

Rate of ESRD Exceeds Mortality among African Americans with Hypertensive Nephrosclerosis

Tahira P. Alves,* Xuelei Wang,[†] Jackson T. Wright, Jr.,[‡] Lawrence J. Appel,[§] Tom Greene,^{||} Keith Norris,[¶] and Julia Lewis,** for the AASK Collaborative Research Group

*Department of Medicine, Division of Nephrology, University of Texas Health Science Center at San Antonio, San Antonio, Texas; [†]Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland, Ohio; [‡]Department of Medicine, William T. Dahms Clinical Research Unit, Clinical and Translational Science Collaborative, and Clinical Hypertension Program, University Hospitals Case Medical Center, Cleveland, Ohio; [§]Department of Medicine, Epidemiology and International Health (Human Nutrition), Johns Hopkins Medical Institutions, Baltimore, Maryland; ^{||}Department of Biostatistics, Division of Epidemiology, University of Utah, Salt Lake City, Utah; [¶]Department of Research, Charles Drew University of Medicine and Science, Clinical Research Center, Lynwood, California; and ^{**}Department of Medicine, Division of Nephrology, Vanderbilt University, Nashville, Tennessee

ABSTRACT

In several studies, patients with CKD seemed to be at greater risk for dying from cardiovascular disease (CVD) than reaching ESRD. The purpose of this study was to compare incident ESRD rates with rates of total mortality, CVD death, and a CVD composite (CVD mortality and CVD hospitalization) among participants who had hypertensive nephrosclerosis and were enrolled in the African American Study of Kidney Disease and Hypertension (AASK). The study period included the AASK trial phase (1996 through 2001) and a subsequent cohort phase (2002 through 2007). The AASK enrolled 1094 participants. Of the 764 participants who completed the trial phase without an event, 691 (90%) enrolled in the cohort phase. During 11 years of follow-up, there were 59 CVD-related deaths and 118 non-CVD-related deaths. The rate of ESRD (3.9/100 patient-years) was significantly higher than the rates of total mortality (2.2/100 patient-years), CVD mortality (0.8/100 patient-years), and the CVD composite (3.2/100 patient-years). The incidence rate ratio of ESRD to CVD mortality was 5.0. The rate of ESRD consistently exceeded the various mortality rates across most of the subgroups defined by age, gender, income, education, previous CVD, baseline urine protein excretion, and baseline estimated GFR. In conclusion, AASK participants were more likely to reach ESRD than to die.

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Cardiovascular disease (CVD) is the leading cause of death for patients with ESRD.¹ In several studies, patients with chronic kidney disease (CKD) seemed to be at greater risk for a CVD death than for reaching ESRD.²⁻⁴ A graded inverse relationship has been observed between estimated GFR (eGFR) and risk for mortality and cardiovascular events in populations with chronic kidney disease (CKD).⁵⁻⁸

Although numerous studies have reported that African American patients have fewer CVD events and lower CVD mortality than white patients in the setting of ESRD, corresponding data in the setting of CKD are sparse and inconsistent.⁹⁻¹¹ Some studies reported increased CVD risk among African

American compared with white patients, although the excess risk was eliminated after the adjustment for socioeconomic factors.^{12,13} A pooled analysis of patients with CKD from four community-based

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Correspondence: Dr. Tahira P. Alves, Department of Medicine, Division of Nephrology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Suite 5.080R, San Antonio, TX 78229. Phone: 210-567-4700; Fax: 210-567-4712; E-mail: tahira.palmer@yahoo.com

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studies reported a greater risk for a composite of death, nonfatal myocardial infarction (MI), and stroke among African American than among white patients, a result in part of a greater severity of hypertension and/or diabetes in the former.¹² These findings underscore the need for appropriately designed studies to document both CVD and renal events in large, well-characterized populations of African American patients with CKD.

The purpose of this report is to compare incident ESRD rates with event rates for total mortality, CVD mortality, and a composite including both CVD mortality and CVD hospitalizations among African American patients with established CKD and well-controlled BP during the course of 11 years of follow-up in the African-American Study of Kidney Disease and Hypertension (AASK).

RESULTS

Patient Characteristics

Figure 1 displays participant flow across all phases of the AASK.¹⁴ There were a total of 149 first CVD and 179 ESRD events during the trial phase and 76 first CVD and 122 ESRD events during the cohort phase of the study. A total of 85 deaths (31 CVD related) occurred during the trial and 74 deaths (28 CVD related) during the cohort phase. Seven participants were lost to follow-up during the trial and another 20 were lost to follow-up during the cohort phase of the study. Another 17 participants progressed to ESRD, 18 died, 24 were lost to follow-up, and 73 declined enrollment during the transition period between the two phases of the study. Of the original 1094 patients who started the trial in 1996, a total of 475 survived and completed the cohort phase without reaching ESRD or experiencing a CVD event.

