Outcomes in Hypertensive Black and Nonblack Patients Treated With Chlorthalidone, Amlodipine, and Lisinopril

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CARDIOVASCULAR DISEASE (CVD) has become the leading cause of morbidity and mortality worldwide, and elevated blood pressure (BP) is a leading contributor to this phenomenon.1,2 The population of blacks with hypertension has the highest morbidity and mortality from hypertension of any population group in the United States and is among the highest in the world.3,4 Mortality related to hypertension and the risk of end-stage renal disease (ESRD), coronary heart disease (CHD), heart failure (HF), and stroke are increased in the black compared with the white population in the United States.4,5 While the benefits of lower-

Context Few cardiovascular outcome data are available for blacks with hypertension treated with angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers (CCBs).

Objective To determine whether an ACE inhibitor or CCB is superior to a thiazide-type diuretic in reducing cardiovascular disease (CVD) incidence in racial subgroups.

Design, Setting, and Participants Prespecified subgroup analysis of ALLHAT, a randomized, double-blind, active-controlled, clinical outcome trial conducted between February 1994 and March 2002 in 33 357 hypertensive US and Canadian patients aged 55 years or older (35% black) with at least 1 other cardiovascular risk factor.

Interventions Antihypertensive regimens initiated with a CCB (amlodipine) or an ACE inhibitor (lisinopril) vs a thiazide-type diuretic (chlorthalidone). Other medications were added to achieve goal blood pressures (BPs) less than 140/90 mm Hg.

Main Outcome Measures The primary outcome was combined fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI), analyzed by intention-to-treat. Secondary outcomes included all-cause mortality, stroke, combined CVD (CHD death, nonfatal MI, stroke, angina, coronary revascularization, heart failure [HF], or peripheral vascular disease), and end-stage renal disease.

Results No significant difference was found between treatment groups for the primary CHD outcome in either racial subgroup. For amlodipine vs chlorthalidone only, HF was the only prespecified clinical outcome that differed significantly (overall: relative risk [RR], 1.37; 95% confidence interval [CI], 1.24-1.51; blacks: RR, 1.46; 95% CI, 1.24-1.73; nonblacks: RR, 1.32; 95% CI, 1.17-1.49; P < .001 for each comparison) with no difference in treatment effects by race (P = .38 for interaction). For lisinopril vs chlorthalidone, results differed by race for systolic BP (greater decrease in blacks with chlorthalidone), stroke, and combined CVD outcomes (P < .001, P = .1, and P = .04, respectively, for interactions). In blacks and nonblacks, respectively, the RRs for stroke were 1.40 (95% CI, 1.10-1.80) and 1.00 (95% CI, 0.85-1.17) and for combined CVD were 1.19 (95% CI, 1.09-1.30) and 1.06 (95% CI, 1.00-1.13). For HF, the RRs were 1.30 (95% CI, 1.10-1.54) and 1.13 (95% CI, 1.00-1.28), with no significant interaction by race. Time-dependent BP adjustment did not significantly alter differences in outcome for lisinopril vs chlorthalidone in blacks.

Conclusions In blacks and nonblack subgroups, rates were not lower in the amlodipine or lisinopril groups than in the chlorthalidone group for either the primary CHD or any other prespecified clinical outcome, and diuretic-based treatment resulted in the lowest risk of heart failure. While the improved outcomes with chlorthalidone were more pronounced for some outcomes in blacks than in nonblacks, thiazide-type diuretics remain the drugs of choice for initial therapy of hypertension in both black and nonblack hypertensive patients.

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For editorial comment see p 1663.
METHODS

Eligibility

The rationale and design of ALLHAT have been presented elsewhere.\textsuperscript{13} Participants were men and women, aged 55 years or older, who had untreated systolic (≥140 mm Hg) and/or diastolic (≥90 mm Hg) hypertension (but ≤180/110 mm Hg at 2 visits) or treated hypertension (≥160/100 mm Hg while receiving 1-2 antihypertensive drugs at visit 1 and ≤180/110 mm Hg at visit 2 when medication may have been withdrawn) with at least 1 additional risk factor for CHD events.\textsuperscript{15,21} The risk factors included left ventricular hypertrophy (LVH) by echocardiography or electrocardiography, history of type 2 diabetes, current cigarette smoking, high-density lipoprotein cholesterol level less than 35 mg/dL (0.9 mmol/L), previous (>6 months) myocardial infarction (MI) or stroke, and documentation of other atherosclerotic CVD. Individuals with a history of hospitalized or treated symptomatic HF, serum creatinine level less than 2.0 mg/dL (176.8 µmol/L), and/or known left ventricular ejection fraction less than 35% were excluded. Race was defined by self-report as black, white, Asian, Native American, and other; the last 4 categories are combined for this report as nonblack (92% white). All participants gave written informed consent, all centers obtained institutional review board approval, and the trial was monitored by a National Heart, Lung, and Blood Institute–appointed data and safety monitoring board.

Enrollment and Study Organization

Unless the drug regimen required tapering for safety reasons, individuals discontinued any prior antihypertensive medications only when they received randomized study drug. Participants included in this report were randomized to receive chlorthalidone, amlodipine, or lisinopril in a ratio of 1.7:1:1, respectively (FIGURE 1). Since all groups were compared with the diuretic, this ratio was chosen to maximize statistical power for a 4-group trial. The concealed randomization scheme was generated by computer at the clinical trials center, stratified by center, and blocked in randomly ordered 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.\textsuperscript{11} The closeout phase began October 1, 2001, and ended March 31, 2002. The range of follow-up was 3 years 8 months to 8 years 1 month. Mean follow-up was 4.9 years.

Intervention and Follow-up

Trained observers using standardized techniques measured BPs during the trial.\textsuperscript{22} Visit BP was the average of 2 seated measurements separated by 30 seconds. Goal BP for all participants 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. Step 1 drugs were identically encapsulated so that each agent was double-masked at each dosage level. Dosages were 12.5, 25, 50, and 10 mg/d for chlorthalidone; 2.5, 5, and 10 mg/d for amlodipine; and 10, 20, and 40 mg/d for lisinopril. The study supplied open-label atenolol, reserpine, and clonidine at step 2, and hydralazine for step 3, if needed for BP control. The choice of step 2 and 3 medications was at the investigator’s discretion. Slow-release potassium chloride was provided for serum potassium levels consistently less than 3.5 mEq/L. After initial monthly titration visits, participants were seen every 3 months during the first year and every 4 months thereafter. Visit adherence was determined by the percentage of participants appearing for their protocol visit within the visit window.

