1.a. Full Title: P-Wave Indices and the CHA2DS2-VASC score for stroke prediction in persons with atrial fibrillation: the Atherosclerosis Risk in Communities Study.

b. Abbreviated Title (Length 26 characters): P-Wave Indices and CHADS2VASC

2. Writing Group:

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]

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

4. **Rationale:**

Atrial fibrillation (AF) is associated with a 5-fold increase in thromboembolic stroke risk.\(^1\) Thrombogenesis in atrial fibrillation is a diverse process relying on synergy between all three elements of Virchow’s triad.\(^2\) Prothrombotic structural changes in the molecular atrial architecture may, in fact, precede development and/or diagnosis of AF, and detecting these early changes poses an opportunity to improve stroke prediction in the general population and in patients with AF. P-wave indices (PWI) are markers derived from P-wave morphology in the electrocardiogram to characterize atrial conduction and these include P-wave axis (PWA), P-wave duration, and P-wave terminal force (PTFV1). Abnormal PWIs have been associated with atrial remodeling, increased risk of atrial fibrillation (AF), and increased risk of ischemic stroke.\(^3\)

Currently, the CHA\(_2\)DS\(_2\)-VASc score is the principal clinical tool used for stroke risk stratification in patients with AF. However, its discriminatory capacity for ischemic stroke is modest (C-statistic, 0.60). We hypothesized that the addition of PWI to the CHA\(_2\)DS\(_2\)-VASc score would improve discriminatory capacity in participants with AF.

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

**AIM:** Evaluate the predictive value of adding P-wave indices to the CHA\(_2\)DS\(_2\)-VASc score for prediction of ischemic stroke in patients with AF.

**Hypothesis:** The addition of PWI (prolonged PWD, abnormal PTFV1, abnormal PWA) to the CHA\(_2\)DS\(_2\)-VASc score will improve discriminatory capacity in patients with 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:** We will include all participants at the baseline visit (V1). We will exclude those with missing covariates and missing ECG data, prevalent AF, stroke before incident AF, and those with use of anti-coagulants within 1 year of AF diagnosis. We will identify all incident cases of AF after V1. We will use the previous EKG (prior to AF incidence) to ascertain PWI. CHA\(_2\)DS\(_2\)-VASc score will be calculated at the time of AF diagnosis.

**Exposure**
- P-Wave Indices (P-Wave Axis, P-Wave Duration, P-wave terminal force).
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.

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

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 will be excluded.

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 stroke. For our study, ischemic stroke was defined as definite and probable ischemic stroke.

Statistical Analysis:

We will estimate the association of abnormal PWA, prolonged PWD, abnormal PTFV1 with incident ischemic stroke using Cox proportional hazard models adjusted for age, sex, race, study center, and CHA2DS2-VASc variables excluding history of stroke or TIA (age, sex, HF, hypertension, diabetes, previous MI and PAD; hereafter called ‘CHA2DS2-VASc adjusted model’).

We will test whether adding (1) each PWI and (2) all 3 PWIs to the CHA2DS2-VASc score will improve risk prediction of 1-year ischemic stroke risk and 5-year ischemic stroke risk. We will compute the C-statistic using methods that accounted for censoring to assess model discrimination. To test model calibration, “goodness-of-fit” of the observed and expected number of events within estimated risk decile groups will be compared using the Grønnesby-Borgan statistic. Finally, to assess improvement in risk classification, categorical and continuous net reclassification improvement (NRI) and relative integrated discrimination improvement (IDI) for 1-year and 5-year risk prediction will be calculated. For categorical NRI, we will use the following categories for 1-year stroke risk: <1%, 1-<2%, and ≥2%.

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.csc.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)?

#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    ___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.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.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.

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 __x__ No.

References


