

# Cardiovascular Outcomes in High-Risk Hypertensive Patients Stratified by Baseline Glomerular Filtration Rate

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**Background:** Chronic kidney disease is common in older patients with hypertension.

**Objective:** To compare rates of coronary heart disease (CHD) and end-stage renal disease (ESRD) events; to determine whether glomerular filtration rate (GFR) independently predicts risk for CHD; and to report the efficacy of first-step treatment with a calcium-channel blocker (amlodipine) or an angiotensin-converting enzyme inhibitor (lisinopril), each compared with a diuretic (chlorthalidone), in modifying cardiovascular disease (CVD) outcomes in high-risk patients with hypertension stratified by GFR.

**Design:** Post hoc subgroup analysis.

**Setting:** Multicenter randomized, double-blind, controlled trial.

**Participants:** Persons with hypertension who were 55 years of age or older with 1 or more risk factors for CHD and who were stratified into 3 baseline GFR groups: normal or increased ( $\geq 90$  mL/min per  $1.73 \text{ m}^2$ ;  $n = 8126$  patients), mild reduction (60 to 89 mL/min per  $1.73 \text{ m}^2$ ;  $n = 18109$  patients), and moderate or severe reduction ( $< 60$  mL/min per  $1.73 \text{ m}^2$ ;  $n = 5662$  patients).

**Interventions:** Random assignment to chlorthalidone, amlodipine, or lisinopril.

**Measurements:** Rates of ESRD, CHD, stroke, and combined CVD (CHD, coronary revascularization, angina, stroke, heart failure, and peripheral arterial disease).

**Results:** In participants with a moderate to severe reduction in GFR, 6-year rates were higher for CHD than for ESRD (15.4% vs.

6.0%, respectively). A baseline GFR of less than 53 mL/min per  $1.73 \text{ m}^2$  (compared with  $>104$  mL/min per  $1.73 \text{ m}^2$ ) was independently associated with a 32% higher risk for CHD. Amlodipine was similar to chlorthalidone in reducing CHD (16.0% vs. 15.2%, respectively; hazard ratio, 1.06 [95% CI, 0.89 to 1.27]), stroke, and combined CVD (CHD, coronary revascularization, angina, stroke, heart failure, and peripheral arterial disease), but less effective in preventing heart failure. Lisinopril was similar to chlorthalidone in preventing CHD (15.1% vs. 15.2%, respectively; hazard ratio, 1.00 [CI, 0.84 to 1.20]), but was less effective in reducing stroke, combined CVD events, and heart failure.

**Limitations:** Proteinuria data were not available, and combination therapies were not tested.

**Conclusions:** Older high-risk patients with hypertension and reduced GFR are more likely to develop CHD than to develop ESRD. A low GFR independently predicts increased risk for CHD. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke, or combined CVD, and chlorthalidone is superior to both for preventing heart failure, independent of level of renal function.

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\*For a complete listing of the ALLHAT Collaborative Research Group, please refer to the following: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA.* 2002;288:2981-97. [PMID: 12479763]

It is estimated that more than 10 million Americans have chronic kidney disease (1, 2). The prevalence of chronic kidney disease is particularly high in older adults; it is estimated to be greater than 25% in persons older than 70 years of age. Patients with chronic kidney disease are at very high risk for cardiovascular disease (CVD) (3–8). However, the long-term outcomes of older patients who have a mild or moderate reduction in glomerular filtration rate (GFR), particularly with regard to CVD, are not well-known. Because of the large population of older adults with chronic kidney disease, it is important, from a public health and a clinical standpoint, to quantify and understand the comparative risks for CVD and renal disease in these patients. Management of hypertension is an important aspect of management in patients with chronic kidney disease; in patients with proteinuria, drugs that inhibit the renin–angiotensin axis have been shown to be superior to conventional antihypertensive drug therapy for preservation of

renal function (1, 9, 10). However, it is uncertain whether the choice of antihypertensive drug therapy affects risk for CVD in patients with chronic kidney disease (11, 12).

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a large clinical

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trial designed to compare the efficacy of treatment with different first-line antihypertensive agents on CVD outcomes in high-risk patients with hypertension who are older than 55 years of age (13–15). The objectives of this report from the ALLHAT data are to 1) compare rates of cardiovascular events with rates of development of end-stage renal disease (ESRD) in high-risk older adults with hypertension who have reduced GFR; 2) determine whether reduced GFR is independently associated with an increased risk for CVD after adjusting for traditional cardiovascular risk factors; and 3) report the efficacy of first-step treatment with a calcium-channel blocker (amlodipine) or an angiotensin-converting enzyme (ACE) inhibitor (lisinopril), each compared with a diuretic (chlorthalidone), in modifying CVD outcomes in high-risk patients with hypertension who are stratified by baseline GFR.

## METHODS

The rationale and design of ALLHAT have been presented in detail elsewhere (13). The study received institutional review board approval, and participants provided written informed consent. Participants were men and women 55 years of age or older who had hypertension with at least 1 additional risk factor for coronary heart disease (CHD). The risk factors included previous (> 6 months) myocardial infarction (MI) or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, history of type 2 diabetes, current cigarette smoking, high-density lipoprotein cholesterol level of less than 0.91 mmol/L (<35 mg/dL), and documentation of other atherosclerotic CVD. Exclusion criteria included a history of symptomatic heart failure and/or a known left ventricular ejection fraction of less than 0.35 and a serum creatinine level greater than 176.8  $\mu\text{mol/L}$  (>2 mg/dL) as reported by the investigator. Participants ( $n = 33\,357$ ) were recruited at 623 centers in the United States, Canada, Puerto Rico, and the U.S. Virgin Islands between February 1994 and January 1998 (Appendix Figure 1, available at [www.annals.org](http://www.annals.org)).

