

ARIC Manuscript Proposal #3907

PC Reviewed: 8/10/21

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title:

Cardiac Structure and Function and the Risk of Incident Atrial Fibrillation in a Community Cohort of Elderly.

b. Abbreviated Title (Length 26 characters): Cardiac Structure and Function and Incident Atrial Fibrillation.

2. Writing Group:

Writing group members:

Riccardo M. Inciardi *, Wendy Wang,* Elsayed Z. Soliman, Alvaro Alonso, Amil M. Shah, Scott D. Solomon, Lin Yee Chen, others welcome

*equally contributed

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

First authors: Riccardo M. Inciardi, MD

Address: Brigham and Women's Hospital, Cardiovascular Division
75 Francis Street Boston, MA 02115
Phone: 393281526343 Fax: 8573071944
E-mail: riccardo.inciardi@libero.it

Wendy Wang

Address: Division of Epidemiology and Community Health
1300 South 2nd St, Suite 300
Minneapolis, MN 55455
Phone: (612) 626-7755
E-mail: wang5694@umn.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: **Lin Yee Chen, MD, MS**

Address: Cardiac Arrhythmia Center, Cardiovascular Division,
Department of Medicine,
University of Minnesota Medical School,
420 Delaware Street SE, MMC 508,

Minneapolis, MN 55455.
Phone: 612-625-4401 Fax: 612-624-4937
E-mail: chenx484@umn.edu

Name: **Scott D. Solomon, MD**
Address: Brigham and Women's Hospital
Cardiovascular Division
75 Francis Street
Boston, MA 02115
Phone: 857.307.1954 Fax: 8573071944
E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline:

Data collection is already completed. Analysis will begin following proposal approval. Manuscript will follow analysis (~6-12 months).

4. Rationale:

Atrial fibrillation (AF) is the most common cardiac arrhythmia among older adults, afflicting approximately 3% of the general population, and its prevalence is expected to increase in the next decades (1,2). AF significantly increases the risk of stroke and heart failure (HF), and the development of AF is associated with poor cardiovascular outcome in several patient populations (3). Thus, early detection of AF is important for stroke and HF prevention as well as for overall improvement in prognosis.

Different standard echocardiographic measures have been proposed as predictors of incident AF, which could help to identify high risk patients. Measures of left ventricle (LV) structure, such as increased left ventricular mass, and LV function, such as reduced LV ejection fraction, have been shown to be associated with the new-onset AF (4-6). Also left atrial (LA) enlargement has also the potential to identify subjects at higher risk of incident AF (7).

However, the long-term prognostic value of a broad range of echocardiographic measures, incorporating conventional assessment of cardiac structure and function and novel deformational imaging technique (i.e. strain analysis derived by speckle-tracking echocardiography) of the LV and the LA is yet to be defined. Also, whether measures of subclinical cardiac impairment portend higher risk of incident AF regardless of history of HF or in subjects with normal LA size is largely unknown.

The Atherosclerosis Risk in Communities (ARIC) (8) study offers a unique opportunity to comprehensively analyze the associations between measures of cardiac structure and function and new-onset AF. We aim to assess whether subclinical markers of cardiac dysfunction are associated with incident AF and whether the associations are modified by prevalent HF and LA size.

5. Main Hypothesis/Study Questions:

The primary objective of this study is to assess the relationship between measures of cardiac structure and function and the risk of incident AF.

We hypothesize that worse alterations in cardiac structure and function portend a higher risk of new onset AF. Parameters of subtle cardiac impairment (such as LV global longitudinal strain and LA strain) will improve the risk estimation more than conventional measures of cardiac structure.

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:

This is a prospective study analyzing eligible subjects without prevalent AF, who participated in the ARIC visit 5 echocardiography study (2011-2013) and have images of acceptable quality for analyses. Visit 5 (2011-2013) will serve as the baseline and incident AF events will be captured through 2019 (or most recent data available).

Exclusion Criteria:

Subjects with incomplete echocardiographic data, history of AF and stroke at visit 5 will be excluded. We will also exclude participants whose race is other than Black or white, as well as Black participants from the Minneapolis and Washington County centers.

