ARIC Manuscript Proposal #2745

PC Reviewed: 4/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: QRS duration and risk of atrial fibrillation in the general population

b. Abbreviated Title (Length 26 characters): QRS duration and AF

2. Writing Group:

Writing group members: Stefanie Aeschbacher
Philipp Krisai
Wesley O'Neal
Laura Loehr
Lin Y. Chen
Alvaro Alonso
Elsayed Z. Soliman
David Conen

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

First author: **Stefanie Aeschbacher, MSc**
Address: Cardiovascular Research Institute Basel
University Hospital Basel
Spitalstrasse 2
CH-4056 Basel
Switzerland

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: Elsayed Z. Soliman, MD, MSc, MS
Address: EPICARE Center, Wake Forest School of Medicine
Medical Center Blvd
Winston-Salem, NC 27157-1063
Phone: 336-716-8632
E-mail: esoliman@wakehealth.edu

3. Timeline:
Statistical analysis can be started immediately after the P&P Committee approval. Manuscript anticipated to be ready 6 months after approval.

4. Rationale:
QRS duration (QRSd) on the resting electrocardiography (ECG) is an independent predictor of mortality in patients with and without atrial fibrillation (AF).[1, 2] Less evidence is available on the association between QRSd and incident AF. A cross sectional study among patients with left ventricular dysfunction found a higher prevalence of AF among patients with prolonged QRSd.[3] A small study investigating patients with septic shock identified QRSd as a predictor of new-onset AF[4] and QRSd was shown to be an independent predictor of incident AF in patients after ischemic stroke.[5] However, a case-control study found an association between AF and incomplete right bundle branch block, but not QRSd.[6] All these studies are limited to small sample size and specific patient groups, and large population based studies on this topic are lacking.
Thus, QRSd could be an easily quantifiable predictor for new-onset AF, potentially representing myocardial fibrosis.[7] Currently no data is available on this association in the general population and possible differences in diverse ethnic groups. The Atherosclerosis Risk in Communities (ARIC) Study provides an ideal opportunity to elucidate these gaps in knowledge.

5. Main Hypothesis/Study Questions:
To examine the independent relationship between QRSd and incident 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).

Inclusion/Exclusion Criteria
We will include ARIC study participants with complete baseline ECG data and follow-up information. We will exclude participants with a history of AF at baseline, non-sinus rhythm (e.g. atrial flutter), pacemaker-rhythm or a Wolff-Parkinson-White pattern on the baseline ECG. Study participants with QRS intervals ≥120ms (except for the conditions mentioned above) will remain in the dataset. Similar to previously published ARIC studies, individuals who are non-white and non-black will be excluded as well as blacks from the Minneapolis and Washington County sites.[8]

Outcomes
The primary outcome is incident AF as defined in prior ARIC publications.[8]

Main Exposure Variables:
- Primary analysis: QRS duration

- Secondary analysis: Right bundle branch block (RBBB), left bundle branch block (LBBB), bifascicular block and indetermined-type ventricular block (IVCD), as defined by Minnesota ECG codes in a prior ARIC publication[9]

Covariates:

Baseline (visit 1):

age, race, sex, study site, education level, body mass index, height, smoking status, systolic blood pressure, diastolic blood pressure, blood pressure lowering medications, diabetes, heart rate, history of myocardial infarction (MI), history of heart failure (HF), PR interval, P wave terminal force.

Statistical Analyses

Table 1: Baseline characteristics

Baseline characteristics will be stratified according to QRS categories (QRS<100ms, QRS 100-119ms and QRS≥120ms). Distribution of continuous variables will be checked using skewness, kurtosis and visual inspection of the histogram. Normally distributed variables will be presented as means ± standard deviations, otherwise as medians (interquartile ranges). Group comparisons will be done using analysis of variance (ANOVA) or Kruskal-Wallis-Test, as appropriate. Categorical variables will be presented as numbers (percentages) and compared using Chi-square tests.

The following variables will be included in *Table 1* to characterize the study population:

Age, race, sex, study site, education level, body mass index, height, smoking status, systolic blood pressure, diastolic blood pressure, blood pressure lowering medications, diabetes, heart rate, history of myocardial infarction (MI), history of heart failure (HF), PR interval, P wave terminal force.

Figure 1: Cumulative incidence of atrial fibrillation across categories of QRS duration

Cumulative incidence of AF will be stratified by categories of the QRS interval (QRS<100ms, QRS 100-119ms and QRS≥120ms) using the Cumulative Incident Function, in order to account for the competing risk of death.

