ARIC Manuscript Proposal # 3003

PC Reviewed: 07/11/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

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:

Writing group members: Mary R Rooney, Faye L Norby, Ryan J Koene, Ankit Maheshwari, Pamela L Lutsey, Elsayed Z Soliman, Laura R Loehr, Tom Mosley, Josef Coresh, Alvaro Alonso, Lin Y Chen

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]**

First author: **Mary R Rooney MPH**

Address: Division of Epidemiology and Community Health
School of Public Health
1300 S 2nd St Suite 300
Minneapolis, MN 55454

Phone: (630) 995-5772 Fax:
E-mail: roone166@umn.edu

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: **Lin Y Chen MD MS**

Address: Cardiovascular Division
Department of Medicine
University of Minnesota Medical School
420 Delaware St SE, MMC 508
Minneapolis, MN, 55455

Phone: (612) 625-4401 Fax: (612) 626-4411
E-mail: chenx484@umn.edu

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

1. Lin CY, Lin YJ, Chen YY, et al. Prognostic Significance of Premature Atrial Complexes Burden in Prediction of Long-Term Outcome. *J Am Heart Assoc.* Aug 27 2015;4(9):e002192.
2. Van Wagoner DR, Piccini JP, Albert CM, et al. Progress toward the prevention and treatment of atrial fibrillation: A summary of the Heart Rhythm Society Research Forum on the Treatment and Prevention of Atrial Fibrillation, Washington, DC, December 9-10, 2013. *Heart Rhythm.* Jan 2015;12(1):e5-e29.
3. Dewland TA, Vittinghoff E, Mandyam MC, et al. Atrial ectopy as a predictor of incident atrial fibrillation: a cohort study. *Ann Intern Med.* Dec 03 2013;159(11):721-728.
4. Chong BH, Pong V, Lam KF, et al. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. *Europace.* Jul 2012;14(7):942-947.
5. Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. *Circulation.* May 04 2010;121(17):1904-1911.
6. Johnson LS, Juhlin T, Juul-Moller S, Hedblad B, Nilsson PM, Engstrom G. A prospective study of supraventricular activity and incidence of atrial fibrillation. *Heart Rhythm.* Sep 2015;12(9):1898-1904.
7. Maurer MS, Shefrin EA, Fleg JL. Prevalence and prognostic significance of exercise-induced supraventricular tachycardia in apparently healthy volunteers. *Am J Cardiol.* Apr 15 1995;75(12):788-792.
8. Hamer ME, Wilkinson WE, Clair WK, Page RL, McCarthy EA, Pritchett EL. Incidence of symptomatic atrial fibrillation in patients with paroxysmal supraventricular tachycardia. *J Am Coll Cardiol.* Apr 1995;25(5):984-988.
9. Alonso A, Arenas de Larriva AP. Atrial Fibrillation, Cognitive Decline And Dementia. *Eur Cardiol.* Summer 2016;11(1):49-53.

10. Udompanich S, Lip GY, Apostolakis S, Lane DA. Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review. *QJM.* Sep 2013;106(9):795-802.

11. Lin T, Wissner E, Tilz R, et al. Preserving Cognitive Function in Patients with Atrial Fibrillation. *J Atr Fibrillation.* Jun-Jul 2014;7(1):980.

12. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis. *Ann Intern Med.* Mar 05 2013;158(5 Pt 1):338-346.

13. Chen LY, Lopez FL, Gottesman RF, et al. Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study. *Stroke.* Sep 2014;45(9):2568-2574.

14. Conen D, Adam M, Roche F, et al. Premature atrial contractions in the general population: frequency and risk factors. *Circulation.* Nov 06 2012;126(19):2302-2308.

15. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation. *J Am Coll Cardiol.* Jul 21 2015;66(3):232-241.

16. O'Neal WT, Kamel H, Kleindorfer D, et al. Premature Atrial Contractions on the Screening Electrocardiogram and Risk of Ischemic Stroke: The Reasons for Geographic and Racial Differences in Stroke Study. *Neuroepidemiology.* 2016;47(1):53-58.

17. Ofoma U, He F, Shaffer ML, Naccarelli GV, Liao D. Premature cardiac contractions and risk of incident ischemic stroke. *J Am Heart Assoc.* Oct 2012;1(5):e002519.

18. Orejarena LA, Vidaillet H, Jr., DeStefano F, et al. Paroxysmal supraventricular tachycardia in the general population. *J Am Coll Cardiol.* Jan 1998;31(1):150-157.

19. Murman DH, McDonald AJ, Pelletier AJ, Camargo CA, Jr. U.S. emergency department visits for supraventricular tachycardia, 1993-2003. *Acad Emerg Med.* Jun 2007;14(6):578-581.

20. Chiang JK, Kao HH, Kao YH. Association of Paroxysmal Supraventricular Tachycardia with Ischemic Stroke: A National Case-Control Study. *J Stroke Cerebrovasc Dis.* Mar 30 2017.

21. Kamel H, Elkind MS, Bhave PD, et al. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. *Stroke.* Jun 2013;44(6):1550-1554.

22. Rawlings AM, Bandeen-Roche K, Gross AL, et al. Factor structure of the ARIC-NCS Neuropsychological Battery: An evaluation of invariance across vascular factors and demographic characteristics. *Psychol Assess.* Dec 2016;28(12):1674-1683.