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STROKE OUTCOMES AMONG PARTICIPANTS RANDOMIZED TO CHLORTHALIDONE, AMLODIPINE OR LISINOPRIL IN ALLHAT

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Abstract

Background—The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind, practice-based, active-control, comparative effectiveness trial in 33,357 high-risk hypertensive participants.

Methods and Results—ALLHAT compared cardiovascular disease outcomes in participants initially treated with angiotensin-converting enzyme inhibitor (lisinopril), calcium channel blocker (amlodipine), or thiazide-type diuretic (chlorthalidone). We report stroke outcomes in 1517 participants in-trial and 1596 additional participants during post-trial passive surveillance, for total follow-up of 8–13 years. Stroke rates were higher with lisinopril (6-year rate/100=6.4) than with chlorthalidone (5.8) or amlodipine (5.5) in-trial but not including post-trial (10-year rates/100=13.2 [chlorthalidone], 13.1[amlodipine], and 13.7 [lisinopril]). In-trial differences were

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Conflicts of Interest/Disclosure Statements

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driven by race (race-by-lisinopril/chlorthalidone interaction $P=0.005$, race-by-amlodipine/lisinopril interaction $P=0.012$) and gender (gender-by-lisinopril/amlodipine interaction $P=0.041$), separately. No treatment differences overall, or by race or gender, were detected over the 10-year period. No differences appeared among treatment groups in adjusted risk of all-cause mortality including post-trial for participants with nonfatal in-trial strokes.

Conclusions—Among Blacks and women, lisinopril was less effective in preventing stroke in-trial than either chlorthalidone or amlodipine, even after adjusting for differences in systolic blood pressure. These differences abated by the end of the post-trial period.

Keywords

ace inhibitor; calcium channel blocker; diuretic; hypertension

Introduction

When considered separately from other cardiovascular diseases (CVDs), stroke is the fourth leading cause of death in the population at large and the second leading cause of death among Blacks and women in the United States (US) (1,2). Importantly, stroke is the leading cause of serious long-term disability in the US (1). High blood pressure (BP) is the most common risk factor (population-attributable fraction ~35%) for stroke, and it is estimated that 77% of persons who experience a first stroke have or have had a systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg (BP $\geq 140/90$) (1,3).

Epidemiologic studies have accurately predicted a 15% decrease in stroke incidence for each 10 mmHg decrease in systolic BP in early clinical trials with diuretics and beta-blockers (4,5). Further, the impressive reductions in stroke incidence and death rates that were achieved in the past 30 years have been attributed in large part to improved detection, treatment, and control of hypertension (6). However, the comparative effects of different BP lowering regimens on stroke risk are uncertain. ALLHAT examined the relative stroke prevention efficacy, a major secondary outcome, of non-diuretic antihypertensive agents (doxazosin, amlodipine, and lisinopril) compared to the diuretic chlorthalidone. The doxazosin arm was stopped early because of the futility of finding a difference in the primary outcome (fatal coronary heart disease [CHD] or nonfatal myocardial infarction) and a higher risk of combined CVD, especially stroke and heart failure in the doxazosin group compared to the chlorthalidone group (7,8). Thus, stroke outcomes in the doxazosin group are not considered in this report. Comparisons between the remaining arms of the study revealed significant differences in stroke during the active-follow-up phase of the study. Randomization to lisinopril was associated with significantly higher stroke risk compared to chlorthalidone (hazard ratio [HR]=1.15, 95% confidence interval [CI]=1.02–1.30) or amlodipine (HR=1.23, 95% CI=1.08–1.41) (8,9). There was an interaction between race and drug assignment such that the overall difference in stroke risk was confined to Black participants (lisinopril/chlorthalidone in Blacks, HR=1.40, 95% CI=1.17–1.68; lisinopril/amlodipine in Blacks, HR=1.51, 95% CI=1.22–1.86). Stroke risk was similar for non-Black participants randomized to each of the 3 treatments (lisinopril/chlorthalidone in non-Blacks, HR=1.00, 95% CI=0.85–1.17; lisinopril/amlodipine in non-Blacks, HR=1.07, 95% CI=0.89–1.28).

We now report, in greater detail than in previously published papers, the experience with regard to stroke among 33,357 ALLHAT participants, randomized to chlorthalidone, amlodipine, or lisinopril, and followed during and after the active-follow-up phase of the trial. This includes greater in-depth look at the amlodipine-lisinopril comparison, subgroup analyses, multiple occurrences of stroke, types of stroke, and length of hospital stay. Although we were not able to ascertain information about medications and BP in the post-trial period, we examine whether in-trial trends persist, diminish, or augment, and whether new beneficial effects develop in long-term passive-surveillance follow-up. Total follow-up (active + passive surveillance using national administrative databases to ascertain deaths and hospitalizations) was 8 to 13 years. We examine by treatment assignment both fatal and nonfatal stroke and in particular, post in-trial stroke death rates and fatal strokes throughout both active- and passive-surveillance phases. We also examine the extent to which differences in stroke rates may be attributed to differences in systolic and diastolic BP during the active surveillance phase of the study.

Methods

Study Design and Participants

The rationale and design of ALLHAT have been presented elsewhere (10) and more extensive details are in the study protocols (11,12). Participants were age 55 years with hypertension and at least one additional CVD risk factor (9,10,13). All participants gave written informed consent and all centers obtained institutional review board approval. The study adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects.

