ARIC Manuscript Proposal #3861

PC Reviewed: 6/8/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Risk of Dementia Associated with Atrial Cardiopathy: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Atrial Cardiopathy and Incident dementia

2. Writing Group:

Writing group members:

Michelle C. Johansen MD (first author), PhD, Wendy Wang, Michael Zhang, David S. Knopman MD, Chiadi Ndumele MD, Thomas H. Mosley PhD, Elizabeth Selvin PhD, Amil M. Shah MD, Scott D. Solomon MD, Rebecca F. Gottesman, MD, PhD, Lin Yee Chen, MD, MS (last author). *Others are 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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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:

1 year, data acquisition and statistical analysis first few months, planned interim abstract submission fall-winter 2021, final manuscript submission planned fall 2022

4. Rationale:

The ARIC study has demonstrated that persistent atrial fibrillation (AF) is associated with cognitive impairment[1], that participants with high burden of PACs have lower cognitive scores[2], and that left atrial enlargement in the presence of AF is associated with dementia.[3] Other cohorts have supported these findings, with AF patients having poorer baseline cognition and incident cognitive impairment that was independent of incident stroke.[4] A meta-analysis with 89,907 AF participants also found a higher risk of cognitive impairment independent of a history of stroke.[5] These results support that AF, even in the absence of stroke, may independently contribute to cognitive impairment.[6]

AF, however, is not a binary entity. While measures of AF burden and other arrhythmias are important, an even earlier state of atrial dysfunction, specifically atrial cardiopathy, is becoming increasingly recognized as an important contributor to ischemic stroke.[7] Since atrial cardiopathy is associated with increased risk of stroke and AF, and both stroke and AF are associated with increased dementia risk, it is essential to determine whether the link between atrial cardiopathy and dementia is independent of AF and stroke. We readily acknowledge that the relationship between a state of atrial cardiopathy and an atrial tachyarrhythmia is complex. It may be that atrial cardiopathy might result in increased dementia risk because it results in AF, or rather is simply mediated through AF, or it may be that a state of atrial cardiopathy independently increases dementia risk, apart from the development of AF.

Atrial cardiopathy has been suggested as another explanation of left atrial embolization than AF alone, and definitions used in other research and in clinical trials have begun to incorporate measures of left atrial size and other biomarkers of cardiac function. We have previously demonstrated an association between atrial cardiopathy, defined using the criteria set forth in a major ongoing clinical trial, and florbetapir PET markers of beta-amyloid in the ARIC PET ancillary study.[8] That work, however, included individuals without dementia, and although it suggests an association with a major mechanism of dementia, it is important to understand the overall role in dementia risk. The overarching goal of this proposed manuscript is to define the association of atrial cardiopathy, defined by three easily obtainable measures in clinical practice, specifically left atrial size, serum NT-proBNP and p-wave terminal force on electrocardiography, and incident dementia.

5. Main Hypothesis/Study Questions:

Aim 1: To determine the association of atrial cardiopathy in old age (defined at visit 5) with incident dementia, accounting for vascular risk factors.

Hypothesis 1a: There is an association of atrial cardiopathy with incident dementia independent of vascular risk factors.

Hypothesis 1b: There is an association of atrial cardiopathy with incident dementia even among people without a diagnosis of AF.

Hypothesis 1c: We do not anticipate that the association between atrial cardiopathy and incident dementia, if found, will be completely mediated through AF.

Aim 2: To determine the association of atrial cardiopathy in old age (defined at visit 5) with incident dementia, accounting for vascular risk factors, in persons without stroke.

Hypothesis 2a: There is an association of atrial cardiopathy with incident dementia independent of vascular risk factors in persons without stroke.

Hypothesis 2b: We do not anticipate that if the association in Aim 1 is found, it will be completely mediated through stroke.

