**ARIC Manuscript Proposal # 3004**

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

**1.a. Full Title**: Ventricular Arrhythmias and Cognitive Function: The Atherosclerosis Risk in Communities Neurocognitive (ARIC-NCS) Study

**b. Abbreviated Title (Length 26 characters)**: NSVT, PVC and cognitive function

**2. Writing Group**:

Writing group members: Faye L. Norby, Mary R. Rooney, Ryan J. Koene, Ankit Maheshwari, Aaron R Folsom, Thomas H. Mosley, Elsayed Z. Soliman, Laura R. Loehr, Josef Coresh, Alvaro Alonso, Lin Y. Chen, others welcome.

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


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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**: Statistical analysis: 12 months
Manuscript preparation: 12 months

We expect to submit an abstract with preliminary results to the AHA Scientific Sessions conference (submission deadline June, 2017; conference is Nov, 2017). We will finalize the manuscript after all data from visit 6 is complete.

## 4. Rationale:

Atrial fibrillation is associated with poorer cognitive function;[1, 2] however, little is known about whether other arrhythmias, particularly ventricular arrhythmias such non-sustained ventricular tachycardia (NSVT) and premature ventricular contractions (PVCs), are associated with cognition.

NSVT is present in individuals encompassing the health spectrum, from apparently healthy individuals to patients with significant heart disease.[3] The prevalence of NSVT had been mostly reported in studies of exercise-induced NSVT, or in studies of concurrent cardiac comorbidities in which patients underwent cardiac monitoring. Therefore, the prevalence in the general population, particularly with monitoring >24 hours is unknown.[4, 5] In the presence of certain comorbidities, NSVT is a marker of increased risk of subsequent sustained tachyarrhythmias, more serious outcomes such as myocardial infarction,[6] and also death, including sudden cardiac death (SCD).[6, 7] Whether NSVT is a surrogate marker of a more severe underlying pathology, or whether it has prognostic significance in healthy individuals needs further clarification.[8]

PVCs are common and also occur in patients encompassing the health spectrum. Mostly asymptomatic, the prevalence of PVCs increases with age, and differs by sex and ethnicity.[9] In adults, hypertension is a major cause of PVCs,[9] and PVCs are associated with increased coronary heart disease (CHD) mortality, independent of cardiovascular risk factors.[10] In ARIC, participants underwent a 2-minute ECG at baseline (mean age 54), and the prevalence of PVC was 6%.[9] PVCs are associated with an increased risk of incident stroke, particularly embolic stroke, in normotensives and non-diabetics.[11, 12] Additionally, the presence of ≥1 PVC on a 2-minute strip was associated with heart failure, independent of CHD.[13] Furthermore, PVCs are associated with an increased risk of SCD, and there is an additive risk in participants with concurrent premature atrial contractions.[14]

Using data from the community-based ARIC study, along with data from a 2-week continuous ambulatory ECG recording device called the Zio®Patch (iRhythm Technologies, Inc, San Francisco, CA), we aim to 1) report the prevalence of these ventricular arrhythmias in a community-based elderly population and 2) assess the cross-sectional association of NSVT and PVCs with cognitive test scores.

**5. Main Hypothesis/Study Questions**:

Aim 1: NSVT: report the prevalence using data from a 2-week wearable device, and evaluate the association of NSVT with cognitive function in ARIC participants

Aim 2: PVCs: report the prevalence using data from a 2-week wearable device, and evaluate the association of PVCs with cognitive function in ARIC participants

Hypothesis: Prevalence of NSVT and PVCs is high in this elderly population. Presence of NSVT or PVCs is independently associated with lower cognitive function. The association is stronger in those with a higher burden of arrhythmia.

**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 using:

1) the Zio®Patch pilot data / visit 5: July 2013 to March 2014, a total of 325 participants at the Minneapolis and Washington County field centers,
2) Zio®Patch and cognitive data from visit 6. For the abstract submission to AHA, we will have data on approximately 1000 participants from this visit. After the completion of visit 6, we hope to have data on approximately 3000 participants.

Study population

Inclusion criteria:

- In July 2013 to March 2014, a total of 325 participants at the Minneapolis and Washington County field centers who presented for their brain MRI scans at visit 5/NCS examinations wore the Zio®Patch.
- ARIC participants who wore the Zio®Patch in conjunction with visit 6, and had cognitive test scores.

Exclusion criteria:

- Participants were exempt from wearing the Zio®Patch if they had skin allergic reactions to adhesive tape, history of pacemaker or defibrillator implantation.

- Additionally, we will exclude anyone who wore the Zio®Patch less than 2 days.

**Exposures**

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

**NSVT** was defined as wide complex tachycardia >4 beats with a rate >100 bpm. It will be analyzed as a dichotomous variable, and additionally as categories of burden, defined as the number of episodes per day. Furthermore, we will explore data of the NSVT episodes, including the maximum rate of beats, the longest duration of NSVT, and the number of beats in the longest episode.

**PVC** count will be calculated based on the number of isolated, couplet and triplet PVCs [e.g. # isolated PVCs + 2 * (# couplet PVCs) + 3 * (# triplet PVCs)]. PVC burden will be defined as PVC count per day divided by the number of days of recorded data, to get a number that is mean PVC count per day. From there, we will split burden into tertiles or quartiles to analyze a dose-response relationship.

