ARIC Manuscript Proposal 1361

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

1.
a. Full Title: Defining Chronic Kidney Disease and its Meaning in the Research Setting: The Atherosclerosis Risk in Communities Study

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

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:

In 1999-2004 national data estimate the prevalence of stages 3 and 4 chronic kidney disease (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]

Generally 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]

Development of a standard definition of chronic kidney disease based on estimated glomerular filtration rate (eGFR) has improved many aspects of kidney disease research and clinical care. However, too little attention has been paid to measures of incident CKD, which are critical for prospective studies and tracking patients over time. A comparison across different definitions of incident CKD, in terms of agreement and associations with risk factors, based on existing ideas in the literature is a useful step in moving forward.

5. Main Hypothesis/Study Questions:

Using data from the ARIC Study, we will compare several definitions of incident CKD. Definitions will be based on rises in serum creatinine, decrements in estimated GFR, and/or incidence of a hospitalization with a kidney-related diagnosis. We will compare agreement in case identification, incidence rates and associations with known (e.g., diabetes, hypertension) and suspected (e.g., triglycerides) CKD risk factors.

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

Data Source and Study population

All participants with relevant covariate information that are free of prevalent CKD (defined here as an estimated GFR below 60 mL/min/1.73 m^2) at Visit 1 will be included in analyses. Incident CKD definitions will dictate varying exclusions to eliminate individuals with prevalent disease at baseline.

Incident CKD (iCKD) will be defined in a number of different ways, including criteria that are visit-based, surveillance-based, or a combination of both. For example, one definition will define iCKD as an estimated GFR falling below 60 mL/min/1.73 m^2 at visit 2 (1990-1992) or 4 (1996-1998), among those with GFR of at least 60 mL/min/1.73 m^2 at visit 1 (1987-1989). A more stringent definition of iCKD requires that this fall in eGFR below 60 mL/min/1.73 m^2 also be a minimum percent drop from the baseline visit (e.g.: 25% drop as in the table). A third definition defines iCKD by a rise in serum creatinine (between visit 1 and the earliest of either visit 2 or visit 4). Incident CKD will also be defined by a hospitalization including kidney disease as captured by specified ICD-9 hospitalization or death codes or ICD-10 death codes.[3] Other definitions of iCKD include patients with either one of the three visit-based definitions of iCKD **or** a related hospitalization.

A modified kinetic Jaffe method was used to measure serum creatinine. Serum creatinine concentration was 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. It was then used to estimate glomerular filtration rate (GFR) using the simplified Modification of Diet in Renal Disease (MDRD) Study equation developed at the Cleveland Clinic:

estimated GFR = 186.3 x (serum creatinine [mg/dL]$^{-1.154}$) x (age$^{-0.203}$) x (0.742 if female) x (1.21 if African American).[4]

Covariates of interest

Covariates will include baseline estimated GFR, 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

We will first look at the degree of agreement in identifying incident CKD (iCKD) cases using the various definitions. We will calculate Kappa statistics for pairwise combinations of iCKD definitions as a measure of agreement beyond that expected by chance alone.

Follow-up time will be calculated from the date of the first ARIC examination to the first date of CKD diagnosis, (defined as the earliest of the second or fourth ARIC visit, or the discharge date of a hospitalization or death with kidney disease, depending on the definition used). Participants who do not become a case will be censored at the earliest time of death, withdrawal, or the date of visit 4, or, for surveillance based cases, December 31, 2004. Certain definitions require follow-up (at visits) to become a case; even for definitions combining visit and hospital based data, individuals are no longer at equal risk of being identified as a case after visit 4. For ease of comparison of rates between iCKD definitions, all definitions will use rates with follow-up only as late as the date of visit 4 for comparisons between definitions. Crude incidence rates of each iCKD definition as well as crude relative incidence rates (comparing all pairwise combinations of iCKD definitions) will be calculated. In addition, using Poisson multivariable regression, adjusted incidence rates and their 95% confidence intervals for the rate of development of CKD will be computed. Fully adjusted multivariable models will include age, race, gender, study center, baseline eGFR, BMI, hypertension status, diabetes status, prevalent coronary heart disease (CHD), smoking status, LDL- and HDL-cholesterol and triglyceride concentrations as covariates. Adjusted incidence rates for each of the iCKD definitions overall, and by race, gender and diabetes status will be estimated, adjusting to the stratum-specific mean values of all other covariates.

We will focus on the discordant cases and examine which risk factors (among those in the multivariable Poisson models) are associated with being classified as an iCKD case according to one definition, and not another. In addition, likelihood ratios of case identification will be constructed for dichotomous risk groups (race, gender, diabetes and hypertension status). In so doing, we will calculate the conditional probability of being identified (and not being identified) as a case according to a particular definition of iCKD given one of these characteristics (eg: African American race), and compare it to the conditional probability of being identified (and not being identified) given the opposite characteristic. We will construct ratios comparing, African Americans to whites, men to women, those with diabetes to those without, and hypertensives to normotensives. Lastly, after constructing multivariable Poisson models, the relative risk of key risk factors will be qualitatively compared across definitions of iCKD. For instance, the incidence rate ratios of race, gender, and diabetes status will be compared across iCKD defined by hospitalization versus visit-based creatinine rise defined cases.

7. a. Will the data be used for non-CVD analysis in this manuscript? __ Yes _X_ 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? ___ 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

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)?

N/A

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. International classification of diseases, 9th revision, clinical modification (ICD-9-CM). Washington, D.C.: U.S. Department of Health and Human Services, Public Health Service, Health Care Financing Administration.; 1991.

4. 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.