ARIC Manuscript Proposal #3795

PC Reviewed: 3/9/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Proteomic Measures Linking Kidney Disease to Heart Failure and Adverse Cardiac Remodeling in Late-Life: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Mediators of Heart-Kidney Disease

2. Writing Group:

Writing group members: Leo Buckley, Amil Shah, Pranav Dorbala, Bing Yu, Brian Claggett, Morgan Grams, Josef Coresh, Kunihiro Matsushita, Ryan Demmer, Christie Ballantyne, Ron Hoogeveen [Others Welcome]

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. *LFB* **[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 will begin statistical analysis after manuscript proposal approval. We expect to complete analysis within 3-4 months of the manuscript approval date (April/May 2021). We anticipate submitting an abstract for presentation at the American Heart Association Scientific Sessions by June 2021, and the manuscript for publication in September 2021.

4. Rationale:

Kidney dysfunction and damage are independent predictors of heart failure with reduced and preserved left ventricular ejection fraction[1,2]. Moreover, kidney dysfunction and damage are

independently associated with alterations in cardiac structure and function.[3,4] While traditional cardiovascular risk factors, such as hypertension and diabetes, are known to contribute incident heart failure and incident kidney disease, the mechanisms linking kidney disease to heart failure and adverse cardiac remodeling are not completely understood.[5]

Kidney dysfunction and damage significantly alter the circulating proteome.[6] Proteins with molecular weights less than 50 kDa are filtered through the glomeruli and thus their circulating concentrations may be elevated as a result of reduced glomerular filtration rate. Conversely, impaired kidney synthetic function may lead to decreased concentrations of some other proteins, thus resulting in lower circulating protein concentrations at reduced glomerular filtration rates.

The extent to which proteomic markers associated with kidney dysfunction and damage relate to incident heart failure and cardiac structure and function remains incompletely understood. Among a panel of 196 previously identified protein biomarkers of cardiovascular disease, Yang et al. found that adjustment for estimated glomerular filtration rate eliminated the association with cardiovascular disease for 109 (66%) proteins.[7] Additionally, these authors identified 8 proteins that predicted cardiovascular disease only among patients with chronic kidney disease. This study utilized the 1K Somalogic platform to measure proteins in 937 patients with established coronary artery disease.

We propose to leverage the unique availability of detailed clinical data including renal function and damage, longitudinal echocardiographic data, adjudicated heart failure events, and aptamer-based proteomics (Somalogic Somascan 4.0 assay) in ARIC to identify kidney function/damage-associated circulating proteins and protein networks that associate independently with heart failure risk and adverse cardiac remodeling in late-life. Since the prevalence of heart failure and kidney disease increases in late-life, this analysis focuses on ARIC Visit 5 (mean age of 76 years).

5. Main Hypothesis/Study Questions:

Our overall hypothesis is that kidney function/damage-associated circulating proteins and protein networks will associate with incident heart failure and adverse cardiac remodeling in late-life, and will identify molecular pathways relating renal dysfunction to heart failure risk in late-life.

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).

This study will use clinical covariates, kidney function and damage measures, and aptamer-based proteomics measurements from Visit 5, adjudicated heart failure events after Visit 5 (including reduced vs. preserved ejection fraction), and echocardiographic data from Visits 5 and 7.

Aim 1: To estimate the association of kidney function- and damage-associated circulating proteins with incident heart failure and heart failure with reduced and preserved ejection fraction

- Population:

