

Renal Outcomes in High-Risk Hypertensive Patients Treated With an Angiotensin-Converting Enzyme Inhibitor or a Calcium Channel Blocker vs a Diuretic

A Report From the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

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Background: This study was performed to determine whether, in high-risk hypertensive patients with a reduced glomerular filtration rate (GFR), treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of renal disease outcomes compared with treatment with a diuretic.

Methods: We conducted post hoc analyses of the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertensive participants 55 years or older with at least 1 other coronary heart disease risk factor were randomized to receive chlorthalidone, amlodipine, or lisinopril for a mean of 4.9 years. Renal outcomes were incidence of end-stage renal disease (ESRD) and/or a decrement in GFR of 50% or more from baseline. Baseline GFR, estimated by the simplified Modification of Diet in Renal Disease equation, was stratified into normal or increased (≥ 90 mL/min per 1.73 m², n=8126), mild reduction (60-89 mL/min per 1.73 m², n=18 109), or moderate-severe reduction (< 60 mL/min per 1.73 m², n=5662) in GFR. Each stratum was analyzed for effects of the treatments on outcomes.

Results: In 448 participants, ESRD developed. Compared with patients taking chlorthalidone, no significant differences occurred in the incidence of ESRD in patients taking amlodipine in the mild (relative risk [RR], 1.47; 95% confidence interval [CI], 0.97-2.23) or moderate-severe (RR, 0.92; 95% CI, 0.68-1.24) reduction in GFR groups. Compared with patients taking chlorthali-

done, no significant differences occurred in the incidence of ESRD in patients taking lisinopril in the mild (RR, 1.34; 95% CI, 0.87-2.06) or moderate-severe (RR, 0.98; 95% CI, 0.73-1.31) reduction in GFR groups. In patients with mild and moderate-severe reduction in GFR, the incidence of ESRD or 50% or greater decrement in GFR was not significantly different in patients treated with chlorthalidone compared with those treated with amlodipine (odds ratios, 0.96 [$P=.74$] and 0.85 [$P=.23$], respectively) and lisinopril (odds ratios, 1.13 [$P=.31$] and 1.00 [$P=.98$], respectively). No difference in treatment effects occurred for either end point for patients taking amlodipine or lisinopril compared with those taking chlorthalidone across the 3 GFR subgroups, either for the total group or for participants with diabetes at baseline. At 4 years of follow-up, estimated GFR was 3 to 6 mL/min per 1.73 m² higher in patients assigned to receive amlodipine compared with chlorthalidone, depending on baseline GFR stratum.

Conclusions: In hypertensive patients with reduced GFR, neither amlodipine nor lisinopril was superior to chlorthalidone in reducing the rate of development of ESRD or a 50% or greater decrement in GFR. Participants assigned to receive amlodipine had a higher GFR than those assigned to receive chlorthalidone, but rates of development of ESRD were not different between the groups.

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THE PREVALENCE OF END-stage renal disease (ESRD) has doubled in the United States during the last decade and is expected to double again by the year 2010.¹ Patients with ESRD experience substantial cardiovascular morbidity and mortality; in ad-

dition, health costs related to ESRD exceed \$12 billion annually.¹ It is estimated that more than 10 million Americans have chronic kidney disease and are at high risk of developing ESRD.² Therefore, therapeutic interventions that slow decline in renal function in patients with chronic kidney disease are important.³

Hypertension is a major cause of target organ damage in the kidney and is the most common comorbid condition at the initiation of treatment for ESRD.⁴ It is second only to diabetes as the most commonly reported underlying cause of ESRD in the United States.¹ Several studies^{4,5} have shown that adequate treatment of hypertension in both diabetic and nondiabetic patients with chronic kidney disease is an important determinant in slowing progression of renal disease and in reducing the incidence of ESRD. Most studies⁶⁻⁹ that have evaluated the effects of antihypertensive therapy on progression of renal disease have been conducted in patients with moderate renal disease with proteinuria; in these studies, inhibition of the renin-angiotensin system by angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blockade has been shown to be superior to conventional therapy in preserving renal function. The African American Study of Kidney Disease and Hypertension (AASK) showed that ACE inhibitor-based therapy provided an additional renoprotective effect compared with standard therapy in patients with hypertensive nephrosclerosis.⁶ Most renal clinical trials have included a diuretic as part of the therapeutic regimen in all treatment arms; to our knowledge, no previous large clinical trial has reported a comparison of diuretic- vs non-diuretic-based antihypertensive drug therapy with regard to renal disease outcomes. Small clinical studies¹⁰ in diabetic nephropathy have shown similar reduction in blood pressure and proteinuria comparing ACE and diuretic therapy.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a clinical trial designed to compare the efficacy of treatment with different antihypertensive agents on cardiovascular disease and other outcomes in high-risk hypertensive patients 55 years and older.¹¹ Renal events and changes in renal function were prespecified as secondary outcomes in the ALLHAT protocol, and the results in the study population as a whole have been previously reported; there was no difference in the risk of ESRD between chlorthalidone and amlodipine or lisinopril, and the estimated glomerular filtration rate (GFR) was higher at the end of the study in patients randomized to receive amlodipine compared with those randomized to receive chlorthalidone.¹² However, renal outcomes in ALLHAT participants considered to be at high risk of progression of their renal disease, for example, diabetic patients and those with a reduced GFR at baseline, have not been previously published. The purpose of this article is to report the efficacy of first-step treatment with a calcium channel blocker (amlodipine) or an ACE inhibitor (lisinopril), each compared with a diuretic (chlorthalidone), in modifying renal disease outcomes in high-risk hypertensive patients stratified by baseline GFR and presence or absence of diabetes mellitus.

METHODS

The rationale and design of ALLHAT have been presented in detail elsewhere.¹¹ Participants were men and women 55 years or older who had stage 1 or stage 2 hypertension with at least 1 additional risk factor for coronary heart disease events. The

risk factors included previous (>6 months) myocardial infarction or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, history of type 2 diabetes mellitus, current cigarette smoking, high-density lipoprotein cholesterol level of less than 35 mg/dL (<0.91 mmol/L), or documentation of other atherosclerotic cardiovascular disease. Individuals with a history of symptomatic heart failure and/or a known left ventricular ejection fraction of less than 35% were excluded. Participants with a serum creatinine level greater than 2 mg/dL (176.8 μmol/L) as reported by the investigator were excluded. However, if the serum creatinine level measured at the time of randomization was found to exceed 2 mg/dL (176.8 μmol/L), these participants were maintained in the trial and followed up according to the study protocol. Participants (n=33 357) were recruited at 623 centers in the United States, Canada, Puerto Rico, and the US Virgin Islands between February 1994 and January 1998.

