ARIC Manuscript Proposal #2799

PC Reviewed: 6/12/18 Status: _____ Priority: 2
SC Reviewed: __________ Status: _____ Priority: ____

1.a. Full Title:

Association of left atrial abnormalities and supraventricular tachycardia from 48 hour ambulatory electrocardiography by sex and race: The ARIC study

b. Abbreviated Title (Length 26 characters): LA abnormalities and SVT

2. Writing Group:
   Writing group members:
   
   
   I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MM__ [please confirm with your initials electronically or in writing]

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3. Timeline: Manuscript to be fully drafted in to the ARIC publications committee in the Summer of 2018.
4. Rationale:
Supraventricular tachycardia (SVT) is a common reason for emergency department visits - about 50,000 per year.\(^1\) SVT significantly impairs quality of life with symptoms including palpitations, shortness of breath, and light-headedness, and syncope.\(^2\)\(^-\)\(^5\) Supraventricular ectopic activity, either premature atrial contractions or paroxysmal SVT have been associated with increased risk of stroke independent of the association of these rhythm abnormalities with atrial fibrillation (AF).\(^6\)\(^-\)\(^11\) Thus, there is an emerging concept that supraventricular ectopic activity and AF are part of the same continuum of atrial disease, namely atrial cardiopathy.\(^12\)\(^-\)\(^14\)

Prolonged PR interval and abnormal P-wave indices from resting electrocardiograms ECGs are considered to be intermediate phenotypes of AF and predict the risk of AF.\(^15\)\(^-\)\(^19\) Similarly, abnormalities in left atrial (LA) structure and function from echocardiogram (echo) are important risk factors for AF.\(^20\)\(^-\)\(^22\) The association of PR interval, P-wave indices, and LA structure and function and SVT has not been sufficiently examined and may be associated with SVT risk.

Further, sex and race differences in the association of left atrial abnormalities with SVT have not been examined. SVT increases with age, and in those ≥ 65 years old, men are more likely to have SVT compared with women.\(^23\) Studies have reported differences in the mechanism of SVT by sex and women have a higher risk of SVTs compared with men.\(^4\)\(^,\)\(^23\)\(^,\)\(^24\) Similarly, the distributions of PR interval and P-wave indices may differ by sex, although prior studies are conflicting. Some reports suggest that PR interval and P-wave duration are higher, while P-wave amplitude is lower in men compared with women.\(^25\)\(^-\)\(^27\) Although these differences may increase with age,\(^26\) a meta-analysis did not find significant differences in PR interval or P-wave indices by sex.\(^28\) PR interval, P-wave duration, P-wave amplitude, and P-wave terminal force are consistently greater in blacks than whites.\(^19\)\(^,\)\(^25\)\(^-\)\(^27\) In the Atherosclerosis Risk in Communities (ARIC) study, the incidence of AF is higher in men and whites,\(^29\) even though blacks have longer PR interval and P-wave indices compared with whites.\(^19\)\(^,\)\(^30\) PR interval and P-wave indices at the ARIC baseline visit were associated with the risk of AF among whites and blacks.\(^19\) For echocardiographic measures, studies have shown that whites and blacks have similar atrial volumes, but whites have larger left atrial diameters compared with blacks.\(^31\)\(^,\)\(^32\) Evidence suggests LA volume does not differ by sex after accounting for body size.\(^33\)\(^,\)\(^34\)

The ARIC ancillary study, “The Race-Specific Prevalence of Atrial Fibrillation Measured by 48-Hour Holter” (AS #2012.08) will therefore allow us to examine the association of left atrial abnormalities from ECG and echocardiography and SVT on 48-hour ambulatory ECG by sex and race. Given the risks and treatments associated with SVT, left atrial abnormalities may be subclinical markers of SVT, capable of providing insight into sex- and race-specific differences in prevalence and risk of this arrhythmia.

