ARIC Manuscript Proposal # 1739

PC Reviewed: 1/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Atrial Fibrillation is Associated with Cognitive Decline and Brain MRI abnormalities: The ARIC Study

b. Abbreviated Title (Length 26 characters): Atrial Fibrillation and Cognitive Decline

2. Writing Group:

Writing group members: Lin Y. Chen, Alvaro Alonso, Faye Lopez, Thomas Mosley, Rebecca Gottesman, Rachel Huxley, Sunil K Agarwal, Laura R. Loehr, and others.

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

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3. Timeline:

Statistical Analysis: 3 months
Manuscript preparation: 3 months

4. Rationale:

Atrial fibrillation (AF) is the most common sustained arrhythmia afflicting more than 2 million Americans, a figure that is projected to increase to approximately 5 to 12 million by 2050.[1, 2] AF is not only associated with an increased risk of stroke,[3] heart failure,[4] and death,[5] but it also imposes considerable socioeconomic burden.[6, 7]

Recently, there has been evidence to suggest that AF may contribute to the development of dementia–also a burgeoning public health problem. Notably, a cross-sectional study of the Rotterdam Study demonstrated that cognitive dysfunction was approximately twice as common in subjects with AF than in those without.[8] Other cross-sectional studies have shown that AF was associated with cognitive dysfunction, independent of stroke and other cardiovascular risk factors.[9, 10] In contrast, analyses from some prospective cohort studies have not shown an association between AF and cognitive dysfunction.[11-13] The Cognition in Atrial Fibrillation Evaluation (CAFE)[11]–a prospective, longitudinal, community-based cohort study–did not find any association between AF and cognitive impairment. Similarly, two other prospective cohort studies did not find an association between AF and cognitive impairment in octogenarians.[12, 13]

More recent data from the Intermountain Heart Collaborative Study, an integrated health system database, have rekindled the debate on the association between AF and cognitive function.[14] This study, which included 37,025 patients (10,161 with AF and 1,535 with dementia), not only demonstrated that AF independently predicted all dementia subtypes, but also showed that AF was a predictor of higher mortality among patients with dementia.[14]

ARIC–with more than 1,000 incident AF events, and cognitive assessments and Brain MRI scans in a subset of participants–is uniquely suited to investigate the relationship between AF and cognitive function.

5. Main Hypothesis/Study Questions:

Aim #1: Evaluate the association of AF development with cognitive change over time

Hypothesis #1: Participants in the Brain MRI Ancillary Study who develop AF will experience a more rapid decline in cognitive function than those who do not develop AF, independently of other risk factors for cognitive decline. Cognitive function will be measured at visits 2, 3, 4, and in 2004-2006.

Hypothesis #2: Participants in the entire ARIC cohort who develop AF will experience a more rapid decline in cognitive function than those not who do not develop AF. Cognitive function will be measured at visits 2 and 4.

Aim #2: Examine the association of AF development with brain MRI abnormalities

Hypothesis #3: Participants in the Brain MRI Ancillary Study who develop AF will have more white matter hyper-intensity (WMH) volume and infarct-like lesions (ILL) than those who do not develop AF as assessed by brain MRI in 2004-2006.

Hypothesis #4: Compared with participants who do not develop AF, participants in the Brain MRI Ancillary Study who develop AF will have greater progression of ILL and WMH from 1993-1995 to 2004-2006.

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

Hypothesis #1, #3, and #4

We will focus on participants in the Brain MRI Ancillary Study. These participants were a subset of the ARIC cohort who, over a period of 14 years between 1990-1992 and 2004-2006, had four cognitive assessments (called CA1-CA4). Of 2,891 participants aged 55 or older from two communities, Forsyth County, NC, and Jackson, MS, who were invited to be part of the Brain MRI ancillary study, 1,920 completed a second cognitive assessment (CA2) in 1993-1995. All of the 1,920 who completed CA2 in 1993–1995 were invited to a final cognitive testing (CA4) between 2004 and 2006, 14 years after CA1, and 1,134 successfully completed CA4.

