ARIC Manuscript Proposal #4262

PC Reviewed: 6/13/23 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Left Atrial Abnormalities and Ischemic Stroke or Death in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): **LA myopathy and ischemic stroke**

2. Writing Group: Gabriele Masini, Wendy Wang, Yuekai Ji, Anne Eaton, Riccardo Inciardi, Elsayed Z. Soliman, Scott D. Solomon, Amil M. Shah, Raffaele De Caterina, Lin Yee Chen, and others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _GM__ **[please confirm with your initials electronically or in writing]**

First author: Gabriele Masini
Address: Cardiovascular Division, Department of Medicine
2231 6th Street SE
Minneapolis, Minnesota 55455

Phone: (763) 286-4822
E-mail: gmasini@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
Address: Lillehei Heart Institute and Cardiovascular Division
University of Minnesota Medical School
420 Delaware St SE, MMC 508
Minneapolis, MN 55455

Phone: (612) 625-4401 Fax: (612) 626-4411
E-mail: chenx484@umn.edu

3. Timeline:
Data analysis to begin immediately; pen draft expected summer/fall 2023.

4. Rationale:

A complex interplay exists between the left atrium, atrial fibrillation (AF), and stroke. Mounting evidence suggests that atrial cardiomyopathy, defined as left atrial (LA) structural and functional changes, precede AF and confers a higher thrombotic risk.[1,2] P-waves abnormalities, such as

advanced interatrial block,[3] a P-wave axis deviation,[4] and abnormal P-wave terminal force in V_1 (PTFV1),[5-7] are associated with a higher risk of ischemic stroke, even after adjusting for AF. Furthermore, P-wave abnormalities are also associated with sudden cardiac death and cardiovascular death.[8]

LA enlargement is associated with an increased risk of AF and stroke.[9] More recently, indices of LA mechanical dysfunction, detected by strain analysis, are associated with ischemic stroke, independent of AF and known cerebrovascular risk factors.[10] Among different LA strain parameters, only LA reservoir strain improved ischemic stroke prediction over and above LA volume and CHA_2DS_2-VASc variables in participants without AF.[11]

Among serum biomarkers, N terminal pro-B-type natriuretic peptide (NT-proBNP) improves stroke risk prediction when add to established risk score variables.[12] Elevated levels of NT-proBNP are associated with ischemic stroke independently from AF in the general population.[13]

Indices of LA cardiomyopathy, such as abnormal PTFV1, a reduced LA reservoir strain or an elevated NT-proBNP, are more strongly associated with cerebral infarcts subtype that are more likely to be cardioembolic (i.e. non lacunar thrombotic stroke) than non-cardioembolic, supporting the hypothesis that LA cardiomyopathy is intrinsically prothrombotic.[6,11,14,15,13]

In patients with embolic stroke of undetermined source, anticoagulant treatment does not reduce the risk of recurrent events compared to the standard of care.[16,17] However, in the subgroup of patients with LA cardiomyopathy and who are at higher risk of thromboembolic events, anticoagulation may be beneficial.[18] One ongoing trial is testing whether apixaban is superior to aspirin for the prevention of recurrent stroke in subjects with cryptogenic ischemic stroke and atrial cardiopathy, defined either by either an increase of LA diameter, an increased in levels of natriuretic peptides or an abnormal PTFV1.[19]

However, no consensus exists on which LA cardiomyopathy marker best predicts the risk of ischemic stroke and death in participants without AF. Therefore, using data from the community-based Atherosclerosis Risk in Communities (ARIC) study, we aim to evaluate which LA cardiomyopathy parameter (P-wave abnormalities, LA enlargement or mechanical dysfunction or elevated NT-proBNP) improves risk prediction the most when added to the current paradigm, the CHA_2DS_2-VASc score. The results from this analysis may aid in refining the entry criteria of randomized controlled trials in primary and secondary stroke prevention.

5. Main Hypothesis/Study Questions:

To evaluate the association between different parameters of LA cardiomyopathy at visit 5 with ischemic stroke and death after visit 5 and to assess which parameter improves risk prediction the most.

