Long-Term Renal and Cardiovascular Outcomes in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Participants by Baseline Estimated GFR

Mahboob Rahman, Charles E. Ford, Jeffrey A. Cutler, Barry R. Davis, Linda B. Piller, Paul K. Whelton, Jackson T. Wright Jr., Joshua I. Barzilay, Clinton D. Brown, Pedro J. Colon Sr., Lawrence J. Fine, Richard H. Grimm Jr., Alok K. Gupta, Charles Baimbridge, L. Julian Haywood, Mario A. Henriquez, Ekambaram Ilamaythi, Suzanne Oparil, and Richard Preston, for the ALLHAT Collaborative Research Group

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Dr. Charles E. Ford, The University of Texas School of Public Health, 1200 Herman Pressler Dr., Houston, Texas 77030. Email: Charles.E.Ford@uth.tmc.edu

Summary

Background and objectives CKD is common among older patients. This article assesses long-term renal and cardiovascular outcomes in older high-risk hypertensive patients, stratified by baseline estimated GFR (eGFR), and long-term outcome efficacy of 5-year first-step treatment with amlodipine or lisinopril, each compared with chlorthalidone.

Design, setting, participants, & measurements This was a long-term post-trial follow-up of hypertensive participants (n=31,350), aged ≥55 years, randomized to receive chlorthalidone, amlodipine, or lisinopril for 4–8 years at 593 centers. Participants were stratified by baseline eGFR (ml/min per 1.73 m^2) as follows: normal/increased (≥90; n=8027), mild reduction (60–89; n=17,778), and moderate/severe reduction (<60; n=5545). Outcomes were cardiovascular mortality (primary outcome), total mortality, coronary heart disease, cardiovascular disease, stroke, heart failure, and ESRD.

Results After an average 8.8-year follow-up, total mortality was significantly higher in participants with moderate/severe eGFR reduction compared with those with normal and mildly reduced eGFR (P<0.001). In participants with an eGFR <60, there was no significant difference in cardiovascular mortality between chlorthalidone and amlodipine (P=0.64), or chlorthalidone and lisinopril (P=0.56). Likewise, no significant differences were observed for total mortality, coronary heart disease, cardiovascular disease, stroke, or ESRD.

Conclusions CKD is associated with significantly higher long-term risk of cardiovascular events and mortality in older hypertensive patients. By eGFR stratum, 5-year treatment with amlodipine or lisinopril was not superior to chlorthalidone in preventing cardiovascular events, mortality, or ESRD during 9-year follow-up. Because data on proteinuria were not available, these findings may not be extrapolated to proteinuric CKD.

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Introduction

CKD is an important manifestation of target organ damage from hypertension (1). Substantial morbidity, mortality, and health care costs are associated with CKD due to progression to ESRD and increased risk for cardiovascular disease (CVD) in this population (2). Hypertension treatment is important in preventing CKD progression (3). In patients with proteinuric CKD (proteinuria usually ≥300 mg/d), inhibition of the renin-angiotensin system (RAS) axis is superior to conventional antihypertensive drug therapy in slowing renal function decline (4). However, long-term ESRD outcome data are limited and, importantly, no compelling data show that one class of antihypertensive agents is superior in reducing CKD-associated cardiovascular risks (5,6). Although CKD prevalence is high in older populations, uncertainty remains about whether this reflects aging-related estimated GFR (eGFR) decline or confers increased mortality risk. Given the aging population, understanding the long-term outcomes associated with moderate eGFR reductions in older patients is critical.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, multicenter clinical trial, compared the incidence of major coronary heart disease (CHD) events in high-risk hypertensive patients treated with a calcium channel blocker, an angiotensin converting enzyme (ACE) inhibitor, or an α-blocker, each compared with diuretic treatment

as first-step therapy (7). Newer antihypertensive drug therapies were not superior to diuretic-based therapy in preventing ESRD or CVD, (although less effective in preventing heart failure [HF] in the population as a whole, or when stratified by baseline eGFR) (8,9). However, eGFR was higher at trial completion in participants assigned to amlodipine compared with those assigned to chlorthalidone (8). Whether this represented a hemodynamic effect of amlodipine resulting in a higher eGFR or represented a true renoprotective effect of amlodipine is not known (10).

The extended follow-up of ALLHAT participants presents two important opportunities. First is ascertaining long-term renal and cardiovascular outcomes in older high-risk hypertensive patients stratified by baseline eGFR. Second is efficacy of first-step 5-year treatment with amlodipine or lisinopril, each compared with chlorthalidone, in modifying long-term renal disease and CVD outcomes. We hypothesized that long-term renal and cardiovascular outcomes would be higher in participants with CKD, and that first-step 5-year treatment with amlodipine or lisinopril was not superior to chlorthalidone in modifying long-term renal disease and CVD outcomes.

Materials and Methods

Design Overview

The design, baseline characteristics, and main results of the clinical trial phase of ALLHAT were previously published (7,11,12). After the closeout of the trial in 2002, there was no further contact of trial participants. Passive post-trial mortality and morbidity surveillance used administrative databases to assess long-term effects of in-trial antihypertensive treatment on trial endpoints. Databases from the National Death Index (NDI), Social Security Administration (SSA), Center for Medicare and Medicaid Services (CMS), and the US Renal Data System (USRDS) were searched for post-trial events occurring from 2002 to 2006. All centers obtained institutional review board approval and all participants gave written informed consent. The University of Texas Health Science Center Institutional Review Board approved this extended follow-up study (ClinicalTrials.gov identifier: NCT00000542).

Setting and Participants

Participants were men and women aged ≥55 years with hypertension and at least one additional CHD risk factor (11). Exclusion criteria included history of symptomatic HF, known left ventricular ejection fraction <0.35, or a serum creatinine level >176.8 μmol/L (>2 mg/dl) as reported by the investigator. At 623 sites in the United States, Canada, Puerto Rico, and the US Virgin Islands, 33,357 participants were recruited between February 1994 and January 1998. Canadian sites, representing 553 participants did not participate in the post-trial phase. Morbidity data were not available for Department of Veterans Affairs (VA) participants (n=5403) and non-Medicare participants (n=5363).

Randomization and Interventions

Participants were randomly assigned in a double-blind manner and in a 1.7:1:1 ratio to chlorthalidone, amlodipine, or lisinopril. A fourth arm of the study using the α-blocker doxazosin was stopped early (13); because of a much shorter duration of active treatment and follow-up in the doxazosin arm, these results will be reported separately. Goal BP in each randomly assigned group was <140/90 mmHg. After initial titration, participants had follow-up visits every 3 months during year 1 and every 4 months thereafter, until trial closeout.

Data on antihypertensive treatments, BP level, and outpatient morbidity were obtained at each follow-up visit during the trial. Baseline laboratory test results for glucose, lipids, creatinine, and potassium values were obtained after an overnight fast and were analyzed at a central laboratory. Laboratory, BP, and antihypertensive medication data are not available for the post-trial period.

The simplified Modification of Diet in Renal Disease (MDRD) equation was used to estimate eGFR (ml/min per 1.73 m^2) (14). Participants were classified into three baseline eGFR categories: normal or increased (≥90), mild reduction (60–89), and moderate or severe reduction (<60). In addition, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was also used to obtain the eGFR, using the same three baseline eGFR categories (15,16). Participants were classified as having diabetes mellitus (DM) or not according to baseline history of diabetes or fasting glucose ≥126 mg/dl (or in its absence, a nonfasting glucose ≥200 mg/dl).

