ARIC Manuscript Proposal #3418

PC Reviewed: 6/18/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of diabetes mellitus with incident dementia in patients with atrial fibrillation in the ARIC cohort.

b. Abbreviated Title (Length 26 characters): Diabetes and dementia in Atrial fibrillation

2. Writing Group:

Writing group members: Ashwini Jiayaspathi, Lin Yee Chen, Elizabeth Selvin, Rebecca Gottesman, David Knopman, Thomas Mosley, Faye Norby, Alvaro Alonso

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

First author:

Address: Ashwini Jiayaspathi
1659 Briarcliff Road NE
Apt 1003 B
Atlanta, Georgia 30306

Phone: 408 398 0481
E-mail: ashwini.jiayaspathi@emory.edu

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).

Name: **Alvaro Alonso**
Address: 1518 Clifton Road NE, CNR 3051
Atlanta, Georgia 30322

Phone: 404 727 8714
E-mail: alvao.alonso@emory.edu

3. Timeline: Completion by March 2020

4. Rationale: Numerous prospective studies, including an analysis of the ARIC cohort, have demonstrated association between cardiovascular risk factors like diabetes and occurrence of dementia (1). Additional analyses within the ARIC cohort have also established the role of cardiac arrhythmias like atrial fibrillation (AF) as a risk factor for the development of cognitive decline and dementia (2,3).

We are currently facing an epidemic of both diabetes (9) and dementia (4) among the elderly. While studies have been conducted demonstrating the associations between midlife cardiovascular risk factors like hypertension, AF, or diabetes mellitus and the development of dementia later in life (1), we do not have sufficient evidence to define the role of diabetes mellitus as a risk factor for cognitive impairment or dementia in patients with AF. Understanding this particular relationship is important because persons with AF, due to their increased risk of stroke, associated irregularities in blood supply to the brain, and other potential mechanisms, are particularly vulnerable to the development of vascular cognitive impairment and dementia (2,3,8). In fact, among ARIC participants attending visit 5, prevalent diabetes was a strong risk factor for dementia among those with AF (OR 3.4, 95% CI 1.8, 6.5) (2). However, this was a cross-sectional analysis. The prospective association between diabetes and dementia among persons with AF has not been described.

A better characterization of the role of diabetes as a risk factor for dementia in persons with AF would be important to understand the mechanisms of dementia in AF patients, and to potentially inform studies aiming to prevent dementia in AF. This study will try to determine the associations of blood sugar levels, diabetes and diabetes control with development of dementia in patients with AF.

5. Main Hypothesis/Study Questions:

1) Primary Aim: to study the association between presence of diabetes (yes/no) at the time of AF diagnosis with risk of dementia

2) Secondary Aims:

a. To study the association between the last glycemia and HbA1c values before AF diagnosis with risk of dementia.
b. To study the association between presence of diabetes (yes/no) at the time of AF diagnosis with prevalence of mild cognitive impairment (MCI) at visits 5 and 6.

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).

Design:

This analysis will include all ARIC participants who developed incident AF during follow up (after visit 1 and through 2017, or latest available year). We will exclude those with prevalent dementia at the time of AF diagnosis, those missing covariates at the baseline, those with a race other than white or black or those who are not white in the Minnesota and Maryland centers. Data on prevalent diabetes, blood glucose levels and HbA1c and other covariates will be obtained from the most recent visit or follow-up call prior to AF diagnosis.

AF is ascertained in ARIC through 3 sources. ECG's performed during the study examinations done using MAC PC personal cardiographs where a standard supine 12 lead resting ECG was performed after a 12 hour fast followed by a light snack and at least 1 hour after smoking tobacco or ingestion of caffeine. A trained abstractor obtained and recorded all hospital discharge diagnosis of AF using the ICD 9, where AF was defined as code 427.31 or 427.32. The participants of the cohort were also labelled as AF patients if underlying cause of death was AF (ICD 10 code 148 or ICD 9 code 427.3), though participants diagnosed through this method will not be included in the analysis (6).

Exposure:

The exposure will be prevalence of diabetes mellitus (yes/no) defined in study visits as fasting blood glucose levels >= 126 mg/dl, a non-fasting blood glucose level >= 200 mg/dl, self-reported physician diagnosis of diabetes or self-reported use of diabetes medication. Also, we will define diabetes as self-reported physician diagnosis reported during the AFU calls. Finally, we will include the fasting blood glucose (collected at all study visits) and hemoglobin A1C (measured at visits 2 and 5) prior to AF diagnosis.

Outcome:

The main outcome will be incident dementia defined according to standard ARIC approaches (5). This adjudication was done beginning in visit 5 when 6471 of the 6538 participants who attended this visit underwent a detailed neurocognitive assessment, a subset of which also received a neurological exam and brain MRI. In those who were alive but unwilling or unable to participate in this visit (1461 participants) a validated phone based cognitive assessment, the modified telephone interview for cognitive status (TICSm) was performed. In the full cohort the hospital diagnosis codes were also used to identify incident dementia (7).

