ARIC Manuscript Proposal #4241

PC Reviewed: 5/09/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Evaluating Associations Between Chronic Kidney Disease (CKD) Progression and Adverse Outcomes in People with the *APOL1* Low-and Higher-Risk Genotype

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Carina Flaherty, Aditya Surapaneni, Josef Coresh, Morgan Grams, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _____ *[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-three years of manuscript proposal approval.

4. Rationale:

Chronic kidney disease affects approximately 10% of the US population and is associated with elevated risk of progression to kidney failure, cardiovascular events, and premature mortality.[1-7] African Americans face nearly four times the lifetime risk of kidney failure compared to Americans of European descent.[8] Some of the excess risk is explained by specific variants in the *APOL1* gene that are common in the populations with African ancestry.[9] Multiple

studies established that two copies of the so-called "kidney risk variants" confer higher risk of kidney failure.[9-11] Compared to African Americans with zero or one copies of these variants, African Americans with two variants have 2-5 fold higher risk of requiring kidney replacement therapy.[12] Approximately 12% of the African American population has two risk variants.

The life expectancy of a patient with kidney failure is lower than that with many types of cancers; thus, preventing progression to kidney failure is of utmost importance. Because kidney failure can take decades to develop, the US Food and Drug Administration has accepted markers of CKD progression as surrogates for kidney failure in clinical trials. Specifically, a 40% decline in eGFR and a comparison of eGFR slopes have been deemed "validated" and change in albuminuria deemed "reasonably likely" surrogate endpoints for kidney failure. In work to inform the US Food and Drug Administration's designation, we showed that these outcomes were robustly associated with subsequent kidney failure and mortality. The link between these markers of CKD progression and other adverse outcomes, such as heart failure and myocardial infarction, is less established, as is the application in patients with and without the *APOL1* kidney risk variants.

5. Main Hypothesis/Study Questions:

1. Are individuals with APOL1 high-risk variants higher risk for surrogate endpoints (30-40% decline in eGFR, increase in albuminuria) compared to individuals without high risk variants?
2. Are surrogate endpoints for ESKD similarly associated with clinical endpoints with and without APOL1 high-risk variants?
3. Are surrogate endpoints for ESKD similarly associated with CVD and death in individuals with and without APOL1 high-risk variants?

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 & Study Population
This study will be a longitudinal study of participants in the ARIC data set. Inclusion criteria for the study will be as follows: Participants must be African American and have had 1) *APOL1* genotyping; 2) GFR measures at least three years apart for the purpose of establishing eGFR decline and slope variables; and 3) follow-up for adverse events in the subsequent time period.

Exposure
eGFR decline and albuminuria stratified by APOL1 susceptibility

Primary Outcome Measures
Our primary outcome measure will be ESKD, CVD and mortality

Secondary Outcome Measures

Our secondary outcome measures will be incidence or composites of subtypes of CVD, particularly heart failure, if power allows. We will also analyze all hospitalizations, if power allows.

Additional Covariates
Additional covariates include Demographics, Medical History (history of CVD, presence of hypertension, diabetes, smoking status), glucose levels, cholesterol levels, vital measurements (systolic and diastolic blood pressure, heart rate, body-mass index), and relevant medications (ACE inhibitors, ARBs, SGLT2-inhibitors, GLP-1RAs, MRAs)

Statistical Analysis
We will evaluate the incidence of surrogate endpoints before 3 years using both logistic and time-to-event analyses using the presence of APOL1 risk alleles as the primary exposures (both additive and recessive models). Then, we will shift our time zero to year 3 and evaluate whether each surrogate endpoint is associated with subsequent adverse events. This analysis will also be done using time-to-event methodology, adjusting for standard covariates taken at baseline, as per our standard surrogate analysis evaluation. In sensitivity analyses, we will also evaluate associations using competing risk regression. The adverse events will include: 1. CVD events; 2. ESKD; 3. Death. The surrogate endpoints will include 30% decline in eGFR, 40% decline in eGFR, and change in albuminuria: each of these "exposures" will be coded according their status before year 3.

We will perform our analyses at the individual cohort level and, where indicated, meta-analyze, as we are planning to do similar analyses in CRIC and AASK.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes ___x_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit"? ____ Yes ____ No
(The 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

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 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/aricproposals/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)?

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

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 https://sites.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.

References

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