Outcomes and Follow-Up

Cardiovascular mortality (death due to CHD, stroke, HF, or other CVD) was designated *a priori* as the primary endpoint for extended follow-up. Total mortality and its components, including CHD death, were prespecified as secondary outcomes. In addition, the following fatal/nonfatal outcomes were prespecified as secondary endpoints: CVD (CVD death or hospitalized nonfatal myocardial infarction, stroke, or HF), CHD (CHD death or hospitalized nonfatal myocardial infarction), stroke (fatal or nonfatal hospitalized), HF (fatal or nonfatal hospitalized), and ESRD.

In-trial deaths were determined by investigators and confirmed by death certificates; cause of death was determined by the respective investigators. When cause of death was reported as unknown, the NDI Plus Coded Causes of Death (NDI*Plus*) database was used. Post-trial all-cause mortality was ascertained through searches of the NDI and SSA databases, using Social Security number, name, birth date, and sex (NDI only) as matching criteria. Cause of death was ascertained from the NDI*Plus* database.

Deaths identified through NDI or SSA were verified at the ALLHAT Clinical Trials Center after receipt of a death certificate from the state or other jurisdiction. Death certificates could not be obtained for 3% of the decedents; these deaths were included in analyses because the matching algorithm is known to be highly accurate. Causes of death for deaths occurring before 1999 were provided under the ninth revision of the International Classification of Diseases (ICD); after 1998, the World Health Organization's two-way translator for the ninth and tenth revisions was used to convert ICD-10 codes to ICD-9 (17). Causes of death from NDI*Plus* were collapsed into categories used in these analyses.

During the in-trial period, nonfatal events were ascertained by the investigator and confirmed by the ALLHAT Clinical Trials Center on the basis of the discharge summaries. During

the post-trial period, nonfatal CVD events were ascertained through CMS database searches and classified using the provided ICD-9 codes. In addition, for analysis herein, ESRD was defined as kidney transplantation or start of long-term renal dialysis, and was ascertained from the USRDS for both in-trial and post-trial; the USRDS system had not been previously used to determine in-trial renal endpoints.

Statistical Analyses

Contingency tables and z tests were used to compare characteristics of participants assigned to amlodipine or lisinopril versus chlorthalidone. Cumulative 10-year event rates were estimated using the Kaplan–Meier product-limit method. Evaluations of effect of assigned treatment on risk for study outcomes during follow-up were performed using Cox regression with only treatment assignment as a covariate. The extended follow-up period includes both the randomized trial (mean duration of follow-up, 4.9 years for amlodipine, lisinopril, and chlorthalidone) and subsequent follow-up during the extension period (4 years for amlodipine, lisinopril, and chlorthalidone). Tests for interactions were conducted to determine whether effects of the treatment on ESRD differed between eGFR and diabetes status subgroups. Adjusted Kaplan–Meier 10-year ESRD rates and hazard ratios (HRs) were estimated, adjusting for age, race, sex, baseline diabetes status, baseline systolic BP, and CVD before trial entry. Time-dependent Cox regression was used to estimate HRs associated with treatment assignment separately for in-trial and post-trial follow-up periods. Given the many multivariate, subgroup, and interaction analyses performed, statistical significance at the 0.05 level should be interpreted with caution. A multiple-comparisons procedure was used to account for the multiple analyses (18).

For purposes of power calculations, the 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, using a type 1 error rate of 0.017, the study had 90% power to detect an 11.0% risk reduction (HR, 0.89) for each group compared with chlorthalidone (10-year CVD mortality rate of 16%).

Results

A total of 31,350 participants (94% of 33,357 randomized) were available for mortality and ESRD analyses (Figure 1), excluding Canadian-site participants (absent from US databases) and those missing a baseline eGFR. For combined morbidity and mortality, 20,584 participants were available for analyses, excluding 5403 participants from VA medical centers (due to lack of post-trial hospitalization data for administrative reasons) and 5363 non-Medicare participants (because they could not be included in searches for nonfatal events reported to national databases). The average and maximum follow-up periods were 8.8 and 12.0 years, respectively.

Participant characteristics at baseline and year 4 of the trial are presented in Table 1, stratified by eGFR and treatment group. Overall, the mean age at baseline was 67 years; 47% were women, 36% were black, and 43% had DM. Normal baseline eGFR values (≥90 ml/min per 1.73 m^2) were seen in 26% (n=8027) of participants; 57% (n=17,778) had mild reduction in eGFR (60–89), and 18% (n=5545) had moderate to severe reduction in eGFR (<60). Within eGFR strata, distributions of baseline characteristics were similar in the three treatment groups. Likewise, baseline distributions for all trial participants were nearly identical to those included in the post-trial analyses (data not shown). Participants with reduced eGFR were older and less likely to have DM than those with normal or high eGFR (19). There were 1- to 2-mmHg differences in year 4 BP among the randomized groups in the normal and mild reduction eGFR subgroups. Year 4 mean eGFR was higher in amlodipine compared with chlorthalidone in all subgroups, and higher in lisinopril compared with chlorthalidone only in the subgroup with normal eGFR.

The total number of deaths and ESRD events in each randomized treatment group, during and after the trial, are summarized in Figure 2. Mortality rates were much higher in participants with reduced eGFR compared with those with normal or mildly reduced eGFR (Table 2 and Figure 3). Overall, those with reduced eGFR had a mortality rate nearly twice that of participants in the normal to mildly reduced eGFR range (HR, 1.94; 95% confidence interval [95% CI], 1.86–2.03; $P<0.001$), and after adjustment for age, race, sex, baseline diabetes status, baseline systolic BP, and CVD before trial entry, they were still 1.5 times as likely to die (HR, 1.54; 95% CI, 1.47–1.61; $P<0.001$) (Figure 3). Similarly, rates for all CVD forms studied (CHD, CVD, stroke, and HF) were 1.5- to 2-fold higher in participants with reduced eGFR compared with participants in the normal or high eGFR range (Table 2).

There were no significant differences between the amlodipine and chlorthalidone groups in total, cardiovascular (Figure 4) and noncardiovascular mortality, CHD, CVD, or stroke by baseline eGFR level and in participants with diabetes (Tables 2 and 3). However, amlodipine was less effective than chlorthalidone in preventing HF, overall (HR, 1.12; 95% CI, 1.02–1.22; P=0.02) and in participants with diabetes. There were no significant differences in ESRD incidence between the amlodipine and chlorthalidone groups by baseline eGFR level (Table 4 and Figure 5). This was consistent when stratified by baseline diabetes status.

There were also no significant differences between the lisinopril and chlorthalidone groups in total, cardiovascular and noncardiovascular mortality, CHD, CVD, stroke, HF, or ESRD incidence by baseline eGFR level (Tables 2–4 and Figures 4 and 5). This was consistent when stratified by baseline diabetes status.

