ARIC Manuscript Proposal #2272

PC Reviewed: 12/10/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Subclinical Arrhythmias, Cognitive Function, and Brain MRI Abnormalities in the Elderly: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Arrhythmias and cognitive function

2. Writing Group:

Writing group members: Faye L. Norby, Sunil K. Agarwal, Rebecca F. Gottesman, Laura Loehr, Thomas Mosley, Elsayed Z. Soliman, Josef Coresh, Alvaro Alonso, Lin Y Chen

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

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3. Timeline: Statistical Analysis: 1 month
Manuscript preparation: 2 months

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing over time.[1] AF is associated with an increased risk of stroke,[2] heart failure,[3] and death.[4, 5] Evidence is emerging that AF is also associated with cognitive impairment or dementia even in individuals without a history of clinical stroke.[6] We recently observed in the ARIC study that in the absence of clinical stroke, the association of incident AF with cognitive decline was present only in participants who had prevalent subclinical cerebral infarcts (SCIs) on brain MRI scans or who developed SCIs during follow-up. In individuals without prevalent SCIs or who did not develop SCIs during follow-up, incident AF was not associated with cognitive decline (Chen, submitted). Our observations suggest that the association between incident AF and cognitive decline is mediated by the presence or development of SCIs.

Some knowledge gaps remain. There is little known regarding if a higher arrhythmia burden (% time in arrhythmia) is associated with greater cognitive impairment, faster cognitive decline over time, and/or incident dementia. There are other potential mechanisms that may underlie the association between AF and cognitive impairment: The rapid and irregular rhythm of AF leads to reduced cardiac output and cerebral hypoperfusion. It this is true, it is possible that other tachyarrhythmias (e.g., frequent subclinical premature atrial contractions [PACs], supraventricular tachycardia [SVT], frequent subclinical premature ventricular contractions [PVCs], or non-sustained ventricular tachycardia [NSVT]) may also be associated with cognitive impairment. Further, from recent ARIC reports, PACs[7] and PVCs[7, 8] were found to be associated with incident ischemic stroke. Whether or not these subclinical arrhythmias are also associated with other brain MRI abnormalities seen in patients with cognitive impairment or dementia (e.g., white matter hyperintensities [WMH]) is unknown.

The availability of Zio®Patch−a non-invasive, leadless, 2-week ECG recording device that is easy to use−has now made it possible to record subclinical arrhythmias.[9] We now have Zio®Patch data completed on 325 participants at the visit 5 pilot study, around 4000 participants at visit 6, and we will be applying the Zio®Patch to a select population at visit 7. Coupled with the cognitive test data and brain MRI scans in ARIC, we seek to evaluate the association of subclinical arrhythmias with cognitive function, dementia, and brain MRI abnormalities.

5. Main Hypothesis/Study Questions:

Aim 1: Evaluate the cross-sectional association of subclinical AF, PACs, SVT, PVCs, and NSVT and arrhythmia burden with cognitive test scores and prevalent dementia at visit 6.

Hypothesis 1: Subclinical AF, PACs, SVT, PVCs, and NSVT are associated with lower cognitive function and prevalent dementia, independent of other risk factors for cognitive impairment. Higher burden is associated with lower cognitive function and prevalent dementia.

Aim 2: Evaluate the cross-sectional association of subclinical AF, PACs, SVT, PVCs, and NSVT with brain MRI abnormalities at visit 5.

Hypothesis 2: Subclinical AF, PACs, SVT, PVCs, and NSVT are associated with presence of SCIs and higher WMH volume.

Aim 3: (Longitudinal aim) Evaluate the burden of subclinical arrhythmias with incident

dementia and the change in cognitive scores between visit 6 and 7.

Hypothesis 3: A higher burden of each subclinical arrhythmia will be associated with incident dementia and a greater cognitive decline between visit 6 and visit 7.

