1. 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:

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]

First author: Ankit Maheshwari MD
Address: 9 Founders
         Hospital of the University of Pennsylvania
         3400 Spruce Street
         Philadelphia, PA 19130

Phone: 6309150660 Fax: 612-624-4937
E-mail: ankit.maheshwari@uphs.upenn.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 Y. 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
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 prothrombotic 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\(_2\)DS\(_2\)VASc variables. We aimed to determine whether adding LAVI to the CHA\(_2\)DS\(_2\)VASc 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\(_2\)DS\(_2\)VASc 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\(_2\)DS\(_2\)VASc 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\(_2\)DS\(_2\)VASc 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 probable 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\textsubscript{2}DS\textsubscript{2}VASc variables to evaluate improvement in stroke prediction as assessed by C-statistic, Net Reclassification Index, or Integrated Discrimination Improvement.

**Model A (CHA\textsubscript{2}DS\textsubscript{2}VASc 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  
___ 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.csc.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