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Should Antihypertensive Treatment Recommendations Differ in Patients With and Without Coronary Heart Disease? (From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT])

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Abstract

Thiazide-type diuretics have been recommended for initial treatment of hypertension in most patients, but should this recommendation differ for patients with and without coronary heart disease (CHD)? The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blind hypertension treatment trial in 42,418 participants with high risk of combined cardiovascular disease (CVD) (25% with pre-existing CHD). This post-hoc analysis compares long-term major clinical outcomes in those assigned amlodipine (n=9048) or lisinopril (n=9054) with those assigned chlorthalidone (n=15,255), stratified by CHD status. After 4–8 years, randomized treatment was discontinued. Total follow-up (active treatment + passive surveillance using national databases for deaths and

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hospitalizations) was 8–13 years. For most CVD outcomes, ESRD, and total mortality, there were no differences across randomized treatment arms regardless of baseline CHD status. In-trial rates of CVD were significantly higher for lisinopril compared with chlorthalidone, and rates of heart failure were significantly higher for amlodipine compared with chlorthalidone in those with and without CHD (overall HRs: 1.10, $p<0.001$ and 1.38, $p<0.001$, respectively). During extended follow-up, significant outcomes according to CHD status interactions ($p=0.012$) were noted in amlodipine versus chlorthalidone comparison for CVD and CHD mortality, $HR=0.88$, $p=0.04$ and 0.84 , $p=0.04$, respectively, in those with CHD at baseline and 1.06 , $p=0.15$ and 1.08 , $p=0.17$ in those without. The results of the overall increased stroke mortality in lisinopril compared to chlorthalidone ($HR=1.2$; $p=0.03$) and hospitalized heart failure in amlodipine compared to chlorthalidone ($HR=1.12$; $p=0.01$) during extended follow-up did not differ by baseline CHD status. In conclusion, these results provide no reason to alter our previous recommendation to include a properly dosed diuretic (such as chlorthalidone 12.5–25 mg/day) in the initial antihypertensive regimen for most hypertensive patients.

Keywords

hypertension; coronary heart disease; cardiovascular disease; diuretics; heart disease; antihypertensive treatment

Thiazide-type diuretics are included in agents recommended for initial treatment of hypertension in most patients, including those with chronic coronary heart disease (CHD).^{1,2} Angiotensin-converting enzyme (ACE)-inhibitors and beta-blockers are recommended for initial treatment of hypertension in all patients with chronic CHD.³ The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a randomized, double-blinded, comparative effectiveness trial with 42,418 patients aged 55 and older at high risk of cardiovascular disease (CVD), including pre-existing CHD. The overall results of ALLHAT indicated that neither a calcium channel blocker (CCB) (amlodipine; 2.5–10 mg/day), an angiotensin-converting enzyme (ACE)-inhibitor (lisinopril; 10–40 mg/day), nor an alpha-receptor blocker (doxazosin; 2–8 mg/day) was superior to thiazide-like diuretic (chlorthalidone 12.5–25 mg/day) in preventing CHD or any other major cardiovascular or renal outcome. Chlorthalidone was superior in preventing heart failure (HF) and stroke (for stroke, compared with doxazosin, and for Blacks, with lisinopril).^{4–6} To further assess the relative efficacy of these agents among patients with pre-existing CHD, participants were stratified by presence or absence of pre-existing CHD at time of enrollment and analyzed according to their randomized drug assignment. Incidence of the primary outcome, as well as predefined secondary outcomes (stroke, all-cause mortality, end-stage renal disease [ESRD], combined CHD [CHD and its components], and combined CVD [CVD and its components]) was determined for each subgroup, and hazard ratios (HRs) comparing amlodipine and lisinopril to chlorthalidone were estimated.

METHODS

ALLHAT participants were men and women aged 55 years with stage 1 or 2 hypertension and at least one additional CHD risk factor, including pre-existing CVD. Of 42,418 subjects,

33,357 were randomly assigned to chlorthalidone (n=15,255), amlodipine (n=9048), or lisinopril (n=9,054).⁴ A fourth arm of the study, which included 9,061 participants assigned to doxazosin, was terminated early^{7,8} and is not included in this analysis, along with 250 other participants (0.7%) whom baseline CHD status was not ascertained. Of those with known CHD status at entry, 8,415 participants (25%) had pre-existing evidence of CHD, with medical records indicating 1 of the following: known prior myocardial infarction (MI) (including silent MI), angina, primary cardiac arrest, angiographically-defined coronary stenosis > 50%, reversible perfusion defects on cardiac scintigraphy, or prior coronary revascularization procedures.^{4,9} The rationale and details of the ALLHAT design have been previously published.¹⁰ Study medications were identically-appearing chlorthalidone, lisinopril, or amlodipine capsules. Blood pressure (BP) lowering was achieved by titrating blinded study drug dose and adding open-label step 2 (atenolol, clonidine, or reserpine) or step 3 (hydralazine) agents as necessary to obtain a BP goal of <140/90 mm Hg; each BP result was the average of 2 seated measurements taken by trained observers using standardized techniques.

Follow-up visits were conducted at 1, 3, 6, 9, and 12 months and every 4 months thereafter. Outcomes were analyzed using an intent-to-treat approach. The primary outcome was a composite of fatal CHD or nonfatal MI. Four major prespecified secondary outcomes included all-cause mortality, fatal and nonfatal stroke, combined CHD (primary outcome, coronary revascularization, or hospitalized angina), and combined CVD (combined CHD, stroke, treated angina, HF [fatal, hospitalized, or treated without hospitalization], or peripheral arterial disease). End-stage renal disease (dialysis, renal transplant, or kidney disease death), cancer events, gastrointestinal bleeding, and individual components of major outcomes were also prespecified. Standardized procedures were used for reporting and validating study outcomes and have been published previously in detail.⁸

After trial close-out in March 2002, blinded randomized treatment was discontinued, clinics and patients were unblinded as to the treatment assignment, and ALLHAT participants were passively followed through 2006.¹¹⁻¹³ Post-trial follow-up was accomplished using the National Death Index (NDI), Social Security Administration (SSA), Centers for Medicare and Medicaid Services (CMS), and the United States Renal Data System (USRDS) databases. Post-trial mortality data and non-fatal ESRD were unavailable for Canadian participants (n=553), because necessary identifying information was unavailable. Post-trial nonfatal outcome data on hospitalized events other than ESRD were available only for participants from non-Veterans Affairs U.S. clinical centers who had valid Medicare or Social Security numbers (65% of all participants).

