ARIC Manuscript Proposal # 1559

PC Reviewed: 10/13/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
PR interval, P wave indices and the incidence of atrial fibrillation: the ARIC study

b. Abbreviated Title (Length 26 characters):
PR interval, P wave indices and AF

2. Writing Group:
Alvaro Alonso, Elsayed Soliman, Sunil K Agarwal, Laura Loehr, Aaron Folsom, others welcome

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

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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: 3 months
First draft of manuscript: 3 months

4. Rationale:
ECG-defined PR interval and P wave indices have been identified as potential intermediate phenotypes (endophenotypes) of atrial fibrillation (AF). In fact, these electrocardiographic parameters have been associated with atrial fibrosis and alterations

in cardiac electrical conduction that might reflect the development of a substrate for AF.[1] Few studies, though, have evaluated whether PR interval and P wave indices are associated with the incidence of AF.[2, 3] These studies had a number of limitations, including a limited sample size, a cross-sectional approach or inclusion of only whites.

In a previous ARIC publication including only AF cases identified by ECGs performed in visits 2 to 4 (117 cases), PR interval and P wave indices (P wave duration, P wave area and P wave terminal force in V1) were associated with the incidence of AF.[4] We propose to reexamine this association including additional AF cases identified from hospitalizations during follow-up through 2005. Furthermore, we will specifically explore whether non-linear associations exist between these ECG parameters and the risk of AF. Even though previous analyses have considered that the association of PR interval and other potential AF endophenotypes with AF risk is linear, existing evidence suggest that these associations could be more complex, with both short and long PR interval associated with the risk of AF.[5] Finally, we will explore whether identified associations are different in whites and African-Americans, given the reported lower risk of AF in African-Americans in spite of their higher exposure to risk factors for AF.[6]

5. Main Hypothesis/Study Questions:

In the present proposal we aim to:

1. Evaluate whether PR interval and P wave indices are associated with the incidence of AF, and characterize the dose-response relationship for such putative association.

2. Explore whether associations are different in whites and African-Americans

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 design

We will conduct a time-to-event analysis, with ECG-derived PR interval and P wave indices at baseline as the main exposure, and incidence of AF during follow-up as the main outcome variable.

Inclusion and exclusion criteria

From the 15,792 ARIC participants, we will exclude those who did not have a 12 lead ECG done at baseline, those with poor quality ECG recordings (QC grade 5), those with ECG-defined prevalent AF at baseline, and those with missing information for the main covariates, those with reported race other than black or white. We will apply the typical inclusion criteria based on race and center (only whites in the Minnesota and Washington County field centers; whites and African American in Forsyth County, African-Americans in Jackson). Finally, we will exclude those with pacemakers, those with Wolf-Parkinson-White syndrome, PR interval >320 ms, right bundle branch block (RBBB) or left bundle branch block (LBBB) (the interpretation of PR interval and P wave indices in these individuals could be problematic).

Exposure assessment

At baseline, 12-lead, 10-second ECGs recordings were taken in all ARIC participants. PR interval and P wave indices (P wave duration, P wave amplitude, P wave area and P wave terminal force V1) were measured automatically from electronic ECGs.[4] The main exposures to be considered in this analysis will be: PR interval, P wave duration (maximum, average, and at lead II), P wave amplitude (maximum, average and at lead II), P wave area (maximum, average and in lead II) and P wave terminal force in V1 (defined as the duration in seconds of the negative part of the P wave in lead V1 multiplied by its depth in microvolts). If available, we will also use P wave dispersion (defined as the difference between the maximum and minimum P wave durations).

Outcome

Ascertainment of incident AF in ARIC has been previously described.[6] Briefly, AF was determined from three sources: ECGs done at baseline and follow-up visits, discharge codes from hospitalizations and death certificates. Most AF cases in ARIC are identified from discharge hospitalizations. A validation study in ARIC has determined that the sensitivity of discharge codes for AF is at least 84% and the positive predictive value at least 89%.[6]

Statistical analysis

The association of PR interval and P wave indices with the incidence of AF will be assessed using Cox proportional hazard models. Initial analyses will explore the shape of the association using restricted cubic splines, polynomial models and by several PR interval/P wave index categories based on shape of restricted cubic splines. Models will be adjusted for the following covariates: age, gender, study center, race, education, income, body mass index, height, heart rate, systolic blood pressure, use of antihypertensive medication, diabetes, smoking, alcohol intake, heart murmur, ECG-defined left ventricular hypertrophy, and use of the following medications: beta-blockers, class I or III antiarrhythmics, cardiac glycosides, and calcium channel blockers. In additional analyses, we will adjust for history of myocardial infarction or heart failure at baseline. We will also conduct stratified analysis by age, gender, and race, and test multiplicative interactions with a likelihood ratio test. We will also conduct sensitivity analyses excluding users of medications that might affect the PR interval (beta-blockers, antiarrhythmics, calcium channel blockers, cardiac glycosides). Finally, we will determine if associations differ according to the method of AF ascertainment (ECG, hospital discharge codes).

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?

____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)?

MS #1156. Soliman et al explored the association of PR interval and P wave indices with AF ascertained from ECGs conducted in visit 2 through 4 (117 AF cases). The current proposal will include also AF cases identified from hospitalizations (more than 1200 incident cases through the end of 2005). Dr. Soliman is a coauthor in this proposal and will provide valuable guidance in the interpretation of exposure information and results.

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

_X_ A. primarily the result of an ancillary study (list number* 2008.09)

___ 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/

12. 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.

1. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol 2008;51:802-809.
2. Cheng S, Keyes MJ, Larson MG, et al. Long-term outcomes in individuals with prolonger PR interval or first-degree atrioventricular block. JAMA 2009;301:2571-2577.

3. Magnani JW, Williamson MA, Ellinor PT, Monahan KM, Benjamin EJ. P wave indices. Current status and future directions in epidemiology, clinical, and research applications. Circulation Arrhythmia and Electrophysiology 2009;2:72-79.
4. Soliman EZ, Prineas RJ, Case D, Zhang Z-M, Goff DC, Jr. Ethnic distribution of electrocardiographic predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities Study (ARIC). Stroke 2009;40:1204-1211.
5. Pfeuffer A, van Noord C, Marciante KD, et al. Genome-wide association study of PR interval and relation to risk of atrial fibrillation. Nat Genet 2009; under review.
6. Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2009;158:111-117.