ARIC Manuscript Proposal #2545

PC Reviewed: 5/12/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of ECG-Based Left Atrial Abnormality with Cognitive Decline and Subclinical Cerebral Infarcts: The ARIC Study

b. Abbreviated Title (Length 26 characters): LA abnormality, cognition, and brain infarcts

2. Writing Group:
Writing group members: Lin Y. Chen, Faye L. Lopez, Rebecca F. Gottesman, Thomas H. Mosley, Michael Griswold, Aaron Folsom, Hooman Kamel, 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 a serious public health problem because of its increasing prevalence in the aging population[1] and its association with elevated risks of ischemic stroke,[2] cognitive decline or impairment,[3,4] heart failure,[5] and death.[6,7] Other than anticoagulation which reduces the risk of ischemic stroke, current therapies for AF to prevent other adverse outcomes are disappointing. The lack of effective therapies is, in part, due to our poor understanding of the mechanisms mediating the adverse outcomes. Recent evidence has emerged to suggest that the higher risks of stroke and cognitive decline are also observed in individuals with an abnormal atrial substrate of atrial enlargement or dysfunction, even in the absence of AF.[8-12] Further, studies of patients with implantable cardiac electronic devices indicate that the vast majority of ischemic strokes are not temporally related to AF episodes.[13,14] These observations raise the tantalizing question whether it is AF or the underlying atrial substrate that is the main entity that causes these adverse outcomes.

To answer the aforementioned question, this proposal will define the odds of subclinical cerebral infarcts (SCIs) and cognitive change in ARIC participants with abnormal P-wave terminal force in ECG lead V_1 ($PTFV_1$)—a marker of left atrial abnormality—with and without AF.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the association of AF and abnormal PTFV1 with SCIs

Hypothesis 1: The odds of SCIs in participants with abnormal PTFV1 will be higher than those with normal PTFV1. The presence of AF does not increase the odds further: participants with abnormal PTFV1 and with AF will have similar odds of SCIs as participants with abnormal PTFV1 and without AF.

Aim 2: Evaluate the association of AF and abnormal PTFV1 with cognitive decline

Hypothesis 2: Cognitive decline will be greater in participants with abnormal PTFV1 than those with normal PTFV1. The presence of AF does not exacerbate the decline: participants with abnormal PTFV1 and with AF will have the same rate of cognitive decline as participants with abnormal PTFV1 and without AF.

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

Aim 1

We will include participants with brain MRI scans at visit 3 (1993-95) and 2004-06 or visit 5/ARIC-NCS (2011-13). Hence, the study period is 1993-2013.

Exclusion criteria: Missing or uninterpretable ECG at visit 3, prevalent SCIs on brain MRI scans at visit 3, and missing covariates

Aim 2
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: Missing or uninterpretable ECG at visit 2, race-and sex-specific lowest 5th percentile of cognitive scores at visit 2, and missing covariates

Exposures

PTFVI
For Aim 1, PTFV1 will be obtained from ECGs at visit 3 that show sinus rhythm. For Aim 2, PTFV1 will be obtained from ECGs at visit 2 that show sinus rhythm. PTFV1 will be defined as the duration (ms) x the absolute value of the depth (μV) of the downward deflection (terminal portion) of the median P-wave in lead V1. Abnormal PTFV1 is defined as ≥4000 μV*ms.

AF
AF will be a time-dependent variable. AF cases will be identified from:
1) Hospital discharge records (ICD-9 code 427.31 – Atrial fibrillation)
2) ECGs performed during study visits

Outcomes
SCIs: focal, non-mass lesions ≥3 mm that were bright on T2 and proton density, and dark on T1 images.

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
Age, sex, race, study center, occupation, educational level, smoking (never, former, current), body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, use of anticoagulants, diabetes, stroke, coronary heart disease or myocardial infarction, and heart failure.

Statistical analysis

Hypothesis #1
Participants will be divided into 4 groups: normal PTFV1/no AF, normal PTFV1/AF, abnormal PTFV1/no AF, abnormal PTFV1/AF. We will compute the odds of SCIs for participants in these 4 groups and corresponding odds ratios with normal PTFV1/no AF as the referent group. We will adjust the logistic model for the following covariates:

Model 1: Age, sex, race, study center, occupation, and educational level
Model 2: Model 1 + smoking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, use of anticoagulants, diabetes, stroke, coronary heart disease or myocardial infarction, and heart failure

If our hypothesis is correct, the odds of SCIs in abnormal PTFV1/no AF will be similar to abnormal PTFV1/AF. The odds in these 2 groups will be higher than normal PTFV1/no AF or normal PTFV1/AF.

Hypothesis #2
Participants will be divided into 4 groups: normal PTFV1/no AF, normal PTFV1/AF, abnormal PTFV1/no AF, abnormal PTFV1/AF. We will compute the cognitive decline rates for participants in these 4 groups and corresponding cognitive decline rate differences with normal PTFV1/no AF as the referent group.

To test the association of AF or abnormal PTFV1 with 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 and PTFV1 status (4 categories as described above; time-dependent), time of follow-up (years), a term for the interaction of AF/PTFV1 status 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 5 years of follow-up.

We will also construct models assessing only the relationship of abnormal PTFV1 to cognitive scores. In these models, we will additionally adjust for prevalent and incident SCIs.

Finally, we will conduct sensitivity analysis using multiple imputation chained equations (MICE) to adjust for selection bias due to censoring.

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/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)?**

    #1156 – ECG prediction of AF
    #2408 – P-wave morphology and stroke

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

11.b. If yes, is the proposal

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

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