Outcomes

The primary outcome was the combination of fatal CHD and nonfatal MI.\textsuperscript{13} Four major prespecified secondary outcomes were (1) all-cause mortality, (2) fatal and nonfatal stroke, (3) combined CHD (≥1 of the primary outcome, coronary revascularization, or hospitalized angina), and (4) com-
bined CVD (≥1 of combined CHD, fatal or nonfatal stroke, nonhospitalized treated angina, HF [fatal, hospitalized, or treated nonhospitalized], and treated peripheral arterial disease). Individual components of combined outcomes were also examined. Other pre-specified secondary outcomes included incident cancer, first hospitalization for gastrointestinal bleeding, incident electrocardiographic LVH, and ESRD (dialysis, renal transplant, or renal death). Change in estimated glomerular filtration rate was examined post hoc, and results for incident LVH will be reported separately.

Study end points were assessed at follow-up visits and reported to the clinical trials center. Hospitalized outcomes were primarily based on clinic investigator reports, with copies of death certificates and hospital discharge summaries requested for central review. Among all combined CVD events that resulted in deaths and/or hospitalizations, 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 & Medicaid Services, the Department of Veterans Affairs, the National Death Index, and the Social Security Administration databases. Clinical trials center medical reviewers verified the clinician-assigned diagnoses of outcomes using death certificates and hospital discharge summaries. More detailed information was collected on random (10% subset) CHD and stroke events to validate the procedure of using clinician diagnoses. When a large excess of HF became evident in the doxazosin group, 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 end point, 84% (129/153) for stroke, and 85% (33/39) for HF hospitalizations and were similar in all treatment groups. Subsequent blinded review of 98% of the HF hospitalizations in 97% of the participants with HF has confirmed the validity of this outcome.

**Statistical Methods**

ALLHAT was designed as a superiority trial. Based on its anticipated sample size, assumptions of expected event

### Table: Randomization and Follow-up of ALLHAT Participants

<table>
<thead>
<tr>
<th>Status at Study Closeout</th>
<th>Year 1</th>
<th>Year 5</th>
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<tr>
<td><strong>Black Patients</strong></td>
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<td>4797 Completed Visit</td>
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<td>784 Discontinued Study Drug</td>
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<td>11 Mortal Event</td>
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<td>28 Other</td>
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<tr>
<td>19 Refused Follow-up</td>
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</table>

ALLHAT indicates Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.

*Patients could have more than 1 reason for discontinuation of study drug.

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rate, treatment crossovers, and losses to follow-up, ALLHAT had 83% power to detect a 16% reduction in risk of the primary outcome between the chlorthalidone group and each other group at a 2-sided α of .05/3, or .0178 (z = 2.37) to account for the 3 original comparisons. Baseline characteristics and intermediate outcomes were compared across treatment within baseline racial classification using analysis of variance for continuous covariates and contingency table analyses for categorical data. Data were analyzed according to participants’ randomized treatment assignments regardless of their subsequent medications (ie, intention-to-treat analysis). Six-year cumulative event rates were calculated using the Kaplan-Meier procedure. Cox proportional hazards models were used to obtain hazard ratios (hereafter termed relative risks [RRs]) and 95% confidence intervals (CIs) for time-to-event outcomes and included the participant’s entire trial experience. The proportional hazards assumption was examined by using log-log plots and testing a treatment × time (time-dependent) interaction term; if the assumption was violated, the RR estimate from a cumulative incidence analysis of a 2 × 2 table (ie, event/no event vs amloidipine/chlorthalidone or lisinopril/chlorthalidone) or an alternative Cox regression model that included a treatment × time interaction term was used. In the case of HF, the model used a treatment × time indicator variable (≤1 year vs >1 year).

For the published main ALLHAT results, the HF outcomes for the total group were obtained using 2 × 2 tables, but the results for the subgroups used the results from the Cox regression analyses. For this analysis, the proportional hazards assumption was also violated within the black and nonblack subgroups, so the subgroup results obtained using 2 × 2 tables are reported. Heterogeneity of treatment effects across racial subgroups was examined by testing for treatment × race interaction with the proportional hazards model (or in a logistic model if the proportional hazards assumption was violated) using \( P < .05 \). Where there were significant differences in baseline characteristics by race, these were included as covariates in adjusted models. Given the many multivariate, subgroup, and interaction analyses performed, statistical significance at the .05 level should be interpreted with caution.

To adjust for observed BP differences over time between treatment groups, Cox proportional hazards models with systolic BPs (SBPs) and diastolic BPs (DBPs) as time-varying covariates were used. The time-dependent analyses were performed both with no imputation for missing values and with multiple imputation for the missing SBP and DBP observations. Since the results with and without imputation were similar, the results without imputation for missing values are presented. Stata version 8 (Stata Corp, College Station, Tex) was used for all analyses.

**RESULTS**

Baseline Findings

The baseline characteristics of the ALLHAT study population by race and treatment group are shown in Table I. Compared with nonblacks, black participants were more likely to be women (55% vs 43%), have diabetes (46% vs 39%), smoke cigarettes (25% vs 20%), and have electrocardiographic LVH (24% vs 12%). Black participants were also slightly younger, had higher levels of high-density lipoprotein cholesterol, and were less likely to have a history of CHD, atherosclerotic disease, or both. Baseline BP levels were similar in the black and nonblack subgroups (146/85 and 146/84 mm Hg, respectively), and within subgroups no differences were noted across the 3 treatment groups in baseline BP or in distribution by age, risk factor levels, and history of CVD.

Visit and Medication Adherence by Race

Visit adherence was slightly lower for blacks than nonblacks. For nonblacks, 93% of expected follow-up visits were completed in each of the 3 treatment groups at 1 year, while the corresponding rates were 89% to 91% for blacks. At year 5, 86% to 89% (across treatment groups) of expected visits were completed for nonblacks, while the rates for blacks were 80% to 84%. Of those seen, 83% to 84% of both racial subgroups randomized to receive chlorthalidone or amloidipine were still receiving the blinded drug at year 1 (87%-89% for each treatment group if drugs of the same class are included). At year 5, 71% to 73% were still receiving the blinded study drug (80%-81% were receiving drugs of the same class as the blinded study drug). Among those randomized to receive lisinopril, for nonblacks and blacks respectively, 78% vs 76% were still receiving blinded study drug at year 1 and 63% vs 57% at year 5. Including any ACE inhibitor, the rates were 83% vs 81% at year 1 and 74% vs 69% at year 5 for nonblacks and blacks, respectively.