Participants (n=33,357) were randomized to a thiazide-type diuretic (chlorthalidone), a calcium channel blocker (amlodipine), or an angiotensin-converting enzyme inhibitor (lisinopril) in a ratio of 1.7:1:1, respectively. Goal BP in each randomized group was <140/90 mmHg achieved by titrating the assigned study drug (step 1) and adding open-label agents (step 2 or 3) when necessary. Method of BP measurement is detailed elsewhere (11).

Measurements

Three main types of analyses were conducted, each with different cohorts depending on what data were available. Details of the 3 cohorts used are in Figure 1a,b,c. The active surveillance phase (hereafter referred to as in-trial) stroke analyses were conducted using the entire cohort (cohort 1, n=33,357). Mortality data in the in-trial and post-trial periods were available for the entire cohort, except for Canadian participants (cohort 2, n=32,802). Nonfatal stroke endpoints in the post-trial were available only for participants from non-Veterans Affairs (VA) US clinical centers who had valid Medicare or Social Security numbers (cohort 3, n=21,623), because we did not have access to VA and Canadian databases. In-trial hospital length-of-stay data for in-trial strokes were available for participants who had Medicare, were in the VA, or were non-Canadian, and for whom we were able to match the specific hospitalized stroke with Centers for Medicare and Medicaid or VA databases to obtain the length of stay (n=621).

Outcomes

Stroke was a major pre-specified secondary outcome in ALLHAT (9,10,14). The current study's outcomes included fatal and nonfatal stroke and post-stroke death rates. Nonfatal stroke was defined as either: 1) unequivocal objective findings of a localizing neurological deficit with a duration longer than 24 hours and absence of another cause of neurological deficit (e.g., neoplasm, subdural hematoma, cerebral angiography, or metabolic disorder); and/or 2) finding of an abnormality on computed tomography or magnetic resonance image consistent with current neurological symptoms or signs, or positive lumbar puncture (for subarachnoid hemorrhage). Fatal stroke was defined as having a death certificate listing stroke as consistent with the underlying or the immediate cause of death plus one or more of: 1) pre-terminal hospitalization with stroke as defined above; 2) previous stroke and no known potentially lethal non-cerebrovascular disease process; and/or 3) stroke diagnosed as the cause of death at post-mortem examination.

Standardized procedures were employed for reporting and validation of study outcomes (9,10). During the post-trial period a stroke event was defined using ICD9 codes 430.x-434.x, 436.x, and 997.02. Death certificates (for fatal strokes) and discharge summaries (for all strokes) were examined for agreement with study criteria by endpoints monitors at the Coordinating Center. Detailed information beyond hospital discharge summaries was collected for 10% of all reported stroke events to validate the procedure of using diagnoses provided by clinical site investigators (9). The original reports and additional documents were reviewed by the ALLHAT Endpoints Subcommittee. Agreement rates between the subcommittee and clinic investigators were 84% (129/153) for stroke and were similar in all treatment groups. Information on stroke subtypes was not collected from the clinical centers during the trial. To determine stroke subtype, in-trial stroke events were matched to data from the Center for Medicare and Medicaid (CMS), the Department of Veterans Affairs (VA), and the National Death Index (NDI), and ICD-9 codes were used to assign stroke subtypes for those events where matches were found. For details on the use of national databases for determining outcomes during the post-trial period, see Cushman, et al.(15) and study extension protocol (12). For the post-trial period, data are not available on medications, blood chemistries, or BP levels.

Statistical Analyses

Baseline characteristics were compared across treatments using a 2-sample t-test for continuous covariates and Pearson's chi-square test for categorical data(9,16). In addition to the 2 protocol-specified comparisons of amlodipine and lisinopril with chlorthalidone, a post-hoc comparison was made of amlodipine with lisinopril. An intent-to-treat statistical analysis was conducted. Cumulative event rates were calculated using the Kaplan-Meier procedure. Cohorts one and three were used to estimate 6-year and 10-year rates, respectively. The Cox proportional hazards model was used to obtain the HRs and 95% CIs for time-to-event outcomes (17). The proportional hazard assumption was examined by using log-log plots and testing a treatment by time (time-dependent) interaction term. Heterogeneity of treatment effects across subgroups was examined by testing for treatment-covariate interaction with the proportional hazard model using a $P<0.05$.

To account for differences in systolic and diastolic BP between the randomized treatment groups, Cox regression analyses were done including fixed covariates of baseline systolic and diastolic BP, age, race, gender, diabetes, CHD at baseline, and anti-hypertensive treatment prior to ALLHAT enrollment. Time-dependent covariates of follow-up systolic and diastolic BPs and multiple imputation was used to account for missing BP values (17). The Andersen-Gill method was used to examine the treatment effect on multiple strokes per patient (18). The Wilcoxon rank sum test was used for comparison of non-normally distributed variables between treatments. Analyses of the total number of stroke events over the total person years (Supplemental Table 4) were performed using Poisson regression. Given the many multivariate, subgroup and interaction analyses that were performed, statistical significance at the 0.05 level should be interpreted with caution. Stata version 11 (Stata Corp, College Station, Tex) was used for all analyses.

