Mortality and Morbidity During and After the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

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A randomized, double-blind, active-controlled, multicenter trial assigned 32,804 participants aged 55 years and older with hypertension and ≥1 other coronary heart disease risk factors to receive chlorthalidone (n=15,002), amlodipine (n=8898), or lisinopril (n=8904) for 4 to 8 years, when double-blinded therapy was discontinued. Passive surveillance continued for a total follow-up of 8 to 13 years using national administrative databases to ascertain deaths and hospitalizations. During the post-trial period, fatal outcomes and nonfatal outcomes were available for 98% and 65% of participants, respectively, due to lack of access to administrative databases for the remainder. This paper assesses whether mortality and morbidity differences persisted or new differences developed during the extended follow-up. Primary outcome was cardiovascular mortality and secondary outcomes were mortality, stroke, coronary heart disease, heart failure, cardiovascular disease, and end-stage renal disease. For the post-trial period, data are not available on medications or blood pressure levels. No significant differences ($P<.05$) appeared in cardiovascular mortality for amlodipine (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.93–1.06) or lisinopril (HR, 0.97; CI, 0.90–1.03), each compared with chlorthalidone. The only significant differences in secondary outcomes were for heart failure, which was higher with amlodipine (HR, 1.12; CI, 1.02–1.22), and stroke mortality, which was higher with lisinopril (HR, 1.20; CI, 1.01–1.41), each compared with chlorthalidone. Similar to the previously reported in-trial result, there was a significant treatment-by-race interaction for cardiovascular disease for lisinopril vs chlorthalidone. Black participants had higher risk than non-black participants taking lisinopril compared with chlorthalidone. After accounting for multiple comparisons, none of these results were significant. These findings suggest that neither calcium channel blockers nor angiotensin-converting enzyme inhibitors are superior to diuretics for the long-term prevention of major cardiovascular complications of hypertension. *J Clin Hypertens (Greenwich).* 2012;14: 20–31. ©2011 Wiley Periodicals, Inc.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a multicenter randomized double-blind, active-controlled clinical trial designed to determine whether the primary end point of fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI) was reduced among high-risk hypertensive participants (n=42,418) treated initially with a calcium channel blocker (CCB), an angiotensin-converting enzyme (ACE) inhibitor, or an α-blocker, each compared with participants treated initially with a thiazide-type diuretic.[1,2] Prespecified secondary end points included all-cause and cause-specific mortality, stroke, heart failure (HF), cardiovascular disease (CVD), and end-stage renal disease (ESRD).

Participants in the chlorthalidone (n=15,255), amlodipine (n=9048), and lisinopril (n=9054) treatment groups were followed for a mean of 4.9 years.[3] Neither the primary outcome nor all-cause mortality differed among treatment groups. There was a 38% higher HF rate with amlodipine, and a 10%, 15%, and 19% higher rate of CVD, stroke, and HF, respectively, with lisinopril compared with chlorthalidone. For stroke, there was a statistically significant race-by-treatment interaction (40% higher stroke rate with lisinopril vs chlorthalidone in black participants). Participants in the doxazosin treatment group (n=9061)

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were followed for a mean of 3.2 years. This arm was terminated early due to a 25% higher incidence of CVD events, including a nearly two-fold higher risk of HF, accompanied by very low probability of reaching a statistically significant difference in the primary end point.[4,5] Therefore, in this paper we do not address outcomes in participants treated with doxazosin, who had a shorter in-trial follow-up due to early termination of the treatment arm.

Reasons for post-trial follow-up in long-term clinical trials include assessing (1) whether in-trial trends diminish, remain constant, or increase (a legacy effect) with time;[6] (2) whether new beneficial effects develop (another type of legacy effect);[7] (3) long-term safety issues; and (4) downstream consequences of in-trial events. Research questions can be formulated as a change or persistence of HRs for treatment vs control. Many previous outcome trials have examined long-term follow-up of randomized treatment groups after the randomized interventions were discontinued,[8–15] even though limited to no data on medication use or concomitant variables (eg, blood pressure [BP], cholesterol) are available in the post-trial period. Similar to ALLHAT, the Systolic Hypertension in the Elderly Program (SHEP)[9] did not have any post-trial follow-up data on BP or medication use. When follow-up data have been available in trials, medication use and intervention variables became similar in randomized groups within a few years after removal from randomized interventions.[8,13,14]

The purpose of this paper is to report mortality and morbidity of ALLHAT participants during 8 to 13 years after randomization using in-trial data plus post-trial data from administrative databases to assess long-term effects of first-step antihypertensive treatment with a thiazide-type diuretic, a CCB, or an ACE inhibitor.

Further, we report whether significant differences in clinical outcomes observed during the trial persisted or disappeared post-trial (eg, HF), the latter suggesting a relationship to current treatment, and whether significant differences emerged during the entire follow-up period for outcomes that were not statistically different at the trial's end (eg, CHD), suggesting a lag until maximum effect. Such comparisons of effects of different regimens during various timeframes could inform the initial choice for clinicians interested in long-term benefits. The primary prespecified outcome for these analyses is CVD mortality, the major end point relevant to the tested treatments that includes the most randomized participants.

METHODS

Details of the design and main results of this trial have been previously published.[2–5] Post-trial follow-up of participants through 2006 was accomplished using the National Death Index (NDI), Social Security Administration (SSA), Center for Medicare and Medicaid Services (CMS), and the United States Renal Data System (USRDS) databases. All participants gave written informed consent, and all centers obtained institutional review board approval for the trial. The institutional review board of The University of Texas Health Science Center at Houston approved the long-term follow-up study.

ALLHAT Participants

Eligible participants were men and women 55 years and older with untreated or briefly (<2 months) treated systolic BP (SBP) 140 to 180 mm Hg and/or diastolic BP (DBP) 90 to 110 mm Hg or who took antihypertensive medication (<3 drugs) for at least 2 months with BP $\leq$160/100 mm Hg. Participants also needed to have a prior CVD event, known atherosclerotic CVD, or another risk factor for CHD.[3]

Double-Blind Treatment Protocol

The objective of ALLHAT was to compare newer classes of drugs (CCBs represented by amlodipine and ACE inhibitors by lisinopril) with an established thiazide-type diuretic (represented by chlorthalidone) in a randomized double-blind trial. To optimize statistical power for multiple comparisons, the randomization ratio was 1.7:1 for the thiazide vs each of the comparator drugs. Within the protocol-prescribed daily dose range (chlorthalidone 12.5–25 mg, amlodipine 2.5–10 mg, lisinopril 10–40 mg), the dose of each step 1 blinded medication was titrated in an attempt to achieve BP <140/90 mm Hg. If BP could not be controlled using the maximum dose of step 1 medication, open-label step 2 (reserpine, clonidine, or atenolol) and step 3 (hydralazine) medications were available from the ALLHAT drug distribution center. After initial titration visits, participants were seen routinely every 3 months during year 1 and every 4 months thereafter.