Table 2: Relationship of QRS duration with incident atrial fibrillation

Multivariable adjusted Cox regression models will be constructed to assess the association between QRSd and AF, using incident AF as the outcome variable. In a first model, QRSd will be included using categories (QRS<100ms (reference group), 100-119ms and ≥120ms) to evaluate the shape of the association. In a second model, QRSd will be used as a continuous variable per 1-standard deviation increase. Models will be adjusted as follows:

Model 1: age, sex, race, educational status and study site

Model 2: additionally adjusted for body mass index, height, smoking status, systolic blood pressure, diastolic blood pressure, blood pressure lowering medications, diabetes, heart rate, history of MI, history of HF.

Model 3: additionally adjusted for PR-interval and P-wave terminal force

Cumulative Incidence of AF per 1000 person-years stratified by QRS category, will be included in this table.

Table 3: Subgroup analyses of the relationship between QRS duration and incident atrial fibrillation

Multivariable adjusted Cox regression analyses will be performed stratified by sex, age (<median vs ≥median) and race. Multiplicative interaction terms will be included in the multivariable adjusted models (Model 2) to calculate p values for interaction.

Table 4: Relationship between QRS duration and incident atrial fibrillation in individuals with a QRS duration <120ms

Multivariable adjusted Cox regression analysis will be performed as described in *Table 2*, however participants with a QRS interval ≥120ms will be excluded.

Table 5: Relationship between ventricular conduction defects and incident atrial fibrillation

Multivariable adjusted Cox regression analysis will be performed using incident AF as the outcome variable and the following ventricular conduction defect categories as the independent variable: complete RBBB, complete LBBB, bifascicular block (Minnesota code 7.8), IVCD (QRS >100 ms but no specific morphology, Minnesota code 7.6 or 7.4) and QRS<100 ms (reference group). Models will be adjusted as follows:

Model 1: age, sex, race, educational status and study site

Model 2: additionally adjusted for body mass index, height, smoking status, systolic blood pressure, diastolic blood pressure, blood pressure lowering medications, diabetes, heart rate, history of MI, history of HF.

Model 3: additionally adjusted for PR-interval and P-wave terminal force

Cumulative incidence of AF per 1000 person-years stratified by QRS category will be included in this table.

Figure 2: Cumulative incidence of atrial fibrillation by ventricular contraction defect category

Cumulative incidence of AF will be calculated by ventricular conduction defect category using the Cumulative Incidence Function in order to account for the competing risk of death. Ventricular contraction defects will be categorized as follows: Isolated RBBB, LBBB, bifascicular block, IVCD and QRS<100 ms.

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. Whitbeck MG, Charnigo RJ, Shah J, Morales G, Leung SW, Fornwalt B, Bailey AL, Ziada K, Sorrell VL, Zegarra MM, Thompson J, Hosn NA, Campbell CL, Gurley J, Anaya P, Booth DC, Di Biase L, Natale A, Smyth S, Moliterno DJ and Elayi CS. QRS duration predicts death and hospitalization among patients with atrial fibrillation irrespective of heart failure: evidence from the AFFIRM study. *Europace*. 2014;16:803-11.
2. Zhang ZM, Rautaharju PM, Prineas RJ, Loehr L, Rosamond W and Soliman EZ. Bundle branch blocks and the risk of mortality in the Atherosclerosis Risk in Communities study. *J Cardiovasc Med*. 2015.
3. El-Chami MF, Brancato C, Langberg J, Delurgio DB, Bush H, Brosius L and Leon AR. QRS duration is associated with atrial fibrillation in patients with left ventricular dysfunction. *Clin Cardiol*. 2010;33:132-8.
4. Guenancia C, Binquet C, Laurent G, Vinault S, Bruyere R, Prin S, Pavon A, Charles PE and Quenot JP. Incidence and Predictors of New-Onset Atrial Fibrillation in Septic Shock Patients in a Medical ICU: Data from 7-Day Holter ECG Monitoring. *PloS one*. 2015;10:e0127168.
5. Baturova MA, Lindgren A, Carlson J, Shubik YV, Olsson SB and Platonov PG. Predictors of new onset atrial fibrillation during 10-year follow-up after first-ever ischemic stroke. *Int J Cardiol*. 2015;199:248-52.
6. Nielsen JB, Olesen MS, Tango M, Haunso S, Holst AG and Svendsen JH. Incomplete right bundle branch block: a novel electrocardiographic marker for lone atrial fibrillation. *Europace*. 2011;13:182-7.
7. Rosenberg MA, Das S, Pinzon PQ, Knight AC, Sosnovik DE, Ellinor PT and Rosenzweig A. A Novel Transgenic Mouse Model of Cardiac Hypertrophy and Atrial Fibrillation. *J Atr Fibrillation*. 2012;2:1-15.
8. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ and Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;158:111-7.
9. Zhang ZM, Rautaharju PM, Prineas RJ, Loehr L, Rosamond W and Soliman EZ. Ventricular conduction defects and the risk of incident heart failure in the Atherosclerosis Risk in Communities (ARIC) Study. *J Card Fail*. 2015;21:307-12.