Results

A total of 33,357 participants were randomized to the ALLHAT chlorthalidone, lisinopril, or amlodipine arms (cohort 1), and 683 of the 15,255 chlorthalidone participants (4.5%), 382 of the 9,048 amlodipine participants (4.2%), and 460 of the 9,054 lisinopril participants (5.1%) had a stroke during 4.9 years of in-trial follow-up (Figure 1a). In cohort 3, 1051 of 9,914 chlorthalidone participants (10.6%), 622 of 5,864 amlodipine participants (10.6%), and 643 of 5,845 lisinopril participants (11.0%) had a stroke either in-trial or post-trial (Figure 1c). Among the participants who had a stroke in-trial, 71.0% in the chlorthalidone arm, 72.7% in the amlodipine arm, and 68.7% in the lisinopril arm died by the end of the extension period, including in-trial stroke deaths (Figure 1b). In contrast, among participants who did not have a stroke in-trial, total in-trial and post-trial mortality rates were only 33.4% (4,792 of 14,326) in the chlorthalidone arm, 33.1% (2,820 of 8,517) in the amlodipine arm, and 32.4% (2,738 of 8,444) in the lisinopril arm.

Baseline characteristics for those with and without in-trial nonfatal/fatal stroke are provided in Table 1. Those who did have a stroke were more likely to be older, Black, male, on aspirin at baseline, have atrial fibrillation on baseline ECG (16), or have history of atherosclerotic CVD, myocardial infarction or stroke, coronary revascularization, left ventricular hypertrophy, CHD, or type 2 diabetes. Additionally, those who had a stroke had higher baseline systolic BP (visit 2), fasting glucose, total cholesterol, and low-density lipoprotein cholesterol; and had lower baseline high-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m², diastolic BP (visit 2), and BMI; and were slightly more likely to be on an antihypertensive treatment and were less well-educated.

Stroke outcomes adjusted for characteristics associated with the initial in-trial stroke during the active surveillance phase and during the extension period are shown in Table 2. Stroke rates were higher in the lisinopril arm than in the other arms at 6 years but not at 10 years (6-year stroke rates/100 persons=5.8 for chlorthalidone, 5.5 for amlodipine, and 6.4 for lisinopril; 10-year stroke rates/100 persons=13.2 for chlorthalidone, 13.1 for amlodipine, and 13.7 for lisinopril). This suggests that for every 167 treated with chlorthalidone versus 167 treated with lisinopril, there would be one less stroke in the chlorthalidone group.

Similarly, the number to treat to prevent a stroke for lisinopril versus amlodipine is 111 patients. In-trial differences were mainly driven by race (race-by-lisinopril/chlorthalidone interaction $P=0.005$, race-by-amlodipine/lisinopril interaction $P=0.012$), where 6-year rates/100 persons were 6.2 for chlorthalidone, 5.8 for amlodipine, and 8.2 for lisinopril for Blacks, and separately by gender (gender-by-amlodipine/lisinopril interaction $P=0.041$), where 6-year rates/100 persons were 5.3 for chlorthalidone, 4.5 for amlodipine, and 6.3 for lisinopril for women (Table 2, Figures 2–3) (19). In-trial stroke rates were similar among treatment comparisons in non-Blacks and in men. Adjusting for time-dependent terms of annual systolic and diastolic BPs using Cox regression for in-trial data resulted in similar race subgroup results (Supplemental Table 1).

No differences in the 10-year rates for the 3 treatment arms were detected, and rates did not differ by race or gender (Table 2). No in-trial versus post-trial treatment interactions affecting stroke were detected. Among women, lisinopril treatment was less effective than either chlorthalidone (HR=1.22, 95% CI 1.01–1.46) or amlodipine (HR=1.45, 95% CI 1.17–1.79) treatment in preventing in-trial stroke (19). These differences occurred in both Black and non-Black women, but were particularly marked in Black women, in whom lisinopril treatment was associated with a 35% higher rate of stroke compared to chlorthalidone treatment and a 48% higher rate compared with amlodipine treatment. The observed disadvantage of lisinopril treatment compared with the other regimens in Black women can be attributed in part to less effective BP lowering; this is not true for non-Black women, in whom the average systolic BP differed by only ~1 mmHg between treatment arms. There was a statistically non-significant reduction in risk of stroke with amlodipine compared with chlorthalidone treatment (HR=0.84, 95% CI 0.69–1.03); that was more apparent among non-Black (HR=0.78, 95% CI 0.60–1.03) than Black (HR=0.91, 95% CI 0.68–1.22) women and appeared to be independent of BP.

The HR of multiple in-trial strokes was higher in the lisinopril arm compared to the amlodipine arm (HR=1.16, 95% CI 1.00–1.35) but not compared to the chlorthalidone arm (HR=1.12, 95% CI 0.98–1.28) in unadjusted analyses (Supplemental Table 2). After adjustment for covariates, the HR of multiple strokes was higher in the lisinopril arm than in either the chlorthalidone or amlodipine arm and there was a significant interaction between lisinopril/chlorthalidone and race ($P=0.013$) and between lisinopril/amlodipine and race ($P=0.008$), mainly driven by the statistically significant difference for Blacks in the lisinopril arm. No significant interactions between treatment and gender were observed.

There were no differences among treatment groups in the adjusted risk of all-cause mortality through the extension period for participants who had a nonfatal in-trial stroke (Table 3, Supplemental Figure 1). However, there was a difference in other CVD deaths. Compared with the amlodipine group, the HR of other CVD death was lower for the lisinopril group (HR=0.66, 95% CI 0.45–0.96).

