseline	4.3 (0.7)	4.3 (0.7)	4.4 (0.7)	.59	.001
2 Years	4.0 (0.7)	4.3 (0.7)	4.5 (0.7)	<.001	<.001
4 Years	4.1 (0.7)	4.4 (0.7)	4.5 (0.7)	<.001	<.001
<3.5 mEq/L, No. (%)					
Baseline	493 (3.4)	292 (3.4)	223 (2.6)	.99	.001
2 Years	1254 (12.7)	151 (2.6)	83 (1.5)	<.001	<.001
4 Years	707 (8.5)	93 (1.9)	37 (0.8)	<.001	<.001
Fasting Glucose, mg/dL					
No. of participants (%)					
Baseline	11 273 (73.9)	6648 (73.5)	6752 (74.6)		
2 Years	5980 (39.2)	3506 (38.7)	3333 (36.8)		
4 Years	4972 (32.6)	2954 (32.6)	2731 (30.2)		
Mean (SD)					
Baseline	123.5 (58.3)	123.1 (57.0)	122.9 (56.1)	.71	.54
2 Years	127.6 (59.2)	122.4 (54.2)	120.8 (54.0)	<.001	<.001
4 Years	126.3 (55.6)	123.7 (52.0)	121.5 (51.3)	.20	.002
≥126 mg/dL, No. (%)					
Baseline	3258 (28.9)	1941 (29.2)	1985 (29.4)	.68	.55
2 Years	1967 (32.9)	1048 (29.9)	947 (28.4)	<.001	<.001
4 Years	1626 (32.7)	901 (30.5)	784 (28.7)	.11	<.001
Fasting Glucose Among Nondiabetics With Baseline Fasting Glucose <126 mg/dL					
No. of participants (%)					
Baseline	6766 (100)	3954 (100)	4096 (100)		
2 Years	3074 (45.4)	1787 (45.2)	1737 (42.4)		
4 Years	2606 (40.3)	1567 (39.6)	1464 (35.7)		
Mean (SD)					
Baseline	93.1 (11.7)	93.0 (11.4)	93.3 (11.8)	.52	.45
2 Years	102.2 (27.1)	99.0 (22.5)	97.4 (20.0)	<.001	<.001
4 Years	104.4 (28.5)	103.1 (27.7)	100.5 (19.5)	.11	<.001
≥126 mg/dL, No. (%)					
2 Years	295 (9.6)	132 (7.4)	101 (5.8)	.006	<.001
4 Years	302 (11.6)	154 (9.8)	119 (8.1)	.04	<.001

(continued)

amlodipine-based therapy in ALLHAT. In the Systolic Hypertension in the Elderly Program and the Systolic Hypertension in Europe trial, in which a thiazide-like diuretic (chlorthalidone) or a DHP-CCB was compared with a placebo, major CHD events were reduced by 27% and 30%, and stroke by 37% and 42%, respectively.[8,9] More direct evidence comes from 2 large active-controlled trials that compared DHP-CCB and traditional first-step drugs. The Swedish Trial in Old Patients with Hypertension-2 and the International Nifedipine GITS (long-acting gastrointestinal formulation) Study: Intervention as a Goal in Hypertension Treatment (INSIGHT), found no significant differences for major CHD or stroke rates between the treatment groups.[32,33] Some of these individual trials have had limited power to evaluate differences between treatments.[34] In meta-analyses of 5 positive-controlled trials, which included both DHP-CCB and non–DHP-CCB trials, there were trends that favored CCB-based therapy for stroke and traditional treatment for CHD, with no difference for all-cause mortality.[13,14] However, ALLHAT observed approximately the same number of strokes and nearly twice as many CHD events as all 5 trials combined, which suggests that the aggregate of the evidence would indicate no difference between CCB-based treatment and diuretic-based treatment for these outcomes.

The amlodipine vs chlorthalidone findings for HF reinforce previous trial results. In the diuretic-based Systolic Hypertension in the Elderly Program, active therapy reduced HF occurrence by 49% compared with placebo ($P<.001$), although in the DHP-CCB–based Systolic Hypertension in Europe trial, it was reduced by 29% (not statistically significant).[9,35] In the INSIGHT trial, HF was approximately twice as frequent in the CCB vs the diuretic arm.[33] The previously cited meta-analyses reported a higher rate of HF with CCB-based treatment than traditional regimens, with no difference in RR for DHPs compared with non–DHPs.[13,14]

A body of literature based on observational studies and secondary CHD prevention trials of short-acting CCBs has suggested that CCBs, especially DHP-CCBs, may increase the risk of cancer, gastrointestinal bleeding, and all-cause mortality.[14,36,37] The results of ALLHAT do not support these findings. In fact, the mortality from noncardiovascular causes was significantly lower in the CCB group (Table 6).

