ARIC Manuscript Proposal #2594

PC Reviewed: 8/11/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Electrocardiographic Interatrial Block and Risk of Ischemic Stroke: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Atrial block and stroke

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. WTO

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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).

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3. Timeline:

Analysis to begin after Publication Committee approval. Manuscript anticipated for initial P&P review 4 months after proposal approval.

4. Rationale:

Advanced interatrial block (aIAB) exists when a delay of conduction occurs over the Bachmann bundle and the left atrium is depolarized by retrograde activation via muscle connections near the coronary sinus.[1] These abnormal properties often are observed among persons with risk factors for myocardial fibrosis and abnormal cardiac remodeling, suggesting that aIAB represents underlying left atrial disease.

Recent reports have suggested that electrocardiographically-detected left atrial abnormality, as measured by P-wave terminal force in lead V_1, is associated with an increased risk for ischemic stroke.[2-4] This association was limited to non-lacunar infarcts and remained after accounting for incident atrial fibrillation.[4] These data suggest that left atrial disease itself possibly results in thromboembolism independent of atrial fibrillation and identifies atrial cardiopathy as a risk factor for stroke.[5]

We have recently shown that aIAB is associated with the development of atrial fibrillation (ARIC MS#2563). Given that recent reports have suggested that left atrial thromboembolism is possible without documented atrial fibrillation,[2-4] it is plausible that aIAB also represents a risk factor for ischemic stroke. Therefore, the purpose of this proposal is to examine the association between aIAB and ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:

The aims of this study are:

1) To examine the association between aIAB (as time-dependent variable) with ischemic stroke.
2) To determine if atrial fibrillation mediates the association between aIAB and stroke.

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).

Design: Secondary analysis from prospective cohort.

Inclusion/Exclusion Criteria: We will include all participants with baseline ECG data. We will exclude participants with prevalent stroke or atrial fibrillation at baseline. The few ARIC participants with race other than black or white will also be excluded, including the small number of black participants from Washington County and Minneapolis.

Outcomes: The outcome of interest will be incident ischemic stroke. Secondary outcomes will be incident non-lacunar and lacunar ischemic strokes.

Variables: Cases of aIAB will be identified during study visits 1-4 due to the small number of cases in the initial study visit. aIAB will be derived by the ARIC ECG Reading Center (EPICARE) and defined as a P-wave duration ≥120 ms and biphasic (positive negative) morphology in leads II, III and AV_F.[1] Other variables needed from the baseline study visit will include the following: demographics (age, sex, race/ethnicity) stroke risk factors (systolic blood pressure, LDL cholesterol, body mass index, smoking, diabetes, coronary heart disease, heart failure), and baseline medication use (blood pressure lowering drugs, lipid-lowering therapies, and aspirin).

Statistics: Baseline characteristics will be examined by the presence of aIAB. Categorical variables will be reported as frequency and percentage while continuous variables will be recorded as mean ± standard deviation. Follow-up will be defined as time between the baseline exam until ischemic stroke, loss to follow-up, or end of follow-up. For those with incident aIAB, time between baseline and aIAB diagnosis will be considered as non-aIAB follow-up. Kaplan-Meier estimates will be used to examine the cumulative incidence of ischemic stroke by the presence of aIAB as time-dependent variable. Cox regression will be used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between aIAB and ischemic stroke. Multivariable models will be constructed as follows: Model 1 adjusted for age, sex, and race/ethnicity; Model 2 adjusted for Model 1 covariates plus smoking, systolic blood pressure, diabetes, body mass index, LDL cholesterol, antihypertensive medication use, coronary heart disease, and heart failure; Model 3 adjusted for Model 2 covariates plus incident atrial fibrillation. The variables included in the multivariable models will be from the initial study visit. Due to the known association between left atrial abnormality and ischemic stroke in ARIC,[4] a sensitivity analysis will be performed with adjustment for P-wave terminal force in lead V_1 ($PTFV_1$) to determine if both markers independently predict stroke. We also will examine the association between aIAB and ischemic stroke by non-lacunar and lacunar ischemic stroke subtypes, separately.

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)?

ARIC MS#2563- O'Neal
ARIC MS#2408- Kamel

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.

References

1. Bayes de Luna A, Platonov P, Cosio FG, et al. Interatrial blocks. A separate entity from left atrial enlargement: a consensus report. *J Electrocardiol.* 2012;45(5):445-451.
2. Kamel H, Soliman EZ, Heckbert SR, et al. P-wave morphology and the risk of incident ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. *Stroke.* 2014;45(9):2786-2788.
3. Kamel H, Bartz TM, Longstreth WT, Jr., et al. Association between left atrial abnormality on ECG and vascular brain injury on MRI in the Cardiovascular Health Study. *Stroke.* 2015;46(3):711-716.
4. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic Left Atrial Abnormality and Stroke Subtype in ARIC. *Ann Neurol.* 2015.
5. Kamel H, Okin PM, Longstreth WT, Jr., Elkind MS, Soliman EZ. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. *Future Cardiol.* 2015;11(3):323-331.