Data were summarized as means and standard deviations for continuous variables and number of subjects and percentage for categorical variables. Baseline characteristics were compared in participants across baseline CHD strata, and BP and medication use data at 36 months of follow-up were compared in participants across baseline CHD and treatment strata. Glomerular filtration rate (GFR) was estimated using the simplified Modification of Diet in Renal Disease (MDRD) Study equation.¹⁴ Significance testing was performed using the t-test for continuous covariates and contingency table analyses for categorical covariates.

The proportional hazards model was used to determine time-to-event HRs and 95% confidence intervals (CI). Heterogeneities of treatment effects across baseline CHD strata were examined by testing for treatment-CHD stratum interactions using *P* values <0.05. Given the many subgroup and interaction analyses performed, statistical significance at the *P* <0.05 level should be interpreted with caution. All statistical analyses were carried out using STATA version 11.0 (College Station, Texas).

All participants gave written informed consent, and all centers obtained institutional review board approval. The investigational review board of The University of Texas Health Science Center at Houston approved the long-term follow-up study.

RESULTS

The number of participants by CHD status who entered the trial and their status at the end of the in-trial period (March, 2002) are shown in Figure 1. There were 8,415 participants with CHD at baseline and 24,692 participants without randomized into ALLHAT, of whom 6,768 (80%) and 20,911 (85%), respectively, were known alive at the end of the in-trial period.

Those with CHD compared with those without were slightly older, more likely to be male, less likely to be Black, more likely to have higher education attainment, and more likely to be on antihypertensive treatment prior to enrollment (Table 1). Also, they had slightly lower systolic blood pressure (SBP), lower HDL- and LDL-cholesterol, lower BMI, lower estimated GFR, and were less likely to be in the lipid-lowering trial due to study eligibility criteria. In addition, they were less likely to have diabetes and fewer were smokers—also likely due to eligibility criteria. The prevalence of atrial fibrillation at baseline was low but greater in those with CHD. There were almost no significant differences across the 3 drug treatment groups in baseline BP or other characteristics at enrollment within either CHD subgroup. During the post-trial period, we passively followed 8,238 participants with and 24,316 participants without evidence of CHD at baseline for mortality status and 6,456 participants with and 20,629 participants without CHD for morbidity status¹¹ (see online supplemental Figures S1 and S2).

BP decreased substantially during the first year and showed modest further decreases over subsequent years in both CHD subgroups in all treatment groups, although decreases in SBP were less in those without CHD than in those with across treatment groups (Figure 2 and Table 2). Together with ~1 mm Hg higher baseline BPs, this resulted in 1–2 mm Hg higher SBPs in those without CHD than in those with during the study. Diastolic BPs showed similar differences between CHD subgroups. In those with CHD, mean reduction in SBP from baseline was 1–2 mm Hg greater with chlorthalidone than with lisinopril or amlodipine. Mean attained SBP in those with CHD was 1–2 mm Hg lower in chlorthalidone versus lisinopril and amlodipine arms. Randomized treatment-related differences were greater in those without CHD: follow-up SBPs were 2–3 mm Hg lower in the chlorthalidone than in either amlodipine or lisinopril arm.

While BP control rates were lower with lisinopril compared to chlorthalidone or amlodipine, more than 60% of participants were controlled to <140/90 mm Hg at year 4, and mean BP

was <140/90 mm Hg in both CHD subgroups. The percent of participants with controlled BP (<140/90 mm Hg) was higher in those with CHD than in those without by 2%–5% at baseline across treatment groups, and this difference increased to 3%–8% after 4 years of follow-up. BP control rates at year 4 were lowest with lisinopril in both CHD subgroups.

Diabetes prevalence (based on examining only fasting blood glucose levels at baseline rather than glucose levels and/or history of diabetes, as in Table 1) was lower in those with baseline CHD than in those without (Table 2).¹⁵ During follow-up, fasting blood glucose increased least in the lisinopril arm and most in the chlorthalidone arm in both CHD subgroups (Table 2). The percentage of participants with fasting blood glucose >126 mg/dL at 2 and 4 years of follow-up increased by 3%–5% with chlorthalidone, by 1%–2% with amlodipine, and changed by between 0% and –1% with lisinopril in both CHD subgroups. During follow-up, changes in serum K⁺, serum cholesterol, and serum creatinine were similar in both CHD subgroups to that reported previously overall (data not shown).⁸ For the post-trial period, data are not available on glucose, potassium, cholesterol or creatinine levels, or BP.

Six-year event rates for the primary outcome of nonfatal MI and fatal CHD were higher in those with versus those without baseline CHD, 17.2 vs. 9.9 per 100 participants (Tables 3 and 4). Rates for the 4 major secondary endpoints of all-cause mortality, combined CHD, combined CVD, and fatal and non-fatal stroke were all lower in those without baseline CHD (Figure 3). Rates for other prespecified secondary endpoints, including fatal or treated with or without hospitalization HF, angina, coronary revascularization, peripheral arterial disease, and ESRD, as well as for a *post-hoc* endpoint of fatal or hospitalized HF were also lower in those without CHD compared to those with baseline CHD.

There was only one statistically significant treatment by CHD subgroup interaction (interaction $p=0.04$), for CHD mortality in the amlodipine comparison with chlorthalidone. Notably, the HRs did not reach statistical significance in either CHD stratum, with amlodipine/chlorthalidone HR, 0.82 [95% CI, 0.64–1.03] for those with CHD versus HR, 1.09 [95% CI, 0.92–1.29] for those without CHD. In the absence of other significant interactions and given the non-significant HRs, this single significant interaction is not convincing.

Similar to 6-year rates, 10-year event rates were higher in those with baseline CHD compared to those with no pre-existing CHD. There were statistically significant outcomes according to CHD status interactions ($p=0.012$) in amlodipine versus chlorthalidone comparison for CVD and CHD mortality. For CVD mortality, HRs (95% CI) were 0.88 (0.78–0.99) in those with baseline CHD and 1.06 (0.98–1.15) in those without. For CHD mortality, the HRs (95% CI) were 0.84 (0.71–1.00) in those with CHD at baseline and 1.08 (0.97–1.22) in those without (Supplemental Tables S1 and S2). For other outcomes, the previously reported overall HRs, including HF for amlodipine comparison with chlorthalidone and stroke mortality for lisinopril comparison with chlorthalidone, apply to both strata.⁹

DISCUSSION

Subgroup analyses of ALLHAT extend findings of this trial and other studies by confirming the consistency of results in those with and without evidence of CHD at baseline. In ALLHAT, no differences in outcomes by CHD status at baseline were detected for either the in-trial or extension periods with the exception of the amlodipine-chlorthalidone comparison for (1) CHD mortality in-trial and (2) CHD and CVD mortality through the extension period (in-trial + post-trial). For (1), the comparison was not significant in either CHD subgroup or overall whereas for (2) the comparisons were significant among those with CHD at baseline ($p=0.04$ for both) but not among those without CHD at baseline. Given the many analyses performed, this may just be the play of chance.