There were no significant differences in the incidence of ESRD between chlorthalidone and amlodipine, consistent with findings from the INSIGHT trial.[33] Comparison of the reciprocal serum creatinine slopes suggested a slower decline in kidney function in the amlodipine group. However, this finding requires cautious interpretation because studies assessing glomerular filtration rate more directly have shown a hemodynamically mediated acute increase in glomerular filtration rate followed by a more rapid rate of decline with chronic therapy using amlodipine and other CCBs.[38-40]

Comparison of the lisinopril and chlorthalidone groups revealed better drug tolerance and BP control with chlorthalidone. Angioedema, a rare but potentially serious adverse effect of ACE inhibitor use, occurred 4 times more frequently in participants randomized to lisinopril than in those randomized to chlorthalidone. Cholesterol levels, the prevalence of hypokalemia (serum potassium <3.5 mEq/L), and new diabetes (fasting glucose ≥126 mg/dL [≥7.0 mmol/L]) were higher in the chlorthalidone than the other groups following 2 and 4 years of follow-up. Overall, these metabolic differences did not translate into more cardiovascular events or into higher all-cause mortality in the chlorthalidone group compared with the other 2 groups.

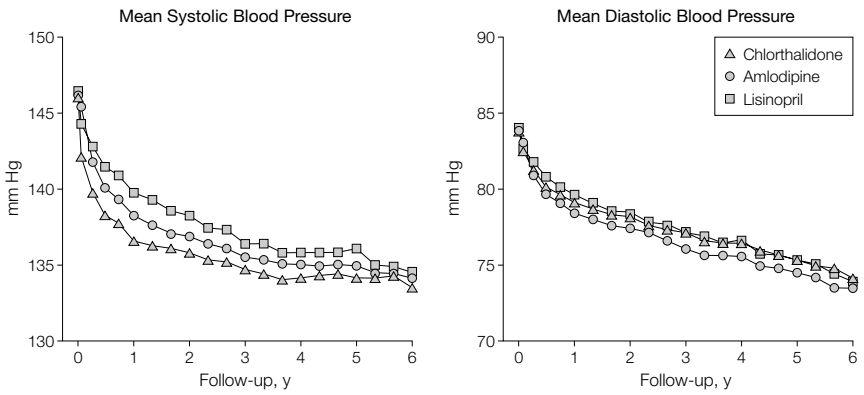
The ALLHAT findings for some major outcomes are consistent with predictions from placebo-controlled trials involving ACE inhibitors and diuretics. Specifically, for ACE inhibitor and diuretic trials, respectively, the reductions in CHD rates were 20% and 18%, and for all-cause mortality, 16% and 10%.[13] The 10% greater rate of combined CVD in the lisinopril than in the chlorthalidone group was due to increased occurrences of stroke, HF, angina, and coronary revascularization. Results for some of these outcomes may seem surprising, because of reports of beneficial effects of ACE inhibitors on surrogate markers of atherosclerosis and reductions in vascular and renal events in individuals with HF, diabetes, kidney disease, and cerebrovascular disease in placebo-controlled trials.[41-43] However, the finding in ALLHAT that HF incidence was lower in the diuretic vs the ACE inhibitor group is also consistent with previous reports. In the Systolic Hypertension in the Elderly Program trial (chlorthalidone vs placebo), there was a 49% decrease in the development of HF, whereas in the Studies of Left Ventricular Dysfunction Prevention (enalapril vs placebo) and Heart Outcomes Prevention Evaluation trials (ramipril vs placebo), there were only 20% and 23% reductions, respectively.[8,10,44] In published meta-analyses of placebo-controlled trials, the reductions in rates for stroke with ACE inhibitor and diuretics were 30% and 34%, translating into nearly equivalent results.[3,13] The 15% relative increase in stroke incidence for lisinopril compared with chlorthalidone treatment in ALLHAT must be considered in the context of heterogeneity of the results by race. The Swedish Trial in Old Patients with Hypertension-2 trial, which compared ACE inhibitors with conventional treatment (diuret-

Table 4. Biochemical Changes by Treatment Group* (cont)

				P Value	
	Chlorthalidone	Amlodipine	Lisinopril	Amlodipine vs Chlorthalidone	Lisinopril vs Chlorthalidone
Estimated Glomerular Filtration Rate, mL/min per 1.73 m²†					
No. of participants (%)					
Baseline	14 492 (95.0)	8589 (94.9)	8577 (94.7)		
2 Years	9877 (64.7)	5794 (64.0)	5516 (60.9)		
4 Years	8316 (54.5)	4924 (54.4)	4621 (51.0)		
Mean (SD)					
Baseline	77.6 (19.7)	78.0 (19.7)	77.7 (19.9)	.08	.57
2 Years	73.3 (19.9)	78.0 (20.5)	74.0 (20.0)	<.001	.002
4 Years	70.0 (19.7)	75.1 (20.7)	70.7 (20.1)	<.001	.03

*To convert serum cholesterol to mmol/L, multiply by 0.0259; fasting glucose to mmol/L, multiply by 0.0555.
†Simplified 4-variable Modification of Diet in Renal Disease Study formula.[24,25]