Block randomization was stratified by center. 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  $\alpha$ -blocker doxazosin was stopped early and is not considered in this report (16). The goal blood pressure in each randomly assigned group was less than 140/90 mm Hg, to be achieved by titrating the assigned study drug (step 1) and by adding study-supplied, open-label agents (atenolol, clonidine, or reserpine [step 2] or hydralazine [step 3]) when necessary, at the physician's discretion (16, 17). Nonpharmacologic lifestyle approaches to treatment of hypertension were recommended according to national guidelines. Other drugs, including low doses of open-label step 1 drug classes, were permitted if clinically indicated.

### Context

Long-term outcomes of patients with a reduced glomerular filtration rate (GFR) who are treated for hypertension are not well-known.

### Contribution

This analysis of a large multicenter trial found that coronary heart disease (CHD) was much more common than end-stage renal disease (15% vs. 6%) in hypertensive patients with moderate to severe reductions in GFR who were followed for 6 years. Lower baseline GFR was associated with higher risk for CHD independent of other risk factors. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke, or combined CVD, and chlorthalidone is superior to both for preventing heart failure, independent of level of renal function.

### Cautions

These are post hoc subgroup findings, and proteinuria was not measured.

—The Editors

Follow-up visits were at 1 month; 3, 6, 9, and 12 months; and every 4 months thereafter.

Levels of serum creatinine were measured in a single central laboratory using VITROS (Ortho Clinical Diagnostics, Rochester, New York), which had a coefficient of variation of approximately 2%. Creatinine measurements were calibrated to the Modification of Diet in Renal Disease (MDRD) laboratory, and no additional correction was found to be necessary (18). A total of 1460 participants (4.4%) were missing creatinine values, and thus estimated GFR, at baseline.

The simplified MDRD Study equation was used to estimate GFR ( $\text{mL}/\text{min}$  per  $1.73\text{ m}^2$ ) according to the following formula:  $186.3 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times 1.212$  (if black)  $\times 0.742$  (if female) (19). Patients were classified into 3 baseline categories of GFR consistent with recommendations in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines on Chronic Kidney Disease: normal or increased ( $\geq 90\text{ mL}/\text{min}$  per  $1.73\text{ m}^2$ ), mild reduction (60 to 89  $\text{mL}/\text{min}$  per  $1.73\text{ m}^2$ ), and moderate or severe reduction ( $<60\text{ mL}/\text{min}$  per  $1.73\text{ m}^2$ ) (1). Because a serum creatinine level of greater than 176.8  $\mu\text{mol/L}$  (>2 mg/dL) was an exclusion criterion, the percentage of patients with severe chronic kidney disease (estimated GFR  $\leq 29\text{ mL}/\text{min}$  per  $1.73\text{ m}^2$ ) at baseline was very small (0.6%). Therefore, as in another study (6), these participants were considered along with those with moderate chronic kidney disease (GFR 30 to 59  $\text{mL}/\text{min}$  per  $1.73\text{ m}^2$ ). Patients were also classified as diabetic or not diabetic by baseline history of diabetes.

The primary outcome was fatal CHD or nonfatal MI. Combined CVD was defined as a composite of the primary

outcome, coronary revascularization, hospitalized angina, stroke, other treated angina, heart failure (fatal, hospitalized, or treated nonhospitalized), and peripheral arterial disease. Coronary revascularization included coronary artery bypass grafting, percutaneous angioplasty, insertion of stents, and atherectomy. Peripheral vascular disease included intermittent claudication or arterial disease of the lower extremities leading to procedures, such as revascularizations, angioplasty of peripheral arteries, or amputation. End-stage renal disease included death from kidney disease, kidney transplantation, and start of long-term kidney dialysis. Study outcomes were defined in the ALLHAT Manual of Operations (available from the authors on request), were assessed by site investigators at follow-up visits, and were reported to the Clinical Trials Center. Medical reviewers from the Clinical Trials Center reviewed all events for concordance with study criteria. More detailed information was collected on a random (10%) subset of CHD

and stroke events and was reviewed by the Endpoints Subcommittee to validate the procedure of using physician diagnoses.

**Statistical Analyses**

Data were analyzed according to the participants' randomly assigned treatments regardless of their subsequent medications (intention-to-treat analysis). Baseline characteristics were compared across treatments and the 3 GFR groups by using the Z-test for continuous covariates and contingency table analyses for categorical data. Cox proportional hazards models were used to obtain hazard ratios and 95% CIs for time to CHD, combined CVD, and stroke to assess the effects of treatment within each of the 3 GFR strata. Because baseline characteristics are similar across treatment groups, no adjustment was deemed necessary. Additional models were used to assess the impact of baseline GFR (using deciles) on CHD and combined

**Table 1. Baseline Characteristics Stratified by Estimated Baseline Glomerular Filtration Rate and Treatment Group\***

Variable	Normal or Increased GFR (≥90 mL/min per 1.73 m <sup>2</sup> )			Mild Decrease in GFR (60–89 mL/min per 1.73 m <sup>2</sup> )			Moderate or Severe Decrease in GFR (<60 mL/min per 1.73 m <sup>2</sup> )		
	Chlorthalidone Group	Amlodipine Group	Lisinopril Group	Chlorthalidone Group	Amlodipine Group	Lisinopril Group	Chlorthalidone Group	Amlodipine Group	Lisinopril Group
Participants randomly assigned, n	3648	2274	2204	8360	4850	4899	2613	1516	1533
Mean age (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, n (%)									
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, n (%)	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)
Mean body mass index (SD), kg/m <sup>2</sup>	30.3 (6.5)	30.6 (6.5)	30.3 (6.5)	29.6 (6.0)	29.6 (5.9)	29.7 (6.0)	29.1 (6.0)	29.0 (5.7)	29.2 (5.8)
Mean baseline systolic blood pressure (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)
Mean baseline diastolic blood pressure (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 CHD, n (%)	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)
Mean estimated GFR (SD), mL/min per 1.73 m <sup>2</sup> †	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‡									
Current cigarette smoking, n (%)	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 CVD, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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, n (%)	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 cholesterol level, n (%)	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 on ECG, n (%)	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 on echocardiography, n (%)	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)

\* CHD = coronary heart disease; CVD = cardiovascular disease; ECG = electrocardiography; GFR = glomerular filtration rate; HDL = high-density lipoprotein; LVH = left ventricular hypertrophy; MI = myocardial infarction.