For the in-trial period, there were significantly higher rates of HF, stroke, and combined CVD for lisinopril compared to chlorthalidone and of HF for amlodipine compared to chlorthalidone. Of these, only the HF result for amlodipine versus chlorthalidone persisted through the extension period, with a 12% ($p=0.16$) and 13% ($p=0.02$) increased risk for amlodipine versus chlorthalidone in those with and without CHD at baseline, respectively (P for interaction was not statistically significant; overall HR, 1.12 [$p=0.01$]). The significantly higher stroke mortality during the extension period overall (HR, 1.20; 95% CI 1.10–1.41) for lisinopril versus chlorthalidone did not differ significantly by CHD status. 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.

Our findings of similarity of antihypertensive drug effects on major clinical outcomes in those with and without CHD are consistent with results of other trials and with recent hypertension treatment guidelines.^{2,16,17} They also constitute a substantial and substantive addition to a sparse body of evidence in this important area of treatment of hypertension. A recently published meta-analysis¹⁸ showed a similar effect on subsequent CHD events compared to placebo or drugs other than beta-blockers regardless of prior CHD status. However, comparisons of beta-blockers with placebo included trials that enrolled patients immediately post-acute MI and trials that evaluated treatment of HF with systolic dysfunction. Notably, the definition of “history of CHD” included “history of HF.” ALLHAT was included as a trial with no CHD at baseline.

In a systematic review of evidence from randomized controlled trials for primary prevention of CVD,¹⁹ including ALLHAT, the authors confirmed our established clinical conclusion that none of the commonly used antihypertensive drugs was superior to the diuretics in preventing any major cardiovascular outcome or total mortality and that diuretics were superior in preventing HF. Specifically, in this multiple treatment meta-analysis, diuretic was superior to beta-blockers, CCBs, angiotensin-receptor blockers and alpha blockers in preventing HF. The HF outcome for the ACE-inhibitors comparison with diuretics (HR, 0.88; 95% CI, 0.76–1.06) was also consistent with the overall ALLHAT result for the unadjudicated endpoint of hospitalized HF²⁰ – a post-hoc outcome which we then centrally adjudicated²¹ and further analyzed by left ventricular ejection fraction (LVEF),²² before concluding that the diuretic chlorthalidone (12.5–35 mg/day) was superior to the ACE-

inhibitor lisinopril (10–40 mg/day) in preventing HF, especially HF with preserved LVEF. As would have been expected, ACE-inhibitors, alpha-receptor blockers and CCBs, but not beta-blockers, were superior to diuretics in preventing diabetes, or, specifically, in not inducing dysglycemia, which we and others^{5,23} have shown to have no long-term clinical consequences for major morbidity and mortality. However, we were surprised to see, in the same systematic review (17), that diuretics were not superior to alpha-blockers for preventing stroke (HR=0.85; 95% CI; 0.66–1.12), especially that this outcome was based on a single clinical trial which had to be ALLHAT. Yet, in ALLHAT, the HR for stroke in doxazosin compared to chlorthalidone was 1.26 (95% CI; 1.10–1.46, p=0.001) and for stroke mortality, 1.39 (95% CI; 1.03–1.89, p=0.03).⁸ However, we understand that the ACE-inhibitor result for stroke was different than in ALLHAT, given the race-by-treatment interaction for this outcome absence in other trials of meaningful numbers of Blacks among whom stroke is known to be more frequent than in other populations. Specifically, within ALLHAT for those without CHD at baseline, the HR for lisinopril vs. chlorthalidone for stroke among Blacks was 1.43 (95% CI, 1.15–1.75) and for non-Blacks, 0.94 (95% CI, 0.78–1.15).

Only 3 major clinical trials reported outcomes stratified by the presence or absence of CVD or CHD at baseline: (1) the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial²⁴ excluded those with prior MI and showed no differences between those with and without otherwise-defined CVD; (2) the Intervention as a Goal in Hypertension Treatment (INSIGHT) trial²⁵ showed no differences between those with and without prior MI; and (3) the Heart Outcomes Prevention Evaluation (HOPE) trial²⁶ included both hypertensive and non-hypertensive high-risk patients with diabetes or evidence of CVD and showed no difference in outcomes among those with and without history of baseline CHD. The International Verapamil-Trandolapril Study (INVEST),²⁷ which enrolled 22,576 hypertensive patients with CHD, compared a CCB verapamil sustained release-based strategy (Step 2 treatment: trandolapril 2 mg once or twice a day) with an atenolol-based strategy (Step 2 treatment: hydrochlorothiazide 25 mg once or twice a day). It showed both strategies to be equally effective in preventing death and major cardiovascular outcomes. In ALLHAT, diuretic chlorthalidone-based treatment was superior to the CCB amlodipine-based treatment in preventing HF and unsurpassed for preventing mortality and other major cardiovascular and renal outcomes. While some advocate use of beta-blockers other than atenolol for treatment of hypertension in patients with preexisting CHD, evidence is lacking beyond acute MI settings.

This analysis has many strengths, including the size and rigorous conduct of ALLHAT and clinical event follow-up for 99% of participants. There are also some known and potential limitations, including the *post hoc* nature of this analysis.^{4,11}

The similarity of the treatment effects in ALLHAT by CHD status at baseline is robust because of its large sample size and rigorous design and execution. Given the totality of to-date evidence, we believe that the ALLHAT conclusion reported for the entire cohort that neither lisinopril nor amlodipine is superior to chlorthalidone for initial therapy of hypertension and that properly dosed chlorthalidone is superior in preventing HF and stroke (for stroke, compared with lisinopril in Blacks) also applies to the subgroups defined by