Participants were randomly assigned in a double-blind manner and a 1.7:1:1 ratio to receive chlorthalidone, amlodipine, or lisinopril. A fourth arm of the study that used the α-blocker doxazosin mesylate was stopped early and is not considered in this report.¹³ Goal blood pressure in each randomized group was less than 140/90 mm Hg, achieved by titrating the assigned study drug (step 1) and adding study supplied open-label agents when necessary at the physician's discretion. Nonpharmacologic lifestyle approaches to treatment of hypertension were recommended according to national guidelines. Dosages were 12.5, 12.5 (sham titration), and 25 mg/d for chlorthalidone; 2.5, 5, and 10 mg/d for amlodipine; and 10, 20, and 40 mg/d for lisinopril. Doses of open-label step 2 drugs were 25 to 100 mg/d of atenolol, 0.05 to 0.2 mg/d of reserpine, or 0.1 to 0.3 mg twice a day of clonidine; step 3 was 25 to 100 mg twice a day of hydralazine hydrochloride. Other drugs, including low doses of open-label step 1 drug classes, were permitted if clinically indicated. Follow-up visits were at 1, 3, 6, 9, and 12 months and every 4 months thereafter.

Serial determinations of serum creatinine were obtained in a single central laboratory using the Ortho Clinical Diagnostics Vitros Chemistry System (Rochester, NY), which had a coefficient of variation of approximately 2%. An indirect calibration was performed based on analyzing 148 frozen ALLHAT samples at the Third National Health and Nutrition Examination Survey (NHANES III)¹⁴ White Sands Laboratory, White Sands, NM, which has recently been compared with The Cleveland Clinic Laboratory, Cleveland, Ohio, using 212 frozen Modification of Diet in Renal Disease (MDRD) study samples¹⁵ and 342 frozen NHANES III samples. Analyses of these data indicated that the ALLHAT serum creatinine measurements averaged only 0.02 mg/dL (SE, 0.02 mg/dL) (1.76 μmol/L [SE, 1.76 μmol/L]) higher than the measurements during the MDRD study. Six hundred thirty-four participants were missing creatinine values and thus estimated GFR at baseline. Serum creatinine measurements were repeated at 1 month, 1 year, 2 years, and then every other year during follow-up.

The simplified MDRD study equation, which incorporated age, race, and sex in addition to serum creatinine, was used to estimate GFR according to the following formula¹⁵:

$$186.3 \times \text{Serum Creatinine}^{-1.154} \times \text{Age in Years}^{-0.203} \\ \times 1.212 \text{ (If Black)} \times 0.742 \text{ (If Female)}.$$

Although the MDRD equation has not been validated in larger populations (particularly diabetic patients), it is the current standard tool to estimate GFR recommended in the National Kidney Foundation–Kidney/Dialysis Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines on Chronic Kidney Disease and National Kidney Disease Education Program.² Patients were classified into 3 baseline categories of GFR: normal or increased (≥ 90 mL/min per 1.73 m²), mild reduction (60–89 mL/min per 1.73 m²), and moderate-severe reduc-

tion (<60 mL/min per 1.73 m²); these categories are also consistent with the NKF-K/DOQI guidelines. Since a serum creatinine level greater than 2 mg/dL was an exclusion criterion, the percentage of patients with severe chronic kidney disease (GFR, ≤29 mL/min per 1.73 m²) at baseline was small (0.6%). Therefore, as in other studies,¹⁶ these participants are considered along with those with moderate chronic kidney disease (GFR, 30-59 mL/min per 1.73 m²).

The following clinical renal outcomes were assessed: (1) development of ESRD, defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis as reported from the clinical sites; (2) a composite end point of ESRD or 50% or greater decline in GFR from baseline; and (3) mean GFR during study follow-up. Details of the clinical events at the time of initiation of long-term dialysis, such as assessment of acute renal failure, were not evaluated. Only the first of these was prespecified in the ALLHAT protocol. The classification of ESRD (kidney disease death, renal transplantation, or start of long-term renal dialysis) was defined in the ALLHAT manual of operations and assigned by the investigators. In addition, medical reviewers at the Clinical Trials Center reviewed all events for concordance with the aforementioned criteria. Events that were judged as possibly misclassified were returned to the investigator for reconsideration and possible reclassification by the investigator. The investigator's judgment always took precedence; the cause of ESRD and any precipitating clinical circumstances, such as acute renal failure, were not evaluated. The slope of the reciprocal serum creatinine was also prespecified but has been replaced by the preferred estimated GFR based on the MDRD equation in this report.

Data were analyzed according to participants' randomized treatment assignments regardless of their subsequent medications (intent-to-treat analysis). Baseline characteristics were compared across treatment and baseline GFR groups using the z test for continuous covariates and contingency table analyses for categorical data. Mean GFRs for participants assigned to receive amlodipine or lisinopril were compared with those from patients assigned to receive chlorthalidone at each follow-up point using t tests. The Cox proportional hazards model was used to obtain hazard ratios (hereafter called *relative risks* [RRs]) and 95% confidence intervals (CIs) for time to ESRD. Because the "time to event" is less certain for a 50% or greater decline in GFR, the odds ratios and their 95% CIs were obtained from logistic models and Cox regression models for the composite outcome of ESRD or a 50% or greater decline in GFR. To assess possible bias from censoring due to competing causes of death, vital status (non-kidney disease deaths, unknown vital status, known alive) was tabulated for those without renal end points, and a combined end point of ESRD, 50% or greater decline in renal function, and total mortality was analyzed using methods already described. Tests for differences in treatment effects across GFR groups (interactions) were performed by calculating the differences in the log likelihoods for models with and without interaction terms.

RESULTS

Baseline characteristics of the study population stratified by GFR and treatment group are presented in **Table 1**. Within each GFR stratum, no significant difference occurred in the characteristics of participants randomized to receive amlodipine or lisinopril compared with those randomized to receive chlorthalidone. Participants with reduced GFRs had older mean age and lower body mass index and diastolic blood pressure. Participants with mild or moderate-severe reductions in baseline GFR were more likely than

those with normal GFRs to be white non-Hispanic; have a history of coronary heart disease or atherosclerotic cardiovascular disease, low high-density lipoprotein cholesterol level, and left ventricular hypertrophy by echocardiography; and were less likely to be current cigarette smokers. They also had higher systolic blood pressure, lower diastolic blood pressure, and a lower prevalence of reported diabetes. Baseline characteristics and cardiovascular risk factors of ALLHAT participants with reduced GFRs have been reported in detail in a separate publication.¹⁷

Four hundred forty-eight patients had an ESRD event. Of participants without an ESRD event, 4533 (13.8%) died and 1147 (3.5%) refused to continue study participation or were lost to follow-up. The proportion of participants who died was higher in the GFR less than 60 mL/min per 1.73 m² stratum (21.8%) and the GFR 60 to 89 mL/min per 1.73 m² stratum (12.5%) than the GFR 90 mL/min per 1.73 m² or greater stratum (10.6%). The mean ± SD duration of follow-up was 59.0 ± 16.5 months and did not differ among the treatment groups.

