

ARIC Manuscript Proposal #3396

PC Reviewed: 5/14/19

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Arterial Stiffness and AF risk in the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Arterial Stiffness and AF

2. Writing Group:

Writing group members: Zakaria Almuwaqqat, Lin Y. Chen, Pamela L. Lutsey, Faye Norby, Elsayed Soliman, Gerardo Heiss, Kunihiro Matsushita, Alvaro Alonso, others welcome.

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

First author: Zakaria Almuwaqqat

Address: Dept of Medicine

Emory University School of Medicine

1354 Clifton Rd

Atlanta, GA 30322

Phone: 203-824-7207

E-mail: zalmuwa@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: Dept of Epidemiology, Rollins School of Public Health

Emory University

1518 Clifton Rd NE, CNR 3051

Atlanta, GA 30322

Phone: 404-727-8714

E-mail: alvaro.alonso@emory.edu

3. Timeline:

April 2019 – Submit proposal

May-June 2019 – Complete primary data analysis

June-July 2019 – Manuscript preparation and submission

4. Rationale:

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and confers increased risks of morbidity and mortality. [1, 2] Prevalence of AF, frailty and arterial stiffness greatly increase with age. [3-6] Evidence from previous studies suggests that arterial system structural and functional changes might be associated with left atrial remodeling. [7-10] In fact, arterial stiffness is a well-known marker for poor cardiovascular outcomes in the community. [11] Stiff arteries increase left ventricular (LV) end-systolic pressure and workload, and over time, this can lead to left ventricular remodeling which may ultimately lead to left atrial changes. [12] Recent studies have indicated that arterial stiffness might be associated with AF. However, they have been limited by the relatively younger age of subjects and the presence of significant comorbidities. [13] [14] We propose to investigate the association of arterial stiffness and incident AF in ARIC who completed visit 5 and have pulse wave velocity (PWV) measurements available. Our hypothesis is that higher PWV, as a marker of arterial stiffness, is associated with greater AF risk. To further study the impact of this association on AF related clinical endpoints, we also propose, as an exploratory aim, to study the association of arterial stiffness and AF-related outcomes among subjects with prevalent AF at visit 5.

5. Main Study Question and Hypothesis:

Hypothesis:

- Increased central arterial stiffness as measured by carotid-femoral PWV (cfPWV) is associated with higher incidence of AF.

Aims:

- 1- To investigate if increased central arterial stiffness as measured by cfPWV is associated with an increased risk of AF in ARIC subjects.
- 2- As an exploratory analysis due to limited sample size, to study the association of increased arterial stiffness with adverse cardiovascular outcomes among ARIC subjects with prevalent AF.

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 participants

Eligible participants will be from the ARIC cohort who participated in visit 5 and have information on PWV at that visit.

Exclusion criteria

- Participants with AF at or prior to visit 5 (for aim 1).

- Subjects who had conditions potentially compromising the quality of PWV measurements: major arrhythmias (Minnesota code 8-1-3, 8-3-1, and 8-3-2; (n=74), Minnesota code 8-1-2 with evidence of low quality PWV waveforms (n=9), self-reported history of aortic or peripheral revascularization or aortic graft (n=40), and echocardiographic evidence of aortic stenosis or moderate or greater aortic regurgitation (n=11). (for aims 1 and 2)
- Participants with no prior history of AF at or prior to visit 5 (for aim 2).
- Participants with race other than white or black, as well as non-whites from the Minnesota and Washington County field sites (because of very small numbers).
- Participants with prevalent MI, ischemic stroke, heart failure who are being evaluated for any of these outcomes in AIM #2.

Main exposure

Aim 1:

PWV- primarily central arterial stiffness through cfPWV.

This variable will be transformed to a 4-level variable based on the cohort's quartiles. We will only use variables collected at visit 5 as this was the only visit those measures were collected with the presence of follow up data for AF.

Aim 2:

PWV at visit 5 as a continuous variable- will also create a dichotomous variable based on cohort's median, among subjects with established history of AF. Since our sample size might be limited, we will consider this as an exploratory analysis and our outcome of interest will be a composite outcome of MI, heart failure, stroke and CV mortality.

Outcome definition

Aim 1:

Incident AF from the end of visit 5 through the end of 2017 for those who completed visit 5. Prevalent AF will be defined according to 12-lead electrocardiograms (ECGs) obtained at study exams or prior history of AF hospitalization. Incident AF will be defined according to hospital discharge codes captured continuously during the follow-up, and death certificates. We will exclude AF cases related to open cardiac surgery. A similar detailed description and validity of this approach has been previously published.²³ Follow-up will be administratively censored at December 31st, 2017.