Variables:

Outcomes

- Our primary outcome is first occurrence of AF (after visit 5) through December 31, 2019. We defined the incidence date of AF as the date for the first ECG showing AF, the first hospital discharge coded as AF, or when AF was listed as a cause of death, whichever occurred earlier. AF was ascertained by hospital discharge International Statistical Classification of Diseases (ICD) codes, and death certificates (9). Hospitalizations were detected with annual follow-up telephone calls and review of local hospital discharges. AF events were identified by the presence of the ICD, 9th Revision, Clinical Modification code of 427.31 (AF) or 427.32 (atrial flutter), listed as a discharge diagnostic code at any position. We excluded AF events associated with cardiac surgery. AF events were also identified if ICD-9 code 427.3 or ICD-10 code I48 was listed as a cause of death.
- Secondary outcome: intermittent vs. continuous AF (based on Zio XT Patch at V6)

Exposure variables

Echocardiographic Variables

- LV dimensions, volumes and EF
- Global LV systolic strain (GLS and GCS)
- Significant Mitral Regurgitation

- LV mass
- LV diastolic function (E/A, E/e')
- LA Structure: LA maximal and minimal volume and derived LA emptying fraction and expansion index
- LA function: LA Reservoir, LA Contraction, LA Conduit

Analysis:

Echocardiographic measures and confounders will be analyzed continuously and linear relationship with incident AF will be assessed. Cox proportional hazard models will be used to assess the association of cardiac structure and function and incident AF.

Planned multivariable-adjusted models:

Model 1: age, gender, race/center

Model 2: model 1 + body mass index, systolic and diastolic blood pressure, height, antihypertensive medication use, heart rate, chronic kidney disease, history of coronary artery disease, diabetes mellitus, history of HF

Model 3: model 2 + log NTproBNP.

Interactions by age (median split), sex, and race will be explored. Stratified results will be reported when appropriate. We will also perform a multivariable Cox regression with the inclusion of the CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology–Atrial Fibrillation) score (10). We will test whether adding LA or LV variables to the CHARGE-AF score improves risk prediction of atrial fibrillation risk. LA or LV variables with the strongest association with AF events will be incorporated into the CHARGE-AF score. We will evaluate the performance of the new model using the C-statistic, calibration chi-square, and the categorical net reclassification improvement.

We will furthermore perform interaction analysis to test whether history of HF and LA size modify the relationship between significant cardiac measures and incident AF.

A two-sided p-value of <0.05 will be considered statistically significant.

Limitations

- Residual confounding remains a possibility.
- Most of the events relied on hospitalization ICD codes leading to the potential for misclassification of AF, though validation studies have shown adequate validity of this case definition (11).
- Power might be limited, given multiple stratification steps.

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 ICTDER03 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 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>

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)?

MP2105

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

Yes No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2015.29)

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.csc.unc.edu/alic/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/alic/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. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJL. Worldwide epidemiology of atrial fibrillation: A Global Burden of Disease 2010 study. *Circulation* 2014;129:837–47.
2. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year followup of the Renfrew/Paisley study. *Am J Med* 2002;113:359–64.
3. Santhanakrishnan R, Wang N, Larson M, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ, Ho JE. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;133:484–492.
4. Vaziri SM, Larson MG, Benjamin EJ, Levy D. Echocardiographic predictors of nonrheumatic atrial fibrillation. The Framingham Heart Study. *Circulation*. 1994;89(2):724–730. 13.
5. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96(7):2455–2461
6. Bekwelem W, Misialek JR, Konety S, Solomon SD, Soliman EZ, Loehr LR, Lopez FL, Fox ER, Mosley TH, Alonso A. Echocardiographic measures of cardiac structure and function are associated with risk of atrial fibrillation in blacks: the Atherosclerosis Risk in Communities (ARIC) study. *PLoS One*. 2014 Oct 16;9(10):e110111.
- 7 Olsen FJ, Møgelvang R, Jensen GB, Jensen JS, Biering-Sørensen T. Relationship Between Left Atrial Functional Measures and Incident Atrial Fibrillation in the General Population The Copenhagen City Heart Study. *J Am Coll Cardiol Img* 2018, DOI 10.1016/j.jcmg.2017.12.016
8. White A, Folsom A, Chambless L, Sharret R, Yang K, Conwill D et al., ARIC investigators. ScienceDirect-Journal of Clinical Epidemiology: community surveillance of coronary heart disease in the Atherosclerosis Risk in Communities (ARIC) study: methods and initial two years' experience. *Journal of Clinical Epidemiology* 1996;49:223–233
9. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;158:111–117.
10. Christophersen IE, Yin X, Larson MG, et al. A comparison of the CHARGE-AF and the CHA2DS2-VASc risk scores for prediction of atrial fibrillation in the Framingham Heart Study. *Am Heart J* 2016;178:45–54.

11. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ, Folsom AR. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J.* 2009; 158:111–117