CHD status. Consequently, these results provide further support for the original ALLHAT conclusion that properly dosed thiazide-type diuretics such as chlorthalidone (12.5–25 mg/day) should be included in the initial treatment regimen in most patients with hypertension. Further research is needed to define drug combinations for optimal health outcomes in patients with and without CHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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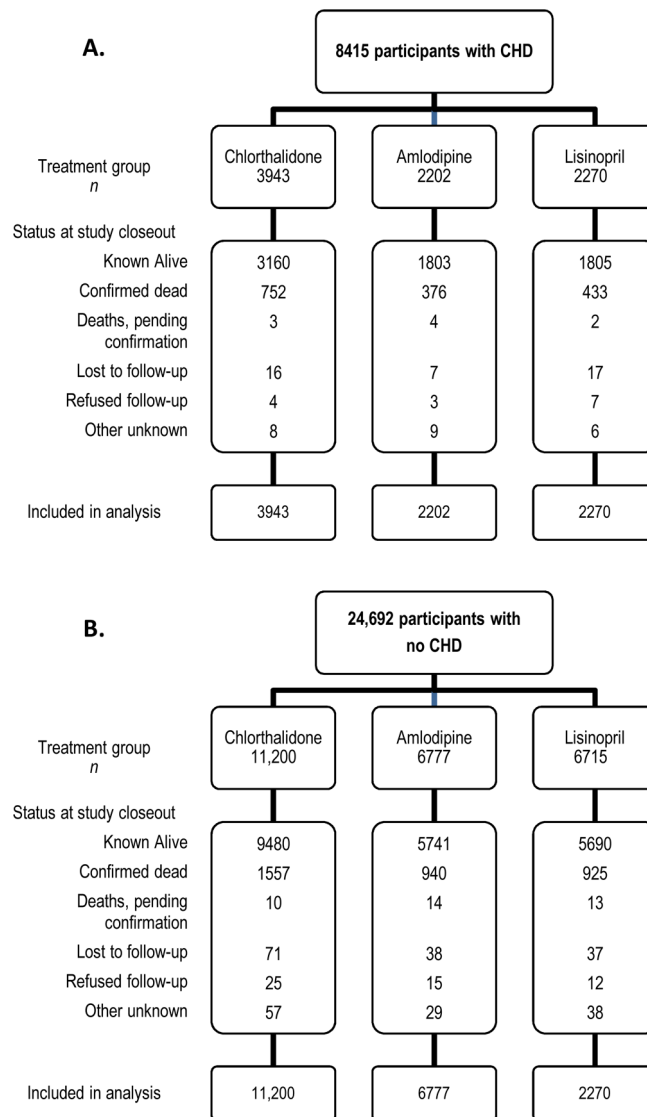


Figure 1. Consort diagram for participants with coronary heart disease at baseline (A) and participants without coronary heart disease at baseline (B)

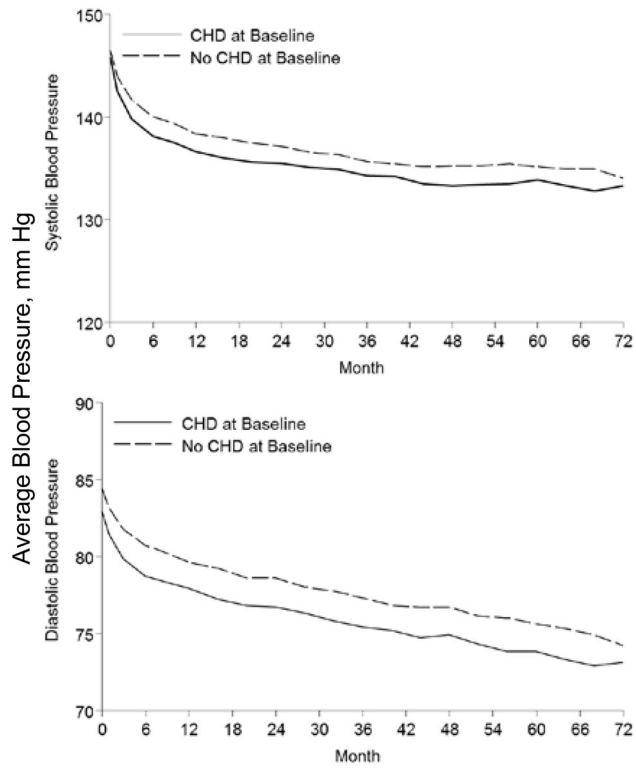


Figure 2. Average systolic and diastolic blood pressures by coronary heart disease status at baseline

