

## ARIC Manuscript Proposal # 1581

PC Reviewed: 12/8/09  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Novel markers of kidney function and prediction of incident chronic kidney disease and end-stage renal disease: the Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters):** Novel markers and incident CKD

### 2. Writing Group:

Writing group members: Brad Astor (lead), Nrupen Bhavsar, Josef Coresh, Christie Ballantyne, Ron Hoogeveen, others welcome

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

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**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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**3. Timeline:** Assays on of Visit 2 specimens have recently been sent to the coordinating center. We expected to complete analyses on these data in the next 3 months. We anticipate that the manuscript will be prepared within 6 months.

### 4. Rationale:

Individuals with decreased kidney function are at a substantially higher risk of end-stage renal disease (ESRD) and mortality than the general population.<sup>1-3</sup> Early detection of individuals at increased risk of decreased kidney function is important to tailor therapy to minimize the incidence of these outcomes.

Serum creatinine is the most commonly used marker of kidney function. Creatinine is a byproduct of muscle breakdown and, therefore, serum levels are affected by an individual's muscle mass.<sup>4,5</sup> Equations accounting for age, race and sex improve the estimation of

glomerular filtration rate (eGFR<sub>creat</sub>) by accounting for average differences in muscle mass across these factors.<sup>6,7</sup> Estimating equations, however, cannot account for individual differences in muscle mass. Muscle wasting due to chronic illness is associated with lower creatinine generation, leading to an overestimation of GFR in such individuals. Therefore, using eGFR<sub>creat</sub> to assess kidney function may miss individuals that have reduced kidney function or be at higher risk of decreasing kidney function.

Cystatin C is less affected by muscle mass than serum creatinine and is thought to be a better marker of kidney function.<sup>8,9</sup> Equations adjusting for age, race and sex also improve estimation of GFR by cystatin C (eGFR<sub>cys</sub>).<sup>10</sup>

Additional analytes, including beta trace protein (BTP) and  $\beta_2$  microglobulin ( $\beta_2$ M), have recently been examined as alternative markers of kidney function. Serum levels of beta-trace protein (BTP) levels were strongly correlated with GFR in a study of kidney transplant patients and in a small study (n=60) of individuals with various types of kidney diseases.<sup>11-15</sup> In a combined analysis using data from the Modification of Diet in Renal Disease (MDRD) and African American Study of Kidney Disease and Hypertension (AASK), GFR estimated by an equation including serum creatinine, cystatin C and  $\beta_2$ M levels correlated with directly-measured GFR more closely than equations based on any single marker, and was nearly as highly correlated as a repeated GFR.[Coresh, unpublished data]. Higher  $\beta_2$ M levels predict early onset atherosclerosis and mortality in hemodialysis patients.<sup>16-18</sup> Data are limited in other populations. It is currently unknown whether other factors affect BTP and/or  $\beta_2$ M levels.

As these novel markers are investigated for use in estimating GFR, it is important to understand how these markers are associated with subsequent changes in kidney function. To our knowledge, no studies have evaluated the associations of BTP and  $\beta_2$ M with the risk of incident CKD.

## **5. Main Hypothesis/Study Questions:**

- a. Do serum levels of BTP and  $\beta_2$ M independently predict incident CKD (as defined by an increase in cystatin C or a decrease in eGFR<sub>cys</sub>) among individuals with normal eGFR<sub>creat</sub> at baseline?
- b. Do serum levels of BTP and  $\beta_2$ M predict incident end-stage renal disease (ESRD) independent of other risk factors?