We hypothesize that among different markers of LA cardiomyopathy, LA reservoir strain will have the greatest prognostic value.

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:

Prospective cohort from visit 5 to 2020 (or most recent data available).

Inclusion/Exclusion:

Participants who had both echocardiogram and ECG measurements done at visit 5 will be included in this analysis. We will exclude those with prevalent atrial fibrillation or stroke, and missing LA function data, P-wave data, or NT-proBNP. Those whose race was other than Black or White will be excluded. We will also exclude those with missing covariates.

Variables

Exposure:

The following variables (obtained at visit 5) will be assessed continuously (per 1-SD)

1. LA minimal volume index
2. LA maximal volume index
3. LA reservoir strain
4. LA contractile strain
5. LA conduit strain
6. NT-proBNP

For P-wave abnormalities, we will use the definitions most used in clinical practice and reviewed in a recent document.[20] LA enlargement will be defined using the cutoff for LA volume recommended by the American Society of Echocardiography.[21] For LA strain parameters and NT-proBNP, if there is a non-linear relationship with the primary outcome, we will assess potential binary cutoffs (see statistical analysis section).

The following categorical variables (obtained at visit 5) will be assessed in the primary analysis:

1. Increased P-wave duration (≥120 ms)
2. Advanced interatrial block (Increased P-wave duration + biphasic P-wave morphology in leads II, III, or aVF)
3. Abnormal P-wave axis (any value outside 0 to 75°)
4. Abnormal P-wave terminal force in V_1 (> 4,000 μV x ms)
5. LA enlargement (maximal volume index > 34 mL/m^2)

Primary outcome: composite outcome of ischemic stroke or death from visit 5 to 2020 (or latest data available).

Confounders/covariates (obtained from visit 5): age, sex, race, ARIC field center, smoking status, diabetes, arterial hypertension, coronary heart disease, peripheral artery disease, heart failure, left ventricular (LV) ejection fraction, E/e', incident atrial fibrillation.

Statistical analysis

- Baseline characteristics will be described using mean (± standard deviation) or median (1^{st}- 3^{rd} quartile) for continuous variables and number (percentages) for categorical variables.
- Incidence of ischemic stroke and death after visit 5 will be calculated.
- Cox proportional hazards models will be used to assess the relationship between exposure variables with the composite outcome of incident ischemic stroke or death. Models will be adjusted as follows:
    - Model 1: age, sex, race/ARIC field center
    - Model 2: smoking status, diabetes, arterial hypertension, coronary heart disease, peripheral artery disease, heart failure, left ventricular (LV) ejection fraction, E/e'
    - Model 3: incident atrial fibrillation as a time-varying covariate
- Linearity will be assessed using restricted cubic splines that display the fully adjusted relationship between each exposure variable and the primary outcome.
- Among exposures that are associated with and demonstrate a non-linear relationship with the primary outcome, we will assess potential binary cutoffs using Youden's J-statistic.
- We will evaluate whether each exposure variable improves risk prediction. The following models will be used:

- The benchmark model (model 0) will include CHA_2DS_2-VASc variables (age, sex, heart failure, diabetes, coronary heart disease, peripheral artery disease)
- From model 0, we will individually add each exposure variable into the model. Model performance will be determined by calculating the Harrell's C-statistic, net reclassification improvement, and relative integrated discrimination improvement. Reclassification categories will be defined as <2.5%, 2.5% to 5%, and >5% 5-year risk. We will also compute the model AIC.

-The following sensitivity and secondary analyses will be performed:

- A secondary outcome events will include thrombotic lacunar and non-lacunar stroke, and non-carotid cardioembolic stroke.
- A secondary analysis will include only patients with prevalent heart failure at visit 5.

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/mantrack/maintain/search/dtSearch.html

___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)?

#3089: age-related left atrial remodeling as a predictor of stroke in patients with normal sinus rhythm: relationship between echocardiographic structural and functional left atrial parameters and cerebral infarcts – Francesco Bianco
#3960: electrocardiographic deep terminal negative of the P wave in V1 and risk of ischemic stroke – Mingfang Li

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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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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