Table 1 summarizes baseline characteristics for the 1094 patients who enrolled in the AASK and for the 691 participants who enrolled in the cohort study. In general, the baseline characteristics (Table 1) were similar at the start of the

Table 1. Participant characteristics at baseline

Characteristic	Start of Trial (n = 1094)	Start of Cohort (n = 691)
Female (n [%])	425 (38.8)	273 (39.5)
Age (years; n [%])		
≤35	56 (5.1)	9 (1.3)
35 to 49	270 (24.7)	98 (14.2)
50 to 69	705 (64.4)	416 (60.2)
≥70	63 (5.8)	168 (24.3)
Smoking status (n [%])		
current	321 (29.3)	289 (42.5)
past	312 (28.5)	114 (16.8)
never	461 (42.1)	277 (40.7)
Diabetes (n [%])	58 (5.3)	91 (13.4)
No high school education (n [%])	444 (40.7)	272 (39.4)
Income (n [%])		
<\$15,000	521 (47.6)	279 (40.4)
≥\$15,000	370 (33.8)	251 (36.3)
declined to answer	203 (18.6)	161 (23.3)
BMI (kg/m ² ; mean ± SD)	30.60 ± 6.59	31.40 ± 7.10
Serum creatinine (mg/dl; mean ± SD)	2.00 ± 0.70	2.32 ± 1.52
UP/Cr (mean ± SD)	0.33 ± 0.52	0.38 ± 0.82
SBP (mmHg; mean ± SD)	150.3 ± 23.9	136.0 ± 22.0
DBP (mmHg; mean ± SD)	95.5 ± 14.2	80.7 ± 12.5
Years with hypertension (mean ± SD)	14.20 ± 10.10	19.70 ± 9.86
Total cholesterol (mg/dl; mean ± SD)	211.6 ± 45.5	201.4 ± 46.2
HDL cholesterol (mg/dl; mean ± SD)	48.3 ± 16.1	47.7 ± 15.4
Non-HDL (mg/dl; mean ± SD)	163.4 ± 45.0	153.7 ± 44.2
Triglycerides (mg/dl; mean ± SD)	140.5 ± 80.9	143.3 ± 91.3

The patient characteristics for the cohort phase include only the participants who did not develop ESRD or receive a renal transplant and who consented to participate in the AASK cohort phase after the completion of the AASK trial phase. BMI, body mass index; DBP, diastolic BP; SBP, systolic BP.

AASK trial and cohort periods; however, mean BP values were lower at the beginning of the cohort phase compared with the trial phase (136.0/80.7 *versus* 150.3/95.5, respectively). Mean age was 54.6 years, and mean GFR as measured by iodine 125-iothalamate (iGFR) was 46.4 ml per 1.73 m² at the beginning of the trial. As expected, patients who were followed during the cohort period were older and had more years of hypertension (14.2 *versus* 19.7). Serum creatinine and urine protein-creatinine ratios (UP/Cr) were slightly lower during the trial phase than during the cohort phase (2.0 ± 0.7 *versus* 2.3 ± 1.5 mg/dl, and 0.3 ± 0.5 *versus* 0.4 mg/dl ± 0.8, respectively).

Mean BP was 136/82 during the trial and 132/78 during the cohort phase. Consistent with the randomized design, 40% of trial participants received angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) during the trial phase. During the cohort phase, 84% of patients received ACEI or ARB therapy.

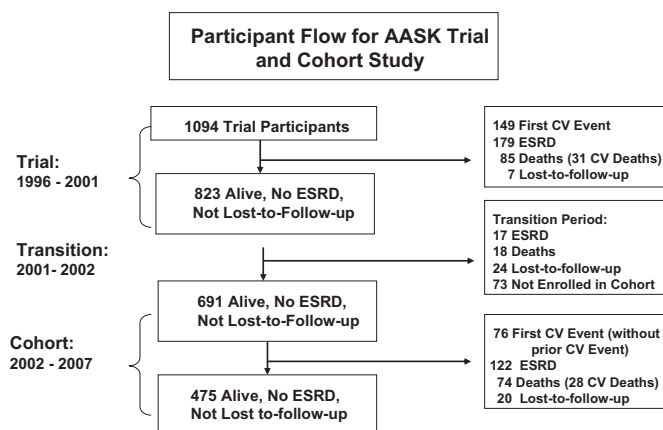


Figure 1. Study design for the AASK trial and cohort phases.

Rate of ESRD Exceeded Rates of Total and Cardiovascular Mortality

During the 11 years of follow-up, there were 177 deaths, 59 (33%) of which were CVD related and 118 (67%) of which were non-CVD related (Figure 1). By comparison, a total of 318 ESRD events occurred during the trial and cohort periods of study. The higher rate of ESRD compared with CVD mortality is reflected in a substantially higher cumulative incidence of patients' reaching ESRD compared with either CVD or non-CVD death throughout the follow-up period (Figure 2).

