ARIC Manuscript Proposal # 3376

PC Reviewed: 4/9/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Refining Prediction of Atrial Fibrillation-Related Ischemic Stroke and Transient Ischemic Attack Using Left Atrial Volume Index : The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): LAVI and Stroke

2. Writing Group:

Writing group members: Ankit Maheshwari, Faye L. Norby, Mary R. Rooney, Michael Zhang, Pamela L. Lutsey, Alvaro Alonso, Elsayed Z. Soliman, Amil M. Shah, Scott D. Solomon, Lin Y. Chen, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _AM____ **[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: Statistical Analysis: 1 month
Manuscript Preparation: 2 months

4. Rationale:

Atrial fibrillation (AF) is associated with a 5-fold increase in thromboembolic stroke risk.[1] Thrombogenesis in atrial fibrillation is a diverse process relying on synergy between all three elements of Virchow's triad.[2] Prothrombotic structural changes in the molecular atrial architecture may, in fact, precede development and/or diagnosis of AF, and detecting these early changes poses an opportunity to improve stroke prediction in the general population and in patients with AF.

Left atrial volume index (LAVI) has been identified as a marker of pro-thrombotic left atrial remodeling and associated with embolic stroke.[3,4] It is not clear whether use of LAVI can help improve prediction of AF-related ischemic stroke and TIA, over and above the CHA_2DS_2VASc variables. We aimed to determine whether adding LAVI to the CHA_2DS_2VASc variables would augment prediction of AF-related ischemic stroke and TIA

5. Main Hypothesis/Study Questions:

Aim :
Evaluate improvement in prediction of ischemic stroke and TIA by adding LAVI to CHA_2DS_2VASc variables

Hypotheses:
a) Higher LAVI (based on Visit 5 2D-echocardiograms) will be associated with higher risk of ischemic stroke and TIA, independent of CHA_2DS_2VASc variables in participants with AF and without AF.

b) Consideration of LAVI (based on Visit 5 2D-echocardiograms) will improve prediction of ischemic stroke and TIA, over CHA_2DS_2VASc variables in participants with 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 Population: We will include all participants who attended the Visit 5 examination with echocardiogram data. We will exclude those with missing left atrial volume index data.

Exposure
Left atrial volume index. We will evaluate as a binary variable (cutoff at 34 ml/m2) and also as a continuous variable.

Outcome

Definite and Probable ischemic stroke.. A secondary outcome will be definite and propable ischemic stroke + transient ischemic attack.

Covariates:

Age, Sex, Race, Heart Failure, Hypertension, Coronary Artery Disease, Peripheral Artery Disease, Stroke/TIA, Diabetes, anticoagulant use

Statistical Analysis:

First, we will use multivariable cox proportional hazard models to assess the association of LAVI with Stroke/TIA. We will conduct this analysis in both participants with and without prevalent AF at visit 5.

Model 1: Unadjusted
Model 2: Model 1+Age, Sex, Heart Failure, Coronary Artery Disease, Peripheral Artery Disease, Stroke/TIA, Diabetes
Model 3: Model 2+ AF
Model 4: Model 3 + anticoagulant use

Next, in people with AF, we will add LAVI to CHA_2DS_2VASc variables to evaluate improvement in stroke prediction as assessed by C-statistic, Net Reclassification Index, or Integrated Discrimination Improvement.

Model A (CHA_2DS_2VASc variables): Age, Sex, Heart Failure, Hypertension, Coronary Artery Disease, Peripheral Artery Disease, Stroke/TIA, Diabetes, anticoagulant use
Model B: LAVI+Model A

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 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?
____ 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)?

MP 2893, MP1559

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

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 ____ Yes __x__ No.

References

1. Katsnelson, M., Koch, S. & Rundek, T. Stroke Prevention in Atrial Fibrillation. *J. Atr. Fibrillation* **3,** 53–64 (2007).
2. Watson, T., Shantsila, E. & Lip, G. Y. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* **373,** 155–166 (2009).
3. Fatema, K. *et al.* Increased Left Atrial Volume Index: Potent Biomarker for First-Ever Ischemic Stroke. *Mayo Clin. Proc.* **83,** 1107–1114 (2008).
4. Biteker, M. *et al.* The Role of Left Atrial Volume Index in Patients with a First-ever Acute Ischemic Stroke. *J. Stroke Cerebrovasc. Dis.* **26,** 321–326 (2017).