5. Main Hypothesis/Study Questions:
1. PR interval, P-wave duration, P-wave area, P-axis, and P-wave terminal force measured by 12-lead ECG and measures of LA structure and function by echo will be associated with the burden of SVT on 48-hour Holter recording.
2. The association of these left atrial abnormalities and SVT on 48-hour Holter recording will be stronger among men compared with women and among whites compared with blacks.
6. Design and analysis

Study design:
This analysis will include a subset of ARIC Visit 5 participants that were selected for a 48-hour ambulatory electrocardiography ancillary study. The ancillary study included participants at two ARIC sites, Forsyth County, NC, and Jackson, MS. Only ARIC participants that attended Visit 5, self-reported as black or white, and had echocardiography measurements were invited to participate.

Participants were invited to attend a one-hour clinic visit to review medications, have anthropometric and blood pressure measurements, and answer a questionnaire on AF symptoms. The study visit included placement of a Holter monitor, education on wearing the monitor, and start of the recording. Study staff attached 7 electrodes to the participant using a “modified V3 placement” method and placed the Holter monitor (SEER Light Extend Compact Digital Holter Recorder; GE, Milwaukee, WI) in a carrying case that the participant could connect to a belt or wear using a strap across their body.

Technicians at EPICARE (Wake Forest School of Medicine, Winston Salem, NC) centrally processed the recordings using the GE MARS 8.0.2 (GE, Milwaukee, WI) with a standardized protocol. Resting, standard, 12-lead, 10-second ECGs were recorded following a standardized protocol during the ARIC visit 5. ECGs were recorded using the GE MAC 1200 electrograph (GE, Milwaukee, Wisconsin) with a 10 mm/mV calibration at a speed of 25 mm/s and centrally processed at EPICARE using the GE 12-SL Marquette Version 2001 (GE, Milwaukee, Wisconsin). Echo measurements were obtained at ARIC visit 5 and centrally read at the ARIC Echo reading center.

Inclusions: All participants that attended the AF ancillary study and wore a Holter monitor.

Exclusions: Participants with poor quality measures (defined as noise >10%), <20 hours of Holter recording time, no Holter recording, an ECG diagnosis of AF, bundle branch block, permanent pacemaker from ARIC visit 5, and missing covariates of interest. We will also exclude three participants with Holter transmission issues, and one participant that came to the visit, but did not wear a monitor. We will also exclude participants with AF detected by Holter.

Outcomes:
1. Presence of SVT on 48-hour Holter recording calculated as SVT/hour and percent SVT and treated as highest quartile (upper 25th percentile) versus other (lower 75th percentile). Depending on the numbers of participants with SVTs, we would also consider a binary variable (presence vs. absence of SVT).

Exposure:
P waves: PR interval and P-wave indices derived from 10-second, standard, 12-lead ECG recordings from ARIC visit 5. Variables will be treated as continuous measures, as a 1 SD change, and as an abnormal index (the upper 25th percentile), unless otherwise noted.
The P-wave indices for the analysis include the following:

1. P-wave duration (ms)- maximum
   a. Lead-specific P-wave duration = P duration in lead * + P’ duration in lead *
      where * in (AVF, AVL, AVR, I, II, III, V1, V2, V3, V4, V5, V6)

2. P-wave terminal force (μV*s)- at lead V1
   a. P’ duration in lead V1 multiplied by the P’ amplitude in lead V1
   b. Treated as a binary variable defined as normal/abnormal with a cut-off point an absolute value of 4000

3. P axis
   a. Treated as a binary normal/abnormal defining abnormal as any value outside the range of 0-75

4. HR-adjusted PR interval duration (PRa) (ms)
   a. Adjusted for heart rate using Soliman and Rautharju method where heart rate–adjusted PR interval (PRa) is calculated using the formula PRa = PR + 0.26 (HR – 70) for age < 60 years and PRa = PR + 0.42 (HR – 70) for age 60 years or older