Laboratory Tests During Active Phase

Baseline laboratory test results for glucose, lipids, creatinine, and potassium levels were obtained after an overnight fast. Central laboratory performed the analyses. At years 2, 4, and 6, fasting total cholesterol and glucose levels were evaluated. Serum potassium and creatinine levels were measured at 1 month and years 1, 2, 4, and 6.

Extended Follow-Up Outcomes: Definitions and Determination

Mortality Only End Points. Mortality data were available during both in-trial and post-trial periods for the entire cohort except for Canadian participants (n=553) due to lack of availability of necessary identifying information (Figure 1). In-trial deaths were ascertained by investigators and confirmed by death certificates and post-trial deaths were ascertained from NDI and SSA. In-trial causes of death were determined by investigators. When the cause of death was reported as unknown, we used the NDI Plus database, which also

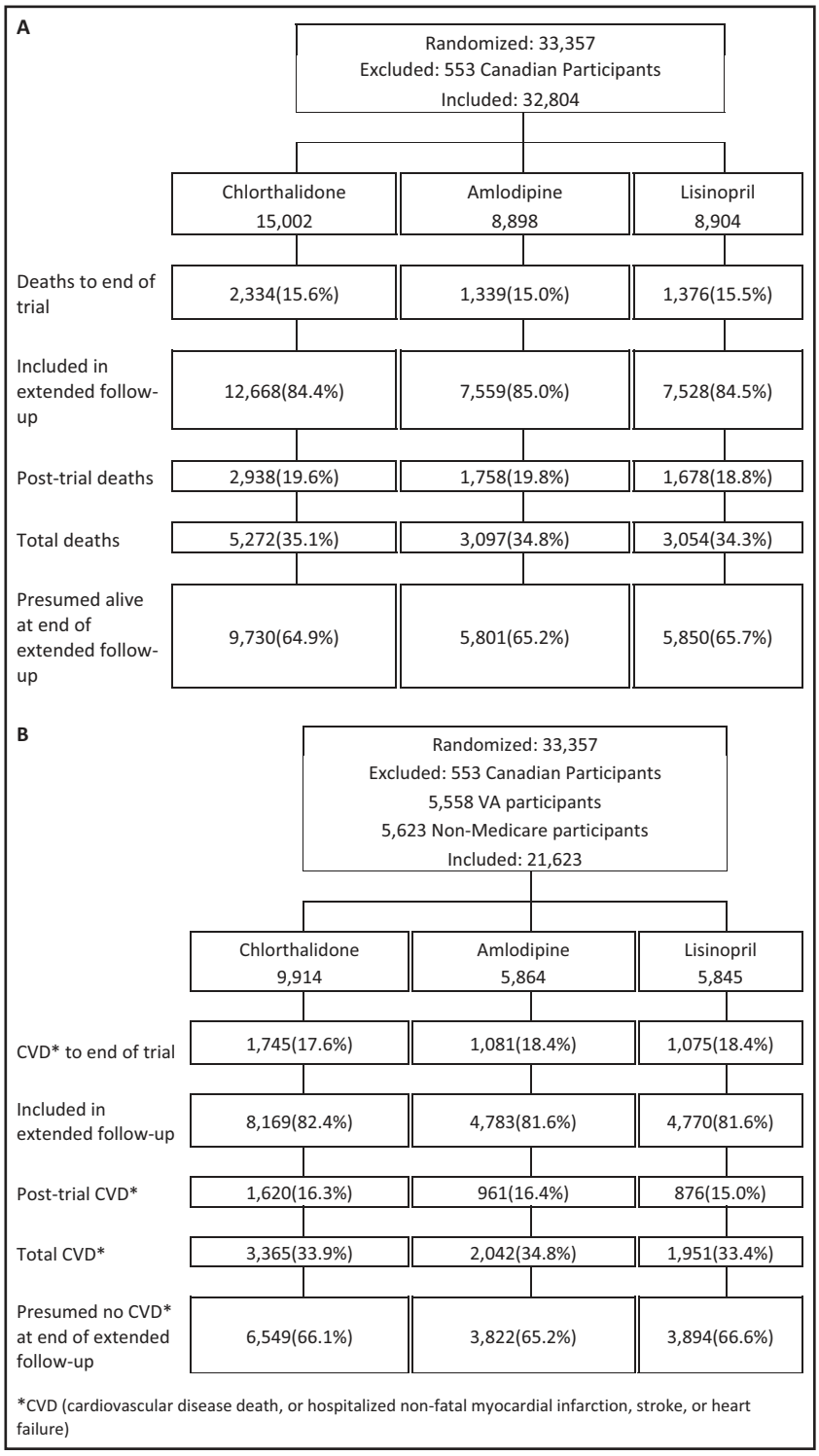

FIGURE 1. (A) CONSORT diagram for all-cause mortality. (B) CONSORT diagram for CVD.

provided cause-specific mortality for the post-trial period. Data from NDI and SSA used Social Security number, name, date of birth, and sex (NDI only) as matching criteria.

CVD mortality (death due to CHD, stroke, HF, or other CVD) was designated a priori as the primary end point. Total mortality and categories of death were prespecified and assessed as important secondary outcomes.[1]

A death identified through NDI or SSA was verified at the ALLHAT Clinical Trials Center (CTC) after receipt and review of a death certificate from the state or other jurisdiction. Of 6492 death certificates requested for the groups compared herein, 6488 (99.9%) were received and 6367 (98.1% of those received) were determined to be for an ALLHAT participant. Death certificates were not obtainable for 4 deaths; these deaths and their reported causes were included in the main analyses, as the matching algorithm had been demonstrated to be highly reliable. Causes of death (*International Statistical Classification of Diseases and Related Health Problems–Tenth Revision* [*ICD-10*] coding) from NDI Plus were collapsed into 11 categories.[1] These were initally provided under the *ICD-9* revision, and for deaths occurring in 1999 forward, the *ICD-10*. The World Health Organization's Two-way Translator for the Ninth and Tenth Revisions (1997) was used to convert *ICD-10* to *ICD-9* codes.[16]

Fatal and Nonfatal End Points. Hospitalization data were available for both in-trial and post-trial periods for the majority of participants. During the in-trial period, events were ascertained and classified by investigators and confirmed by the ALLHAT CTC based on discharge summaries. Unlike previous reports from ALLHAT, in-trial ESRD events (chronic dialysis or kidney transplant) were ascertained from the USRDS. During the post-trial period, nonfatal events were ascertained from the CMS (formerly HCFA) and the USRDS. Events identified through CMS data were classified using the provided *ICD-9* codes from those sources.

