

**ARIC Manuscript Proposal #2378**

**PC Reviewed: 6/10/14**  
**SC Reviewed: \_\_\_\_\_**

**Status: A**  
**Status: \_\_\_\_\_**

**Priority: 2**  
**Priority: \_\_\_\_\_**

**1.a. Full Title:** The significance of left atrial size and function in the elderly general population

**b. Abbreviated Title (Length 26 characters):** LA function in the general population

**2. Writing Group:**

Writing group members: Alexandra Gonçalves, Chung-Lieh Hung, Cristina Quarta, Dalane Kitzman, Amil M Shah, Scott D. Solomon. Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **AG** [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:** Analysis will begin following proposal approval. Anticipating 3 months of echocardiography analysis, a manuscript will be completed within 6 months of the date.

#### **4. Rationale:**

Left atrial enlargement is a robust predictor of cardiovascular outcomes in the general population<sup>1</sup> and a marker of poor prognosis in patients with various cardiovascular diseases.<sup>2 3</sup> LA volume has been recognized to predict first atrial fibrillation, heart failure (HF), stroke, transient ischemic attack, acute myocardial infarction and cardiovascular death.<sup>4</sup> Moreover, there is an independent association between LA volume and incidence and prevalence of systolic and diastolic HF,<sup>5</sup> and it has been recognized as an independent predictor of HF hospitalization in subjects with coronary heart disease and preserved baseline LV ejection fraction.<sup>6</sup>

Above and beyond LA volume, LA function has been suggested to increment the strengths of the association with cardiovascular outcomes, and perhaps to better represent underlying LV dysfunction. Decreasing LA function, but not LA volume was independently associated with mortality and added incremental power to a predictive model in the general population,<sup>7</sup> and LA ejection fraction was associated with increased risk for new-onset AF and atrial flutter after adjustment for several risk factors, including LA volume.<sup>8</sup> Nevertheless, the best LA predictive parameter for cardiovascular risk is yet to be defined. As well, the parameters of normality of LA ejection fraction are unclear and the relation between LA function and cardiovascular risk factors, as arterial hypertension and diabetes, and HF and is relatively unexplored.

Quantifying LA size is difficult, because of the LA's complex geometry and intricate fiber orientation and the variable contributions of the appendage and pulmonary veins. LA size is most often measured from M-mode and 2-dimensional echocardiography (2DE), but 3D echocardiography (3DE) is more accurate, overcoming 2DE geometric assumptions and it has shown reproducibly estimating LA volume compared with cardiac magnetic resonance<sup>9</sup> and superior clinical value than 2D methods.<sup>10</sup> However, up to now, there are no cut points of LA volume, as data using 3DE are relatively scant and most studies have been performed in patients with cardiovascular disease referred for echocardiography.

The ARIC cohort presents a unique opportunity for the evaluation of cardiac structure and function in the general population, using 3DE, which will develop the recognition of the importance of LA function and its relation with cardiovascular risk factors, risk markers and cardiovascular outcomes.

## **5. Main Hypothesis/Study Questions:**

1. Larger LA volume is related with advanced age and arterial hypertension
2. Decreased LA function is related with cardiovascular outcomes (HF, stroke, myocardial infarction)
3. LA function is lower in patients with HF than controls of the same age
4. Hypertensive patients present higher LA function than patients with HF and preserved ejection fraction, but lower than controls of the same age
5. LA function is inversely related with cardiac biomarkers (BNP, high sensitivity troponin T)
6. Decreased LA function is related with left ventricular function abnormalities, as lower left ventricular global strain and increased LV twist/torsion

## **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).**

This study will analyze ARIC cohort participants presenting to visit 5, who have acceptable echocardiography image quality for 3D analysis. Participants will be excluded if they are neither White nor African American or with missing data for other covariates utilized in the analysis.

### **Variables of interest**

Echocardiographic variables (Visit 5) of cardiac structure and LV systolic and diastolic function

Clinical covariates (Visit 5): age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, heart failure and prior hospitalization for heart failure, prior stroke or TIA.

Laboratory values (visit 5): high sensitivity troponin T, NT-proBNP, serum creatinine, hemoglobin and hematocrit, hemoglobin A1C, total cholesterol, triglycerides, HDL, LDL

### **Analytical approach:**

Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be shown as a total sample and proportion. Categorical variables will be compared via  $\chi^2$  or Fischer exact test, while continuous data will be compared between groups via Wilcoxon Rank Sum or Kruskal-Wallis tests. P values < 0.05 will be considered significant.

Univariable and multivariable linear or logistic regression analysis will be used to assess associations between categories of participants and echocardiographic characteristics.

Limitations:

This study will be a cross sectional analysis using data collected at visit 5. Besides, the visit 5 echocardiogram will not be performed concurrently with an event as the use of ICD-9 coding limits our analysis to those participants who have had a prior event.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**

Yes  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

**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.cscce.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)?**

#2039 Feasibility and reference values for left ventricular size, function, and deformation in an elderly cohort determined by 3D echocardiography: the ARIC study

#2017 Comparison of left ventricular torsion mechanics derived from two-dimensional and three-dimensional echocardiography in a community-dwelling elderly cohort: The ARIC study

#1917 Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community – A preliminary analysis from the ARIC study

#1943 Performance of two echocardiographic schema for grading diastolic dysfunction in an elderly community-based cohort – A preliminary analysis from the ARIC study

#2092 Association of Age with Diastolic Dysfunction in the Community

#1942 Cardiac structure and function in elderly African-Americans with heart failure with preserved ejection fraction

**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\* \_\_\_\_\_)**

**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/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](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

## References

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