† Derived from application of the simplified Modification of Diet in Renal Disease equation based on serum creatinine level, age, race, and sex (19).

‡ 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.

**Table 2. Six-Year Event Rates and Hazard Ratios Compared across Baseline Glomerular Filtration Rate Subgroups\***

Variable	ESRD				CHD				Combined CVD			
	6-Year Rates per 100 ± SE	Events, n	HR (95% CI)†	P Value	6-Year Rates Per 100 ± SE	Events, n	HR (95% CI)†	P Value	6-Year Rates Per 100 ± SE	Events, n	HR (95% CI)†	P Value
<b>All participants</b>												
GFR ≥ 90 mL/min per 1.73 m <sup>2</sup> (n = 8126)	0.4 ± 0.1	27	–	–	8.5 ± 0.4	550	–	–	26.5 ± 0.6	1816	–	–
GFR 60–89 mL/min per 1.73 m <sup>2</sup> (n = 18 109)	1.0 ± 0.1	125	2.90 (1.80–4.67)	<0.001	10.8 ± 0.3	1588	1.09 (0.97–1.23)	0.136	30.5 ± 0.4	4767	1.08 (1.01–1.15)	0.027
GFR < 60 mL/min per 1.73 m <sup>2</sup> (n = 5662)	6.0 ± 0.4	259	20.33 (12.74–32.42)	<0.001	15.4 ± 0.6	696	1.38 (1.20–1.59)	<0.001	40.0 ± 0.8	1954	1.35 (1.24–1.46)	<0.001
<b>Participants with diabetes at baseline</b>												
GFR ≥ 90 mL/min per 1.73 m <sup>2</sup> (n = 3674)	0.5 ± 0.2	15	–	–	9.7 ± 0.6	284	–	–	29.6 ± 0.9	915	–	–
GFR 60–89 mL/min per 1.73 m <sup>2</sup> (n = 5944)	2.0 ± 0.2	78	4.18 (2.24–7.83)	<0.001	13.9 ± 0.6	655	1.15 (0.97–1.37)	0.105	34.8 ± 0.7	1795	1.13 (1.02–1.24)	0.017
GFR < 60 mL/min per 1.73 m <sup>2</sup> (n = 1888)	10.8 ± 0.9	153	25.90 (14.01–47.86)	<0.001	19.6 ± 1.1	281	1.54 (1.25–1.90)	<0.001	45.5 ± 1.4	743	1.44 (1.27–1.63)	<0.001

\* GFR derived from application of the simplified Modification of Diet in Renal Disease equation based on serum creatinine level, age, race, and sex (19). CHD = coronary heart disease; CVD = cardiovascular disease; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HR = hazard ratio.

† Compared with the group with GFR ≥ 90 mL/min per 1.73 m<sup>2</sup>; adjusted for age, ethnicity, sex, body mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, fasting triglyceride level, history of diabetes, and cigarette smoking. Combined cardiovascular disease refers to death from coronary heart disease, nonfatal myocardial infarction, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).

CVD. Baseline characteristics are not expected to be similar across the various GFR groups defined by deciles; therefore, adjustments are necessary. Cox test assumptions were examined using log–log plots and tests of treatment by time (time-dependent) interaction terms. Because the assumptions were violated in the case of heart failure, logistic models were used to estimate odds ratios for this endpoint. The consistency of treatment effects across subgroups was examined in the Cox and logistic models by calculating the differences in the log likelihood for models with and without the interaction terms. Treatment effects by GFR subgroup were also analyzed for participants with a history of diabetes by using the aforementioned methods. A *P* value less than 0.05 indicated statistical significance for the results.

### Role of the Funding Sources

This study was supported by contract NO1-HC-35130 from the National Heart, Lung, and Blood Institute (NHLBI); the NHLBI was involved in the collection, analysis, and interpretation of the data and the decision to submit the manuscript for publication but was not involved in the direct operations of the study centers. Study medications were supplied by Pfizer Inc. (New York, New York) (amlodipine), AstraZeneca (Wilmington, Delaware) (atenolol and lisinopril), and Bristol-Myers Squibb (New York, New York) (pravastatin), and financial support was provided by Pfizer Inc. These companies had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation or ap-

proval of the manuscript. All data analyses were performed at the Clinical Trials Center at the University of Texas School of Public Health, Houston, Texas. All data collected during the study were available for analysis. The authors who were not at the Clinical Trials Center did not have direct access to the data files.

### RESULTS

Baseline characteristics of the study population stratified by GFR and treatment group are shown in Table 1. Within each GFR stratum, there were no statistically significant differences in the characteristics of participants randomly assigned to amlodipine or lisinopril compared with those randomly assigned to chlorthalidone. Baseline characteristics and cardiovascular risk factors of ALLHAT participants with a reduced GFR have been reported in detail previously (14).

