The Rationale and Design of the AASK Cohort Study

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Abstract. Hypertensive kidney disease commonly progresses. The primary objective of the AASK (*A*frican *A*merican *S*tudy of *K*idney Disease and Hypertension) Cohort Study is to determine prospectively the course of kidney function and risk factors for kidney disease progression in African Americans with hypertensive kidney disease who receive recommended anti-hypertensive therapy. The AASK Cohort Study is a prospective, observational study that is an extension of the AASK trial. The AASK trial tested the effects of three medications used as initial anti-hypertensive therapy (ramipril, metoprolol, and amlodipine) and two levels of BP control. Of the 1094 trial participants, approximately 650 to 700 individuals who have not reached ESRD will likely enroll in the Cohort Study. Risk factors to be studied include environmental, genetic, physiologic, and socioeconomic variables. The primary renal outcome is a composite clinical outcome defined by doubling of serum creatinine, ESRD, or death. Medication treatment for hypertension, beginning with the angiotensin converting enzyme inhibitor ramipril, is offered to all participants. In this fashion, the study directly controls two of the major determinants of kidney disease progression: treatment of hypertension and use of renoprotective, anti-hypertensive medication. The minimum duration of follow-up in the Cohort Study is 5 yr (total of 9 to 12 yr, including the period of the AASK trial). Ultimately, data from the AASK Cohort Study should enhance our understanding of the risk factors and processes that determine the progression of kidney disease. Such results might eventually lead to new strategies that delay or prevent ESRD.

During the past three decades, mortality from cardiovascular and cerebrovascular disease has progressively declined. In contrast, no such reduction in the mortality from ESRD has occurred. In fact, the number of patients entering the ESRD program in the United States has doubled during the past decade (1989 to 1998). Consequently, the number of individuals with ESRD in the United States exceeds 300,000, and the annual cost to the Medicare ESRD Program is over $15 billion (1).

ESRD disproportionately affects African Americans. Although African Americans comprise only 13% of the general US population, 29% of incident ESRD cases in 1999 occurred in African Americans (1). After adjustment for age and gender, the incidence of all-cause ESRD is nearly four times greater in African Americans than in Caucasians (953 *versus* 237 cases per million in 1999). The corresponding incidence of hypertensive ESRD is over six times higher in African Americans than Caucasians (3187 *versus* 515 incident cases per 10 million). Two strategies that might prevent hypertensive ESRD are (*1*) use of anti-hypertensive medications that have renoprotective effects apart from their effects on BP, and (*2*) aggres-

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sive BP control, that is, a BP goal that is below current recommendations.

The African American Study of Kidney Disease and Hypertension (AASK) was a 2 × 3 factorial trial that tested these two strategies. Participants were 1094 African-American hypertensives, ages 18 to 70 yr, with a GFR of 20 to 65 ml/min per 1.73 m^2, and no other apparent cause of renal insufficiency other than hypertension. Participants were randomized to a usual mean arterial pressure (MAP) goal of 102 to 107 mmHg or a low MAP goal of <92 mmHg, and to initial treatment with one of three anti-hypertensive study drugs: a sustained-release β-blocker (metoprolol), an angiotensin converting enzyme inhibitor (ACEI, ramipril), or a dihydropyridine calcium channel blocker (amlodipine). The primary outcome was GFR slope, as assessed by ^{125}I-iothalamate clearance. A secondary renal outcome was a composite clinical outcome defined by the occurrence of a reduction in GFR by 50% or by 25-ml/min per 1.73 m^2 from baseline, ESRD, or death.

Trial results have been published (2,3). In brief, the presence of even small amounts of proteinuria at baseline (urinary protein to creatinine ratio [UP/Cr] of >0.22) was associated with rapid progression of kidney disease. Despite a sustained 10 mmHg MAP difference between the two MAP groups, progression of kidney disease was similar in both groups. Ramipril compared with metoprolol appeared to slow renal disease progression independent of protein level, whereas ramipril and metoprolol slowed progression compared with amlodipine in patients with baseline UP/Cr >0.22.

