

ARIC Manuscript Proposal #2689

PC Reviewed: 1/12/16
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Association of Abnormal P-Wave Axis with Atrial Fibrillation and Ischemic Stroke.

b. Abbreviated Title (Length 26 characters): aPWA associated with AF and ischemic stroke

2. Writing Group:

Writing group members: Ankit Maheshwari, Faye L. Norby, Wesley T. O’Neal, Selcuk Adabag, Alvaro Alonso, Elsayed Z. Soliman, Lin Y. Chen, others welcome.

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

First author: Ankit Maheshwari MD

Address: Cardiac Arrhythmia Center, Cardiovascular Division
Department of Medicine,
University of Minnesota Medical School
420 Delaware Street SE, MMC 508
Minneapolis, MN 55455

Phone: 630-915-0660 Fax: 612-624-4937
E-mail: mahes046@umn.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, MD, MS
Address: Cardiac Arrhythmia Center, Cardiovascular Division
Department of Medicine
University of Minnesota Medical School
420 Delaware Street SE, MMC 508
Minneapolis, MN 55455

Phone: 612-625-4401 Fax: 612-624-4937
E-mail: chenx484@umn.edu

- 3. Timeline:** Statistical Analysis: 1 month
Manuscript Preparation: 2 months

4. Rationale:

P-wave axis (PWA) is a routine measure on 12-lead ECGs that reflects the net vector component of atrial depolarization in the frontal plane. Abnormal P-wave axis (aPWA) is defined as any value outside 0-75 degrees. It has been linked to incident atrial fibrillation (AF) in the Cardiovascular Health Study (CHS) and all-cause mortality in the National Health and Nutrition Examination Survey (NHANES)^{1,2}. AF is independently associated with an increased risk of ischemic stroke in the general population. Of note, markers of left atrial abnormality which predict AF are also independently associated with ischemic stroke³⁻⁶. These markers—with the exception of PR interval which is weakly associated with stroke—are not routinely reported on ECGs. The association of aPWA with ischemic stroke is not well established. We hypothesized that aPWA—a routine measure on 12-lead ECGs—is independently associated with ischemic stroke in the general population secondary to cardiac thromboembolism. As such, we expect a stronger association with nonlacunar stroke as opposed to lacunar stroke.

5. Main Hypothesis/Study Questions:

AIM : Evaluate the association of aPWA with AF and ischemic stroke

Hypothesis: aPWA will be significantly associated with an increased risk of each of the following cardiovascular outcomes: AF, ischemic stroke, and lacunar stroke. aPWA will not be significantly associated with nonlacunar 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).

Study Population: We will include all participants at the baseline visit (V1). We will exclude those with missing covariates and missing ECG data. For analysis of stroke as the outcome, we will exclude prevalent stroke. For analysis of AF as the outcome, we will exclude prevalent AF.

Exposure

Normal P-wave axis will be defined as a value between 0 and 75 degrees. Abnormal P-wave axis (aPWA) will be defined as P-wave axis with values outside this window.

Outcome

AF: Incident AF was determined from resting ECGs obtained during 4 study examinations, hospital discharge codes, and death certificates. AF events identified during cardiac surgery were excluded⁷.

Ischemic Stroke: Cases of ischemic stroke were identified by annual phone interviews, hospital discharge records, and death certificates. Each case was classified in accordance with criteria from the National Survey of Stroke by a computer algorithm and physician reviewer as previously described. Discrepancies were reviewed by a second physician. In cases of definite thrombotic stroke, cases were classified as lacunar or nonlacunar stroke⁸. For our study, ischemic stroke was defined as definite and probable ischemic stroke.

Covariates

Age, sex, race, study center, smoking (never, former, current), body mass index, hypertension, systolic and diastolic blood pressure, use of antihypertensive medication, use of anticoagulants, diabetes, stroke, CHD, ECG-based left ventricular hypertrophy (LVH) defined by the Cornell criteria, and heart failure.

Statistical Analysis: AF

Follow-up will be defined as time between the baseline exam until the date of AF diagnosis. We will use Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals of aPWA for incident AF. We will exclude patients with prevalent AF.

Model 1: Age, sex, race, study center

Model 2: Model 1 + smoking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, CHD, LVH by ECG, and heart failure

Statistical Analysis: Ischemic Stroke, nonlacunar stroke, and lacunar stroke

Follow-up will be defined as time between the baseline exam until the date of ischemic stroke. We will use Cox proportional hazards models to estimate hazard ratios and 95% confidence intervals of aPWA for incident ischemic stroke, nonlacunar stroke, and lacunar stroke.

Model 1: Age, sex, race, study center

Model 2: Model 1 + smoking, body mass index, hypertension, use of anticoagulants, diabetes, CHD, and heart failure

Model 3: Model 2 + time-dependent AF

For all outcomes, we will also consider restricted cubic spline regression to evaluate association with outcome across the continuum of P wave axis.

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>

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)?

#1557 – ECG Predictors of SCD - Soliman

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes 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)* 2004.03)

*ancillary studies are listed by number at <http://www.csc.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.csc.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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 No.

References

1. Li, Y., Shah, A. J. & Soliman, E. Z. Effect of electrocardiographic P-wave axis on mortality. *Am J Cardiol* **113**, 372–6 (2014).
2. Rangel, M. O., O’Neal, W. T. & Soliman, E. Z. Usefulness of the Electrocardiographic P-Wave Axis as a Predictor of Atrial Fibrillation. *Am. J. Cardiol.* (2015). doi:10.1016/j.amjcard.2015.10.013
3. Soliman, E. Z., Prineas, R. J., Case, L. D., Zhang, Z. M. & Goff, D. C. Ethnic distribution of ecg predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the atherosclerosis risk in communities (ARIC) study. *Stroke* **40**, 1204–1211 (2009).
4. Kamel, H. *et al.* Association Between Left Atrial Abnormality on ECG and Vascular Brain Injury on MRI in the Cardiovascular Health Study. *Stroke* 711–716 (2015). doi:10.1161/STROKEAHA.114.007762
5. Kamel, H. *et al.* Electrocardiographic Left Atrial Abnormality and Risk of Stroke. *Stroke* STROKEAHA.115.009989 (2015). doi:10.1161/STROKEAHA.115.009989
6. Kamel, H. *et al.* Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. *Ann Neurol* (2015).
7. Alonso, A. *et al.* Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am. Heart J.* **158**, 111–7 (2009).
8. Rosamond, W. D. *et al.* Stroke Incidence and Survival Among Middle-Aged Adults. 736–743 (1999).