ARIC Manuscript Proposal #3738

PC Reviewed: 11/16/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Proteomics and risk prediction for incident cardiovascular disease, recurrent cardiovascular disease, and chronic kidney disease progression: A validation analysis

b. Abbreviated Title (Length 26 characters): Proteomics and adverse outcomes in CKD

2. Writing Group:
Raj Deo, Peter Ganz, Josef Coresh, Ruth Dubin, Adi Surapaneni, Kuni Matsushita, Bing Yu, Christie Ballantyne, Morgan Grams, *others welcome*

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

First author: RD
Address:

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). Using large-scale, aptamer-based proteomics, investigators from the CRIC study have developed proteomic risk models for a) incident cardiovascular disease; b) recurrent cardiovascular disease; and c) CKD progression. Each of these protein models has been 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. 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. The 20 million Americans with CKD (defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/m^2)[1] suffer high rates of atherosclerotic heart disease, acute myocardial infarction and heart failure that are on average 2-fold higher than persons without CKD and increase with severity of CKD.[5] Studies in both community-based[2-4] and high-risk populations[6-9] have confirmed that CKD and proteinuria confer increased cardiovascular risk. However, little is known about the extent of biologic pathways linking CKD to cardiovascular disease (CVD). While traditional risk factors such as hypertension and diabetes predict adverse cardiovascular outcomes in these patients,[10] non-traditional risk factors involved in inflammation and altered mineral and bone metabolism are also thought to play an important role.[11,12] However, these risk factors and markers do not fully explain the excess risk of CVD among CKD patients. Further, these non-traditional measures of risk do not acceptably predict CVD risk in this population. Finally, many of these risk factors are not modifiable or pharmacologically "druggable" (e.g. age, sex, race, eGFR).

In addition to having high rates of CVD, patients with CKD are at increased risk of developing end-stage kidney disease (ESKD), becoming dependent on dialysis, and suffering from complications leading to poor health including bone disease,[13] frailty,[14] and decreased cognitive function.[15] Preventing the progression of CKD is thus imperative not only to avoid progression to ESKD, but also to avoid these complications of CKD and to maintain quality of life.

5. Main Hypothesis/Study Questions:

Aim 1: To evaluate prediction measures of proteomic risk models, which were derived in the CRIC study, for incident cardiovascular disease.
Aim 2: To evaluate prediction measures of proteomic risk models, which were derived in the CRIC study, for recurrent cardiovascular disease.
Aim 3: To evaluate prediction measures of proteomic risk models, which were derived in the CRIC study, for CKD progression.

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, using study visit 3 as baseline. In secondary analysis, we will use study visit 5 as a baseline, with follow-up through December 31, 2018 (or the most recent surveillance year).

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 for the visit 5 cohort, at visit 5). Incident cardiovascular disease analysis will exclude those with a history of cardiovascular disease (defined as CHD, stroke, or heartfailure) at visit 3. Recurrent CVD analyses will include people with a history of CHD, heart failure, or stroke. All analyses 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 outcomes are incident CVD, recurrent CVD, and incident ESKD. CVD will be defined as the composite of MI, stroke, heart failure and CVD mortality. Incident CVD will be evaluated over a 10-year time horizon. Recurrent CVD will be evaluated over a 5-year time horizon. We will also evaluate individual component outcomes.

Incident ESKD will be defined as the initiation of renal replacement therapy (either dialysis or transplant) and cases will be defined through linkage of the ARIC study with the United States Renal Data System (USRDS) registry. CKD progression will be defined as ESKD, or 50% decline in GFR using subsequent visit data. CKD progression will be evaluated with a 10-year time horizon and over the entire ARIC follow-up.

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, diabtes, hypertension, anti-hypertension treatment, BMI, current smoking, total cholesterol, HDL, eGFR, and albuminuria.

We will test the three developed models for incident CVD (32 proteins), recurrent CVD (19 proteins), and CKD progression (56 proteins) in the respective study samples. 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
ARIC Manuscript Proposal #3389: Proteomic Profiling and Heart Failure Risk in the Atherosclerosis Risk in Communities (ARIC) Study

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* 2017.27, 2013.21)
___ 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.

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4. Shlipak MG, Sarnak MJ, Katz R, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med.* 2005;352(20):2049-2060.
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13. Drueke TB, Massy ZA. Changing bone patterns with progression of chronic kidney disease. *Kidney international.* 2016;89(2):289-302.
14. Walker SR, Brar R, Eng F, et al. Frailty and physical function in chronic kidney disease: the CanFIT study. *Canadian journal of kidney health and disease.* 2015;2:32.
15. Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol.* 2007;18(7):2205-2213.