Time-dependent Cox regression analyses were done to assess for differences between the in-trial and post-trial time periods; among participants with eGFR<60, no statistically significant differences were observed by time period between amlodipine and chlorthalidone, or lisinopril and chlorthalidone for all of the above outcomes (Table 5). Cox proportional hazards modeling used to test for two-way (drug treatment by eGFR) and three-way (drug treatment

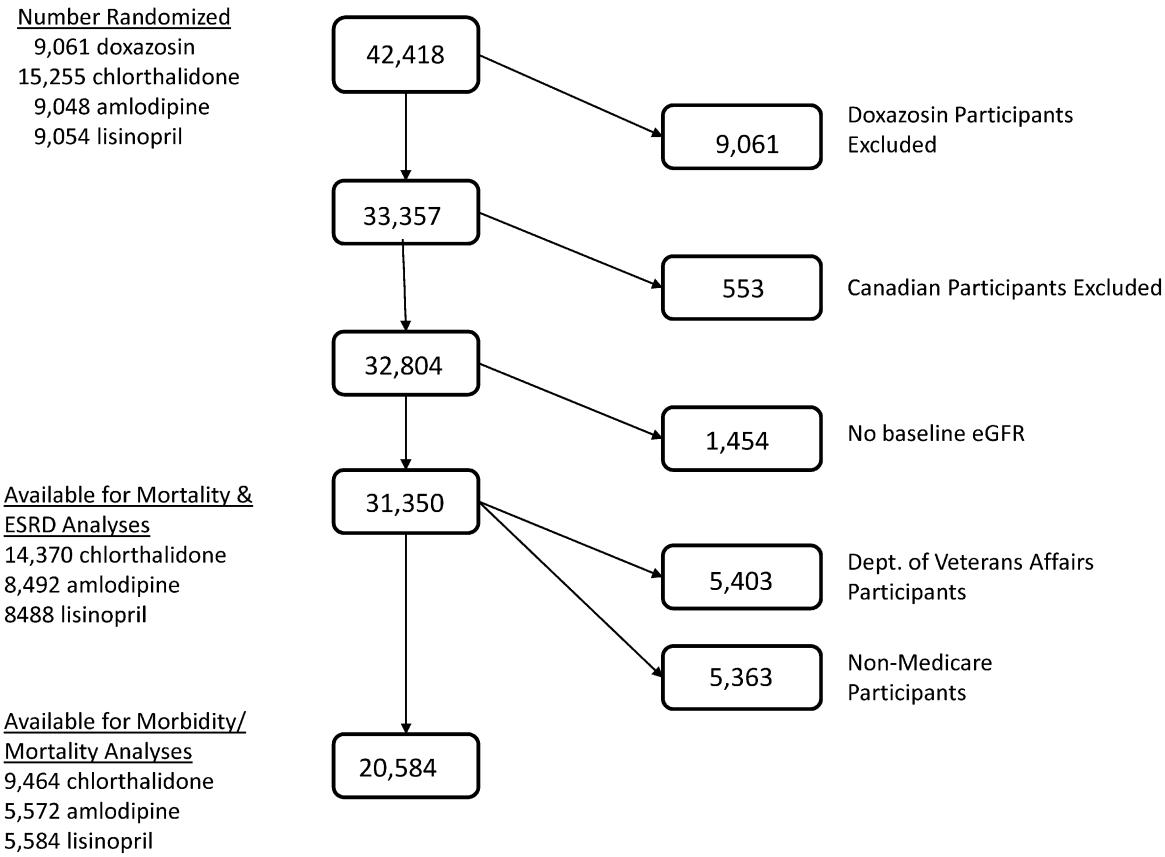

Figure 1. | **Participant flow for long-term follow-up of participants in the ALLHAT participants.** ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; eGFR, estimated GFR.

by eGFR and diabetes) interactions for the ESRD outcomes showed no statistically significant interactions (data not presented).

We performed 202 statistical comparisons and interaction tests, including the 56 each shown in Tables 2 and 3 (7 outcomes × 4 categories [overall + 3 subgroups] × 2 treatment outcomes), 24 shown in Table 4, and the 48 shown in Table 5, as well as 16 interaction tests for treatment by eGFR and treatment by eGFR by diabetes status and the 2 overall comparisons of reduced eGFR with higher eGFR levels (adjusted and unadjusted HRs). Our results showed that there were only four HRs that differed significantly from 1.0 using a nominal P value of 0.05. Using the Bonferroni step-down Holm's procedure, only the adjusted and unadjusted comparisons of total mortality by eGFR level were significant by a strict multiple-comparisons criterion. All analyses were repeated using the CKD-EPI equation to estimate the GFR (Supplemental Tables 1–5 and Supplemental Figure 1). The results were qualitatively unchanged.

Discussion

The long-term follow-up of ALLHAT demonstrates that CKD is associated with a significantly higher risk of mortality in older hypertensive patients. In each stratum by baseline eGFR, 5-year treatment with amlodipine or lisinopril is not superior to chlorthalidone-based antihypertensive drug therapy in preventing cardiovascular events, mortality, or ESRD over a 9-year follow-up period.

Our findings illustrate that older patients with CKD are at very high risk for cardiovascular events and mortality. Although participants in the reduced eGFR strata were older, and adjustment for age and other relevant risk factors attenuated the risk, even after adjustment participants with reduced eGFR were still 50% more likely to die than those with higher levels of eGFR. In older patient populations, it has been debated whether CKD, as currently defined, confers increased risk for long-term morbidity and mortality or simply reflects decreased muscle mass and loss of eGFR with aging (20,21). Our data strongly support the concept that CKD predicts higher cardiovascular risk and mortality in older hypertensive patients. In the long term, older patients with reduced eGFR are much more likely to develop CVD than to progress to ESRD. Therefore, it is important to evaluate the effects of antihypertensive drugs on cardiovascular outcomes in patients with CKD. Few studies have addressed this issue, and most of these are *post hoc* analyses of large clinical trials.

The composite of morbidity and mortality from cardiovascular causes was similar between the ACE/angiotensin receptor blocker (ARB) and comparator groups in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study, the Irbesartan in Diabetic Nephropathy Trial, and the African American Study of Kidney Disease and Hypertension (AASK) (5,6,22). In some

Table 1. Characteristics of ALLHAT chlorthalidone, amlodipine, and lisinopril participants at baseline and during follow-up by baseline eGFR and antihypertensive treatment group