During the post-trial period, nonfatal outcome data, except for ESRD, were only available for participants from non-VA US clinical centers who had valid Medicare or Social Security numbers (65% of all participants) due to lack of access for administrative reasons. The following fatal/nonfatal composites were prespecified as secondary end points: CVD (CVD death or hospitalized non-fatal MI, stroke, or HF), CHD (CHD death or hospitalized nonfatal MI), stroke (fatal or nonfatal hospitalized), HF (fatal or nonfatal hospitalized), and ESRD.

Details on how the databases were used to identify events are noted in our online protocol.[1] For the post-trial period, data are not available on medications, BP levels, outpatient morbidity, or laboratory values.

Statistical Analysis

To compare baseline characteristics of participants assigned to amlodipine or lisinopril vs chlorthalidone, contingency tables and z tests were used. Intermediate outcomes of BP and laboratory measures are presented at baseline and year 4. Evaluations of the effect of assigned treatment on primary and secondary outcomes for the entire follow-up period were performed using Cox regression. Prespecified tests for interactions were conducted to determine whether the effects of the treatment intervention differ between subgroups, defined by age, race, sex, or diabetes status. Time-dependent Cox regression was used to estimate HRs associated with treatment assignment separately for in-trial and post-trial periods. Given the many multivariate, subgroup, and interaction analyses performed, statistical significance at the .05 level should be interpreted with caution. A Bonferroni step-down or Holm's procedure[17] was also utilized to give further perspective on the multiple analyses examined.

Estimated 10-year event rates for CVD mortality, total mortality, CHD, stroke, HF, CVD, and ESRD in the chlorthalidone group were calculated using a Weibull survival model of the observed results in the original study projected out to 10 years. Statistical power for each analysis was obtained using these rates and sample sizes within various treatment groups and subgroups of ALLHAT. For the primary outcome, for example, we estimated a 90% power with an α=.017 to detect a reduction in risk of 11.0% (HR, 0.89) for each group compared with the chlorthalidone group (10-year CVD mortality rate of 16%).[1,18] For other power estimations, see the extension protocol.[1]

RESULTS

Patient Characteristics

Table I presents patient characteristics at baseline for all participants included in the analyses of extension mortality and ESRD data. Mean baseline age was 67 years; 47% were women, 36% were black, 16% were Hispanic, and 43% had diabetes. There were nearly identical distributions of baseline factors in the 3 treatment groups for those included in the post-trial analyses and for all trial participants.[19]

Follow-Up Cohorts

Figure 1A shows the number of participants randomized and followed to the end of 2006 for all-cause mortality and ESRD. The mean length of follow-up including the post-trial period was 8.8 years. The maximum follow-up was 12.9 years. Figure 1B shows the number of participants randomized and followed up to the end of 2006 for fatal/nonfatal CVD.

Intermediate Outcomes

Intermediate outcome results were explored for the mortality cohort and the morbidity/mortality cohort defined for these extension analyses. Since the mortality cohort only excludes the 553 Canadian participants (1.7% of the total cohort), intermediate outcome results are very similar to those for the total cohort and are not presented or described here.[5] Intermediate outcome data for the morbidity/mortality cohort are shown in Table II. Four-year mean SBP was similar among participants randomized to amlodipine (+0.3 mm Hg, P=.33) to that among participants randomized to chlorthalidone and significantly higher

TABLE I. Baseline Characteristics of the ALLHAT Antihypertensive Component Participants (Excluding Canadian Participants)

	Total Randomized
No.	32,804
Age, mean (SD), y	66.9 (7.7)
65+, No. (%)	18,905 (57.6)
Non-Hispanic	
White, No. (%)	15,251 (46.5)
Black, No. (%)	10,682 (32.6)
Hispanic	
White, No. (%)	4152 (12.7)
Black, No. (%)	1090 (3.3)
Other, No. (%)	1629 (5.0)
Women, No. (%)	15,393 (46.9)
Years of education, mean (SD)	11.0 (4.0)
Taking antihypertensive treatment at baseline, No. (%)	29,633 (90.3)
Blood pressure, mean (SD), mm Hg	146/84 (16/10)
Treated at baseline, mean (SD), mm Hg	145/83 (16/10)
Untreated at baseline, mean (SD), mm Hg	156/89 (12/9)
Eligibility risk factors[a]	
Cigarette smoker, No. (%)	7169 (21.9)
ASCVD,[b] No. (%)	16,868 (51.4)
History of MI or stroke, No. (%)	7584 (23.1)
History of coronary revascularization, No. (%)	4224 (12.9)
Other ASCVD, No. (%)	7715 (23.5)
ST-T wave, No. (%)	3366 (10.3)
HDL-C <35 mg/dL, No. (%)	3812 (11.6)
LVH by ECG or echocardiography, No (%)	5440 (16.6)
LVH by Minnesota code, No. (%)	1480 (5.3)
Diabetes, No. (%)[c]	13,010 (42.7)
History of CHD at baseline, No. (%)	8238 (25.3)
Body mass index, mean (SD) kg/m^2	29.8 (6.2)
Lipid trial participants, No. (%)	8036 (24.5)

Abbreviations: CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; SD, standard deviation. [a]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. [b]History of myocardial infarction or stroke; history of coronary revascularization; major ST-segment depression on T-wave inversion on any electrocardiogram (ECG) in the past 2 years; other arteriosclerotic cardiovascular disease (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% documented by angiography or Doppler studies; ischemic heart disease documented by reversible or fixed ischemia on stress thalium or dipyridamole thalium, ST depression ≥1 mm for ≥1 minute on exercise testing or Holter monitoring; reversible wall motion abnormality on stress echocardiography; ankle-arm index <0.9; abdominal aortic aneurysm detected by ultrasonography, computed tomography scan, or x-ray; or carotid or femoral bruits. [c]Diabetes=history of diabetes or baseline fasting glucose ≥126 mg/dL or, in the case of missing fasting glucose, nonfasting glucose ≥200 mg/dL. No diabetes=no history of diabetes and baseline fasting glucose <126 mg/dL or, in the case of missing fasting glucose, nonfasting glucose <100 mg/dL.

among participants randomized to lisinopril (approximately 2 mm Hg, $P<.001$) than among participants randomized to chlorthalidone. At 4 years, total cholesterol was slightly higher (approximately 2 mg/dL), serum potassium levels were lower (approximately 0.3–0.4 mEq/L), and fasting glucose levels were higher (approximately 3–4 mg/dL) in the chlorthalidone group compared with amlodipine and lisinopril groups. Incident diabetes was higher in the chlorthalidone group compared with the amlodipine (approximately 1%, not significant) and lisinopril (approximately 3%, $P=.008$) groups. Follow-up estimated glomerular filtration rate was lower among participants assigned to chlorthalidone compared with those assigned to amlodipine ($P<.001$) but similar to those assigned to lisinopril.