**Intermediate Outcomes**

Nonblacks assigned to receive chlorthalidone or amloidipine had progressive BP declines to approximately 134/76 mm Hg by the end of 4 years of follow-up (Table 2). In black participants, amloidipine produced a decline in DBP similar to that produced by chlorthalidone, although SBP decline with amloidipine was approximately 2 mm Hg less. The BP decline in nonblacks randomized to receive lisinopril was also similar to that for those receiving chlorthalidone, with less than 1 mm Hg separating the treatment groups at 4 years. Blood pressure decline while receiving lisinopril was significantly less in blacks compared with nonblacks and less than in blacks randomized to receive chlorthalidone, especially during the early time periods. At 2 years, blacks experienced a 5/2-mm Hg greater BP reduction on average with chlorthalidone than with lisinopril; this difference decreased to 4/1 mm Hg at 4 years. Among nonblacks, BP’s averaged over 5 years of follow-up were 137/78 mm Hg in the chlorthalidone and amloidipine groups, respectively, and 138/78 mm Hg.
Table 1. Baseline Characteristics by Race and Treatment Group

<table>
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<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>All Black</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
<th>Lisinopril</th>
<th>All Nonblack</th>
<th>Chlorthalidone</th>
<th>Amlodipine</th>
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<td>66.3 (7.8)</td>
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<td>67.3 (7.6)</td>
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<td>67.2 (7.6)</td>
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<td>16.6</td>
<td>17.0</td>
<td>17.4</td>
<td>28.8</td>
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<td>44.6 (13.7)</td>
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<td>1508</td>
<td>4.5</td>
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</table>

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction.

*All results are presented as percentages of the number of participants randomized to the treatment groups unless otherwise indicated. Left ventricular hypertrophy by echocardiogram (P = .02) and treatment (P = .06) are the only variables in the table for which the total black vs total nonblack comparison is not statistically different. For each of the other variables, the P value for the black vs nonblack comparison is <.001.

†Diabetes was defined as history of diabetes at baseline or fasting glucose level ≥126 mg/dL (7.0 mmol/L); impaired fasting glucose, as no history and baseline fasting glucose level of 110 to 125 mg/dL (6.1-6.9 mmol/L), inclusive; and normoglycemic, as not classified as impaired fasting glucose, no history, and fasting glucose and/or nonfasting glucose level <110 mg/dL.

‡Participants randomized to the ALLHAT Lipid Trial, an open-label subset of pravastatin vs usual care in participants with elevated cholesterol levels.

§History of CHD is by self-report. Other atherosclerotic CVD is any of the following: 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 thallium or dipyridamole thallium; ST-segment depression ≥1 mm for ≥1 min during exercise testing or Holter monitoring; reversible wall-motion abnormality on stress echocardiogram; ankle-arm index <0.9; abdominal aortic aneurysm detected by ultrasoundography, computed tomography scan, or radiograph; or carotid or femoral bruits.

| Value for the black vs nonblack comparison is | .001. |
Table 2. Blood Pressure and Fasting Glucose Levels at Baseline and Follow-up*