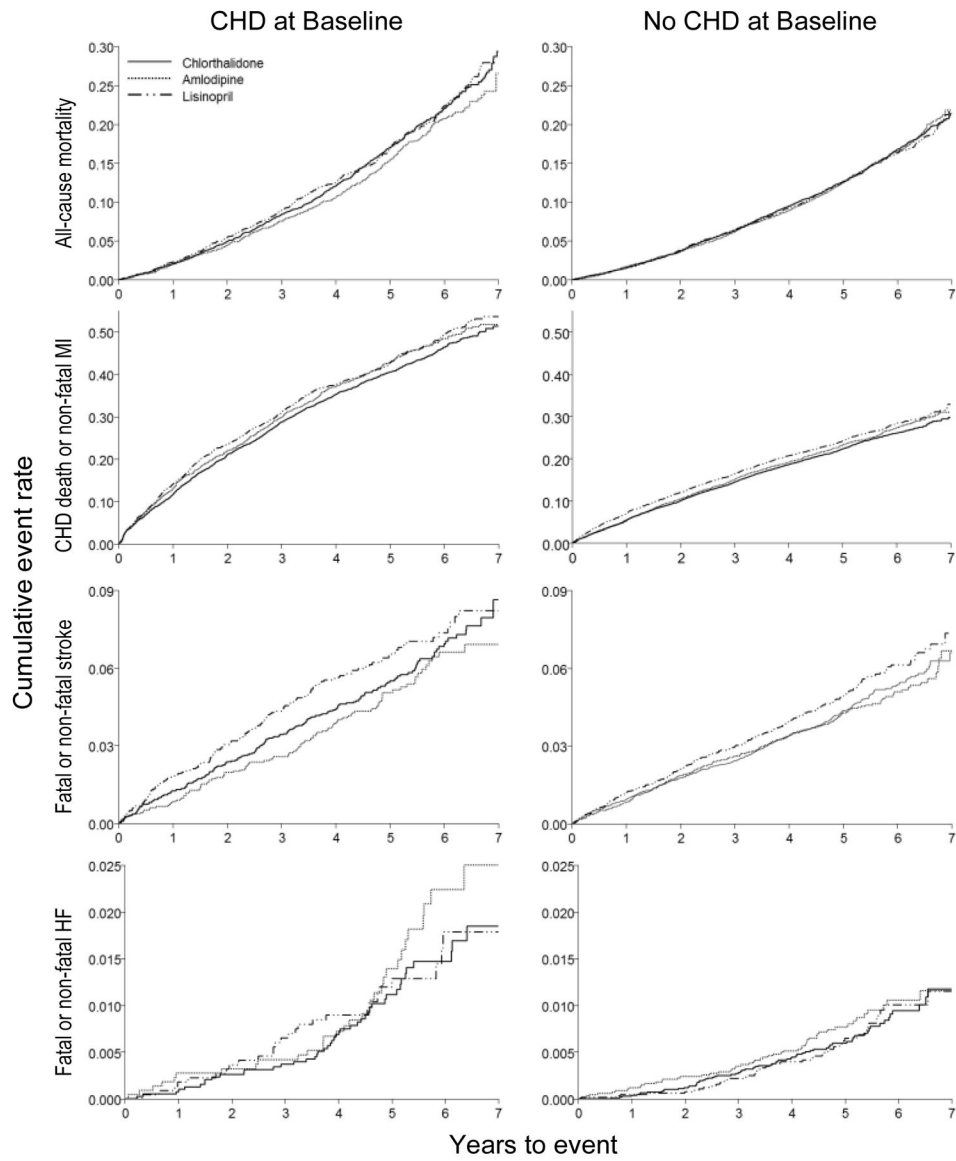


Figure 3. Kaplan-Meier curves for morbidity and mortality rates by treatment group and coronary heart disease status at baseline

Table 1 Baseline characteristics of ALLHAT participants by coronary heart disease status at baseline*

Characteristic	CHD at baseline				No CHD at baseline			
	Chlorthalidone	Amlodipine	Lisinopril	All	Chlorthalidone	Amlodipine	Lisinopril	All
Number randomized	3,943	2,202	2,270	8,415	11,200	6,777	6,715	24,692
Men	2523(64.0)	1402(63.7)	1496(65.9)	5421(64.4)	5492(49.0)	3342(49.0)	3329(49.6)	12,163(49.2)
Age,years, mean (sd)	68.10(7.48)	67.86(7.50)	68.08(7.46)	68.03(7.48)	66.46(7.74)	66.55(7.76)	66.44(7.80)	66.48(7.76)
55-64 n (%)	1,396(35.4)	804(36.5)	789(34.8)	2,989(35.5)	5,031(44.9)	3,019(44.6)	3,059(45.6)	11,109(45.0)
65-79	2,255(57.2)	1,253(56.9)	1,313(57.8)	4,821(57.3)	5,469(48.8)	3,318(49.0)	3,241(48.3)	12,028(48.7)
80+	292(7.4)	145(6.6)	168(7.4)	605(7.2)	700(6.3)	440(6.5)	415(6.2)	1,555(6.3)
Ethnicity [†]								
Black	953(24.2)	525(23.84)	539(23.74)	2,017(24.0)	4,342(38.77)	2,637(38.9)	2,628(39.14)	9,607(38.9)
Non-Black	2,990(75.83)	1,677(76.2)	1,731(76.3)	6,398(76.03)	6,858(61.23)	4,140(61.09)	4,087(60.86)	15,085(61.1)
White, non-Hispanic	2,392(60.66)	1,367(62.08)	1,396(61.50)	5,155(61.26)	4,778(42.66)	2,924(43.15)	2,847(42.40)	10,549(42.7)
Black, non-Hispanic	822(20.85)	453(20.57)	468(20.62)	1,743(20.71)	3,975(35.49)	2,408(35.53)	2,410(35.89)	8,793(35.61)
White Hispanic	475(12.05)	253(11.49)	264(11.63)	992(11.79)	1,435(12.81)	852(12.57)	871(12.97)	3,158(12.79)
Black Hispanic	131(3.32)	72(3.27)	71(3.13)	274(3.26)	367(3.28)	229(3.38)	218(3.25)	814(3.30)
Other	123(3.12)	57(2.59)	71(3.13)	251(2.98)	645(5.76)	364(5.37)	369(5.50)	1,378(5.58)
Education,yrs, mean (sd)	11.28(3.86)	11.36(3.92)	11.39(4.11)	11.33(3.95)	10.87(4.10)	10.82(3.95)	10.81(4.07)	10.84(4.05)
Receiving antihypertensive treatment, n(%)	3,649(92.54)	2,040(92.64)	2,076(91.45)	7,765(92.28)	10,001(89.30)	6,067(89.52)	6,024(89.7)	22,092(89.5)
Blood pressure, mmHg, mean (sd)								
SBP	146.01(16.1)	145.42(16.2)	146.0(16.2)	145.85(16.1)	146.35(15.5)	146.54(15.5)	146.6(15.3)	146.46(15.5)
DBP	82.94(10.2)	82.65(10.16)	83.07(10.19)	82.90(10.2)	84.43(9.93)	84.36(10.12)	84.48(9.91)	84.42(10.0)
Treated at baseline								
SBP	145.21(16.1)	144.59(16.12)	144.99(16.22)	144.99(16.1)	145.18(15.5)	145.35(15.4)	145.49(15.24)	145.31(15.4)
DBP	82.47(10.20)	82.22(10.11)	82.61(10.14)	82.44(10.16)	83.81(9.84)	83.69(10.0)	83.92(9.84)	83.80(9.88)
Untreated at baseline								
SBP	155.94(12.25)	155.86(12.63)	156.5(12.33)	156.07(12.4)	156.06(12.03)	156.7(12.08)	156.06(12.4)	156.2(12.13)
DBP	88.70(8.64)	88.13(9.29)	87.9(9.55)	88.33(9.07)	89.60(9.19)	90.07(9.42)	89.43(9.09)	89.68(9.23)
Baseline lipid profile, mg/dL,-mean (sd)								
Cholesterol								