ESRD OUTCOMES

No significant difference was apparent in the overall 6-year rates of ESRD between those randomized to receive chlorthalidone (1.8/100) and either amlodipine (2.1/100, $P=.33$) or lisinopril (2.0/100, $P=.38$). This overall study finding was similar in diabetic and nondiabetic participants in all 3 strata of baseline GFRs and in all of the baseline GFR strata in diabetic participants (**Table 2**). In diabetic participants with mildly reduced GFRs (60-89 mL/min per 1.73 m²), participants assigned to receive amlodipine had a higher risk of ESRD than those assigned to receive chlorthalidone (RR, 1.72; 95% CI, 1.01-2.95; $P=.05$), and participants assigned to receive lisinopril had a higher risk of ESRD than those assigned to receive chlorthalidone (RR, 1.74; 95% CI, 1.00-3.01; $P=.05$). However, no significant treatment group by GFR interaction occurred in the total group or among diabetic participants.

COMPOSITE RENAL OUTCOMES

The composite end point, defined as a 50% or greater decline in GFR or ESRD, occurred in 1049 study participants. There were no significant differences in the overall rates of this end point between the chlorthalidone (3.2%), amlodipine (2.8%, $P=.08$), or lisinopril (3.3%, $P=.65$) groups (**Table 3**). This finding was consistent across diabetes, GFR, and GFR-diabetic subgroups. Results using Cox regression analyses, in which time to 50% or greater decline in GFR was determined by the date of the blood draw, were similar to those using the logistic regression model approach (data not shown). The risk of ESRD or this composite end point was significantly higher in patients in the moderate-severe reduction in GFR group compared with the normal or increased GFR group; this was particularly marked in the diabetic participants regardless of treatment assignment.

Another composite end point that included ESRD, 50% or greater decline in GFR, or death from any cause was compared among the groups. The RRs for patients taking amlodipine compared with those taking chlorthali-

Table 1. Baseline Characteristics Stratified by Baseline Estimated GFR and Treatment Group

Characteristic	Normal or Increased GFR (≥90 mL/min per 1.73 m ²)			Mild Decrease in GFR (60-89 mL/min per 1.73 m ²)			Moderate or Severe Decrease in GFR (<60 mL/min per 1.73 m ²)		
	Chlorthalidone	Amlodipine	Lisinopril	Chlorthalidone	Amlodipine	Lisinopril	Chlorthalidone	Amlodipine	Lisinopril
No. randomized	3648	2274	2204	8360	4850	4899	2613	1516	1533
Age, mean (SD), y	63.4 (6.4)	63.3 (6.5)	63.2 (6.3)	67.2 (7.4)	67.4 (7.5)	67.3 (7.5)	70.8 (7.9)	70.8 (7.6)	70.6 (7.9)
Ethnicity, No. (%)									
White non-Hispanic	1223 (33.5)	766 (33.7)	754 (34.2)	4302 (51.5)	2524 (52.0)	2494 (50.9)	1489 (57.0)	882 (58.2)	877 (57.2)
Black non-Hispanic	1569 (43.0)	985 (43.3)	945 (42.9)	2303 (27.6)	1363 (28.1)	1354 (27.6)	675 (25.8)	369 (24.3)	400 (26.1)
White Hispanic	401 (11.0)	244 (10.7)	249 (11.3)	1150 (13.8)	636 (13.1)	686 (14.0)	296 (11.3)	184 (12.1)	170 (11.1)
Black Hispanic	259 (7.1)	154 (6.8)	137 (6.2)	195 (2.3)	112 (2.3)	123 (2.5)	27 (1.0)	19 (1.3)	22 (1.4)
Other	196 (5.4)	125 (5.5)	119 (5.4)	410 (4.9)	215 (4.4)	242 (4.9)	126 (4.8)	62 (4.1)	64 (4.2)
Women, No. (%)	1710 (46.9)	1087 (47.8)	988 (44.8)	3726 (44.6)	2145 (44.2)	2189 (44.7)	1368 (52.4)	829 (54.7)	763 (49.8)
BMI, mean (SD)	30.3 (6.5)	30.6 (6.5)	30.3 (6.5)	29.6 (6.00)	29.6 (5.9)	29.7 (6.0)	29.1 (6.0)	29.0 (5.7)	29.2 (5.8)
Baseline systolic blood pressure, mean (SD), mm Hg	145.8 (15.2)	145.7 (15.7)	146.3 (15.1)	146.2 (15.7)	146.4 (15.5)	146.4 (15.5)	146.9 (16.2)	146.3 (16.3)	146.8 (16.4)
Baseline diastolic blood pressure, mean (SD), mm Hg	84.9 (9.7)	84.7 (9.9)	85.2 (9.4)	84.1 (10.0)	84.0 (10.1)	84.1 (10.0)	82.5 (10.5)	82.4 (10.4)	82.8 (10.6)
History of coronary heart disease, No. (%)	775 (21.4)	455 (20.2)	478 (21.8)	2216 (26.7)	1253 (26.0)	1252 (25.8)	824 (31.8)	423 (28.1)	466 (30.7)
Estimated GFR, mean (SD), mL/min per 1.73 m ² *	102.5 (13.0)	102.7 (12.9)	102.7 (13.2)	75.1 (8.1)	75.1 (8.0)	75.1 (8.1)	50.1 (8.7)	50.6 (8.5)	50.1 (8.6)
Eligibility risk factors, No. (%)†									
Current cigarette smoking	995 (27.3)	596 (26.2)	639 (29.0)	1766 (21.1)	1013 (20.9)	970 (19.8)	452 (17.3)	276 (18.2)	283 (18.5)
Atherosclerotic cardiovascular disease	1575 (43.2)	991 (43.6)	921 (41.8)	4420 (52.9)	2529 (52.1)	2595 (53.0)	1579 (60.4)	888 (58.6)	945 (61.6)
History of MI or stroke	720 (19.7)	450 (19.8)	427 (19.4)	1989 (23.8)	1148 (23.7)	1113 (22.7)	755 (28.9)	403 (26.6)	435 (28.4)
History of coronary revascularization	329 (9.0)	198 (8.7)	205 (9.3)	1123 (13.4)	641 (13.2)	692 (14.1)	467 (17.9)	235 (15.5)	278 (18.1)
Other atherosclerotic CVD	668 (18.3)	436 (19.2)	390 (17.7)	2026 (24.2)	1169 (24.1)	1190 (24.3)	743 (28.4)	446 (29.4)	464 (30.3)
ST-segment depression or T-wave inversion on ECG	329 (9.1)	206 (9.1)	202 (9.2)	879 (10.6)	500 (10.4)	503 (10.4)	286 (11.1)	159 (10.6)	174 (11.5)
Type 2 diabetes mellitus	1667 (45.7)	1026 (45.1)	981 (44.5)	2755 (33.0)	1626 (33.5)	1563 (31.9)	881 (33.7)	506 (33.4)	501 (32.7)
Low HDL-C	362 (9.9)	208 (9.2)	207 (9.4)	1053 (12.6)	601 (12.4)	621 (12.7)	323 (12.4)	177 (11.7)	189 (12.3)
LVH by ECG	570 (15.6)	392 (17.2)	361 (16.4)	1328 (15.9)	820 (16.9)	785 (16.0)	434 (16.6)	250 (16.5)	255 (16.6)
LVH by echocardiography	131 (3.6)	83 (3.7)	67 (3.1)	409 (4.9)	218 (4.5)	241 (5.0)	129 (5.0)	91 (6.1)	73 (4.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CVD, cardiovascular disease; ECG, electrocardiography; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MI, myocardial infarction. *Derived from the application of the simplified Modified Diet in Renal Disease equation based on serum creatinine, age, race, and sex.¹⁵