Characteristic	Normal or Increased eGFR (≥90 ml/min per 1.73 m^2)			Mild Reduction in eGFR (60-89 ml/min per 1.73 m^2)			Moderate/Severe Reduction in eGFR (<60 ml/min per 1.73 m^2)		
	C	A	L	C	A	L	C	A	L
Baseline									
sample size	3606	2245	2176	8199	4768	4811	2565	1479	1501
age (yr), mean (SD)	63.4 (6.4)	63.3 (6.6)	63.3 (6.4)	67.2 (7.4)	67.4 (7.5)	67.3 (7.5)	70.8 (7.9)	70.8 (7.6)	70.6 (7.9)
black, *n* (%)	1825 (50.6)	1138 (50.7)	1079 (49.6)	2491 (30.4)	1472 (30.9)	1475 (30.7)	701 (27.3)	388 (26.2)	422 (28.1)
women, *n* (%)	1697 (47.1)	1080 (48.1)	975 (44.8)	3657 (44.6)	2104 (44.1)	2144 (44.6)	1346 (52.5)	811 (54.8)	747 (49.8)
SBP (mmgHG), mean (SD)	145.8 (15.2)	145.7 (15.7)	146.3 (15.1)	146.2 (15.8)	146.3 (15.6)	146.3 (15.5)	146.9 (16.3)	146.1 (16.3)	146.8 (16.4)
DBP (mmgHG), mean (SD)	84.9 (9.7)	84.7 (9.9)	85.2 (9.4)	84.1 (10.0)	84.0 (10.2)	84.1 (10.0)	82.5 (10.5)	82.4 (10.4)	82.8 (10.6)
eGFR (ml/min per 1.73 m^2), mean (SD)	102.6 (13.0)	102.7 (12.9)	102.8 (13.2)	75.1 (8.1)	75.2 (8.0)	75.1 (8.1)	50.1 (8.7)	50.6 (8.5)	50.1 (8.6)
diabetic, *n* (%)	1794 (51.5)	1104 (51.0)	1074 (50.9)	2976 (38.0)	1755 (38.8)	1722 (37.5)	953 (39.5)	548 (39.1)	529 (37.5)
Follow-up in-trial at 4 yr									
sample size[a]	2244	1438	1279	5197	3073	2961	1482	842	796
SBP (mmgHG), mean (SD)	133.5 (15.2)	134.7 (14.5)[b]	135.7 (17.4)[c]	133.7 (15.6)	134.6 (14.7)[c]	135.3 (17.0)[c]	135.5 (17.2)	135.9 (17.1)	136.5 (18.3)
DBP (mmgHG), mean (SD)	76.8 (9.5)	76.5 (9.0)	77.6 (10.1)[b]	76.5 (9.6)	75.8 (9.6)[c]	76.3 (10.2)	75.7 (10.0)	74.2 (9.8)[c]	75.8 (11.2)
Taking statins, *n* (%)[a]	823 (30.6)	489 (28.8)	503 (32.1)	2074 (33.8)	1259 (34.7)	1179 (33.3)	605 (34.1)	332 (33.2)	320 (32.7)
eGFR (ml/min per 1.73 m^2), mean (SD)[d]	86.9 (18.4)	93.2 (18.5)[c]	88.4 (18.4)[b]	68.8 (14.4)	73.0 (14.7)[c]	69.1 (14.7)	48.2 (14.3)	51.5 (15.2)[c]	48.3 (14.2)

A total of 31,350 patients participated in the ALLHAT trial. Comparisons are with the chlorthalidone group. ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; eGFR, estimated GFR; C, chlorthalidone; A, amlodipine; L, lisinopril; SBP, systolic blood pressure; DBP, diastolic blood pressure.

[a]The sample size is based on the number of participants with SBP/DBP measurements. The percentage of participants taking statins is based on participants with a visit, and the denominators are larger than the indicated sample size. For the year-4 percentage of participants taking statins, sample sizes are as follows: normal or increased eGFR: 2687 for C, 1699 for A, and 1568 for L; mild reduction in eGFR: 6139 for C, 3626 for A, and 3539 L; and moderate reduction in eGFR: 1775 for C, 999 for A, and 980 for L.

[b]$P<0.05$.

[c]$P<0.01$.

[d]Due to participants with missing eGFR values, the year-4 sample sizes for mean eGFR are as follows: normal or increased eGFR, 1996 for C, 1247 for A, and 1098 for L; mild reduction in eGFR: 4662 for C, 2741 for A, and 2625 for L; and moderate reduction in eGFR: 1278 for C, 706 for A, and 662 for L.

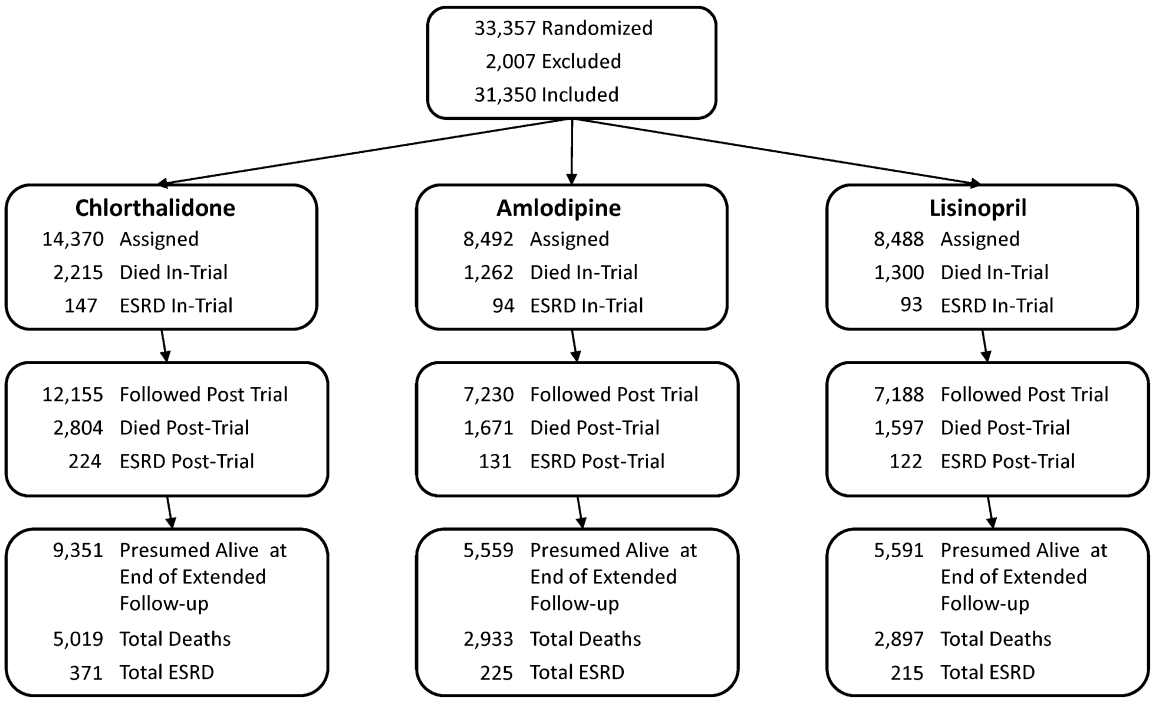

Figure 2. | **Long-term outcomes in each randomized group in participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial.**

studies, ACE inhibitor–based treatment has been associated with reduced risk of major vascular events among patients with CKD, although the effect of BP differences between the groups is unclear (23,24). Other studies indicate that, independently of the BP-lowering effect, no antihypertensive drug class has significant advantages over others in preventing stroke in CKD patients (25). Our findings demonstrate no difference in risk of cardiovascular events and mortality between chlorthalidone and lisinopril or amlodipine groups when stratified by baseline eGFR. Amlodipine was less effective than chlorthalidone in preventing HF; this effect was consistent in eGFR subgroups. This is particularly important in the setting of CKD in which HF is common and is associated with substantial morbidity and mortality (26).

With regard to effects on ESRD, long-term post-trial follow-up of clinical trial participants can provide important information. The MDRD (27) and AASK studies (28) showed no differences in outcomes between the usual and low BP arms at trial conclusion. However, extended follow-up in both studies indicated that randomization to the lower BP goal was beneficial in patients with proteinuria at baseline (29,30). At the conclusion of the ALLHAT clinical trial, neither amlodipine nor lisinopril was superior to chlorthalidone in preventing ESRD (8). We now extend these findings to report that 5-year treatment with amlodipine or lisinopril was not associated with lower ESRD outcomes over a 9-year follow-up period. This is important because most studies of comparative effects of antihypertensive drug therapy on ESRD outcomes have had follow-up periods of <5 years (22,28). Therefore, this study represents one of the longest durations of follow-up for ascertainment of ESRD outcomes in the context of a hypertension clinical trial. Participants assigned to amlodipine had a higher eGFR at the end of the clinical trial phase compared with chlorthalidone (7). We now demonstrate that this did not translate into lower ESRD incidence. We hypothesize that, early in the course of therapy with amlodipine, eGFR is often higher due to its effects on renal microcirculation resulting from afferent vasodilatation (31). Over time, as seen in the AASK study, this may not necessarily result in improved clinical renal outcomes (32).