**Echo measures:**
LA size
1. Maximal left atrial anterior-posterior diameter (cm)
2. Left atrial volume (ml)
3. LA volume index (ml per m²) (LA volume adjusted for body surface area)

LA function:
1. Peak A wave velocity (cm/s)
2. Lateral late diastolic myocardial velocity (cm/s)
3. Septal late diastolic myocardial velocity (cm/s)

**Covariates:** Field center, age, sex, race, history of coronary artery disease or heart failure, hypertension, diabetes, valvular disease by Visit 5 echocardiography, left atrial volume index by visit 5 echocardiography, systolic blood pressure (SBP), body mass index (BMI), smoking status, and use of antihypertensive drugs, antiarrhythmic drugs, β-blockers, calcium-channel blockers, and vasoactive medications.

**Statistical Analysis:**
Participant characteristics will be estimated as means and standard deviations, medians and 25th and 75th percentiles, or frequencies and percent, where appropriate and stratified by distribution-based cut points for SVT (e.g. upper 25th percentile vs. lower 75th percentile). We will use general linear models to calculate means for P-wave indices and echo measures (for continuous measures) by SVT status (upper 25th percentile vs. lower 75th percentile), stratified by race and sex and adjusted for age.

Associations between P-wave indices and echo measures with the burden of SVT (upper 25th percentile vs. lower 75th percentile) will be evaluated using multivariable weighted logistic regression using sampling weights that account for the complex sampling design. Each P-wave index and echo measure will be evaluated in separate models with a Bon Ferroni-corrected significance threshold of 0.05 / 10 = 0.005.
Independent variables will include race, sex, age, field center, and current smoking. Subsequent models will include potential confounders known to be associated with P-wave indices, echo measures, and SVT, such as BMI, SBP and antihypertensive medications (or hypertension), heart rate, heart failure, diabetes, and medications (antiarrhythmic drugs, β-blockers, calcium-channel blockers, and vasoactive medications). We will investigate first order interactions between P-wave indices, echo measures, race, and sex. Results will be stratified if significant interactions are detected (P<0.2).

**Sensitivity analysis:** In a sensitivity analysis, we will investigate whether excluding participants who reported the use of antiarrhythmic or vasoactive medications affects the estimates as well as those with prevalent heart failure. To reassure the robustness of the results, we will consider analyses of multiply imputed outcome, exposure, and covariate data that will be less prone to selection bias than the analysis of complete data, as proposed here.

Additionally, we will consider evaluating supraventricular ectopic beats (PACs) and ventricular ectopic beats (PVCs). The following measures will be defined separately for PACs and PVCs and categorized using distribution-based cut points or pre-defined points (e.g. rare <1%, occasional 1-5%, frequent ≥5) depending on the numbers:

a. Log of the total number of PACs, Log of the total number of PVCs
b. Percentage of counts: total number of ectopic beats divided by the total number of beats recorded during the length of Holter monitoring x 100
   - % PACs = (number of PACs / number of QRS complexes) x 100
   - % PVCs = (number of PVCs / number of QRS complexes) x 100

**Limitations:** Holter recordings and SVT are only available at visit 5, however, the prevalence and incidence of AF has been assessed in prior visits (1-4). ARIC visit 5 and the Holter recordings were an average of 1098 days apart on average (range 359 days to 1665 days) and may limit our ability to evaluate temporal associations.

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 ___x__ 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.cscu.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)? There are related manuscripts and co-authors from those papers have been invited to collaborate on this project.

MP 1559: PR interval, P wave indices and the incidence of atrial fibrillation: the ARIC study. Alvaro Alonso, Elsayed Soliman, Sunil K Agarwal, Laura Loehr, and Aaron Folsom


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* _2012.08 _) )

___ 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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](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

Independent Predictor of Incident Atrial Fibrillation: A Community-Based Cohort Study. 
*Circulation Cardiovascular imaging*. 2015;8:e003520.