These results have implications for the AASK Cohort Study, which is an extension of the AASK trial. First, the incidence of clinical outcomes and the progression of kidney disease was high, even in the group that received the most effective therapy. Specifically, in the ramipril group, the cumulative incidence of clinical outcomes was approximately 30% over 5 yr, and the average decline in GFR was 1.9 ml/min per 1.73 m^2 per yr. This documented decline in renal function, which is roughly twice the average age-associated decline in GFR in the general population, highlights the importance of identifying factors other than BP that predict, if not determine, progression of hypertensive kidney disease. Second, of the three medications tested in AASK, ramipril had the most beneficial effects on kidney function. These results support provision of ramipril therapy to all participants in the AASK Cohort Study.

In view of these results, the primary objective of the AASK Cohort Study is to determine prospectively the long-term course of kidney function and risk factors for kidney disease progression in African Americans with hypertensive kidney disease. We hypothesize that in addition to BP control and use of recommended renoprotective, anti-hypertensive medication, other factors determine the progression of kidney disease. A secondary objective is to determine the occurrence of cardiovascular disease and assess its risk factors. In this context, the AASK Cohort Study addresses the following research questions:

1. What is the long-term course of kidney function in this population?
2. What are the environmental, genetic, physiologic, and socioeconomic factors that predict the progression of kidney disease?
3. What are the long-term effects of the AASK trial interventions on the progression of kidney disease?
4. Does the development of proteinuria predict the progression of kidney disease?
5. What is the effect of recommended BP therapy, as determined by the AASK trial, on the progression of kidney disease in comparison with usual care in the community? This question will be addressed using parallel analyses from the Chronic Renal Insufficiency Cohort (CRIC) study.
6. What comorbidities, particularly cardiovascular disease, occur in the setting of hypertension-related kidney disease?
7. What risk factors predict the occurrence of cardiovascular disease?
8. What are the patterns of change in metabolic variables and cardiovascular-renal risk factors during the transition from pre-ESRD to ESRD?

Materials and Methods

The AASK Cohort Study is a multicenter, prospective, observational study that is an extension of the AASK trial (see Figure 1). Institutional review boards at each center approved the study protocol. A data and safety monitoring board provides external oversight.

Study Population

The study population of the AASK Cohort Study consists of all randomized individuals in the AASK trial who did not reach ESRD by the end of the trial. Those individuals who reached ESRD during the trial are invited for one visit at which time DNA is collected; otherwise no additional data are collected in those persons.

Data Collection

The purpose of the study visits is to collect risk factors (exposure) data, ascertain outcomes, and manage anti-hypertensive therapy. Data collection for exposures and outcomes are collected at baseline and every 12 mo thereafter. Management of anti-hypertensive therapy occurs at these visits and at an additional 2 to 4 visits per yr. Although participants are encouraged to receive their anti-hypertensive care

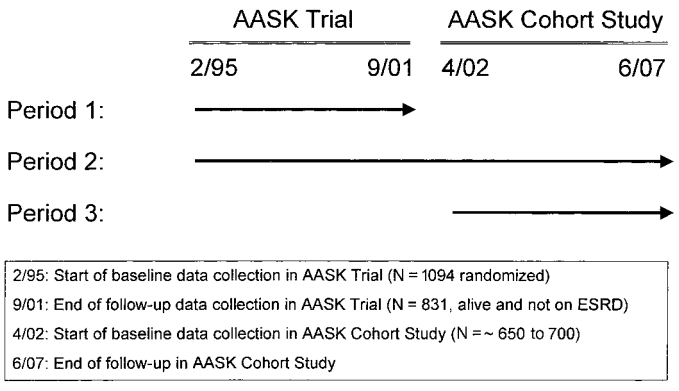

Figure 1. Overview of the African American Study of Kidney Disease and Hypertension (AASK) Cohort Study in relation to the AASK Trial.

through the AASK Cohort Study, some persons may decide not to accept such care. In this case, they are asked to attend just the semiannual data collection visits. Clinical outcomes are ascertained at each contact.

