ARIC Manuscript Proposal #1362

PC Reviewed: 4/8/08 **Status: A** **Priority: 2**
SC Reviewed: ____ **Status: ____** **Priority: ____**

1.
a. Full Title: Chronic kidney disease and risk of end-stage renal disease: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): CKD and ESRD

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. LB **[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 December 2008

4. Rationale:

The purpose of this study is to investigate the relationship between kidney function and risk of subsequent development of end-stage renal disease.

In 1999-2004 national data estimated the prevalence of stages 3 and 4 CKD in the U.S. to be 8.04% (~16.2 million adults) and stages 1 and 2 CKD to be 5.02% (10.1 million adults).[1] Characterized by moderately decreased kidney function, chronic kidney disease (CKD) is a silent, slowly developing disease which may progress to a complete loss of kidney function. In addition to the number of individuals affected (more than 26 million in the U.S. alone),[1] CKD is quite threatening because affected individuals often

remain asymptomatic until it reaches advanced stages. Most individuals with CKD are not aware that they have the condition.[2]

End-stage renal disease (ESRD) affects approximately one-half million individuals in the U.S. It poses a substantial health burden to afflicted individuals and a substantial cost burden to the US healthcare system. Increased risk for ESRD is experienced by those with CVD, hypertension, diabetes, and tobacco smoking.[3] Patients with ESRD have mortality rates much greater than those without, independent of age, gender, race and diabetes.[4] The risk of death is estimated to be four-fold greater than the general population.[5]

The clinical course taken by adults across the full range of estimated kidney function is currently unknown. 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 that may occur earlier in the progression of disease.

There is generally a decline in glomerular filtration rate (GFR) with age.[6] There is interest in nonlinear relationships between estimated GFR (eGFR) and adverse outcomes, particularly among the aging population. 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. Among the missions of the United States Renal Data System (USRDS) is to characterize the ESRD population. Despite the wealth of information that can be obtained through this system, individuals with ESRD are likely to have experienced kidney function decline and adverse health events prior to their ESRD diagnosis and entrance into the Medicare system.[7]

Active and ongoing hospital surveillance that takes place as part of a longitudinal cohort study such as ARIC makes for an important avenue to obtain such information. However, capturing this information in this setting is limited by potential for misclassification error. Linking the database from the United States Renal Data System with the ARIC cohort will provide an opportunity to confirm previously identified ESRD cases as well as gain insight into the capabilities of hospital surveillance, prospective longitudinal studies and a qualitative review of the long-term clinical history of ESRD patients, for a period of time before which their clinical data were available to the Centers for Medicare & Medicaid Services (CMS) and USRDS.

5. Main Hypothesis/Study Questions:

We hypothesize that baseline factors of kidney function (eGFR) and damage (urinary albumin:creatinine) will predict ESRD. While we hypothesize for this to be true among all individuals, we also hypothesize that these relationships will differ by age, race, sex, and diabetes status. We will also explore associations with hospitalizations for ESRD ascertained by ARIC surveillance.

Hospitalization data has been collected for over 17 years with continuous active surveillance in ARIC. Despite the breadth of information captured, ESRD cases have not been clinically confirmed. Through linkage of ARIC data to the United States Renal Data System (USRDS), we will confirm incident ESRD cases identified through hospital-based surveillance data and acquire additional information on hospitalizations following ESRD. We will examine agreement of cases identified and if substantial disagreement is

identified we will examine risk factors of discordant ESRD case identification.

We will estimate the relationship between baseline eGFR and ESRD over 17 years of follow-up. We will examine whether this relationship differs by demographics (age, race and gender) and diabetes status with a focus on the risk associated with CKD Stage 3.

Using data from visit 4, in which both eGFR and albuminuria were measured, we will examine how these two factors are associated with the risk of ESRD among individuals, with a focus on individuals with CKD stage 3 over 8 years of follow-up. We will examine whether these relationships differ by demographics (race and gender) and diabetes status and compare the risk to individuals without CKD and with CKD stage 3. Lastly, we will also repeat these analyses among individuals free of any evidence of CKD and compare findings between the groups.

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 ESRD through December 31, 2004.

Exposures

Estimated GFR will be based on serum creatinine, age, race, and sex at visit 1 and visit 4. 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. The simplified Modification of Diet in Renal Disease (MDRD) equation will be used to estimate GFR.[8, 9-12]

Urinary albumin excretion was measured at visit 4 (1996-1998) from frozen urine specimens collected from each participant (untimed and frozen within 12 hours and stored at -70°C) and shipped to the University of Minnesota in aliquots of 40 mL each for albumin and creatinine. Albumin was measured by a nephelometric method either on the Dade Behring BN100 (assay sensitivity, 2.0 mg/L), or on the Beckman Image Nephelometer. Urinary creatinine was measured using the Jaffe method. Urinary albumin excretion was determined as the ratio of albumin to creatinine (ACR, in ug/mg). The urinary albumin:creatinine ratio (ACR) will be used to determine levels of albuminuria according to American Diabetes Association[13] and National Kidney Foundation recommendations.[14] Microalbuminuria will be defined as ACR 30-299 ug/mg, and macroalbuminuria defined as an ACR $\geq$ 300 ug/mg. Alternative categories of urinary albumin excretion and examination of continuous relationships with ACR also may be used.

Covariates of interest

Covariates will include sociodemographic 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).

