ARIC Manuscript Proposal #1348

PC Reviewed: 3/18/08    Status: A    Priority: 2
SC Reviewed: ______    Status: __    Priority: __

1. a. Full Title: Chronic kidney disease and risk of hospitalization: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): CKD Progression

2. Writing Group:
   Writing group members:
   Anna Kottgen MD, MPH; Josef Coresh MD, PhD; Brad Astor PhD, M.P.H

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. [please confirm with your initials electronically or in writing]

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3. Timeline: a draft of the manuscript is expected to be available September 2008

4. Rationale:
   The purpose of this study is to investigate the relationship between chronic kidney disease (CKD) and risk of subsequent hospitalization and death. CKD is a silent, slowly developing disease which may progress from moderately decreased kidney function to a complete loss of kidney function. In addition to the large number of people with CKD (26 million in the U.S. alone), CKD is quite threatening because affected individuals often remain asymptomatic until the condition reaches advanced stages. Most individuals with CKD are not aware that they have the condition. The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (K/DOQI) recommends staging chronic kidney disease (CKD) based on creatinine-based
estimated GFR (eGFR), with Stage 5 being <15 mL/min/1.73 m² body surface area, Stage 4 being 15-30 mL/min/1.73 m², and Stage 3 being 30-60 mL/min/1.73 m². Stages 1 and 2 are based on evidence of kidney damage (e.g., urinary albumin excretion) in conjunction with estimated GFR. In 1999-2004 national data estimate the prevalence of stages 1 and 2 CKD to be 5% (10.1 million adults), and stages 3 and 4 CKD in the U.S. to be 8% (~16.2 million adults). Along with these stages are guidelines on appropriate action. However, the evidence for action is fairly limited and more data are needed, particularly in relation to level of kidney function and albuminuria. The effects of moderately reduced kidney function on subsequent hospitalizations and deaths are not well defined. A short term study of adults within a healthcare group has shown that the hazards of death, cardiovascular events and hospitalization increase with lower estimated GFR. Another short term study of kidney function has shown kidney function to be an independent predictor of both CVD and all-cause mortality in the elderly (CHS population, a mean age of 73). In the ARIC population, lower eGFR was related to increased risk of atherosclerotic cardiovascular disease over a 6.2 year follow-up period. Incident CHD and HF have also been shown to increase with lower eGFR in ARIC. Over 12 years of follow-up, decreased kidney function (along with anemia) was also associated with increased risk of recurrent CHD events as well as CHD and all-cause mortality in ARIC.

However, the long term implications of moderately decreased kidney function among the middle-aged population, where decreased kidney function is common, and still early enough to intervene, has not been well studied. It is important to examine these estimates not only in the context of well known complications such as end-stage renal disease and cardiovascular deaths, but also in the context of other adverse outcomes, (such as other types of hospitalizations) that may occur earlier in the disease. There is generally a decline in glomerular filtration rate (GFR) with age.

How these endpoints are related to population specific characteristics and kidney function estimates are also quite relevant to the health of heterogeneous populations worldwide. Details on the extent of healthcare utilization and adverse outcomes of patients with moderately decreased kidney function have not yet been fully explored. Whether the degree of albuminuria experienced gives additional information on their propensity towards adverse events is also unknown.

5. Main Hypothesis/Study Questions:

1. Baseline measures of kidney function (eGFR) and damage (urinary albumin:creatinine) will be risk factors for all-cause hospitalizations and death.

   We will also describe how the absolute risk and thresholds for risk vary between older and younger individuals, blacks and whites, men and women and individuals with and without diabetes.

   We will then explore associations with cause-specific hospitalizations, including the following causes: chronic and acute kidney injury, cardiovascular disease, cancer, and infectious causes.

2. Both eGFR and albuminuria (measured at ARIC visit 4) will be independent risk factors for subsequent hospitalizations.

6. Data (variables, time window, source, inclusions/exclusions):

   Data Source and Study population
All ARIC participants with serum creatinine and other necessary covariates will be included in the analyses. Follow-up data will consist of information on hospitalizations and deaths through December 31, 2004.

Exposures

Estimated GFR will be based on serum creatinine, age, race, and sex at visit 1 and visit 4 as done previously.\textsuperscript{4, 5} Albuminuria was assessed only at visit 4. A modified kinetic Jaffe’s method was used to measure serum creatinine. Measured serum creatinine will be corrected for interlaboratory differences and calibrated to the Cleveland Clinic measurement by subtraction of 0.24 mg/dL at visits 1 and 2, and addition of 0.18 mg/dL at visit 4. Values will then be multiplied by 0.95 to convert to standard serum creatinine and the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation will be used to estimate GFR (this is numerically equivalent to applying the original equation with the original calibration).\textsuperscript{10}

Urinary albumin excretion was measured at visit 4 (1996-1998) from frozen urine specimens. Urinary albumin excretion was determined as the ratio of albumin to creatinine (ACR, in ug/mg). The urinary albumin:creatinine ratio (ACR) will be categorized according to American Diabetes Association\textsuperscript{11} and National Kidney Foundation recommendations.\textsuperscript{12} Microalbuminuria will be defined as ACR 30-299 ug/mg, and macroalbuminuria defined as an ACR > 300 ug/mg. Alternative sex-specific categories of urinary albumin excretion and examination of continuous relationships with ACR will also be explored in secondary analyses.

Covariates of interest

Covariates will include socio-demographic characteristics (age, race, gender), smoking status, diabetes status, body mass index, CHD prevalence, hypertension status, use of blood pressure-lowering medications, and lipid parameters (HDL cholesterol, LDL cholesterol, triglycerides).

