ARIC Manuscript Proposal #3698

PC Reviewed: 9/8/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations between atrial arrhythmias and brain amyloid deposition: The ARIC-PET Study

b. Abbreviated Title (Length 26 characters): AF/PAC and brain amyloid

2. Writing Group:

Writing group members: Michelle C. Johansen (first author), Rebecca F. Gottesman, Wendy Wang, Michael Zhang, Alvaro Alonso, Dean Wong, Lin Yee Chen (last author) (others welcome)

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

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3. Timeline: Analysis will begin as soon as the proposal is approved. Planned abstract submission winter 2021, with manuscript submission fall 2021.

4. Rationale:

Cognitive decline in the setting of clinical stroke is well-documented[1,2], but it is possible that vascular risk factors act independently and result in either silent infarcts or by some other mechanism yet to be understood, contribute to brain pathologic changes sufficient to cause cognitive impairment.[3-5]

Atrial fibrillation (AF) and other atrial tachyarrhymias (e.g., frequent premature atrial contractions [PACs] and atrial tachycardia [AT]) are potential risk factors for cognitive decline and dementia. AF can cause cardioembolic strokes or silent infarction, thereby potentially leading to later development of cognitive impairment from direct insult.[6] AF is certainly

associated with other cardiac conditions, such as heart failure, that increase risk of dementia.[7,8] AF is also associated with vascular risk factors, which themselves are associated with elevated risk for dementia,[9] but data from ARIC show that AF's association with cognitive decline and dementia is independent not only of these comorbid vascular risk factors but also stroke.[10,11] It is unknown, therefore, if the effect of AF on cognition is mediated entirely through these pathways or these shared risk factors, or there is a more direct mechanism by which AF impacts cognition, apart from stroke or silent brain infarction.[12] There has been a suggestion that AF may impact brain volumes via cerebral hypoperfusion or cerebral emboli, with permanent AF more strongly associated with global brain atrophy than paroxysmal AF, suggesting a cumulative effect, but other work saw such associations attenuated after adjusting for vascular risk factors.[13,14] There may also be a multi-hit phenomenon with literature suggesting that in patients with Alzheimer's disease (AD), the APOE Ɛ4 allele, and permanent AF have lower mini-mental state exam (MMSE) scores and the highest risk of cognitive deterioration when compared with individuals without AF.[15]

One way to evaluate potential mechanisms by which AF might impact cognition and increase dementia risk is to consider specific markers of diseases processes that impact cognition: the availability of tracers that bind to beta-amyloid (Aβ) allows consideration specifically of AD-specific pathology. Although demonstrating an association between AF and brain amyloid does not rule out other mechanisms connecting the two (including shared confounding risk factors), evidence of elevated brain amyloid in individuals with AF would further demonstrate the potential importance of treatment and prevention of AF.

The aim of this study is to leverage the ARIC-PET study, which provides cerebral beta-amyloid (Aβ) imaging (florbetapir PET) in a group of nondemented individuals, and information on prevalent AF to begin to answer these questions. Of note, among those patients who have AF, there is a suggestion of race differences in the epidemiology of the disease, the severity of the disease and treatment of the disease.[16,17] We have also described similar disparities in amyloid deposition, with higher rates of Aβ positivity in blacks vs whites in ARIC-PET.[18] As a result, it is of interest and importance to explore the potential for effect measure modification by race of the association between a history of AF and brain amyloid. Therefore, we aim to determine if there is an association between prevalent AF and brain amyloid on PET, and explore differences in these associations by race.

Additionally, we will leverage the Zio XT Patch data at ARIC visit 6 to define those who may have some atrial electrical remodeling, characterized by the present of premature atrial contractions (PACs) or atrial tachycardia (AT), a well-established precursor to AF[19] and determine the association between the presence and frequency of PACs/AT and brain amyloid on PET. We have previously shown that there was a higher odds of elevated cerebral beta-amyloid (Aβ) among those with a larger left ventricular diameter.[20] We will expand these considerations to include early evidence of atrial remodeling manifesting as frequent PACs or AT on Zio XT Patch in this analysis. As the sample size allows, we will also explore differences in these associations by race.

