ARIC Manuscript Proposal # 3654

PC Reviewed: 6/9/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Subclinical Primary Aldosteronism and Future Risk of Heart Failure in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Subclinical PA & HF

2. Writing Group:

Writing group members: Jenifer M. Brown, Magnus O. Wijkman, Brian Claggett, Christie Ballantyne, Joe Coresh, Morgan Grams, Stephen Turner, Zhiying Wang, Bing Yu, Eric Boerwinkle, Anand Vaidya, [OTHERS WELCOME], Scott Solomon

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

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3. Timeline: Analysis to begin immediately, first draft by September 2020

4. Rationale:

Cardiometabolic traits, including obesity, hypertension, diabetes, and the metabolic syndrome are important risk factors for heart failure and have been associated with maladaptive activation of the mineralocorticoid receptor (MR) through multiple pathways including the

promotion of myocardial fibrosis[1]. While patients with high circulating renin and aldosterone indicative of renin-dependent neurohormonal activation (e.g. due to low cardiac output, renal artery stenosis) are at high risk of adverse cardiovascular outcomes[2–5], autonomous aldosterone production, independent of upstream renin-angiotensin activation, is also a prevalent and largely unrecognized cause of cardiovascular events. The most extreme form of autonomous aldosterone production, overt primary aldosteronism, has been associated with an increased risk of left ventricular hypertrophy (OR 2.29, 95% CI 1.65-3.17) and of heart failure (OR 2.05, CI 1.11-3.78) compared to patients with essential hypertension[6].

Autonomous aldosterone production is a common state of renin-independent aldosterone excess that exists across a spectrum from unrecognized and subclinical to overt primary aldosteronism. In its mildest forms in normotension, aldosterone that is produced in the context of renin suppression is associated with future incident hypertension risk[7–9] and has been associated with subclinical atherosclerosis and mortality[10]. With increasing severity of hypertension, renin-independent aldosterone production is increasingly common, detectable in at least 15-20% of the hypertensive population and at least a quarter of resistant hypertensives, and is associated with evidence of MR activity[11]. In a trial of add-on therapy for resistant hypertension, even when patients with primary aldosteronism were putatively excluded, the efficacy of MR antagonist therapy for blood pressure lowering was directly correlated with the degree of renin suppression and renin-independent aldosterone production, consistent with a ubiquitous but entirely unrecognized syndrome of autonomous aldosterone production[12,13].

Given the central importance of hypertension in the pathogenesis of heart failure, especially heart failure with preserved ejection fraction, there has been previous interest in exploring aldosterone as a marker of heart failure risk. While the aldosterone-to-renin ratio (ARR), the standard primary aldosteronism screening metric, has been largely unrevealing in predicting heart failure in other epidemiologic cohorts[14], we have recently demonstrated the sensitivity of a positive ARR to be poor (at best 50%) compared to confirmatory sodium suppression testing for primary aldosteronism across the spectrum of normal to resistant hypertension[11]. This is likely due to documented variability of circulating aldosterone levels[15], may explain why this ratio has not been prognostically useful, and is the rationale for focusing on the more stable phenotype of renin suppression.

We propose to investigate the relationship between renin-independent aldosterone production and the incidence of cardiovascular death and heart failure. In contrast to prior studies, which have focused on aldosterone and renin in the context of reduced ejection fraction or have emphasized the insensitive ARR, we will use a physiologic framework to evaluate whether renin suppression and aldosterone, specifically in the context of renin suppression, can identify a population subset enriched in heart failure and at increased risk for future events, paralleling the known excess risk in overt clinical primary aldosteronism.

5. Main Hypothesis/Study Questions:

We hypothesize that autonomous, or renin-independent, aldosterone production will be a prevalent pathophysiologic phenotype and will be associated with increased risk of incident

heart failure, potentially through chronic activation of the MR, volume retention, and myocardial and vascular fibrosis.

Specific Aims:

1. **To assess the cross-sectional relationship between renin suppression and aldosterone in the context of renin suppression at Visit 5 with prevalent heart failure. We hypothesize that renin suppression (and relative aldosterone excess in that context) will be enriched in patients with existing heart failure, in particular HFpEF.**
2. **To assess the relationship of renin suppression and aldosterone levels in the context of renin suppression at Visit 5 with subsequent cardiovascular events (primarily cardiovascular death and incident heart failure). We hypothesize that renin suppression and higher aldosterone levels (though potentially in the "normal" range) in the context of renin suppression will be associated with an increased risk of adverse cardiovascular events.**
3. **To assess the relationship of renin suppression and aldosterone levels in the context of renin suppression at Visit 5 with echocardiographic markers of ventricular remodeling and diastolic function. We hypothesize that renin suppression and higher aldosterone levels in that context will be associated with more adverse metrics of LV remodeling and diastolic dysfunction.**
4. **To assess whether antihypertensive drug use modifies the association between baseline Visit 5 renin suppression and subsequent cardiovascular risk.**

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).

Subjects with prevalent heart failure or cardiomyopathy at Visit 5 will be excluded.

Analysis Methods:

Primary Exposure Variable:

- Renin status will be defined based on Visit 5 plasma renin activity (PRA) as suppressed (≤ 0.5ng/mL/h) or unsuppressed (>0.5ng/mL/h).
- Aldosterone by renin phenotype (suppressed vs unsuppressed) will be defined.

Primary Endpoint: Composite of cardiovascular death and heart failure (defined as heart failure hospitalizations or heart failure-related death).