We hypothesize that the risk of incident dementia will be higher among those with atrial cardiopathy independent of demographics and vascular risk factors. We also hypothesize that there will be an attenuation of the effect when excluding participants with prevalent AF or prevalent stroke, but that the effect estimates will remain significant. We also hypothesize that the effect of atrial cardiopathy on incident dementia will be partially mediated by AF, and stroke, each, but that full mediation will not be present.

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:

Our study design will be a prospective cohort study with study entrance at visit 5, with follow up through visit 7 (or most recent data).

Inclusion criteria: Non-demented ARIC participants who attended visit 5 and had echo measurements will be included in this analysis.

Exclusion criteria: Participants whose race is other than black or white, or blacks from the MN and MD centers will be excluded. Participants will be excluded if they are missing NT-proBNP or covariates of interest.

Exposure:

We will define atrial cardiopathy as a combination of enlarged left atrial diameter, the p wave terminal force measure in lead 1 on electrocardiogram, and elevated serum NT-proBNP. Specifically, atrial cardiopathy will be defined as present if the participants have ≥ 1 of the following: P-wave terminal force >5000 mV x ms in electrocardiogram (ECG) lead V1, serum amino terminal pro-B-type natriuretic peptide (NTproBNP)>250 pg/mL, and LA diameter index ≥3cm/m2. Other work has demonstrated an association between p-wave terminal force in lead V1 and atrial abnormalities such as fibrosis and myocyte hypertrophy.[9,10] Left-atrial chamber dilatation is also associated with atrial dysfunction independent of AF.[11-13] Finally serum NT-proBNP reflects atrial myocyte dysfunction, and has been associated with ischemic stroke independent of AF.[14] These three markers together help form a picture of the function of the left atrium, apart from tachyarrhythmia alone. It was also chosen as the definition of atrial cardiopathy used to enroll participants in ARCADIA, a major, ongoing stroke clinical trial designed to test if patients who have atrial cardiopathy go on to have recurrent stroke after being randomized to receive either aspirin or apixaban.[15] This was also the definition used in our prior ARIC work determining the association between atrial cardiopathy and florbetapir PET.[8] As a result of this, we believe that this is an optimal definition by which to define atrial cardiopathy in a way that can be easily applicable in clinical practice as it requires no advanced imaging (LA diameter easily obtained from standard, routine clinical transthoracic echocardiography). In this

study, P-wave terminal force will be calculated by multiplying amplitude by duration from participant ECG.

Outcomes:
We will use the level 3 definition of dementia in ARIC that includes participants with adjudicated dementia by in person exam, by telephone assessment, informant telephone interview, or by medical records (identified through surveillance for hospitalization discharge codes (ICD-9) or death certificate codes related to dementia).

Statistical Analysis:
Covariates:
Covariates will include age, race-center, sex, education (visit 1), Apo E4 allele, current alcoholic use, current cigarette smoking, body mass index, history of coronary artery disease, history of prevalent heart failure, low density lipoprotein cholesterol and hypertension. Adjudicated atrial fibrillation (defined by ECGs, hospital discharge records and ICD-9 codes) will be included in the adjustment model for Aim 2. ARIC adjudicated ischemic stroke will be included in the adjustment model for Aim 1. We will additionally consider the use of anticoagulants or antiplatelet medications as covariates.

Primary Analysis:
We will use an adjusted Cox proportional hazards regression models to determine the association of atrial cardiopathy with incident dementia. We will follow participants over time until either the participant has the event of interest (dementia), death, or censoring (drop out or end of follow-up). We will perform this analysis among all participants who meet inclusion criteria, and then will additionally exclude those with prevalent AF (Hypothesis 1b) or prevalent ischemic stroke (Hypothesis 2a). We will then perform a formal mediation analysis using structural equation modeling to estimate the direct and indirect mediation effects of atrial fibrillation (Aim 1) or ischemic stroke (Aim 2) on the association between atrial cardiopathy and dementia. We will also consider a competing risks analysis depending on the number of outcomes.