†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.

done for this end point were 0.90 (95% CI, 0.78-1.04; *P* = .16) in the GFR of 90 mL/min per 1.73 m² or greater stratum, 0.90 (95% CI, 0.82-0.99; *P* = .02) in the GFR stratum of 60 to 89 mL/min per 1.73 m², and 1.02 (95% CI, 0.90-1.15; *P* = .78) in the GFR of less than 60 mL/min per 1.73 m² stratum. The RRs for patients taking lisinopril compared with those taking chlorthalidone were 1.04 (95% CI, 0.90-1.20; *P* = .57) in the GFR of 90 mL/min per 1.73 m² or greater stratum, 1.00 (95% CI, 0.91-1.09; *P* = .93) in the GFR stratum of 60 to 89 mL/min per 1.73 m², and 1.02 (95% CI, 0.90-1.15; *P* = .80) in the GFR less than 60 mL/min per 1.73 m² stratum.

CHANGE IN ESTIMATED GFR DURING THE STUDY

Amlodipine vs Chlorthalidone

Participants assigned to receive amlodipine had higher estimated GFRs during follow-up compared with their

counterparts who were assigned to receive chlorthalidone at years 1, 2, 4, and 6, regardless of their baseline GFR. This pattern was consistent for diabetic participants (**Table 4**).

Lisinopril vs Chlorthalidone

Estimated GFRs were similar between participants assigned to receive lisinopril and chlorthalidone at years 1, 2, 4, and 6. This pattern was consistent for diabetic participants and when stratified by baseline GFR with the exception of the baseline stratum of GFR of 90 mL/min per 1.73 m² or greater, where participants assigned to receive lisinopril had a higher GFR at years 2 and 4 compared with those assigned to receive chlorthalidone (Table 4).

BLOOD PRESSURE CONTROL

At year 4, systolic blood pressure was slightly higher in the amlodipine and lisinopril groups compared with the

Table 2. End-stage Renal Disease in the Blood Pressure Component of ALLHAT by Treatment Group by Diabetic Status and GFR Group at Baseline*

Variable	Total No. of Events/ Total No. of Participants			Mean (SE) 6-Year Rates per 100 Population			RR (95% CI) [P Value]	
	Chlorthalidone	Amlodipine	Lisinopril	Chlorthalidone	Amlodipine	Lisinopril	Amlodipine- Chlorthalidone	Lisinopril- Chlorthalidone
Total†	193/15 255	129/9048	126/9054	1.8 (0.1)	2.1 (0.2)	2.0 (0.2)	1.12 (0.89-1.40) [.33]	1.11 (0.88-1.38) [.38]
By baseline diabetic status								
Diabetic participants	109/5528	86/3323	73/3212	2.7 (0.3)	3.6 (0.4)	3.3 (0.4)	1.30 (0.98-1.73) [.07]	1.17 (0.87-1.57) [.31]
Nondiabetic participants†	84/9727	43/5725	53/5842	1.3 (0.2)	1.0 (0.1)	1.3 (0.2)	0.86 (0.60-1.25) [.43]	1.05 (0.74-1.48) [.78]
By GFR stratum for all participants, mL/min per 1.73 m ² ‡								
≥90	11/3648	9/2274	7/2204	0.27 (0.10)	0.60 (0.22)	0.40 (0.15)	1.31 (0.54-3.17) [.54]	1.08 (0.42-2.78) [.88]
60-89	47/8360	41/4850	37/4899	0.84 (0.14)	1.24 (0.21)	1.06 (0.18)	1.47 (0.97-2.23) [.07]	1.34 (0.87-2.06) [.18]
<60	124/2613	65/1516	70/1533	6.23 (0.59)	5.69 (0.76)	6.00 (0.76)	0.92 (0.68-1.24) [.57]	0.98 (0.73-1.31) [.89]
By GFR stratum for diabetic participants, mL/min per 1.73 m ² §								
≥90	8/1667	5/1026	2/981	0.54 (0.21)	0.76 (0.39)	0.27 (0.19)	1.03 (0.34-3.16) [.95]	0.43 (0.09-2.04) [.29]
60-89	26/2755	27/1626	25/1563	1.38 (0.30)	2.62 (0.54)	2.35 (0.49)	1.72 (1.01-2.95) [.05]	1.74 (1.00-3.01) [.05]
<60	68/881	44/506	41/501	10.05 (1.25)	11.55 (1.84)	11.12 (1.79)	1.11 (0.77-1.63) [.56]	1.07 (0.73-1.58) [.72]

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CI, confidence interval; GFR, glomerular filtration rate; RR, relative risk.

*Differences among treatment group effects by baseline history of diabetes and baseline GFR group are not statistically significant. End-stage renal disease is defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis.

†Includes participants with unknown baseline estimated GFR.

‡A total of 634 participants are missing baseline GFRs.