<table>
<thead>
<tr>
<th></th>
<th>Black Chlorthalidone</th>
<th>Black Amlodipine</th>
<th>Black Lisinopril</th>
<th>Nonblack Chlorthalidone</th>
<th>Nonblack Amlodipine</th>
<th>Nonblack Lisinopril</th>
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<td><strong>Blood Pressure Measures</strong></td>
<td></td>
<td></td>
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<td>No. of participants</td>
<td>5369</td>
<td>3213</td>
<td>3210</td>
<td>9886</td>
<td>5835</td>
<td>5844</td>
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<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>4439</td>
<td>2646</td>
<td>2581</td>
<td>8425</td>
<td>4963</td>
<td>4940</td>
</tr>
<tr>
<td>2 y</td>
<td>3949</td>
<td>2347</td>
<td>2246</td>
<td>7791</td>
<td>4536</td>
<td>4454</td>
</tr>
<tr>
<td>4 y</td>
<td>3145</td>
<td>1895</td>
<td>1741</td>
<td>6237</td>
<td>3742</td>
<td>3584</td>
</tr>
<tr>
<td>SBP, mean (SD), mm Hg</td>
<td>146.3 (15.7)</td>
<td>146.1 (15.9)</td>
<td>146.2 (15.8)</td>
<td>146.2 (15.6)</td>
<td>146.3 (15.6)</td>
<td>146.5 (15.4)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>−7.7 (19.2)</td>
<td>−5.7 (19.4)</td>
<td>−2.5 (21.8)</td>
<td>−9.8 (18.4)</td>
<td>−8.4 (18.5)</td>
<td>−8.1 (19.9)</td>
</tr>
<tr>
<td>2 y</td>
<td>−8.6 (20.1)</td>
<td>−7.1 (19.9)</td>
<td>−3.4 (22.0)</td>
<td>−10.6 (18.9)</td>
<td>−9.8 (18.8)</td>
<td>−9.5 (19.7)</td>
</tr>
<tr>
<td>4 y</td>
<td>−10.5 (20.4)</td>
<td>−8.8 (20.3)</td>
<td>−6.8 (22.4)</td>
<td>−12.3 (19.4)</td>
<td>−12.3 (19.2)</td>
<td>−12.0 (20.0)</td>
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<tr>
<td>DBP, mean (SD), mm Hg</td>
<td>84.9 (10.1)</td>
<td>84.7 (10.3)</td>
<td>84.9 (10.2)</td>
<td>83.5 (10.0)</td>
<td>83.5 (10.1)</td>
<td>83.7 (9.9)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>−3.9 (11.0)</td>
<td>−4.1 (11.2)</td>
<td>−2.3 (12.0)</td>
<td>−4.7 (10.8)</td>
<td>−5.6 (10.6)</td>
<td>−4.9 (10.9)</td>
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<tr>
<td>2 y</td>
<td>−5.0 (11.5)</td>
<td>−5.2 (11.5)</td>
<td>−3.4 (12.1)</td>
<td>−5.8 (11.0)</td>
<td>−6.6 (11.0)</td>
<td>−6.1 (11.0)</td>
</tr>
<tr>
<td>4 y</td>
<td>−6.6 (11.6)</td>
<td>−6.6 (11.7)</td>
<td>−5.6 (12.7)</td>
<td>−7.6 (11.5)</td>
<td>−8.7 (11.3)</td>
<td>−8.0 (11.5)</td>
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<tr>
<td>Blood pressure &lt;140/90 mm Hg, No. (%)</td>
<td>1449 (27.0)</td>
<td>900 (28.0)</td>
<td>837 (26.1)</td>
<td>2705 (27.4)</td>
<td>1596 (27.3)</td>
<td>1546 (26.5)</td>
</tr>
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<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 y</td>
<td>2364 (53.3)</td>
<td>1336 (50.5)</td>
<td>1085 (42.0)</td>
<td>5068 (60.2)</td>
<td>2862 (67.7)</td>
<td>2717 (55.0)</td>
</tr>
<tr>
<td>2 y</td>
<td>2254 (57.1)</td>
<td>1213 (51.7)</td>
<td>993 (44.2)</td>
<td>4903 (62.9)</td>
<td>2735 (60.3)</td>
<td>2634 (59.1)</td>
</tr>
<tr>
<td>4 y</td>
<td>1994 (63.4)</td>
<td>1140 (60.2)</td>
<td>943 (54.2)</td>
<td>4296 (68.9)</td>
<td>2567 (68.6)</td>
<td>2417 (67.4)</td>
</tr>
<tr>
<td><strong>Fasting Glucose‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No. of participants</td>
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<td>2180</td>
<td>2200</td>
<td>7636</td>
<td>4484</td>
<td>4575</td>
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<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 y</td>
<td>1757</td>
<td>1052</td>
<td>969</td>
<td>4223</td>
<td>2454</td>
<td>2364</td>
</tr>
<tr>
<td>4 y</td>
<td>1458</td>
<td>873</td>
<td>783</td>
<td>3514</td>
<td>2081</td>
<td>1948</td>
</tr>
<tr>
<td>Baseline, mean (SD), mg/dL</td>
<td>127.2 (66.2)</td>
<td>126.3 (61.9)</td>
<td>126.8 (62.3)</td>
<td>121.7 (64.7)</td>
<td>121.5 (64.2)</td>
<td>120.8 (52.4)</td>
</tr>
<tr>
<td>Baseline if have 2-y follow-up</td>
<td>122.6 (57.8)</td>
<td>122.9 (55.7)</td>
<td>123.1 (66.2)</td>
<td>118.8 (50.4)</td>
<td>118.7 (51.1)</td>
<td>118.1 (48.7)</td>
</tr>
<tr>
<td>2 y</td>
<td>130.2 (64.0)</td>
<td>128.0 (64.1)</td>
<td>124.3 (61.7)</td>
<td>126.4 (67.0)</td>
<td>119.9 (49.1)</td>
<td>119.4 (50.4)</td>
</tr>
<tr>
<td>4 y</td>
<td>129.6 (63.0)</td>
<td>126.1 (56.4)</td>
<td>124.6 (59.7)</td>
<td>125.0 (52.2)</td>
<td>122.7 (50.0)</td>
<td>120.2 (47.4)</td>
</tr>
<tr>
<td>Change from baseline, mean (SD), mg/dL †</td>
<td>7.3 (57.0)</td>
<td>5.2 (60.9)</td>
<td>1.9 (57.0)</td>
<td>7.7 (47.7)</td>
<td>1.1 (42.2)</td>
<td>1.3 (43.9)</td>
</tr>
<tr>
<td>2 y</td>
<td>6.9 (64.8)</td>
<td>6.0 (59.7)</td>
<td>2.3 (59.7)</td>
<td>5.5 (52.5)</td>
<td>3.6 (48.4)</td>
<td>2.1 (43.4)</td>
</tr>
<tr>
<td>Fasting glucose ≥126 mg/dL, No. (%)</td>
<td>1133 (30.9)</td>
<td>686 (31.5)</td>
<td>691 (31.4)</td>
<td>2144 (28.1)</td>
<td>1262 (28.1)</td>
<td>1293 (28.3)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 y</td>
<td>616 (35.1)</td>
<td>355 (33.8)</td>
<td>280 (28.9)</td>
<td>1351 (32.0)</td>
<td>694 (28.3)</td>
<td>666 (28.2)</td>
</tr>
<tr>
<td>4 y</td>
<td>493 (33.8)</td>
<td>286 (32.8)</td>
<td>222 (28.4)</td>
<td>1133 (32.2)</td>
<td>616 (29.8)</td>
<td>561 (28.8)</td>
</tr>
</tbody>
</table>

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.  
SI conversion factor: To convert glucose values to mmol/L, multiply by 0.0555.  
*The only total black vs total nonblack comparisons at baseline that are not significant are SBP (P = .72) and blood pressure/H11021 140/90 mm Hg (P = .86).  
†Mean changes are calculated using only those participants who have a value both at baseline and at the indicated year of follow-up. All other means are calculated for all participants at the designated time point.  
‡The number of participants with fasting glucose values is smaller than the numbers for the other measurements because the participants frequently arrived nonfasting and were asked to return fasting but did not. The mean at baseline was also calculated for fasting glucose levels for only those participants who had a fasting glucose level at the 2-year follow-up. Thus, the mean changes are calculated only for participants with measurements at both time points.
The change in the cholesterol levels at 4 years for chlorthalidone vs amlo
dipine did not differ between blacks and nonblacks.

**Clinical Outcomes**

Overall, 6-year event rates were significantly lower in black vs nonblack participants for the primary outcome, nonfatal MI plus fatal CHD (9.7% vs 12.3%, *P* < .001), combined CHD (15.9% vs 22.5%, *P* < .001), and combined CVD (28.4% vs 33.7%, *P* < .001). Black participants had significantly higher rates of stroke (6.5% vs 5.3%, *P* < .001) and ESRD (2.6% vs 1.5%, *P* < .001) and higher overall mortality (17.7% vs 16.8%, *P* = .003). These differences are unadjusted for the numerous baseline differences between blacks and nonblacks.