RAS axis inhibition with ACE inhibitors or ARBs has been shown to improve renal outcomes in patients with diabetic and nondiabetic proteinuric CKD. This forms the basis for most guideline recommendations for use of an ACE inhibitor or an ARB as the preferred agent in hypertensive patients with CKD (33).The ALLHAT clinical trial (8) and now extended follow-up results do not show that lisinopril is superior to chlorthalidone in preventing ESRD. As discussed previously (8), several factors need to be considered in interpreting the renal outcomes comparison between lisinopril and chlorthalidone in this study. First, most renal studies used ACE inhibitors in combination with diuretic therapy; ALLHAT is different in comparing ACE inhibitors directly with diuretic therapy with little cross-over. Second, patients who had a specific indication for ACE inhibition and could not be withdrawn from their antihypertensive therapy before enrollment could not be enrolled into the study. As a result, patients with high-grade proteinuria and diabetic nephropathy who were already taking ACE inhibitors may have been excluded. Third, unlike renal outcomes studies that involve patients at high risk of renal disease progression, ALLHAT participants were older than those in most CKD trials and selected for their high CVD risk. Thus,

Table 2. All-cause, CVD, and non-CVD mortality, as well as cardiovascular outcomes and mortality by baseline eGFR for the chlorthalidone, amlodipine, and lisinopril antihypertensive treatment groups

eGFR	Total Number of Events/Participants			10-Yr Rate/100 Participants			HR (95% CI)	*P*	HR (95% CI)	*P*
	C	A	L	C	A	L	A Compared with C		L Compared with C	
All-cause mortality	5019/14370	2933/8492	2897/8488	33.4	32.9	32.6	0.98 (0.94–1.03)	0.40	0.97 (0.93–1.02)	0.23
≥90	1033/3606	619/2245	616/2176	27.8	26.4	27.1	0.96 (0.87–1.06)	0.39	0.99 (0.90–1.10)	0.88
60–89	2659/8199	1536/4768	1529/4811	30.6	30.4	30.3	0.98 (0.92–1.04)	0.52	0.97 (0.91–1.04)	0.40
<60	1327/2565	778/1479	752/1501	49.9	50.8	47.7	1.03 (0.94–1.13)	0.51	0.96 (0.88–1.05)	0.36
CVD mortality	2198	1300	1263	16.3	16.0	15.7	0.99 (0.93–1.06)	0.84	0.97 (0.90–1.04)	0.36
≥90	387	252	241	11.6	11.6	11.2	1.04 (0.89–1.22)	0.63	1.04 (0.88–1.22)	0.66
60-89	1191	684	669	15.3	14.8	14.6	0.97 (0.89–1.07)	0.58	0.95 (0.87–1.05)	0.30
<60	620	364	353	27.0	27.5	26.6	1.03 (0.91–1.17)	0.64	0.96 (0.84–1.10)	0.56
Non-CVD mortality	2637	1511	1520	19.2	18.8	18.8	0.96 (0.90–1.02)	0.22	0.97 (0.91–1.03)	0.36
≥90	598	340	348	17.1	15.6	16.7	0.91 (0.79–1.04)	0.15	0.97 (0.85–1.11)	0.64
60-89	1376	795	796	17.1	17.3	17.2	0.98 (0.90–1.07)	0.64	0.98 (0.90–1.07)	0.63
<60	663	376	376	29.8	29.9	27.5	1.00 (0.88–1.13)	0.96	0.96 (0.85–1.09)	0.53
CHD, total	1507/9464	884/5572	865/5548	18.8	18.6	18.2	0.98 (0.91–1.07)	0.70	0.98 (0.90–1.07)	0.66
≥90	278/2048	161/1253	147/1222	15.9	14.7	14.1	0.94 (0.78–1.15)	0.56	0.89 (0.73–1.09)	0.25
60–89	819/5436	511/3173	485/3180	17.5	18.6	17.4	1.05 (0.94–1.18)	0.36	1.02 (0.91–1.14)	0.73
<60	410/1980	212/1146	233/1146	26.3	23.1	25.4	0.88 (0.75–1.04)	0.14	0.97 (0.82–1.14)	0.70
CVD, total	3203	1922	1832	38.5	37.9	37.2	1.02 (0.96–1.07)	0.59	0.98 (0.93–1.04)	0.53
≥90	597	381	341	33.0	33.3	31.4	1.05 (0.92–1.19)	0.46	0.97 (0.85–1.11)	0.64
60–89	1756	1038	995	36.3	35.8	35.0	1.01 (0.93–1.09)	0.89	0.98 (0.90–1.05)	0.53
<60	850	503	496	50.7	49.5	49.8	1.02 (0.92–1.14)	0.69	1.01 (0.90–1.13)	0.89
Stroke, total	992	582	612	12.9	12.9	13.8	0.98 (0.89–1.09)	0.74	1.06 (0.96–1.17)	0.27
≥90	188	113	120	11.2	10.5	11.6	0.97 (0.77–1.23)	0.83	1.09 (0.86–1.37)	0.48
60–89	558	315	340	12.4	12.2	13.3	0.95 (0.83–1.09)	0.45	1.05 (0.92–1.20)	0.49
<60	246	154	152	16.6	18.0	17.9	1.08 (0.88–1.32)	0.46	1.06 (0.87–1.30)	0.55
HF, total	1143	749	651	15.3	15.9	14.7	1.12 (1.02–1.22)	0.02	0.98 (0.89–1.08)	0.64
≥90	210	143	114	12.9	13.0	11.6	1.12 (0.91–1.39)	0.29	0.92 (0.73–1.15)	0.47
60–89	617	402	342	13.9	14.8	13.3	1.12 (0.99–1.27)	0.08	0.96 (0.84–1.09)	0.51
<60	316	204	195	22.7	23.0	22.4	1.12 (0.94–1.33)	0.22	1.07 (0.89–1.27)	0.49

The mortality cohort included 31,350 participants whereas the morbidity and mortality cohort included 20,584 participants. HF indicates those participants with heart failure who were hospitalized or had a fatal event; CVD indicates CVD mortality or first hospitalized nonfatal CVD event such as MI, stroke, or HF; and ESRD indicates start of dialysis or renal transplant. CVD mortality includes death due to CHD, stroke, HF, or other CVD. There were 10,849 deaths: 4761 due to CVD, 5668 due to non-CVD causes, and 420 unknown causes. CVD, cardiovascular disease; eGFR, estimated GFR; C, chlorthalidone; A, amlodipine; L, lisinopril; HR, hazard ratio; 95% CI, 95% confidence interval; CHD, coronary heart disease; HF, heart failure.