In each stratum of baseline GFR, 6-year event rates for CHD and combined CVD were considerably higher than those for ESRD (Table 2). In the category of a GFR less than 60 mL/min per 1.73 m<sup>2</sup>, patients were more than twice as likely to experience a CHD event and more than 6 times as likely to experience a combined CVD event than to develop ESRD. In diabetic patients with a GFR less than 60 mL/min per 1.73 m<sup>2</sup>, 6-year event rates were higher than for the overall population in the same GFR stratum: 19.6% for CHD, 45.5% for combined CVD, and 10.8% for ESRD. The risk for ESRD was approximately 3

**Table 3. Coronary Heart Disease, Combined Cardiovascular Disease, Stroke, and Heart Failure by Treatment Group by Glomerular Filtration Rate at Baseline\***

Variable	6-Year Rates per 100 ± SE			Total Events, n/n			Amlodipine/ Chlorthalidone Comparison		Lisinopril/ Chlorthalidone Comparison	
	Chlorthalidone Group	Amlodipine Group	Lisinopril Group	Chlorthalidone Group	Amlodipine Group	Lisinopril Group	Unadjusted HR or OR (95% CI)	P Value	Unadjusted HR or OR (95% CI)	P Value
<b>Nonfatal MI and fatal CHD</b>										
Total	11.5 ± 0.3	11.3 ± 0.4	11.4 ± 0.4	1362/15 255	798/9048	796/9054	0.98 (0.90–1.07)	0.648	0.99 (0.91–1.08)	0.807
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	8.7 ± 0.6	7.6 ± 0.7	9.0 ± 0.8	252/3648	141/2274	157/2204	0.90 (0.73–1.10)	0.293	1.04 (0.86–1.27)	0.669
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	10.9 ± 0.4	10.9 ± 0.6	10.6 ± 0.6	740/8360	427/4850	421/4899	0.98 (0.87–1.10)	0.718	0.97 (0.86–1.09)	0.594
GFR <60 mL/min per 1.73 m <sup>2</sup>	15.2 ± 0.9	16.0 ± 1.2	15.1 ± 1.1	318/2613	194/1516	184/1533	1.06 (0.89–1.27)	0.500	1.00 (0.84–1.20)	0.968
<b>Combined CVD</b>										
Total	30.9 ± 0.5	32.0 ± 0.6	33.3 ± 0.6	3941/15 255	2432/9048	2514/9054	1.04 (0.99–1.09)	0.121	1.10 (1.05–1.16)	<0.001
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	25.6 ± 0.9	25.3 ± 1.1	29.1 ± 1.2	803/3648	487/2274	526/2204	0.97 (0.86–1.08)	0.560	1.11 (0.99–1.24)	0.062
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	29.6 ± 0.6	31.2 ± 0.8	31.3 ± 0.8	2125/8360	1312/4850	1330/4899	1.06 (0.99–1.14)	0.081	1.09 (1.02–1.17)	0.015
GFR <60 mL/min per 1.73 m <sup>2</sup>	38.7 ± 1.2	41.1 ± 1.5	41.3 ± 1.5	870/2613	537/1516	547/1533	1.08 (0.97–1.20)	0.175	1.12 (1.01–1.25)	0.038
<b>Stroke</b>										
Total	5.6 ± 0.2	5.4 ± 0.3	6.3 ± 0.3	675/15 255	377/9048	457/9054	0.93 (0.82–1.06)	0.278	1.15 (1.02–1.30)	0.021
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	4.0 ± 0.4	3.5 ± 0.5	5.7 ± 0.6	118/3648	70/2274	101/2204	0.95 (0.70–1.27)	0.712	1.43 (1.10–1.87)	0.008
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	5.2 ± 0.3	4.7 ± 0.4	5.9 ± 0.4	366/8360	185/4850	239/4899	0.85 (0.71–1.02)	0.076	1.12 (0.95–1.31)	0.188
GFR <60 mL/min per 1.73 m <sup>2</sup>	7.6 ± 0.6	8.8 ± 1.0	7.9 ± 0.8	157/2613	100/1516	99/1533	1.12 (0.87–1.44)	0.377	1.10 (0.86–1.42)	0.452
<b>Heart failure‡</b>										
Total	7.7 ± 0.3	10.2 ± 0.4	8.7 ± 0.4	870/15 255	706/7048	612/9054	1.40 (1.26–1.55)	<0.001	1.20 (1.08–1.33)	0.001
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	5.1 ± 0.5	6.4 ± 0.6	6.1 ± 0.6	147/3648	121/2274	110/2204	1.34 (1.05–1.71)	0.020	1.25 (0.97–1.61)	0.083
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	6.7 ± 0.4	9.8 ± 0.5	6.9 ± 0.4	435/8360	380/4850	278/4899	1.55 (1.34–1.79)	<0.001	1.10 (0.94–1.28)	0.246
GFR <60 mL/min per 1.73 m <sup>2</sup>	13.1 ± 0.9	15.0 ± 1.2	15.8 ± 1.1	259/2613	174/1516	191/1533	1.18 (0.96–1.44)	0.114	1.29 (1.06–1.58)	0.011

\* Differences among treatment group effects by baseline GFR are not statistically significant. Combined CVD refers to death from CHD, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization). CHD = coronary heart disease; CVD = cardiovascular disease; GFR = glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio.

† A total of 1460 participants were missing baseline GFRs.