**Outcomes**

Cognitive function: We will use factor scores for each of the main cognitive domains: general cognitive performance, memory, executive function and language.[15] Within the latter 3 domains, we will report associations with z-scores for each individual test.

- Memory (delayed word recall, logical memory, incidental learning)
- Executive functioning/processing speed (digit symbol, Trail Making Test parts A and B)
- Language (using phonemic and semantic fluency, Boston Naming test)

**Covariates**

Variables include: age, sex, race/study center, educational level, occupation, APOE genotype, smoking, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, diabetes, coronary heart disease, heart failure, atrial fibrillation (prevalent at visit and also prevalent on Zio®Patch recordings), and stroke.

**Statistical analysis**

Aims1 and 2:

We will report the prevalence of NSVT and PVCs in this elderly population, by age, race, and sex.

Analyses involving the pilot study participants (n=325) will be weighted for selection into the brain MRI study at visit 5.

We will use multivariable linear regression to assess the associations of NSVT and PVCs with factor scores and standardized z-scores of cognitive tests. We will report associations with dichotomous yes/no variable, along with the burden of arrhythmia. Distributions of burden will be assessed, and likely be categorized into quartiles.

- Model 1 is adjusted for age, sex and race/center
- Model 2 is adjusted for adjusted for model 1, education, occupation, APOE genotype, smoking (not current vs. current), body mass index, diabetes, systolic and diastolic blood pressure, and use of antihypertensive medication
- Model 3 is adjusted for model 2 plus CHD, heart failure, atrial fibrillation, and stroke

We will consider the following:

- Interactions by sex, race, diabetes status, hypertension status, CHD, and heart failure
- Sensitivity analysis in which we exclude those with stroke and/or atrial fibrillation (AF prevalent at visit and also prevalent on Zio®Patch recordings)

**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)?**
Similar manuscripts include:
#2667: Predictors of premature ventricular complexes (Maan)
#2677: 12-lead ectopy, AF and HF (Nguyen)
#2076: VPC and risk of dementia (Wang)
#2272 Arrhythmias & Cognitive Function (Chen)
-Unassigned: PACs & cognitive function (Rooney)

**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. Chen, L.Y., et al., *Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study.* Stroke, 2014. **45**(9): p. 2568-74.
2. Chen, L.Y., et al., *Persistent but not Paroxysmal Atrial Fibrillation Is Independently Associated With Lower Cognitive Function: ARIC Study.* J Am Coll Cardiol, 2016. **67**(11): p. 1379-80.
3. Katritsis, D.G., W. Zareba, and A.J. Camm, *Nonsustained ventricular tachycardia.* J Am Coll Cardiol, 2012. **60**(20): p. 1993-2004.
4. Marine, J.E., et al., *Prevalence and prognostic significance of exercise-induced nonsustained ventricular tachycardia in asymptomatic volunteers: BLSA (Baltimore Longitudinal Study of Aging).* J Am Coll Cardiol, 2013. **62**(7): p. 595-600.
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6. Frishman, W.H., et al., *Twenty-four-hour ambulatory electrocardiography in elderly subjects: prevalence of various arrhythmias and prognostic implications (report from the Bronx Longitudinal Aging Study).* Am Heart J, 1996. **132**(2 Pt 1): p. 297-302.
7. Bikkina, M., M.G. Larson, and D. Levy, *Prognostic implications of asymptomatic ventricular arrhythmias: the Framingham Heart Study.* Ann Intern Med, 1992. **117**(12): p. 990-6.
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9. Simpson, R.J., Jr., et al., *Prevalence of premature ventricular contractions in a population of African American and white men and women: the Atherosclerosis Risk in Communities (ARIC) study.* Am Heart J, 2002. **143**(3): p. 535-40.
10. Massing, M.W., et al., *Usefulness of ventricular premature complexes to predict coronary heart disease events and mortality (from the Atherosclerosis Risk In Communities cohort).* Am J Cardiol, 2006. **98**(12): p. 1609-12.
11. Agarwal, S.K., et al., *Premature ventricular complexes and the risk of incident stroke: the Atherosclerosis Risk In Communities (ARIC) Study.* Stroke, 2010. **41**(4): p. 588-93.
12. Ofoma, U., et al., *Premature cardiac contractions and risk of incident ischemic stroke.* J Am Heart Assoc, 2012. **1**(5): p. e002519.
13. Agarwal, S.K., et al., *Relation of ventricular premature complexes to heart failure (from the Atherosclerosis Risk In Communities [ARIC] Study).* Am J Cardiol, 2012. **109**(1): p. 105-9.
14. Cheriyath, P., et al., *Relation of atrial and/or ventricular premature complexes on a two-minute rhythm strip to the risk of sudden cardiac death (the Atherosclerosis Risk in Communities [ARIC] study).* Am J Cardiol, 2011. **107**(2): p. 151-5.
15. Gross, A.L., et al., *Application of Latent Variable Methods to the Study of Cognitive Decline When Tests Change over Time.* Epidemiology, 2015. **26**(6): p. 878-87.