ARIC Manuscript Proposal #2664

PC Reviewed: 11/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Components of the PR Interval and the Risk of Atrial Fibrillation

b. Abbreviated Title (Length 26 characters): **PR segment and atrial fibrillation**

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. [JS]

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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 to begin immediately after the P&P Committee approval. Manuscript anticipated to be ready 6 months after approval.

4. Rationale:

PR interval on the resting electrocardiogram (ECG) has been suggested as a potential predictor for future risk of developing atrial fibrillation (AF) (1). Currently, prolongation of the PR interval is a component of the Framingham AF risk score (2), which was validated in the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES) and the Cardiovascular Health Study (CHS) (3). However, inconsistencies have been reported regarding the association between prolonged PR and AF, especially among racially diverse cohorts. For example, prolonged PR interval did not add to the prediction of AF in the Atherosclerosis Risk in Communities (ARIC) study (4), and paradoxically short PR interval was more predictive of AF than prolonged PR interval in a meta-analysis using data from multiple cohorts in the United States and Europe (5).

An explanation for the observed inconsistencies stems from the fact that the PR interval consists of three different components: time from P-wave onset to peak P wave (which represents conduction within the right atrium), time from peak P-wave to the end of P-wave (which represents conduction within the left atrium), and the PR segment (representing AV conduction) (8). Since each part of the PR interval represents an independent entity, the association between each component of the PR interval with AF may be independent, suggesting that abnormalities detected in the PR interval are not uniform (6). Therefore, an examination of the the association between each component of the PR interval with future development of AF possibly will help to explain the aforementioned inconsistencies and aid in our ability to predict AF events in the general population. To address these gaps in knowledge, we propose to examine the association between each component of the PR interval with AF in the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:

The purpose of this study is to examine the association between each component of PR interval (P onset to P peak duration, P peak to P end duration and PR segment) with incident AF in ARIC.

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).

Inclusion/Exclusion Criteria

We will include all participants with baseline ECG data and incident AF data. We will exclude participants with non-sinus rhythms at baseline, including AF or with ECG conditions that impact PR interval measurements (e.g. advanced AV block, WPW). Also, participants on anti-arrhythmic drugs or digoxin will be excluded. Similar to prior ARIC

papers, non-white and non-black individuals will be excluded, as well as blacks from the Minnesota and Washington sites.

Outcomes

The primary outcome will be incident AF as defined as in prior ARIC publications (7).

Main Exposure Variables:

Baseline P onset to P peak duration, P peak to P end duration and PR segment identified from baseline ECG data.

Covariates:

Baseline (visit 1) age, race, sex, education level, study site, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medications, total cholesterol, high-density lipoprotein (HDL) cholesterol, smoking status, serum glucose, hypertension, diabetes, and heart rate.

Statistical Analyses

Baseline characteristics (visit 1) of the analysis population will be tabulated and compared across different components of PR interval **(**P onset to P peak duration, P peak to P end duration and PR segment). The 95^{th} percentile of each component will be used as the cut-point defining an abnormality. Age-adjusted incidence rates of AF per 1000 person-years in the study participants, overall and across different components of PR interval (P onset to P peak duration, P peak to P end duration and PR segment) will be computed using Kaplan-Meier estimates.

Cox regression will be used to examine the association between each component of the PR interval (P onset to P peak duration, P peak to P end duration and PR segment) with AF. These components will be used in the models as binary variables (using the 95^{th} percentile as the cut-point defining abnormality) and as continuous variables (per 1-standard deviation increase). Models will be adjusted as follows: Model 1 adjusted for age, sex, race, study site, and education level; Model 2 adjusted for Model 1 covariates plus heart rate, body mass index, prevalent coronary artery disease, prevalent congestive heart failure, diabetes, hypertension, dyslipidemia, and smoking status.

Subgroup analyses will be performed by age (dichotomized at median age), sex, and race (white vs. black). Additionally, we will examine the graphical dose-response relationship between each component of the PR interval (P onset to P peak duration, P peak to P end duration and PR segment) with AF using a restricted cubic spline model at the 5th, 50th, and 95th percentiles.

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.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)?

ARIC MS #1156 Soliman**:** Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke.

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.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.

References

1. Soliman EZ, Prineas RJ, Case D, Zhang ZM, Goff D 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;40,1204-11.

2. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. Lancet 2009;373:739.

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4. Chamberlain AM, Agarwal SK, Folsom AR, et al. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). Am J Cardiol. 2011; 107:85osis

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6. Soliman EZ, Cammarata M, Li Y. Explaining the inconsistent associations of PR interval with mortality: the role of P-duration contribution to the length of PR interval. Heart Rhythm. 2014 Jan;11(1):93-8.

7. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J. 2009 Jul;158(1):111-7

8. Human Gp Fau - Snyman, H. W., & Snyman, H. W. (1963). The value of the Macruz index in the diagnosis of atrial enlargement. *Circulation, 27*(5), 935-938.