    - Aim 1 will include all participants who were free from heart failure through Visit 5 and had available exposure measurements at Visit 5.
- Exposures:
    - The exposures for Aim 1 will include proteins that significantly associate with kidney damage (urine albumin-creatinine ratio [UACR]) and dysfunction (CKD-EPI serum creatinine and cystatin C estimated glomerular filtration rate) at Visit 5. Proteins associated with UACR and eGFR will be identified using multivariable linear regression with statistical significance defined using Bonferroni correction for multiple testing. Models will adjust for demographics and standard HF risk factors assessed at Visit 5. Additional analyses will employ LASSO regularized regression with an initial Bonferroni filter.
- Outcomes:
    - Incident adjudicated heart failure
    - Incident adjudicated heart failure or death
    - Incident adjudicated heart failure with reduced ejection fraction
    - Incident adjudicated heart failure with preserved ejection fraction
    - Sensitivity analysis with incident adjudicated heart failure with reduced or unknown ejection fraction and incident adjudicated heart failure with preserved or unknown ejection fraction
- Analysis:
    - We will use Cox proportional hazards regression models to estimate the association of kidney-related protein biomarkers (derived as above) with incident heart failure outcomes. We will sequentially adjust regression models for Visit 5 demographic characteristics (model 1: age, sex, race/ethnicity and field center), clinical characteristics (model 2: coronary artery disease, smoking, diabetes mellitus, hypertension, smoking) and other risk factors (BMI and NTproBNP). Additional analyses will employ LASSO regularized regression with an initial Bonferroni filter.
    - We will test key assumptions of the linear and Cox proportional hazards regression models and adjust (e.g., time-dependent covariates, stratify cohort) as appropriate. We will assess non-linearity using restricted cubic splines. We will conduct sensitivity analyses using inverse probability of attrition weights to account for non-random non-attendance. We will repeat analyses with censoring after incident myocardial infarction. We will conduct separate analyses according to age, gender, race/ethnicity and prevalent CVD subgroups.

Aim 2: To estimate the association of kidney function- and damage-associated circulating proteins with alterations in cardiac structure and function

- Population:
    - Aim 2A will include all participants who were free from heart failure through Visit 5, had available exposure measurements at Visit 5 and underwent transthoracic echocardiography at Visit 5.
    - Aim 2B will include all participants who were free from heart failure through Visit 7, had available exposure measurements at Visit 5 and underwent transthoracic echocardiography at Visits 5 and 7.
- Exposures:

    - As in Aim 1
- Outcomes:
    - Aim 2A: Visit 5 cardiac structure and function (cross-sectional)
    - Aim 2B: Change in cardiac structure and function from Visit 5 to Visit 7
    - Specific echocardiographic parameters of interest are listed below.
- Analysis:
    - We will use linear regression to model the cross-sectional association of each protein exposure with Visit 5 cardiac structure and function (Aim 2A) and to model the association of each protein exposure with change in cardiac structure and function from Visit 5 to Visit 7 (Aim 2B). All models will be adjusted for systolic blood pressure and heart rate at Visit 5 (Aims 2A and 2B) and Visit 7 (Aim 2B). Additional additive models will adjust for Visit 5 demographic characteristics (model 1: age, sex, race/ethnicity and field center), clinical characteristics (model 2: coronary artery disease, smoking, diabetes mellitus, hypertension, smoking) and other risk factors (BMI and NTproBNP).
    - We will test key assumptions of the linear regression model and adjust appropriately. We will assess non-linearity with restricted cubic splines. We will use inverse probability of attrition weights to adjust for non-random non-attendance at Visits 5 and 7. We will conduct separate analyses according to age, gender, race/ethnicity and prevalent CVD subgroups

Additional Statistical Analysis: Continuous and categorical data will be summarized using means and standard deviations, medians and interquartile ranges and numbers and percentages, respectively.

Echocardiographic Parameters of Interest: Echocardiographic measures of cardiac structure and function (1) at Visit 5; and (2) their change from Visits 5 to 7. Primary measures of interest will be those reflective of LV structure (left ventricular wall thickness, dimensions, mass, RWT), LV diastolic function (E wave, e', E/e', LA diameter, LA volume index), left ventricular systolic function (LVEF, longitudinal strain, circumferential strain), PASP, RV measures (area, fractional area change, tricuspid annular s').