The treatment comparisons by racial subgroup for the prespecified clinical outcomes are shown in **Table 5**.

### Table 3. Potassium, Cholesterol, and Creatinine Levels at Baseline and Follow-up*

<table>
<thead>
<tr>
<th></th>
<th>Black</th>
<th>Nonblack</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>Amlodipine</td>
</tr>
<tr>
<td><strong>Potassium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>5027</td>
<td>3001</td>
</tr>
<tr>
<td>2 y</td>
<td>3162</td>
<td>1925</td>
</tr>
<tr>
<td>4 y</td>
<td>2656</td>
<td>1591</td>
</tr>
<tr>
<td>Mean (SD), mEq/L</td>
<td>4.3 (0.7)</td>
<td>4.3 (0.7)</td>
</tr>
<tr>
<td>2 y</td>
<td>4.0 (0.6)</td>
<td>4.3 (0.7)</td>
</tr>
<tr>
<td>4 y</td>
<td>4.1 (0.7)</td>
<td>4.4 (0.8)</td>
</tr>
<tr>
<td>Potassium &lt;3.5 mEq/L, No. (%)</td>
<td>301 (6.0)</td>
<td>162 (5.4)</td>
</tr>
<tr>
<td>2 y</td>
<td>492 (15.6)</td>
<td>89 (4.6)</td>
</tr>
<tr>
<td>4 y</td>
<td>293 (11.0)</td>
<td>46 (2.9)</td>
</tr>
</tbody>
</table>

|                  |                    |                      |           |                    |                      |           |
| **Cholesterol**  |                    |                      |           |                    |                      |           |
| No. of participants | 5006       | 2991          | 2971       | 9551           | 5614        | 5630       |
| 2 y               | 3302         | 2011          | 1805       | 6904           | 4014        | 3934       |
| 4 y               | 2721         | 1631          | 1452       | 5774           | 3394        | 3259       |
| Mean (SD), mg/dL  | 217.6 (45.2)  | 217.5 (44.7)  | 216.7 (44.6) | 215.3 (42.8)  | 216.0 (43.7) | 215.0 (41.0) |
| 2 y               | 209.0 (44.4)  | 204.4 (43.3)  | 204.0 (45.6) | 203.6 (40.9)  | 201.5 (41.6) | 201.1 (41.5) |
| 4 y               | 202.0 (43.3)  | 199.3 (43.8)  | 197.5 (41.4) | 194.9 (41.3)  | 193.8 (39.5) | 193.9 (40.2) |
| Change from baseline, mean (SD), mg/dL | -9.1 (37.4) | -13.1 (37.4) | -13.2 (38.3) | -11.7 (37.4) | -14.0 (37.9) | -13.6 (37.5) |
| 2 y               | -15.6 (40.6)  | -17.6 (40.2)  | -20.9 (39.6) | -19.8 (40.6)  | -21.4 (40.3) | -21.3 (41.1) |
| Cholesterol $\geq$240 mg/dL, No. (%) | 1426 (28.5) | 839 (28.1)   | 799 (26.9)  | 2437 (25.5)    | 1452 (25.9)  | 1384 (24.4) |
| 2 y               | 729 (22.1)    | 380 (18.9)    | 341 (18.9)  | 1174 (17.0)    | 640 (15.9)   | 636 (16.2)  |
| 4 y               | 469 (17.2)    | 272 (16.7)    | 205 (14.1)  | 758 (13.1)     | 403 (11.9)   | 396 (12.2)  |

|                  |                    |                      |           |                    |                      |           |
| **Creatinine**   |                    |                      |           |                    |                      |           |
| No. of participants | 5007       | 3006          | 2992       | 9485           | 5583        | 5585       |
| 2 y               | 3162         | 1925          | 1721       | 6715           | 3869        | 3795       |
| 4 y               | 2656         | 1593          | 1418       | 5658           | 3331        | 3203       |
| Mean (SD), mg/dL  | 1.1 (0.4)    | 1.1 (0.3)     | 1.1 (0.3)  | 1.0 (0.3)      | 1.0 (0.3)   | 1.0 (0.3)  |
| 2 y               | 1.2 (0.5)    | 1.1 (0.5)     | 1.1 (0.5)  | 1.1 (0.3)      | 1.0 (0.3)   | 1.1 (0.3)  |
| 4 y               | 1.2 (0.6)    | 1.1 (0.7)     | 1.2 (0.7)  | 1.1 (0.4)      | 1.0 (0.4)   | 1.1 (0.4)  |

SI conversion factors: To convert cholesterol values to mmol/L, multiply by 0.0259; creatinine values to µmol/L, multiply by 88.4.

*All black vs nonblack comparisons were significant (*P* < .001) at baseline.

†Mean changes are calculated using only those participants who have a value both at baseline and at the indicated year of follow-up. All other means are calculated for all participants at the designated time point.
TABLE 6, and FIGURE 2. As previously reported, no difference was noted between treatment groups in the primary outcome of MI and fatal CHD in either racial subgroup. For amlo- dipine compared with chlorthalidone, a higher rate of HF (RR, 1.46 and 1.32 in blacks and nonblacks, respectively; 1.37 [95% CI, 1.24-1.51] overall) was the only prespecified clinical outcome that differed significantly in either subgroup. There was no evidence of

Table 4. Serious Adverse Events by Race*

<table>
<thead>
<tr>
<th></th>
<th>Black</th>
<th>Nonblack</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>Amlodipine</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>Amlodipine</td>
</tr>
<tr>
<td>No. of participants randomized</td>
<td>5369</td>
<td>3213</td>
</tr>
<tr>
<td>Total adverse events, No. (No. per 1000 participants)</td>
<td>38 (0.71)</td>
<td>20 (0.62)</td>
</tr>
<tr>
<td>Adverse events by body system, No. (% of participants)</td>
<td>14 (0.26)</td>
<td>9 (0.28)</td>
</tr>
<tr>
<td>Circulatory</td>
<td>2 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>0</td>
<td>1 (0.03)</td>
</tr>
<tr>
<td>Nervous system and sense organs</td>
<td>4 (0.07)</td>
<td>3 (0.09)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (0.04)</td>
<td>0</td>
</tr>
<tr>
<td>Angioedema, No. (% of participants)</td>
<td>2 (0.04)</td>
<td>2 (0.06)</td>
</tr>
<tr>
<td>Total participants with adverse events, No. (%)</td>
<td>30 (0.56)</td>
<td>16 (0.50)</td>
</tr>
</tbody>
</table>

*All rows present numbers of events except for the last row, which present numbers of participants; thus, an individual can appear in more than 1 category or more than once in the same category.