Characteristic	CHD at baseline			No CHD at baseline				
	Chlorthalidone	Amlodipine	Lisinopril	All	Chlorthalidone	Amlodipine	Lisinopril	All
Total	213.91(44.31)	213.25(41.11)	212.55(41.28)	213.37(42.7)	217.04(43.35)	217.63(44.9)	216.65(42.48)	217.10(43.5)
HDL	44.63(13.86)	44.92(13.57)	44.47(13.26)	44.67(13.62)	47.57(15.11)	47.90(15.02)	47.29(14.88)	47.59(15.02)
LDL	134.55(36.25)	133.76(35.36)	134.13(35.31)	134.23(35.8)	136.50(37.68)	136.18(37.7)	136.50(36.7)	136.41(37.4)
Fasting triglycerides	177.9(133.6)	176.5(123.4)	176.0(121.9)	177.0(127.9)	170.85(128.6)	171.5(137.3)	171.8(145.2)	171.3(135.7)
Total Glucose mg/dL	119.48(57.51)	117.36(53.9)	119.0(55.3)	118.80(56.0)	126.95(62.74)	126.91(62.6)	125.5(60.3)	126.54(62.1)
Fasting Glucose mg/dL	118.17(54.81)	114.6(48.61)	117.21(50.6)	117.0(52.15)	125.43(59.5)	125.77(59.2)	124.7(57.4)	125.32(58.8)
Diabetes classification								
Diabetes [‡]	1,226(32.9)	656(31.46)	696(32.43)	2,578(32.41)	4,717(44.57)	2,907(45.38)	2,789(44.04)	10,413(44.7)
Impaired fasting glucose [§]	194(5.21)	104(4.99)	128(5.96)	426(5.36)	430(4.06)	254(3.97)	275(4.34)	959(4.11)
Normoglycemic	2,304(61.87)	1,325(63.55)	1,322(61.60)	4,951(62.24)	5,437(51.37)	3,245(50.66)	3,269(51.62)	11,951(51.2)
Lipid trial participants ^{**}	526(13.34)	318(14.44)	302(13.3)	1,146(13.62)	3,229(28.83)	1,922(28.36)	1,865(27.77)	7,016(28.41)
History of CHD								
Cigarette smoker	593(15.04)	328(14.90)	331(14.58)	1,252(14.88)	2,729(24.37)	1,639(24.18)	1,637(24.38)	6,005(24.32)
Atherosclerotic CVD	3,805(96.5)	2,137(97.05)	2,190(96.48)	8,132(96.64)	4,060(36.25)	2,452(36.18)	2,463(36.68)	8,975(36.35)
History of MI or stroke	2,270(57.57)	1,267(57.54)	1,277(56.26)	4,814(57.21)	1,290(11.52)	816(12.04)	763(11.36)	2,869(11.62)
History of coronary revascularization	1,640(41.59)	921(41.83)	1,012(44.58)	3,573(42.46)	340(3.04)	182(2.69)	201(2.99)	723(2.93)
Other Atherosclerotic CVD ^{††}	1,617(41.01)	928(42.14)	928(40.88)	3,473(41.27)	1,974(17.63)	1,206(17.80)	1,213(18.06)	4,393(17.79)
ST-T wave ^{‡‡}	452(11.48)	249(11.32)	250(11.02)	951(11.32)	1,120(10.04)	659(9.76)	690(10.32)	2,469(10.04)
History of LVH on Electrocardiogram	423(10.73)	209(9.49)	251(11.06)	883(10.49)	2,009(17.94)	1,302(19.21)	1,200(17.87)	4,511(18.27)
History of LVH on Echocardiogram	141(3.58)	77(3.50)	67(2.95)	285(3.39)	554(4.96)	334(4.95)	335(5.01)	1,223(4.97)
Estimated GFR (ml/min/1.73 m ²), mean (sd)	75.03(19.32)	75.73(18.69)	75.49(19.6)	75.34(19.24)	78.41(19.71)	78.90(20.0)	78.47(19.9)	78.56(19.83)
Body mass index, mean (sd)	29.21(5.61)	29.28(5.61)	29.10(5.53)	29.20(5.60)	29.90(6.33)	29.97(6.51)	30.03(6.36)	29.96(6.39)
Atrial Fibrillation /Flutter, n(%)	49(1.41)	32(1.66)	26(1.33)	107(1.45)	88(0.92)	56(0.97)	50(0.88)	194(0.92)

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular diseases; DBP, diastolic blood pressure; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; sd, standard deviation; yrs, years; SBP, systolic blood pressure.

* All results are presented as percentages of the number of participants randomized to the treatment groups unless otherwise indicated.

[‡] Ethnicity is self-reported

[§] Diabetes=History of diabetes at baseline or fasting glucose > 126 mg/dL;

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§ Impaired fasting glucose=No history and baseline fasting glucose is 110 to 125 mg/dL inclusive;

// Normoglycemic=Not classified as impaired fasting glucose, no history of DM and at least one fasting glucose or non-fasting glucose is < 110 mg/dL.

** Participants randomized to the ALLHAT Lipid Trial, an open label randomized trial of pravastatin versus usual care in a subset (N=10,350) of ALLHAT participants with moderately elevated lipid levels

†† Other atherosclerotic CVD is any of 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 dipyridamol thallium.

‡‡ ST-T wave is any major ST segment depression or T-wave inversion on any electrocardiogram in the past two years. ST depression 1 mm for 1 minute on exercise testing or Holter monitoring; reversible wall motion abnormality on stress echocardiogram; ankle-arm index < 0.9; abdominal aortic aneurysm detected by ultrasonography, computed tomography scan, or radiograph; carotid or femoral bruits.

Table 2
Blood pressure and fasting glucose results at baseline and follow-up by coronary heart disease status at baseline