The crude incidence rates for total mortality, CVD mortality, the CVD composite, and ESRD are shown in Table 2, and incidence rate ratios (IRRs) are shown in Table 3. Among all participants, the rate of ESRD (3.9/100 patient-years) exceeded the crude rate of total mortality (2.2/100 patient-years; Table 2). The corresponding IRR of ESRD/total mortality was 1.8 ($P < 0.001$; Table 3). The rate of ESRD exceeded the rate of total mortality in most subgroups (Table 2). In all subgroups, the IRR either was significantly greater than 1 or did not differ from 1 (Table 3).

Among all participants, the rate of ESRD (3.9/100 patient-years) substantially exceeded the crude rate of CVD mortality (0.8/100 patient-years). Incident ESRD rates also exceeded incident CVD mortality, and the corresponding ESRD/CVD IRRs were significantly greater than 1 in all subgroups considered. Still, the ESRD/CVD mortality IRR did vary substantially across patient subgroups: The ESRD/CVD mortality IRR was higher in younger compared with older individuals (8.8 versus 2.8; $P < 0.001$), lower compared with higher eGFR (11.1 versus 2.4; $P < 0.001$), higher compared with lower UP/Cr (12.2 versus 2.4; $P < 0.001$), and those without previous CVD compared with those with previous CVD (8.8 versus 3.3; $P < 0.001$).

Cumulative Incidence Based on Competing Risk Analysis

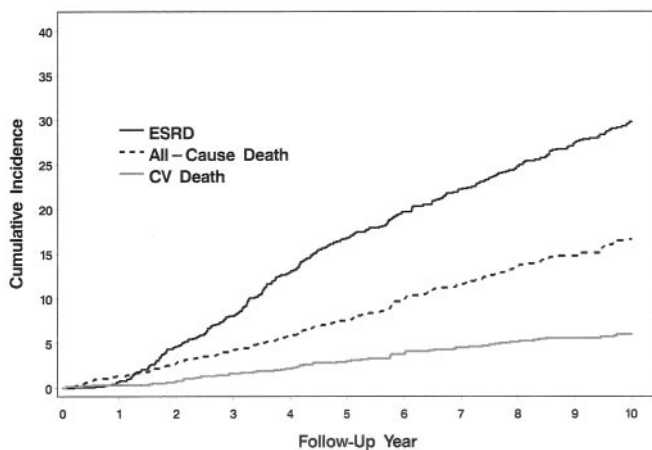


Figure 2. Cumulative incidence of ESRD is greater than the incidences for CVD death and non-CVD death for the 1094 AASK participants during 10 years of follow-up. The cumulative incidence curves were constructed under a competing risk framework.²⁶

Rate of ESRD Exceeded the Rate of the CVD Composite in Most Subgroups

Among all participants (Table 2), the rate of ESRD (3.9/100 patient-years) also exceeded the rate of the CVD composite, which included both CVD mortality and the first occurrence of a CVD hospitalization (3.2/100 patient-years). The corresponding IRR between ESRD and the CVD composite was 1.2 ($P = 0.025$; Table 3). In most subgroups, the ESRD/CVD composite IRR was significantly greater than 1 or did not differ significantly from 1; however, the rate of the CVD composite significantly exceeded the rate of ESRD (IRR significantly less than 1) in three subgroups: Participants who were older than 55 years, those with a UP/Cr ≤ 0.22 , and those with a GFR > 40 ml/min per 1.73 m^2 .

DISCUSSION

In the AASK, African American patients with hypertensive CKD were more likely to progress to ESRD than experience all-cause or CVD mortality during the course of 11 years of follow-up. The lower rate of CVD mortality compared with the rate of ESRD observed in AASK contrasts with reports from other studies. Keith *et al.*² reported a graded and inverse relationship among total mortality, ESRD, and the level of eGFR among 28,000 managed care enrollees who were followed for a 5 year; patients with stage 2 and 3 CKD were 20 times more likely to die than reach ESRD and those with stage 4 CKD were twice as likely to die than reach ESRD. Foley *et al.*¹⁵ reported mortality rates ranging from 5 (diabetic CKD) to 10 (nondiabetic CKD) times greater than renal replacement therapy in a 5% sample ($n = 1091,201$) of the US Medicare population stratified by administrative reporting of CKD. They found high and similar rates of CVD and ESRD. Neither Keith *et al.* nor Foley *et al.* explored potential racial/ethnic differences in mortality and ESRD. Newsome *et al.*¹⁶ evaluated data on $> 125,000$ African American and white Medicare beneficiaries who were aged ≥ 65 years and admitted to a hospital with acute MI and found similar overall adjusted pre-ESRD mortality rates across race and ethnicity but found that African American patients were 16% less likely to die ($P < 0.01$) at lower levels of eGFR (< 60 ml/min). The same graded and inverse relationship between total mortality and level of eGFR was also observed as in the study by Keith *et al.*² O'Hare *et al.*¹⁷ reported that older patients who belonged to a Veteran's Administration cohort and had an eGFR ≤ 45 ml/min per 1.73 m^2 at baseline were more likely to die than to experience a worsening progression of renal function. The average age of patients who were enrolled in the cohort was 73 years.

