ARIC Manuscript Proposal #4016

PC Reviewed: 3/8/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Association of Left Atrial Function with the Risk of Chronic Kidney Disease in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study.

b. Abbreviated Title (Length 26 characters): LA function and CKD risk

2. Writing Group: Jorge Reyes,* Abayomi Oyenuga,* Anne Eaton, Wendy Wang, Romil Parikh, Riccardo M. Inciardi, Alvaro Alonso, Charles Herzog, Junichi Ishigami, Kunihiro Matsushita, Josef Coresh, Amil M. Shah, Scott D. Solomon, Lin Yee Chen, and others welcome

*both will contribute equally to the paper

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

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3. Timeline:
Data collection for the present study has been already completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Chronic kidney disease (CKD) is associated with a higher risk of cardiovascular diseases such as coronary heart disease, heart failure, atrial fibrillation, and peripheral artery disease.[1,2] Current literature indicates a bidirectional relationship between CKD and cardiovascular disease and the spectrum of cardiorenal syndrome provides a clear example of how acute or chronic dysfunction in one organ might lead to acute or chronic dysfunction in the other.[3] Although the mechanisms underpinning the effects of subclinical cardiovascular disease on worsening kidney function are not completely understood, growing evidence suggests a complex multifactorial process that includes neurohormonal changes in the renin angiotensin system, endothelial dysfunction, and inflammatory processes.[4,5]

Additionally, previous epidemiological studies have reported that greater left ventricular mass, higher pulmonary artery pressure, and lower right ventricular systolic function, as measured by transthoracic echocardiography (2D echo), are associated with greater decline in kidney function.[6-9] However, data on the association of left atrial (LA) size and function with change in kidney function or incident CKD are limited.[9,10] One study of patients with residual kidney function on peritoneal dialysis found that a greater LA size was associated with worsening kidney function.[8] A more recent study of patients free of diabetes, heart failure and chronic kidney disease showed that a poor LA expansion index (a marker of LA function) was associated with worsening kidney function.[11]

Emerging data suggest that lower (worse) LA function, as measured by 2D echo, is associated with a higher risk of adverse health outcomes including atrial fibrillation, ischemic cerebrovascular events, and death, independent of LA size.[12-15] To date, the association between LA function and risk of adverse kidney outcomes has not been reported. Therefore, the ARIC study is well suited to assess the relationship between LA function and risk of adverse kidney outcomes such as incident chronic kidney disease (CKD), incident end-stage kidney disease (ESKD), and CKD progression. At visit 5 (2011-2013), participants underwent 2D-echocardiograms with speckle tracking, which enabled the measurement of LA function by strain analysis. Therefore, we will evaluate the prospective association between LA function measures and adverse kidney outcomes in the ARIC study.

5. Main Hypothesis/Study Questions:

Aim: Evaluate the association of 2D echo measures of LA function at Visit 5 with CKD outcomes.

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 from visit 5 to visit 6 and 7.

Inclusion/Exclusion:

Inclusion:

Our analytic sample will include all ARIC participants who attended visit 5 and who have LA strain measures.

Exclusion:

-Participants who reported race other than Black or White or non-White participants at the Minneapolis and Forsyth County field centers due to low numbers
-eGFR <60/ml/min/1.73m^2 for the primary outcome of incident CKD
-eGFR <15 ml/min/1.73m^2 for the secondary outcome of incident ESKD
-Those missing covariates

Variables:

Exposures: The following LA function measures (obtained at visit 5) will be assessed continuously (per 1-SD) and also as quintiles (highest quintile as referent)

1. LA reservoir strain
2. LA contractile strain
3. LA conduit strain

Exploratory exposures:

1. LA minimum volume index (LAVi min)
2. LA emptying fraction (LAEF)
3. LA maximum volume index (LAVi max)

Primary outcome:

1. The primary outcome of interest is incident CKD which is defined as a composite of developing eGFR <60 ml/min/1.73m$^{2.}$ accompanied by at least 25% decline from baseline visit 5, end-stage kidney disease identified through the USRDS or hospitalizations or deaths with the ICD 9-10[16]

Secondary outcomes:

1. Incident ESKD using data from USRDS (with or without death due to CKD)
2. eGFR decline between visit 5 and visit 6 and 7

Exploratory outcomes:

1. Incident albumin creatine ratio (ACR) ≥30 mg at visit 6 or 7

Other confounders/covariates (obtained from visit 5): age, sex, race/center, education (from visit 1), body mass index (BMI), smoking status, CKD measures (eGFR, urinary albumin to creatinine ratio [ACR]), systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1C, use of antidiabetic medications, stroke, coronary heart disease, heart failure, atrial fibrillation, peripheral artery disease, LAVi min, LAVi Max, LAEF,, left ventricular (LV) ejection fraction, E/e', LV mass index, and antihypertensive medications..

Additional variables of interest:

- All-cause mortality
- Incident CVD: defined as a composite variable consisting of incident stroke, coronary heart disease (CHD), or heart failure (HF) at visits 6 or 7
- Incident diabetes at visit 6 or visit 7

Statistical analysis:

Baseline characteristics will be described using mean ± SD for continuous variables and proportions for categorical variables.

-Poisson regression models will be used to estimate incidence rate and 95% confidence intervals for our primary and secondary binary outcomes

-Cox proportional hazard models will be used to estimate hazard ratios and 95% confidence intervals for our primary and secondary binary outcomes

- Multiple linear regression models will be used to estimate the rate of decline of eGFR between visit 5, 6, and 7

-For all analyses, the following models will be used:

- Model 1 will be adjusted for baseline egfr, age, sex, race/center, education
- Model 2 will be adjusted for model 1 plus BMI, smoking status, SBP, DBP, stroke, CHD, HF, atrial fibrillation, peripheral artery disease, HbA1C, use of antidiabetic medications, and use of antihypertensive medications
- Model 3 will be adjusted for model 2 plus LV ejection fraction, E/e', LV mass index
- Model 4 will be model 3 plus LA volume

-Sensitivity analysis: separately, adjusting for incident diabetes and incident CVD as a time-varying covariate.

-We will test effect modification by sex, age (dichotomized using the median as the cut-off), race/center, prevalent CVD, and ACR (<30 vs ≥30 mg/g).

- For our secondary outcome of incident ESKD, we will conduct a competing risk analysis with all-cause mortality

- Models will be fit to explore the effects of LAVi min, LAVi Max, and LAEF. We will compare the associations of these LA measures to those from the measures of LA strain

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

7b. 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.)

8a. Will the DNA data be used in this manuscript? ____ Yes _X_ No

8b. 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/mantrack/maintain/search/dtSearch.html

__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)?

MP#1972 The association of kidney disease measures with left ventricular and atrial structure and function: The Atherosclerosis Risk in Communities (ARIC) Study.

MP#3529 Echocardiographic parameters and subsequent risk of chronic kidney disease

(CKD). Ishigami et al.

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

11b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* (Chen, 2015.29). **_____) ___**

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 https://www2.cscc.unc.edu/aric/approved-ancillary studies

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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