Data Analysis

Follow-up time will be calculated from the time of visit 1 (or visit 4) to the earliest date of ESRD. Adjusted incidence rates and their 95% confidence intervals for the time to ESRD will be computed using Poisson regression models.

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 m^2) will be the first step to explore the relationship. Splines will be used next 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 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 are more informative.

ACR is classified clinically as normal <30 mg/g, microalbuminuria 30-299 mg/g, and macroalbuminuria 300+ mg/g. However, for 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 as recommended by Warram, (with cut-offs for microalbuminuria in men and women of 17 mg/g and 25 mg/g, respectively, and cut-offs for macroalbuminuria in men and women of 250 mg/g and 355 mg/g, respectively),[15] or modeling continuously, throughout the "normal" range are more informative. Next, we will compare the risk 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. Incidence rates of ESRD for each category of eGFR will be estimated by adjusting to the population mean of all other covariates.

The association of eGFR levels with ESRD will be compared between risk groups using Poisson multivariable regression and stratifying by race, gender, and baseline diabetes status.

We will be comparing hospital-based surveillance- and USRDS identified ESRD cases. Follow-up time will be calculated from the date of the first ARIC examination to the first date of ESRD diagnosis. Participants who do not become a case will be censored at the earliest time of death, withdrawal, or December 31, 2004. Likewise, crude and adjusted incidence rate estimates will be made using multivariable Poisson regression models, and the risk factors predicting ESRD will be examined. Likelihood ratios of case identification will be calculated, incidence rate ratios examined, and discordant cases will be assessed for association with previously mentioned risk factors. The USRDS cannot be used as the gold standard in these analyses. Among the limitations of USRDS data is that individuals undergoing dialysis for less than three months are not identified as cases. Cases identified through USRDS and not through ARIC surveillance are expected to be ESRD cases. Cases identified through ARIC, and not USRDS may be rapid mortality cases, or misclassified. All available hospitalization and/or death data for these discordant cases will be reviewed to determine correct case status. If these individuals experienced previous coronary or cerebrovascular events, an abstraction of hospital records will be available. However, if these individuals have not, all hospitalizations and discharge diagnoses should still be available.

Once correct case status is determined (by resolving discordant cases through available hospital record review), it will be used as the comparison group along with concordant cases, where the sensitivity, specificity, positive and negative predictive values of both methods used to identify ESRD cases (hospital surveillance captured information in ARIC, and USRDS identified cases) will be calculated.

Lastly, ROC analyses will be conducted, using the adjudicated and the concordant ESRD cases as the reference group. The discriminatory quality of the hospital-based surveillance data will be compared to the USRDS data using ROC plots and quantified with summary statistics. The relative predictability of each will be quantified by calculating the area under the ROC curve (AUC).

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? _X___ Yes ____ 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"? __X_ Yes ____ No

9.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)?

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? ___ Yes __*X*_ No

11.b. If yes, is the proposal

___ 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

1. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the united states. *JAMA*. 2007;298:2038-2047.

2. Coresh J, Byrd-Holt D, Astor BC, et al. Chronic kidney disease awareness, prevalence, and trends among U.S. adults, 1999 to 2000. *J Am Soc Nephrol*. 2005;16:180-188.

3. Roblin DW, Khoury A, Pisanelli W, Dahar W, Roth M. Risk for incident renal dialysis in a managed care population. *Am J Kidney Dis*. 2006;48:205-211.

4. Levin A, Foley RN. Cardiovascular disease in chronic renal insufficiency. *Am J Kidney Dis*. 2000;36:S24-30.

5.
U.S. renal data system, USRDS 2006 annual data report: Atlas of end-stage renal disease in the
united states, national institutes of health, national institute of diabetes and digestive and kidney diseases, bethesda, MD, 2006. .

6. Robinson BE. Epidemiology of chronic kidney disease and anemia. *J Am Med Dir Assoc*. 2006;7:S3-6.

7. United states renal data system, *researcher's guide to the USRDS database*, national institutes of health national institute of diabetes and digestive and kidney diseases. Bethesda, MD:2006.

8. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. modification of diet in renal disease study group. *Ann Intern Med*. 1999;130:461-470.

9. Weiner DE, Tighiouart H, Elsayed EF, et al. The framingham predictive instrument in chronic kidney disease. *J Am Coll Cardiol*. 2007;50:217-224.

10. Kottgen A, Russell SD, Loehr LR, et al. Reduced kidney function as a risk factor for incident heart failure: The atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol*. 2007;18:1307-1315.

11. Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney function and risk of peripheral arterial disease: Results from the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol*. 2007;18:629-636.

12. Wattanakit K, Coresh J, Muntner P, Marsh J, Folsom AR. Cardiovascular risk among adults with chronic kidney disease, with or without prior myocardial infarction. *J Am Coll Cardiol*. 2006;48:1183-1189.

13. Molitch ME, DeFronzo RA, Franz MJ, et al. Nephropathy in diabetes. *Diabetes Care*. 2004;27 Suppl 1:S79-83.

14. Eknoyan G, Hostetter T, Bakris GL, et al. Proteinuria and other markers of chronic kidney disease: A position statement of the national kidney foundation (NKF) and the national institute of diabetes and digestive and kidney diseases (NIDDK). *Am J Kidney Dis*. 2003;42:617-622.

15. Warram JH, Gearin G, Laffel L, Krolewski AS. Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol*. 1996;7:930-937.