There are several possible explanations for these observations. The cohorts in the studies by Keith *et al.* and O'Hare *et al.* were unselected groups of managed care enrollees. This contrasts with the AASK participants, all of whom met the study's inclusion and exclusion criteria defining hypertensive nephrosclerosis. Foley *et al.* also examined an unselected group of Medicare recipients us-

Table 2. Crude event rates for CVD death, total mortality, CVD Composite Events, and ESRD for the AASK

Patient Subgroup	All ESRD		CVD Composite Event		All Death (Censoring Follow-up at ESRD)		CVD Death	
	Total N (No. of Events; %)	Rate/100 patient-years	Total N (No. of Events; %)	Rate/100 patient-years	Total N (No. of Events; %)	Rate/100 patient-years	Total N (No. of Events; %)	Rate/100 patient-years
All patients	1094 (318; 29)	3.9	1094 (225; 21)	3.2	1094 (177; 16)	2.2	1094 (59; 5)	0.8
Age (years)								
≤55	524 (207; 40)	5.4	524 (95; 18)	2.9	524 (52; 10)	1.4	524 (22; 4)	0.6
>55	570 (111; 19)	2.6	570 (130; 23)	3.5	570 (125; 22)	2.9	570 (37; 6)	0.9
Baseline UP/Cr								
≤0.22	733 (109; 15)	1.8	733 (155; 21)	3.0	733 (123; 17)	2.0	733 (43; 6)	0.8
>0.22	357 (208; 58)	10.5	357 (69; 19)	4.0	357 (53; 15)	2.7	357 (16; 4)	0.9
Education								
high school or higher	648 (209; 32)	4.3	648 (115; 18)	2.7	648 (88; 14)	1.8	648 (30; 5)	0.7
lower than high school	444 (109; 25)	3.3	444 (110; 25)	4.0	444 (88; 20)	2.7	444 (29; 7)	1.0
Gender								
female	425 (135; 32)	4.2	425 (82; 19)	3.0	425 (52; 12)	1.6	425 (20; 5)	0.7
male	669 (183; 27)	3.7	669 (143; 21)	3.4	669 (125; 19)	2.5	669 (39; 6)	0.8
Income								
<\$15,000	521 (152; 29)	4.0	521 (118; 23)	3.7	521 (87; 17)	2.3	521 (29; 6)	0.8
≥\$15,000	370 (107; 29)	3.8	370 (68; 18)	2.7	370 (56; 15)	2.0	370 (17; 5)	0.6
declined to answer	203 (59; 29)	4.0	203 (39; 19)	3.0	203 (34; 17)	2.3	203 (13; 6)	0.9
Mean baseline GFR								
>40	718 (106; 15)	1.7	718 (160; 22)	3.1	718 (112; 16)	1.8	718 (41; 6)	0.7
≤40	376 (212; 56)	10.2	376 (65; 17)	3.5	376 (65; 17)	3.1	376 (18; 5)	0.9
Preexisting CVD								
yes	564 (147; 26)	3.5	564 (132; 23)	3.7	564 (105; 19)	2.5	564 (41; 7)	1.1
no	530 (171; 32)	4.2	530 (93; 18)	2.7	530 (72; 14)	1.8	530 (18; 3)	0.5

Shown are unadjusted incidence rates. Follow-up for CVD events and mortality was terminated at occurrence of ESRD. The follow-up time for ESRD and mortality outcomes included the trial, cohort, and transition periods. The follow-up time for CVD events and CVD deaths included the trial and cohort periods. Similar incidence rates were obtained for each outcome in a sensitivity analysis in which the transition period between the trial and cohort periods was excluded for all events.

Table 3. IRRs for CVD death, total mortality, CVD composite events, and ESRD for the AASK

