ARIC Manuscript Proposal # 3089

PC Reviewed: 12/12/2017 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

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

b. Abbreviated Title (Length 26 characters): Left atrial dysfunction and prediction of stroke

2. Writing Group:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.
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3. Timeline: The analysis will begin immediately following the proposal approval. A manuscript will be completed within 6 months of the date.

4. Rationale:

Changes in left atrial (LA) structure and function are well-recognized factors that contribute not only to the development of heart failure (HF), [1] but also to other outcomes, including ischemic stroke. [2, 3] The latter is a major public health problem that affects 795,000 people every year in the United States. The magnitude of the problem is even larger if we consider asymptomatic or silent cerebral infarctions (SCIs). [4] Stroke is a subtle disease and is clinically evident only in 0.2-0.4% of the cases. [4] The presence of SCIs exposes itself to a higher risk of symptomatic strokes in the last decades of life [5] and have been yet correlated to cardio-embolisms. [4, 6]

Traditionally the pathophysiology of cardio-embolic stroke implies the occurrence of atrial fibrillation (AF), and is ascribed to stasis and thrombus formation in a structurally abnormal or dilated atrium, due to the occurrence of components of Virchow's triad: blood stasis, parietal abnormalities (endothelial dysfunction) and blood hypercoagulability.[7, 8]

Some emerging evidence suggests a higher risk of SCIs and cognitive decline can also be observed in individuals with LA enlargement or dysfunction, even in the absence of AF. [9-11] Nevertheless, little is known about differences in the association of LA structure and function with clinical stroke and subclinical cerebral infarct.

LA enlargement is a robust and well-established predictor of cardiovascular outcomes in the general population and a marker of poor prognosis in patients with various cardiovascular diseases, [12] with connective tissue deposition as an important contributor and precursor.[13] LA remodeling is also strictly related to the senescence process, in part driven by age-related comorbidities, such as elevated hemodynamic load due to a long-standing hypertension and vascular stiffness. [1] Among elderly, a subclinical marker of LA dysfunction or LA enlargement, if associated with increased odds of SCIs and clinical evident stroke, may suggest that minor forms of LA dysfunction may cause LA stasis and predispose to possibly preventable cerebral embolization.

5. Main Hypothesis/Study Questions:

1. To assess the association of alterations in LA structure and function with clinical ischemic stroke or subclinical cerebral infarcts in community-dwelling elderly individuals without AF and reduced ejection fraction.
2. To examine age-related changes in LA structure and function, in terms of left atrial volume, anterior-posterior diameter, ejection fraction, empting fraction and global longitudinal strain, in healthy individuals, individuals with clinical stroke, and individuals with subclinical cerebral infarct, in the absence of AF and reduced ejection fraction
3. To assess the association of alterations in LA structure and function with cortical versus subcortical infarcts and the number of infarcts in community-dwelling elderly individuals without AF and reduced ejection fraction.

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 methodological limitations or challenges if present).

The Atherosclerosis Risk in Communities (ARIC) is an ongoing prospective observational study, which involves a population-based cohort composed from four communities in North Carolina, Mississippi, Minnesota and Maryland. A total of 15792 participants were enrolled in this cohort between 1987 and 1989, during Visit 1, and 2011 and 2013, during Visit 5. A detailed rationale of the study, design, and procedures has been previously published.[16] Of the 6538 (n=2693 male, 41.2% and n=4977 white, 76.1%) participants who attended Visit 5, 1,906 of the surviving consented to undergo an extensive cognitive assessment, as part of the ARIC Neurocognitive Study (ARIC-NCS), which included a brain MRI examination.[17]

Inclusion and exclusion criteria

All participants who underwent echocardiograms and brain MRI scans at visit 5/ARIC- NCS (2011-13) will be included.

Exclusion criteria:

Missing covariates
Prevalent atrial fibrillation cases at visit 5, defined by:
1) Hospital discharge records (ICD-9 code 427.31 and 427.32– Atrial fibrillation)
2) ECGs performed during study visits
Ejection fraction < 50 % (Visit 5 ech10 variable)

Echocardiographic parameters of LA enlargement/dysfunction:

Left atrial volume index ≥ 28 ml/m^2

Maximal left atrial anterior-posterior diameter ≥ 2.3 cm/m^2
LA ejection fraction, cut off at 50 %
LA empting fraction, cut off at 45 %
LA global longitudinal strain (GLS), cut off at 20 %

Covariates:

Age, sex, race, body mass index, CHA_2DS_2-VASc, cigarette-smoking status, coronary heart disease, heart failure, diabetes mellitus, use of antihypertensive medications, systolic and diastolic blood pressure, blood samples and medications, including anticoagulants and antiplatelet agent use

Outcomes

Number of lesions and location of lesions based on visit 5/ARIC- NCS (2011-13) MRI cerebral definitions.

Sub clinical cerebral infarct: focal, non-mass, non-lacunar lesions ≥3 mm that were bright on T2 and proton density, and dark on T1 images.

Clinical ischemic stroke: prevalent stroke by the end of Visit-5
Cases of ischemic stroke were identified by annual phone interviews, hospital discharge records, and death certificates. Each case was classified in accordance with criteria from the National Survey of Stroke by a computer algorithm and physician reviewer as previously described. Discrepancies were reviewed by a second physician. In cases of definite thrombotic stroke, cases were classified as lacunar or non-lacunar stroke[8]. For our study, ischemic stroke was defined as definite and probable ischemic stroke.