Primary and Secondary Outcomes

Study events by treatment group are provided in Tables III and IV and Figures 2 and 3.

Amlodipine vs Chlorthalidone. No significant differences were observed between amlodipine and chlorthalidone for CVD mortality (HR, 1.00; 95% CI, 0.93–1.06) or for the secondary outcomes of all-cause mortality, non-CVD mortality, and cancer mortality (Table III, Figure 2). Other cause-specific mortality rates were also similar for the two groups. Fatal/hospitalized HF was higher among participants randomized to amlodipine (HR, 1.12; 95% CI, 1.02–1.22). No significant differences were observed for the other combined fatal/nonfatal end points. There was a significant interaction by race ($P=.04$) for HF with a significantly increased hazard for amlodipine vs chlorthalidone for black participants (HR, 1.26; 95% CI, 1.09–1.46) but not for non-blacks (HR, 1.04; 95% CI, 0.93–1.17) (Figure 3A). There were 2 other significant treatment interactions noted: stroke mortality ($P=.01$) for treatment by age (younger than 65: HR, 1.53; 95% CI, 1.06–2.21 [$P=.02$]; age 65+: HR, 0.89; 95% CI, 0.73–1.09 [$P=.26$]; when analyzed using age as a continuous variable, interaction of age*treatment was not significant [$P=.18$]); and cancer mortality ($P=.01$) for treatment by sex (female: HR, 1.20; 95% CI, 1.02–1.40; [$P=.02$]; male: HR, 0.93; 95% CI, 0.82–1.05 [$P=.26$]).

No significant differences were observed between amlodipine and chlorthalidone by time period for the primary outcome of CVD mortality or for stroke mortality (Table IV). For HF mortality, cancer mortality, and mortality due to accidents, suicides, and homicides, there were significant treatment by time period interactions ($P=.02$–$.04$). Post-trial HRs for these were not significant, except for HF mortality (post-trial HR, 0.71; 95% CI, 0.51–0.98). In-trial HRs for HF mortality, cancer mortality, and trauma mortality were 1.17 (95% CI, 0.89–1.54); 0.92 (95% CI, 0.80–1.06) and 0.51 (95% CI, 0.31–0.83), respectively. No significant differences were observed between amlodipine and chlorthalidone by time period for fatal/nonfatal CVD or stroke. For HF, there was a significant interaction ($P<.001$) with in-trial HR of 1.37 (95% CI, 1.20–1.55) and post-trial HR of 0.93 (95% CI, 0.82–1.06).

TABLE II. BP and Biochemical Results at 4 Years (In-Trial) by Treatment Group for the Mortality/Morbidity Cohort

				Treatment Group Differences and *P* Values			
	Chlorthalidone	Amlodipine	Lisinopril	A vs C		L vs C	
Systolic BP, mean (SD/No.), mm Hg	134.7 (15.8/5891)	135.0 (15.0/3514)	136.2 (17.2/3291)	0.3	.33	1.5	<.001
Diastolic BP, mean (SD/No.), mm Hg	76.4 (9.5/5889)	75.5 (9.4/3513)	76.4 (10.3/3291)	−0.9	<.001	−0.1	.76
				P value			
Controlled BP (<140/90 mm Hg), No. (%)	3839 (65.2)	2292 (65.2)	2008 (61.0)	.97		<.001	
Total cholesterol, mean (SD/No.), mg/dL	199.2 (42.2/5248)	197.6 (41.0/3077)	196.8 (40.9/2866)	−1.7	.08	−2.4	.01
Serum potassium, mean (SD/No.), mEq/L	4.1 (0.5/5111)	4.4 (0.5/2985)	4.5 (0.5/2788)	0.3	<.001	0.4	<.001
Fasting glucose, mean (SD/No.), mg/dL	126.1 (56.2/2928)	122.2 (50.1/1747)	121.3 (50.7/1609)	−3.9	.02	−4.8	.005
				P value			
Incident diabetes (among participants without diabetes at baseline), % (n/N)	8.5 (204/2412)	7.2 (105/1463)	6.0 (81/1340)	.15		.008	
Estimated glomerular filtration rate, mean (SD/No.) mL/min/1.73 m^2	68.3 (19.4/5129)	72.9 (20.3/3008)	68.7 (19.7/2810)	4.6	<.001	0.4	.41

Abbreviations: A, amlodipine; BP, blood pressure; C, chlorthalidone; L, lisinopril; SD, standard deviation.

TABLE III. Outcomes Through the Extension Period by Antihypertensive Treatment Group

	Chlorthalidone	Amlodipine			Lisinopril		
	10-y Rate (SE) per 100 Persons	10-y Rate (SE) per 100 Persons	Unadjusted HR[a] (95% CI)	*P* Value	10-y Rate (SE) per 100 Persons	Unadjusted HR[a] (95% CI)	*P* Value
Mortality outcomes							
All-cause mortality	33.6 (0.4)	33.2 (0.5)	0.98 (0.94–1.03)	.44	32.8 (0.5)	0.97 (0.93–1.02)	.19
CV mortality	16.4 (0.3)	16.3 (0.4)	1.00 (0.93–1.06)	.89	15.9 (0.4)	0.97 (0.90–1.03)	.33
CHD	8.7 (0.3)	8.5 (0.3)	0.99 (0.90–1.09)	.80	8.3 (0.3)	0.95 (0.86–1.04)	.26
Stroke	2.6 (0.1)	2.6 (0.2)	1.01 (0.84–1.20)[b]	.95	3.1 (0.2)	1.20 (1.01–1.41)	.03
Heart failure	1.9 (0.1)	1.7 (0.2)	0.94 (0.77–1.17)	.59	1.6 (0.2)	0.88 (0.71–1.10)	.26
Other CVD	4.3 (0.2)	4.4 (0.2)	1.03 (0.90–1.17)	.70	3.9 (0.2)	0.91 (0.79–1.04)	.17
Non-CV mortality	19.3 (0.4)	18.9 (0.5)	0.96 (0.90–1.02)	.22	18.8 (0.5)	0.97 (0.91–1.03)	.31
Cancer	8.1 (0.2)	8.4 (0.3)	1.02 (0.93–1.13)[c]	.65	8.4 (0.3)	1.01 (0.92–1.11)	.82
Kidney disease	1.1 (0.1)	1.1 (0.1)	1.02 (0.77–1.34)	.92	1.1 (0.1)	1.04 (0.79–1.37)	.77
Accident/suicide/homicide	1.0 (0.1)	0.8 (0.1)	0.79 (0.58–1.07)	.13	0.9 (0.1)	0.90 (0.67–1.20)	.47
Other non-CVD	10.3 (0.3)	9.8 (0.4)	0.93 (0.85–1.01)	.08	9.5 (0.3)	0.93 (0.86–1.02)	.13
Unknown cause	1.5 (0.1)	1.6 (0.1)	1.12 (0.89–1.39)	.33	1.6 (0.1)	1.05 (0.84–1.32)	.66
Combined fatal or nonfatal hospitalized events							
CHD	18.7 (0.5)	18.8 (0.6)	0.99 (0.92–1.08)	.89	18.2 (0.6)	0.98 (0.90–1.07)	.66
CVD	38.7 (0.6)	38.5 (0.7)	1.02 (0.97–1.08)	.41	37.6 (0.7)	0.99 (0.94–1.05)[d]	.70
Heart failure	15.4 (0.4)	16.1 (0.6)	1.12 (1.02–1.22)[e]	.01	15.1 (0.6)	1.00 (0.91–1.09)[f]	.94
Stroke	13.2 (0.4)	13.1 (0.5)	0.99 (0.89–1.09)	.81	13.7 (0.5)	1.04 (0.94–1.15)	.41
Cancer	14.3 (0.4)	15.5 (0.5)	1.08 (0.99–1.18)	.10	14.6 (0.5)	1.02 (0.93–1.11)	.74
ESRD	3.0 (0.2)	3.1 (0.2)	1.02 (0.87–1.20)	.77	3.0 (0.2)	0.98 (0.83–1.15)	.79