Our preliminary analysis indicates there are 478 participants from those who presented for visit 5 had experienced AF during the follow up time.

Aim 2:

Incident adverse cardiovascular composite outcomes (MI, ischemic stroke, heart failure and cardiovascular death) as a composite outcome.

Our preliminary analysis indicates there are 547 participants from those who presented for visit 5 had experienced AF prior to visit 5 (prevalent AF). Among those, 124 subjects experienced at least one event [MI (n=66), ischemic stroke (n=44), heart failure (n=140) or CV death (n=74)].

Other Variables of Interest

Sex, age, race, study center, education, BMI, height, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, alcohol using status, diabetes, use of antihypertensive medications, LVH by ECG, prevalent HF, and prevalent myocardial infarction (MI). We will also consider Echocardiographic data; LVH and LV dimensions as explanatory variables, and use of oral anticoagulants for the Aim 2 analysis.

Analysis plan

For Aim 1, we will study association with incident AF using Cox proportional hazards models, adjusting for the variables described above.

For Aim 2, we will study the association of PWV and incident composite outcomes, among subjects with prior history of AF, using Cox proportional hazards models and adjusting for the variables described above. Depending on the number of events, we may limit the number of covariates or use a composite variable such as the CHA2DS2-VASc score.

As a limitation, we acknowledge that we may not include asymptomatic AF or AF managed exclusively in an outpatient setting. Also, exclusion of participants with missing data on arterial indices could introduce selection biases into our analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript? 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? 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.csc.unc.edu/ARIC/search.php>

No overlap with existing proposals

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 #1578: Prediction of atrial fibrillation in the community: the CHARGE consortium (Alonso)
- Carotid Intima-Media Thickness and Arterial Stiffness and the Risk of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study (Lin Chen and Alonso).
- Correlates of Segmental Pulse Wave Velocity in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study (Meyer, ML)
10.1093/ajh/hpv079

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* _____)
 B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2008.10 and 2009.16)

*ancillary studies are listed by number at <http://www.csc.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.csc.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: No

References:

1. Mozaffarian, D., et al., *Executive Summary: Heart Disease and Stroke Statistics—2016 Update*. A Report From the American Heart Association, 2016. **133**(4): p. 447-454.
2. Chugh, S.S., et al., *Worldwide Epidemiology of Atrial Fibrillation: A Global Burden of Disease 2010 Study*. *Circulation*, 2013.
3. Cavalcante, J.L., et al., *Aortic stiffness: current understanding and future directions*. *J Am Coll Cardiol*, 2011. **57**(14): p. 1511-22.
4. Fumagalli, S., et al., *Atrial fibrillation is a possible marker of frailty in hospitalized patients: results of the GIFA Study*. *Aging Clin Exp Res*, 2010. **22**(2): p. 129-33.
5. Miyasaka, Y., et al., *Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence*. *Circulation*, 2006. **114**(2): p. 119-25.
6. Scardia, A., et al., *Arterial stiffness and atrial fibrillation: a new and intriguing relationship*. *European Heart Journal Supplements*, 2017. **19**(suppl_B): p. B35-B39.
7. Mitchell, G.F., et al., *Pulse pressure and risk of new-onset atrial fibrillation*. *JAMA*, 2007. **297**(7): p. 709-15.
8. Proietti, M., et al., *Relationship between carotid intima-media thickness and non valvular atrial fibrillation type*. *Atherosclerosis*, 2015. **238**(2): p. 350-5.
9. Larstorp, A.C., et al., *Association of pulse pressure with new-onset atrial fibrillation in patients with hypertension and left ventricular hypertrophy: the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study*. *Hypertension*, 2012. **60**(2): p. 347-53.
10. Chen, L.Y., et al., *Increased carotid intima-media thickness and arterial stiffness are associated with lone atrial fibrillation*. *Int J Cardiol*, 2013. **168**(3): p. 3132-4.
11. Mitchell, G.F., et al., *Arterial stiffness and cardiovascular events: the Framingham Heart Study*. *Circulation*, 2010. **121**(4): p. 505-11.
12. Roman, M.J., et al., *Impact of arterial stiffening on left ventricular structure*. *Hypertension*, 2000. **36**(4): p. 489-94.
13. Chen, L.Y., et al., *Carotid Intima-Media Thickness and Arterial Stiffness and the Risk of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study*. *J Am Heart Assoc*, 2016. **5**(5).
14. Bonapace, S., et al., *Echocardiographically Derived Pulse Wave Velocity and Diastolic Dysfunction Are Associated with an Increased Incidence of Atrial Fibrillation in Patients with Systolic Heart Failure*. *Echocardiography*, 2016. **33**(7): p. 1024-31.

