ARIC Manuscript Proposal #2546

PC Reviewed: 5/8/2018	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of Left Atrial Enlargement with Lower Cognitive Function and Dementia: The ARIC-NCS Study

b. Abbreviated Title (Length 26 characters): LA enlargement, cognition, and dementia

2. Writing Group:
Writing group members: Michael J. Zhang, Faye L. Norby, Rebecca F. Gottesman, Thomas H. Mosley, Suma H. Konety, Rebecca J. Cogswell, Amil M. Shah, Scott D. Solomon, Alvaro Alonso, Lin Y. Chen, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MJZ____ **[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: Statistical analysis: 1 month
Manuscript preparation: 2 months

4. Rationale:

Atrial fibrillation (AF) is a serious public health problem because of its increasing prevalence in the aging population[1] and its association with elevated risks of ischemic stroke,[2] cognitive decline or impairment,[3,4] heart failure,[5] and death.[6,7] Other than anticoagulation which reduces the risk of ischemic stroke, current therapies for AF to prevent other adverse outcomes are disappointing. The lack of effective therapies is, in part, due to our poor understanding of the mechanisms mediating the adverse outcomes. Recent evidence has emerged to suggest that the higher risks of stroke and cognitive decline are also observed in individuals with an abnormal atrial substrate of atrial enlargement or dysfunction, even in the absence of AF.[8-12] Further, studies of patients with implantable cardiac electronic devices indicate that the vast majority of ischemic strokes are not temporally related to AF episodes.[2,13] These observations raise the tantalizing question whether it is AF or the underlying atrial substrate that is the main entity that causes these adverse outcomes.

To answer the aforementioned question, this proposal will evaluate the cross-sectional association of echocardiographic-defined left atrial enlargement (LAE) with cognitive test scores and prevalent mild cognitive impairment (MCI) and dementia, with and without AF.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the association of LAE and AF with cognitive test scores

Hypothesis 1: Cognitive test scores will be lower in participants with LAE than those with normal atrial size. The presence of AF is not associated with lower scores in participants with LAE; those with LAE and with AF will have similar cognitive scores as participants with LAE and without AF.

Aim 2: Evaluate the association of LAE and AF with prevalent MCI and dementia

Hypothesis 2: Participants with LAE will have a higher risk of prevalent MCI and dementia than those with normal atrial size. The presence of AF is not associated with MCI or dementia in participants with LAE; participants with both LAE and AF will have similar prevalence of MCI or dementia as participants with LAE but without AF.

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 Population

Aim 1 and 2
We will include participants with echocardiograms, cognitive test data and adjudicated MCI and dementia at visit 5/ARIC-NCS (2011-13).
Exclusion criteria: Missing covariates

Exposures
LAE: left atrial volume index ≥28 ml/m^2

AF
Prevalent AF cases at visit 5 will be defined by:
1) Hospital discharge records (ICD-9 code 427.31 and 427.32– Atrial fibrillation)
2) ECGs performed during study visits

Outcomes
Cognitive scores: z-scores for different domains (memory, language and verbal fluency, executive function, and visuo-spatial). For this analysis, we will follow recommendations from the ARIC-NCS analysis committee.

MCI and dementia: For this analysis we will use the adjudicated MCI and dementia variables from ARIC visit 5. MCI and dementia were adjudicated by a panel of neurologists and neuropsychologists following criteria proposed by the National Institute of Aging-Alzheimer's Association workgroups [14]

Covariates
Age, sex, race, study center, occupation, and educational level, smoking (never, former, current), body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, use of anticoagulants, diabetes, stroke, coronary heart disease or myocardial infarction, and heart failure.

Statistical analysis
Hypothesis #1
Participants will be divided into 4 groups: normal atrial size/no AF, normal atrial size/AF, LAE/no AF, LAE/AF. We will use the general linear model to assess association between atrial size/AF status and each z-score:

Model 1: Adjusted for age, sex, race, and study center
Model 2: Model 1 + smoking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, stroke, coronary heart disease or myocardial infarction, and heart failure.

Hypothesis #2

The association between LAE and the prevalence of MCI and dementia will be assessed using logistic models.. We will use the same 2 models listed above. We may also look at the association by type of dementia if we have enough events in each group.

Sensitivity analysis:

- In addition, we will conduct sensitivity analysis using inverse probability of attrition weighting to adjust for selection bias due to censoring.
- We will explore interactions by age, race and sex through stratified analysis and including multiplicative terms in the models.

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

___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)?

#2378 – LA function in the general population
#2384 – Cardiac and Brain Structure and Function Associations

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 at http://www.cscc.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.

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.

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