ARIC Manuscript Proposal #4043

PC Reviewed: 5/17/22	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Proteomics and incident atrial fibrillation among individuals with chronic kidney disease: A validation analysis

b. Abbreviated Title (Length 26 characters): Proteomics and incident atrial fibrillation in CKD

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ RD___ **[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: Analysis will begin upon receipt of the data and approval of the manuscript proposal. Manuscript will be written and submitted for ARIC Publications Committee review within one year of manuscript proposal approval.

4. Rationale:

As part of a large collaboration in the Chronic Kidney Disease Biomarkers Consortium and the field of aptamer-based proteomics, our research group has been working closely with investigators from the Chronic Renal Insufficiency Cohort (CRIC) Study to understand proteomic risk prediction for cardiorenal disease in participants with chronic kidney disease (CKD). Recently, using large-scale, aptamer-based proteomics, investigators from the CRIC study have developed proteomic risk models for incident atrial fibrillation among individuals with CKD. The protein and clinical models will be transferred from the University of

Pennsylvania's Biostatistics group to our research team, and we hope to validate them in the ARIC subset of individuals with CKD. In additional analysis, we will evaluate the list of proteins from CRIC that are independently associated with incident atrial fibrillation after multivariable analysis. Specifically, we will "look-up" these proteins and their hazard ratios for associations with incident AF.

ARIC has evaluated proteomics across multiple study visits using the same version of the SomaScan platform. The development of the SomaScan proteomics assay affords the opportunity to screen nearly 5000 soluble plasma proteins in search of novel, potentially modifiable risk factors.

Developing novel models of cardiorenal risk in CKD patients remains a research priority. Multiple studies have demonstrated the strong, independent associations between chronic kidney disease (CKD) and the development of atrial fibrillation (AF).[1-5] Many of these studies have also demonstrated that the combination of CKD and AF leads to a higher risk of thromboembolic complications and heart failure than either condition alone. Unfortunately, clinical prediction models such as the CHARGE-AF risk score are limited to the general population and are not specific to CKD patients.[6]

In this manuscript, we hypothesize that large-scale proteomics will identify novel biological markers that are associated and predictive of incident atrial fibrillation in individuals with CKD. We also hypothesize that proteomic models will be superior to clinical models for predicting AF.

5. Main Hypothesis/Study Questions:

Aim 1: Among participants with chronic kidney disease, we aim to evaluate prediction measures of proteomic risk models, which were derived in the CRIC study, for incident atrial fibrillation.

Aim 2: Among participants with chronic kidney disease, we aim to evaluate prediction measures of clinical risk models (CHARGE AF) for incident atrial fibrillation.

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: We will conduct a prospective analysis of the ARIC cohort. Since our proteomic and clinical risk model are evaluating incident AF outcomes over 5 years, we will use study visit 3 and visit 5 as baseline. We will have follow-up through December 31, 2019.

Study Population: The study population will include all members of the ARIC cohort with available SOMAscan data, consent to participate in cardiovascular research, and eGFRcrcys<60 ml/min per 1.73 m^2 at visit 3 or visit 5. The analysis will exclude those with a history of atrial fibrillation. Further, the analysis will exclude those with ESKD at the study visit.

Exposure: We will use select protein levels as the primary predictor. Proteins will be scaled to the median absolute deviation (MAD) and centered on the median of the training (CRIC) dataset, with outliers > 5 MAD units removed.

Outcomes:

The main outcome is incident AF. Incident AF will be evaluated over a 5-year time horizon.

Statistical Analysis:

Baseline characteristics of the study sample will be tabulated for each of the aims. Characteristics of interest include age, sex, race, study center, systolic blood pressure, diastolic blood pressure, diabetes, hypertension, anti-hypertension treatment, height, weight, current smoking, total cholesterol, HDL, eGFR, and albuminuria. We will also assess for any history of heart failure, coronary heart disease / MI, or stroke. We will also assess electrocardiographic features including the PR interval and left ventricular hypertrophy (by electrocardiogram) obtained from the ECG corresponding to the time of proteomic measurements.

We will test the models for incident AF using the proteomics (17 proteins) and CHARGE-AF risk scores (simple and augmented) in the respective study sample. Harrel's C-statistics will be used to evaluate the discrimination of the models, and calibration will be evaluated by plotting the observed vs. predicted risk by quintile of predicted risk in each study population. We will use the Greenwood-Nam-D'Agostino test to tet for significant deviations.

Limitations:

SOMAscan provides aptamer levels, which may not perfectly correlate with protein levels. The absolute risk of outcomes may differ substantially between CRIC and ARIC, which can affect calibration.

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/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)?

ARIC Manuscript Proposal #3533: Proteomics and CKD (Grams)
ARIC Manuscript Proposal #3389: Proteomic Profiling and Heart Failure Risk in the Atherosclerosis Risk in Communities (ARIC) Study (Yu)
MS #3398 Proteomics and the risk of AF in the elderly (Norby)
MS #3555 Association of plasma proteomic markes with LA function (Zhang / Chen)
MS #3905 Changes in proteomic levels and risk of AF (Misialek / Lutsey)

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
___ 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

REFERENCES

1. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation.* 2009;119(10):1363-1369.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation.* 2014;129(3):e28-e292.
3. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med.* 2012;367(7):625-635.
4. Nelson SE, Shroff GR, Li S, Herzog CA. Impact of chronic kidney disease on risk of incident atrial fibrillation and subsequent survival in medicare patients. *Journal of the American Heart Association.* 2012;1(4):e002097.
5. Alonso A, Lopez FL, Matsushita K, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation.* 2011;123(25):2946-2953.
6. Alonso A, Roetker NS, Soliman EZ, Chen LY, Greenland P, Heckbert SR. Prediction of Atrial Fibrillation in a Racially Diverse Cohort: The Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of the American Heart Association.* 2016;5(2).