**ARIC Manuscript Proposal #3522**

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| **PC Reviewed: 12/10/19** | **Status: _____** | **Priority: 2** |
| **SC Reviewed: _____** | **Status: _____** | **Priority: ____** |

**1a. Full Title**: Association of P-wave indices and Brain MRI abnormalities: The ARIC Study

**1b. Abbreviated Title (Length 26 characters)**: PWIs and Brain MRI abnormalities

**2. Writing Group**:
Writing group members: Jorge L. Reyes, Faye L. Norby, Wendy Wang, Michael Zhang, Romil Parikh, Joseph Decker, Niki Oldenburg, Elsayed Z. Soliman, Alvaro Alonso, Lin Y. Chen, and others welcome

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


**First author**: Jorge L. Reyes, MD
Address: Hennepin County Medical Center,
Department of Medicine,
701 Park Ave, Minneapolis, MN 55415
Minneapolis, MN 55415.
Phone: 312-576-6306 Fax: 612-624-4937
E-mail: jorge.reyescastro@hcmed.org


**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: 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**:

Atrial fibrillation (AF) is a serious public health problem that is highly prevalent in the aging population.[1] This disease currently affects approximately 2.3 million people in the United States; this number is expected to increase to 5.6 million people by 2050.[2] AF is associated with an increased risk of stroke,[3] cognitive impairment,[4] dementia[5] and brain magnetic resonance imaging (MRI) morphological changes.[6] Left atrial (LA) abnormality—such as LA enlargement or impaired LA function—is also related to some of the aforementioned outcomes, independent of AF.

P-wave indices (PWIs) are ECG markers of LA abnormality and they include P-wave axis, P-wave duration, advanced inter-atrial block (aIAB), and P-wave terminal force in lead V1 (PTFV1). PWIs have also been shown to be associated with increased risk of ischemic stroke[7, 8] and brain vascular injury,[9] independent of AF. However, whether PWIs are associated with other brain MRI changes (e.g., brain volume, ventricular volume, and WMH volume) is unknown.

Therefore, we aim to evaluate the association between PWIs and brain MRI measures.

**5. Main Hypothesis/Study Questions**:

**Aim 1: Evaluate the cross-sectional association of PWIs with brain MRI abnormalities in late life.**

Hypothesis Aim 1: Abnormal P-wave axis, PTFV1, P-wave duration, and presence of aIAB will be associated with lower brain volume; greater ventricular volume and WMH volume; and more brain infarcts at visit 5.

**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 5 and those with ECGs at visit 5.

Exclusion criteria:
Missing covariates.
Uninterpretable ECGs

**Exposures measurement**

P-wave indices (P-wave Axis, P-wave duration, P-wave terminal force, advanced inter-atrial block). P-wave indices will be based on 12-lead ECGs from visit 5 for aim 1 and visit 3 for aim 2.

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, similar to previous ARIC papers.

Normal PWA will be defined as a value between 0 and 75 degrees. Abnormal PWA will be defined as PWA with values outside this window.

Prolonged P-wave duration is defined as >120 ms.

Advanced inter-atrial block will be defined as P-wave duration >120ms + biphasic P-wave morphology in leads III and aVF with biphasic morphology or notched morphology in lead II.

**Outcomes measurement**
**Aim 1**: We will look at the following structural brain MRI measures at visit 5.

- Cerebrovascular Lesions
    - Cortical infarcts
    - Subcortical infarcts
    - Lacunar infarcts
    - Microhemorrhages

- White matter disease
    - White matter hyperintensities

- Volumes
    - Total brain
    - Frontal lobe
    - Temporal lobe
    - Occipital lobe
    - Parietal lobe
    - Hippocampal

- Deep gray matter
- AD signature region
- Total cortical (sum of frontal, parietal, occipital, and temporal lobe volumes)

**Covariates**

Variables will be obtained from visit 5 except for education and APOE e4 status which was included from visit 1. These variables include age, sex, race and center (black–Mississippi, black–North Carolina, white–North Carolina, white–Maryland, white–Minnesota), smoking status (current, former, never). Hypertension was defined as a systolic blood pressure ≥140, diastolic blood pressure ≥90, or use of antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose ≥ 126 mg/dL, a nonfasting glucose ≥200 mg/dL, using medication for diabetes mellitus, or self-reported physician diagnosis of diabetes mellitus. Heart failure, coronary heart disease, and stroke were defined based on presence of adjudicated events according to previously published criteria.

**Statistical analysis**

**Aim 1:** Weighted multivariable linear (for continuous MRI measures) or logistic (for categorical MRI measures) regression models will be used to estimate the cross-sectional association of PWIs (categorized as normal vs. abnormal) with subclinical brain MRI abnormalities.

All analyses will incorporate sampling weights in order to account for the ARIC brain MRI sampling strategy. Each brain volume will be scaled on the basis of its standard deviation to facilitate comparison of the magnitude of association across brain regions in regression models. WMH volume is highly skewed, and therefore will be log base 2 ($\log_2$) transformed for normality. The multivariable models to be used in the present study are constructed as follows:

Model 1 will be adjusted for demographics (age, sex, race and center, and education) and total intracranial volume (for volume measures only).

Model 2 will be adjusted for all variables in model 1 and also cardiovascular risk factors (smoking, diabetes, hypertension), prevalent cardiovascular disease (past history of coronary heart disease, heart failure, or atrial fibrillation) and APOE4.

Model 3 (for volume measures only) will include all variables in model 2 in addition to markers of subclinical cerebrovascular disease (lobar microhemorrhages, subcortical microhemorrhages, cortical infarcts, subcortical infarcts, lacunar infarcts, and Log2 WMH).

For secondary analyses, we will estimate the association between PWIs and brain MRI measures for subgroups of interest including age, sex, race, or cardiovascular risk factors/prevalent cardiovascular disease. Effect modification will be formally tested using interaction terms.

We will also conduct a sensitivity analysis excluding participants with atrial fibrillation.

**7a. Will the data be used for non-CVD analysis in this manuscript?____ Yes __x__ No**

**7b. 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.)

**8a. Will the DNA data be used in this manuscript?____ Yes _x___ No**

**8b. 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)?**

#2408 – P-wave morphology and stroke (Kamel)
#2689 Association of abnormal P-Wave axis with atrial fibrillation and ischemic stroke (Maheshwari)
#2545 - Association of ECG-Based Left Atrial Abnormality with Cognitive Decline and Subclinical Cerebral Infarcts: The ARIC Study (Gutierrez)
#3279 - Association between atrial fibrillation and brain volumes: the ARICNeurocognitive (ARIC-NCS) Study (Moazzami)

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

**11b. 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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