Table 5. Clinical Outcomes in Black Subgroup, by Antihypertensive Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>6-y Rate per 100 Persons</th>
<th>Cox Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>Amlodipine</td>
</tr>
<tr>
<td></td>
<td>No. Rate (SE)</td>
<td>No. Rate (SE)</td>
</tr>
<tr>
<td>Total randomized</td>
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<td>3213</td>
</tr>
<tr>
<td>Primary End Point</td>
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<td></td>
</tr>
<tr>
<td>CHD (nonfatal MI + fatal CHD)</td>
<td>400 9.6 (0.5)</td>
<td>243 9.5 (0.6)</td>
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<tr>
<td>Secondary End Points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>821 17.9 (0.8)</td>
<td>481 17.0 (0.8)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>362 8.1 (0.5)</td>
<td>215 8.4 (0.6)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>655 15.2 (0.8)</td>
<td>407 15.8 (0.8)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1211 26.8 (0.7)</td>
<td>767 28.4 (1.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>257 6.0 (0.4)</td>
<td>145 5.7 (0.5)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>93 2.3 (0.3)</td>
<td>65 2.7 (0.4)</td>
</tr>
<tr>
<td>Cancer</td>
<td>417 9.4 (0.5)</td>
<td>245 9.8 (0.7)</td>
</tr>
<tr>
<td>Hospitalized for gastrointestinal bleeding</td>
<td>282 8.9 (0.5)</td>
<td>169 8.6 (0.7)</td>
</tr>
</tbody>
</table>

Components of Secondary End Points

| Heart failure (fatal, nonfatal hospitalized, or nonhospitalized treated) | 283 6.8 (0.4) | 248 9.6 (0.6) | 220 8.8 (0.6) | 1.46 (1.24-1.73) | <.001 | 1.30 (1.10-1.54) | .003 |
| Heart failure (hospitalized/fatal)                                     | 236 5.5 (0.4) | 204 7.9 (0.6) | 176 7.1 (0.6) | 1.44 (1.20-1.73) | <.001 | 1.25 (1.03-1.51) | .02   |
| Angina (hospitalized or treated)                                    | 401 8.8 (0.5) | 257 9.7 (0.6) | 293 11.2 (0.7) | 1.07 (0.91-1.25) | .42   | 1.24 (1.07-1.44) | .01   |
| Angina (hospitalized)                                               | 259 5.9 (0.4) | 164 6.1 (0.5) | 203 8.2 (0.6) | 1.05 (0.87-1.28) | .60   | 1.33 (1.11-1.60) | .002  |
| Coronary revascularization                                         | 213 4.9 (0.4) | 137 5.5 (0.5) | 152 6.0 (0.5) | 1.07 (0.86-1.32) | .56   | 1.21 (0.98-1.49) | .08   |
| Peripheral arterial disease (hospitalized or treated)               | 167 3.7 (0.3) | 86 3.3 (0.4) | 103 4.1 (0.4) | 0.85 (0.65-1.10) | .22   | 1.04 (0.81-1.33) | .75   |

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; RR, relative risk.
Table 6. Clinical Outcomes in Nonblack Subgroup, by Antihypertensive Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>6-y Rate per 100 Persons</th>
<th>Cox Regression</th>
<th>Amlodipine vs Chlorthalidone</th>
<th>Lisinopril vs Chlorthalidone</th>
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</thead>
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<td>Chlorthalidone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. Rate (SE)</td>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
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<td>Total randomized</td>
<td>9886</td>
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</tr>
<tr>
<td>Primary End Point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD (nonfatal MI + fatal CHD)</td>
<td>962 12.5 (0.4)</td>
<td></td>
<td>0.97 (0.87-1.08)</td>
<td>0.94 (0.85-1.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>.57</td>
<td>.29</td>
</tr>
<tr>
<td>Secondary End Points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1382</td>
<td>16.9 (0.5)</td>
<td>0.94 (0.87-1.03)</td>
<td>0.97 (0.89-1.06)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>634 8.0 (0.4)</td>
<td>8.6 (0.5)</td>
<td>1.03 (0.91-1.17)</td>
<td>1.05 (0.93-1.19)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>1796 22.5 (0.5)</td>
<td>22.2 (0.7)</td>
<td>0.99 (0.92-1.07)</td>
<td>1.01 (0.93-1.09)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>2730 33.1 (0.6)</td>
<td>34.0 (0.8)</td>
<td>1.04 (0.97-1.10)</td>
<td>1.06 (1.00-1.13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>418 5.4 (0.3)</td>
<td>5.2 (0.4)</td>
<td>0.93 (0.79-1.10)</td>
<td>1.00 (0.85-1.17)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>100 1.5 (0.2)</td>
<td>1.6 (0.2)</td>
<td>1.08 (0.79-1.48)</td>
<td>0.93 (0.67-1.30)</td>
</tr>
<tr>
<td>Cancer</td>
<td>753 9.9 (0.4)</td>
<td>10.1 (0.5)</td>
<td>1.04 (0.92-1.17)</td>
<td>1.02 (0.90-1.14)</td>
</tr>
<tr>
<td>Hospitalized for</td>
<td>535 8.8 (0.4)</td>
<td>7.6 (0.5)</td>
<td>0.88 (0.76-1.01)</td>
<td>1.02 (0.89-1.17)</td>
</tr>
<tr>
<td>gastrointestinal bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Components of Secondary End Points

| Heart failure (fatal, nonfatal hospitalized, or nonhospitalized treated) | 587 8.2 (0.4) | 458 10.5 (0.5) | 392 8.6 (0.5) | 1.32 (1.17-1.49) | <.001 | 1.13 (1.00-1.28) | .05 |
| Heart failure (hospitalized/fatal)                                    | 488 7.0 (0.4) | 374 8.7 (0.5) | 295 6.7 (0.4) | 1.30 (1.14-1.48) | <.001 | 1.02 (0.89-1.18) | .76 |
| Angina (hospitalized or treated)                                      | 1166 13.9 (0.4) | 693 14.1 (0.6) | 726 14.8 (0.6) | 1.00 (0.91-1.10) | .96 | 1.06 (0.97-1.17) | .19 |
| Angina (hospitalized)                                                | 819 10.0 (0.4) | 466 9.6 (0.5) | 490 10.2 (0.5) | 0.96 (0.85-1.07) | .46 | 1.02 (0.91-1.14) | .75 |
| Coronary revascularization                                           | 900 11.6 (0.4) | 588 12.4 (0.5) | 566 12.5 (0.6) | 1.10 (1.00-1.23) | .06 | 1.07 (0.97-1.19) | .19 |
| Peripheral arterial disease (hospitalized or treated)                | 343 4.2 (0.2) | 179 3.8 (0.3) | 208 4.5 (0.3) | 0.88 (0.73-1.05) | .16 | 1.03 (0.87-1.23) | .71 |

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; RR, relative risk.