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 population

Inclusion criterion:

1. Participants in ARIC with analyzable Zio Patch ECG data of ≥48 hours

Exclusion criteria:

1. Participants with symptoms correlating with AF, PACs, SVT, PVCs, and NSVT recorded by Zio Patch (data on symptoms are available from the participants' symptom diaries).
2. Non-white participants
3. Participants with history of stroke

Independent variables, measured by Zio Patch

AF (present or absent, % burden)
PAC (present or absent, % burden)
SVT (present or absent, no. of episodes)
PVC (present or absent, % burden)
NSVT (present or absent, no. of episodes)

Dependent variables - Cognitive tests (all continuous variables)
z-scores for different domains (memory, language and verbal fluency, executive function, and visuo-spatial). For this analysis, we will follow recommendations from the ARIC-NCS analysis committee. These tests were measured at visits 5, 6, and 7.

Dependent variables - Brain MRI abnormalities Subclinical cerebral infarcts
(present or absent) WMH volume (cm^3)
These were measured at visit 5

Dependent variables – Dementia

Dementia: The main analysis will use dementia diagnosis (all-cause), defined as diagnosis level 3 (per MS#2020 (Gottesman et al). As a secondary analysis, we will explore the association of arrhythmia and types of dementia.

Covariates

Age, sex, educational level, smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction. All variables were collected at all visits (5-7), except LVEF, which was not collected at visit 6, so when addressing cross-sectional association at visit 6, we will adjust for LVEF from visit 5.

Statistical analysis

Aim 1

Mean and standard deviation (SD) of z-scores will be shown by presence or absence of each subclinical arrhythmia.

We will use the general linear model to assess association between presence/absence of each subclinical arrhythmia and each z-score:

Model 1: Adjusted for age, race/center, and sex

Model 2: Model 1 + educational level, smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

We will use the general linear model to assess association of % burden or no. of episodes of each subclinical arrhythmia with each z-score:

Model 1: Adjusted for age, race/center, and sex

Model 2: Model 1 + educational level, smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

We will use multivariable logistic regression to access association between presence / absence of each subclinical arrhythmia and prevalent dementia.

Model 1: Adjusted for age, race/center, and sex

Model 2: Model 1 + educational level, smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

Aim 2

Mean and standard deviation (SD) of WMH volume will be shown by presence or absence of each subclinical arrhythmia and no. (%) of SCI will be shown by presence or absence of each subclinical arrhythmia.

Multivariable logistic regression will be used to assess association between presence/absence of each subclinical arrhythmia and presence/absence of SCI. Multivariable logistic regression will also be used to assess association of % burden or no. of episodes of each subclinical arrhythmia with presence/absence of SCI:

Model 1: Adjusted for age and sex

Model 2: Model 1 + smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

We will use the general linear model to assess association between presence/absence of each subclinical arrhythmia and WMH volume:

Model 1: Adjusted for age and sex

Model 2: Model 1 + smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

We will use the general linear model to assess association of % burden or no. of episodes of each subclinical arrhythmia with WMH volume:

Model 1: Adjusted for age and sex

Model 2: Model 1 + smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

Aim 3

This longitudinal Aim will use Zio Patch data and covariates from visit 6 and address incident dementia and cognitive change (visit 6 to visit 7) outcomes.

We will use a general linear model to assess the association of % burden of arrhythmias at visit 6 with the change in cognitive scores between visits 6 and 7.

Model 1: Adjusted for age, race/center, and sex

Model 2: Model 1 + educational level, smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

We will use a Cox proportional hazards model to assess the association between presence / absence of each subclinical arrhythmia at visit 6 and incident dementia.

Model 1: Adjusted for age, race/center, and sex

Model 2: Model 1 + educational level, smoking status, body mass index, prevalent hypertension, diabetes, coronary heart disease, heart failure, and left ventricular ejection fraction

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

8b. 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

The authors of the proposals above will be included as co-authors in the current proposal.

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* 2013.14)
___ 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. References

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