Table 1 displays the data collection items and procedures by visit during the first 2 yr. The pattern of data collection items and visits during all subsequent years is similar to that of year 2, except that ambulatory BP monitoring and echocardiography occur every other year. For those persons who reach ESRD during the Cohort Study, data collection visits still occur. Core measurements are as follows:

BP. BP is measured in a standardized fashion by trained, certified observers using the Tycos Classic Handheld Aneroid device. Two BP measurements are obtained in the seated position and one measurement in the upright position.

Biological Specimens. Blood is obtained twice at baseline and then every 6 mo thereafter. Serum creatinine is measured at each point. On an annual basis, fasting lipids (total cholesterol, LDL cholesterol [calculated], HDL cholesterol, and triglycerides), glucose, insulin, routine chemistry panel, and CBC are measured. Other analytes include homocysteine, C-reactive protein (CRP), and potentially other measures of inflammation, measures of oxidative stress and other lipid risk factors, *e.g.*, Lp(a). From each collection, aliquots of serum and plasma are banked for future analyses.

Blood for DNA is collected once. From this specimen, blood is spotted on filter paper and then stored. Also, lymphocytes are immortalized. A 24-h urine collection is obtained annually. Analytes include creatinine, protein, albumin, sodium, and potassium. From each collection, aliquots are banked. Fingernails are collected once each year. Participants are asked to trim each of their 10 fingernails with a chromium-free nail clipper. From these stored clippings, the levels of 50 heavy metals, including elemental mercury, chromium, and lead, can be measured using neutron activation analyses.

Questionnaires. Questionnaires that focus on potential risk factors are administered annually. Surveillance for outcomes (ESRD and cardiovascular outcomes) occurs at each visit. Risk factors of interest include health habits (alcohol, smoking, analgesic use, drug use), medications, exposure to intravenous contrast, and psychosocial factors. Instruments include the SF-36, the Jackson Heart Study Approach to Life, the Beck Depression Inventory II, and the Diener Satisfaction of Life Form.

Cardiovascular (CVD) Procedures. All CVD procedures are done locally and read centrally by the Cardiovascular Procedures Core Laboratory at Lenox Hill Hospital. Each year, an ECG is obtained. Specific codes of interest are the presence of LVH and myocardial infarction.

At baseline and every other year, a two-dimensional, M-mode, pulsed Doppler and pulsed tissue Doppler echocardiogram is obtained to evaluate left ventricular (LV) structure, LV mass, cardiac output, and aortic valve structure; as well as to obtain measures of systolic and diastolic function.

At baseline and every other year, 24-h ambulatory BP recordings are obtained. The study uses the SpaceLabs 90217 Ultralite or SpaceLabs 90207 devices. During each 24-h recording, measurements are obtained every 30 min throughout the day and night, from which awake and asleep averages are calculated, along with other variables including dipping status.

Table 1. Data collection items and activities by visit during the first 2 years of the AASK Cohort Study

	Visit[a]									
	C0	C0.1	C3	C6	C9	C12	C15	C18	C21	C24
Informed consent	X									
Contact information	X		X	X	X	X	X	X	X	X
BP measurement	X	X	X	X	X	X	X	X	X	X
BP management	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X
Demographics and baseline medical history questionnaire	X									
Medication questionnaire	X	X	X	X	X	X	X	X	X	X
Other risk factors	X					X				X
Surveillance for outcomes			X	X	X	X	X	X	X	X
Fasting blood for lipids, glucose, insulin, routine chemistry, complete blood count (CBC)	X					X				X
Creatinine	X	X		X		X		X		X
DNA	X									
24-Hr urine	X					X				X
Finger nail clippings	X					X				X
Stored specimens	X			X		X		X		X
Electrocardiogram	X					X				X
Ambulatory BP	X									X
Echocardiogram	X									X

[a] Visit code: C followed by a number which corresponds to months after enrollment (*e.g.*, C18 is the cohort visit which is 18 months after enrollment). Visit C0.1 occurs just after the initial visit.

Outcomes

Major outcomes of interest are renal and cardiovascular events. The primary renal outcome is a composite clinical outcome defined as the occurrence of a marked reduction in kidney function, ESRD, or death (G1 or S1, see Table 2). A coprimary outcome only includes the renal events (marked reduction in kidney function or ESRD) without deaths (G2 or S2, see Table 2). Secondary outcomes are GFR slope, to be used in mechanistic analyses, and proteinuria. During the trial, GFR was measured using ^{125}I-iothalamate clearance. After the end of the trial, eGFR is calculated from serum creatinine using an equation developed from baseline data in the AASK trial (4).

