ARIC Manuscript Proposal # 1583

1.a. Full Title: The impact of inflammation on prediction of mortality by glomerular filtration rate estimated by serum creatinine and cystatin C: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Kidney function, CRP and death

2. Writing Group:
Writing group members: Brad Astor (lead), 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: We anticipate that the manuscript will be prepared within six months from approval of the proposal.

4. Rationale:

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.\textsuperscript{1,2} Equations accounting for age, race and sex improve the estimation of glomerular filtration rate (GFR) by accounting for average differences
in muscle mass across these factors. Estimating equations, however, cannot account for individual differences in muscle mass.

Cystatin C is less affected by muscle mass than serum creatinine and is thought to be a better marker of kidney function. The improvement in GFR estimation is more pronounced among individuals with better kidney function (GFR > 60 mL/min/1.73m²) than in those with more severe kidney dysfunction. Some reports, however, have shown that cystatin C levels are affected by non-renal factors, including smoking and inflammation, independent of kidney function.

Several studies have found that estimated GFR (eGFR) based on cystatin C predicts mortality and cardiovascular events better than eGFR based on serum creatinine. Similar to the findings for GFR estimation, the improvement in prediction is most substantial at higher levels of kidney function, where serum creatinine may overestimate GFR. Estimated GFR based on serum creatinine has a J-shaped relationship with mortality risk, in which higher eGFR is associated with higher risk at eGFR levels above 90 mL/min/1.73m², while the relationship with eGFR based on cystatin C is approximately linear across the entire range of eGFR levels.

It has been suggested that the improved prediction of mortality risk by eGFR based on cystatin C is partially due to its association with inflammation. This hypothesis, however, has not been directly investigated.

5. Main Hypothesis/Study Questions:

**Hypotheses:** The association of lower estimated GFR based on cystatin C (eGFRcys) and risk of mortality will be weaker among individuals with elevated hsCRP as compared to individuals with lower hsCRP levels. The association of estimated GFR based on serum creatinine (eGFRcreat) will be independent of hsCRP level.

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).

Cystatin C and high sensitivity CRP (hsCRP) were measured on Visit 4 samples as part of Ancillary Study 2006.16, “Longitudinal Study of Predictors and Consequences of Chronic Kidney Disease.” The most recent follow-up data will be used to assess the association between these Visit 4 measures and subsequent mortality.

All analyses will be performed locally by Dr. Astor. Estimates of GFR (eGFRcreat and eGFRcys) will be calculated using the CKD-EPI equations. Participants with missing values for these variables or with severely decreased kidney function (<15 ml/min/1.73m²) will be excluded from analyses.

The association of hsCRP levels with eGFRcreat and eGFRcys will be evaluated graphically and by quantile regression, due to the skewed distribution of hsCRP values. The association between eGFR and risk of mortality will be assessed by multivariate Cox proportional hazards regression models. These models will be run for eGFRcreat and eGFRcys separately. Models also will be run after stratification by hsCRP levels (e.g.,
upper quartile compared to lower three quartiles), and interaction assessed by likelihood ratio tests.

An important component of the analyses will be an attempt to define the risk of events across the entire range of eGFR, by hsCRP levels. This analysis will use nonlinear models, and the shape of these curves will be qualitatively compared between eGFRcreatin and eGFRcys.

Additional variables required for analyses include demographic factors (age, race, sex, center), comorbid conditions (blood pressure, diabetes status, prior CHD events), anthropometric data (waist circumference, waist:hip ratio, BMI), smoking status, medication use (antihypertensives, lipid-lowering medications), and laboratory variables (lipids, blood glucose).

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 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? __X__

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 __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 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.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)?

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? __X__ Yes    ____ No

11.b. If yes, is the proposal

__X__  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.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.

Agreed
Reference List


