ARIC Manuscript Proposal #3845

PC Reviewed: 5/11/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Contemporary Assessment and Clinical Implications of Measures of Left Atrial Structure and Function Among Older Adults in the Community. The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Left Atrium, Incident Heart Failure and Mortality.

2. Writing Group:
Writing group members: Riccardo M. Inciardi, Brian Claggett, Masatoshi Minamisawa, Wendy Wang, Narayana G. Prasad, Dalane Kitzman, Kunihiro Matsushita, Amil M. Shah, Lin Yee Chen, Scott D. Solomon …..Other welcome….

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

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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:

Data collection is already completed. Analysis will begin following proposal approval. Manuscript will follow analysis (~3-6 months).

4. Rationale:

Left atrium (LA) plays an important role in the prognosis of the general population and patients with different established cardiac diseases (1-4). Although the role of measures of cardiac structure and function for defining the risk of incident HF events among subjects without prevalent HF is established (5-7), the additional value of novel measures of left atrial (LA) structure and function, compared to the standard assessment of LA dimension, is unclear.
It has been shown that measures of LA structure and function are significantly associated with cardiovascular events in subjects with heart failure (HF) with preserved and reduced ejection fraction (HFpEF and HFrEF), in subjects at heightened risk for stroke or after an acute myocardial infarction (1-2). Although LA dimension or volume is considered the standard measures, several novel measures of LA structure and function have been proposed.

A promising technique to evaluate LA function is two-dimensional speckle-tracking echocardiography (2D-STE), which is based on the analysis of the speckle pattern (acoustic backscatter generated by the reflected ultrasound beam) followed frame-by-frame during the cardiac cycle (1).
These parameters have the potential to better assess the overall intrinsic LA phasic function being less influenced by loading conditions and by left ventricle (LV) systolic function. These parameters are also able to identify subclinical abnormalities of LA function, even before the structural changes occur, and may potentially better stratify the risk of CV events with more accuracy than standard measure by LA maximal volume. However, limited data exist on normative values of LA structure and function in older adults, their association with circulating biomarkers of HF risk, and their prognostic relevance for incident HF and mortality.

The Atherosclerosis Risk in Communities (ARIC) (8) study is well suited to investigate the association of novel measures of LA structure and function and the incidence of overall HF, HFpEF, HFrEF and mortality.

5. Main Hypothesis/Study Questions:

The primary objectives of this study are as follows:

- To determine reference values for LA structure and function measures in a subgroup of participants who were free of prevalent CV disease or major CV risk factors
- Cross-sectional association of LA structure and function with NT-proBNP
- To assess the relationship between measures of LA structure and function the risk of death or incident HF (overall and both HFrEF and HFpEF).

We hypothesize that worse alterations in LA structure and function portend a higher risk of events in subjects without prevalent HF, more than standard LA assessment by LA maximal volume. These

parameters will improve the risk stratification and will be associated with increased risk of events also in subjects without LA dilatation.

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 post-hoc analysis using measures of LA structure and function derived from an LA-dedicated software (Philips Qlab13) from ARIC visit 5 participants. Visit 5 (2011-13) will serve as the baseline and events will be capture through 2019 (or most recent data available).

Exclusion Criteria:
Subjects with incomplete echocardiographic data, atrial fibrillation at the time of the echocardiogram and prevalent HF at visit 5 will be excluded.

Variables:
Outcomes

- NTproBNP plasma values at visit 5
- The composite of incident HF hospitalization or all cause death. HF events underwent physician adjudication (9) and included events after visit 5. All-cause mortality was ascertained by ARIC surveillance or the National Death Index. Additional analysis for performed for incident HF with preserved ejection fraction (HFpEF) and reduced EF (HFrEF). Left ventricle (LV) EF abstracted from the first incident adjudicated HF hospitalization was used to classify heart failure as HFpEF (LVEF ≥50%) or HFrEF (LVEF < 50%). When LVEF was unavailable from this hospitalization, the most recent abstracted LVEF from a prior hospitalization – if available - was used. If the prior LVEF was normal, it was only used if it was from within 6 months before the HF hospitalization and without an interval myocardial infarction (MI) (10).

Exposure variables
Echocardiographic Variables
- LA Structure: LA maximal and minimal volume and derived LA emptying fraction and expansion index
- LA function: LA Reservoir, LA Contraction, LA Conduit

Reproducibility for LA stain analysis
We will randomly select up to 40 studies with adequate or good image quality to evaluate intra-observer and inter-observer reproducibility of LA peak LS measurements performed blinded to participant demographic and clinical information. Reproducibility of measures will be assessed using Bland-Altman plots, coefficients of variation, and intra-class correlation coefficients.

Analysis:
Echocardiographic measures of LA structure and function will be described in the HF stages "0" as a reference group using the quantile regression (STATA qreg) to define 10th, 50th, and 90th percentile limits with associated 95% confidence interval (CI) overall and stratified by sex.
The resulting 10th and 90th percentile limits will be considered reference limits for these measures in the overall ARIC sample. The cross-sectional continuous association of LA structure and function with log-transformed NT-proBNP levels will be assessed with restricted cubic splines. The number of knots that minimized model Akaike information criterion will be selected. Also, Cox proportional hazard models will be used to assess the association of these measures and incident HF and mortality. Sensitivity analysis will be performed among participants without LA enlargement.

Planned multivariable-adjusted models:
Model 1: age, gender, race/center
Model 2: model 1 + body mass index, systolic blood pressure, heart rate, history of hypertension, estimated glomerular filtration rate, history of coronary artery disease, diabetes mellitus, left-ventricle ejection fraction, E/e`, LV mass;
Model 3: model 2 + log NTproBNP.

For time-to-event analyses with incident HFpEF as an outcome, participants with incident HFmrEF or HFrEF were censored at the time of heart failure and vice versa for incident HFmrEF or HFrEF.
A two-sided p-value of <0.05 will be considered statistically significant.

Limitations

- The LA strain analysis will be performed using 2D speckle tracking imaging obtained using 4-chamber view alone, and hence the findings may not be generalizable to all methods of longitudinal strain.
- Given the small number of black participants in the low-risk reference subgroup (8%), we will be unable to determine normative cut-point separately by race
- Residual confounding remains a possibility.
- 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 __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/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)?

MP2378
MP3530
MP2278
MP3645

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* ____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.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.

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6. Shah AM, Claggett B, Loehr LR, Chang PP, Matsushita K, Kitzman D et al., Heart Failure Stages Among Older Adults in the Community. The Atherosclerosis Risk in Communities Study. Circulation. 2017;135:224–240

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8. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol. 1989;129:687–702.