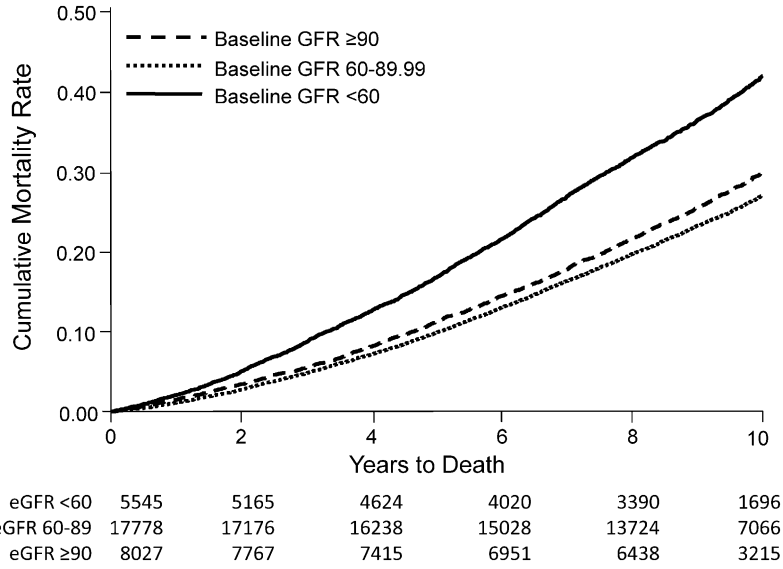

Figure 3. | **Adjusted all-cause mortality by baseline eGFR strata.** Adjusted for age, race, sex, baseline diabetes status, baseline systolic BP, and cardiovascular disease before trial entry. eGFR, estimated GFR.

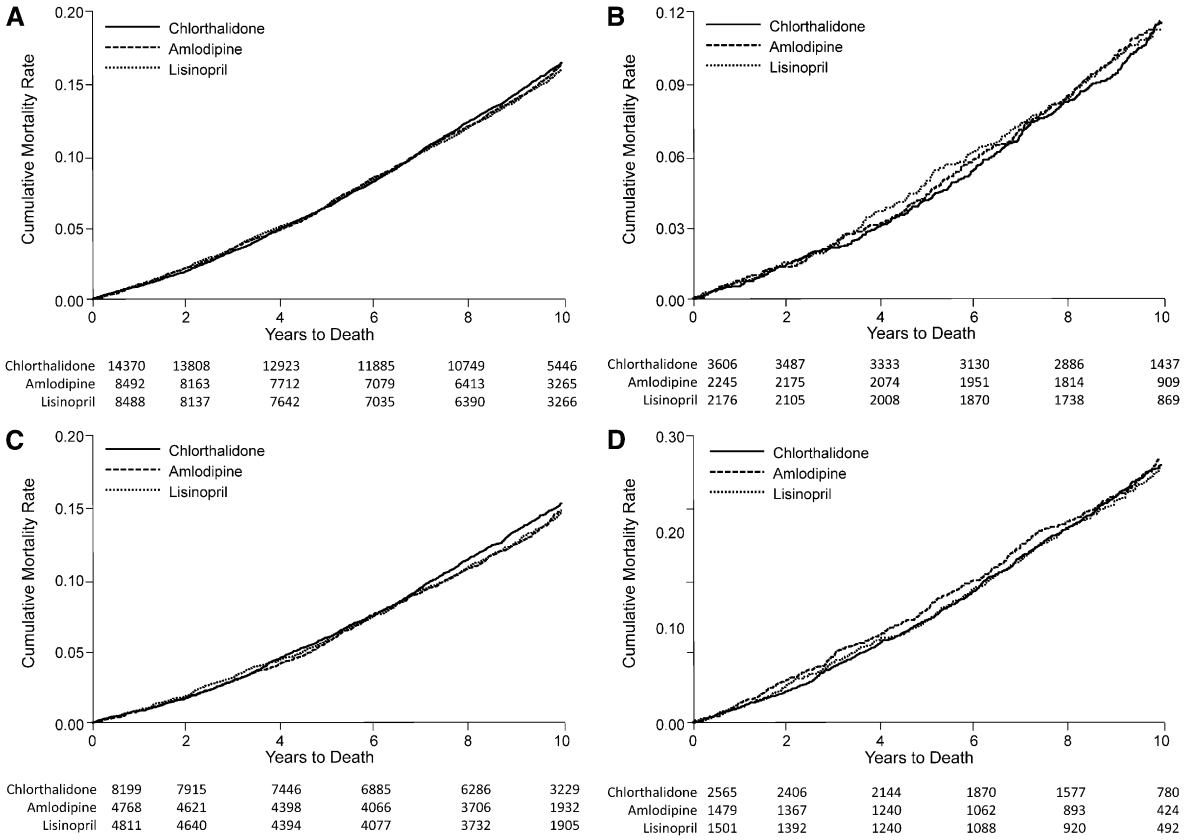

Figure 4. | **Cardiovascular disease mortality by baseline estimated GFR (eGFR) stratum.** (A) Cardiovascular disease mortality by treatment group for all participants. (B) Rates for participants with eGFR≥90 ml/min per 1.73 m^2. (C) Rates for participants with eGFR=60–89 ml/min per 1.73 m^2. (D) Rates for participants with eGFR<60 ml/min per 1.73 m^2.

participants at high risk of adverse renal outcomes may have had a CVD event or could have died from a competing cause before experiencing a renal event. Finally, proteinuria data were not obtained in ALLHAT participants. Proteinuria is an important marker of CKD and a predictor of decline in renal function and response to therapy, especially level of BP control (34). If the proportion of participants with minimal or modest proteinuria was high in

Table 3. All-cause, CVD, and non-CVD mortality in participants with diabetes, as well as cardiovascular outcomes and mortality in participants with diabetes by baseline eGFR for chlorthalidone, amlodipine, and lisinopril antihypertensive treatment groups

