

ARIC Manuscript Proposal #2955

PC Reviewed: 10/8/19
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Priority: _____

1.a. Full Title: Cardiac dysfunction and brain amyloid deposition: The ARIC-PET Study

b. Abbreviated Title (Length 26 characters): Cardiac echo and brain amyloid

2. Writing Group:

Writing group members: Michelle Johansen (first and corresponding author); Thomas Mosley; David Knopman; Dean Wong; Yun Zhou; Lynne Wagenknecht; Chiadi Ndumele; Amil Shah; Scott Solomon; Rebecca Gottesman (last author); Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. MJ [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: 3-6 months; planned abstract submission spring 2017; manuscript submission fall 2017. The addition to this manuscript proposal is planned for abstract submission in the fall of 2019 with the paper in the spring of 2020.

4. Rationale:

Congestive heart failure's (CHF) adverse effect on the brain is increasingly recognized, with evidence for cognitive impairment in individuals with marked cardiac dysfunction,¹ in addition to

evidence for an increased risk of dementia in individuals with heart failure.² More subclinical cardiac dysfunction, however, has less clear associations with brain outcomes, including cognitive decline.³ A difference of 25g in higher left ventricular mass was associated with significantly lower hippocampal volume and higher degrees of cerebral white matter disease.⁴ Higher levels of pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin T (hs-cTnT) were associated with cortical cerebral microinfarcts among a cohort seeking treatment for memory complaints.⁵

There has also been an increasing recognition of the role that atrial cardiopathy, or subclinical atrial disease, has in the role of cerebrovascular disease, such as embolic stroke, and has been shown to occur independently of atrial fibrillation. Atrial cardiomyopathy is defined as any complex of structural, architectural, contractile or electrophysiological changes affecting the atrial with a potential to produce clinically-relevant results.⁶ It may be that frank atrial disease is not necessary for a change in cognitive trajectory, but more subtle signs of cardiac structural and functional changes may be sufficient. Additionally, there has been no work investigating changes in the atrium, apart from atrial fibrillation, and its impact on cognition.

A potential mechanism for the association between cardiac dysfunction and brain amyloid deposition might be via shared risk factors; hypertension, for example, is a known risk factor for cardiac dysfunction, but also may adversely effect clearance of brain amyloid, leading to greater amyloid accumulation. Our study design will not allow us to rule out this order of an association (amyloid accumulation leading to both cardiac and brain dysfunction), but evaluation of longitudinal data as the ARIC-PET repeat PET scan is obtained will allow these possibilities to be teased apart.

In this study, we will evaluate the association between echo markers of systolic and diastolic dysfunction, and left ventricular structure, and brain amyloid by PET, and explore differences in these associations by race. We will also define markers that have been associated with subclinical atrial dysfunction, also called atrial cardiopathy, and look at the associations between these markers and brain amyloid by PET. Similar explorations of effect measure modification will be performed.

5. Main Hypothesis/Study Questions:

1. Global cortical A β deposition by PET will be associated with markers of left ventricular structure; A β will be elevated in individuals with evidence of abnormal left ventricular structure.
2. Global cortical A β deposition by PET will be associated with markers of left ventricular systolic dysfunction; A β will be elevated as systolic function decreases.
3. Global cortical A β deposition by PET will be associated with markers of diastolic dysfunction; A β will be elevated in association with evidence of diastolic function.
4. Global cortical A β deposition by PET will be associated with defined atrial cardiopathy; A β will be elevated in association with evidence of atrial cardiopathy.
5. Associations observed in #1, 2, 3, and 4 above, will be stronger in blacks compared to white participants, and will be independent of other vascular risk factors including hypertension and diabetes.

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).

Analysis of all participants in completed ARIC-PET study (N= 346 completed scans (one additional person was not able to complete the scan so her data is not usable). All analyses will be

cross-sectional, using echocardiogram (echo), electrocardiogram (ECG) and laboratory data from ARIC visit 5 and PET data from ARIC-PET.

Inclusion criteria (for inclusion in ARIC-PET; all of these persons will be included in analysis): persons with a CDR of 3 or lower, and also with a FAQ of 5 or lower, and with a brain MRI (from ARIC-NCS) within 12 months of recruitment. MMSE cannot be “low” (<19 for African-Americans and <21 for Caucasians) at the time of visit 5/ NCS. All participants were required to be able to give their own consent.