Patient Subgroup	ESRD/CVD Death		ESRD/CVD Composite		ESRD/All Death	
	IRR (95% CI)	P	IRR (95% CI)	P	IRR (95% CI)	P
All patients	5.01 (3.77 to 6.66)	<0.001	1.21 (1.02 to 1.43)	0.025	1.80 (1.48 to 2.17)	<0.001
Age (years)						
≤55	8.76 (5.66 to 13.55)	<0.001	1.89 (1.49 to 2.38)	<0.001	3.98 (2.92 to 5.42)	<0.001
>55	2.78 (1.90 to 4.07)	<0.001	0.72 (0.57 to 0.92)	0.009	0.89 (0.68 to 1.16)	0.38
Baseline UP/Cr						
≤0.22	2.35 (1.65 to 3.34)	<0.001	0.60 (0.47 to 0.76)	<0.001	0.89 (0.69 to 1.14)	0.35
>0.22	12.18 (7.13 to 20.8)	<0.001	2.62 (2.01 to 3.41)	<0.001	3.92 (2.89 to 5.32)	<0.001
Education						
high school or higher	6.48 (4.35 to 9.63)	<0.001	1.59 (1.26 to 2.00)	<0.001	2.37 (1.84 to 3.06)	<0.001
lower than high school	3.49 (2.28 to 5.34)	<0.001	0.82 (0.63 to 1.06)	0.13	1.24 (0.93 to 1.64)	0.14
Gender						
female	4.37 (3.08 to 6.19)	<0.001	1.41 (1.08 to 1.84)	0.01	2.60 (1.87 to 3.61)	<0.001
male	6.26 (3.90 to 10.05)	<0.001	1.09 (0.89 to 1.34)	0.40	1.46 (1.17 to 1.84)	0.001
Income						
<\$15,000	4.86 (3.26 to 7.26)	<0.001	1.07 (0.86 to 1.35)	0.54	1.75 (1.33 to 2.30)	<0.001
≥\$15,000	5.86 (3.44 to 10.00)	<0.001	1.38 (1.02 to 1.86)	0.04	1.91 (1.39 to 2.62)	<0.001
declined to answer	4.21 (2.20 to 8.08)	<0.001	1.32 (0.89 to 1.96)	0.16	1.74 (1.11 to 2.71)	0.02
Mean baseline GFR						
>40	2.39 (1.66 to 3.45)	<0.001	0.56 (0.44 to 0.71)	<0.001	0.95 (0.73 to 1.23)	0.68
≤40	11.05 (6.70 to 18.20)	<0.001	2.89 (2.22 to 3.76)	<0.001	3.26 (2.49 to 4.28)	<0.001
Preexisting CVD						
yes	3.33 (2.37 to 4.67)	<0.001	0.95 (0.76 to 1.17)	0.61	1.40 (1.09 to 1.80)	0.009
no	8.83 (5.33 to 14.64)	<0.001	1.58 (1.24 to 2.02)	0.0002	2.38 (1.79 to 3.16)	<0.001

Shown are unadjusted IRRs. Follow-up for CVD events and mortality was terminated at occurrence of ESRD. The interaction *P* value tested whether IRRs differed between the indicated subgroups.

ing administrative data. The patients analyzed by Newsome *et al.* were older (mean age 77.1 years) with a history of a recent MI, increasing the likelihood of death rather than survival to ESRD; however, even in their study, they did report a lower mortality rate at a reduced GFR for African American patients in comparison with their white counterparts, suggesting that, in part, the unexpectedly low rate of death to ESRD in our study may reflect a survival benefit among African American patients with reduced GFR. In the AASK, patients with a history of diabetes, a major CVD event within 6 months, or an indication such as coronary artery disease potentially requiring use of a β blocker or calcium channel blocker were excluded. Thus, it is likely that the baseline CVD risk in AASK was lower than in high-risk populations without these exclusions.^{6,8,15} Still, in participants with self-report of previous CVD, the rate of ESRD exceeded the rate of CVD mortality.

Our data, however, are consistent with the recent report by Derose *et al.*,¹⁸ who noted that during a 9-year period, despite equivalent health insurance benefits in an integrated health system, the age- and gender-adjusted hazard ratios for ESRD and death before ESRD in African American patients with stage 3 or 4 CKD compared with non-African American patients were 1.83 and 1.15, respectively. Although that study was limited by the use of an administrative database of all-cause ESRD and race/ethnicity were not directly ascertained in nearly half of the study cohort and were imputed by zip code-based estimates, it is intriguing that they also found higher ESRD rates in comparison with total mortality among the African American subgroup.

An additional factor that may have contributed to a higher rate of ESRD compared with total and CVD mortality in AASK is that the aggressive BP control in AASK may have selectively reduced CVD but not CKD progression. Previous AASK studies reported that there were no significant differences between the two BP groups (low *versus* normal) or among the three antihypertensive groups (ACEI/ARB, β blocker, calcium channel blocker) in the risk for cardiovascular death, cardiovascular composite outcome, or overall cardiovascular event. Cardiovascular events were censored after ESRD in the AASK.¹⁹ Because of the possible bias that may have occurred when censoring post-ESRD events, the study specifically analyzed the differences in the occurrences of ESRD and cardiovascular events as a composite and found no statistically significant difference in the outcome among the treatment groups. The AASK, however, was underpowered to analyze cardiovascular mortality *versus* ESRD as a possible competing risk among the various BP control groups. The National Institutes of Health-sponsored Systolic Blood Pressure Intervention Trial (SPRINT), a large ($n > 7500$) multiracial trial of different systolic BP goals in hypertension with and without CKD on renal and cardiovascular outcomes is under way and will hopefully provide further insight into this question. Other explanations for the increased rates of ESRD compared with total and CVD mortality include routine and easy access to health care providers in our study, along with special efforts to improve compliance with medications and follow-up visits.²⁰ Indeed, it is

quite possible that multiple factors contributed to our observed findings.