eGFR	Total Number of Events/Participants			10-Yr Rate/100 Participants			HR (95% CI)	*P*	HR (95% CI)	*P*
	C	A	L	C	A	L	A Compared with C		L Compared with C	
All-cause mortality	2292/5723	1329/3407	1270/3325	38.5	37.2	36.4	0.96 (0.90–1.03)	0.23	0.94 (0.88–1.01)	0.10
≥90	560/1794	326/1104	320/1074	30.2	28.2	29.2	0.93 (0.81–1.06)	0.28	0.95 (0.83–1.09)	0.44
60–89	1169/2976	674/1755	659/1722	37.3	36.3	36.0	0.96 (0.87–1.06)	0.40	0.97 (0.89–1.07)	0.58
<60	563/953	329/548	291/529	57.5	58.0	52.6	1.04 (0.90–1.19)	0.62	0.90 (0.78–1.03)	0.13
CVD mortality	1023	597	552	19.4	18.3	17.9	0.97 (0.87–1.07)	0.51	0.92 (0.83–1.02)	0.11
≥90	228	138	125	13.9	12.7	12.6	0.96 (0.78–1.19)	0.74	0.91 (0.73–1.13)	0.39
60–89	530	308	289	19.1	18.1	17.8	0.97 (0.84–1.12)	0.66	0.94 (0.82–1.09)	0.42
<60	265	151	138	32.0	32.0	29.7	1.01 (0.82–1.23)	0.95	0.90 (0.73–1.11)	0.33
Non-CVD mortality	1180	684	660	22.2	21.8	21.1	0.96 (0.87–1.05)	0.38	0.95 (0.87–1.05)	0.31
≥90	311	177	179	18.0	16.9	17.7	0.91 (0.75–1.09)	0.29	0.95 (0.79–1.15)	0.61
60–89	589	348	341	20.9	21.4	20.6	0.98 (0.86–1.12)	0.80	1.00 (0.87–1.14)	0.99
<60	280	159	140	35.9	35.3	30.6	1.01 (0.83–1.23)	0.92	0.86 (0.71–1.06)	0.16
CHD, total	710/3802	401/2233	385/2194	22.5	20.8	20.2	0.94 (0.83–1.06)	0.29	0.93 (0.82–1.06)	0.27
≥90	168/1042	91/631	84/615	19.1	15.8	16.1	0.86 (0.67–1.11)	0.24	0.83 (0.64–1.07)	0.16
60–89	362/2026	222/1188	207/1179	21.0	21.5	19.9	1.02 (0.87–1.21)	0.79	1.00 (0.84–1.18)	0.97
<60	180/734	88/414	94/400	33.0	27.9	28.3	0.86 (0.66–1.11)	0.24	0.92 (0.72–1.19)	0.54
CVD, total	1483	887	821	44.9	43.6	42.5	1.00 (0.92–1.09)	0.93	0.96 (0.88–1.04)	0.33
≥90	366	220	201	40.1	36.8	37.3	0.96 (0.81–1.14)	0.65	0.93 (0.78–1.10)	0.41
60–89	760	460	425	42.4	42.8	40.4	1.02 (0.91–1.15)	0.73	0.97 (0.89–1.09)	0.62
<60	357	207	195	60.3	57.3	57.2	1.04 (0.88–1.24)	0.64	0.99 (0.83–1.18)	0.89
Stroke, total	463	274	285	15.4	15.1	16.7	0.98 (0.85–1.14)	0.82	1.07 (0.92–1.24)	0.40
≥90	105	70	71	12.4	12.3	14.4	1.06 (0.78–1.43)	0.72	1.16 (0.86–1.57)	0.34
60–89	248	139	155	15.1	14.6	16.4	0.93 (0.76–1.15)	0.50	1.08 (0.89–1.33)	0.43
<60	110	65	59	21.6	22.4	22.8	1.07 (0.79–1.45)	0.67	0.95 (0.69–1.30)	0.75
HF, total	579	391	337	20.0	20.8	19.7	1.15 (1.01–1.31)	0.03	1.01 (0.88–1.15)	0.91
≥90	142	89	79	17.6	16.1	15.9	0.99 (0.76–1.30)	0.97	0.94 (0.71–1.24)	0.65
60–89	297	204	167	18.5	20.2	18.5	1.19 (0.99–1.42)	0.06	0.98 (0.81–1.19)	0.85
<60	140	98	91	29.0	31.1	30.2	1.28 (0.98–1.65)	0.07	1.17 (0.90–1.52)	0.26

The Modified Diet in Renal Disease equation was used to estimate baseline GFR. The mortality cohort included 12,455 participants whereas the morbidity and mortality cohort included 8229 participants. HF indicates those participants with heart failure who were hospitalized or had a fatal event; CVD indicates CVD mortality or first hospitalized nonfatal CVD event such as MI, stroke, or HF; and ESRD indicates start of dialysis or renal transplant. CVD mortality includes death due to CHD, stroke, HF, or other CVD. There were 4891 deaths, 2172 due to CVD, 2524 due to non-CVD causes, and 195 unknown causes. CVD, cardiovascular disease; eGFR, estimated GFR; C, chlorthalidone; A, amlodipine; L, lisinopril; HR, hazard ratio; 95% CI, 95% confidence interval; CHD, coronary heart disease; HF, heart failure.

Table 4. ESRD in ALLHAT chlorthalidone, amlodipine, and lisinopril participants

eGFR	Total Number of Events/ Participants			10-Yr Rate/100 Participants			HR (95% CI)	*P*	HR (95% CI)	*P*
	C	A	L	C	A	L	A Compared with C		L Compared with C	
Total	371/14370	225/8492	215/8488	3.0	3.0	2.9	1.02 (0.86–1.20)	0.83	0.98 (0.82–1.15)	0.78
≥90	39/3606	26/2245	23/2176	1.2	1.4	1.2	1.06 (0.65–1.74)	0.81	0.98 (0.59–1.65)	0.95
60–89	112/8199	76/4768	74/4811	1.6	1.7	1.8	1.15 (0.86–1.54)	0.34	1.12 (0.83–1.50)	0.46
<60	220/2565	123/1479	118/1501	10.9	10.9	9.9	0.98 (0.79–1.22)	0.87	0.91 (0.73–1.14)	0.41
Diabetic[a]	245/5723	156/3407	158/3325	5.1	5.3	5.7	1.06 (0.86–1.29)	0.59	1.10 (0.90–1.34)	0.35
≥90	34/1794	24/1104	21/1074	2.0	2.7	2.3	1.12 (0.66–1.89)	0.68	1.02 (0.59–1.76)	0.94
60–89	76/2976	52/1755	59/1722	3.1	3.3	4.3	1.14 (0.80–1.62)	0.47	1.35 (0.96–1.89)	0.09
<60	135/953	80/548	78/529	19.0	19.0	18.9	1.06 (0.81–1.40)	0.67	1.00 (0.76–1.32)	0.99
Nondiabetic[a]	110/7993	61/4689	52/4786	1.5	1.5	1.1	0.94 (0.69–1.29)	0.70	0.79 (0.57–1.09)	0.16
≥90	5/1691	1/1063	2/1033	0.4	0.1	0.1	0.32 (0.04–2.72)	0.30	0.67 (0.13–3.44)	0.63
60–89	31/4845	19/2771	11/2857	0.7	0.8	0.3	1.06 (0.60–1.87)	0.85	0.59 (0.30–1.17)	0.13
<60	74/1383	41/855	39/844	6.3	6.6	5.5	0.96 (0.65–1.40)	0.82	0.89 (0.60–1.31)	0.54

This study included 31,350 participants. ESRD indicates start of dialysis or renal transplant, on the basis of data from the US Renal Data System. ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; eGFR, estimated GFR; C, chlorthalidone; A, amlodipine; L, lisinopril; HR, hazard ratio; 95% CI, 95% confidence interval.

[a]Baseline history of diabetes or fasting glucose ≥126 mg/dl (or nonfasting glucose ≥200 mg/dl if baseline fasting glucose missing). Participants missing a baseline glucose measure (*n*=1427) were excluded from diabetic status subgroups