The classification of clinical cardiovascular outcomes is displayed in Table 3. "Total" cardiovascular outcomes include both "definite" and "probable" outcomes. In most analyses, cardiovascular outcomes are grouped together as a composite outcome; however, in some instances, cause-specific events are of interest. A Cardiovascular Outcome Committee, blinded to risk factor status, reviews medical records and assigns outcome status.

BP Management

AASK participants who have not reached ESRD are encouraged to have their BP managed by AASK Cohort investigators and staff. The recommended approach to hypertension control, both initial medication and BP goal, is based on the results of the AASK trial. The initial drug is the ACEI, ramipril. A loop diuretic is the next step. Subsequent medications are beta-blocker, calcium channel blocker, centrally-acting alpha adrenergic blocker, and direct vasodilators. Within each class, medications donated by manufacturers are preferentially used. In contrast to the AASK trial, in which the medication algorithm was fixed, there is investigator latitude during the cohort phase. The BP goal is a systolic BP $<$140 mmHg and diastolic BP $<$90 mmHg. However, in certain clinical settings, *e.g.* heavy proteinuria or diabetes, a lower BP goal may be warranted (5).

Analyses

The analytic approach depends on the point at which risk factors are collected, and the types of risk factors and outcomes (see Figure 1, Tables 2 and 3).

Clinical Outcomes. The association of risk factors with the clinical outcomes (renal or cardiovascular) will be evaluated with Cox regression models including predictor variables of interest and indicator variables for the six cells of the 2×3 factorial trial design. The period 2 analyses will include a separate set of time-dependent indicator variables for the time period that the patient was actually assigned to the randomized intervention to allow for different relative risks during and after the randomized trial. Analyses of the composite outcomes G1 or S1 will be administratively censored at the end of the designated study period (*i.e.*, the end of period 1, 2, or 3) or final loss of contact with the patient; analyses of G2 and S2 will be censored at these times and at death.

GFR Slope. The association of risk factors with GFR (or eGFR) slope will be examined with mixed effects models containing fixed effects terms for the predictor variables of interest along with additional terms to control for differences in the mean GFR (or eGFR) slopes among the six cells of the 2×3 factorial design of the randomized trial. For period 2, the latter terms will include interactions between the six cells and linear spline terms in time to allow for different mean slopes during the first 3 mo of the randomized trial (to account for initial acute effects of the interventions), the subsequent follow-up of the randomized trial (the chronic phase of the trial), the period between the final assessment of the trial, and the first assessment of the cohort (to account for a second acute effect on termination

Table 2. Renal outcomes by period

Composite Clinical Outcomes (primary outcomes)

Period 1 (AASK Trial)

- G1: the occurrence of a 25 ml/min per 1.73 m^2 or 50% reduction in GFR from trial baseline, ESRD (dialysis or transplantation), or death
- G2: the occurrence of a 25 ml/min per 1.73 m^2 or 50% reduction in GFR from trial baseline or ESRD (dialysis or transplantation)

Period 2 (AASK Trial and AASK cohort)

- S1: Doubling of serum creatinine from trial baseline, ESRD (dialysis or transplantation), or death
- S2: Doubling of serum creatinine from trial baseline or ESRD (dialysis or transplantation)

Period 3 (AASK Cohort)

- S1: Doubling of serum creatinine from cohort baseline, ESRD (dialysis or transplantation), or death
- S2: Doubling of serum creatinine from cohort baseline or ESRD (dialysis or transplantation)

GFR Slope (secondary outcome):

Period 1 (AASK Trial)

- Mean slope from serial GFR measurements (^{125}I-iothalamate clearance)

Period 2 (AASK Trial and AASK Cohort) and period 3 (AASK Cohort):

- Mean slope of estimated GFR (eGFR) in which eGFR = $329 \times (\text{Scr})^{-1.096} \times (\text{age})^{-0.294} \times$ (0.736 for women). This equation was developed from baseline data of the AASK trial ((4)).

