ARIC Manuscript Proposal # 1423

PC Reviewed: 09/09/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cystatin C-based estimated GFR and albuminuria as predictors of coronary heart disease (CHD) events and mortality

b. Abbreviated Title (Length 26 characters): Cystatin C and CVD events

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: Cystatin C measurements have recently been completed for all participants at Visit 4. Analyses and manuscript preparation will begin when the data are received from the coordinating center.

4. Rationale: Moderately decreased kidney function is associated with an elevated risk of mortality.[1-3] As direct measurements of glomerular filtration rate (GFR) are expensive and inconvenient, most large studies use GFR estimated from serum creatinine. Serum levels of creatinine, however, are affected by factors other than GFR, most importantly variations in creatinine generation due to differences in muscle mass.[4] Estimating equations that include age, sex and race as indicators of average muscle mass improve the accuracy of GFR estimation, but cannot account for individual differences.

GFR estimates based on serum creatinine ($eGFR_{SCr}$) are less accurate at higher levels of kidney function.[5]

Cystatin C is a marker of kidney function that is less sensitive to differences in muscle mass than is serum creatinine.[4] Nonetheless, adjustment for age, sex, and race improves cystatin C-based estimates of GFR ($eGFR_{CysC}$) , and GFR estimating equations incorporating these factors have recently become available.[6] Cystatin C predicted total and cardiovascular mortality risk more strongly than creatinine-based estimates of GFR in prospective studies of older adults,[7;8] but this association has not been evaluated in the general population.

Leakage of protein in the urine is a sensitive indicator of early kidney damage, especially in persons with diabetes. The prevalence and severity of albuminuria increase with lower GFR, and are significantly higher at each stage among individuals with diabetes. National Kidney Foundation (NKF) clinical practice guidelines define microalbuminuria, based on a random spot urine sample, as albumin:creatinine ratio (ACR) >30 mg/g, and macroalbuminuria as ACR >300 mg/g. The presence of albuminuria is one of the strongest predictors of progression of kidney disease, and is associated with a higher risk of cardiovascular disease and mortality in both diabetic and non-diabetic individuals.[9]

The combined impact of decreased kidney function, as estimated by cystatin C, and albuminuria on CHD and mortality has not been investigated in the general population. It is unknown whether these relationships differ by race.

5. Main Hypothesis/Study Questions:

Decreased kidney function, as estimated by cystatin C or serum creatinine, will predict subsequent CHD and mortality, independent of other risk factors. The association between $eGFR_{CysC}$ and outcomes will be observed throughout the entire range of $eGFR_{CysC}$, whereas the association between $eGFR_{SCr}$ and outcomes will only be observed at $eGFR_{SCr} < 60$ mL/min/1.73m^2.

Albuminuria will predict subsequent CHD and mortality, independent of other risk factors. Even minimally higher ACR, below current clinical cut-offs, will be associated with greater risk of events.

Decreased kidney function, as estimated by cystatin C or serum creatinine, will be moderately correlated with severity of albuminuria, and each will independently predict subsequent events.

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 was measured on Visit 4 samples as part of Ancillary Study 2006.16, "Longitudinal Study of Predictors and Consequences of Chronic Kidney Disease." Serum creatinine and u[10]rinary albumin and creatinine were measured at Visit 4 for all

participants. The most recent follow-up data will be used to assess the association between these Visit 4 measures and subsequent CHD events and mortality.

All analyses will be performed locally by Dr. Astor. Participants with missing values for these variables or with severely decreased kidney function (<15 l/min/1.73m^2) will be excluded from analyses. Urinary albumin:creatinine ratio (ACR) will be calculated and analyzed using clinical cutoff (microalbuminuria 30-300 mg/g, macroalbuminuria 300+ mg/g) and as a continuous variable (including levels below the cutoff for microalbuminurai). Sex-specific cut-offs (>17 mg/g in men, >25 mg/g in women) also will be used. An important component of the analyses will be an attempt to define the risk of events across the entire range of ACR and eGFR. The latter analysis will use nonlinear models, and the shape of these curves will be qualitatively compared between estimated GFR (eGFR) based on cystatin C and serum creatinine, using published estimating equations.[6]

Additional analyses will be stratified by race, and interaction terms added to test for different relationships in African Americans and whites.

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, wasit:hip ratio, BMI), smoking status, alcohol intake, medication use (antihypertensives, lipid-lowering medications), and laboratory variables (lipids, blood glucose, insulin).

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 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 __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

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2. Coresh J, Astor BC, Sarnak MJ: Evidence for increased cardiovascular disease risk in patients with chronic kidney disease. *Curr Opin Nephrol Hypertens* 13:73-81, 2004

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5. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, van Lente F, Levey AS: Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis* 39:920-929, 2002

6. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van LF, Bruce RD, III, Zhang YL, Greene T, Levey AS: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51:395-406, 2008

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10. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van LF, Bruce RD, III, Zhang YL, Greene T, Levey AS: Estimating GFR using

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11. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van LF, Bruce RD, III, Zhang YL, Greene T, Levey AS: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51:395-406, 2008