ARIC Manuscript Proposal #3865

PC Reviewed: 6/8/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Mediation of atrial fibrillation-related ischemic stroke and dementia by left atrial size and function: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): **AF & LA with stroke & dementia**

2. Writing Group: Michael J. Zhang, Yuekai Ji, Anne A. Eaton, Wendy Wang, Riccardo M. Inciardi, Romil Parikh, Alvaro Alonso, Elsayed Z. Soliman, Thomas H. Mosley, Rebecca F. Gottesman, Michelle C. Johansen, Amil M. Shah, Scott D. Solomon, Lin Yee 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:

Data analysis to begin immediately; pen draft expected Summer 2021.

4. Rationale:

Atrial fibrillation is a serious public health problem because it is the most common sustained arrhythmia, its prevalence is increasing in the aging population[1, 2] and it is associated with elevated risks of ischemic stroke and dementia.[3-9] Although the AF-stasis hypothesis has been the accepted mechanism of AF-related thromboembolism and morbidity,[10] recent compelling evidence has emerged to suggest an alternate hypothesis: Novel insights into the temporal dissociation between AF episodes and ischemic stroke events,[11, 12] and data linking markers of abnormal atrial substrate with ischemic stroke independent of AF,[13-16] suggest that another mechanism—other than the dysrhythmia of AF—may drive AF-related thromboembolism and morbidity.

The left atrium (LA) is a significant contributor to cardiovascular performance, and its size and function have important prognostic implications in health and disease.[17] *Increased size or lower function of the LA* manifest as "structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations", and is thus termed atrial cardiomyopathy (or atrial cardiopathy or atrial myopathy).[18-20] As early as 1968, extensive fibrosis, loss of muscle mass and marked LA enlargement was first noted in LA biopsies of patients undergoing mitral valve surgery with valvular AF.[21] This evidence was corroborated by imaging of LA fibrosis using delayed-enhancement cardiac MRI in patients with non-valvular AF.[22] Experimentally, atrial cardiomyopathy can be induced in goats and dogs with pacing-induced AF.[23, 24] In the latter study, extensive mural thrombi were also found in the LA upon necropsy.[24] Collectively, current evidence indicates that AF and atrial cardiomyopathy frequently co-exist with a possible bidirectional relationship.

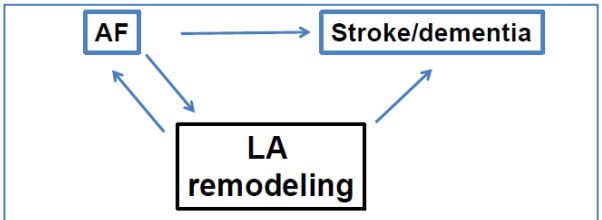
Importantly, recent evidence has emerged to indicate that thromboembolism can occur in the setting of atrial cardiomyopathy even in the absence of AF: First, greater LA size is associated with higher risk of ischemic stroke, even in patients without AF or adjusting for AF.[25, 26] Second, lower LA function has been linked to brain infarcts on MRI and ischemic stroke, independent of AF.[27, 28] Third, ECG markers of atrial cardiomyopathy have been associated with increased risk of ischemic stroke and vascular brain injury.[13, 15, 16, 19, 29, 30] In aggregate, current evidence suggests that atrial cardiomyopathy may be an alternate mechanism of thromboembolism that mediates the morbidity previously attributed to AF.

Despite this recent evidence, whether there is a causal link, and bidirectional relationship, between atrial cardiomyopathy and AF that results in thromboembolism to cause stroke or dementia remains unknown. Mediation analysis can clarify the extent to which atrial cardiomyopathy vs. AF contributes to AF-related thromboembolism and morbidity.[31] The ARIC study thus presents an opportunity to address this knowledge gap. The aim of this study is to clarify the relationship between atrial cardiomyopathy and AF, and their associations with incident ischemia stroke and incident dementia.

5. Main Hypothesis/Study Questions:

1: Evaluate the association between prevalent AF at Visit 5 and incident ischemic *stroke* (after Visit 5). We will adjust for measures of LA size and function, and assess mediation of the association between AF and ischemic *stroke* by LA size and function.

2: Evaluate the association between prevalent AF at Visit 5 and incident *dementia* (after Visit 5). We will adjust for measures of LA size and function, and assess mediation of the association between AF and *dementia* by LA size and function.



Conceptual model. Bidirectional relationship between AF and LA remodeling and their associations with stroke/dementia

Based on our conceptual model above, we hypothesize
1) The associations of AF with incident ischemic stroke and dementia will be substantially attenuated after adjusting for LA size and function.

2) The associations of AF with incident ischemic stroke and dementia are substantially mediated by LA size and function.