§A total of 225 participants are missing baseline GFRs.

chlorthalidone group in those with a normal or increased GFR and in those with mild reduction in GFR at baseline (**Table 5**). For the corresponding comparison, diastolic blood pressure was slightly but significantly lower in those assigned to amlodipine. In the subset of patients who reached ESRD, blood pressure was not significantly different between the treatment groups at baseline and 2 and 4 years of follow-up (except the amlodipine group had a lower diastolic blood pressure at year 4 compared with the chlorthalidone group, 68.0 vs 75.0 mm Hg, $P < .05$).

ADHERENCE TO STUDY MEDICATION AND ANTIHYPERTENSIVE MEDICATION USE

Amlodipine vs Chlorthalidone

Adherence to study drug or equivalent and use of step 2 or step 3 medications was similar between the amlodipine and chlorthalidone groups in all 3 GFR strata.

Lisinopril vs Chlorthalidone

Participants randomized to receive lisinopril were less likely to be taking the study drug or another medication of the same class compared with those randomized to receive chlorthalidone regardless of estimated baseline GFR. In the lisinopril group at year 2, 74.3% of patients in the GFR less than 60 mL/min per 1.73 m² stratum, 79.9% in the GFR of 60 to 89 mL/min per 1.73 m² stratum, and 79% in the GFR of 90 mL/min per m² or 1.73 greater stratum were using lisinopril or equivalent anti-

hypertensive medication. In the chlorthalidone group at year 2, 82.7% in the GFR less than 60 mL/min per 1.73 m² stratum, 85.6% in the GFR stratum of 60 to 89 mL/min per 1.73 m², and 85% in the GFR stratum of 90 mL/min per 1.73 m² or greater were using chlorthalidone or an equivalent antihypertensive medication ($P < .001$ for all 3 comparisons). At year 2, use of step 2 or 3 medications was not significantly different between the lisinopril and chlorthalidone groups among participants with baseline GFRs of less than 60 mL/min per 1.73 m² (39.1% vs 37.0%, $P = .22$) and higher for lisinopril vs chlorthalidone among participants with GFRs of 60 to 89 mL/min per 1.73 m² (36.3% vs 32.1%, $P < .001$) and GFRs of 90 mL/min per 1.73 m² or greater (36.6% vs 30.3%, $P < .001$).

In the small subset of patients with a GFR less than 30 mL/min per 1.73 m², no statistically significant difference existed between patients taking amlodipine ($n = 45$) and those taking chlorthalidone ($n = 83$) for risk of development of ESRD (amlodipine-chlorthalidone RR, 0.67; $P = .23$). Similarly, no statistically significant difference occurred between patients taking lisinopril ($n = 54$) and those taking chlorthalidone ($n = 83$) for risk of development of ESRD (lisinopril-chlorthalidone RR, 0.67; $P = .23$).

COMMENT

In ALLHAT participants with reduced renal function, neither amlodipine nor lisinopril was superior to chlorthalidone in reducing incidence of ESRD or a composite of

Table 3. End-stage Renal Disease or a 50% or Greater Decline in GFR in the Blood Pressure Component of ALLHAT by Treatment Group by Diabetic Status and GFR Group at Baseline*

Variable	Total No. of Events (% of Participants)/ Total No. of Participants			RR (95% CI) [P Value]	
	Chlorthalidone	Amlodipine	Lisinopril	Amlodipine- Chlorthalidone	Lisinopril- Chlorthalidone
Total†	493 (3.2)/15 255	256 (2.8)/9048	300 (3.3)/9054	0.87 (0.74-1.01) [.08]	1.03 (0.89-1.20) [.65]
By baseline diabetic status					
Diabetic participants‡	279 (5.0)/5528	164 (4.9)/3323	168 (5.2)/3212	0.98 (0.80-1.19) [.82]	1.04 (0.85-1.26) [.71]
Nondiabetic participants‡	214 (2.2)/9727	92 (1.6)/5725	132 (2.3)/5842	0.73 (0.57-0.93) [.01]	1.03 (0.83-1.28) [.81]
By GFR stratum for all participants, mL/min per 1.73 m ² ‡					
≥90	112 (3.1)/3648	46 (2.0)/2274	57 (2.6)/2204	0.65 (0.46-0.92) [.02]	0.84 (0.61-1.16) [.28]
60-89	190 (2.3)/8360	106 (2.2)/4850	125 (2.6)/4899	0.96 (0.76-1.22) [.74]	1.13 (0.90-1.41) [.31]
<60	180 (6.9)/2613	90 (5.9)/1516	106 (6.9)/1533	0.85 (0.66-1.11) [.23]	1.00 (0.78-1.29) [.98]
By GFR stratum for diabetic participants, mL/min per 1.73 m ² §					
≥90	77 (4.6)/1667	30 (2.9)/1026	35 (3.6)/981	0.62 (0.40-0.96) [.03]	0.76 (0.51-1.15) [.20]
60-89	99 (3.6)/2755	68 (4.2)/1626	67 (4.3)/1563	1.17 (0.85-1.60) [.33]	1.20 (0.88-1.65) [.26]
<60	96 (10.9)/881	56 (11.1)/506	61 (12.1)/501	1.02 (0.72-1.44) [.92]	1.13 (0.81-1.60) [.47]

Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CI, confidence interval; GFR, glomerular filtration rate; RR, relative risk.

*Differences among treatment group effects by baseline history of diabetes and baseline GFR group are not statistically significant. End-stage renal disease is defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis.

†Includes participants with unknown baseline estimated GFR.

‡A total of 634 participants are missing baseline GFRs.

§A total of 225 participants are missing baseline GFRs.

ESRD and a 50% or greater decline in GFR. Participants assigned to receive amlodipine had a higher GFR than those assigned to receive chlorthalidone, but rates of development of ESRD were not different among the groups.

End-stage renal disease is an important public health concern worldwide. The prevalence of ESRD has been increasing, and the estimated cost of ESRD programs in the United States was \$12 billion in 1998 and is projected to exceed \$28 billion by 2010.¹ Several epidemiologic studies identify hypertension as an independent predictor of renal insufficiency.^{18,19} In addition, regardless of whether hypertension is the cause or the consequence of kidney disease, when the two present together, high blood pressure is associated with rapid progression, and adequate treatment of hypertension slows progression of kidney disease and reduces the risk of ESRD.²⁰⁻²² Therefore, great interest exists in whether the choice of antihypertensive drug therapy has an impact on renal disease progression. In diabetic and nondiabetic hypertensive patients with established chronic renal insufficiency and proteinuria, drugs that inhibit the renin-angiotensin system have been suggested to be superior to conventional therapy in slowing decline in renal function.⁵ However, few studies have compared the efficacy of different classes of antihypertensive drug therapy on decline in renal function in hypertensive patients with a mild reduction in GFR.

