ARIC Manuscript Proposal Form

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Publication Committee Review Date: **05/14/24**
ARIC Manuscript Proposal Number: **# 4444**

1.a. Full Title: Aldosterone dysregulation and risk of cardiovascular outcomes

b. Abbreviated Title (Length 26 characters): Aldosterone dysregulation and long-term outcomes

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Mats C. H. Lassen*, John W. Ostrominski, Brian Claggett, [others welcome], Scott D. Solomon, Muthiah Vaduganathan

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MCHL_ **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6 months of data becoming available.

4. Rationale:

Aldosterone is a key regulator of salt and water homeostasis, blood pressure, and other central physiologic actions in the human system[1]. When dysregulated, however, elevated aldosterone levels drive genomic and non-genomic signaling that contribute to downstream excess salt and water retention, systemic hypertension, endothelial dysfunction, and pathological fibrosis, hypertrophy, and inflammation of the end organs, including the heart and kidneys[2]. These core mechanisms of disease progression appear operative across the cardio-kidney-metabolic spectrum. Inhibition of this pathway through mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, or other therapies appears beneficial in blood pressure control and in disease states such as heart failure(HF)[3,4] and chronic kidney disease[5,6].

However, less is known about the contemporary epidemiology of elevated aldosterone levels (aldosterone dysregulation) in the general population. Indeed, aldosterone dysregulation may in fact be frequently under-recognized at the population level. The challenges in providing clarity to the population distributions of aldosterone levels have been 1) lack of standardization of measurement; 2) restriction to small, single center studies; 3) focus on specific populations with established cardio-kidney-metabolic diseases; and 4) lack of indexing to blood pressure around the time of measurement. To address these limitations and research gaps, we aim to conduct a contemporary description of aldosterone levels with association of clinical outcomes in a general US cohort.

5. Main Hypothesis/Study Aims:

We hypothesize that aldosterone dysregulation (aldosterone-to-renin ratio ≥20 ng/dL per ng/mL per hour and renin suppression) is underrecognized at the population level and that aldosterone dysregulation is associated with clinical outcomes during follow-up particular in all-cause mortality, hospitalization with HF, atrial fibrillation/flutter, hospitalization with myocardial infarction (MI), and stroke. We further hypothesize that aldosterone dysregulation will be evident across the spectrum of blood pressure but will be particularly elevated in patients with uncontrolled hypertension.

<u>Study objectives:</u>

1. To assess the population distribution of aldosterone levels, indexed to baseline blood pressure (including in persons with uncontrolled hypertension and in those without hypertension) in context to plasma renin activity to identify aldosterone dysregulation threshold associated with increased clinical risk.
2. To understand key correlates (patient phenotypes) that associate closely with aldosterone dysregulation (including in persons with uncontrolled hypertension and in those without hypertension)

3. To examine associations with clinical outcomes during follow-up particular in all-cause mortality, hospitalization with HF, atrial fibrillation/flutter, and MACE+ (all-cause mortality or hospitalization with MI, stroke, HF) between patients with and without aldosterone dysregulation.

6. Design and analysis - please address the following aspects:

a) Inclusion/Exclusion

This analysis will include all ARIC participants who participated at Visit 5 and had aldosterone measured. Participants with missing data for key variables used for categorizing aldosterone dysregulation (aldosterone, plasma renin activity, and blood pressure) will be excluded from this analysis.

b) Study design

This will be a longitudinal analysis of the participants who participated in Visit 5 with variables for categorizing aldosterone dysregulation available. The population will be assessed for presence of aldosterone dysregulation and the association between aldosterone dysregulation and risk of adverse clinical outcomes during follow-up will be evaluated. Furthermore, we will examine which baseline characteristics are associated with aldosterone dysregulation to better understand the patient phenotypes.

c) Outcome and other variables of interest with specific reference to the time of their collection

1. Physical examination variables (Visit 5): age, sex, race/ethnicity, height, weight, waist circumference, hip circumference, blood pressures, heart rate, history of hypertension, diabetes, dyslipidemia, chronic kidney disease, and prior cardiovascular disease (coronary artery disease, MI or revascularization procedure, heart failure, atrial fibrillation, stroke, peripheral artery disease).

2. Laboratory values (Visit 5): Aldosterone, plasma renin activity, NT-proBNP, eGFR, high sensitivity troponin T, serum albumin and creatinine, urine albumin and creatinine, HbA1c, fasting glucose, high-sensitivity C-reactive protein, lipoprotein (a), triglycerides, LDL, HDL, and total cholesterol.

3. Outcome data during follow-up: All-cause mortality, hospitalization with HF, atrial fibrillation/flutter, and MACE+ (all-cause mortality or hospitalization with MI, stroke, HF)

Summary of data analysis

At Visit 5, all participants will be categorized according to presence of aldosterone dysregulation and the distribution in the population will be described to identify the optimal threshold for aldosterone indexed to blood pressure associated with clinical risk. Baseline characteristics will be compared using descriptive statistics according to aldosterone dysregulation presence. Uni- and multivariable linear regressions will be used to assess associations between clinically meaningful baseline characteristics and aldosterone dysregulation. Adjustments for differences in clinical characteristics (based upon p-value <0.05 and/or clinically important covariates) will be

performed. Cox proportional hazard regression models will be used to assess the association between aldosterone dysregulation and risk of clinical outcomes during follow-up. In addition, beyond conventional predictive analytics, we will plan to undertake a machine learning-based approach to identify those with subclinical hyperaldosteronism incorporating all available laboratory and clinical data. If associations are sufficiently robust, we will generate a simple clinically applicable score to flag individuals who should be considered for more formal renin and aldosterone phenotyping.

d) Any anticipated methodologic limitations or challenges if present
Not all participants at Visit 5 had aldosterone and plasma-renin measurements available so the present study would be limited to the part of the population with the relevant laboratory variables available. As this is a prospective cohort study, an inherent limitation is that we can assess associations but never establish causality.

e) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 ☒ 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"? ☐ Yes ☐ No

9. The lead author or the "sponsoring" ARIC 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 website at:

https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?

Brown JM, Wijkman MO, Claggett BL, Shah AM, Ballantyne CM, Coresh J, Grams ME, Wang Z, Yu B, Boerwinkle E, Vaidya A, Solomon SD. Cardiac Structure and Function Across the Spectrum of Aldosteronism: the Atherosclerosis Risk in Communities Study. Hypertension 2022;79:1984–1993.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☐ Yes ☒ No → Skip to question 12

11.b. If yes to 11.a., 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)**

11.c. If yes to 11.a., list number* __

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website□Ancillary Studies□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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website□Publications□Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References: ____

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3. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348(14):1309-1321. doi:10.1056/NEJMoa030207
4. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364(1):11-21. doi:10.1056/NEJMoa1009492
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6. Ando K, Ohtsu H, Uchida S, et al. Anti-albuminuric effect of the aldosterone blocker eplerenone in non-diabetic hypertensive patients with albuminuria: a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2014;2(12):944-953. doi:10.1016/S2213-8587(14)70194-9

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