In secondary analysis, we will consider adjudicated prevalent MCI at visits 5 or 6 as an outcome.

Covariates:

Factors considered to be potential confounders include the participants age, sex, race, study site, education levels, APOE genotype, body mass index, systolic and diastolic blood pressure, use of antihypertensive medication, use of oral anticoagulants, hyperlipidemia, statin use, smoking and alcohol consumption, and prior history of cardiovascular disease (myocardial infarction, heart failure, incident and prevalent stroke).

Statistical Analysis:

We will use Cox proportional hazards regression models to estimate hazard ratios and 95% confidence intervals of dementia by presence or absence of diabetes, adjusting for potential confounders like age and calendar year when AF was diagnosed. All additional covariates in the study will be assessed at the time of diagnosis of AF. We will conduct parallel analyses using fasting glucose and HbA1c as primary independent variables. The primary endpoint will be time to dementia diagnosis from initial diagnosis with AF. Initial models will adjust for age, sex, race-site and education. A second model will include potential confounders (listed above), with a final model adjusting for additional variables that could be considered confounders or mediators (e.g. history of CVD prior to diagnosis of AF). We will also adjust for prevalent stroke at the time of

AF diagnosis in addition to adjusting for incident stroke as a potential mediator between AF and development of dementia. We will conduct additional analyses stratifying by sex and race. Depending on the degree of missingness for the exposure and covariates, we will consider using multiple imputation approaches.

The analysis of prevalent MCI will be done with logistic regression to evaluate the association of diabetes at AF diagnosis with prevalent MCI (vs normal cognition) at visits 5 and 6. This analysis will exclude participants with diagnosed dementia at visits 5 and 6. Covariate adjustments will follow the same approach as for the incident dementia analysis.

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__ 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/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)?

2120C (Gottesman) Dementia incidence and midlife risk factors (published in JAMA Neurology; reports association between midlife risk factors, including diabetes and dementia in the entire ARIC population)

1740 (Chen) AF and dementia (published in JAHA: reports association between AF and dementia incidence)

2804 (Alonso) Correlates of MCI and dementia in AF (published in JAHA: cross-sectional association between CV risk factors, including diabetes, and prevalent dementia in participants with AF attending visit 5).

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* 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 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) Gottesman, R. F., Albert, M. S., Alonso, A., Coker, L. H., Coresh, J., Davis, S. M., . . . Knopman, D. S. (2017). Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *JAMA Neurol, 74*(10), 1246-1254. doi:10.1001/jamaneurol.2017.1658
2) Alonso, A., Knopman, D. S., Gottesman, R. F., Soliman, E. Z., Shah, A. J., O'Neal, W. T., . . . Chen, L. Y. (2017). Correlates of Dementia and Mild Cognitive Impairment in Patients With Atrial Fibrillation: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *J Am Heart Assoc, 6*(7). doi:10.1161/jaha.117.006014
3) Chen, L. Y., Norby, F. L., Gottesman, R. F., Mosley, T. H., Soliman, E. Z., Agarwal, S. K., . . . Alonso, A. (2018). 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, 7*(6). doi:10.1161/jaha.117.007301
4) Alzheimer's association, Alzheimer's and Dementia: Global Resources
5) Knopman, D. S., Gottesman, R. F., Sharrett, A. R., Wruck, L. M., Windham, B. G., Coker, L., . . . Mosley, T. H., Jr. (2016). Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst), 2*, 1-11. doi:10.1016/j.dadm.2015.12.002
6) Alonso, A., Agarwal, S. K., Soliman, E. Z., Ambrose, M., Chamberlain, A. M., Prineas, R. J., & Folsom, A. R. (2009). Incidence of atrial fibrillation in whites and African-

Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J, 158*(1), 111-117. doi:10.1016/j.ahj.2009.05.010

7) Lutsey, P. L., Chen, N., Mirabelli, M. C., Lakshminarayan, K., Knopman, D. S., Vossel, K. A., . . . Alonso, A. (2018). Impaired Lung Function, Lung Disease and Risk of Incident Dementia. *Am J Respir Crit Care Med*. doi:10.1164/rccm.201807-1220OC
8) Alonso, A., & Arenas de Larriva, A. P. (2016). Atrial Fibrillation, Cognitive Decline And Dementia. *Eur Cardiol, 11*(1), 49-53. doi:10.15420/ecr.2016:13:2
9) Tabish, S. A. (2007). Is Diabetes Becoming the Biggest Epidemic of the Twenty-first Century? *Int J Health Sci (Qassim), 1*(2), V-viii.