The results presented in Tables 2 and 3 demonstrate that as level of proteinuria increases, the risk for progressing to ESRD becomes much stronger than the risk for a participant's experiencing a CVD event or death. The increase in risk for CVD morbidity and mortality was relatively modest in comparing those with UP/Cr >0.22 *versus* those with UP/Cr <0.22 compared with the magnitude of increase seen for ESRD in these subgroups. Reasons for the lesser effect of proteinuria on CVD morbidity and mortality than on renal outcomes in the AASK cohort are unclear but may be related to a greater effect of aggressive follow-up care and control of CVD factors (including BP) once CVD risk factors were identified. To date, there are limited data to assess whether there is a significant correlation between change in level of proteinuria and the risk for CVD morbidity and mortality in African American populations with hypertensive nephrosclerosis. This, too, is a question worth considering in future studies.

Our study has several limitations. First, as previously noted, this is a report of cardiovascular outcomes in a study that was originally designed to evaluate renal outcomes. In addition, the study did not include a comparison group without CKD and enrolled only African American individuals. Without a comparison group of non-African American individuals, we cannot determine whether our findings, specifically the high rate of ESRD in comparison with CVD, reflects a more rapid CKD progression in African American than non-African American individuals. Second, individuals at high risk for CKD progression (*e.g.*, those with marked proteinuria [baseline UP/Cr >2.5]) were excluded from the study.¹⁴ Although the AASK shares these limitations with other renal and cardiovascular studies, the observation of low rates of mortality and CVD events compared with ESRD events is noteworthy and warrants further evaluation within both a clinical and a public health context.

In conclusion, we report that participants in the AASK were more likely to progress to ESRD than experience CVD mortality, all-cause mortality, or a major CVD event. This study remains novel in that it is the only study to analyze cardiovascular and renal outcomes in an exclusively African American cohort with CKD and well-controlled BP during an 11-year follow-up period. Furthermore, we demonstrated the risk for total mortality and CVD death is not uniform in all CKD populations. More research is needed to determine the specific reasons, including possible genetic or socioeconomic factors, that may explain the observed lower cardiovascular mortality in this high-risk minority population.

CONCISE METHODS

Participants

The design and inclusion and exclusion criteria for the AASK trial and cohort phases were reported in detail previously.^{20–22} In the AASK

trial phase, participants were self-identified African American individuals with hypertensive nephrosclerosis (diastolic BP ≥ 95 mmHg with a GFR 20 to 65 ml/min per 1.73 m²).¹⁴ Participants with a history of a CVD event within 6 months, New York Heart Association class 3 or 4 heart failure, diabetes, malignant or accelerated hypertension within 6 months of enrollment, UP/Cr > 2.5 , or evidence of renal disease other than hypertensive nephrosclerosis were excluded at trial baseline.²²

A total of 1094 individuals were enrolled for a median follow-up of 4.1 years.²² Of the original 1094 individuals, a total of 264 died, initiated dialysis therapy, or received a kidney transplant by the end of the AASK trial phase.²² Of the 795 individuals who were eligible to participate in the AASK cohort phase, a total of 691 were enrolled and followed up from April 2003 through June 2007. On the basis of the results of the AASK trial, an antihypertensive regimen with an ACEI or ARB was recommended for the participants in the AASK cohort study.^{23,24} In the cohort study, a BP goal of 130/80 mmHg was recommended. The rationale and design of the AASK cohort were previously reported in detail.²⁵

Outcome Variables

In this report, total mortality and the occurrence of ESRD, defined by initiation of dialysis or transplantation, were respectively designated as the main outcomes. Also of interest were CVD-related mortality and a CVD composite outcome, defined as CVD death or the first hospitalized MI, congestive heart failure, stroke, or revascularization procedure. Only deaths and CVD hospitalizations that occurred before ESRD are considered in this report. A detailed description of cardiovascular events has been previously published.^{19,25} All events were adjudicated by the same cardiovascular review committee throughout the study.¹⁹

There was an 8-month transition period between the administrative censoring date (September 30, 2001) of the trial phase and the median cohort study enrollment date (June 4, 2002). During the transition period, occurrence of ESRD and all-cause mortality was ascertained using the same protocol that was used during the trial and cohort studies. A total of 18 deaths during the interim period were classified by the cardiovascular review committee on the basis of summaries of the circumstances of the death provided by the patient's clinical center without the availability of data on hospitalizations.

Measurements

Baseline information was obtained through participant self-report and chart review.¹⁴ The GFR was assessed by iodine 125-iothalamate clearance in the AASK trial. Because iGFR measurements were not obtained during the cohort study, a separate eGFR was calculated from serum creatinine, age, and gender using an equation developed from baseline data in the AASK trial.^{26,27}

Statistical Analyses

Patient characteristics were summarized at the start of the trial phase for all 1094 randomly assigned participants and at the start of the cohort phase for the subset of 691 AASK participants who enrolled in the cohort study. Means and SD are provided for quantitative variables and frequencies and percentages for categorical variables. For the trial phase, mean

follow-up systolic and diastolic BP levels were computed for each patient by averaging BP measurements from all clinic visits that did not include GFR measurement between 4 months after randomization and the end of follow-up. For the cohort phase, mean follow-up BP levels were computed by averaging all clinic systolic and diastolic BP measurements over the duration of the cohort study. BP levels are summarized by the averages of these mean follow-up values for the trial and cohort phases and by the percentage of visits at which follow-up BP levels fell below or above designated thresholds.