Abbreviations: CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; ESRD, end-stage renal disease; SE, standard error. [a]Comparisons are amlodipine (A) with chlorthalidone (C) and lisinopril (L) with C. [b]Stroke mortality=significant treatment × age interaction (*P*=.01 for interaction) for A vs C. Age younger than 65: hazard ratio (HR), 1.53 (95% confidence interval [CI], 1.06–2.21; *P*=.02). Age 65+: HR, 0.89 (95% CI, 0.73–1.09; *P*=.26). When analyzed using age as a continuous variable, interaction of age*treatment was not significant (*P*=.18). [c]Cancer mortality=significant treatment × sex interaction (*P*=.01 for interaction) for A vs C. Women: HR, 1.20 (95% CI, 1.02–1.40; *P*=.02). Men: HR, 0.93 (95% CI, 0.82–1.05; *P*=.26). [d]Fatal/nonfatal cardiovascular disease (CVD)=significant treatment × race interaction (*P*=.04 for interaction) for L vs C. Non-black: HR, 0.95 (95% CI, 0.88–1.01, *P*=.12), black: HR, 1.07 (95% CI, 0.98–1.17; *P*=.15). [e]Fatal/nonfatal HF=significant treatment × race interaction (*P*=.04 for interaction) for A vs C. Non-black: HR, 1.04 (95% CI, 0.93–1.17; *P*=.49), black: HR, 1.26 (95% CI, 1.09–1.46; *P*=.002). [f]Fatal/nonfatal HF=significant treatment × race interaction (*P*=.03 for interaction) for L vs C. Non-black: HR, 0.92 (95% CI, 0.82–1.04; *P*=.17), black: HR, 1.14 (95% CI, 0.98–1.33; *P*=.09).

There were no significant treatment–time period–race interactions (data not shown).

Lisinopril vs Chlorthalidone. No significant differences were observed between lisinopril and chlorthalidone for CVD mortality (HR, 0.97; 95% CI, 0.90–1.03) or for secondary outcomes of all-cause mortality, non-CVD mortality, or cancer mortality (Table III, Figure 2). Other cause-specific mortality rates were also similar in the 2 groups (Table III), except that the

TABLE IV. In-Trial and Post-Trial Hazard Ratios

	Hazard Ratio (95% Confidence Interval)					
	Amlodipine vs Chlorthalidone			Lisinopril vs Chlorthalidone		
	In Trial	Post Trial	*P* Value	In Trial	Post Trial	*P* Value
All-cause mortality	0.96 (0.90–1.03)	1.00 (0.94–1.06)	.43	0.99 (0.93–1.06)	0.95 (0.90–1.01)	.43
CV mortality	1.02 (0.92–1.13)	0.97 (0.89–1.07)	.51	1.02 (0.93–1.13)	0.92 (0.84–1.01)	.12
CHD	0.97 (0.85–1.11)	1.00 (0.88–1.14)	.74	0.99 (0.87–1.14)	0.90 (0.79–1.03)	.33
Stroke	0.99 (0.77–1.27)	1.02 (0.80–1.30)	.86	1.25 (0.99–1.58)	1.14 (0.90–1.44)	.59
Heart failure	1.17 (0.89–1.54)	0.71 (0.51–0.98)	.02	0.96 (0.71–1.28)	0.81 (0.59–1.11)	.44
Other CVD	1.09 (0.87–1.37)	0.99 (0.84–1.17)	.50	0.95 (0.75–1.21)	0.88 (0.74–1.05)	.59
Non-CV mortality	0.89 (0.81–0.98)	1.01 (0.93–1.09)	.05	0.95 (0.87–1.05)	0.98 (0.90–1.06)	.69
Cancer	0.92 (0.80–1.06)	1.12 (0.99–1.28)	.04	0.96 (0.84–1.11)	1.06 (0.93–1.21)	.34
Kidney disease	1.09 (0.66–1.78)	0.98 (0.70–1.38)	.74	1.30 (0.81–2.08)	0.93 (0.66–1.31)	.26
Accident/suicide/homicide	0.51 (0.31–0.83)	1.11 (0.75–1.66)	.02	0.73 (0.48–1.12)	1.09 (0.73–1.63)	.19
Other non-CVD	0.90 (0.78–1.05)	0.94 (0.84–1.05)	.67	0.95 (0.82–1.10)	0.93 (0.83–1.03)	.82
Unknown cause	1.10 (0.85–1.42)	1.17 (0.76–1.80)	.81	1.04 (0.80–1.36)	1.07 (0.69–1.67)	.91
Combined fatal or nonfatal hospitalized events						
CHD	0.97 (0.87–1.08)	1.03 (0.91–1.16)	.49	0.99 (0.89–1.10)	0.97 (0.86–1.10)	.83
CVD	1.05 (0.97–1.13)	1.00 (0.92–1.08)	.37	1.05 (0.98–1.14)	0.92 (0.85–1.00)	.02
Heart failure	1.37 (1.20–1.55)	0.93 (0.82–1.06)	<.001	1.11 (0.97–1.27)	0.91 (0.80–1.04)	.04
Stroke	0.93 (0.80–1.08)	1.03 (0.90–1.18)	.32	1.17 (1.02–1.35)	0.94 (0.82–1.07)	.03
Cancer	1.02 (0.91–1.15)	1.17 (1.02–1.35)	.15	1.02 (0.90–1.14)	1.02 (0.87–1.18)	>.99
ESRD	1.16 (0.91–1.48)	0.94 (0.76–1.16)	.20	1.10 (0.86–1.42)	0.90 (0.72–1.11)	.21