Having an in-trial stroke was associated with a statistically significant increase in the HR of all mortality outcomes (Supplemental Table 3) through the extension period. For other CVD deaths, we observed a statistically significant interaction for stroke and treatment (chlorthalidone versus amlodipine), suggesting an increased risk of other CVD mortality for

participants who had a stroke in the amlodipine arm. The higher risk of mortality for the amlodipine arm (versus the lisinopril arm in Table 3 and the chlorthalidone arm in Supplemental Table 3) is not consistent with our other results. This might be explained by an inflated type I error due to multiple comparisons since they are of uncertain clinical significance. Stroke subtype matches were found for 918 (61%) of the 1525 total in-trial strokes. Twenty percent of the non-matches were due to the participants not being eligible for inclusion in the CMS or VA databases; the remaining 80% were due to not finding matches in the databases within ± 1 month of the event date. There were no differences in the total number of in-trial nonfatal strokes, length of hospital stay, or type of stroke among treatment groups (Supplemental Tables 4–5).

Discussion

ALLHAT is the first large-scale outcome trial to compare the ability of different classes of antihypertensive drugs to prevent stroke in an ethnically diverse population of high-risk older hypertensive persons. ALLHAT enrolled the largest number of minority participants, including 15,084 Blacks (both African-American and Afro-Caribbean) (36%) and 8,342 Hispanics (19%), ever studied in a hypertension trial. A total of 1517 first strokes, roughly half of the number of fatal and nonfatal coronary events ($n=2956$) were reported during the active trial, reflecting the relative incidence of these conditions in the US population (1). This study was a detailed examination of these strokes that occurred including the amlodipine-lisinopril comparison, subgroup analyses, occurrence of multiple strokes, types of stroke, and length of hospital stay.

The finding of greater reductions in in-trial stroke risk with the CCB- and diuretic-based regimens compared to the ACE-inhibitor-based regimen in ALLHAT is generally consistent with results of previous trials (20). The second-cycle meta-analysis of data from 29 randomized trials, including ALLHAT, with 162,341 participants by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) showed trends toward greater stroke risk reduction with diuretic or β -blocker-based regimens compared to those based on ACE inhibitors (21). Stroke risk reduction tended to be greater with CCB-based regimens compared to those based on diuretics or β -blockers, or ACE inhibitors. However, these differences were of borderline statistical significance. BP reduction was slightly (1–2 mmHg) less with ACE inhibitors than with other drugs, and it was uncertain whether the results could be entirely accounted for by differences in achieved BP levels.

The finding that ACE inhibitor treatment was less effective, even after adjusting for BP, than either diuretic or CCB treatment in preventing in-trial stroke among women in ALLHAT is consistent with results of a prospectively designed overview by the Blood Pressure Lowering Treatment Trialists' Collaboration (22). Among women, ACE inhibitor treatment was less effective than CCB (HR 1.27; 95% CI 1.05–1.55) or diuretic/ β -blocker treatment (HR 1.13; 95% CI 0.99–1.30) in preventing stroke. Among men, all 4 drug classes were equally effective in stroke prevention. Evidence for this interaction was of borderline ($P=0.05$) statistical significance and was attributed by the authors to chance in view of the large number of subgroup analyses made in the study.

Observational data have documented increased impact of systolic BP elevation on stroke risk in Blacks compared to non-Blacks (23). Over 4.5 years of follow-up, a 10 mm Hg difference in systolic BP was associated with a 24% (95% CI, 14%–35%) increase in stroke risk for Blacks compared to 8% (95% CI, 0%–16%) for non-Blacks (*P*-value for interaction=0.02) in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. This effect persisted after adjustment for demographic factors, use of antihypertensive medications and other risk factors for stroke, suggesting that differences in control of BP, particularly systolic BP, may have contributed to the increased incidence of stroke in Blacks with ACE inhibitor compared to diuretic or CCB treatment in ALLHAT.

Racial/ethnic differences in BP responses to different classes of antihypertensive drugs have been reported previously (24–28). The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents study showed that Blacks responded better to diuretics and CCBs than to drugs that inhibit components of the renin-angiotensin-aldosterone system, including β -blockers and ACE inhibitors, and that ACEs and β -blockers were less effective in reducing BP in Blacks than in whites (24). Among Blacks in ALLHAT, systolic BP was higher in the ACE inhibitor arm by 5 mmHg at year 1 and by 4 mmHg at year 5 compared to the diuretic arm; in the CCB arm, systolic BP was higher by 2 mmHg at year 1 and by 1 mmHg at year 5 compared to the diuretic arm. Among non-Blacks, the ACE inhibitor-diuretic difference was only 2 mmHg at year 1 and 0.9 mmHg at year 5, while the CCB-diuretic difference was 1.4 mmHg at year 1 and 0.5 mmHg at year 5. Adjustment for follow-up BP as a time-dependent covariate in a Cox-proportional hazards regression model reduced the HR for stroke in Blacks only slightly from 1.40 to 1.36, and in the study as a whole, from 1.15 to 1.12, and the results remained statistically significant(9). Thus, most of the excess stroke risk in Blacks randomized to the ACE inhibitor cannot be explained by less effective BP control as assessed by brachial artery BP measurements in the clinic setting. However, because 24-hour ambulatory, night time, or central BP were not assessed in ALLHAT, we cannot accurately determine what proportion of the excess stroke risk in Blacks randomized to the ACE inhibitor can be explained by less effective BP control.