‡ Logistic analyses used for heart failure analyses because of nonproportional hazards. Results expressed as ORs.

times higher in patients with a GFR of 60 to 89 mL/min per 1.73 m<sup>2</sup>, and approximately 20-fold higher in those with a GFR of less than 60 mL/min per 1.73 m<sup>2</sup>, compared with the patients with a GFR of 90 mL/min per 1.73 m<sup>2</sup> or greater. Similarly, patients with a baseline GFR less than 60 mL/min per 1.73 m<sup>2</sup> had a 38% higher risk for a CHD event and a 35% higher risk for a combined CVD event when compared with patients with a GFR of 90 mL/min per 1.73 m<sup>2</sup> or greater. In a separate multivariate model, the relationship between baseline GFR (in deciles) and risk for a CHD or combined CVD event was exam-

ined by adjusting for age, ethnicity, sex, body mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, fasting triglyceride level, history of diabetes, and cigarette smoking. Patients with a GFR less than 53 mL/min per 1.73 m<sup>2</sup> (the lowest decile) had a 32% higher risk for CHD and a 50% higher risk for CVD when compared with the patients with a GFR greater than 104 mL/min per 1.73 m<sup>2</sup>. The increased risk for CHD was observed in the bottom 2 deciles of baseline GFR (<62 mL/min per 1.73 m<sup>2</sup>), and increased risk for combined

CVD was seen in the lowest 4 deciles ( $<72$  mL/min per  $1.73$  m<sup>2</sup>) (Appendix Figure 2, available at [www.annals.org](http://www.annals.org)).

Differences in blood pressure and medication adherence between the groups stratified by baseline GFR have been reported in detail previously (15). At years 2 through 6, systolic blood pressure was slightly higher in the amlodipine and lisinopril groups than in the chlorthalidone group, regardless of baseline estimated GFR, although differences in systolic blood pressure were small and statistically nonsignificant at years 4 and 6. Diastolic blood pressure was generally similar between the randomly assigned groups. Prescription of study drugs and prescription of additional antihypertensive medications were similar between the amlodipine and chlorthalidone groups in all 3 GFR strata. At 2 and 4 years, patients randomly assigned to lisinopril were less likely to be taking the study drug or an equivalent medication compared with those randomly assigned to chlorthalidone, regardless of the estimated baseline GFR. Use of step 2 or 3 medications was similar between the lisinopril and chlorthalidone groups among participants with a baseline GFR of less than 60 mL/min per  $1.73$  m<sup>2</sup> and was higher for the lisinopril versus chlorthalidone groups among participants with higher baseline GFR levels.

There were no statistically significant differences in risk for CHD, combined CVD, or stroke between the chlorthalidone and amlodipine groups in the overall population or in participants with baseline GFR less than 60 mL/min per  $1.73$  m<sup>2</sup> (Table 3; Appendix Table, available at [www.annals.org](http://www.annals.org)). Among diabetic participants with a baseline GFR of less than 60 mL/min per  $1.73$  m<sup>2</sup>, the risk for combined CVD was 20% higher in those receiving amlodipine than in those receiving chlorthalidone. However, there were no statistically significant interactions between treatment group and GFR in the total group or among diabetic participants.

In the overall study population, participants randomly assigned to lisinopril had a similar risk for CHD, a 10% higher risk for combined CVD, and a 15% higher risk for stroke when compared with those randomly assigned to chlorthalidone. Among participants with a baseline GFR less than 60 mL/min per  $1.73$  m<sup>2</sup>, similar trends were observed, except that the 10% higher risk for stroke in those taking lisinopril was not statistically significant. However, no statistically significant interactions between treatment effect and GFR groups were identified in the overall study population or in diabetic patients.

Patients assigned to amlodipine or lisinopril had higher risks for heart failure than did those assigned to chlorthalidone. There was no statistically significant interaction between treatment group and GFR in the total group or among diabetic participants (Table 3; Appendix Table, available at [www.annals.org](http://www.annals.org)). Similar results were seen when the more stringent criterion of hospitalized or fatal heart failure was used (data not shown).

## DISCUSSION

These data indicate that in older ( $\geq 55$  years of age) high-risk patients with hypertension who have a moderate or severe reduction in GFR, the 6-year risk for a cardiovascular event is considerably higher than that for ESRD. Despite the frequent coexistence of risk factors for atherosclerotic disease, presence of a low GFR is independently predictive of CVD. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing fatal CHD and nonfatal MI in patients with hypertension who have reduced GFR. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke, or combined CVD, and chlorthalidone is superior to both for preventing heart failure, independent of level of renal function. Relatively few longitudinal studies define long-term outcomes in older patients with a mild or moderate reduction in GFR (1, 5–8). Our study makes an important contribution to this body of knowledge. In older patients with hypertension who have a moderate or severe reduction in GFR, the 6-year rate of developing ESRD is 6% overall and 10% in diabetic patients. Of importance, the rate of CHD (15.4%) or combined CVD (40%) was considerably higher in the same strata of GFR. The risk for ESRD was, as would be expected, much higher in patients with a moderate or severe reduction in GFR than in those with a preserved GFR. However, even in this stratum, patients were much more likely to experience a cardiovascular event than to develop ESRD. A substantial proportion of patients (approximately 25%) had CHD at baseline; therefore, these data may not reflect the true incidence rates of CHD (17). However, because subclinical CVD is also common in this population (3), true incidence rates may be more difficult to establish. Our data provide a practical and realistic estimate of the burden of disease that can be expected in this population and are consistent with previous literature. In a Medicare population, Foley and colleagues (20) reported that the 2-year rates were higher for patients with atherosclerotic vascular disease than for those with renal replacement therapy (35.7 per 100 patient-years vs. 1.6 per 100 patient-years). However, the relative outcomes may be influenced by age; in the younger population enrolled in the MDRD Study (mean age, 51 years), ESRD was more common than death as an outcome (21). Our data in this large representative sample of patients with hypertension reinforce the concept that even a moderate reduction in GFR is associated with a high risk for CVD. In addition, they support recent recommendations that cardiovascular risk stratification should include chronic kidney disease as a risk factor for future CVD.