Figure 2. Mean Systolic and Diastolic Blood Pressure by Year During Follow-up



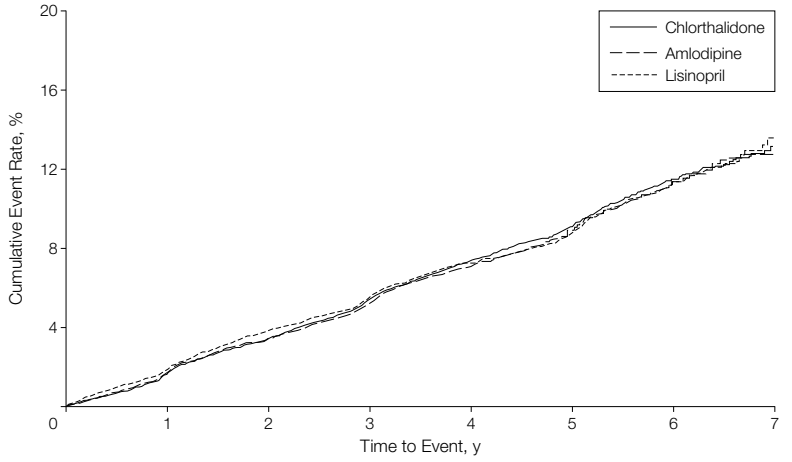
Number measured at baseline through 5 years is given in Table 3; numbers at 6 years for chlorthalidone, amlodipine, and lisinopril are 2721, 1656, and 1551, respectively.

Table 5. Clinical Outcomes by Antihypertensive Treatment Group*

	Chlorthalidone		Amlodipine		Lisinopril		Amlodipine vs Chlorthalidone			Lisinopril vs Chlorthalidone		
	No. of Total Events	6-Year Rate per 100 Persons (SE)	No. of Total Events	6-Year Rate per 100 Persons (SE)	No. of Total Events	6-Year Rate per 100 Persons (SE)	RR (95% CI)	Z Score	P Value	RR (95% CI)	Z Score	P Value
Primary outcome												
CHD†	1362	11.5 (0.3)	798	11.3 (0.4)	796	11.4 (0.4)	0.98 (0.90-1.07)	−0.46	.65	0.99 (0.91-1.08)	−0.24	.81
Secondary outcomes												
All-cause mortality	2203	17.3 (0.4)	1256	16.8 (0.5)	1314	17.2 (0.5)	0.96 (0.89-1.02)	−1.27	.20	1.00 (0.94-1.08)	0.12	.90
Combined CHD‡	2451	19.9 (0.4)	1466	19.9 (0.5)	1505	20.8 (0.5)	1.00 (0.94-1.07)	0.04	.97	1.05 (0.98-1.11)	1.35	.18
Stroke	675	5.6 (0.2)	377	5.4 (0.3)	457	6.3 (0.3)	0.93 (0.82-1.06)	−1.09	.28	1.15 (1.02-1.30)	2.31	.02
Combined CVD‡	3941	30.9 (0.5)	2432	32.0 (0.6)	2514	33.3 (0.6)	1.04 (0.99-1.09)	1.55	.12	1.10 (1.05-1.16)	3.78	<.001
End-stage renal disease	193	1.8 (0.1)	129	2.1 (0.2)	126	2.0 (0.2)	1.12 (0.89-1.40)	0.98	.33	1.11 (0.88-1.38)	0.87	.38
Cancer	1170	9.7 (0.3)	707	10.0 (0.4)	703	9.9 (0.4)	1.01 (0.92-1.11)	0.30	.77	1.02 (0.93-1.12)	0.42	.67
Hospitalized for gastrointestinal bleeding§	817	8.8 (0.3)	449	8.0 (0.4)	526	9.6 (0.4)	0.92 (0.82-1.03)	−1.44	.15	1.11 (0.99-1.24)	1.82	.07
Components of secondary outcomes												
Heart failure	870	7.7 (0.3)	706	10.2 (0.4)	612	8.7 (0.4)	1.38 (1.25-1.52)	6.29	<.001	1.19 (1.07-1.31)‖	3.33	<.001
Hospitalized/fatal heart failure	724	6.5 (0.3)	578	8.4 (0.4)	471	6.9 (0.4)	1.35 (1.21-1.50)	5.37	<.001	1.10 (0.98-1.23)‖	1.59	.11
Angina (hospitalized or treated)	1567	12.1 (0.3)	950	12.6 (0.4)	1019	13.6 (0.4)	1.02 (0.94-1.10)	0.42	.67	1.11 (1.03-1.20)	2.59	.01
Angina (hospitalized)	1078	8.6 (0.3)	630	8.4 (0.4)	693	9.6 (0.4)	0.98 (0.89-1.08)	−0.41	.68	1.09 (0.99-1.20)	1.85	.06
Coronary revascularizations	1113	9.2 (0.3)	725	10.0 (0.4)	718	10.2 (0.4)	1.09 (1.00-1.20)	1.88	.06	1.10 (1.00-1.21)	1.95	.05
Peripheral arterial disease (hospitalized or treated)	510	4.1 (0.2)	265	3.7 (0.2)	311	4.7 (0.4)	0.87 (0.75-1.01)	−1.86	.06	1.04 (0.90-1.19)	0.48	.63

*RR indicates relative risk; CI, confidence interval; CHD, coronary heart disease; and CVD, cardiovascular disease. CHD includes nonfatal myocardial infarction (MI) and fatal CHD; end-stage renal disease: kidney disease death, kidney transplant, or start of chronic renal dialysis; and heart failure: fatal, nonfatal hospitalized, or treated.
†Nonfatal MIs comprise 64% to 66% of the primary outcome.
‡Combined CHD indicates CHD death, nonfatal MI, coronary revascularization procedures, and hospitalized angina. Combined CVD indicates CHD death, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).
§Denominators are 11 361 chlorthalidone, 6757 amlodipine, and 6665 lisinopril.
‖Proportional hazards assumption violated; data are RRs from a 2 × 2 table.