In addition to diurnal variation in BP, increased visit-to-visit variability (VVV) of systolic BP has been associated with increased risk for CVD events, particularly stroke, in several studies (29–32). Further, a meta-analysis of randomized controlled trials of antihypertensive therapy that used interindividual variance of systolic BP as surrogate for intraindividual variability showed that calcium channel blockers and non-loop diuretics lowered BP variability, while ACE inhibitors increased BP variability compared with all other antihypertensive classes (33). Compared head-to-head, calcium channel blockers were associated with lower interindividual BP variability than diuretics. A recent post-hoc comparison of VVV of systolic BP by treatment arm in ALLHAT showed that variability was lower in participants randomized to chlorthalidone or amlodipine than in those randomized to lisinopril (34). After multivariable adjustment, those in the amlodipine arm had slightly lower VVV of systolic BP than those in the chlorthalidone arm. This difference was no longer significant when participants taking antihypertensive medications other than the randomized study drug were excluded. Ongoing analyses are examining the association between VVV of systolic BP and CVD outcomes, including stroke, in ALLHAT.

The in-trial stroke differences abated by the end of the post-trial period. We were not able to follow what medications participants remained on or switched to after the active follow-up phase of the trial; however, we hypothesize that the dissipation of differences when post-trial follow-up is included is likely due to crossovers in treatment.

A limitation of our study is the number of statistical comparisons conducted resulting in a higher likelihood of finding spurious statistical differences. For example, in Table 2 there are 64 total interaction tests. However, pre-specified subgroups in ALLHAT included race, gender, and age. Atrial fibrillation and baseline CHD subgroups were post-hoc. In general, the reader should interpret p-values with caution. In addition, there were many participants that were omitted from cohort 3 analyses due to unavailability of this data. There exists the possibility of bias in the analyses due to differences in the distribution of age and gender. However, we have tried to reduce this bias by adjusting for covariates associated with incident stroke.

Stroke rates were higher in the lisinopril arm than in the chlorthalidone or the amlodipine arms during the trial but not for the period including the post-trial. Among Blacks and women in ALLHAT, lisinopril treatment was less effective in preventing in-trial stroke than either chlorthalidone or amlodipine treatment, even after adjusting for treatment differences in systolic BP. Stroke severity, as judged by likelihood of dying during its initial occurrence or over the next 5 years, length of stroke hospitalization, or recurrence of stroke, was similar in the 3 treatment groups. These results suggest that initial therapy with a diuretic or a calcium channel blocker is superior to an ACE inhibitor in preventing fatal and nonfatal stroke, particularly among older Blacks and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014 Jan 21; 129(3):e28–e292. [PubMed: 24352519]
2. Towfighi A, Ovbiagele B, Saver JL. Therapeutic milestone: stroke declines from the second to the third leading organ- and disease-specific cause of death in the United States. *Stroke*. 2010 Mar; 41(3):499–503. [PubMed: 20075347]
3. Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF. Lifetime cost of stroke in the United States. *Stroke*. 1996 Sep; 27(9):1459–1466. [PubMed: 8784113]

4. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990 Apr 7; 335(8693):827–838. [PubMed: 1969567]
5. MacMahon S, Rodgers A. Blood pressure, antihypertensive treatment and stroke risk. *J Hypertens Suppl*. 1994 Dec; 12(10):S5–14. [PubMed: 7769492]
6. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, et al. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke*. 2014 Jan; 45(1):315–353. [PubMed: 24309587]
7. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2000 Apr 19; 283(15):1967–1975. [PubMed: 10789664]
8. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertens*. 2003 Sep; 42(3):239–246.
9. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 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). *JAMA*. 2002 Dec 18; 288(23):2981–2997. [PubMed: 12479763]
10. Davis BR, Cutler JA, Gordon DJ, Furberg CD, Wright JT Jr, Cushman WC, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. *Am J Hypertens*. 1996 Apr; 9(4 Pt 1):342–360. [PubMed: 8722437]
11. [Accessed 29 May 2014] Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Protocol. Available at: <https://allhat.sph.uth.tmc.edu/Forms/protocol.pdf>
12. [Accessed 29 May 2014] Extension Protocol: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Available at: <https://allhat.sph.uth.tmc.edu/Forms/ExtensionProtocol.pdf>
13. Grimm RH Jr, Margolis KL, Papademetriou V, Cushman WC, Ford CE, Bettencourt J, et al. Baseline Characteristics of Participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Hypertension*. 2001; 37:19–27. [PubMed: 11208751]
14. Leenen FH, Nwachuku CE, Black HR, Cushman WC, Davis BR, Simpson LM, et al. Clinical events in high-risk hypertensive patients randomly assigned to calcium channel blocker versus angiotensin-converting enzyme inhibitor in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Hypertension*. 2006 Sep; 48(3):374–384. [PubMed: 16864749]
15. Cushman WC, Davis BR, Pressel SL, Cutler JA, Einhorn PT, Ford CE, et al. Mortality and morbidity during and after the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *J Clin Hypertens (Greenwich)*. 2012 Jan; 14(1):20–31. [PubMed: 22235820]
16. Haywood LJ, Ford CE, Crow RS, Davis BR, Massie BM, Einhorn PT, et al. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). *J Am Coll Cardiol*. 2009 Nov 24; 54(22):2023–2031. [PubMed: 19926008]
17. Klein, JP.; Moeschberger, ML. Survival analysis: Techniques for censored and truncated regression. 2. New York, NY: Springer-Verlag; 2003.
18. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *The annals of statistics*. 1982:1100–1120.
19. Oparil S, Davis BR, Cushman WC, Ford CE, Furberg CD, Habib GB, et al. Mortality and morbidity during and after Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial: results by sex. *Hypertension*. 2013 May; 61(5):977–986. [PubMed: 23529173]

20. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001 Sep 29; 358(9287):1033–1041. [PubMed: 11589932]
21. Turnbull F. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet*. 2003 Nov 8; 362(9395):1527–1535. [PubMed: 14615107]
22. Turnbull F, Woodward M, Neal B, Barzi F, Ninomiya T, Chalmers J, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. *Eur Heart J*. 2008 Nov; 29(21):2669–2680. [PubMed: 18852183]
23. Howard G, Lackland DT, Kleindorfer DO, Kissela BM, Moy CS, Judd SE, et al. Racial differences in the impact of elevated systolic blood pressure on stroke risk. *JAMA Intern Med*. 2013 Jan 14; 173(1):46–51. [PubMed: 23229778]
24. Materson BJ, Reda DJ, Cushman WC, Massie BM, Freis ED, Kochar MS, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med*. 1993 Apr 1; 328(13):914–921. [PubMed: 8446138]
25. Saunders E, Weir MR, Kong BW, Hollifield J, Gray J, Vertes V, et al. A comparison of the efficacy and safety of a beta-blocker, a calcium channel blocker, and a converting enzyme inhibitor in hypertensive blacks. *Arch Intern Med*. 1990 Aug; 150(8):1707–1713. [PubMed: 2200382]
26. Rahman M, Douglas JG, Wright JT Jr. Pathophysiology and treatment implications of hypertension in the African-American population. *Endocrinol Metab Clin North Am*. 1997 Mar; 26(1):125–144. [PubMed: 9074856]
27. Johnson, E.; Wright, J. Management of hypertension in black populations. In: Weber, M.; Oparil, S., editors. *Hypertension*. Philadelphia, PA: Elsevier; 2005. p. 587-595.
28. Flack JM, Oparil S, Pratt JH, Roniker B, Garthwaite S, Kleiman JH, et al. Efficacy and tolerability of eplerenone and losartan in hypertensive black and white patients. *J Am Coll Cardiol*. 2003 Apr 2; 41(7):1148–1155. [PubMed: 12679215]
29. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet*. 2010; 375:895–905. [PubMed: 20226988]
30. Muntner P, Shimbo D, Tonelli M, et al. The relationship between visit-to-visit variability in systolic blood pressure and all-cause mortality in the general population: findings from NHANES III, 1988 to 1994. *Hypertension*. 2011; 57:160–166. [PubMed: 21200000]
31. Shimbo D, Newman JD, Aragaki AK, et al. Association between annual visit-to-visit blood pressure variability and stroke in postmenopausal women: data from the Women's Health Initiative. *Hypertension*. 2012; 60:625–630. [PubMed: 22753206]
32. Mancia G, Facchetti R, Parati G, Zanchetti A. Visit-to-visit blood pressure variability in the European Lacidipine Study on Atherosclerosis: methodological aspects and effects of antihypertensive treatment. *J Hypertens*. 2012; 30:1241–1251. [PubMed: 22499291]
33. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive- drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet*. 2010; 375:906–915. [PubMed: 20226989]
34. Muntner P, Levitan EB, Lynch AI, Simpson LM, Whittle J, Davis BR, Kostis JB, Whelton PK, Oparil S. Effect of chlorthalidone, amlodipine, and lisinopril on visit-to-visit variability of blood pressure: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *J Clin Hypertens (Greenwich)*. 2014 May; 16(5):323–30. [PubMed: 24739073]

Highlights

- We studied how well lisinopril, amlodipine, and chlorthalidone prevented stroke.
- We studied older, high-risk, ethnically diverse patients with hypertension.
- Patients taking lisinopril, especially Blacks and women, had strokes more often.
- Stroke severity was similar in all three treatment groups.
- Amlodipine and chlorthalidone prevent more strokes among Blacks and women.

Figure 1. CONSORT diagrams: (A) Cohort 1 for in-trial stroke analyses; (B) Cohort 2 for in-trial and post-trial deaths after in-trial stroke analyses; (C) Cohort 3 for in-trial and post-trial strokes analyses. [†]Excluding incident stroke deaths with no prior stroke.

Figure 2.

Forest plots of in-trial (Cohort 1 at 6-year) and in-trial and post-trial (Cohort 3 at 10 year) stroke outcomes by treatment group and subgroups.

Abbreviations: A, amlodipine; afib, atrial fibrillation; C, chlorthalidone; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; L, lisinopril;

Figure 3.
In-trial blood pressure and stroke rates

Table 1

Baseline characteristics of ALLHAT participants with vs. without in-trial stroke or fatal stroke (Cohort 1)

