ARIC Manuscript Proposal #3924

PC Reviewed: 9/14/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between clonal hematopoiesis of indeterminate potential (CHIP) status and incident acute kidney injury events

b. Abbreviated Title (Length 26 characters): CHIP and AKI risk

2. Writing Group:
Caitlyn Vlasschaert, Bryan Kestenbaum, Morgan E. Grams, Cassianne Robinson-Cohen, Michael Rauh, Matthew Lanktree, Alex Bick, Bruce Psaty, Russell Tracy, Alvaro Alonso, Dan Arking, Josef Coresh, Christie Ballantyne, and Eric Boerwinkle

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CV **[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: Data analysis Fall 2021 and manuscript first draft prepared by January 2022.

4. Rationale (*references linked below**):
Clonal hematopoiesis of indeterminate potential (CHIP) is a newly recognized clinical entity that links immune system aging to organ senescence. With age, clonal populations of circulating myeloid cells emerge as a result of mutations in bone marrow progenitor cells, typically in genes encoding epigenetic regulators such as TET2 and DNMT3A. This state is called CHIP, and it portends a higher risk for all-cause mortality and hematologic malignancy [1] as well as worse outcomes in a number of cardiovascular conditions [2-5]. Myeloid cells carrying CHIP mutations display impaired inflammatory responses, and experimental recapitulation of CHIP by transplanting a small fraction of HSCs with pathogenic TET2 mutations leads to kidney tubulointerstitial fibrosis [6,7]. We hypothesize that persons harboring a CHIP mutation would be predisposed to acute kidney injury since myeloid cells play pivotal roles in response to injury

and management of the kidney microenvironment. Moreover, CHIP has been associated with pathologic processes such as accelerated atherogenesis that also can predispose to AKI [2].

5. Main Hypothesis/Study Questions:

We propose to examine whether the rate of acute kidney injury is greater in persons with CHIP compared to persons without CHIP in Atherosclerosis Risk In Communities (ARIC) study, where both the exposure (CHIP) and the outcome (AKI) have previously been adjudicated [8-10]. During the 10.2-year follow-up period of 5,781 CHS participants, there were 225 AKI events [9]. Additionally, there were 1,970 AKI events in 10,056 ARIC participants over a period of 12 years [10]. Given these data, our aims are as follows:

Aim 1: Assess whether CHIP is associated with incident acute kidney injury events.

Aim 1 hypothesis: Participants with CHIP will have higher rates of incident AKI and a correspondingly higher risk of AKI in Cox regression analyses.

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).

Aim 1*:* We will calculate unadjusted incidence rates for AKI by CHIP status, followed by univariate Cox regression analyses. As noted above, both the exposure (CHIP status) and the outcome (AKI) have been adjudicated in previous studies. We will also perform multivariable regression controlling for age, sex, and baseline eGFR, and comorbidities including history of smoking, diabetes, CVD, and hypertension.

For these analyses we will require access to the following variables for ARIC participants:

1. Existing CHIP calls (*via* TOPMed; approval has been granted by TOPMed for this).
2. Inflammatory biomarker measurements: Serum measurements for IL-6, CRP, fibrinogen.
3. Kidney function measurements: Baseline creatinine and adjudicated AKI events.
4. All available baseline demographic information including age, sex, history of smoking, diabetes, CVD, hypertension.

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" ? **N/A**
(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? X Yes ____ No

8.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"? X 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)?
Dr. Morgan E. Grams has adjudicated AKI events in this cohort and performed several analyses (https://jasn.asnjournals.org/content/25/8/1834, https://jasn.asnjournals.org/content/27/9/2842). She has agreed to collaborate and serve as co-author for the proposed manuscript.

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

11.b. If yes, is the proposal **N/A**

___ 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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