Abbreviations: CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; ESRD, end-stage renal disease

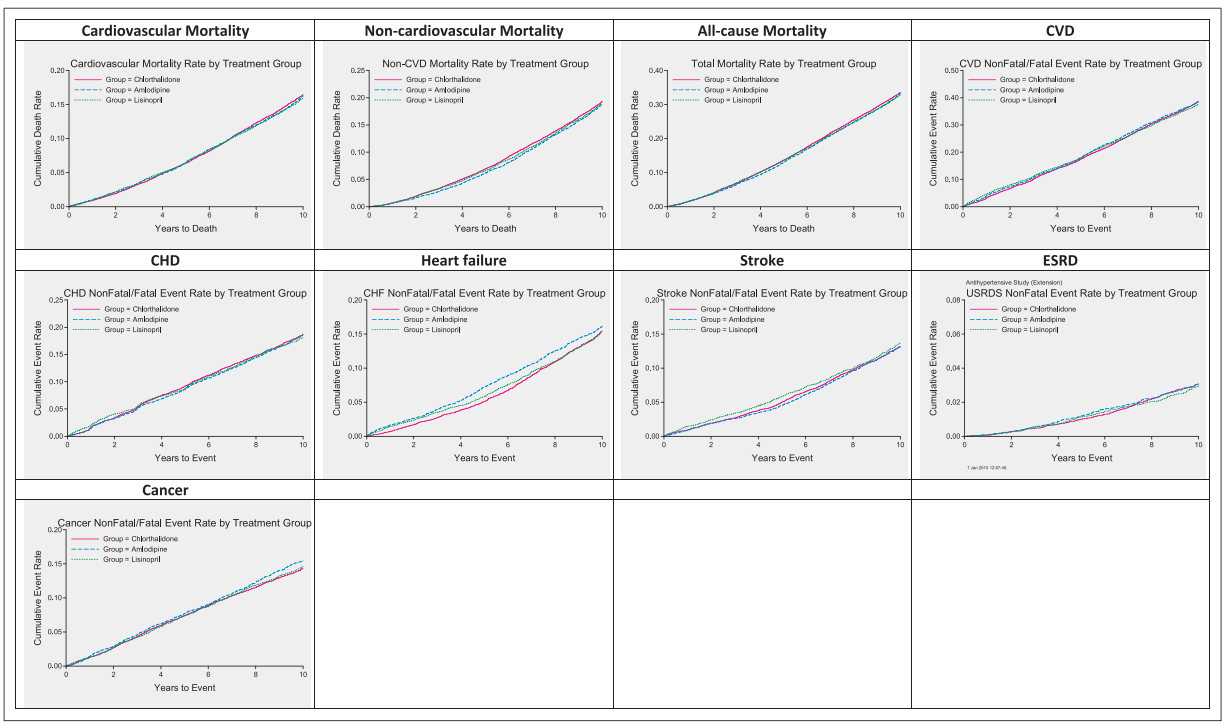

FIGURE 2. Kaplan-Meier plots.

lisinopril group had a 20% higher risk for stroke mortality (*P*=.03) with no significant interaction by race. Rates of combined fatal/nonfatal events, including stroke, were similar in the lisinopril and chlorthalidone groups. There was a significant interaction (*P*=.04) by race for the CVD outcome, but the HR

estimates for lisinopril vs chlorthalidone included 1.0 for both blacks (HR, 1.07; 95% CI, 0.98–1.17) and non-blacks (HR, 0.95; 95% CI, 0.88–1.01). There was a significant interaction (*P*=.03) by race for the HF outcome but the HR estimates for lisinopril vs chlorthalidone included 1.0 both for blacks (HR, 1.14;