Exclusions: Missing information on study covariates and indeterminate AF status.

Hypotheses #2

We will study the entire ARIC cohort, using data from CA1 (1990-1992) and CA3 (1996-1998).

Exclusions: Missing information on study covariates and indeterminate AF status.

Exposure measurement

AF

AF cases will be identified from:
1) Hospital discharge records (ICD-9 code 427.31 – Atrial fibrillation)
2) ECGs performed during study visits 1 – 4
3) Death certificates

Outcomes measurement

Cognitive decline

Scores from three neuropsychological tests: Delayed Word Recall (DWR) Test, Digit Symbol Substitution (DSS) Test, and Word Fluency (WF) Test will be used to determine cognitive decline.

Brain MRI assessment

- White matter hyper-intensity (WMH) volume: Volumetric measurements will be determined using an automated protocol. Fully quantitative WMH volumes will not be possible from all 1993-1995 scans. Therefore, WMH volumes in 1993-1995 will be estimated using a prediction equation that relates volume from visual grades.[15]

- Infarct-like lesions (ILL): defined as ≥3mm in diameter.
- Ventricular volume.
- Total brain volume and atrophy: defined as difference between total intracranial volume and brain volume.
- Sulcal grade: graded 0 – 9.

Covariates
Age, gender, race, study center, educational level, occupation, current smoking, body mass index, hypertension, diabetes, stroke, history of coronary heart disease or myocardial infarction, and heart failure.

Given that stroke is a probable intermediary in the causal pathway between AF and cognitive decline, we will repeat the analyses with and without adjustment for stroke in the models. This will enable us to determine whether the association between AF and cognitive decline, if any, is independent of stroke.

Statistical analysis

Hypotheses #1 and #2
To test the association between AF and cognitive decline rate, we will use random-effects linear models (PROC MIXED, SAS Software 9.2; SAS Institute, Cary, NC). The models will consist of AF status, time of follow-up (per annual change), a term for the interaction of AF x time, and covariates: age, gender, race, educational level, occupation, current smoking, body mass index, hypertension, diabetes, history of coronary heart disease or myocardial infarction, and heart failure. The coefficient for time estimates the average annual rate of change in the cognitive test score, and the coefficient for the interaction term estimates the difference in average annual rate of change associated with the presence of AF. In addition, we will include a term for prevalent AF to estimate the effect of AF on baseline (visit 2) cognitive function, and a term for incident AF as a time-varying predictor (the value is 1 at a given visit if AF occurred before the visit, and 0 otherwise).

Missing data on cognitive scores will be addressed using inverse-probability weighting.

Hypothesis #3
We will conduct multivariable linear regression analysis to determine whether AF status is associated with WMH volume, ILL, ventricular volume, total brain volume, brain atrophy, and sulcal grade.

Hypothesis #4
To test the association between AF and brain MRI abnormalities (WMH volume, ILL, ventricular volume, total brain volume and atrophy, and sulcal grade), we will use random-effects linear models (PROC MIXED, SAS Software 9.2; SAS Institute, Cary, NC). The models will consist of AF status, time of follow-up (per annual change), a term for the interaction of AF x time, and covariates. The coefficient for time estimates the average annual rate of change in brain MRI parameters, and the coefficient for the

interaction term estimates the difference in average annual rate of change associated with the presence of AF. In addition, we will include a term for prevalent AF to estimate the effect of AF on 1993–1995 brain MRI parameters, and a term for incident AF as a time-varying predictor.

Missing data on brain MRI parameters will be addressed using inverse-probability weighting.

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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)?

#1700: Cognitive function and incident dementia
#1365: Cardiovascular risk factors and dementia hospitalization

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

___ A. primarily the result of an ancillary study (list number* _____)

_x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 1999.01 – ARIC MRI Study, 2008.12 AF ancillary study)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. 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.

References

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