Figure 3. Cumulative Event Rates for the Primary Outcome (Fatal Coronary Heart Disease or Nonfatal Myocardial Infarction) by Treatment Group



No. at Risk								
Chlorthalidone	15255	14477	13820	13102	11362	6340	2956	209
Amlodipine	9048	8576	8218	7843	6824	3870	1878	215
Lisinopril	9054	8535	8123	7711	6662	3832	1770	195

No significant difference was observed for amlodipine (relative risk [RR], 0.98; 95% confidence interval [CI], 0.90-1.07; $P = .65$) or lisinopril (RR, 0.99; 95% CI, 0.91-1.08; $P = .81$) vs chlorthalidone with a mean follow-up of 4.9 years.

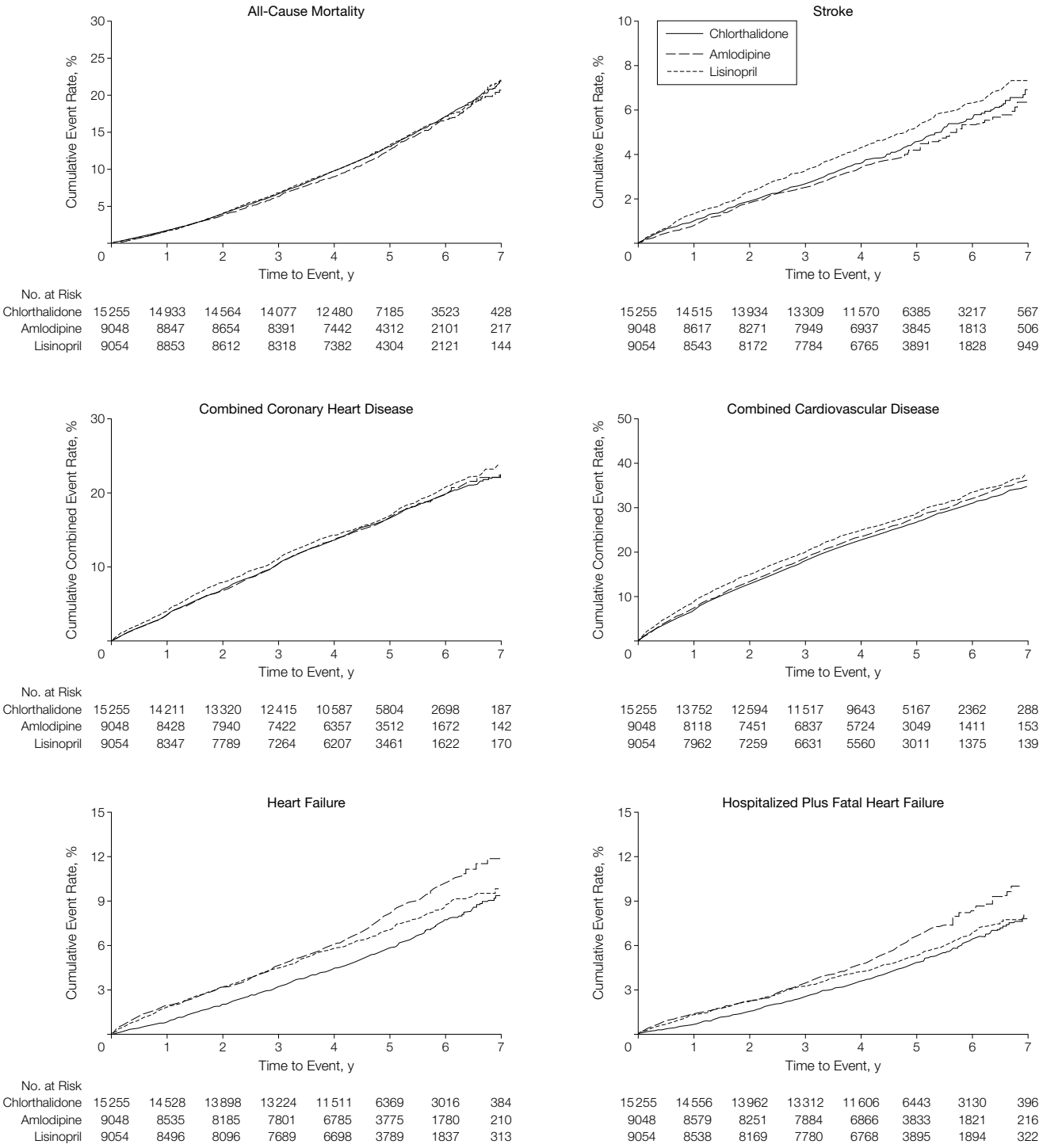
ics and/or β-blockers), showed no significant differences in CHD, stroke, HF, or all-cause mortality.[32] Although these findings are somewhat different from the experience in ALLHAT, consideration needs to be given to respective confidence limits, population differences (especially race), and study designs (open vs double-blind).