ALLHAT is the largest antihypertensive trial ever conducted and was designed to compare the effects of different antihypertensive agents on cardiovascular disease outcomes. The primary outcome of the study was cardiovascular disease, but renal outcomes were pre-

specified as a secondary outcome. (GFR subgroup analyses were not prespecified.) The large number of participants with reduced GFRs and diabetes allowed the opportunity to do a head-to-head comparison of the effects of amlodipine and lisinopril with chlorthalidone on renal disease outcomes. Unlike previous renal function trials that included diuretics as an add-on agent in most trial participants, ALLHAT is able to compare the effects of a diuretic-based regimen vs other antihypertensive drug classes on renal outcomes. The proportion of patients with an estimated GFR of less than 90 mL/min per 1.73 m² was higher in ALLHAT compared with the general population; although this likely reflects higher prevalence of chronic kidney disease due to the older age and multiple risk factors in the study population, an inherent bias in the MDRD equation to estimate GFR in patients with normal and near-normal renal function cannot be excluded.

There was no difference in risk of ESRD between the amlodipine and chlorthalidone groups when stratified by baseline GFR or diabetes. However, the composite end point of a 50% or greater decline in GFR or ESRD was less common in some subgroups with amlodipine, and the estimated GFR was higher in the amlodipine group compared with the chlorthalidone group. This may reflect a true difference in the ability to preserve renal function or a hemodynamic effect of amlodipine, resulting in an initial increase in GFR. Effects of amlodipine on the renal microcirculation have been well documented. Amlodipine induces vasodilation of constricted preglomerular renal resistance vessels in isolated perfused kidneys, with preferential augmentation of GFR with a re-

Table 4. Estimated GFR During the Study by Treatment Group and Baseline GFR

Estimated Baseline GFR	Baseline		1 Year		2 Years		4 Years		6 Years	
	Mean (SD)	P Value	Mean (SD)	P Value	Mean (SD)	P Value	Mean (SD)	P Value	Mean (SD)	P Value
All Participants										
≥90 mL/min per 1.73 m ²										
Chlorthalidone	102.5 (13.0) (n = 3648)		93.4 (17.2) (n = 2394)		91.9 (18.1) (n = 2368)		86.9 (18.4) (n = 2026)		83.3 (19.4) (n = 548)	
Amlodipine	102.7 (12.9) (n = 2274)	.66	98.6 (16.9) (n = 1513)	<.001	97.7 (17.6) (n = 1485)	<.001	93.2 (18.6) (n = 1267)	<.001	89.9 (19.9) (n = 342)	<.001
Lisinopril	102.7 (13.2) (n = 2204)	.58	94.5 (17.0) (n = 1375)	.05	93.4 (17.0) (n = 1335)	.01	88.3 (18.4) (n = 1116)	.04	84.9 (22.0) (n = 286)	.28
60-89 mL/min per 1.73 m ²										
Chlorthalidone	75.1 (8.1) (n = 8360)		72.8 (19.2) (n = 5734)		72.2 (13.6) (n = 5649)		68.9 (14.4) (n = 4776)		65.5 (15.5) (n = 1406)	
Amlodipine	75.1 (8.0) (n = 4850)	.82	76.7 (13.0) (n = 3321)	<.001	75.9 (13.6) (n = 3224)	<.001	73.0 (14.7) (n = 2797)	<.001	69.7 (16.5) (n = 883)	<.001
Lisinopril	75.1 (8.1) (n = 4899)	.58	73.2 (12.7) (n = 3209)	.25	72.5 (13.7) (n = 3138)	.30	69.0 (14.7) (n = 2689)	.60	66.7 (15.8) (n = 803)	.09
<60 mL/min per 1.73 m ²										
Chlorthalidone	50.1 (8.7) (n = 2613)		50.6 (12.6) (n = 1677)		50.2 (13.3) (n = 1615)		48.1 (14.3) (n = 1307)		45.6 (15.4) (n = 386)	
Amlodipine	50.6 (8.5) (n = 1516)	.06	54.9 (13.4) (n = 956)	<.001	54.3 (14.1) (n = 918)	<.001	51.5 (15.1) (n = 732)	<.001	49.9 (14.4) (n = 215)	.001
Lisinopril	50.1 (8.6) (n = 1533)	.98	51.1 (12.2) (n = 950)	.30	50.6 (14.1) (n = 888)	.41	48.3 (14.4) (n = 679)	.81	46.9 (14.8) (n = 233)	.30
Participants With Diabetes at Baseline										
≥90 mL/min per 1.73 m ²										
Chlorthalidone	104.5 (14.5) (n = 1667)		94.3 (19.0) (n = 1071)		92.1 (20.3) (n = 1065)		84.4 (20.2) (n = 896)		79.8 (20.5) (n = 252)	
Amlodipine	104.9 (14.3) (n = 1026)	.52	100.2 (17.7) (n = 673)	<.001	99.5 (18.7) (n = 645)	<.001	92.4 (19.9) (n = 548)	<.001	87.1 (21.7) (n = 156)	<.001
Lisinopril	104.6 (14.8) (n = 981)	.89	95.5 (18.1) (n = 608)	.22	93.1 (18.4) (n = 591)	.31	87.2 (20.0) (n = 482)	.01	81.9 (24.5) (n = 140)	.39
60-89 mL/min per 1.73 m ²										
Chlorthalidone	75.8 (8.2) (n = 2755)		72.9 (14.0) (n = 1795)		72.0 (14.8) (n = 1780)		67.7 (15.6) (n = 1456)		63.6 (17.0) (n = 466)	
Amlodipine	75.7 (8.0) (n = 1626)	.72	77.3 (13.8) (n = 1060)	<.001	75.6 (14.8) (n = 998)	<.001	71.7 (16.7) (n = 827)	<.001	67.5 (18.5) (n = 292)	.003
Lisinopril	75.4 (8.2) (n = 1563)	.09	72.9 (13.3) (n = 969)	.90	72.2 (14.8) (n = 972)	.73	66.9 (16.1) (n = 789)	.25	63.8 (16.1) (n = 227)	.84
<60 mL/min per 1.73 m ²										
Chlorthalidone	49.6 (9.3) (n = 881)		48.9 (13.3) (n = 515)		48.6 (13.2) (n = 475)		44.8 (14.4) (n = 376)		42.0 (16.3) (n = 113)	
Amlodipine	49.7 (9.1) (n = 506)	.88	52.6 (13.7) (n = 306)	<.001	51.7 (15.7) (n = 275)	.004	48.3 (15.7) (n = 202)	.007	46.5 (16.4) (n = 61)	.09
Lisinopril	49.2 (9.0) (n = 501)	.41	49.7 (13.3) (n = 294)	.42	49.1 (16.0) (n = 271)	.66	45.1 (15.3) (n = 205)	.81	42.4 (17.3) (n = 68)	.89