Proteinuria (secondary outcome):

Same outcomes in periods 1, 2, and 3:

- Urine protein/urine creatinine ratio (UP/Cr), a continuous variable
- The occurrence of UP/Cr $>$0.22 (roughly 300 mg/day of proteinuria)
- The occurrence of UP/Cr $>$0.66 (roughly 1 g/day of proteinuria)

Table 3. Clinical cardiovascular outcomes

"Definite" cardiovascular outcomes:
- Cardiovascular death; or
- Cardiac revascularization procedure; or
- Nonfatal myocardial infarction, defined as a clinical report of myocardial infarction from the investigator and the presence of one of the following:
  - Elevation of CPK >twice the upper limit of normal for the given hospital supported by the elevation of cardiac specific enzyme above the normal range such as MB fraction or cardiac troponin, OR
  - In the absence of cardiac specific enzymes, determination of a typical evolutionary pattern defined as an elevation of CPK to twice the upper limit of normal for the given hospital followed by a fall of at least 50% or the appearance of new pathological Q-waves in two or more contiguous leads, or
  - The appearance of a R-wave with R/S ratio in lead V1 >1.0 in the absence of another explanation or a loss of progression of R-waves V2 through V5.
- Heart failure requiring hospitalization and therapy with an inotropic agent, vasodilator ACE inhibitor, increased diuretic dose, ultra filtration, or dialysis: or
- Stroke, defined as a permanent neurological deficit of at least 24 h, attributed to stroke by the personal physician, requiring hospitalization and confirmation by radiographic imaging.

"Probable" cardiovascular outcome:
- Nonfatal myocardial infarction, defined by a clinical report from the investigator but lacking confirmation of elevated enzymes or ECG changes: or
- Nonfatal myocardial infarction, defined by centrally read ECG that documents a new myocardial infarction in comparison with the baseline ECG but without clinical event: or
- Stroke, defined as above but lacking confirmation by radiographic imaging.

of the trial interventions), and the remaining follow-up period of the Cohort Study (the chronic phase of the Cohort Study). Periods 1 and 3 analyses will include the terms from the period 2 model that are relevant to the randomized trial (period 1) or the cohort follow-up (period 3), respectively.

A potential complication of the slope-based analyses is informative censoring from loss-to-follow-up due to death, dialysis, or dropout. If censoring is informative, the standard mixed effects models may give biased estimates. Therefore, the results of the standard mixed effects models will be compared with extensions of these models which account for informative censoring. If substantial bias is identified for important predictor variables, informative censoring models will be used in place of the standard mixed effects models.

Sample Size and Power

Of the 1094 randomized participants, 263 died or reached ESRD by September 30, 2001. We anticipate that an additional 154 participants will be lost-to-follow-up or be unwilling to participate in the AASK Cohort Study. Hence, the projected sample size is approximately 675.

Table 4 provides the projected numbers of events for each composite outcome, as the associated projected minimum detectable treatment effects (with 80% or 90% power based on an alpha level of 0.05, 2-sided test) for increases in risk associated with (*1*) a dichotomous risk factor with 50% prevalence; (*2*) a dichotomous risk factor with 20% prevalence; and (*3*) a 1-SD change in a continuous risk factor which is linearly related to the log-transformed relative risk. The power calculations correspond to unadjusted risk ratios.

The following two examples illustrate the power calculations. Consider analyses done in period 3 that compare nondippers (individuals with <10% BP decline from daytime to nighttime on ambulatory BP monitoring) to dippers (individuals with >10% BP decline). If 50% of AASK participants are nondippers, the study should have 80% power to detect a 47% or greater increase in the rate of composite endpoint of doubling of serum creatinine, ESRD, or death for nondippers compared with dippers. As a second example, consider a period 3 analysis relating the same composite outcome to total serum cholesterol, which has a SD of approximately 45 mg/dl. This analysis should have 80% power to detect a 21% or greater increase in the event rate per one SD (45 mg/dl) difference in total serum cholesterol.