No substantial differences in incidence of ESRD, glomerular filtration rate, or reciprocal creatinine slopes were noted for the lisinopril vs chlorthalidone comparisons. The ALLHAT study population was selected for high CVD risk and had a baseline mean creatinine of only 1.0 mg/dL (88.4 μmol/L). More detailed analyses of high renal risk subgroups (ie, diabetic, renal-impaired, and black patients) will be the subject of subsequent reports.

Analyses of RRs for stroke and HF adjusted for follow-up BP suggest that the 2-mm Hg systolic BP difference over-

all (4 mm Hg in black patients) between the lisinopril and chlorthalidone groups only partially accounts for the observed CVD event difference. However, such analyses are limited by the infrequency and imprecision of BP measurements for individual participants and regression dilution, which underestimates CVD risk associated

Figure 4. Cumulative Event Rates for All-Cause Mortality, Stroke, Combined Coronary Heart Disease, Combined Cardiovascular Disease, Heart Failure, and Hospitalized Plus Fatal Heart Failure by Treatment Group



No. at Risk

Chlorthalidone	15255	14933	14564	14077	12480	7185	3523	428
Amlodipine	9048	8847	8654	8391	7442	4312	2101	217
Lisinopril	9054	8853	8612	8318	7382	4304	2121	144

Chlorthalidone	15255	14515	13934	13309	11570	6385	3217	567
Amlodipine	9048	8617	8271	7949	6937	3845	1813	506
Lisinopril	9054	8543	8172	7784	6765	3891	1828	949

No. at Risk

Chlorthalidone	15255	14211	13320	12415	10587	5804	2698	187
Amlodipine	9048	8428	7940	7422	6357	3512	1672	142
Lisinopril	9054	8347	7789	7264	6207	3461	1622	170

Chlorthalidone	15255	13752	12594	11517	9643	5167	2362	288
Amlodipine	9048	8118	7451	6837	5724	3049	1411	153
Lisinopril	9054	7962	7259	6631	5560	3011	1375	139