Abbreviation: GFR, glomerular filtration rate.

duced effect on plasma flow.^{23,24} Under these conditions, higher GFR is achieved via higher intraglomerular pressure with increased proteinuria and glomerulosclerosis. These complex responses in the renal microvasculature are also modified by the effects of amlodipine on general peripheral resistance and cardiac output. In a large, well-designed clinical trial that directly compared amlodipine and ramipril to metoprolol in nondiabetic hypertensive patients, the AASK, amlodipine increased the GFR initially, but the slope of decline of the GFR was steeper during the study compared with ramipril.²⁵ This initial increase in GFR in the amlodipine group may have contributed to keeping the absolute difference in GFR between the amlodipine and ramipril groups nonsignifi-

cant. However, more patients in the amlodipine group reached ESRD than in either the ramipril or metoprolol groups.⁶ In the Irbesartan Diabetic Nephropathy Treatment Study,⁸ the effect of amlodipine on renal outcomes in patients with diabetic nephropathy was similar to that of placebo. In summary, the apparent increase in MDRD-estimated GFR with amlodipine should be interpreted with caution and in our study did not translate into improved clinical renal disease outcomes during follow-up. In addition, interactions based on levels of proteinuria could not be assessed. This may be particularly relevant to this comparison, since amlodipine was less effective than an ACE inhibitor in reducing proteinuria in AASK.²⁵

Table 5. Blood Pressure by Treatment Group and Baseline GFR*

Variable	Baseline GFR, mL/min per 1.73 m ²	Chlorthalidone	Amlodipine	Lisinopril
Baseline				
Systolic blood pressure	≥90	145.8 (15.2) (n = 3648)	145.7 (15.7) (n = 2274)	146.3 (15.1) (n = 2204)
	60-89	146.2 (15.7) (n = 8360)	146.4 (15.5) (n = 4850)	146.4 (15.5) (n = 4899)
	<60	146.9 (16.2) (n = 2613)	146.3 (16.3) (n = 1516)	146.8 (16.4) (n = 1533)
Diastolic blood pressure	≥90	84.9 (9.7) (n = 3648)	84.7 (9.9) (n = 2274)	85.2 (9.4) (n = 2204)
	60-89	84.1 (10.0) (n = 8360)	84.0 (10.1) (n = 4850)	84.1 (10.0) (n = 4899)
	<60	82.5 (10.5) (n = 2613)	82.4 (10.4) (n = 1516)	82.8 (10.6) (n = 1533)
2 y				
Systolic blood pressure	≥90	135.3 (15.8) (n = 2763)	136.5 (14.2) (n = 1742)	138.6 (17.2) (n = 1625)
	60-89	135.4 (15.2) (n = 6601)	136.8 (14.8) (n = 3774)†	137.7 (17.5) (n = 3727)†
	<60	137.9 (17.7) (n = 1968)	138.6 (16.2) (n = 1114)	140.4 (19.2) (n = 1087)†
Diastolic blood pressure	≥90	79.0 (9.5) (n = 2763)	78.4 (9.1) (n = 1742)†	79.7 (10.0) (n = 1625)†
	60-89	78.2 (9.4) (n = 6601)	77.6 (9.6) (n = 3774)†	78.3 (10.2) (n = 3727)
	<60	77.4 (9.9) (n = 1968)	76.8 (10.4) (n = 1114)	78.0 (11.0) (n = 1087)
4 y				
Systolic blood pressure	≥90	133.4 (15.2) (n = 2276)	134.6 (14.4) (n = 1462)†	135.6 (17.3) (n = 1301)†
	60-89	133.6 (15.5) (n = 5310)	134.5 (14.6) (n = 3127)†	135.2 (16.9) (n = 3024)†
	<60	135.5 (17.1) (n = 1511)	135.9 (17.0) (n = 869)	136.4 (18.2) (n = 813)
Diastolic blood pressure	≥90	76.8 (9.5) (n = 2276)	76.4 (9.0) (n = 1462)	77.6 (10.1) (n = 1301)†
	60-89	76.5 (9.6) (n = 5308)	75.8 (9.6) (n = 3127)†	76.3 (10.2) (n = 3024)
	<60	75.6 (9.9) (n = 1511)	74.2 (9.8) (n = 869)	75.7 (11.2) (n = 813)
6 y				
Systolic blood pressure	≥90	133.6 (15.2) (n = 610)	135.3 (16.4) (n = 368)	135.2 (18.3) (n = 336)
	60-89	133.0 (15.5) (n = 1572)	134.1 (15.2) (n = 976)	133.8 (17.7) (n = 889)
	<60	136.4 (18.4) (n = 454)	133.9 (16.2) (n = 255)	134.2 (17.2) (n = 269)
Diastolic blood pressure	≥90	74.2 (10.0) (n = 610)	74.8 (9.8) (n = 368)	75.5 (10.8) (n = 336)
	60-89	74.5 (9.8) (n = 1571)	73.7 (9.4) (n = 976)	73.9 (10.4) (n = 889)
	<60	73.5 (10.9) (n = 454)	72.8 (10.7) (n = 255)	72.9 (10.9) (n = 269)

Abbreviation: GFR, glomerular filtration rate.

*Data are presented as mean (SD) unless otherwise indicated.

†P<.05 compared with chlorthalidone.

Although a large number of studies have demonstrated that ACE inhibitors and/or angiotensin receptor blockers, generally in combination with thiazide diuretics, are effective in slowing progression of both diabetic and nondiabetic kidney diseases, few studies have compared ACE inhibitors to diuretics directly with respect to renal outcomes. In both the diabetic and nondiabetic participants in ALLHAT, the 6-year rate of ESRD for those assigned to receive chlorthalidone was no different from that experienced by those assigned to receive lisinopril, although the ESRD rate in diabetic patients was about twice that seen in nondiabetic patients by the end of the 6-year follow-up. Similarly, there was no difference in the composite end point of ESRD and/or a 50% or greater decline in GFR between those assigned to receive lisinopril or chlorthalidone. When changes in estimated GFR by treatment group stratified by baseline estimated GFR were evaluated, participants assigned to receive lisinopril had a similar GFR compared with those assigned to receive chlorthalidone in the GFR less than 60 mL/min per 1.73 m² and 60 to 89 mL/min per 1.73 m² strata; in the GFR of 90 mL/min per 1.73 m² or greater stratum, participants in the lisinopril group had a higher GFR at years 2 and 4. In summary, lisinopril did not emerge as being superior to chlorthalidone with respect to renoprotection in the ALLHAT study.

