ARIC Manuscript Proposal # 3335

PC Reviewed: 1/8/18  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: ECG Predictors of Subclinical Atrial Fibrillation: the ARIC Study

b. Abbreviated Title (Length 26 characters): ECG predictors of subclinical AF

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.

   Importantly, subclinical AF poses a significant public health risk. Even short paroxysms of the arrhythmia are associated with non-trivial risk of stroke. Furthermore, at least 16% of cryptogenic strokes have AF identified on further cardiac monitoring, a number that is likely underestimated. Collectively, these findings highlight the importance of detecting subclinical AF to help inform stroke risk assessment.\(^3,4\)

   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.\(^5\) However, whether these PWIs are associated with increased risk of subclinical AF is unknown.

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

   **AIM:** Evaluate the association of abnormal PWI based on Visit 5 12-lead ECGs with subclinical AF detected by the Zio Patch at Visit 6.

   **Hypothesis:** Abnormal PWI will be associated with higher odds of subclinical 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 who attended the Visit 6 examination. We will exclude those with missing Zio Patch data at V6, missing ECG data at V5, and missing covariates at V5. We will also exclude those with prevalent AF at V5.

   **Exposure**
   P-Wave Indices (P-Wave Axis, P-Wave Duration, P-wave terminal force, advanced inter-atrial block). P-wave indices will be based on V5 12-lead ECGs.
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.

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.

**Outcome**

Subclinical AF: AF detected only by the Zio Patch at Visit 6 (i.e., those detected by ARIC ascertainment at V6 will not be counted as subclinical AF).

Clinical AF: Any AF identified through standard ARIC ascertainment (study visit ECGs, review of hospitalization records)

**Covariates:**

Age, sex, race, field center, body mass index, height, systolic and diastolic blood pressure, use of hypertension medications, diabetes, coronary heart disease, heart failure, LA volume index, and LV mass index. All covariates will be based on V5 data.

**Statistical Analysis:**

We will use multivariable logistic regression to assess the association of PWI with subclinical AF. We will construct separate models for each PWI.

Model 1: Age, sex, race-field center

Model 2: Model 1 + body mass index, height, systolic and diastolic blood pressure, use of hypertension medications, diabetes, coronary heart disease, and heart failure

Model 3: Model 2 + LA volume index

Model 4: Model 2 + LV mass index

Model 5: Model 2 + LA volume index and LV mass index

We will also conduct a multinomial logistic regression with a 3-level endpoint: clinical AF, subclinical AF, no AF to determine whether associations of the PWIs are different for subclinical vs clinical AF.

We will conduct a sensitivity analysis to deal with non-participation at Visit 6 using inverse probability weighting.
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.cscce.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)?
MP 2893, MP1559

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

11.b. If yes, is the proposal
   ____ A. primarily the result of an ancillary study (list number*)
   ___2014.18______
   ____ 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.cscce.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