ARIC Manuscript Proposal #1972

PC Reviewed: 7/10/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The association of kidney disease measures with left ventricular and atrial structure and function: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): **Kidney & left cardiac echo**

2. Writing Group:

Writing group members: Kunihiro Matsushita, Amil M. Shah, Hicham Skali, Josef Coresh, Scott D. Solomon, Others welcome

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

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3. Timeline: Analysis will begin following proposal approval and completion of visit 5 data collection (anticipated in 2013). A manuscript will be completed within 6 months after receiving necessary data for this proposal.

4. Rationale:

Chronic kidney disease (CKD), kidney damage or reduced kidney function, is a major global public health problem.[1, 2] CKD affects one to two out of ten adults in the world[3-6] and is an independent predictor of adverse outcomes including cardiac disease.[7, 8] Of note, individuals with CKD are more likely to die due to cardiac disease before they reach end-stage renal disease (ESRD).[9] Therefore, prevention and management strategy for heart

disease in CKD patients is clinically important, and better understanding of pathophysiological link between the kidney and the heart would create basis for establishing that strategy.

To elucidate cardiac manifestation due to kidney disease, several clinical and epidemiological studies have assessed the association between kidney disease measures and cardiac structure and function.[10-19] However, most of these studies have focused on structure (particularly left ventricular hypertrophy), did not evaluate function (diastolic function is particularly understudied), investigated selected population with hypertension, diabetes, and/or ESRD, and include a small number of participants (often n<1000). Thus, a comprehensive examination for two key kidney measures, glomerular filtration rate (GFR) and albuminuria, and both cardiac structure and function (systolic and diastolic) in a large sample from the general population with broad range of kidney function is needed.

Echocardiography in the fifth visit of the Atherosclerosis Risk in Communities (ARIC) Study, therefore, provides an excellent opportunity to assess the associations of estimated GFR and albuminuria with cardiac structure and function including state-of-art indices in a bi-ethnic community-based population with ~9000 individuals. This proposal will focus on structure and function of the left-sided heart, and a separate proposal led by Dr. Hicham will focus on the right-sided heart and measures of pulmonary circulation in the context of kidney dysfunction/damage.

5. Main Hypothesis/Study Questions:

1. Kidney disease measures are associated with abnormalities of cardiac structure (e.g., left ventricular hypertrophy and left ventricular/atrial dilation)
2. Kidney disease measures are associated with abnormalities of cardiac function (e.g., systolic and diastolic function)

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).

Inclusions:

- All black and white ARIC subjects with data of kidney disease measures (serum creatinine and cystatin C and urinary albumin) and echocardiography at visit 5

Exclusions:

-Ethnicity other than black or white

-Missing data on kidney disease measures and echocardiography

Exposure (independent variables):

-estimated GFR (eGFR)

eGFR will be calculated using the recently proposed CKD-EPI equation[20] incorporating data of serum creatinine concentration, age, gender, and race at visit 5 and measured in ml/min/1.73 m^2. We will also evaluate the consistency of our results by using eGFR incorporating age, gender, race, serum creatinine and cystatin C[21].

-albuminuria

As recommended in clinical guidelines,[2] urinary albumin-to-creatinine ratio (ACR) will be used as a measure of albuminuria.

Outcome (dependent variables):

-Echocardiographic variables

- Left-sided cardiac structure: left ventricular mass, relative wall thickness, left ventricular diameter/volume, left atrial diameter/volume (we will use values of these parameters indexed to body size)
- Left-sided systolic function: ejection fraction, fraction shortening, tissue Doppler mitral annular peak systolic velocity (TDI S')
- Left-sided diastolic function: E wave, A wave, E/A, E wave deceleration time, tissue Doppler imaging (TDI) E', E/E', left atrial volume

Other variables of interest and covariates:

-Sociodemographics: age, race, gender, education level
-Physical information: body mass index, waist circumference, blood pressure
-Lifestyle: smoking status, alcohol habit, and physical activity
-Comorbidities: obesity, dyslipidemia, diabetes, hypertension, and history of coronary heart disease, stroke, and heart failure

Statistical Analysis Plan:

The primary analysis will use linear regression models to quantify the association between kidney disease measures and echocardiographic measures. eGFR and ACR will be treated as continuous variables with splines and categorical variables based on clinical categories (eGFR: <15, 15-29, 30-44, 45-59, 60-89, and 90+ ml/min/1.73m^2 and ACR: <30, 30-299, and 300+ mg/g) in the models. We will adjust for the covariates listed above. We will test interaction of these kidney measures on the associations with echo parameters. We will repeat the analysis after stratifying the study sample by age, gender, race, and presence/absence of comorbidities such as obesity and diabetes. For echocardiographic variables with clinical cutoff points (ejection fraction), we will also run logistic regression models with dichotomized dependent variables.

We will conduct a few sensitivity analyses. Firstly, to evaluate the impact of extreme values, we will exclude individuals with CKD stage 5 (eGFR <15) or ESRD at visit 5. Secondly, we will exclude individuals with history of coronary heart disease and heart failure. Thirdly, we will exclude individuals with moderate or greater mitral or aortic valve disease. Finally, we will exclude participants who are taking medications that can affect kidney measures and cardiac load/function, such as renin angiotensin system inhibitors and diuretics.

Limitations:

A cross-sectional design will not allow us to evaluate causality of the associations. As with any observational study, we will not be able to rule out the possibility of residual confounding. A single measurement of kidney measures is an additional limitation.

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

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)?
863: Brad Astor, Josef Coresh, Donna K. Arnett, Andy Brown. The risk of left ventricular hypertrophy associated with moderate kidney dysfunction and anemia among African Americans

#954: Brad Astor, Josef Coresh, Donna K. Arnett. Electrocardiographic left ventricular growth associated with anemia and moderate kidney dysfunction

#1917: Shah AM, Ballantyne C, Kitzman D, Fox E, Butler K, Matsushita K, Konety S, Solomon SD. Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community – A preliminary analysis from the ARIC study.

The most relevant proposal in terms of study question would be #863. However, this proposal used echocardiography obtained at Jackson at visit 3.

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/

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.cscc.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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