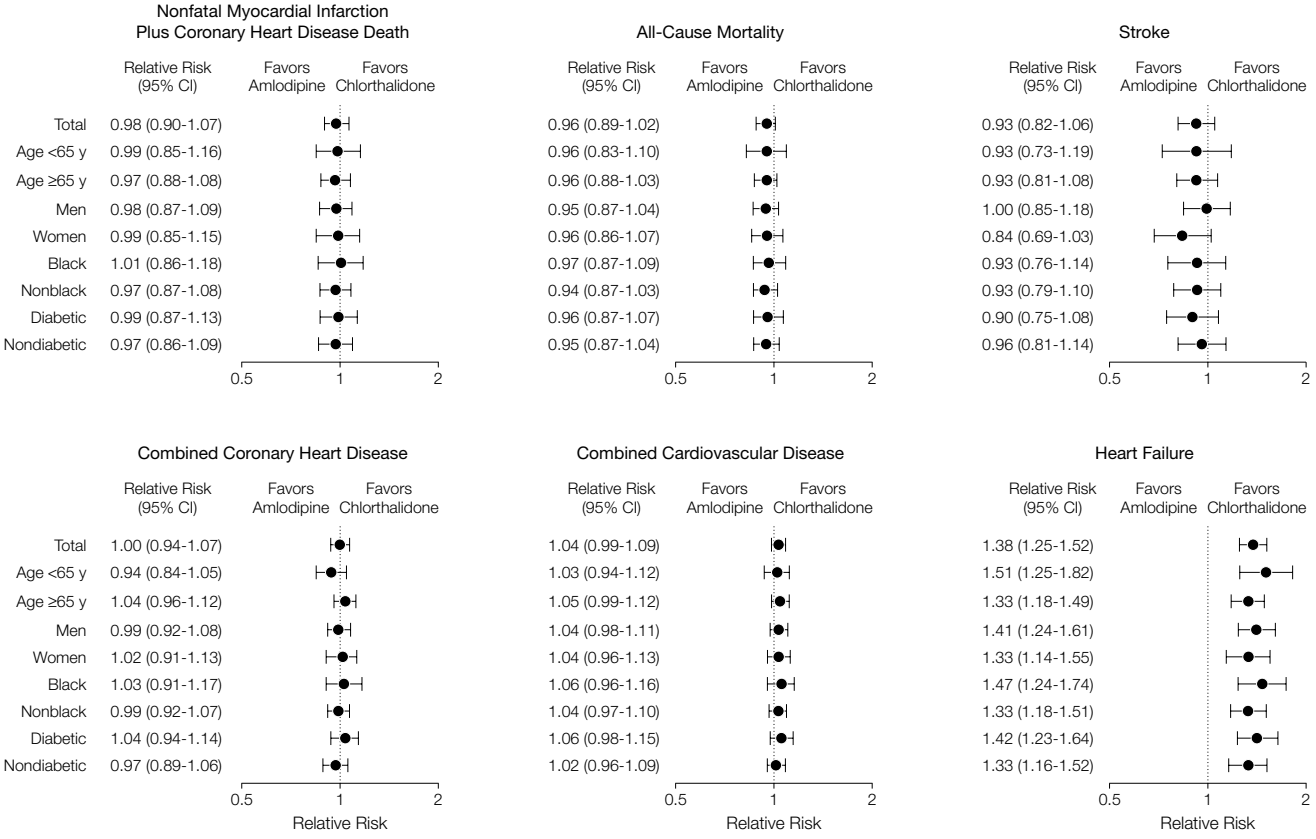
No. at Risk

Chlorthalidone	15255	14528	13898	13224	11511	6369	3016	384
Amlodipine	9048	8535	8185	7801	6785	3775	1780	210
Lisinopril	9054	8496	8096	7689	6698	3789	1837	313

Chlorthalidone	15255	14556	13962	13312	11606	6443	3130	396
Amlodipine	9048	8579	8251	7884	6866	3833	1821	216
Lisinopril	9054	8538	8169	7780	6768	3895	1894	322

with BP differences based on single-visit (or even visit-averaged) measurements.[45] Such modeling is also unable to account for differences among individuals due to other unmeasured or poorly represented risk factors; thus, participants who lower their BP by a given amount with one drug may not be comparable to those who lower their

Figure 5. Relative Risks and 95% Confidence Intervals (CIs) for Amlodipine/Chlorthalidone Comparisons in Prespecified Subgroups



Scales are shown in natural logarithm.

Table 6. Causes of Death by Antihypertensive Treatment Group*

	No. (6-Year Rate per 100 Persons)			*P* Value	
	Chlorthalidone (n = 15 255)	Amlodipine (n = 9048)	Lisinopril (n = 9054)	Amlodipine vs Chlorthalidone	Lisinopril vs Chlorthalidone
Total deaths	2187 (17.1)	1237 (16.5)	1303 (17.0)	.12	.90
Cardiovascular	992 (8.0)	592 (8.4)	609 (8.4)	.98	.53
Myocardial infarction	298 (2.4)	168 (2.3)	157 (2.2)	.56	.22
Definite CHD	118 (1.1)	74 (1.2)	78 (1.1)	.73	.47
Possible CHD	123 (1.1)	69 (1.1)	93 (1.4)	.68	.08
Stroke	163 (1.4)	91 (1.4)	116 (1.6)	.62	.14
Heart failure	116 (1.1)	79 (1.3)	68 (1.1)	.36	.92
Other CVD	174 (1.4)	111 (1.7)	97 (1.5)	.58	.62
Noncardiovascular	1058 (8.9)	559 (7.8)	606 (8.3)	.02	.47
Cancer	513 (4.3)	280 (3.7)	297 (4.0)	.23	.72
Kidney disease	36 (0.4)	23 (0.5)	28 (0.5)	.80	.29
Unintentional injury/suicide/homicide	65 (0.6)	18 (0.3)	27 (0.4)	.004	.12
Other non–CVD	444 (3.9)	238 (3.6)	254 (3.7)	.18	.62
Unknown	137 (1.2)	86 (1.2)	88 (1.3)	.72	.58

*CHD indicates coronary heart disease; CVD, cardiovascular disease.