Additional Analyses:

We will additionally test for center*race-based interactions in the association between atrial cardiopathy and incident dementia. Given that there is a lower rate of AF in Blacks but a higher rate of dementia in Blacks, it is plausible that a similar pattern may be seen for atrial cardiopathy and thus hypothesize that atrial cardiopathy may be a more important risk factor for dementia in Whites versus Blacks.

Limitations:
We recognize that there will be limitations in our analysis. It may be that we may miss asymptomatic AF or silent cerebral infarction, not captured in the ARIC adjudication process. It may be that another definition of atrial cardiopathy may be superior to the one chosen for this manuscript, but it is a definition that has been used in other research, and by ongoing clinical trials and will therefore offer the ability to compare our findings to other's work. We also recognize that the participants who develop either AF or stroke during the duration of follow up may be small.

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/mantrack/maintain/search/dtSearch.html

__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-Atrial fibrillation is associated with hospitalization for dementia
#1739-Atrial fibrillation is associated with cognitive decline and brain MRI abnormalities
#2546-Association of left atrial enlargement with lower cognitive function and dementia
All are included as co-authors

**There is also an ongoing manuscript proposal that is being submitted by Dr. Michael Zhang et al. building off the prior work of Dr. Chen (Atrial fibrillation, incident dementia) with one of the manuscript's goals being to determining if the association between AF and dementia are mediated by LA size and function using echocardiography measures to include LA strain. Once this submission came to my attention, we discussed our approach to ensure that the concepts represented in his proposal are distinct. He will be submitting his proposal concurrently. We are both co-authors on each other's manuscript proposals and will review the science of each other to ensure that this is not work that is being duplicated.

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* __2008.06_____)
___ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

References:

1. 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.

2. Rooney MR, Norby FL, Maheshwari A, et al. Frequent premature atrial contractions are associated with poorer cognitive function in the atherosclerosis risk in communities (ARIC) study. *Mayo Clin Proc*. 2021.

3. 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.

4. Bailey MJ, Soliman EZ, McClure LA, et al. Relation of atrial fibrillation to cognitive decline (from the REasons for geographic and racial differences in stroke [REGARDS] study). *Am J Cardiol*. 2021.

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

6. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(5):612-619.

7. Johansen MC, De Vasconcellos HD, Gottesman RF. Understanding atrial cardiopathy: An under-recognized contributor to cardioembolic stroke. *Curr Treat Options Neurol*. 2019;21(7):32-019-0571-4.

8. Johansen MC, Mosley TH, Knopman DS, et al. Associations between atrial cardiopathy and cerebral amyloid: The ARIC-PET study. *J Am Heart Assoc*. 2020;9(24):e018399.

9. Goyal SB, Spodick DH. Electromechanical dysfunction of the left atrium associated with interatrial block. *Am Heart J*. 2001;142(5):823-827.

10. Ariyarajah V, Mercado K, Apiyasawat S, Puri P, Spodick DH. Correlation of left atrial size with p-wave duration in interatrial block. *Chest*. 2005;128(4):2615-2618.

11. Anaissie J, Monlezun D, Seelochan A, et al. Left atrial enlargement on transthoracic echocardiography predicts left atrial thrombus on transesophageal echocardiography in ischemic stroke patients. *Biomed Res Int*. 2016;2016:7194676.

12. Barbarossa A, Guerra F, Capucci A. Silent atrial fibrillation: A critical review. *J Atr Fibrillation*. 2014;7(3):1138.

13. Chen LY, Chung MK, Allen LA, et al. Atrial fibrillation burden: Moving beyond atrial fibrillation as a binary entity: A scientific statement from the american heart association. *Circulation*. 2018;137(20):e623-e644.

14. Folsom AR, Nambi V, Bell EJ, et al. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: The atherosclerosis risk in communities study. *Stroke*. 2013;44(4):961-967.

15. Kamel H, Longstreth WT,Jr, Tirschwell DL, et al. The AtRial cardiopathy and antithrombotic drugs in prevention after cryptogenic stroke randomized trial: Rationale and methods. *Int J Stroke*. 2019;14(2):207-214.