Limitations: There are certain limitations to this analysis. We cannot exclude reverse causality between kidney disease and protein biomarker measurements at Visit 5. Missing LVEF data from time of incident heart failure hospitalization will reduce the number of classifiable HFpEF and HFrEF events. We will perform sensitivity analysis by assigning all incident HF cases with missing LVEF as either HFpEF or HFrEF and re-evaluating our models. Non-random non-attendance at Visits 5 and 7 due to survivor bias and attendance bias may bias the results of our echocardiographic analyses towards the null since we expect Visit 5 and 7 non-attendees to be at higher risk of adverse remodeling and to have more severe CKD than attendees. We will adjust for non-random non-attendance using inverse probability of attrition weights. It is possible that HFpEF cases were underreported or other conditions were misclassified as HFpEF due to the challenges associated with diagnosing this condition. We do not expect the number of misclassified cases to alter our estimates since all events have been adjudicated by an independent committee according to standardized definitions. Regardless, underreporting of

HFpEF cases may bias estimates towards the null. Absolute quantification of protein biomarkers is not provided.

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 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 _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/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)?

1. Zhi Yu, Christie Ballantyne, Ron Hoogeveen, Bing Yu, Josef Coresh, et al: Proteomic Profiling and Kidney Function in the Atherosclerosis Risk in Communities (ARIC) Study (#3497)
2. Morgan Grams, Bing Yu, Christie Ballantyne, Josef Coresh, et al: Proteomics and kidney disease in a community-based population (#3533)
3. Bing Yu, Brian Claggett, Ron Hoogeveen, Kuni Matsushita, Christie Ballantyne, Josef Coresh, Amil Shah, et al: Proteomic profiling and heart failure risk in the ARIC Study (#3389)
4. Amil Shah, Brian Claggett, Ron Hoogeveen, Kuni Matsushita, Christie Ballantyne, Josef Coresh, Bing Yu, et al. Proteomic profiling and cardiac structure and function in the ARIC study (#3539)
5. Michael Zhang, Christie Ballantyne, Josef Coresh, Bing Yu, Amil Shah, et al. Association of proteomic markers with left atrial function in the elderly (#3555)

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* 2015.34; 2017.27, 2018.19, 2019.03, 2019.10)

___ 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.

The writing group agrees to complete the manuscript within this timeframe.

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.

The writing group agrees to upload the manuscript to PubMed Central.

References

1. Bansal N, Zelnick L, Bhat Z, et al. Burden and Outcomes of Heart Failure Hospitalizations in Adults With Chronic Kidney Disease. *Journal of the American College of Cardiology.* 2019;73(21):2691-2700.
2. Matsushita K, Coresh J, Sang Y, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: A collaborative meta-analysis of individual participant data. *The Lancet Diabetes and Endocrinology.* 2015;3(7):514-525.
3. Matsushita K, Kwak L, Sang Y, et al. Kidney Disease Measures and Left Ventricular Structure and Function: The Atherosclerosis Risk in Communities Study. *Journal of the American Heart Association.* 2017;6(9):e006259.
4. Park M, Hsu CY, Li Y, et al. Associations between kidney function and subclinical cardiac abnormalities in CKD. *Journal of the American Society of Nephrology.* 2012;23(10):1725-1734.
5. Wang X, Shapiro JI. Evolving concepts in the pathogenesis of uraemic cardiomyopathy. *Nature reviews Nephrology.* 2019;15(3):159-175.
6. Christensson A, Ash JA, DeLisle RK, et al. The Impact of the Glomerular Filtration Rate on the Human Plasma Proteome. *Proteomics Clin Appl.* 2018;12(3):e1700067.
7. Yang J, Brody EN, Murthy AC, et al. Impact of Kidney Function on the Blood Proteome and on Protein Cardiovascular Risk Biomarkers in Patients With Stable Coronary Heart Disease. *J Am Heart Assoc.* 2020;9(15):e016463.