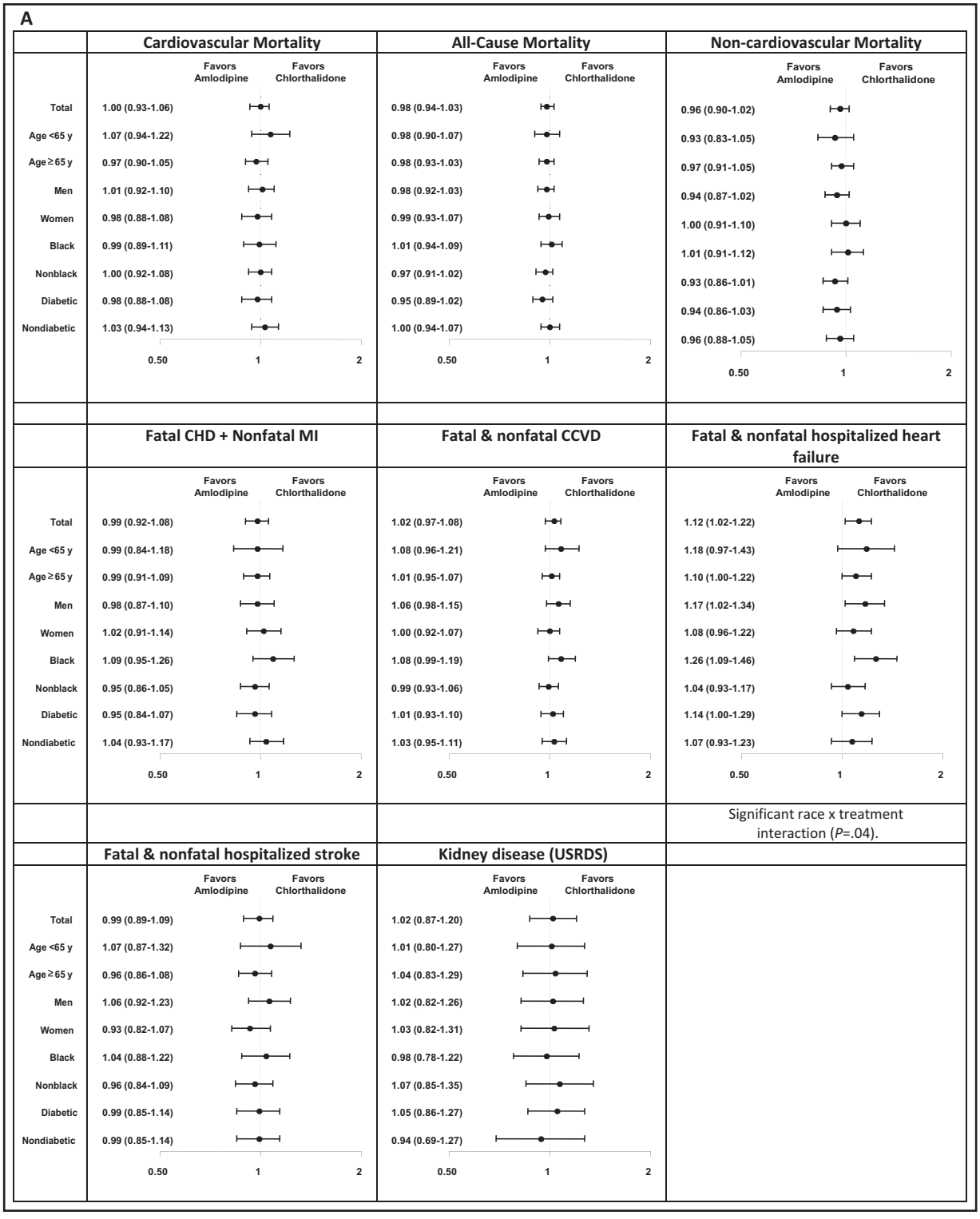

FIGURE 3. (A) Subgroup results through the extended follow-up – amlodipine vs chlorthalidone. (B) Subgroup results through the extended follow-up – lisinopril vs chlorthalidone.

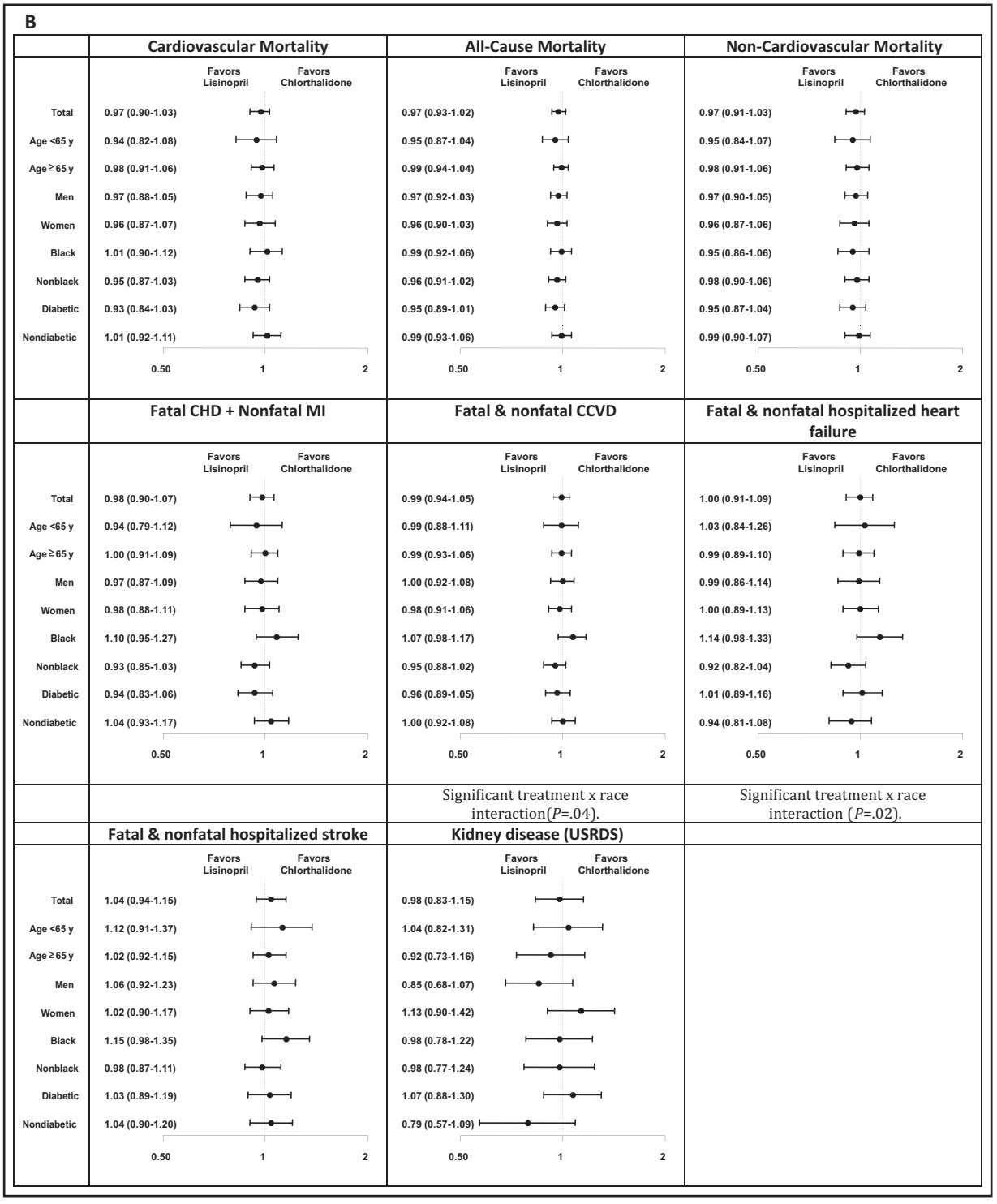

FIGURE 3. (A) Subgroup results through the extended follow-up – amlodipine vs chlorthalidone. (B) Subgroup results through the extended follow-up – lisinopril vs chlorthalidone.

95% CI, 0.98–1.33) and non-blacks (HR, 0.92; 95% CI, 0.82–1.04) (Figure 3B).

No significant differences were observed between lisinopril and chlorthalidone by time period for CVD mortality, stroke mortality, or HF mortality (Table IV). For the CVD mortality/morbidity outcome, there was a significant interaction (*P*=.02) with an in-trial HR of 1.05 (95% CI, 0.98–1.14) and post-trial HR of 0.92

(95% CI, 0.85–1.00). For HF, there was a significant interaction (P=.04) with an in-trial HR of 1.11 (95% CI, 0.97–1.27) and post-trial HR of 0.91 (95% CI, 0.80–1.04). For stroke, there was a significant interaction (P=.03) with an in-trial HR of 1.17 (95% CI, 1.02–1.35) and post-trial HR of 0.94 (95% CI, 0.82–1.07). There were no significant treatment–time period–race interactions (data not shown).

Using $P<.05$, there were 6 significant interactions (Table III, Figure 3A and 3B) of 180 analyses on the entire follow-up (18 outcomes × 5 [overall + 4 subgroups] categories × 2 treatment comparisons) and 7 significant interactions (Table IV) of 36 analyses (18 outcomes × 2 treatment comparisons across time periods). Using the Holm's procedure, in either case, the only significant result was for the amlodipine vs chlorthalidone comparison for HF for the in-trial HR of 1.37 vs the post-trial HR of 0.93 (see above).

Secondary sensitivity analyses using data captured entirely from databases (as in the post-trial period) for both the in-trial and post-trial periods showed similar results (data not shown).