Discussion

The incidence and prevalence of hypertensive ESRD are relentlessly increasing, despite evidence from national surveys that rates of BP-related cardiovascular disease are declining. In view of the substantial public health burden of hypertensive kidney disease, particularly among African Americans, and evidence that the condition is progressive, even among persons with well controlled and appropriately treated hypertension, efforts to understand the determinants of disease progression are a high national priority.

The AASK Cohort Study is well positioned to accomplish this task. First, this study is, to our knowledge, the only cohort study that specifically focuses on progression of kidney disease in African Americans with hypertensive kidney disease. Second, participants in this study are extremely well characterized. Baseline data on many exposures, including extensive medical history, detailed medication records, and numerous laboratory measurements, are already available, as is a bank of biologic specimens. Third, the study is enriched with individuals who have progressive disease. To date, over 300 individuals have had a major decline in renal function, ESRD, or death. If another 200 outcomes occur during the Cohort Study, there will be >500 incident ESRD cases, a number that vastly exceeds the incidence of all-cause ESRD cases in most popu-

Table 4. Minimum detectable increases in relative risk of renal composite clinical outcomes in time-to-event analyses

Period	Outcome[a]	Number of Outcomes	Minimum detectable effect sizes					
			80% Power			90% Power		
			Risk Factor with 50% Prevalence	Risk Factor with 20% Prevalence	1 SD Δ in quantitative variable	Risk Factor with 50% Prevalence	Risk Factor with 20% Prevalence	1 SD Δ in quantitative variable
Period 1 AASK trial only	ESRD, GFR Evt, or death	340	35%	46%	16%	42%	55%	19%
	ESRD, GFR Evt	263	41%	54%	19%	49%	64%	22%
	ESRD or death	249	43%	56%	19%	51%	67%	22%
Period 2 AASK trial + cohort	ESRD, Scr Evt, or death	530	28%	36%	13%	33%	42%	15%
	ESRD, Scr Evt	413	32%	41%	15%	38%	49%	17%
	ESRD or death	452	30%	39%	14%	36%	46%	16%
Period 3 AASK cohort only	ESRD, Scr Evt, or death	210	47%	62%	21%	56%	75%	25%
	ESRD, Scr Evt	173	53%	70%	24%	64%	85%	28%
	ESRD or death	176	53%	69%	23%	63%	84%	28%

[a] See Table 2 for definitions of outcomes. ESRD: End-stage renal disease; GFR Evt: event defined by a reduction in GFR; Scr Evt: event defined by a doubling of serum creatinine.

lation-based cohort studies, few of which enrolled large numbers of African Americans. Fourth, the long duration of follow-up (9 to 12 yr across trial and cohort phases) should allow us to identify and characterize individuals with slow, but clinically important, renal disease progression.

Design considerations included the selection of exposures and outcomes, and the approach to anti-hypertensive therapy. The number of candidate risk factors is vast. In this setting, we focused on a few biologically plausible factors. Salient new risk factors include markers of inflammation, diurnal BP from ambulatory BP, measurements of LV function and structure from transthoracic echocardiography, and a battery of psychosocial questionnaires. Specimens of urine, blood, and fingernails are collected and stored to assess the potential effect of other risk factors (*e.g.*, heavy metals from fingernails). For cost and logistic considerations, we decided to estimate GFR from creatinine-based formula (4) rather than measure GFR from ^{125}I-iothalamate clearance.

A major design consideration pertained to anti-hypertensive drug therapy. In the end, we decided to offer anti-hypertensive drug therapy to all cohort participants. Provision of such therapy has scientific, practical, and ethical roles. The scientific role is to directly control, rather than statistically adjust for, two of the major determinants of kidney disease progression (treatment of hypertension and use of renoprotective, anti-hypertensive medication). The practical role is to promote retention of individuals who otherwise might not participate in the Cohort Study after the trial ends. The ethical role is to avoid the situation of studying the effect of inadequately treated hypertension among individuals who received excellent care in the trial yet have inadequate resources to cover their own care after the trial ends.

In summary, results from the AASK Cohort Study should greatly enhance our understanding of the risk factors and processes that determine the progression of kidney disease. Such results might eventually lead to new strategies that delay or prevent ESRD.

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