Figure 2. Relative Risks for Comparisons of Amlodipine vs Chlorthalidone and Lisinopril vs Chlorthalidone in Blacks and Nonblacks

Scales are shown in natural logarithm. The proportional hazards assumption was violated for heart failure, so relative risks and 95% confidence intervals (CIs) were calculated using $2 \times 2$ tables. *Includes fatal, nonfatal hospitalized, and nonhospitalized treated. CHD indicates coronary heart disease; MI, myocardial infarction.
Comparing lisinopril vs chlorthalidone, different treatment effects by race were seen for BP reduction (P = .001 for interaction) (Table 2), stroke (P = .01), and combined CVD outcomes (P = .04). In blacks, compared with randomization to chlorthalidone, randomization to lisinopril significantly increased risk of stroke (RR, 1.40; 95% CI, 1.17-1.68). No such effect was seen in nonblacks (RR, 1.00; 95% CI, 0.85-1.17). The RR for combined CVD was 1.19 (95% CI, 1.09-1.30) for blacks vs 1.06 (95% CI, 1.00-1.13) for nonblacks. For HF, although the effect was somewhat larger in blacks (1.30; 95% CI, 1.10-1.54) than in nonblacks (1.13; 95% CI, 1.00-1.28), there was no significant interaction, so the previously reported overall RR (1.19; 95% CI, 1.07-1.31) is the best estimate for both racial subgroups.11

The relative differences in HF event rates between treatment groups in both racial categories occurred early (during the first year) and decreased over time (Figure 3). For example, in blacks, the RRs for HF at 1 year were 2.26 (95% CI, 1.56-3.27) for amlodipine vs chlorthalidone and 2.17 (95% CI, 1.49-3.13) for lisinopril vs chlorthalidone. In nonblacks, the RRs for HF at 1 year were 2.37 (95% CI, 1.75-3.22) for amlodipine vs chlorthalidone and 2.26 (95% CI, 1.66-3.07) for lisinopril vs chlorthalidone. The RRs declined after 1 year, with larger declines in nonblacks.

When time-dependent adjustment for BP was applied to the data presented above, these findings did not change significantly in either racial subgroup (Table 7). For example, for lisinopril vs chlorthalidone in blacks, time-dependent BP adjustment reduced the RR from 1.40 to 1.36 for stroke, from 1.30 to 1.26 for HF,11 and from 1.19 to 1.17 for combined CVD.

Finally, adjusting for baseline differences in age, sex, history of CHD, diabetic status, treatment for hypertension, aspirin use, SBP, DBP, glucose levels, and years of education in both racial subgroups had no effect on the stroke outcome, whether or not results also were adjusted for time-dependent BP.

COMMENT

ALLHAT is the first large-scale trial with a substantial number of black participants to evaluate the effect of dihydropyridine CCBs and ACE inhibitors on preventing cardiovascular outcomes. The findings by race mostly parallel those in the whole cohort and in

Table 7. Clinical Outcomes by Antihypertensive Treatment Group vs Chlorthalidone After Time-Dependent Blood Pressure Adjustment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI) Black</th>
<th>RR (95% CI) Nonblack</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>0.99 (0.82-1.19)</td>
<td>0.97 (0.85-1.10)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.97 (0.85-1.10)</td>
<td>0.92 (0.83-1.02)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.71 (0.60-1.15)</td>
<td>0.76 (0.66-1.00)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.03 (0.93-1.15)</td>
<td>1.04 (0.94-1.08)</td>
</tr>
<tr>
<td>Heart failure*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First year</td>
<td>2.85 (1.75-4.66)</td>
<td>2.49 (1.68-3.68)</td>
</tr>
<tr>
<td>Beyond first year</td>
<td>1.23 (0.99-1.52)</td>
<td>1.16 (1.00-1.35)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; RR, relative risk.

*The proportional hazards assumption was violated for the heart failure outcome.

The proportional hazards assumption was violated for the heart failure outcome.
nonblacks, who comprised two thirds of the participants. The major exception was the outcome for stroke (as discussed below); effects on SBP also differed in blacks and nonblacks. In both racial subgroups as in the whole cohort, neither the ACE inhibitor nor the CCB was more effective than the thiazide-type diuretic in preventing the primary outcome of MI or fatal CHD or any other major cardiovascular or renal outcome, and diuretic-based treatment was superior to ACE inhibitors and CCBs in reducing HF incidence.

While the CCB conferred a higher rate of HF compared with the diuretic in both blacks and nonblacks (37% overall), the other prespecified outcomes did not differ in either subgroup. The small BP difference in both subgroups between the CCB and diuretic treatment groups is unlikely to account for the higher HF incidence with the CCB. This finding confirms and specifically establishes in both blacks and nonblacks previous findings that suggested that CCBs are less effective than diuretics in preventing or treating HF.

As previously reported,11 stroke was significantly less likely with the diuretic than with the ACE inhibitor in blacks but not in nonblacks, and the difference in the composite CVD outcome was greater in blacks. The diuretic also was more effective in lowering and controlling BP in blacks, and the difference in effect on stroke in blacks and nonblacks is likely explained in part by the BP differences. In considering the race-specific differences between treatment groups, BP correlated less with HF than with stroke, a finding confirmed by the recent prospective meta-analysis of hypertension outcome trials.28 Importantly, the overall improved HF outcomes with diuretics did not differ in blacks and nonblacks.