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 design:
Prospective cohort from visit 5 to 2019 (or most recent data available).

Study population:

1. Inclusion criteria: Only participants with prevalent AF at Visit 5, who also underwent echocardiographic examination Visit 5.

2. Exclusion criteria: Participants with prevalent stroke, prevalent dementia and missing LA size and function data at Visit 5.

Variables

Exposure: Prevalent AF at Visit 5, as diagnosed by study ECGs or hospitalization codes

Outcomes: After Visit 5, until 2019 (or the most recent data available)

1. Incident ischemic stroke: We will include definite ischemic stroke, which includes all definite thrombotic strokes and all definite cardioembolic strokes[32]
2. Incident dementia: Adjudicated dementia events as previously identified in ARIC will be used.[33] Level 3 dementia diagnosis will be used.
   - Level 1 includes adjudicated outcomes from visits 5 and 6 NCS evaluations, including evidence of cognitive decline based on assessments from prior visits.
   - Level 2 includes cases identified in level 1, as well as participants who did not attend NCS visits, but had their cognitive status evaluated through a validated phone-based cognitive assessment interview.
   - Level 3 includes level 1 and 2 cases, as well as participants identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia.

Left atrial size and function: the following measures (obtained at visit 5) will be assessed continuously (per 1-SD)

1. LA max volume, indexed to body surface area
2. LA min volume, indexed to body surface area
3. LA reservoir strain
4. LA contractile strain
5. LA conduit strain
6. LA total emptying fraction
7. LA passive emptying fraction
8. LA active emptying fraction

Other confounders/covariates (obtained from Visit 5): age, sex, race/center, education (from visit 1), APOE ε4, body mass index (BMI), smoking status, diabetes, hypertension, stroke, coronary heart disease, heart failure, left ventricular (LV) ejection fraction, LV mass index, use of anticoagulants or antiplatelets

Statistical analysis

- Cox proportional hazards regression will be used to assess the relationship between AF with incident ischemic stroke and incident dementia (level 3 cases).
- For all analyses, the following models will be used:
  - Model 1 will be adjusted for age, sex, race/center, education, APOE ε4
  - Model 2 will be adjusted for model 1 plus BMI, smoking status, diabetes, hypertension, coronary heart disease, and heart failure
  - Model 3 will be adjusted for model 2 plus use of statins, and use of antihypertensives
  - Model 4 will be adjusted for model 3 plus LA size and function variables (together or individually)
  - Model 5 will be adjusted for model 3 plus use of anticoagulants and anti-platelet agents

- LA variables will be evaluated as continuous variables (e.g., per 1-SD change) and as categories (e.g., highest versus lowest tertile, middle versus lowest tertile).
- We will then perform mediation analysis to quantify direct effects (AF → stroke and dementia) vs. indirect effects (AF → LA function changes → stroke and dementia). Specifically, we will conduct mediation analyses to examine the controlled direct effect, the natural direct effect, and the natural indirect effect of AF on outcomes with mediation by LA size and function using an approach developed by Valeri and Vanderwheel[34, 35]

Sensitivity analyses

- Depending on the number of outcomes, we will consider using the Fine-Gray subdistribution hazards model to account for the competing risk of death if outcomes are rare,[36, 37] or we will use an accelerated failure time model if outcomes are not rare.[38]

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/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)?

Unassigned MS proposal: The Risk of Dementia Associated with Atrial Cardiopathy: The Atherosclerosis Risk in Communities (ARIC) Study (Johansen) – submitting to P&P concurrently

Of note, a co-author, Dr. Michelle Johansen, is submitting a related manuscript proposal examining the association of atrial cardiopathy/cardiomyopathy with dementia. However, there are sufficient differences such that 2 separate proposals and manuscripts are warranted: the *exposures are different* and the *atrial cardiopathy criteria are different*. In Dr. Johansen's proposal, atrial cardiopathy is the exposure, whereas AF is the exposure in this proposal. In Dr. Johansen's proposal, atrial cardiopathy is defined as a combination of enlarged left atrial diameter, the P wave terminal force measure in lead V1 on electrocardiogram, and elevated serum NT-proBNP (ARCARDIA criteria).[39] In this proposal, atrial cardiomyopathy is defined solely by echocardiographic indices. All effort will be undertaken to avoid overlap in the analyses and reporting of results in the 2 manuscripts.

#3750: LA function and cognition (Wang)
#3089: Left atrial dysfunction and prediction of stroke (Bianco)

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

11.b. If yes, is the proposal
_x_ A. primarily the result of an ancillary study (list number* _2008.06 (NCS), 2015.29_)

___ 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 https://www2.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.

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