Baseline Characteristic	Amlodipine/Lisinopril/Chlorthalidone Comparison		P-value
	No in-trial stroke N=31,832	In-trial nonfatal or fatal stroke N=1,525	
Age in years, mean (SD)	66.74 (7.68)	69.84 (7.76)	<0.0001
Age group, n (%)			
55–64	13,767 (43.25)	417 (27.34)	<0.001
65	18,065 (56.75)	1108 (72.66)	
Race, n (%)			
Black	11,172 (35.10)	620 (40.66)	<0.001
Non-Black	20,660 (64.90)	905 (59.34)	
Men, n (%)	16,828 (52.87)	891 (58.43)	<0.001
Education in years, mean (SD)	10.98 (4.03)	10.56 (3.94)	0.0001
Medication use, n (%)			
Antihypertensive treatment	28,691 (90.14)	1398 (91.67)	0.049
Aspirin	11,333 (35.60)	619 (40.59)	<0.001
Lipids medications	7447 (23.39)	326 (21.38)	0.069
Blood Pressure in mm Hg, mean(SD)			
SBP at Visit 2	146.15 (15.63)	148.94 (15.43)	<0.0001
DBP at Visit 2	84.05 (10.04)	83.52 (10.52)	0.0476
Pulse in beats/minute, mean(SD)	73.57 (10.68)	73.91 (11.24)	0.2217
Eligibility risk factors, n (%) *			
Current smoker	6977 (21.92)	326 (21.38)	0.617
ASCVD [†]	16,291 (51.18)	907 (59.48)	<0.001
History MI or stroke	7189 (22.58)	548 (35.93)	<0.001
History coronary revascularization	4073 (12.80)	237 (15.54)	0.002
Other ASCVD	7514 (23.61)	387 (25.38)	0.112
Major ST depression or T-wave inversion	3259 (10.33)	161 (10.70)	0.643
Type 2 diabetes	12,436 (39.07)	732 (48.00)	<0.001
HDL-C < 35 mg/dL	3745 (11.76)	132 (8.66)	<0.001
LVH by echo or ECG	6273 (19.71)	343 (22.49)	0.008
History CHD	7962 (25.20)	453 (30.08)	<0.001
Atrial fibrillation on baseline ECG, n (%)	287 (0.98)	47 (3.31)	<0.001
Body mass index, mean (SD)	29.79 (6.21)	29.23 (6.01)	0.0005
Baseline GFR < 60 ml/min/1.73m ² , n (%)	5302 (17.41)	360 (24.81)	<0.001
Biochemical measures, mean (SD)			
Total cholesterol (mg/dL)	215.98 (43.15)	218.56 (48.25)	0.0271
LDL cholesterol (mg/dL)	135.68 (36.95)	139.21 (39.65)	0.0006
HDL cholesterol (mg/dL)	46.90 (14.75)	45.37 (14.13)	0.0001
Potassium (mmol/L)	4.31 (0.51)	4.32 (0.53)	0.6726
Fasting glucose (mg/dL)	122.96 (57.25)	128.10 (57.92)	0.0033

Amlodipine/Lisinopril/Chlorthalidone Comparison			
Baseline Characteristic	No in-trial stroke N=31,832	In-trial nonfatal or fatal stroke N=1,525	P-value
eGFR (ml/min/1.73m ²)	77.91 (19.70)	73.76 (20.09)	<0.0001

Abbreviations: SBP/DBP=systolic blood pressure/diastolic blood pressure; ASCVD=atherosclerotic cardiovascular disease; MI=myocardial infarction; HDL-C=high density lipoprotein cholesterol; LVH=left ventricular hypertrophy; CHD=coronary heart disease; body mass index calculated by the weight in kilograms divided by the square of height in meters; eGFR=estimated glomerular filtration rate (derived from application of the following simplified MDRD equation based on serum creatinine level, age, race, and sex; Estimated GFR=186.3× (Serum creatinine)^{-1.154} × (Age, y)^{-0.203} × 1.212 (if black) × 0.742 (if female).

* 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 myocardial infarction or stroke; history of coronary revascularization; major ST segment depression or T wave inversion on any ECG in the past 2 years; other ASCVD (history of angina pectoris; history of intermittent claudication, gangrene, or ischemic ulcers; history of transient ischemic attack; coronary, peripheral vascular, or carotid stenosis 50% or more documented by angiography or Doppler studies; ischemic heart disease documented by reversible or fixed ischemia on stress thallium or dipyridamole thallium, ST depression 1 mm for 1 minute on exercise testing or Holter monitoring; reversible wall motion abnormality on stress echocardiogram; ankle-arm index <.9; abdominal aortic aneurysm detected by ultrasonography, CT scan, or X-ray; carotid or femoral bruits).

Table 2
Stroke outcomes by treatment group and subgroups (cohort 1 for in-trial and cohort 3 for in-trial and post-trial)