The reasons why patients with chronic kidney disease are at high risk for CVD are complex; it is thought that at least part of the increase in risk may relate to the clustering of traditional atherosclerotic risk factors, such as diabetes, hypertension, and hyperlipidemia, all of which are commonly seen in this population (22). In a previous cross-

sectional analysis, we showed that GFR was independently associated with left ventricular hypertrophy and prevalent CVD (14). Our current data expand on this concept, documenting in a more robust prospective manner that a low GFR at baseline is independently predictive of occurrence of CVD. Several factors associated with decline in renal function ("nontraditional" risk factors), including anemia, abnormalities of calcium and phosphorus metabolism, and altered hemostatic factors, may also contribute to increased CVD in this population (23, 24). It is possible that chronic kidney disease may be a marker for severity of traditional risk factors (for example, longer duration of diabetes or hypertension); however, we cannot confirm this in our study. Ongoing prospective studies may provide a better mechanistic understanding and novel therapeutic targets to reduce risk for CVD in this population (25, 26).

Hypertension is very common in patients with chronic kidney disease (1). Current guidelines recommend that achieving adequate blood pressure control and inhibition of the renin-angiotensin axis, particularly in patients with proteinuria, is important in slowing the decrease in GFR (27, 28). Relatively few data, however, relate the choice of antihypertensive drug therapy to the risk for CVD in patients with chronic kidney disease.

We previously reported that neither amlodipine nor lisinopril is superior to chlorthalidone in preventing ESRD in this population as a whole (17) and when this population is stratified by baseline renal function (15). This paper focused on comparing cardiovascular outcomes between participants taking these drugs who were stratified by baseline renal function. Our data suggest that amlodipine is not superior to chlorthalidone in preventing CHD or combined CVD events regardless of the level of baseline renal function. The amlodipine and chlorthalidone groups were comparable within each GFR strata regarding relevant clinical characteristics at baseline. Our data are consistent with the results of the Irbesartan Type 2 Diabetic Nephropathy Trial (IDNT) (11), in which the secondary composite end point (time to first event: cardiac death; nonfatal MI; or hospitalization for heart failure, stroke, and revascularization) was not statistically significantly different among the amlodipine, irbesartan, or placebo groups, although IDNT was not adequately powered to address this outcome. We also found that risk for heart failure is higher with amlodipine than with chlorthalidone and that this risk is consistent across all strata of baseline GFR.

We previously reported that lisinopril is not superior to chlorthalidone in preventing CHD or nonfatal MI and is less effective than chlorthalidone in preventing combined CVD events in high-risk patients with hypertension (17). We now extend those observations to demonstrate that this effect is consistent regardless of baseline renal function. Lisinopril was less effective than chlorthalidone in preventing stroke in the overall population; this effect was most marked in patients with preserved GFR. Similarly, lisinopril was less effective than chlorthalidone in preventing

heart failure. It is possible that differences in systolic blood pressure overall may contribute to this difference in outcome. However, there was no statistically significant difference in systolic blood pressure between the 2 groups in those with a GFR of less than 60 mL/min per 1.73 m<sup>2</sup>. Patients in all 3 GFR strata were less likely to continue lisinopril therapy than to continue chlorthalidone therapy during the course of the study. It is not known whether this was caused by increased side effects or laboratory abnormalities associated with the use of ACE inhibitors. Similarly, use of add-on antihypertensive medication was more common in the lisinopril group, particularly in patients with a high GFR.

These data are consistent with data from other studies that have reported cardiovascular outcomes with ACE inhibitors in patients with decreased renal function. However, none of these studies directly compared ACE inhibitors with diuretics. In fact, most trials used diuretics as additional antihypertensive therapy in all randomly assigned groups. In IDNT and in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, there was no difference between the angiotensin-receptor blocker and conventional therapy in the primary composite cardiovascular outcomes; however, in both studies, time to first heart failure with hospitalization was longer in the angiotensin-receptor blocker group (11, 12).

The major strength of our study is the large number of patients (>5500) with a moderate to severe reduction in GFR, which allowed robust subgroup analyses. The methodologic strengths of ALLHAT, including double-blinding of randomly assigned treatments and careful ascertainment of cardiovascular and renal outcomes, enhance the credibility of the data. However, several limitations in our study also need to be considered. Perhaps the biggest limitation is the lack of data regarding proteinuria, which not only is a potent predictor of renal and CVD outcomes in this population (4, 29) but may also have an interaction effect with antihypertensive therapy (30). Lack of information about proteinuria also makes these data less readily comparable with traditional trials of renal disease. Participants in ALLHAT were selected because of their high risk for CVD; therefore, the estimates of event rates for renal disease and CVD should be extrapolated with caution to patients with hypertension who are at lower risk for atherosclerotic disease. Although there were small differences in blood pressure between some groups, it is unlikely that these differences contributed meaningfully to the overall results of these analyses. Multiple subgroup comparisons were done, and some of them may have reached statistical significance simply by chance. There is no consensus, however, on the appropriate statistical procedure for handling multiplicity attributable to secondary outcomes (or multiple analyses such as subgroups and regression) in the absence or presence of statistically significant findings with the primary end point (31, 32). However, the absence of statistically

significant interactions suggests that the results in the subgroups were similar to those of the overall population. Most participants received multiple drugs; therefore, these results may not reflect the effects of monotherapy with the agents studied. Because participants were randomly assigned to ACE inhibitors, diuretics, or calcium antagonists, combinations of these agents (such as ACE inhibitors plus a diuretic) were not tested. Finally, these are post hoc analyses, and therefore the results have to be interpreted with caution.

