ARIC Manuscript Proposal # 3279

PC Reviewed: 11/13/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between atrial fibrillation and brain volumes: the ARIC-Neurocognitive (ARIC-NCS) Study

b. Abbreviated Title (Length 26 characters): **AF and brain volumes**

2. Writing Group: Kasra Moazzami, Iris Yuefan Shao, Lin Yee Chen, Pamela L. Lutsey, Clifford Jack, Thomas Mosley, David A. Joyner, Rebecca Gottesman, Alvaro Alonso

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

First author: **Kasra Moazzami**
Address: 1516 Clifton Rd NE, Room 4053
Rollins School of Public Health
Emory University
Atlanta, GA 30322
Phone: 857-294-6186
E-mail: kmoazza@emory.edu

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).
Name: **Alvaro Alonso**
Address: 1516 Clifton Rd NE, Room 3051
Rollins School of Public Health
Emory University
Atlanta, GA 30322
Phone: 404 727 8714
E-mail: alvaro.alonso@emory.edu

3. Timeline:
Analysis to be started immediately. We expect a manuscript draft to be prepared over the next 6 months.

4. Rationale:
Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia, and its prevalence increases dramatically with age[1]. Emerging evidence suggests that AF is associated with

cognitive impairment [2-5]. While earlier studies have shown that such association is strongest in individuals with prevalent stroke[2], two meta-analyses have demonstrated that the association is also present in patients without a history of clinical stroke [6, 7]. Additionally, studies have indicated that in the absence of clinical stroke, patients with AF experience more rapid cognitive decline than those without [3, 5], thus highlighting the importance of atrial fibrillation as a risk factor for cognitive impairment, independent of clinically recognized stroke.

Even though increasing evidence has shown that cognitive performance is worse in patients with AF compared with those without, studies investigating the potential underlying brain morphometric changes in this patient population are scarce [4, 8, 9]. Total cerebral brain volume has shown to correlate directly with various domains of cognitive performance including attention, executive function, and visuospatial function [10]. Additionally, it has previously been shown that in stroke-free individuals with AF, cognitive decline is mediated by the presence of subclinical cerebral infarcts [3]. As a result, it is important to understand the relationship between AF and brain structure, as it might provide additional insights into the pathophysiological mechanisms of cognitive impairment in AF patients. In the largest study to date among 4,251 non-demented participants, in an age and sex matched analysis, AF was associated with lower volume of total brain, and gray matter volume [4]. However, in a more recent study from the Framingham Offspring cohort, such associations only held for frontal brain volume after additional adjusting for vascular risk factors and APOE4. [8]. Given the conflicting evidences, this study aims to assess whether prevalent AF is associated with total or regional brain volumes and whether such association holds among patients without evidence of silent cerebral infarcts and microbleeds.

5. Main Hypothesis/Study Questions:

Aim 1. To investigate the association of prevalent AF with total and regional brain volumes, adjusting for sociodemographic information, cardiovascular risk factors (diabetes, hypertension, heart rate, obesity, smoking, dyslipidemia, kidney function), and prevalent cardiovascular disease (past history of myocardial infarction, heart failure, or stroke), and presence of white matter hyperintensity.
Hypothesis: We hypothesize that AF is associated with lower total and regional brain volumes, and that the association is independent of demographics, cardiovascular risk factors, prevalent cardiovascular disease, and APOE4 status.

Aim 2. To assess the role of silent cerebral infarcts, microbleeds, or volume of white matter hyperintensities as mediators of the association between AF and brain volumes.
Hypothesis: We also hypothesize that presence of silent cerebral infarcts and microbleeds mediatethe association between AF and brain volumes.

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

We will include all participants who attended ARIC visit 5 and underwent brain Magnetic Resonance Imaging (MRI) scans.
Of these, we will exclude those with incomplete MRI data or poor image quality, and those with missing values for AF ascertainment.

Prevalent AF

Participants are considered to have AF if there is evidence of AF in any of the study ECGs (Visit 1-5) or had a hospitalization with an ICD-9-CM code for AF/atrial flutter not associated with open cardiac surgery prior to visit 5.[11]

Outcome of interest

The following brain volumes will be used as outcomes in our analysis:
1. Total brain volume
2. Lobar volumes (frontal, parietal, temporal, and occipital)
3. Total volume of deep gray subcortical structures defined as the total volume of the thalamus, caudate, putamen, and globus pallidum
4. The hippocampal volume
5. Total volume of an Alzheimer disease signature region defined as the total volume of parahippocampal, entorhinal, and inferior parietal lobules; hippocampus; precuneus; and cuneus [12]

Covariates of interest

We will explore the following variables as potential mediators of the association between AF and brain volumes. Covariate information will come from visit 5, with the exception of static sociodemographic variables which were collected at baseline:
1. Sociodemographic variables: age, sex, race-center, education
2. Cardiovascular risk factors and prevalent cardiovascular disease: diabetes, hypertension, heart rate, obesity, smoking, dyslipidemia, kidney function, past history of myocardial infarction, heart failure, or stroke.
3. AF-related medications: rate and rhythm-control therapies (beta-blockers, calcium-channel blockers, digoxin, type I and III anti-arrhythmics, anticoagulants).
4. Presence of silent cerebral infarcts, microbleeds, volume of white matter hyperintensities.
We will include total intracranial volume as a covariate in all analyses.

Statistical analysis

Characteristics of the study population will be presented by AF status. Adjusted multivariable linear regression models will be used to assess the associations between AF and brain volumes.
Model 1 will be adjusted for total intracranial volume.
Model 2 will be adjusted for sociodemographic factors and total intracranial volume
Model 3 will include all variables in model 2 in addition to cardiovascular risk factors, prevalent cardiovascular disease, and APOE4 status.
Model 4 will adjust for all variables in model 4 and presence of silent cerebral infarcts, microbleeds, and volume of white matter hyperintensities. All analyses will be weighted to the ARIC visit 5 / NCS sample using weights provided by the Coordinating Center.

Among a total of 1968 participants who underwent brain MRI studies, 130 patients have AF. This sample size will be adequate to detect differences in brain volumes between patients with and without AF.

Limitations

The proposed analysis has 2 major limitations:

1. Cross-sectional design: temporal relationships between presence of AF and brain volumes cannot be determined
2. AF ascertainment: a large proportion of AF cases has been ascertained from hospital discharge codes without evidence of AF in an ECG

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? _ X _ 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? ___X_ 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"? _X___ 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)?
MS #1739 (Chen) Atrial fibrillation and cognitive decline
MS #1740 (Chen) Atrial fibrillation and dementia
MS #2405 (Chen) Atrial fibrillation and 20-year cognitive decline
Lin Chen and Alvaro Alonso are coauthors in this proposal and the previous related proposals. There is no overlap of this proposal with those listed above.

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 ARIC NCS)

___ 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.

References

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