

ARIC Manuscript Proposal #2405

PC Reviewed: 8/12/14
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Atrial Fibrillation and its Association with Cognitive Decline over 20 years: The ARIC Neurocognitive Study (ARIC-NCS)

b. Abbreviated Title (Length 26 characters): Atrial fibrillation and cognitive function

2. Writing Group:

Writing group members: Lin Y. Chen, Faye L. Lopez, Rebecca F. Gottesman, Lisa Wruck, Thomas H. Mosley, Elsayed Z. Soliman, Alvaro Alonso, others welcome.

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: 1 month
Manuscript preparation: 2 months

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing over time.¹ AF is associated with an increased risk of stroke,² heart failure,³ and death.^{4,5} Evidence is emerging that AF is also associated with cognitive impairment or dementia even in individuals without a history of clinical stroke.⁶ We recently reported in the ARIC study over a follow-up period of 10 years, that in the absence of clinical stroke, the association of incident AF with cognitive decline was present only in participants who had prevalent subclinical cerebral infarcts (SCIs) on brain MRI scans or who developed SCIs during follow-up. In individuals without prevalent SCIs or who did not develop SCIs during follow-up, incident AF was not associated with cognitive decline (Chen et al., In Press–*Stroke*). Our observations suggest that the association between incident AF and cognitive decline is mediated by the presence or development of SCIs.

In the proposed study, we aim to extend our investigation to include brain MRI and cognitive test data in the ARIC Neurocognitive Study (ARIC-NCS, 2011-2013). To date, the proposed study will be one of the largest and with the longest follow-up (~20 years) to investigate prospectively the association of incident AF with cognitive decline in a stroke-free population. We will also evaluate whether or not this association is dependent on the presence of SCIs as assessed by brain MRI scans.

The findings of this study will have important clinical and public health implications. If the relationship between AF and cognitive impairment is found to be dependent on the presence of SCIs, the study would provide additional evidence to support another indication for anticoagulation in AF patients—to prevent cognitive decline or dementia.

5. Main Hypothesis/Study Questions:

Aim #1: Evaluate the association of incident AF with cognitive change in stroke-free participants

Hypothesis #1: Compared with participants who do not develop AF, those who develop AF will experience a greater decline in cognitive function.

Aim #2: Evaluate the association of prevalent AF with cognitive test scores, stratified by the presence of SCIs in stroke-free participants

Hypothesis #2: The association of prevalent AF with lower cognitive test scores is significant only in the presence of SCIs.

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

We will include participants with cognitive test data at visit 2 (1990-92) and visit 4 (1996-98) or visit 5/ARIC-NCS (2011-13). Hence, the study period is 1990-2013.

Exclusion criteria: Prevalent AF at visit 2, prevalent stroke at visit 2, missing or uninterpretable ECG, prevalent dementia or race-and sex-specific lowest 5th percentile of cognitive scores at visit 2, and missing covariates. Cognitive test scores after incident stroke will be excluded.

Hypothesis #2

We will include participants with brain MRI scans and cognitive test data at visit 5/ ARIC-NCS (2011-13).

Exclusion criteria: Prevalent stroke at visit 5 and missing covariates.

Exposure

AF

AF cases will be identified from:

- 1) Hospital discharge records (ICD-9 code 427.31 – Atrial fibrillation)
- 2) ECGs performed during study visits

Outcomes

Cognitive decline

z-scores of 3 neuropsychological tests: Delayed Word Recall (DWR) Test, Digit Symbol Substitution (DSS) Test, and Word Fluency (WF) Test; and a global cognitive score will be used to assess cognitive function and determine cognitive decline.

Covariates

Visit 2 variables: age, gender, race, study center, and occupation. Visit 1 variable: educational level. Time-dependent variables: smoking (never, former, current), body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, stroke (as an exclusion variable), coronary heart disease or myocardial infarction, and heart failure.

Subclinical cerebral infarcts

SCIs will be defined as focal, non-mass lesions ≥ 3 mm that are bright on T2 and proton density, and dark on T1 images.

Statistical analysis

Hypotheses #1

AF and cognitive decline

To test the association between AF and cognitive decline rate, we will follow recommendations from the ARIC-NCS Analysis Committee. Specifically, we will use GEE models (PROC GENMOD, SAS Software 9.2; SAS Institute, Cary, NC). Separate models will be run for each cognitive test (DWR, DSS, and WF) and a global cognitive score. The models will consist of AF status (time-dependent), 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, coronary heart disease or myocardial infarction, and heart failure, as well as interactions

between time and covariates. Time will be modeled as a spline variable with a knot at 6 years of follow-up.

To evaluate whether incident AF is associated with cognitive decline in participants with a low risk of stroke, we will repeat the analysis above excluding cognitive test scores of participants with CHADS₂ score ≥ 2 .

In addition, we will conduct sensitivity analysis using inverse probability weighting to adjust for selection bias due to censoring.

Hypotheses #2

AF and cognitive test scores, stratified by presence of SCIs

We will use multivariable linear regression to evaluate the association of prevalent AF with cognitive test scores, stratified by the presence of SCIs.

As a secondary analysis, we will compare cognitive change in participants with prevalent AF at visit 5 to those without AF at visit 5, stratified by presence of SCIs. Cognitive change will be computed based on cognitive test data at visit 2 (1990-92) or visit 4 (1996-98) and visit 5/ARIC-NCS (2011-13).

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

4. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10):946-952.
5. Chen LY, Sotoodehnia N, Bůžková P, et al. Atrial Fibrillation and the Risk of Sudden Cardiac Death: The Atherosclerosis Risk in Communities (ARIC) Study and Cardiovascular Health Study (CHS). *JAMA Intern Med*. 2013;173(1):29-35.
6. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive Impairment Associated With Atrial Fibrillation A Meta-analysis. *Ann Intern Med* 2013;158(5_Part_1):338-346.