## **6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

Serum creatinine was measured at ARIC Visits 2 and 4. Cystatin C was measured on all Visit 4 samples as part of Ancillary Study 2006.16, “Longitudinal Study of Predictors and Consequences of Chronic Kidney Disease.” This ancillary study also funded assays of Cystatin C, BTP and  $\beta_2$ M in case-control studies of incident CKD and incident ESRD, using samples from Visit 2. Cystatin C measurements at Visit 2 and 4 will be used to identify cases and non-cases of incident CKD from Visit 2 to Visit 4. The eligibility criteria and case definitions for these case-control studies are described below:

### Incident CKD study

#### Eligibility criteria:

- eGFR<sub>creat</sub> at Visit 2  $\geq 60$  mL/min/1.73m<sup>2</sup>
- Non-missing at Visit 2: hypertension  
diabetes status  
smoking status  
lipids (LDL, HDL, TG)
- Non-missing eGFR<sub>creat</sub> at Visit 4
- White or black; black in Jackson, white in Minneapolis and Washington County

#### Cases:

Three overlapping case groups were defined:

- 1) eGFR<sub>cys</sub> (N = 867 cases; 1,126 non-cases):  
eGFR<sub>cys</sub> at Visit 2  $\geq 60$  mL/min/1.73m<sup>2</sup> and  
eGFR<sub>cys</sub> at Visit 4  $< 60$  mL/min/1.73m<sup>2</sup>
- 2) Cystatin C (N = 777 cases; 1,058 non-cases):  
Cystatin C at Visit 2  $\leq 1.0$  mg/dL and  
Cystatin C at Visit 4  $> 1.0$  mg/dL
- 3) Combined (N = 872 cases; 1,043 non-cases):  
eGFR<sub>cys</sub> at Visit 2  $\geq 60$  mL/min/1.73m<sup>2</sup> and cystatin C at Visit 2  $< 1.0$  mg/dL and  
eGFR<sub>cys</sub> at Visit 4  $< 60$  mL/min/1.73m<sup>2</sup> or cystatin C at Visit 4  $> 1.0$  mg/dL

#### Controls:

A random sample of eligible participants was selected to serve as controls (N=1,289). A different subset of these meet the eligibility criteria for each of the three case groups above.

### Incident ESRD study

#### Eligibility criteria:

- Non-missing eGFR<sub>creat</sub> at Visit 2
- Non-missing diabetes status at Visit 2
- No ESRD prior to Visit 2
- White or black; black in Jackson, white in Minneapolis and Washington County

#### Cases:

- 4) ESRD (N = 171; 148 non-cases)  
ESRD after Visit 2 (through 2005)

#### Controls:

No ESRD, frequency matched to cases on:

- Sex, race, diabetes at Visit 2
- Visit 2 eGFR<sub>creat</sub> categories (10-19, 20-29, 30-39, etc ...)

## Analysis

All analyses will account for the frequency-matched selection of controls. Baseline characteristics will be examined in the overall population and stratified by quartiles of BTP and  $\beta_2M$ . T-tests and chi-square tests will be used to test differences across quartiles for continuous and categorical covariates, respectively.

The odds of declining kidney function or ESRD across quartiles of BTP and  $\beta_2M$  will be examined separately using conditional logistic regression, with and without adjustment for relevant covariates. Based on the results of these models, subsequent models will utilize different categories or will include risk factor levels modeled as continuous variables. Additional models will adjust for eGFR<sub>creat</sub> or eGFR<sub>cys</sub> at Visit 2 to assess the added predictive capability of BTP and  $\beta_2M$  for declining kidney function. We also will model the change in eGFR<sub>cys</sub> or eGFR<sub>creat</sub> between Visit 2 and Visit 4 as continuous outcome variables, and investigate whether the change in either estimate is predicted by levels of BTP and/or  $\beta_2M$  at Visit 2.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**     Yes     No

**b. If Yes, is the author aware that the file ICTDER03 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 ICTDER03 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     No

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES\_DNA = "No use/storage DNA"?**     Yes     No

**8.c. If yes, is the author aware that the participants with RES\_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?**  
       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.csc.unc.edu/ARIC/search.php>

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)?**

MS1123: Albuminuria and Kidney Function as Predictors of Cardiovascular Events and Mortality (lead author: Astor).

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

**11.b. If yes, is the proposal**

**A. primarily the result of an ancillary study (list number\* 2006.16)**

**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.csc.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.**

Agreed

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