Incidence rates for renal or cardiovascular events were computed as the ratio of the number of events to the total patient-years of follow-up and expressed as the number of events per 100 patient-years. Incidence rates are presented for the combined trial and cohort periods. Follow-up time for CVD death and the CVD composite was terminated at the occurrence of non-CVD deaths, occurrence of ESRD, time of loss to follow-up, or administrative end of the study period. Follow-up time for ESRD was ended at the occurrence of death, loss to follow-up, and the administrative end of the study period. IRRs were computed to compare rates of renal and CVD events. The bootstrap method (with 1000 independent bootstrap samples) was applied to estimate the SEs of the log-transformed IRRs between renal and CVD outcomes in the full cohort, and a normal approximation was then used to compute *P* values and 95% confidence intervals. Separate bootstrap procedures (each with 1000 independent bootstrap samples) were used to compute the SEs of log-transformed IRRs within subgroups defined by age, gender, education, income levels, baseline UP/Cr, baseline iGFR, and preexisting CVD. Using the bootstrap SEs, a normal approximation was used to test whether the log-transformed IRRs differed between the indicated subgroups. Although statistical analyses were performed for log-transformed IRRs, IRRs were re-expressed on their original scale when presenting the final results.

The IRRs described in the previous paragraph compare overall event rates throughout the follow-up period. To compare the cumulative proportions of patients who reached renal and CVD events over time, we estimated cumulative incidence curves for renal events, CVD mortality, and death from non-CVD causes in a competing risk framework using the approach of Gray.²⁸ In the competing risk framework, only loss to follow-up and the administrative end date of the study were treated as censoring events.

For analyses presented in this article, both the numerator (the number of events) and the denominator (the total patient-years of follow-up) used to compute event rates include the 8-month transition period between the trial and cohort phases for mortality and ESRD but exclude this period for the CVD composite end point. In sensitivity analyses, similar results (data not shown) were found when both the event counts and the follow-up times used to determine the event rates were computed after excluding the interim period, thereby maintaining a constant follow-up period for all outcomes.

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REFERENCES

1. US Renal Data System: *USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive Kidney Diseases, 2007
2. Keith D, Nichols G, Gullien C, Brown J, Smith D: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 164: 659–663, 2004
3. Sarnak M, Levey A, Schoolweth A, Coresh J, Culeton B, Hamm L, McCoullough P, Kasiske B, Kelepouris E, Klag M, Parfrey P, Pfeffer M, Raij L, Spinosa D, Wilson P: Kidney disease is a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 42: 1050–1065, 2003
4. Foley R, Parfrey P, Sarnak M: Clinical epidemiology of cardiovascular disease in chronic renal failure. *Am J Kidney Dis* 32: S112–S119, 1998
5. Go A, Chertow G, Fan D, Mcculloch C, Hsu C: Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *N Engl J Med* 351: 1296–1305, 2004
6. Brenner B, Cooper M, de Zeeuw D, Keane W, Mitch W, Remuzzi G, Snappinn S, Zhang Z, Shahinfar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
7. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic. *JAMA* 288: 2981–2997, 2002
8. Rahman M, Pressel S, Davis B, Nwachuku C, Wright J, Whelton P, Barzilay J, Bahtman V, Eckfeldt J, Farber M, Henriquez M, Kopyt N, Louis G, Saklayen M, Stanford C, Walworth C, Ward H, Weigman T: Renal outcomes in high-risk hypertensive patients treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic. *Arch Intern Med* 165: 936–946, 2005
9. Norris K, Agodoa L: Unraveling the racial disparities associated with kidney disease. *Kidney Int* 68: 914–924, 2005
10. Powe N: To have and have not: Health and health care disparities in chronic kidney disease. *Kidney Int* 64: 763–772, 2003
11. Agodoa L, Eggers P: Racial and ethnic disparities in end-stage kidney failure-survival paradoxes in African Americans. *Semin Dial* 20: 577–585, 2007
12. Weiner D, Tighiouart H, Amin M, Stark P, MacLeod B, Griffith J, Salem D, Levey A, Sarnak M: Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: A pooled analysis of community-based studies. *J Am Soc Nephrol* 15: 1307–1315, 2004
13. Mehrotra R, Kermah D, Fried L, Adler S, Norris K: Racial differences in mortality among those with chronic kidney disease. *J Am Soc Nephrol* 19: 1403–1410, 2008
14. Appel L, Bakris G, Gabbai J, Greene T, Kopple J, Lipkowitz M, Norris K, Rahman M, Rostand S, Schulman G, Wang X, Wright J, African-American Study of Kidney Disease and Hypertension Investigators: Progression of hypertensive chronic kidney disease is common among African Americans with excellent blood pressure control and high rates of use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. *Arch Intern Med* 168: 832–839, 2008
15. Foley R, Murray A, Herzog C, McBean A, Eggers P, Collins A: Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 16: 489–495, 2005
16. Newsome BB, McClellan WM, Allison JJ, Eggers PW, Chen SC, Collins AJ, Kiefe CI, Coffey CS, Warnock DG: Racial differences in the competing risks of mortality and ESRD after acute myocardial infarction. *Am J Kidney Dis* 52: 251–261, 2008
17. O'Hare A, Choi A, Bertenthal D, Bacchetti P, Garg A, Kaufman J, Walter L, Mehta K, Steinman M, Allon M, McClellan W, Landefeld C: Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 18: 2758–2765, 2007
18. Derose SF, Rutkowski MP, Levin NW, Liu IL, Shi JM, Jacobsen SJ, Crooks PW: Incidence of end-stage renal disease and death among insured African Americans with chronic kidney disease. *Kidney Int* 76: 629–637, 2009
19. Norris K, Bourgoigne J, Gassman J, Herbert L, Middleton J, Phillips R, Randall O, Rostand S, Shaper S, Toto R, Wright J, Wang X, Greene T, Appel L, Lewis J: Cardiovascular Outcomes in the African-American Study of Kidney Disease and Hypertension (AASK) Trial. *Am J Kidney Dis* 48: 739–751, 2006
20. Wright J, Bakris G, Greene T, Agodoa L, Appel L, Charleston J, Creek D, Douglas-Baltimore J, Gassman J, Glassock R, Herbert L, Jamerson K, Lewis J, Phillips R, Toto R, Middleton J, Rostand S: Design and baseline characteristics of participation in the African-American Study of Kidney Disease and Hypertension. *Controlled Clinical Trials* 16: 35–165, 1996
21. Gassman J, Greene T, Wright J, Agodoa L, Bakris G, Beck G, Douglas J, Jamerson K, Lewis J, Kutner M, Randall O, Wang S: Design and statistical aspects of African American Study of Kidney Disease and Hypertension. *J Am Soc Nephrol* 14: 5154–5165, 2003