Our findings have significant clinical implications for care of patients with hypertension and a reduced GFR. We confirmed that patients with a reduced GFR are at high risk for a cardiovascular event. In addition, we showed that patients with moderate to severe reduction in GFR are much more likely to have a cardiovascular event than to develop ESRD. Therefore, in addition to interventions to slow decline in renal function, this patient population may benefit from modification of risk factors for atherosclerotic vascular disease. We also demonstrated that amlodipine and lisinopril are not superior to diuretic-based therapy in preventing cardiovascular events, even in patients with a moderate to severe reduction in GFR, and that diuretics are superior for preventing heart failure. Current guidelines, such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and guidelines from the American Diabetes Association, recommend an ACE inhibitor or angiotensin-receptor blocker as initial antihypertensive drug therapy in patients with chronic kidney disease primarily on the basis of renal outcome data. The hypertension guidelines from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommend ACE inhibitors or angiotensin-receptor blockers as the preferred agents in diabetic patients with kidney disease and in nondiabetic patients with kidney disease who have a urine spot total protein-to-creatinine ratio greater than 200 mg/g; in chronic kidney disease in nondiabetic patients, no specific agent is preferred. In all chronic kidney disease subtypes, the National Kidney Foundation guidelines (33) recommend diuretics as add-on agents to reduce risk for increased blood pressure and CVD. Our findings from these analyses of ALLHAT subgroups support this approach. Although the ALLHAT data do not directly address combined therapy with a diuretic and an ACE inhibitor or angiotensin-receptor blocker, recent guidelines recognize that a diuretic should be used in most patients for both blood pressure control and optimal prevention of CVD (33). Future clinical trials may need to evaluate the optimal combination regimens to reduce CVD and renal disease in this high-risk population.

In conclusion, we demonstrate that in older high-risk patients with hypertension and a moderate to severe reduction in GFR, risk is considerably higher for a cardiovascular event than for ESRD. Despite the frequent coexistence of risk factors for atherosclerotic disease, presence of a low

GFR is independently predictive of CVD. Neither amlodipine nor lisinopril is superior to chlorthalidone in preventing CHD, stroke, or combined CVD, and chlorthalidone is superior to both for preventing heart failure, independent of level of renal function. Because of their post hoc nature, our findings are to be interpreted with caution and additional prospective studies are needed to verify these conclusions.

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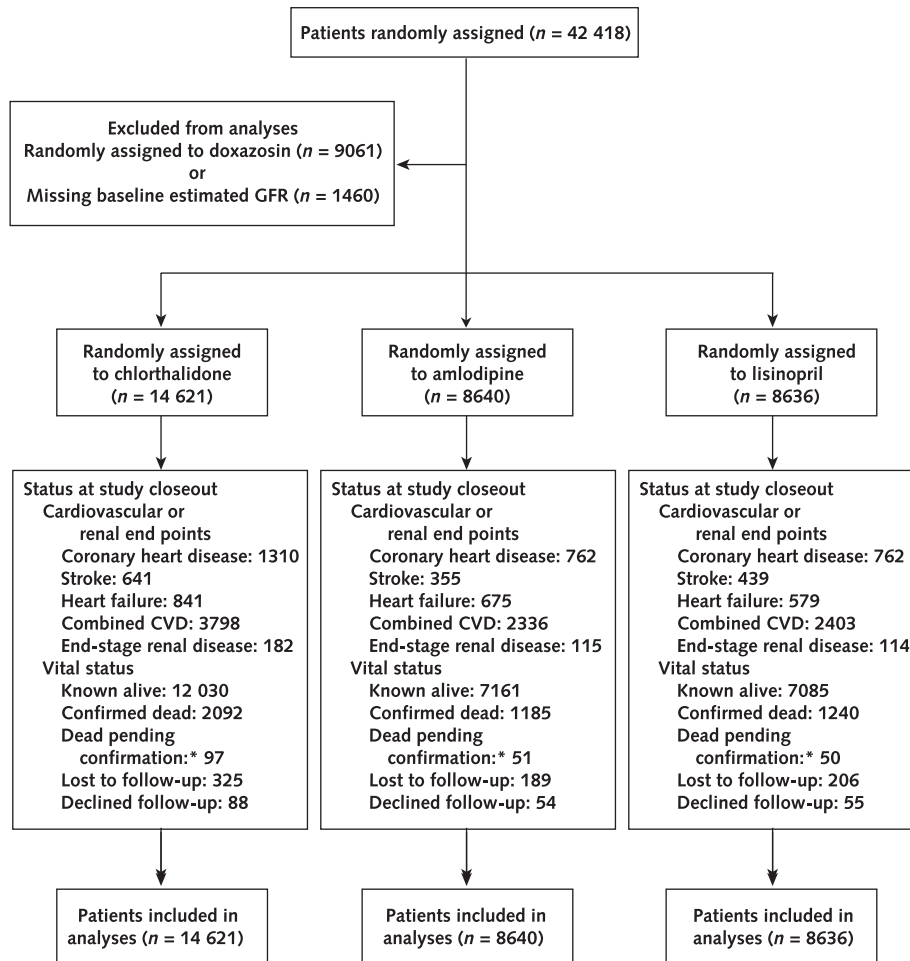
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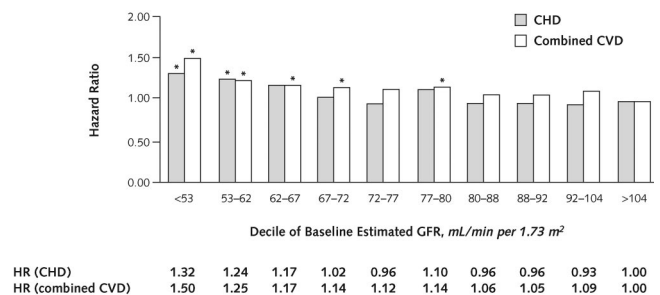
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**Appendix Figure 1. Randomization and follow-up of participants in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) by treatment group.**



CVD = cardiovascular disease; GFR = glomerular filtration rate. \*As of 30 September 2002 database (17).