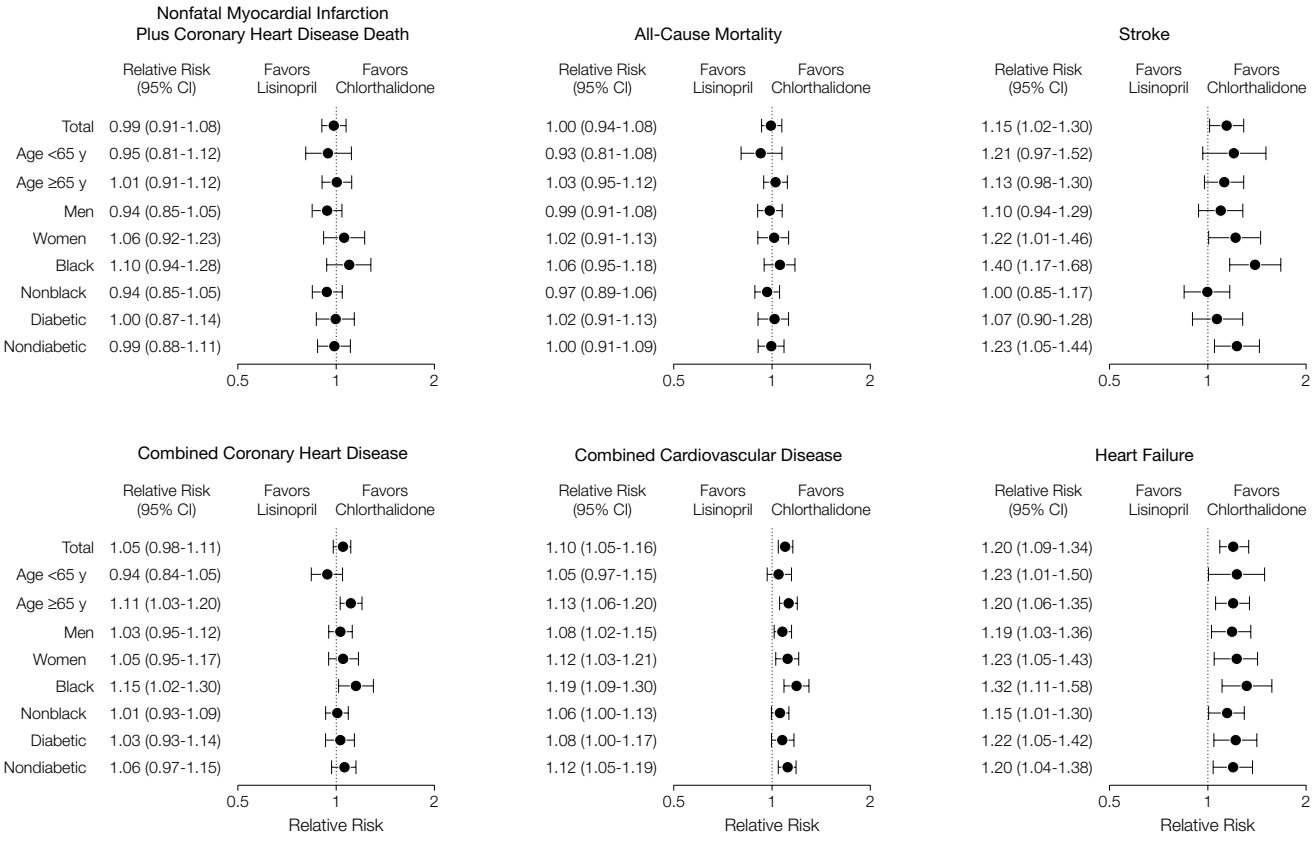
BP by the same magnitude with another drug.

Using an external standard of pooled results of long-term hypertension treatment trials and observational studies (10-12 mm Hg systolic BP difference associated with 38% stroke reduction), a 2- to 3-mm Hg difference in BP might account for a 6% to 12% difference in stroke rates.[45,46] This is consistent with the observed 15% difference for stroke overall but not with the difference seen in black patients (13%-16% expected, 40% observed). For the HF outcome, trial results in isolated systolic hypertension suggest that a 3-mm Hg higher systolic BP could explain a 10% to 20% increase in risk.[8,47] The forgoing ignores the absence of a diastolic BP difference in ALLHAT; however, the relationship of diastolic pressure and CVD events in elderly persons who often have increased pulse pressure is not entirely clear.[48]

The primary and secondary outcome results for the amlodipine vs chlorthalidone group comparisons were consistent for all subgroups of participants: older and younger, men and women, black and nonblack, diabetic and nondiabetic. For the lisinopril vs chlorthalidone comparisons, results were generally consistent by age, sex, and diabetic status. Thus, for the important diabetic population, lisinopril appeared to have no special advantage (and amlodipine no particular detrimental effect) for most CVD and renal outcomes when compared with chlorthalidone. In fact, chlorthalidone was superior to lisinopril for several CVD outcomes and superior to amlodipine for HF in both diabetic and nondiabetic participants. The consistency of the ALLHAT findings across multiple patient subgroups provides confidence in the ability to generalize the findings to most patients with hypertension.

In the lisinopril vs chlorthalidone comparisons, there were 2 outcomes with significant interactions. The greater differences observed in black vs nonblack patients for combined CVD and stroke, along with a similar trend for HF and lesser BP lowering with lisinopril, are in accord with the multiple reports of poorer BP response with ACE inhibitor in black patients.[49-51] They are also consistent with reports of lesser effects of ACE inhibitors in secondary prevention of HF in this population,[52,53] although these findings have been recently questioned.[54] The differential responses for disease outcomes parallel the lesser response in the black subgroup for BP, although the differences in outcomes are not substantially reduced by statistically adjusting for systolic BP.

Figure 6. Relative Risks and 95% Confidence Intervals (CIs) for Lisinopril/Chlorthalidone Comparisons in Prespecified Subgroups



Scales are shown in natural logarithm.

Although subordinate to safety and efficacy, the cost of drugs and medical care for the individual and society is a factor that should be considered in the selection of antihypertensives. One of the stated objectives of ALLHAT was to answer the question, "Are newer types of antihypertensive agents, which are currently more costly, as good or better than diuretics in reducing CHD incidence and progression?"[18] Consideration of drug cost could have a major impact on the nation's health care expenditures. Based on previous data that showed that diuretic use declined from 56% to 27% of antihypertensive prescriptions between 1982 and 1992, the health care system would have saved $3.1 billion in estimated cost of antihypertensive drugs had the pattern of prescriptions for treatment of hypertension remained at the 1982 level.[55] Further economic analyses based on the results of ALLHAT are under way.