BP and fasting glucose results	CHD at baseline				No CHD at baseline			
	Chlorthalidone	Amlodipine	Lisinopril	All	Chlorthalidone	Amlodipine	Lisinopril	All
Participants, n								
Baseline	3,943	2,202	2,270	8,415	11,200	6,777	6,715	24,692
Year-1	3,343	1,869	1,876	7,088	9,416	5,678	5,578	20,672
Year-2	3,041	1,669	1,651	6,361	8,607	5,154	4,991	18,752
Year-4	2,468	1,395	1,362	5,225	6,838	4,199	3,917	14,954
Systolic Blood Pressure mmHg, mean (sd)								
Baseline	146.01(16.1)	145.4(16.2)	146.0(16.2)	145.84(16.1)	146.3(15.5)	146.5(15.5)	146.6(15.3)	146.5(15.5)
Year-1	135.8(15.7)	137.2(14.7)	138.0(18.1)	136.7(16.1)	137.2(15.8)	138.9(15.0)	140.6(18.5)	138.6(16.4)
Year-2	134.9(15.8)	136.2(14.9)	136.7(18.0)	135.7(16.2)	136.3(15.9)	137.4(15.0)	138.9(17.7)	137.3(16.2)
Year-4	132.8(16.3)	133.2(14.9)	133.4(17.1)	133.1(16.2)	134.4(15.5)	135.4(15.0)	136.2(17.1)	135.1(15.8)
Mean change in SBP mean(SD) from baseline, mmHg,								
Year-1	-10.1(18.5)	-8.0(18.8)	-7.8(20.3)	-8.9(19.1)	-8.7(18.8)	-7.4(18.9)	-5.8(20.8)	-7.6(19.4)
Year-2	-11.0(19.3)	-9.1(18.9)	-8.7(20.2)	-9.9(19.4)	-9.7(19.3)	-8.9(19.1)	-7.2(20.8)	-8.8(19.7)
Year-4	-13.1(19.9)	-12.1(19.6)	-11.9(20.6)	-12.5(20.0)	-11.2(19.6)	-10.8(19.6)	-9.8(21.0)	-10.8(20.0)
Diastolic blood pressure mmHg, mean(sd)								
Baseline	82.9(10.2)	82.7(10.2)	83.1(10.2)	82.9(10.2)	84.4(9.9)	84.4(10.1)	84.5(9.9)	84.4(10.0)
Year-1	78.04(9.4)	77.8(9.1)	78.2(10.4)	78.03(9.6)	79.8(9.7)	79.0(9.6)	80.5(10.5)	79.8(9.9)
Year-2	76.9(9.4)	76.6(9.5)	76.9(10.0)	76.8(9.6)	78.8(9.6)	78.1(9.6)	79.2(10.3)	78.7(9.8)
Year-4	75.3(9.6)	74.3(9.5)	74.6(10.4)	74.9(9.8)	76.9(9.6)	76.2(9.5)	77.3(10.2)	76.8(9.8)
Mean change in DBP mean(SD) from baseline, mg/dL,								
Year-1	-4.7(10.9)	-4.7(10.2)	-4.6(11.3)	-4.7(10.8)	-4.4(10.9)	-5.2(11.0)	-3.9(11.3)	-4.5(11.1)
Year-2	-5.8(11.4)	-6.0(10.9)	-5.6(11.6)	-5.8(11.3)	-5.4(11.1)	-6.2(11.3)	-5.1(11.4)	-5.5(11.2)
Year-4	-7.5(11.8)	-7.9(11.1)	-8.0(11.9)	-7.7(11.6)	-7.2(11.5)	-8.0(11.6)	-7.0(12.0)	-7.4(11.6)
Blood Pressure <140/90 mmHg, n(%)								
Baseline	1,136(28.8)	667(30.3)	652(28.7)	2,455(29.2)	2,973(26.5)	1,802(26.6)	1,707(25.4)	6,482(26.3)
Year-1	2,080(62.3)	1,100(58.9)	1,044(55.7)	4,224(59.6)	5,297(56.3)	3,065(54.0)	2,733(49.0)	11,095(53.7)
Year-2	1,961(64.5)	980(58.7)	972(58.9)	3,913(61.5)	5,149(60.0)	2,938(57.0)	2,633(52.8)	10,720(57.2)

BP and fasting glucose results	CHD at baseline				No CHD at baseline			
	Chlorthalidone	Amlodipine	Lisinopril	All	Chlorthalidone	Amlodipine	Lisinopril	All
Year-4	1,713(69.4)	986(70.7)	909(66.7)	3,608(69.1)	4,534(66.3)	2,692(64.1)	2,432(62.1)	9,658(64.6)
Fasting glucose, mg/dL †								
Participants at baseline, n								
Year-2	2,987	1,614	1,725	6,326	8,023	4,866	4,879	17,768
Year-4	1,519	855	803	3,177	4,276	2,540	2,417	9,233
Mean (SD) Baseline	1,327	732	663	2,722	3,486	2,120	1,974	7,580
Baseline if have 2 yr follow-up*	118.1(55.0)	114.9(49.0)	117.4(50.9)	117.1(52.4)	125.5(59.6)	125.9(59.3)	124.9(57.6)	125.4(59.0)
Year-2	113.8(46.4)	111.8(45.4)	113.7(45.5)	113.3(45.9)	122.1(54.6)	122.4(54.6)	121.9(53.2)	122.1(54.2)
Year-4	121.6(53.6)	114.0(46.0)	115.6(49.3)	118.1(50.7)	129.8(61.2)	125.1(56.5)	123.2(56.1)	126.8(58.7)
Change from baseline, mg/dL, mean(sd)	122.1(51.4)	115.5(41.8)	116.7(41.5)	119.0(46.7)	128.0(57.8)	126.9(55.5)	123.2(54.1)	126.5(56.1)
Year-2	8.3(49.0)	1.9(43.9)	2.6(45.0)	5.2(46.8)	7.4(51.1)	2.5(50.4)	1.3(49.5)	4.4(50.6)
Year-4	6.1(54.3)	5.4(41.0)	3.8(38.3)	5.3(47.4)	5.9(57.4)	4.1(55.8)	1.6(51.9)	4.3(55.6)
Fasting glucose 126 mg/dL, n(%)								
Baseline	724(24.2)	353(21.9)	423(24.5)	1,500(23.7)	2,469(30.8)	1,548(31.8)	1,519(31.1)	5,536(31.2)
Year-2	424(27.9)	190(22.2)	198(25.0)	812(25.6)	1,491(34.9)	822(32.4)	728(30.1)	3,041(32.9)
Year-4	389(29.3)	171(23.4)	163(24.6)	723(26.6)	1,180(33.9)	705(33.3)	598(30.3)	2,483(32.8)

* Mean changes are calculated using only those participants who have both a value at baseline and a value at indicated year of follow-up. All other means are calculated for all participants at designated time point.

† Number of participants with fasting glucose values is smaller than numbers for other measurements because participants frequently arrived non-fasting, were asked to return fasting, and did not. The mean at baseline was also calculated for fasting glucose for only those participants who had a fasting glucose at year-2 follow-up. This is to make it easier for readers to understand mean changes, which are calculated only for participants with measurements at both time points.

Table 3
Clinical outcomes by antihypertensive treatment group for participants with coronary heart disease at baseline

