

ARIC Manuscript Proposal #2225

PC Reviewed: 9/10/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Change in Kidney Filtration Markers and Risk of Kidney Disease, Cardiovascular Disease, and All-Cause Mortality: Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 25 characters): Change in Filtration Markers

2. Writing Group:

Writing group members: Casey Rebholz, Kunihiro Matsushita, Elizabeth Selvin, Morgan Grams, Josef Coresh, others TBD

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

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3. Timeline:

Upon manuscript proposal approval, data analysis will begin. The authors intend to write an abstract based on the results from this proposal to be submitted to American Heart Association - Epidemiology and Prevention / Nutrition, Physical Activity and Metabolism 2014 Scientific Sessions as well as the NHLBI Cardiovascular, Epidemiology, Biostatistics, and Prevention Trainee Session (submission deadline for both meetings: October 14, 2013). The goal is to prepare a draft manuscript by mid-March 2014.

4. Rationale:

There is substantial evidence that lower glomerular filtration rate (GFR) is associated with kidney disease, cardiovascular disease, and all-cause mortality (1-4). Severity of kidney disease is classified primarily based on GFR levels (5). GFR is directly measured after administering an exogenous substance, such as iothalamate, EDTA, diethylene triamine pentaacetic acid, or iohexol, and assessing the plasma or urine clearance of that substance. Due to the difficulty of this procedure, estimation of GFR through measurement of renally-cleared endogenous substances, most often creatinine, has become commonplace (6). However, the use of creatinine as a marker of glomerular filtration is limited by its variability due to non-GFR determinants, such as muscle mass and dietary protein intake (6). Consequently, alternative markers of kidney filtration have been proposed (7).

There is considerable interest in alternative kidney function markers for clinical and research purposes. The Food and Drug Administration and National Kidney Foundation have sponsored a large project to evaluate the prognostic ability of changes in kidney function markers. Recently, several publications have reported an association between change in estimates of GFR and kidney disease outcomes, cardiovascular disease, and mortality (8-10). Cystatin C and β_2 -microglobulin may be useful as alternative markers of kidney filtration since these markers have been shown to be strongly associated with kidney outcomes, cardiovascular disease and overall mortality, perhaps even more so than creatinine-based eGFR (11-14). However, the relationship between change in these novel kidney filtration markers and adverse outcomes is not well known.

We propose to estimate the association between six-year change in cystatin C and β_2 -microglobulin and risk of adverse outcomes (chronic kidney disease, end-stage renal disease, acute kidney injury, cardiovascular disease, and all-cause mortality) during 10-12 years of follow-up among ARIC study participants. We will relate the main findings to estimates of association for change in creatinine and eGFR and adverse outcomes.

5. Main Hypothesis/Study Questions:

1. Changes in kidney filtration markers (cystatin C, β_2 -microglobulin, creatinine and eGFR) over a 6-year period will be independently associated with increased risk of adverse outcomes (chronic kidney disease, end-stage renal disease, acute kidney injury, cardiovascular disease, and all-cause mortality).
2. The relative hazard of future adverse outcomes will be greater for changes in novel kidney filtration markers (cystatin C, β_2 -microglobulin) than a similar change in eGFR since the latter is blunted by muscle loss.

Secondary analyses will examine albuminuria.

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).

Study Design: Prospective cohort study

Inclusion/Exclusion

The study population will include ARIC study participants with measured values for cystatin C, β_2 -microglobulin, and creatinine at study visit 2 (1990-1992, baseline) as well as study visit 4 (1996-1998).

Exposure

The primary exposure of interest is change in circulating levels of cystatin C and β_2 -microglobulin between visit 2 (1990-1992) and visit 4 (1996-1998). For comparison purposes, we will also assess change in creatinine and estimated glomerular filtration rate (eGFR). eGFR will be calculated using creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation (15). Cystatin C, β_2 -microglobulin, and creatinine values will be standardized and calibrated according to the recommendations from the recent calibration study.

Change will be operationalized as the absolute difference (visit 4 – visit 2), percent change ((visit 4 – visit 2) / visit 2), and change in tertiles, focusing on the highest tertile vs. lower two tertiles (no change – remained low, no change – remained high, increased, decreased). Categories of change in tertiles are detailed in the table below.

Tertile of Marker Level at Time 1	Tertile of Marker Level at Time 2	Change Category
Tertile 1-2	Tertile 1-2	No change – remained low
Tertile 1-2	Tertile 3	Increased
Tertile 3	Tertile 3	No change – remained high
Tertile 3	Tertile 1-2	Decreased

Outcome

Outcomes will be assessed after study visit 4. The adverse outcomes of interest are as follows:

- 1) incident chronic kidney disease,
- 2) incident end-stage renal disease,
- 3) incident acute kidney injury,
- 4) cardiovascular disease,
- 5) all-cause mortality, and
- 6) incident albuminuria (sensitivity analysis).