The strengths of ALLHAT include its randomized double-blind design, statistical power to detect clinically meaningful differences in CVD outcomes of interest, diverse population with adequate representation from subgroups of special interest in the treatment of hypertension, and varied practice-based settings. In addition, the agents that were directly compared represent 3 of the most commonly used newer classes of antihypertensives vs the best studied of the older classes.

Some limitations are worth noting. After ALLHAT was designed, newer agents have been or may soon be released (eg, angiotensin-receptor blockers, selective aldosterone antagonists), which were not evaluated. Although clinical centers were blinded to the regimen and urged to achieve recommended BP goals, equivalent BP reduction was not fully achieved in the treatment groups. Furthermore, because diuretics, ACE inhibitors, CCBs, and α-blockers were evaluated in the trial, the agents available for step-up led to a somewhat artificial regimen (use of sympatholytics rather than diuretics and CCBs) of step-up drugs in the ACE inhibitor group. This may have contributed to the higher BPs in the ACE inhibitor group, especially in the black subgroup. However, mean follow-up BPs were well below 140/90 mm Hg in all treatment groups. Although ALLHAT did not compare a β-blocker to chlorthalidone, previous trials have suggested equivalence[45] or even inferiority[3] for major CVD events.

The ALLHAT results apply directly to chlorthalidone, amlodipine, and lisinopril. Combined with evidence from other trials, we infer that the findings also broadly apply to the drug classes (or subclass in the case of the dihydropyridine CCBs) that the study drugs represent. The evidence base for selection of antihypertensive agents has been markedly strengthened by the addition of ALLHAT.

In conclusion, the results of ALLHAT indicate that thiazide-type diuretics should be considered first for pharmacologic therapy in patients with hypertension. They are unsurpassed in lowering BP, reducing clinical events, and tolerability, and they are less costly. For patients who cannot take a diuretic (which should be an unusual circumstance), first-step therapy with CCBs and ACE inhibitors could be considered with due regard for their higher risk of 1 or more major manifestations of CVD. Since a large proportion of participants required more than 1 drug to control their BP, it is reasonable to infer that a diuretic be included in all multidrug regimens, if possible. Although diuretics already play a key role in most antihypertensive treatment recommendations, the findings of ALLHAT should be carefully evaluated by those responsible for clinical guidelines and be widely applied in patient care.

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CORRECTIONS

Incorrect Byline: In the Original Contribution entitled "Myocardial Perfusion Imaging for Evaluation and Triage of Patients With Suspected Acute Cardiac Ischemia: A Randomized Controlled Trial" published in the December 4, 2002, issue of THE JOURNAL (2002;288:2693-2700), the order of authors in the byline was incorrect. Jonathan Handler, MD, should have been listed between John L. Griffith, PhD, and Gary V. Heller, MD, PhD.

Incorrect Data in Table: In the Original Contribution entitled "Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)" published in the December 18, 2002, issue of THE JOURNAL (2002;288:2981-2997), there were incorrect data in **TABLE 6**. This table replaces the one on page 2992. The new data do not affect the results or conclusions of the original article.

Table 6. Causes of Death by Antihypertensive Treatment Group*

	No. (6-Year Rate per 100 Persons)			*P* Value	
	Chlorthalidone (n = 15 255)	Amlodipine (n = 9048)	Lisinopril (n = 9054)	Amlodipine vs Chlorthalidone	Lisinopril vs Chlorthalidone
Total deaths	2203 (17.3)	1256 (16.8)	1314 (17.2)	.20	.90
Cardiovascular	996 (8.0)	603 (8.5)	618 (8.5)	.76	.39
Myocardial infarction	296 (2.4)	169 (2.3)	157 (2.2)	.66	.25
Definite CHD	118 (1.1)	72 (1.2)	77 (1.0)	.88	.52
Possible CHD	128 (1.1)	71 (1.1)	95 (1.4)	.62	.10
Stroke	162 (1.4)	92 (1.4)	121 (1.7)	.71	.06
Heart failure	114 (1.0)	83 (1.4)	68 (1.1)	.17	.98
Other CVD	178 (1.4)	116 (1.7)	100 (1.5)	.46	.66
Noncardiovascular	1067 (8.9)	571 (8.0)	616 (8.6)	.04	.57
Cancer	515 (4.3)	285 (3.8)	302 (4.1)	.31	.86
Kidney disease	36 (0.4)	24 (0.5)	27 (0.5)	.68	.37
Unintentional injury/suicide/homicide	66 (0.6)	19 (0.4)	28 (0.4)	.005	.14
Other non–CVD	450 (4.0)	243 (3.7)	259 (3.9)	.21	.68
Unknown	140 (1.2)	82 (1.2)	80 (1.1)	.89	.78

*CHD indicates coronary heart disease; CVD, cardiovascular disease.

in digestion, absorption, and metabolism further increase demand and decrease utilization of critical nutrients. When restricted diets are necessary, alternative methods of delivering essential nutrients should be considered.

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CORRECTION

Investigator Omitted: In the Original Contribution entitled "Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)" published in the December 18, 2002, issue of THE JOURNAL (2002;288:2981-2997), Pasquale F. Nestico, MD, was inadvertently omitted from the list of ALLHAT investigators. His name should appear on page 2996 under "Pennsylvania."