ARIC Manuscript Proposal # 3045

PC Reviewed: 9/12/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of atrial fibrillation with white matter microstructural integrity using diffusion tensor imaging – The ARIC-NCS

b. Abbreviated Title (Length 26 characters): **AF and DTI**

2. Writing Group:

Writing group members: Yuefan Shao (first author), Melinda C. Power, Thomas Mosley, Clifford Jack (invited), Rebecca Gottesman, Lin Y. Chen, Faye Norby, Elsayed Soliman, Alvaro Alonso (senior author)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __YS___ **[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:

Finish primary data analysis and complete an abstract submission for AHA – EPI lifestyle 2018; Complete all data analysis and manuscript writing within 6 months after proposal submission.

4. Rationale:

It is known that atrial fibrillation (AF) is associated with increased risk for stroke[1,2], which can further cause cognitive impairment or dementia among patients[3]. Mounting evidence suggests that AF might be directly associated with an increased risk of cognitive impairment,[4,5] and one proposed mechanism is through the increased risk of stroke in patients with AF [4,6]. However, recent studies have also shown that AF is associated with an increased risk of cognitive impairment and dementia even in the absence of prevalent stroke[6,7]. Studies have suggested alternative explanations linking AF to cognitive impairment and dementia. For example, lower cardiac output among AF patients might induce brain hypoperfusion[5], which might further compromise cerebrovasculature and brain tissues[8]. Therefore, it is critical to investigate the direct association between AF and cognitive impairment in those with and without stroke in order to elucidate potential underlying mechanisms for prevention purposes.

Cerebral white matter disease plays an important role in cognitive impairment. White matter hyperintensity (WMH) assessed through MRI as a consequence of cerebral small vessel disease is associated with increased risk of cognitive impairment and dementia[9]. Recent technology - Diffusion Tensor Imaging (DTI) – supplements WMH volume measured with traditional MRI and can provide information on more subtle damages to white matter microstructures. DTI tracks the diffusion distribution of water molecules in the tissue. Fractional anisotropy (FA) and mean diffusivity (MD) are the two most common measures. FA captures the directionality of water flow whereas MD informs the mean diffusivity of water molecules in all directions[10]. Thus, when applied to the white matter, DTI measures are considered highly sensitive markers of neuropathology[10] and provide information that can be critical to early detection of white matter integrity change that could prevent worsened outcomes.

Several studies have suggested that vascular risk factors such as hypertension are associated with worse white matter microstructural integrity[4,6]. Studies have also examined the association between AF and WMH dependent and independent of cerebral infarcts[11,12]. However, there are no studies to date investigating the direct association between AF and white matter microstructural integrity using DTI measures. Moreover, few studies have investigated etiologic pathways from AF to cognitive impairment or dementia independent of stroke or silent cerebral infarcts (SCI) [13,14]. Therefore, in order to better understand the potential mechanistic pathway linking AF to cognitive impairment and dementia, we propose to examine the association of prevalent AF with WMH and white matter microstructural integrity (assessed with FA and MD) among persons with and without the presence of clinical stroke and SCI in the ARIC-NCS cohort using a cross-sectional study at Visit. 5.

Also, we will conduct a quantitative bias analysis to examine the impact of selection bias and information bias on the above estimates of associations.

5. Main Hypothesis/Study Questions:

Aim 1: Examine the association of AF with WM microstructural integrity (measured by FA and MD) and WMH volume

Aim 1.1.1: Examine the association of AF with WM microstructural integrity and WMH in the ARIC sample, as well as the association of AF with WM microstructural integrity independent of WMH.

Aim 1.1.2: Examine the association of AF with WM microstructural integrity and WMH among persons without clinical stroke and silent cerebral infarcts (SCI).

Hypothesis: We hypothesize that AF is associated with reduced WM microstructural integrity as defined by MD and FA, and with increased volume of WMH, independently of presence of stroke and SCI.

Aim 2: Methodological aims. Apply a quantitative bias analysis on the estimates of association detected in Aim 1

Aim 2.1: Identify the appropriate bias model for bias analysis.

Aim 2.2: Assess the impact of selection bias and misclassification bias over the association detected in Aim 1.