Secondary Endpoint: Echocardiographic parameters reflecting morphologic remodeling and diastolic function to include chamber dimensions and Doppler and tissue Doppler measurements.

Analysis:

1. Baseline characteristics will be compared between individuals with and without renin suppression (PRA ≤ 0.5ng/mL/h vs >0.5ng/mL/h).
2. Cross-sectional comparisons of biological indicators of MR activation including systolic blood pressure, diastolic blood pressure, and serum potassium will be compared between renin phenotypes.
3. Cross-sectional comparisons of prevalence of renin suppression will be made between those with and without prevalent heart failure.
4. Renin status and aldosterone by renin status at Visit 5 will be related to incident cardiovascular events with Cox regression analysis in univariate and multivariable models adjusting for potential confounders including demographic variables, biomarkers, and medical history components. We will also test for interactions with subsequent antihypertensive drug class usage, if available in sufficient detail.
5. Echocardiographic structural and functional parameters will be compared based on renin status and aldosterone by renin status at Visit 5 in univariate and multivariable regression models.

Limitations:

- Data on dietary sodium intake are unavailable, which could influence individuals' baseline renin and aldosterone values measured at Visit 5.
- Changes in subsequent antihypertensive medication use (especially renin-angiotensin-aldosterone system inhibitors) and blood pressure control may be incompletely characterized, may reflect underlying renin and aldosterone physiology, and likely influences the risk of subsequent cardiovascular events.

References

1. Brown NJ. Contribution of aldosterone to cardiovascular and renal inflammation and fibrosis. Nat Rev Nephrol 2013;9(8):459–69.
2. Masson S, Solomon S, Angelici L, et al. Elevated plasma renin activity predicts adverse outcome in chronic heart failure, independently of pharmacologic therapy: Data from the Valsartan heart failure trial (Val-HeFT). J Card Fail 2010;16(12):964–70.
3. Cohen JB, Schrauben SJ, Zhao L, et al. Clinical Phenogroups in Heart Failure With Preserved Ejection Fraction. JACC Hear Fail 2020;8(3):172–84.
4. Vaduganathan M, Cheema B, Cleveland E, et al. Plasma renin activity, response to aliskiren, and clinical outcomes in patients hospitalized for heart failure: the ASTRONAUT trial. Eur J Heart Fail 2018;20(4):677–86.
5. De Boer RA, Schroten NF, Bakker SJL, et al. Plasma renin and outcome in the community: Data from PREVEND. Eur Heart J 2012;33(18):2351–9.
6. Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2018;6(1):41–50.
7. Vasan RS, Evans JC, Larson MG, et al. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. N Engl J Med 2004;351(1):33–41.
8. Newton-Cheh C, Guo C-YY, Gona P, et al. Clinical and genetic correlates of aldosterone-to-renin ratio and relations to blood pressure in a community sample. Hypertension

2007;49(4):846–56.
9. Brown JM, Robinson-Cohen C, Luque-Fernandez MA, et al. The spectrum of subclinical primary aldosteronism and incident hypertension : A cohort study. Ann Intern Med 2017;167(9):630–41.
10. Inoue K, Goldwater D, Allison M, Seeman T, Kestenbaum BR, Watson KE. Serum Aldosterone Concentration, Blood Pressure, and Coronary Artery Calcium. Hypertension 2020;76.
11. Brown JM, Siddiqui M, Calhoun DA, et al. The Unrecognized Prevalence of Primary Aldosteronism: A Cross-sectional Study. Ann Intern Med 2020;(in press).
12. Williams B, Macdonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): A randomised, double-blind, crossover trial. Lancet 2015;386(10008):2059–68.
13. Williams B, MacDonald TM, Morant S V, et al. Endocrine and haemodynamic changes in resistant hypertension, and blood pressure responses to spironolactone or amiloride: the PATHWAY-2 mechanisms substudies. Lancet Diabetes Endocrinol 2018;6(6):464–75.
14. De Boer RA, Nayor M, DeFilippi CR, et al. Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction. JAMA Cardiol 2018;3(3):215–24.
15. Kline GA, Darras P, Leung AA, So B, Chin A, Holmes DT. Surprisingly low aldosterone levels in peripheral veins following intravenous sedation during adrenal vein sampling: implications for the concept of nonsuppressibility in primary aldosteronism. J Hypertens 2019;37(3):596–602.

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

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 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)?

There are no directly related current manuscript proposals in ARIC. A few relevant publications include the following:

Avery CL, Loehr LR, Baggett C, Chang PP, Kucharska-Newton AM, Matsushita K, Rosamond WD, Heiss G. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. J Am Coll Cardiol. 2012 ;60(17):1640-6.

Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. J Am Soc Nephrol. 2007;18(4):1307-15.

Khalid U, Ather S, Bavishi C, Chan W, Loehr LR, Wruck LM, Rosamond WD, Chang PP, Coresh J, Virani SS, Nambi V, Bozkurt B, Ballantyne CM, Deswal A. Pre-morbid body mass index and mortality after incident heart failure: the ARIC study. J Am Coll Cardiol. 2014;64(25):2743-9.

Ballantyne CM, Hoogeveen RC, McNeill AM, Heiss G, Schmidt MI, Duncan BB, Pankow JS. Metabolic syndrome risk for cardiovascular disease and diabetes in the ARIC study. Int J Obesity. 2008;32:S21-4.

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

___ 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.