5. Main Hypothesis/Study Questions:

Aim 1: To determine the cross-sectional association between global cortical Aβ deposition by PET and AF, diagnosed by ARIC ascertainment.
Hypotheses:

1. Global cortical Aβ will be elevated in individuals with AF compared to participants without AF, independent of demographics and vascular risk factors.
2. The association between the presence of atrial fibrillation and global cortical Aβ will be different between blacks and whites, with blacks with AF having a higher amount of Aβ than whites with AF, when controlling for other demographics and vascular risk factors.

Aim 2: To determine the (nonconcurrent) cross-sectional association between global cortical Aβ deposition by PET and PACs/AT, as assessed by Zio XT Patch diagnosis.

1. Global cortical Aβ will be higher in individuals with frequent PACs (defined per analysis plan) compared to participants with infrequent PACs, independent of demographics and vascular risk factors.
2. Global cortical Aβ will be higher in individuals with a higher AT burden (defined per analysis plan) compared to participants with a lower AT burden or any AT, independent of demographics and vascular risk factors
3. The association between PACs/AT and global cortical Aβ will be different between blacks and whites, with blacks having a greater amount of amyloid with the same incremental increase in PACs/AT.

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 cohort: The analysis will be of all participants in the completed ARIC-PET study (N= 346 completed scans) for Aim 1 and all participants in the ARIC-PET study who also have Ziopatch information available (N=199) for Aim 2. All analyses will be cross-sectional, using echocardiogram (echo), electrocardiogram (ECG) and laboratory data from ARIC visit 5 and PET data from ARIC-PET (scan #1, concurrent to visit 5), although Ziopatch data is from visit 6, so aim 2 will be nonconcurrent (~5 years apart)).

Inclusion criteria (for inclusion in ARIC-PET; all of these persons will be included in analysis): no ARIC diagnosis of dementia at time of florbetapir PET scan, and with a brain MRI (from ARIC-NCS) within 12 months of recruitment. All participants were required to be able to give their own consent. For Aim 2, we will require participants to have Ziopatch data and will exclude participants who wore Ziopatch for less than two days.

Exclusion criteria for involvement in ARIC-PET: We excluded individuals with history of: (1) radiation therapy, chemotherapy, or surgery in the 6 weeks preceding the ARIC-PET visit; or (2) clinically significant liver or renal dysfunction; (3) prolonged QT interval; (4) drug or alcohol abuse. We allowed use of anticholinergic medications or memantine if the dose had been stable for ≥3 months preceding the PET scan.

Outcome: Standardized Uptake Volume Ratio (SUVR) of florbetapir (amyloid) by ARIC-PET, in prespecified regions of interest. Global mean cortical SUVR, which is a weighted average (based on region-of-interest (ROI) volumes) of regions known to be typically impacted in AD. The SUVR's will be evaluated at a cutpoint of 1.2, with values >1.2 considered positive, or elevated.

Exposure: AF will be defined per ARIC ascertainment at visit 5 while PAC burden and AT will be obtained from Zio XT Patch at visit 6 and will be defined as follows:

1) AT: narrow complex tachycardia >4 beats with a rate >100 bpm;
2) AT burden: Number of AT episodes per day
3) PAC burden: Number of PACs per day or % of heart beats that are PACs

Other variables: We will include race, center, sex, and age information from ARIC baseline (race, center, sex) and visit 5 (age), as well as APOE genotype from prior ARIC measurement. In addition, hypertension and systolic and diastolic blood pressures, diabetes, hypercholesterolemia, and smoking status will all be assessed from visit 5. Level of educational attainment as a covariate will be included in the models. Cognitive status (MCI versus normal cognition, since no participants with dementia were included in the cohort), defined based on the ARIC-NCS expert classification, will also be considered in later models as a covariate.