**Appendix Figure 2. Coronary heart disease (CHD) and combined cardiovascular disease (CVD) by baseline glomerular filtration rate (GFR) in deciles.**



HR = hazard ratio. \*  $P < 0.05$  compared with highest decile, adjusted for age, race, sex, body mass index, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol level, low-density lipoprotein cholesterol level, fasting triglyceride level, history of diabetes, and cigarette smoking.

**Appendix Table. Coronary Heart Disease, Combined Cardiovascular Disease, Stroke, and Heart Failure by Treatment Group by Glomerular Filtration Rate at Baseline among Diabetic Participants\***

Variable	6-Year Rates per 100 ± SE			Total Events, n/n			Amlodipine/Chlorthalidone Comparison		Lisinopril/Chlorthalidone Comparison	
	Chlorthalidone Group	Amlodipine Group	Lisinopril Group	Chlorthalidone Group	Amlodipine Group	Lisinopril Group	Unadjusted HR or OR (95% CI)	P Value	Unadjusted HR or OR (95% CI)	P Value
<b>Nonfatal MI and fatal CHD</b>										
Total	13.5 ± 0.6	13.8 ± 0.8	12.8 ± 0.7	592/5528	358/3323	339/3212	0.99 (0.87–1.13)	0.927	1.00 (0.87–1.14)	0.967
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	10.0 ± 0.9	9.2 ± 1.2	9.7 ± 1.1	133/1667	72/1026	79/981	0.88 (0.66–1.18)	0.400	1.02 (0.77–1.35)	0.874
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	13.9 ± 0.8	14.4 ± 1.1	13.2 ± 1.1	304/2755	184/1626	167/1563	1.01 (0.84–1.21)	0.957	0.98 (0.81–1.18)	0.808
GFR <60 mL/min per 1.73 m <sup>2</sup>	19.3 ± 1.7	21.1 ± 2.4	18.3 ± 2.0	132/881	83/506	76/501	1.07 (0.81–1.41)	0.629	1.03 (0.78–1.37)	0.831
<b>Combined CVD</b>										
Total	33.9 ± 0.8	36.2 ± 1.0	35.5 ± 1.0	1609/5528	1030/3323	985/3212	1.06 (0.98–1.15)	0.121	1.08 (1.00–1.17)	0.049
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	27.9 ± 1.3	30.4 ± 1.8	31.4 ± 1.8	402/1667	256/1026	257/981	1.04 (0.89–1.22)	0.605	1.12 (0.95–1.31)	0.169
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	34.3 ± 1.1	35.2 ± 1.4	35.0 ± 1.4	814/2755	499/1626	482/1563	1.03 (0.92–1.15)	0.618	1.07 (0.96–1.20)	0.235
GFR <60 mL/min per 1.73 m <sup>2</sup>	43.1 ± 2.0	50.4 ± 2.7	44.2 ± 2.5	326/881	224/506	193/501	1.20 (1.01–1.42)	0.035	1.08 (0.90–1.29)	0.400
<b>Stroke</b>										
Total	7.1 ± 0.4	6.6 ± 0.5	7.6 ± 0.6	314/5528	172/3323	193/3212	0.90 (0.75–1.08)	0.260	1.07 (0.90–1.28)	0.447
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	4.4 ± 0.6	3.9 ± 0.8	7.0 ± 1.1	55/1667	33/1026	53/981	0.98 (0.63–1.50)	0.916	1.66 (1.14–2.43)	0.008
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	7.7 ± 0.6	6.4 ± 0.7	7.8 ± 0.8	176/2755	83/1626	99/1563	0.77 (0.59–1.00)	0.052	1.00 (0.78–1.28)	0.995
GFR <60 mL/min per 1.73 m <sup>2</sup>	8.7 ± 1.1	10.9 ± 1.7	8.3 ± 1.5	63/881	42/506	33/501	1.17 (0.79–1.72)	0.438	0.94 (0.62–1.43)	0.775
<b>Heart failure‡</b>										
Total	9.7 ± 0.5	13.1 ± 0.7	10.9 ± 0.7	410/5528	347/3323	284/3212	1.46 (1.25–1.69)	<0.001	1.21 (1.03–1.42)	0.018
Stratified by baseline GFR†										
GFR ≥90 mL/min per 1.73 m <sup>2</sup>	6.5 ± 0.8	8.0 ± 1.1	8.1 ± 1.0	87/1667	65/1026	68/981	1.23 (0.88–1.71)	0.224	1.35 (0.97–1.88)	0.071
GFR 60–89 mL/min per 1.73 m <sup>2</sup>	9.9 ± 0.7	13.4 ± 1.0	9.1 ± 0.9	203/2755	177/1626	119/1563	1.54 (1.24–1.90)	<0.001	1.04 (0.82–1.31)	0.768
GFR <60 mL/min per 1.73 m <sup>2</sup>	15.6 ± 1.6	22.0 ± 2.4	20.5 ± 2.2	104/881	87/506	81/501	1.55 (1.14–2.11)	0.005	1.44 (1.05–1.97)	0.023

\* Differences among treatment group effects by baseline GFR are not statistically significant. Combined CVD refers to death from CHD, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization). CHD = coronary heart disease; CVD = cardiovascular disease; GFR = glomerular filtration rate; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio.

† A total of 557 diabetic participants were missing baseline GFRs.

‡ Logistic analyses used for heart failure analyses because of nonproportional hazards. Results expressed as ORs.