Several factors need to be considered in interpreting the renal outcomes comparison between lisinopril and

chlorthalidone. Patients who could not be withdrawn from their antihypertensive therapy (if they were taking any of the blinded class medications before enrollment) could not be entered into the study. As a result, patients with glomerular diseases and overt established diabetic nephropathy who were already taking ACE inhibitors may have been excluded. It is also possible that a significant proportion of the renal insufficiency encountered in ALLHAT reflects atherosclerotic or ischemic kidney disease, predominantly a tubulointerstitial disease, a category of kidney disease in which the renoprotective effects of ACE inhibitors are probably less prominent. In addition, unlike studies of renal outcomes that involve patients at high risk of renal disease progression, ALLHAT participants were selected for their high cardiovascular disease risk. This is evidenced by the high number of combined cardiovascular disease events (n=8887) and high number of non-kidney disease deaths (n=4533) compared with the 448 ESRD events and 1049 composite renal disease outcome events.¹¹ Thus, participants at high risk of adverse disease renal outcomes may have had a cardiovascular disease event before experiencing a renal event or could have died from a competing cause. An assessment of a combined end point that included death moved all the comparisons toward the null hypothesis of no difference among treatment groups. The beneficial effects of ACE inhibitors (and later the angiotensin

receptor blockade agents) have been attributed to their effects on the renin-angiotensin system and to the unique antiproteinuric effects of these agents.²⁶ Data regarding the presence of proteinuria were not obtained in ALLHAT participants. If the proportion of patients with minimal or modest proteinuria was high in ALLHAT, as is typical of patients who have atherosclerotic or ischemic nephropathy, the beneficial effects of treatment with an ACE inhibitor would be less likely. Finally, systolic blood pressure was approximately 2 mm Hg higher in the lisinopril group compared with the chlorthalidone group. Although epidemiologic studies have demonstrated a strong association between blood pressure and ESRD outcomes,¹⁸ small differences in blood pressure in treated hypertensive patients are less likely to affect ESRD outcomes. For example, in AASK, a blood pressure difference of 12/8 mm Hg (128/78 mm Hg in the lower blood pressure group and 141/85 mm Hg in the usual blood pressure group) between the 2 blood pressure arms was not associated with a difference in 5-year ESRD risk.⁶ Similar results were seen in the MDRD study, particularly in the nonproteinuric patients.²⁷ Therefore, although possible, it is unlikely that the small differences in systolic blood pressure noted between the lisinopril and chlorthalidone groups account for the lack of difference in renal outcomes noted in our study.

Our findings have particular relevance for the treatment of diabetic patients with chronic kidney disease. In patients with established diabetic nephropathy, inhibitors of the renin-angiotensin system have been shown to be superior to conventional therapy in patients with type 1⁷ and type 2 diabetes mellitus^{8,28}; current guidelines recommend the use of ACE inhibitors and angiotensin receptor blockers as first-line agents for the treatment of diabetic nephropathy.^{22,29} Although less information exists regarding the use of calcium channel blockers or diuretics, some clinical outcome data are available. Although not designed to compare renal outcomes, the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial³⁰ and Appropriate Blood Pressure Control in Diabetes³¹ studies showed equivalent renal outcomes for calcium channel blockers vs ACE inhibitors, as have 2 smaller studies^{32,33} that used reduction in albuminuria as an end point. Two studies^{34,35} showed equivalent albuminuria and renal protection for diuretics and β -blockers vs ACE inhibitors. In the UK Prospective Diabetes Study,³⁶ no differences occurred in renal outcomes for those treated with a β -blocker or an ACE inhibitor. ALLHAT is the first study, to our knowledge, to compare a calcium channel blocker or an ACE inhibitor with diuretic-based therapy with regard to progression of renal disease in hypertensive diabetic patients, and in ALLHAT, neither was superior to the diuretic as first-line therapy. Furthermore, there was no difference in outcomes at any given level of GFR. Lastly, our findings suggest that the reduction in vascular inflammation^{37,38} and glomerular transforming growth factor β 1 expression that are associated with ACE inhibitors,^{39,40} the negative metabolic effects of diuretics,¹² and the increase in vascular inflammation seen with calcium channel blockers⁴¹ may not be sufficiently strong to improve on or offset, respectively, the salutary effect of blood pressure lowering. How-

ever, ALLHAT did not specifically study patients with diabetic nephropathy and proteinuria; therefore, these findings do not refute current recommendations for treatment of these patients.

The main strength of this study is the large number of patients with mild to moderate renal insufficiency who were available for evaluation during a long period of close follow-up. The number of patients in each category of mild and moderate renal insufficiency in ALLHAT exceeded the total number of similar patients in many renal outcome studies. Similarly, the number of patients who reached ESRD in ALLHAT was greater than in any previous renal trial. The methodologic strengths of the study, including small loss to follow-up, accurate event ascertainment, and use of a validated serum creatinine measure in a single central laboratory, all enhance the credibility of these findings.

Several limitations need to be considered when interpreting these data. Renal outcomes were not the primary outcomes in ALLHAT; however, ESRD incidence and a serum creatinine-based measure were predefined as secondary outcomes. Perhaps the most significant limitation is the lack of information about proteinuria at baseline and during the study, since proteinuria may be an independent predictor of decline in renal function and the level of proteinuria may have a significant interaction with effects of drugs on renal outcomes. Often in clinical trials and in practice, ACE inhibitors and diuretics are used in combination rather than as individual agents. For the purposes of this analysis, patients with diabetes mellitus were defined as those who entered ALLHAT with a prior diagnosis of diabetes mellitus. We have shown previously that many of the nondiabetic participants in ALLHAT had glucose disorders.⁴² However, given the fact that the 3 medications had a similar effect on renal function in those with reduced GFR overall and in diabetic patients, our results should not be affected by the particular criteria used to define diabetes mellitus. The numbers of events in some strata are small, and the relatively wide CIs do not rule out clinically important treatment effects. The precise nature of renal disease that results in reduction in the GFR could not be ascertained; therefore, although the results can be generalized to hypertensive patients at high risk of vascular disease, they do not affect the treatment of specific renal syndromes.

In conclusion, in hypertensive patients with reduced GFRs, amlodipine and lisinopril are not superior to chlorthalidone in reducing the rate of development of ESRD or a composite of ESRD and 50% or greater decline in GFR. Participants assigned to receive amlodipine had a higher GFR than those assigned to receive chlorthalidone, but rates of development of ESRD were not different between the groups.

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