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 study of the association between Visit 5 AF status and Visit 5 WM microstructural integrity.

Exclusion Criteria for Aim 1.1.1: Participants of race other than black or white, non-white participants examined at MD or MN; Missing DTI data at Visit 5; no consent to use of genetic data

Exclusion Criteria for Aim 1.1.2: Participants of race other than black or white, non-white participants examined at MD or MN; Missing DTI data at Visit 5; Prior history of either stroke or SCI before Visit 5; no consent to use of genetic data.

Exposure: Atrial fibrillation status (yes /no) at Visit 5 as defined by past AF history based on study ECGs; history of AF hospitalization.

Outcomes: DTI data (regional average FA and MD measurements) measured at ARIC-NCS visit 5; White matter hyperintensity volume measured with MRI at Visit 5.

Covariates:
age, sex, race/center, systolic/diastolic blood pressure, fasting glucose, HDL-C, LDL-C, triglycerides, education, smoking history, alcohol use, BMI, hypertension medication, diabetes, ECG-based left ventricular hypertrophy, plasma CRP, eGFR and ApoE * E4 allele status, and anticoagulant use at Visit 5. Most covariates and biomarker data are collected during Visit 5 of ARIC-NCS except for race/center, education, and sex (using information from visit 1),

Data Analysis:

In our primary analysis, we will investigate the association between AF status and WM microstructural integrity using weighted multiple linear regression models, incorporating the ARIC-NCS MRI sampling weights and adjusting for potential confounders. We will repeat the analysis adjusting for WMH as well as in the participants without prior stroke or without SCI in MRI. Additional analyses will also consider log (WMH volume) as an independent variable.

The impact of selection bias due to loss-to-follow-up and information bias due to misclassification of AF on the association between AF and WH microstructural integrity will be performed through a formal bias analysis as described in *Applying Quantitative Bias Analysis to Epidemiologic Data*[15]. We will examine different sets of bias parameters and perform multidimensional bias analysis to each bias scenario separately. Based on our results from bias analysis, we will then determine whether to perform multiple imputation on missing exposure/covariates data including previous ARIC study visits.

Limitations and Challenges: Our study is limited to a cross-sectional analysis since DTI data is only available during ARIC-NCS visit 5. Moreover, we will only use regional average FA and MD as measurements due to data availability. Due to limited prior knowledge, unknown confounding remains an issue in our analysis, though we are adjusting for the main established risk factors for AF. Certain covariates such as plasma CRP are measured as an indicator for inflammatory response at an immediate time point at visit 5. Even though evidences suggest that inflammatory response could be a potential confounder, the direction of association remains unknown due to temporal ambiguity.

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? __X__ 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)?
MS 2551 Vascular risk factors and DTI (Power). AF not evaluated as an exposure in that manuscript. Melinda Power has been invited to be a coauthor in the current proposal.
MS 2999 PWV and DTI (Wei). AF not evaluated as an exposure in the manuscript.
MS 2804 Correlates of MCI/dementia in AF (Alonso). This manuscript examined risk factors for dementia/MCI in ARIC participants with AF, while in this manuscript we will examine association of AF with markers of WM disease.
MS 1739. AF and cognitive decline (Chen). This manuscript proposed examining the association of AF with cognitive decline and brain MRI abnormalities, but it did not include DTI-derived measures of WM structural integrity.

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 [ARIC-NCS])
___ 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.

Citations:

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4. Power, M. C. *et al.* Midlife and late-life vascular risk factors and white matter microstructural integrity: The atherosclerosis risk in communities neurocognitive study. *J. Am. Heart Assoc.* **6,** (2017).
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13. Ott, A. *et al.* Atrial Fibrillation and Dementia in a Population-Based Study. *Stroke* **28,** 316 LP-321 (1997).
14. Shah, A. D., Merchant, F. M. & Delurgio, D. B. Atrial Fibrillation and Risk of Dementia/Cognitive Decline. *J. Atr. Fibrillation* **8,** 1353 (2016).
15. Lash, T., Fox, M. and Fink, A. (2009). Applying Quantitative Bias Analysis to Observational Epidemiologic Research. New York, NY: Springer Science Business Media, LLC.