Data analysis: Our primary analysis for Aims 1 and 2 will utilize logistic regression models with evaluation of elevated SUVR as a binary dependent variable; the SUVR data are highly skewed, not easily handled with transformation, so we will not plan to use continuous SUVR data. AF will be considered as either present or absent up to and including visit 5.

For Aim 2 (Hypothesis 1) PAC burden will be considered as number of PACs per day/% of heart beats that are PACs. As there is no clinical cutoff for frequent PACs, different modeling strategies will be considered. PACs will first be categorized using the Zio reports which is <1%, 1-5%, >5%. It will also be considered as a continuous variable, per 1-SD increase. Finally, the PACs will be considered as tertiles with the lowest category as the reference group. (Hypothesis 2). Given that participants who are in continuous AF will not have PACs, we will consider excluding those participants with continuous AF when PAC is the exposure.
AT burden will be considered as a count (number of AT episodes per day) as well as either AT is present/AT is absent. Given that the analysis is non-concurrent, it is possible that both Aβ and cardiovascular risk factors/PAC burden at visit 5 may affect participation in visit 6 (when the Zio data were collected). This could lead to selection bias, and as such, we will consider using either multiple imputation methods or inverse probability weighting to account for selection bias.

All models will include adjustment for demographics (model 1); other covariates (model 2), with addition of APOE and cognitive status in model 3. We will add race interaction terms when appropriate (Aims 1+2).

Sensitivity analysis: We recognize that stroke may represent a confounder in the relationship between AF and global mean cortical SUVR, or between PACs/AT and global mean cortical SUVR. However it is also possible that As such, we will include stroke in the adjustment model (model 2) in the primary analysis. There are not many participants in the ARIC-PET cohort with stroke, but in a sensitivity analysis we will exclude these participants due to the possibility of stroke as a mediator between the exposure and outcome. We also recognize that there are participants who will have AF at the time of visit 6, but not at the time of visit 5. We will adjust for prevalent AF at visit 6 in the main analysis (model 2) and in a sensitivity analysis we will exclude those participants who have prevalent AF at visit 6.

Limitations: We recognize that ARIC-PET was performed as an ancillary to visit 5 and Zio XT data was obtained at visit 6 so the analysis is non-concurrent. We acknowledge the timing of PET relative to Zio as a limitation, but we have planned the above sensitivity analysis to address those with prevalent AF at visit 6 and have limited the definition of AF to ARIC ascertainment at visit 5. We will additionally consider the need to address selection bias as mentioned above. Finally, we recognize that the sample size is small and therefore may preclude adequate power to address interactions by race.

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? __x__ 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? __X (Apo E data)__ Yes ____ 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"? _X___ 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)?
--Association of Atrial Fibrillation With White Matter Disease.
Proposal Lead Author: Shao, IY
--Evaluation of Epigenetic Age Acceleration as a Risk Factor for Incident Atrial Fibrillation
Proposal Lead Author: Roberts, JD
--Association of Left Atrial Enlargement with Lower Cognitive Function and Subclinical Cerebral Infarcts: The ARIC Study
Proposal Lead Author: Chen, LY
--Association of ECG-Based Left Atrial Abnormality with Cognitive Decline and Subclinical Cerebral Infarcts: The ARIC Study
Proposal Lead Author: Chen, LY
--Atrial Fibrillation and its Association with Cognitive Decline over 20 years: The ARIC Neurocognitive Study (ARIC-NCS)

Proposal Lead Author: Chen, LY
--Determinants of Heart Rate Variability Change over 10 Years in a Population Sample: The ARIC Study
Proposal Lead Author: Chen, LY
--Cardiac dysfunction and brain amyloid deposition: The ARIC-PET Study
Proposal Lead Author: Johansen, M

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* _2009.29, 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. Levine DA, Galecki AT, Langa KM, et al. Trajectory of cognitive decline after incident

stroke. *JAMA*. 2015;314(1):41-51.