DISCUSSION

Findings from the ALLHAT extension study show that during the entire follow-up period, the only major outcomes that were significantly different were a higher HF rate with amlodipine compared with chlorthalidone (HR, 1.12; P=.01) and a higher stroke mortality rate with lisinopril compared with chlorthalidone (HR, 1.20; P=.03). The former result was mostly attributable to the in-trial difference and the latter result was due to the addition of events post-trial, which converted a not quite significant in-trial result (HR, 1.25; P=.05) to a significant one. Thus, neither for this nor any other outcome, such as CHD, was there evidence of any lagged (late-emerging) effect. In the post-trial period, there were only two differences in major outcomes: a lower HF mortality rate in the amlodipine group compared with the chlorthalidone group (HR, 0.71; 95% CI, 0.51–0.98, P=.02 for heterogeneity comparing in-trial with post-trial) and a lower CVD rate in the lisinopril group compared with the chlorthalidone group (HR, 0.92; 95% CI, 0.85–1.00, P=.02 for heterogeneity comparing in-trial with post-trial). These results could be consistent with many other post-trial results wherein the medications used, including the use of diuretics, likely became more similar across the randomized groups or could be due to chance. There was no difference in HF mortality (HR, 0.94; 95% CI, 0.77–1.17) or in CVD (HR, 0.99; 95% CI, 0.94–1.05) during the entire follow-up period. Although the apparent persistence or emergence (a legacy effect) of post-trial differences may seem plausible (as discussed below), it must be noted that post-trial comparisons are no longer protected by blinded randomized therapy. Legacy effects for antihypertensive treatment due to prevention of nonfatal events, attenuation of left ventricular modeling, or prevention or regression of pathological or functional changes caused by hypertension have been shown for mortality, but mainly where the comparator is placebo or usual care.[6]

In-trial results in this reduced cohort for all-cause mortality, stroke mortality, fatal and nonfatal CVD events, and renal outcomes were similar to what had been reported previously from the entire trial population. Notably, such similarities for lisinopril compared with chlorthalidone included higher HRs for stroke mortality (HR of 1.26 originally, 1.25 here), combined CVD (CVD plus revascularizations and hospitalized angina) (HR 1.07 originally and 1.05 as CVD was defined in this analysis), and HF (1.11 originally and 1.11 here), although the CVD and HF HRs were not statistically significant in this smaller cohort. The similarities for amlodipine compared with chlorthalidone included the significantly higher HR for HF (1.35 originally vs 1.37 here), significantly lower noncardiovascular mortality (0.90 originally and 0.89 here), and significantly lower trauma mortality (0.49 originally and 0.51 here). These noncardiovascular and trauma mortality differences disappeared post-trial, suggesting that they were related to randomized treatment, but we have no plausible explanation and these associations may merit further study.

The overall results suggest that observed in-trial differences dissipated over time as participants were taken off blinded study medications and put on open-label therapy. With the exception of the HF and stroke mortality results, there was no evidence of a legacy effect. Unfortunately, post-trial antihypertensive medications usage is unknown. It is likely that treatments became similar across randomized groups, which would cause post-trial HRs to be close to one. For the lisinopril-chlorthalidone comparison, another possibility is that participants may have received thiazide-type diuretics added to ACE inhibitors, which could lead to decreases in CVD rates compared with those who were simply continued on a thiazide. If such altered regimens were more common among black participants, this could explain the proportionately greater narrowing of differences for stroke, and perhaps for HF, in black compared with non-black participants. These subgroup results contrast with those in the amlodipine-chlorthalidone comparison, where lowered post-trial HRs for HF were proportionately similar in black and non-black participants.

An additional possibility is that the in-trial to post-trial difference for CVD suggests some delayed effects (or a legacy effect) for lisinopril that may make it (or any ACE inhibitor) a desirable adjunct in antihypertensive regimens.[20–23] ACE inhibitors have shown beneficial CVD effects in some other trials, especially in combination with thiazide-type diuretics, in treating participants with hypertension, diabetes, high CVD risk, or after strokes.[23–26]

Overall, these long-term results from passive follow-up suggest that differences in major CVD outcomes

between regimens diminished once the clinical trial stopped and the antihypertensive regimens most likely became similar. In addition, for CVD and all-cause mortality, as well as most other secondary outcomes (except for stroke mortality for lisinopril vs chlorthalidone), there were no new differences that appeared as a net result of any possible intermediate effects observed or not recognized during the trial. For example, differences in effects on glucose, lipids, HF or stroke did not apparently result in overall net differences in CVD or all-cause mortality. Specific effects on post-trial outcomes will be reported further in separate papers addressing participants who developed diabetes or HF, or changes in glucose or renal function, within the ALLHAT trial. Long-term renal outcomes from the USRDS will also be further reported.

STRENGTHS AND LIMITATIONS

The extended follow-up study had several strengths. ALLHAT was the largest antihypertensive randomized controlled outcome trial conducted to date, with 32,804 participants in the 3 arms. Also, ALLHAT was a double-blind, randomized, active-controlled clinical trial with well-documented procedures for outcome ascertainment, which were supplemented by national databases to capture outcomes for both post-trial and in-trial events.

The analyses of the extended data set had several limitations. Participants were taken off blinded therapies at the trial's end, and information about medications participants used post-trial was not available. BP and laboratory data were not obtained post-trial. It should be noted that medication use and/or BPs in other major randomized trials with post-trial follow-up have tended to converge.[8,10] All participants were not included in the analyses, ie, 533 Canadian participants were in neither the mortality nor combined mortality/morbidity analyses, and neither VA participants (n=5558) nor those without a Medicare number (n=5623) were in the combined mortality/morbidity analyses except for ESRD outcomes. Event ascertainment, except for ESRD, was not the same in-trial and post-trial, but when analyses were done capturing information from databases for both in-trial and post-trial periods, results were remarkably similar. Finally, many analyses were performed and only one was significant by a strict multiple comparison standard. Given these limitations, it is noteworthy that the in-trial HRs were quite similar to those observed in the original analyses that included all the participants.

CONCLUSIONS

These long-term follow-up results from ALLHAT show that significant cardiovascular outcome differences observed during the trial did not persist except for an excess of HF in the amlodipine group compared with the chlorthalidone group. No new significant differences were observed during the entire follow-up period that had not been present in-trial with the exception of a higher stroke mortality rate for participants taking lisinopril compared with chlorthalidone. Lastly, no new differences in major outcomes developed post-trial, except for slightly lower major CVD events in the lisinopril group compared with the chlorthalidone group. However, there was no difference in major CVD events or CVD mortality during the entire follow-up period. These findings, therefore, suggest that neither CCBs nor ACE inhibitors are superior to diuretics in long-term prevention of major cardiovascular complications of hypertension.[27,28]

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