Outcomes	6-year Rate per 100 persons (SE), n					From Cox Regression Hazard Ratio and 95% Confidence Interval	
	Chlorthalidone	Amlodipine	Lisinopril	Total	A/C	L/C	
Total randomized, n	3,943	2,202	2,270	8,415			
Primary Endpoint							
CHD (nonfatal MI + fatal CHD)	17.3(0.8),514	16.6(1.0),280	17.7(1.1),292	17.21(0.5),1086	0.96(0.83–1.11)	1.00(0.88–1.16)	
Secondary Endpoints							
Mortality outcomes							
All-Cause Mortality	22.01(0.8),707	20.7(1.1),360	22.3(1.1),407	21.8(0.6),1474	0.90(0.79–1.02)	1.01(0.90–1.14)	
CV Mortality	11.5(0.6),352	11.0(0.9),182	12.6(0.9),215	11.7(0.4),749	0.92(0.77–1.10)	1.09(0.92–1.28)	
CHD	7.1(0.5),211	5.9(0.7),96	6.6(0.7),113	6.7(0.4),420	0.82(0.64–1.03)	0.96(0.77–1.20)	
Stroke	1.8(0.3),49	1.5(0.3),23	2.2(0.4),35	1.8(0.2),107	0.88(0.55–1.42)	1.31(0.86–2.00)	
Heart Failure	1.5(0.2),42	2.2(0.4),31	1.8(0.4),27	1.8(0.2),100	1.27(0.81–2.01)	1.06(0.66–1.70)	
Cancer	5.3(0.5),157	4.1(0.5),67	4.8(0.6),84	4.9(0.3),308	0.74(0.56–0.99)	0.94(0.73–1.22)	
Combined fatal/nonfatal outcomes							
Combined CVD	46.31(0.99),1528	48.4(1.3),897	49.3(1.3),925	47.7(0.7),3550	1.07(0.98–1.16)	1.10(1.01–1.19)	
Stroke	6.8(0.5),202	6.6(0.7),104	7.4(0.7),134	6.9(0.4),440	0.89(0.70–1.12)	1.16(0.94–1.44)	
Renal disease	2.2(0.3),56	2.2(0.5),28	1.8(0.4),26	2.1(0.2),110	0.87(0.56–1.37)	0.84(0.53–1.32)	
Cancer	11.8(0.7),347	10.4(0.8),177	10.7(0.8),179	11.2(0.4),703	0.91(0.76–1.09)	0.92(0.77–1.10)	
Heart Failure (treated/hospitalized/fatal)	11.9(0.7)	15.4(1.0)	12.9(0.9)	13.1(0.5)	1.30(1.11–1.53)	1.18(1.00–1.39)	
Hospitalized/fatal heart failure	9.8(0.6),275	12.1(0.9),194	10.0(0.8),171	10.5(0.4),640	1.25(1.04–1.50)	1.09(0.91–1.32)	
Hospitalized Angina	15.9(0.7),505	16.9(0.9),310	18.1(1.0),325	16.7(0.5),1140	1.09(0.95–1.26)	1.15(1.00–1.32)	
Coronary revascularization	15.6(0.7),466	17.1(0.98),298	18.4(1.0),313	16.7(0.5),1077	1.15(1.00–1.33)	1.19(1.03–1.37)	
Peripheral arterial disease	5.7(0.4),185	5.9(0.6),107	5.9(0.6),102	5.8(0.3),394	1.04(0.82–1.31)	0.96(0.76–1.23)	

Abbreviations: CVD, cardiovascular disease; CV, cardiovascular; MI, myocardial infarction; SE, standard error.

Clinical outcomes by antihypertensive treatment group for participants without coronary heart disease at baseline

Table 4

Outcomes	6-year Rate per 100 persons (SE), n				Total	From Cox Regression Hazard Ratio and 95% Confidence Interval	
	Chlorthalidone	Amlodipine	Lisinopril	Lisinopril		A/C	L/C
Total randomized	11,200	6,777	6,715	24,692			
Primary Endpoint							
CHD (nonfatal MI + fatal CHD)	9.9(0.4),830	10.0(0.5),504	9.6(0.5),486	9.9(0.2),1820	1.01(0.91–1.13)	0.99(0.88–1.10)	
Secondary Endpoints							
Mortality outcomes							
All-Cause Mortality	16.8(0.4),1481	16.5(0.6),881	16.3(0.6),879	16.6(0.3),3241	0.99(0.91–1.07)	0.99(0.91–1.07)	
CV Mortality	7.4(0.3),634	8.3(0.4),428	7.5(0.4),391	7.7(0.2),1453	1.09(0.97–1.23)	1.00(0.89–1.14)	
CHD*	3.8(0.2),327	4.4(0.3),220	4.0(0.3),207	4.0(0.2),754	1.09(0.92–1.29)	1.04(0.88–1.23)	
Stroke	1.3(0.1),109	1.4(0.2),69	1.5(0.2),80	1.4(0.1),258	1.01(0.75–1.37)	1.21(0.91–1.60)	
Heart Failure	0.9(0.1),71	1.1(0.2),52	1.0(0.2),43	1.00(0.09),166	1.18(0.83–1.67)	0.97(0.67–1.41)	
Cancer	4.2(0.2),357	3.8(0.3),208	4.0(0.3),207	4.0(0.2),772	0.99(0.84–1.17)	0.99(0.84–1.17)	
Combined fatal/nonfatal outcomes							
Combined CVD	26.0(0.5),2338	27.2(0.7),1481	28.3(0.7),1535	26.9(0.4),5354	1.05(0.98–1.11)	1.11(1.04–1.19)	
Stroke	5.4(0.3),449	5.1(0.3),263	6.1(0.4),309	5.5(0.2),1021	0.96(0.83–1.12)	1.15(0.99–1.32)	
Renal disease	1.7(0.2),130	2.1(0.2),100	2.1(0.2),99	1.9(0.1),329	1.22(0.94–1.57)	1.23(0.95–1.60)	
Cancer	9.4(0.4),802	10.0(0.5),506	9.9(0.5),499	9.7(0.2),1807	1.05(0.94–1.17)	1.05(0.94–1.17)	
Heart Failure (treated/hospitalized/fatal)	6.5(0.3)	8.8(0.5)	7.5(0.4)	7.4(0.2)	1.46(1.29–1.65)	1.25(1.09–1.42)	
Hospitalized/fatal heart failure	5.5(0.3),420	7.5(0.4),364	6.1(0.4),285	6.2(0.2),1069	1.44(1.25–1.65)	1.14(0.98–1.32)	
Hospitalized Angina	6.0(0.3),531	5.8(0.4),308	6.7(0.4),347	6.2(0.2),1186	0.93(0.81–1.07)	1.08(0.94–1.23)	
Coronary revascularization	7.0(0.3),609	7.8(0.4),396	7.6(0.4),385	7.4(0.2),1390	1.08(0.96–1.23)	1.06(0.94–1.21)	
Peripheral arterial disease	3.5(0.2),310	3.0(0.3),149	4.0(0.3),206	3.5(0.1),665	0.79(0.65–0.96)	1.10(0.92–1.31)	

Abbreviations: CVD, cardiovascular disease; CV, cardiovascular; MI, myocardial infarction; SE, standard error.

* CHD Death: significant treatment x CHD status at baseline interaction (HR 0.74(0.56–0.99), P=0.04) amlodipine vs chlorthalidone