2. Levine DA, Wadley VG, Langa KM, et al. Risk factors for poststroke cognitive decline: The REGARDS study (reasons for geographic and racial differences in stroke). *Stroke*. 2018;49(4):987-994.

3. Nys GM, van Zandvoort MJ, de Kort PL, Jansen BP, de Haan EH, Kappelle LJ. Cognitive disorders in acute stroke: Prevalence and clinical determinants. *Cerebrovasc Dis*. 2007;23(5-6):408-416.

4. Gottesman RF, Coresh J, Catellier DJ, et al. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis risk in communities (ARIC) study. *Stroke*. 2010;41(1):3-8.

5. Gottesman RF, Grega MA, Bailey MM, et al. Association between hypotension, low ejection fraction and cognitive performance in cardiac patients. *Behav Neurol*. 2010;22(1-2):63-71.

6. Snyder HM, Corriveau RA, Craft S, et al. Vascular contributions to cognitive impairment and dementia including alzheimer's disease. *Alzheimers Dement*. 2015;11(6):710-717.

7. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D. Heart failure and alzheimer's disease. *J Intern Med*. 2015;277(4):406-425.

8. Johansen M,C., Langton-Frost,Nicole, Gottesman R,F. The role of cardiovascular disease in cognitive impairment. .

9. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurol*. 2017;74(10):1246-1254.

10. Zhang MJ, Norby FL, Lutsey PL, et al. Association of left atrial enlargement and atrial fibrillation with cognitive function and decline: The ARIC-NCS. *J Am Heart Assoc*. 2019;8(23):e013197.

11. Chen LY, Norby FL, Gottesman RF, et al. Association of atrial fibrillation with cognitive decline and dementia over 20 years: The ARIC-NCS (atherosclerosis risk in communities neurocognitive study). *J Am Heart Assoc*. 2018;7(6):10.1161/JAHA.117.007301.

12. Aldrugh S, Sardana M, Henninger N, Saczynski JS, McManus DD. Atrial fibrillation, cognition and dementia: A review. *J Cardiovasc Electrophysiol*. 2017;28(8):958-965.

13. Piers RJ, Nishtala A, Preis SR, et al. Association between atrial fibrillation and volumetric magnetic resonance imaging brain measures: Framingham offspring study. *Heart Rhythm*. 2016;13(10):2020-2024.

14. Stefansdottir H, Arnar DO, Aspelund T, et al. Atrial fibrillation is associated with reduced brain volume and cognitive function independent of cerebral infarcts. *Stroke*. 2013;44(4):1020-1025.

15. Falsetti L, Viticchi G, Buratti L, Grigioni F, Capucci A, Silvestrini M. Interactions between atrial fibrillation, cardiovascular risk factors, and ApoE genotype in promoting cognitive decline in patients with alzheimer's disease: A prospective cohort study. *J Alzheimers Dis*. 2018;62(2):713-725.

16. Volgman AS, Bairerz CN, Benjamin EJ, et al. Sex and race/ethnicity differences in atrial fibrillation. *J Am Coll Cardiol*. 2019;74(22):2812-2815.

17. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial fibrillation: Epidemiology, pathophysiology, and clinical outcomes. *Circ Res*. 2017;120(9):1501-1517.

18. Gottesman RF, Schneider AL, Zhou Y, et al. The ARIC-PET amyloid imaging study: Brain amyloid differences by age, race, sex, and APOE. *Neurology*. 2016;87(5):473-480.

19. Gunda S, Akyeampong D, Gomez-Arroyo J, et al. Consequences of chronic frequent premature atrial contractions: Association with cardiac arrhythmias and cardiac structural changes. *J Cardiovasc Electrophysiol*. 2019;30(10):1952-1959.

20. Johansen MC, Mosley TH, Knopman DS, et al. Associations between left ventricular structure, function, and cerebral amyloid: The ARIC-PET study. *Stroke*. 2019:STROKEAHA119027220.