Incident chronic kidney disease will be defined as eGFR <60 mL/min/1.73 m² at study visit 5 (2011-2013) and eGFR decline of at least 25% from study visit 4 to study visit 5. Incident end-stage renal disease will be defined by entry into the U.S. Renal Data System (USRDS) registry, which is current through September 30, 2011. Incident acute kidney injury is defined as a hospitalization or death with the ICD-9-CM code 584.X (ICD-10-CM code N17.x) in any position. Cardiovascular disease will include coronary heart disease (hospitalizations for definite/probable myocardial infarction and cardiac procedures including angioplasty/stenting and coronary artery bypass grafting; and deaths

from coronary heart disease), stroke (fatal and non-fatal ischemic stroke), and heart failure (heart failure-related hospitalizations and deaths). All-cause mortality will be defined as death from any cause identified after visit 4 through active surveillance of the National Death Index, state death records, local newspaper obituaries, and hospital discharge status and by annual follow-up phone interview with a proxy. For defining acute kidney injury, cardiovascular disease, and all-cause mortality, we will use the most recent ARIC surveillance dataset for hospitalizations and deaths (currently updated through December 31, 2010).

In a secondary analysis, incident albuminuria will be the outcome variable, defined as moderately-severely increased albuminuria at study visit 5 (≥ 30 mg/g) among those with normal-mildly increased albuminuria (< 30 mg/g) at study visit 4.

Other Variables

Age at visit 2 will be used to calculate visit 2 eGFR, and age at visit 4 will be used to calculate visit 4 eGFR. Sex and race will also be incorporated into the eGFR calculations. To assess the independent effect of kidney filtration markers on kidney disease risk, we will build several multivariate models. In the adjustment for first measurement model, we will include the kidney filtration markers measured at visit 2, as well as the demographic characteristics (age, sex, race) measured at visit 2 and risk factors measured at visit 2, and will be included. Likewise, for the adjustment for last measurement model, we will include the visit 4 kidney filtration markers as well as visit 4 demographics and visit 4 risk factors. The risk factors include body mass index, systolic blood pressure, anti-hypertensive medication use, diabetes status, total and high-density lipoprotein cholesterol, history of coronary heart disease and heart failure, and smoking status.

Data Analysis

First, we will describe change in cystatin C and β_2 -microglobulin for the overall population using measures of central tendency and variation for absolute and percent change, and frequencies and proportions for categorical change. We will compare change estimates and baseline covariates using analysis of variance and χ^2 tests. Cox proportional hazard regression models will be run to estimate the association between change in cystatin C and β_2 -microglobulin and incident end-stage renal disease, incident acute kidney injury, cardiovascular disease, and all-cause mortality. A competing risk regression analysis will be conducted to assess the impact of death and loss-to-follow-up on risk estimation. We will use logistic regression models to estimate risk of chronic kidney disease and albuminuria. Model 1 will be unadjusted. Model 2 will be adjusted for demographic characteristics (age, sex, race). Model 3 will adjust for risk factors in addition to demographic characteristics. Model 4 will adjust for first measurement of kidney filtration markers (visit 2) along with the corresponding visit 2 demographics and risk factors. Model 5 will adjust for last measurement of kidney filtration markers (visit 4) along with the corresponding visit 4 demographics and risk factors. These analyses will be repeated using change in creatinine and eGFR. As a sensitivity analysis, we will stratify the population by prevalent chronic kidney disease at baseline (eGFR < 60 mL/min/1.73 m²).

Limitations

We recognize that there will be informative censoring, particularly for the assessment of incident chronic kidney disease and incident albuminuria at study visit 5, since the definition requires follow-up study visit attendance and the period between study visit 4 (1996-1998) and study visit 5 (2011-2013) is particularly lengthy. There may also be informative censoring during the period between study visit 2 and study visit 4. For this reason, we will utilize an additional kidney disease outcome (end-stage renal disease) that does not require follow-up study visit attendance. In addition, we will perform a competing risk regression analysis.

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 ICTDER 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

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)?

#2202 – Novel kidney filtration markers and incident sudden cardiac death: the Atherosclerosis Risk in Communities (ARIC) Study – Takeki Suzuki, Kunihiro Matsushita, Sunil Agarwal, Morgan Grams, Elizabeth Selvin, Hugh Calkins, Josef Coresh

#1944 – Risk factors for acute kidney injury – Morgan Grams, Josef Coresh, W.H. Linda Kao, Mara McAdams-DeMarco, Kunihiro Matsushita

#2183 – Progression of CKD focusing on kidney function – Josef Coresh, Kunihiro Matsushita, Yingying Sang, Mark Woodward, Morgan Grams, Shoshana Ballew

#1574 – Comparison of novel markers of kidney function and prediction of cardiovascular events, mortality, and kidney failure: the Atherosclerosis Risk in Communities (ARIC) Study – Brad Astor, Josef Coresh, Christie Ballantyne, Ron Hoogeveen

#1581 – Novel markers of kidney function and prediction of incident chronic kidney disease and end-stage renal disease: the Atherosclerosis Risk in Communities (ARIC) Study – Brad Astor, Nrupen Bhavsar, Josef Coresh, Christie Ballantyne, Ron Hoogeveen

#1395 – Change in kidney function and coronary heart disease, stroke, and all-cause mortality: the Atherosclerosis Risk in Communities (ARIC) study – Kunihiro Matsushita, Elizabeth Selvin, Lori Bash, Brad Astor, Josef Coresh

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* 2009.16, 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/>

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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2. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney international*. 2011;80(1):93-104.
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4. van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney international*. 2011;79(12):1341-52.
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6. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. *The New England journal of medicine*. 2006;354(23):2473-83.
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