ARIC Manuscript Proposal #2804

PC Reviewed: 7/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Correlates of mild cognitive impairment and dementia in patients with atrial fibrillation: The ARIC-Neurocognitive (ARIC-NCS) Study

b. Abbreviated Title (Length 26 characters): Correlates of MCI/dementia in AF

2. Writing Group: Alvaro Alonso, Faye L. Norby, Rebecca F. Gottesman, Tom H. Mosley, David S. Knopman, Elsayed Z. Soliman, Amit J. Shah, Lin Y. Chen

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

First author: **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

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: **Lin Y. Chen**
Address: Cardiovascular Division
University of Minnesota
Minneapolis, MN 55455
Phone: 612 624 8022
E-mail: chenx484@umn.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 a common cardiac arrhythmia associated with increased risk of stroke, heart failure, myocardial infarction, and mortality.[1-3] Previous studies have also

shown that AF increases the risk of cognitive decline and dementia, even among individuals without clinical strokes.[4, 5] Different mechanisms have been proposed to explain the impact of AF on cognitive function, including a prothrombotic state predisposing to cerebrovascular disease, brain hypoperfusion derived from inadequate left ventricular filling, or a proinflammatory state in the context of AF.[6] The relative importance of these mechanisms, however, is unknown. Moreover, the specific predictors of cognitive impairment and dementia among AF patients have been studied only in selected populations,[7] or relying in suboptimal cognitive phenotyping.[8, 9] A better characterization of the risk factors and correlates of cognitive impairment and dementia in patients with AF will shed light into the pathways linking AF and negative cognitive outcomes. This may contribute to identifying patients at high-risk of cognitive complications, and eventually may be useful to develop therapeutic approaches specifically tailored to prevent cognitive impairment and dementia in this patient population.

To address these gaps, we propose to explore correlates of cognitive impairment and dementia in individuals with AF who participated in ARIC-NCS/visit 5. The availability of rich data on cardiovascular risk factors, biomarkers, and cardiac imaging, together with the detailed cognitive phenotyping of the ARIC visit 5 participants, provides a unique opportunity to answer this significant question.

5. Main Hypothesis/Study Questions:

We will address the following specific aims:

1. To identify correlates of mild cognitive impairment (MCI) and dementia in patients with a history of AF participating in ARIC-NCS/visit 5
2. To determine whether associations are different for Alzheimer disease (AD)-type MCI and dementia compared to vascular MCI and dementia
3. To assess the role of any identified correlate as a mediator of the association between AF and dementia/MCI.

We hypothesize that scores used for stroke risk stratification in patients with AF, such as the CHA2DS2-VASc score, will be associated with prevalence of dementia/MCI in participants with AF, even after adjustment for age. We also hypothesize that the association will be similar for AD-type dementia/MCI and vascular dementia/MCI, and that some of the identified correlates will mediate the association between AF and dementia/MCI.

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).

<u>Study population</u>

We will include individuals who attended ARIC visit 5 and had AF at the time of the visit. Participants who did not undergo cognitive assessment and those with missing values for relevant covariates will be excluded, as well as those not meeting the usual

ARIC race-center inclusion criteria (race other than white or black; non-whites in Minneapolis and Washington County).

Prevalent AF

Participants will be 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.[10]

Covariates of interest

We will explore the following variables as potential correlates of MCI / dementia in AF patients:

1. Sociodemographic variables: age, sex, race, 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, APOE genotype
3. Selected biomarkers: C-reactive protein, NT-proBNP, troponin T
4. AF-related medications: rate and rhythm-control therapies (beta-blockers, calcium-channel blockers, digoxin, type I and III anti-arrhythmics, anticoagulants).
5. Composite scores used for risk stratification in AF patients: $CHADS_2$, CHA_2DS_2-Vasc, HAS-BLED
6. Basic echocardiographic measurements: left atrial volume index, ejection fraction, left ventricular mass index
7. Among participants with brain MRI: presence of silent cerebral infarcts, microbleeds, volume of white matter hyperintensities. We may consider dropping these variables if sample size is inadequate.

Outcome of interest

The primary endpoint will be a composite MCI/dementia, as adjudicated by ARIC-NCS.[11] If sample size is adequate, we will differentiate between MCI and dementia. Similarly, we will separate primary AD MCI/dementia and primary vascular MCI/dementia in a secondary, exploratory analysis.

Statistical analysis

For the primary analysis, we will calculate the association of correlates with the prevalence of MCI/dementia using logistic regression. Initial models for each separate covariate will adjust for age, sex, race/center and education. Because of the exploratory character of this analysis, we will use results from these models to inform additional multivariable models. Additional analyses differentiating between MCI and dementia, and between AD and vascular MCI/dementia will be done using multinomial logistic regression. Secondary analyses will be conducted excluding participants with a history of stroke, to evaluate correlates of MCI/dementia in those without prior clinical cerebrovascular disease. Finally, we will evaluate the role that any strong correlate of dementia/MCI has in explaining the association between AF and dementia/MCI by running models including all visit 5 participants and assessing whether inclusion of any specific correlates attenuate/explain the association between AF and dementia/MCI. We

recognize the limitations and assumptions of this analysis and will exert caution in its interpretation.

Among 6538 participants in ARIC-NCS/visit 5, we have identified 604 individuals with AF and, among them, 234 have been diagnosed with MCI (n=174) or dementia (n=60). This sample size will be adequate to identify strong predictors of MCI/dementia in this population. We will also assess effect modification by age, sex, race, and prior history of other CVD (CHD/HF), though these analyses will be considered exploratory given the limited sample size.

Limitations

The proposed analysis has 2 major limitations:

1. Cross-sectional design: temporal relationships between most of the explored variables and prevalence of MCI/dementia 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? ____ 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__ (APOE genotype) **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/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)?

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 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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