	In-trial 6-year rates per 100 (se) Total events/number at risk			In-trial and post-trial 10-year rates per 100 (se) Total events/number at risk		
	Chlor	Aml	Lis	Chlor	Aml	Lis
Total	5.81 (0.24) 683/15255	5.47 (0.31) 382/9048	6.40 (0.32) 460/9054	13.17 (0.41) 1051/9914	13.14 (0.53) 622/5864	13.71 (0.54) 643/5845
Black*	6.19 (0.41) 260/5369	5.83 (0.52) 146/3213	8.23 (0.58) 214/3210	13.45 (0.69) 385/3536	13.98 (0.90) 241/2133	15.22 (0.94) 255/2083
Non-Black*	5.61 (0.30) 423/9886	5.27 (0.38) 236/5835	5.41 (0.38) 246/5844	13.01 (0.51) 666/6378	12.67 (0.65) 381/3731	12.88 (0.66) 388/3762
Men†	6.27 (0.34) 395/8084	6.38 (0.44) 237/4768	6.53 (0.43) 259/4867	13.04 (0.61) 460/4369	14.60 (0.85) 283/2524	14.31 (0.83) 294/2644
Women‡	5.26 (0.34) 288/7171	4.45 (0.42) 145/4280	6.27 (0.48) 201/4187	13.27 (0.55) 591/5545	12.07 (0.67) 339/3340	13.22 (0.70) 349/3201
Men						
Black	6.93 (0.64) 134/2434	6.86 (0.84) 77/1464	9.41 (0.90) 113/1464	13.44 (1.14) 142/1267	16.05 (1.64) 90/776	18.34 (1.73) 107/756
Non-Black	5.99 (0.40) 261/5650	6.13 (0.51) 160/3304	5.32 (0.47) 146/3403	12.87 (0.72) 318/3102	14.01 (0.99) 193/1748	12.73 (0.94) 187/1888
Women						
Black	5.52 (0.51) 126/2935	4.94 (0.65) 69/1749	7.25 (0.75) 101/1746	13.40 (0.86) 243/2269	12.90 (1.07) 151/1357	13.52 (1.11) 148/1327
Non-Black	5.11 (0.46) 162/4236	4.15 (0.56) 76/2531	5.59 (0.64) 100/2441	13.14 (0.71) 348/3276	11.51 (0.86) 188/1983	13.00 (0.91) 201/1874
Age <65 years	3.67 (0.30) 183/6471	3.25 (0.36) 103/3844	4.11 (0.39) 131/3869	8.80 (0.59) 228/2939	9.71 (0.82) 146/1746	9.51 (0.78) 152/1754
Age 65+ years	7.38 (0.35) 500/8784	7.10 (0.45) 279/5204	8.11 (0.47) 329/5185	15.31 (0.54) 14823/6975	14.76 (0.68) 476/4118	15.85 (0.71) 491/4091
Diabetes	7.34 (0.42) 338/6024	6.67 (0.53) 184/3612	7.82 (0.58) 210/3532	15.76 (0.70) 494/3972	15.55 (0.91) 297/2358	16.53 (0.94) 296/2315
No diabetes	4.83 (0.29) 345/9231	4.69 (0.37) 198/5436	5.53 (0.37) 250/5522	11.51 (0.49) 557/5942	11.58 (0.64) 325/3506	11.93 (0.65) 347/3530
Atrial fibrillation	16.36 (3.81) 17/147	27.62 (6.21) 18/99	18.12 (5.37) 12/88	30.42 (5.93) 22/108	36.66 (7.07) 20/75	28.46 (6.56) 15/66
No atrial fibrillation	5.64 (0.25) 614/13915	5.31 (0.31) 343/8229	6.28 (0.33) 416/8226	12.90 (0.42) 940/8945	12.90 (0.55) 551/5266	13.71 (0.57) 582/5252

	In-trial 6-year rates per 100 (se) Total events/number at risk			In-trial and post-trial 10-year rates per 100 (se) Total events/number at risk		
	Chlor	Aml	Lis	Chlor	Aml	Lis
CHD at baseline	6.83 (0.51) 210/3943	6.62 (0.70) 105/2202	7.37 (0.66) 138/2270	14.82 (0.85) 314/2597	14.04 (1.11) 157/1456	15.62 (1.14) 186/1499
No CHD at baseline	5.38 (0.27) 463/11200	5.09 (0.34) 273/6777	6.12 (0.37) 317/6715	12.62 (0.47) 729/7245	12.80 (0.60) 457/4365	12.97 (0.61) 448/4301

Abbreviations: Afib, atrial fibrillation; Aml, amlodipine; CHD, coronary heart disease; Chlor, chlorthalidone; Lis, lisinopril; trt, treatment.

* In-trial race-by-lisinopril/chlorthalidone interaction $P=0.005$, in-trial race-by-amlodipine/lisinopril interaction $P=0.012$

† In-trial gender-by-lisinopril/amlodipine interaction $P=0.041$

Table 3

Adjusted in-trial and post-trial mortality outcomes among those with in-trial nonfatal stroke by treatment group comparison (Cohort 2)*

Mortality	Chlorthalidone N=494		Amlodipine N=282		Lisinopril N=337		Amlodipine/Chlorthalidone		Lisinopril/Chlorthalidone		Lisinopril/Amlodipine	
	n	10-y rate/100 persons	n	10-y rate/100 persons	n	10-y rate/100 persons	HR (95% CI)*	P-value	HR (95% CI)*	P-value	HR (95% CI)*	P-value
All-cause	299	49.93	178	51.64	196	49.35	1.06 (0.88–1.28)	0.540	1.04 (0.87–1.25)	0.668	0.97 (0.79–1.19)	0.776
CVD	149	30.13	101	34.33	96	26.33	1.20 (0.93–1.55)	0.154	1.01 (0.78–1.30)	0.970	0.86 (0.65–1.14)	0.285
HF	15	2.24	10	3.27	9	1.25	1.26 (0.56–2.82)	0.574	0.86 (0.37–2.00)	0.734	0.78 (0.31–1.93)	0.588
Stroke	43	8.33	26	9.48	40	12.10	1.03 (0.63–1.69)	0.893	1.50 (0.97–2.31)	0.069	1.38 (0.84–2.27)	0.207
Other CVD	91	20.27	65	23.55	47	13.21	1.27 (0.92–1.75)	0.140	0.79 (0.56–1.13)	0.200	0.66 (0.45–0.96)	0.029
Non-CVD	142	26.67	70	23.95	92	27.11	0.87 (0.65–1.17)	0.360	1.06 (0.81–1.38)	0.671	1.14 (0.83–1.56)	0.421

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

* Adjusted for age, race, gender, diabetes, CHD at baseline, current smoker, baseline SBP, and lipid medications