Exclusion criteria for involvement in ARIC-PET: We excluded individuals with history of: (1) radiation therapy, chemotherapy, or surgery in the 6 weeks preceding the ARIC-PET visit; or (2) clinically significant liver or renal dysfunction; (3) prolonged QT interval; (4) drug or alcohol abuse. We will allow use of anticholinergic medications or memantine if the dose has been stable for ≥ 3 months preceding the PET scan.

Outcome: Standardized Uptake Volume Ratio (SUVR) of florbetapir (amyloid) by ARIC-PET, in prespecified regions of interest. Global mean cortical SUVR, which is a weighted average (based on region-of-interest (ROI) volumes) of regions known to be typically impacted in AD. The SUVR's will be evaluated at a cutpoint of 1.2, with values >1.2 considered positive. Other cutpoints in the literature, including 1.1 and 1.11, will also be explored in sensitivity analyses.

Echo data will include markers of 1) LV structure; End-diastolic left ventricular diameter (cm), Mean LV wall thickness (mm), LV mass index (10g per m²); 2) LV systolic function; Ejection fraction (%), Average Peak Longitudinal Strain (%); 3) LV diastolic function; Lateral early diastolic myocardial velocity (cm per sec), E-Em lateral ratio (cm per sec), LA volume index (ml per m²).

Additional variables that will be evaluated include ECG data, and will include markers of left atrial function, specifically the p-wave terminal velocity in lead I. Laboratory data will include serum NT-proBNP. The Atrial Cardiopathy and Antithrombotic Drugs In prevention After Cryptogenic stroke (ARCADIA) is a large multicenter randomized controlled trial that is defining atrial cardiopathy based on P-wave terminal velocity, left atrial enlargement and elevated NT-proBNP. As a result, we have chosen these variables for our analysis.

For hypothesis 1, the markers of LV structure will be evaluated separately as independent variables, with elevated SUVR as the dependent variable. Hypothesis 2 will explore the above systolic markers separately as independent variables, and hypothesis 3 will evaluate the diastolic markers.⁷

In hypothesis 4 we will define atrial cardiopathy based on variables and features in the literature that have been shown to be associated with subclinical disease of the atrium. Specifically, we will define atrial cardiopathy as a combination of enlarged left atrial diameter, defined using echocardiographic data detailed above, the p wave terminal force measure in lead I on electrocardiogram (ECGRA100) and serum NT-proBNP >250 pg/mL. The analysis will begin by considering atrial cardiopathy as present only if all three conditions are present. If the sample size does not support these criteria, then 2 or more markers will be considered sufficient to define atrial cardiopathy. Atrial cardiopathy will then serve as the independent variable with SUVR (binarized) as per below as the dependent variable. We will also conduct a sensitivity analysis where we will exclude those with a history of atrial fibrillation.

For hypothesis 5, we will repeat the above analyses stratified by race. All models will be adjusted for potential confounders as described below.

Other variables: We will include race, center, sex, and age information from ARIC baseline (race, center, sex) and visit 5 (age), as well as APOE genotype from prior ARIC measurement. In addition, hypertension and systolic and diastolic blood pressures, diabetes, hypercholesterolemia, and smoking status will all be assessed from ARIC-NCS. Level of educational attainment as a covariate will be included in models. Cognitive status (MCI versus normal cognition, since no participants with dementia were included in the cohort), defined based on the ARIC-NCS expert classification, will also be considered in later models as a covariate.

Data analysis: Our primary analysis for hypotheses 1-4 will consider logistic regression models with evaluation of elevated SUVR as a binary dependent variable; the SUVR data are highly skewed, not easily handled with transformation, so we will not plan to use the continuous SUVR data at this point. Models will include adjustment for demographics (model 1); other covariates (model 2), with addition of APOE and cognitive status in model 3. The same sequential covariate adjustment will be made for all of the echocardiographic markers.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes 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 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.csc.unc.edu/ARIC/search.php>

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)?

2544. Arterial stiffness and beta-amyloid deposition in the ARIC-PET study. Hughes et al.
2511. Vascular risk factors and brain amyloid deposition: The ARIC-PET Study. Gottesman et al.
2384. Cardiac and Brain structure and function associations: The ARIC study. Gottesman et al. (first author Johansen)
2227. Relationship of cardiac structure and function with cognitive performance: a study of the Atherosclerosis Risk in Communities (ARIC) study (Jhund et al.)

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

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* 2009.29)**
 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.csc.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.

Yes, we understand.

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.csc.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.

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