ARIC Manuscript Proposal # 3003

1.a. Full Title: Premature atrial contractions, supraventricular tachycardia & cognitive function: The Atherosclerosis Risk in Communities (ARIC) Study

  b. Abbreviated Title (Length 26 characters): PACs, SVT & cognitive function

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

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3.   Timeline:
June 2017: Based on preliminary visit 6 data (including N~1,000 Zio®Patch participants), we will prepare an abstract for AHA's Scientific Sessions (November 2017)

Mid-2018: Once visit 6 data are finalized (including N~3,000 Zio®Patch participants), we will conduct the proposed analysis among all ARIC visit 6 participants and use these results to prepare a full-length manuscript for publication.

4. Rationale:

Premature atrial contractions (PACs) and supraventricular tachycardia (SVT) are commonly encountered arrhythmias and are often considered benign. However, PACs and SVT have been associated with increased risk of atrial fibrillation (AF).[1-8] While AF has been adversely associated with cognitive impairment and/or dementia,[9-13] independently of clinical stroke,[12,13] little is known of the association of other atrial arrhythmias with cognitive function.

PACs are common and can affect those with or without prior heart disease. The prevalence of PACs increases with age. In fact, 99% of Swiss participants aged ≥50y had ≥1 PAC during 24-hour Holter monitoring.[14] While considered benign, PACs have been independently associated with increased risk of AF,[1-6] stroke,[5,15,16] and all-cause mortality.[1] Previously in ARIC, based on 2-minute ECGs at visit 1, presence of PACs had a modest, albeit non-statistically significant association with ischemic stroke risk in the fully-adjusted model [HR=1.30 (95% CI: 0.92-1.83)].[17] However, this short 2-minute monitoring period may underestimate the extent of PAC burden in this population. Another study showed that excessive supraventricular ectopic activity (defined by presence of ≥30 PACs/hour daily or runs of ≥20 PACs) were associated with incident ischemic stroke independent of AF.[15] Additionally, the association of PACs (>76 PACs per day) with all-cause mortality may be stronger in non-diabetics, normotensives, and those without heart failure.[1]

SVT can also affect both those with or without prior heart disease, and is potentially heterogeneous in etiology.[18] In the U.S., SVT accounts for 55,000 emergency department visits,[19] and affects an estimated 2.5 per 1,000 people.[18] SVT prevalence increases with age and appears more common in females.[18,19] However, these prevalence estimates are based on medical records and generally do not include >24 hours monitoring. These methods may not capture asymptomatic SVT and may underestimate SVT burden. In epidemiologic studies, paroxysmal SVT has been associated with greater risk of AF[8] and ischemic stroke.[20,21] Approximately 12% of individuals with paroxysmal SVT may develop AF within 1-year follow-up.[8] Paroxysmal SVT in the absence of AF has been suggested to explain a proportion of cryptogenic strokes.[20,21]

Whether PACs or SVT (other than AF) are associated with cognitive function has not yet been characterized. Using ARIC visit 6 data, we will (1) report the prevalence of PAC and SVT by age, race, and sex; and (2) assess whether PAC and SVT burden are associated with cognitive function among elderly community-dwelling study participants who wore the Zio®Patch (iRhythm Technologies Inc.; San Francisco, CA), a continuous 2-week leadless ECG-recording device.

5. Main Hypothesis/Study Questions:

Aim: Evaluate the cross-sectional association of PAC and SVT burden (as measured using the Zio®Patch) with cognitive test scores, mild cognitive impairment (MCI) and dementia at visit 6.

Hypothesis: Higher PAC and SVT burden will be associated with lower cognitive test scores as well as a higher prevalence of MCI and dementia.

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
Cross-sectional at visit 6

Study population
Inclusion: ARIC visit 6 participants with ≥48 hours of analyzable Zio®Patch ECG data.
Exclusion: Participants with missing cognitive function assessments, covariates of interest, and those with a history of AF (AF as identified by the Zio®Patch monitor or prior ARIC ascertainment).

Exposures
Participants were asked to wear the Zio®Patch for 14 days.

PAC: Data are available on presence and number of isolated, couplet and triplet PACs. PAC burden will be calculated based on the number of isolated, couplet, and triplet PACs [e.g. # isolated PACs + 2 * (# couplet PACs) + 3 * (# triplet PACs)]. PAC burden will be defined as average PAC count per day. We will also consider presence of isolated, couplet, or triplet PACs and their respective burden (e.g. # of isolated PACs per day).

SVT: SVT is defined by narrow complex tachycardia >4 beats with a rate >100 bpm, and will be analyzed by presence of SVT and by burden (# of episodes per day). We will explore other measures of SVT burden, including: maximum rate of beats, longest duration, and number of beats in the longest episode.

Outcomes
We will include 3 cognitive domain scores for memory, executive functioning / processing speed, language, and consider a global composite z-score.[22] We will also provide results for the individual cognitive test z-scores: Delayed Word Recall, Logical Memory, Incidental Learning, Animal Naming, Boston Naming Test, Word Fluency Test, Trail Making Tests (2), Digit Symbol Substitution Test, and Digit Span Backwards.

Once available through visit 6, in the full manuscript, we will incorporate adjudicated dementia and MCI.

Covariates
Age, sex, race, study center, educational attainment, occupation, current smoking status, BMI, diabetes, hypertension medication use, antiarrhythmic medication use, SBP, DBP, CHD, heart failure, stroke

Data analysis

We will report the prevalence of PACs and SVT by age, sex and race. Depending on distributions of burden, we will consider log-transforming or categorizing into tertiles/quartiles. Multiple linear regression will be used to assess the association between PACs and SVTs with cognitive test z-scores. Unconditional logistic regression will be used to assess the association of PACs and SVT with dementia and MCI.

- Model 1 = age, race, sex
- Model 2 = Model 1 + study center, educational attainment, occupation, current smoking status, BMI, diabetes, hypertension medication use, antiarrhythmic medication use, SBP, DBP, CHD, heart failure
- Model 3 = Model 2 + stroke

In sensitivity analyses, we will exclude those with a history of stroke. We will also test for interactions by age, race, sex, diabetes, hypertension status and HF.

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)?
#1740: AF and Dementia (Chen)
#1739: AF and Cognitive Decline (Chen)
#2272: Arrhythmias & Cognitive Function (Chen)
Unassigned: NSVT, PVC and cognitive function

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* __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.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.

13. Per Data Use Agreement Addendum, approved manuscripts using 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

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