22. Sika M, Lewis J, Douglas J, Erlinger T, Dowie D, Lipkowitz M, Lash J, Cornish-Zirker D, Peterson G, Toto R, Kusek J, Appel L, Kendrick C, Gassman J: Baseline characteristics in the African American Study of Kidney Disease and Hypertension (AASK) clinical trial and cohort study. *Am J Kidney Dis* 50: 78–89, 89.e1, 2007
 23. Wright J, Bakris G, Greene T, Agodoa L, Appel L, Chertow J, Cheek D, Douglas-Baltimore J, Gassman J, Herbert L, Jamerson K, Lewis J, Phillips R, Toto R, Middleton J, Rostand S: The effects of blood pressure lowering class of anti-hypertensive therapy on progression of hypertensive kidney disease: Results from the AASK Trial. *JAMA* 288: 2421–2431, 2002
 24. Agodoa L, Appel L, Bakris G, Beck G, Bourgoignie J, Briggs J, Charleston J, Cheek D, Cleveland W, Douglas JG, Douglas M, Dowie D, Faulkner M, Gabriel A, Gassman J, Greene T, Hall Y, Hebert L, Hiremath L, Jamerson K, Johnson CJ, Kopple J, Kusek J, Lash J, Lea J, Lewis JB, Lipkowitz M, Massry S, Middleton J, Miller ER 3rd, Norris K, O'Connor D, Ojo A, Phillips RA, Pogue V, Rahman M, Randall OS, Rostand S, Schulman G, Smith W, Thornley-Brown D, Tisher CC, Toto RD, Wright JT Jr, Xu S, African American Study of Kidney Disease and Hypertension (AASK) Study Group: Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis. *JAMA* 285: 2719–2728, 2001
 25. Appel L, Middleton L, Miller E 3rd, Lipkowitz M, Norris K, Agodoa L, Bakris G, Douglas J, Charleston J, Gassman J, Greene T, Jamerson K, Kusek J, Lewis J, Phillips R, Rostand G, Wright J: The rationale and design of the AASK cohort study. *J Am Soc Nephrol* 14[Suppl 2]: S166–S172, 2003
 26. Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, Ojo A, Philips R, Sika M, Wright J: Comparison of cross-sectional renal function measurements in African-Americans with hypertensive nephrosclerosis and of primary formulas to estimate glomerular filtration rate. *Am J Kidney Dis* 38: 744–775, 2001
 27. Wang X, Lewis J, Appel L, Creek D, Contreras G, Faulkner M, Feldman H, Gassman J, Lea J, Kopple J, Sika M, Toto R, Greene T: Validation of creatinine-based estimated of GFR when evaluating risk factors in longitudinal studies of kidney disease. *J Am Soc Nephrol* 17: 2900–2909, 2006
 28. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat* 16: 1141–1154, 1998
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