The BP findings in ALLHAT are consistent with previous studies reporting lesser BP lowering in blacks receiving monotherapy with ACE inhibitors and other agents whose mechanism of BP lowering is related to inhibiting the renin-angiotensin system (RAS), eg, angiotensin receptor blockers and β-blockers.3,4,16,22 In ALLHAT, this smaller degree of BP reduction was associated with a 19% higher risk of the composite CVD outcome, 40% higher risk of stroke, and 30% higher risk of HF in blacks randomized to receive the ACE inhibitor compared with the diuretic.

Previous studies suggest that the smaller degree of BP reduction could explain the difference in outcomes at least in part. Based on results from the placebo-controlled Systolic Hypertension in the Elderly Program (SHEP)33 and the Systolic Hypertension in Europe Trial (Syst-Eur),18 in which the respective 12- and 10-mm Hg SBP differences were associated with 49% and 29% decreases in HF, respectively, a 5-mm Hg difference could explain a 15% to 20% decrease in this outcome. A meta-analysis of prospective studies suggests that this SBP difference could account for an approximately 18% decrease in stroke.34 ALLHAT demonstrated a 26% decrease in stroke using a time-dependent analysis to adjust for change in BP.35 The stroke reduction can be explained by the change in BP. A report of more detailed analyses of the effects of differences in BP on the results in ALLHAT is forthcoming, but it is worth noting that at 4 years of follow-up, the average BP for blacks in the ACE inhibitors group was 138/79 mm Hg and that more than 54% of blacks in this treatment group had BP’s less than 140/90 mm Hg. Thus, the differences in stroke outcomes occurred despite more than half of the participants achieving the target BP.

ACE inhibitors and angiotensin receptor blockers have slowed decline of renal function in trials of patients with reduced baseline renal function.35-37 In the African American Study of Kidney Disease and Hypertension (AASK), an ACE inhibitor–based regimen slowed progression of renal disease in black participants with hypertension more than a regimen based on a β-blocker or a dihydropyridine CCB.35 However, ALLHAT is the first trial to compare renal outcomes by race and the first in which a diuretic was compared with an ACE inhibitor or CCB for renal outcomes. A diuretic was often used as the first add-on drug in the previous trials of renal outcomes. Participants in both racial subgroups who were randomized to receive the diuretic had rates of ESRD that were not significantly different than the rates for those receiving an ACE inhibitor. More detailed analyses of the renal outcomes in ALLHAT are forthcoming in a separate manuscript.38

The choice of available step 2 or step 3 agents in ALLHAT may have contributed to the poorer BP control in the ACE inhibi tor group, especially in the black subgroup. β-Blockers (followed by clonidine) were the most frequently prescribed add-on agents in all treatment groups. ACE inhibitors and β-blockers are both less effective in lowering BP in blacks in the absence of a diuretic (or CCB).3,39-43 and the combination of a sympatholytic and RAS inhibitor may be less effective than the combination of either class with an agent not affecting the RAS.39,44,45

Since ACE inhibitors, CCBs, and thiazide-type diuretics were being compared as first-line agents, unless a specific clinical indication (including uncontrolled BP) developed, participants randomized to receive ACE inhibitors who required multiple antihypertensive agents to control BP could not receive either diuretics or CCBs. These antihypertensive agents have been shown to be the most effective add-on agents for reducing BP in blacks with hypertension when combined with ACE inhibitors.3,39,41-43 This study design was necessary, since a primary objective of ALLHAT was to determine the optimal antihypertensive agent when selected as the initial agent. For an agent that is less effective in lowering BP to be recommended as initial therapy over a more effective agent, it must exhibit beneficial properties independent of BP lowering. The results of ALLHAT suggest that any non–BP-related benefit of

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ACE inhibition is insufficient to overcome the 5-mm Hg less BP reduction it conferred in black participants (or even the 1-mm Hg SBP disadvantage noted in nonblacks). This implication for RAS inhibition as first-line approach was also seen in a recent study comparing the angiotensin receptor blocker valsartan with the CCB amlo- 
dipine in a predominantly nonblack cohort.39,46 The higher risk of ACE inhibitor–associated angioedema that was noted in the black ALLHAT sub-
group, previously reported,31,47 provides another disadvantage for selecting ACE inhibition as initial therapy in this subgroup. Based on other studies, ACE inhibitors are recommended as part of treatment regimens for black pa-
tients with hypertension and renal dis-
ease or HF.35,48,49 Normally, such pa-
tients would also receive a diuretic for control of BP, fluid retention, or both. Thus, the overall ALLHAT conclu-
sions that thiazide-type diuretics are indi-
cated as the drug of choice for initial therapy of hypertension apply to both black and nonblack patient popula-
tions. Despite more favorable meta-
biologic profiles in the 3 newer classes of drugs, diuretics were either similar or su-
perior in lowering BP, in tolerability, and in preventing the major clinical complica-
tions of hypertension. We previ-
ously recommended that for patients un-
able to take a diuretic, a CCB or an ACE inhibitor may be appropriate first-line therapy.31 In this analysis, nonblacks had a higher risk of HF with the CCB than with the ACE inhibitor when com-
pared with the diuretic. However, the in-
crease in HF in the ACE inhibitor group compared with the diuretic group was large initially and remained so over the course of the trial. Analyses directly com-
paring outcomes for CCBs vs ACE in-
hibitors are currently under way. The Blood Pressure Lowering Treatment Tri-
alis’ Collaboration second-cycle meta-
analysis reported no significant differ-
eence between these classes for aggregated major cardiovascular events, though there were trends favoring CCBs for stroke outcomes and ACE inhibitors for HF outcomes.28

In conclusion, in blacks with hyper-
tension and without renal disease or HF, these results indicate that thiazide-
type diuretics, and CCBs in patients who cannot take a diuretic (eg, those with allergy or confirmed intolerance), are preferred to ACE inhibitors as initial single-drug therapy. The rec-
ommended preference for a CCB over an ACE inhibitor as the first alterna-
tive to a diuretic in blacks is based on the greater risk for stroke, combined CHD, combined CVD, and angio-
edema seen with ACE inhibitors, over-
riding the greater risk for HF with a CCB. This conflicts with the recom-
mandation of one panel that continued to advocate inclusion of a RAS in-
hibitor as first-line antihypertensive therapy,50 but is consistent with the rec-
ommendations from more recent guide-
line panels.36,51,52

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A list of the ALLHAT Collaborative Research Group members has been published previously.31

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