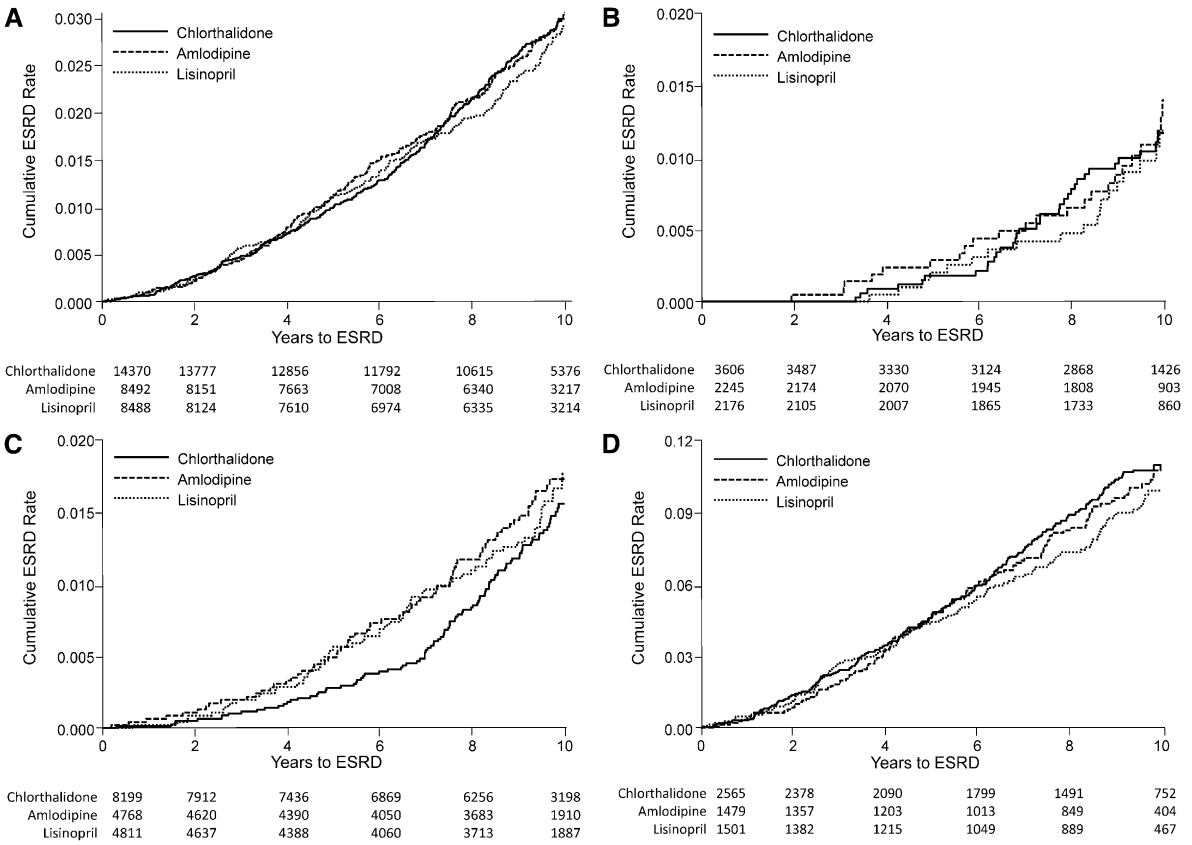

Figure 5. | ESRD by baseline estimated GFR (eGFR) stratum. (A) ESRD rates by treatment group for all participants; (B) rates for participants with eGFR $\geq$ 90 ml/min per 1.73 m^2; (C) rates for participants with eGFR 60-89 ml/min per 1.73 m^2; (D) rates for participants with eGFR $<$ 60 ml/min per 1.73 m^2.

ALLHAT, as is typical of patients who have atherosclerotic or ischemic nephropathy, the selective benefits of ACE inhibitor treatment would likely be diminished. However, because ALLHAT did not specifically study patients with diabetic nephropathy and proteinuria, these findings do not refute current recommendations for treatment of these patients.

These findings have important implications for practice and future research. Given the efficacy of diuretics in preventing cardiovascular and renal outcomes in this population, we agree with recent recommendations that diuretics are an important component of antihypertensive drug regimens in CKD (35). For all CKD subtypes, the hypertension guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (36) recommend diuretics along with RAS axis inhibitors to lower BP and reduce risk for CVD. Our findings support this approach and allay concerns about long-term consequences of renal injury induced by thiazide diuretics in animal models (37). Finally, the high cardiovascular event rate associated with CKD in our study underscores the need for research into novel preventive and treatment strategies for CVD in CKD (38).

The large sample of participants with and without CKD, the high number of cardiovascular and ESRD events, and the long duration of follow-up make ALLHAT a valuable cohort of hypertensive patients. This report extends previous reports on the CKD subgroup in the ALLHAT study. The mean duration of follow-up in the clinical trial phase was 4.9 years; the current analyses extends this to 8.8 years. Antihypertensive drug therapy was not prescribed or managed by the study in the post-trial phase; ascertainment of post-trial events was through databases rather than active adjudication in the clinical trial phase. The consistency of the extended results despite these differences thus reinforces the important conclusions about the association of CKD with very high cardiovascular outcomes over a long time period and effects of antihypertensive drug therapy on cardiovascular and renal outcomes.

Post-trial information about BP levels and antihypertensive medication use was not available, and we are unable to evaluate the influence of proteinuria on long-term outcomes and choice of antihypertensive drug therapy. The lack of long-term morbidity data on some participants (VA, Canadian, and non-Medicare) is a limitation; however, these subgroups did not differ in any consistent manner from other ALLHAT participants.

In summary, the long-term follow-up of the ALLHAT study demonstrates that CKD is associated with a significantly higher long-term risk of cardiovascular events and mortality in older hypertensive patients. In addition, when stratified by baseline eGFR, 5-year treatment with amlodipine or lisinopril is not superior to chlorthalidone-based antihypertensive drug therapy in preventing cardiovascular events,

Table 5. Time-dependent Cox regression analyses of outcome results in-trial and post-trial

	Amlodipine versus Chlorthalidone					Lisinopril versus Chlorthalidone				
	In-Trial		Post-Trial		Time Interaction	In-Trial		Post-Trial		Time Interaction
	HR (95% CI)	*P*	HR (95% CI)	*P*	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	*P*
eGFR <60										
ESRD	0.95 (0.70–1.29)	0.73	1.02 (0.74–1.40)	0.90	0.74	0.95 (0.70–1.29)	0.73	0.87 (0.63–1.21)	0.41	0.71
Nonfatal MI and fatal CHD	0.96 (0.78–1.18)	0.72	0.76 (0.58–1.00)	0.05	0.18	0.94 (0.77–1.16)	0.58	1.01 (0.78–1.30)	0.94	0.68
Combined CVD	1.10 (0.95–1.27)	0.19	0.92 (0.78–1.10)	0.36	0.12	1.07 (0.92–1.23)	0.38	0.94 (0.79–1.11)	0.45	0.25
Stroke	1.12 (0.85–1.48)	0.42	1.03 (0.77–1.38)	0.82	0.69	1.03 (0.78–1.37)	0.82	1.10 (0.83–1.47)	0.51	0.75
Heart failure	1.23 (0.97–1.55)	0.09	1.00 (0.77–1.30)	0.99	0.26	1.24 (0.98–1.57)	0.08	0.88 (0.67–1.16)	0.36	0.07
All-cause mortality	1.06 (0.94–1.21)	0.35	1.00 (0.88–1.13)	0.99	0.51	0.99 (0.87–1.13)	0.91	0.93 (0.82–1.05)	0.24	0.46
CVD mortality	1.16 (0.97–1.38)	0.11	0.91 (0.76–1.10)	0.34	0.07	0.97 (0.80–1.17)	0.75	0.95 (0.79–1.14)	0.61	0.89
Non-CVD mortality	0.91 (0.75–1.11)	0.35	1.07 (0.90–1.26)	0.45	0.23	1.00 (0.83–1.21)	0.97	0.92 (0.78–1.10)	0.38	0.53

HR, hazard ratio; 95% CI, 95% confidence interval; eGFR, estimated GFR; MI, myocardial infarction; CHD, coronary heart disease; CVD, cardiovascular disease.

ESRD, or mortality in this cohort over a 9-year follow-up period. Because data on proteinuria were not available, these findings may not be extrapolated to proteinuric CKD.

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