Outcomes

All hospitalizations captured through acute care hospital surveillance will be examined. From ARIC’s inception in 1987 through 2004, over 11,000 of the cohort members have had more than 40,000 hospitalizations collectively. All hospitalizations, with all discharge diagnoses for each hospitalization for each cohort member were identified through the cohort surveillance component of the ARIC study. In addition, all potential coronary or cerebral vascular disease events were validated. The relationship of hospitalizations to kidney disease in ARIC has not been examined. This study will examine all hospitalizations in detail with respect to risk of onset, duration, and diagnoses codes, including coronary and noncoronary events. Analyses will account for multiple events among individual participants.

Cohort surveillance also captures information on all deaths of cohort members, as well as for all underlying and contributory causes of death as identified in death certificates. By 2004, about 18% of the cohort had died. For this study, we will look at all-cause death as well as cardiovascular disease-related and other deaths separately.

Data Analysis

Follow-up time will be calculated from the time of visit 1 (or visit 4) to the earliest date of the event of interest (hospitalization, death), loss to follow-up, or
December 31, 2004. Adjusted incidence rates and their 95% confidence intervals for the time to hospitalization or death will be computed using Poisson regression models. To account for multiple and recurrent hospitalization events, we will examine the variation in the number of hospitalizations and use an extension to Poisson regression to account for greater than Poisson variation (i.e. the negative binomial regression), as needed. These models will provide more conservative estimates, with wider confidence intervals, than the models based on the standard Poisson distribution. We will then conduct a likelihood ratio test to determine whether the extension to the Poisson provides a significantly improved fit.

Crude associations of eGFR with the outcomes will be estimated by modeling eGFR continuously, as well as looking at quartiles separately. We will explore nonlinear relationships between eGFR and the outcomes of interest. Categories of eGFR (quartiles and clinically relevant categories such as <30, 30-45, 45-60, 60-90, >90 mL/min/1.73 m²), will be used, followed by the use of splines to determine the shape of the continuous relationship. We will examine potential for non-proportionality and whether the short- and long-term predictive ability of eGFR differs. For instance, adjusted risk of hospitalization in the first 6 years and then the next 8 years will be examined. Models will use age as the time scale and stratification by age, sex and race will be important in determining whether overall or stratum-specific cutoffs for eGFR are more informative.

Finally, techniques to evaluate risk prediction will be used. We will examine the performance of such risk prediction with eGFR alone and eGFR added after other hospitalization risk factors are in the model. For the relationship of albuminuria and cardiovascular risk there is evidence of increased risk even in the “normal” category. Therefore we will explore the utility of subdividing this category into “optimal” and high-normal. We will also explore whether using sex-specific cutoffs, or modeling ACR continuously throughout the “normal” range are more informative. Next, we will compare the risk of hospitalizations and death associated with cross-classifying categories of eGFR and ACR.

Multivariable models will include adjustments for age, race, gender, study center, BMI, hypertension status, use of antihypertensives, diabetes status, prevalent coronary heart disease (CHD), smoking status, LDL- and HDL-cholesterol and triglyceride concentrations. Adjusted incidence rates of hospitalization and death for each category of eGFR will be estimated by adjusting to the population mean of all other covariates. The association of eGFR levels with adverse outcomes will be compared between risk groups using Poisson multivariable regression and stratifying by race (African American and white), gender, and baseline diabetes status. First we will report the relative incidence rates of each risk factor within the fully adjusted regression model. In addition, we will also model each of the risk groups separately to examine the relationship of events across a wide range of eGFR values. We will adjust to the mean of all other covariates, and estimate the predicted incidence rate of the outcomes across the observed range of eGFR.

7. a. Will the data be used for non-CVD analysis in this manuscript? X_ Yes ___No
b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? X_ Yes ___No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)
8.a. Will the DNA data be used in this manuscript?  ____ Yes  ___ X__ No
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating
      Center must be used, or the file ICTDER02 must be used to exclude those with
      value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

   The lead author of this manuscript proposal has reviewed the list of existing ARIC
   Study manuscript proposals and has found no overlap between this proposal and
   previously approved manuscript proposals either published or still in active status.
   ARIC Investigators have access to the publications lists under the Study Members Area
   of the web site at: http://www.cscc.unc.edu/ARIC/search.php  ____ X__ Yes  _____ No

10. What are the most related manuscript proposals in ARIC (authors are
    encouraged to contact lead authors of these proposals for comments on the new
    proposal or collaboration)?

   952:  Kidney function and anemia as risk factors for coronary heart disease and
         mortality: The ARIC Study; Astor, BC
   1028:  Cardiovascular risk among adults with chronic kidney disease, with or without
          prior myocardial infarction; Wattanakit, K
   1118:  Reduced Kidney Function as a risk factor for incident heart failure: The ARIC
          Study; Kottgen, A
   1244:  Kidney Dysfunction and Sudden Cardiac Death among Participants in the ARIC
          Study; Deo, R

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use
     any ancillary study data?  ____ X__ Yes  ____ No
     2002.02

11.b. If yes, is the proposal
     _2002.02__  A. primarily the result of an ancillary study (list number*)
     __      B. primarily based on ARIC data with ancillary data playing a minor
           role (usually control variables; list number(s)* ________________________)
*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a
    manuscript is not submitted for ARIC review at the end of the 3-years from the
date of the approval, the manuscript proposal will expire.
REFERENCES