Echocardiography Protocol

All echocardiograms have been performed using dedicated Philips iE33 Ultrasound systems with Vision 2011, using a preprogrammed acquisition protocol. All studies have been acquired and stored digitally and transferred from field centers to a secure server at the Echocardiography Reading Center (ERC; Brigham and Women's Hospital, Boston, MA), where echocardiographic measures have been performed and over-read, using proprietary-validated echocardiographic analysis software, blinded to participants' clinical characteristics.

Left ventricular (LV) dimensions, wall thickness, and anterior-posterior LA dimension were measured from the parasternal long-axis view according to the recommendations of the American Society of Echocardiography [18]. LV mass was calculated from LV linear dimensions and indexed to BSA as recommended by American Society of Echocardiography guidelines. LV volumes and LV ejection fraction were calculated by the modified Simpson method using the apical 4- and 2-chamber views. Two-dimensional echocardiography LA volume was measured by the method of disks using apical 4- and 2-chamber views at an end-systolic frame preceding mitral valve opening. LV diastolic function classified according to Olmsted criteria. Right ventricular (RV) function was assessed by RV fractional area change, calculated as the percent change in cavity area from end-diastolic to end-systolic tracings of the RV cavity in the apical 4-chamber view. Deformation analysis was performed on 2D images throughout the cardiac cycle, acquired at a frame rate of 50 to 80 frames per second, using the TomTec Cardiac Performance Analysis package. The TomTec software automatically selects the 2-, 3-, and 4-chamber views, from 4 consecutive cardiac cycles, in the 3D real-time data set and than detect the blood–tissue interface with an off-line contour-tracking algorithm. Anyway, a manual correction was systematically applied. The LA appendage and the orifices of the pulmonary vein were excluded from the tracing. LA endocardial surface was reconstructed throughout the cardiac cycle, resulting in a dynamic cast of LA cavity; for each consecutive frame, the voxel count inside the 3D surface was used to measure LA volume (LAV), resulting in a smooth interpolated LAV time curve allowing detection of the maximal (LAV max) and minimal (LAV min) LA volumes. LA emptying fraction, an estimate of LA reservoir function was calculated as [(LAV max−LAV min)/ LAV max*100] [(9)]. In addition, 3DE LA speckle-tracking analysis was automatically performed throughout the cardiac cycle, using P wave as the reference point, and LA global longitudinal strain (GLS), also a surrogate of LA reservoir function was determined. Image quality was judged on the basis of stitch/artifacts ratio and quality resolution of LA segments

throughout the whole cardiac cycle. In the presence of stitching artifacts or dropout of more than 2 LA segments the image was excluded of the analysis.

Statistical analysis

Hypothesis 1

Participants will be divided into 3 groups: non-cerebral infarct, silent cerebral infarct and stroke. We will compute the odds of LA echocardiographic enlargement and impaired function in these 3 groups. Non-cerebral infarct is the referent group.
We will adjust the logistic model for the following covariates:
Model 1: Age, sex, race, study center
Model 2: Model 1 + smoking, BMI, use of hypertension medications, systolic and diastolic blood pressure, diabetes, CHD, anticoagulants, and antiplatelet agents

Hypothesis 2

Participants will be divided into 3 groups: non-cerebral infarct, silent cerebral infarct and stroke. We will use the general linear model to assess association between echocardiographic parameters, in terms of left atrial volume, anterior-posterior diameter, ejection fraction, empting fraction and global longitudinal strain with each group
Model 1: Age, sex, race, study center
Model 2: Model 1 + smoking, BMI, use of hypertension medications, systolic and diastolic blood pressure, diabetes, CHD, anticoagulants, and antiplatelet agents

Hypothesis 3

Participants will be divided into 3 groups based on MRI-defined cerebral infarcts: cortical infarcts, subcortical infarcts, and no infarcts. We will compute the odds of LA echocardiographic enlargement and impaired function in these 3 groups. Non-cerebral infarct is the referent group.
We will adjust the logistic model for the following covariates:
Model 1: Age, sex, race, study center
Model 2: Model 1 + smoking, BMI, use of hypertension medications, systolic and diastolic blood pressure, diabetes, CHD, anticoagulants, and antiplatelet agents

We will use the general linear model to assess the association of LA enlargement and impaired LA function with number of cerebral infarcts.

Model 1: Age, sex, race, study center

Model 2: Model 1 + smoking, BMI, use of hypertension medications, systolic and diastolic blood pressure, diabetes, CHD, anticoagulants, and antiplatelet agents

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

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)?

#2378 – LA function in the general population
#2384 – Cardiac and Brain Structure and Function Associations
#2546 - Association of Left Atrial Enlargement with Lower Cognitive Function and Subclinical Cerebral Infarcts: The ARIC Study

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.

References

1. Goncalves A, Hung CL, Claggett B, Nochioka K, Cheng S, Kitzman DW, Shah AM and Solomon SD. Left Atrial Structure and Function Across the Spectrum of Cardiovascular Risk in the Elderly: The Atherosclerosis Risk in Communities Study. *Circ Cardiovasc Imaging*. 2016;9:e004010.

2. Thomas L and Abhayaratna WP. Left Atrial Reverse Remodeling: Mechanisms, Evaluation, and Clinical Significance. *JACC Cardiovasc Imaging*. 2017;10:65-77.

3. Blume GG, McLeod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM and Tsang TS. Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr*. 2011;12:421-30.

4. Hassell ME, Nijveldt R, Roos YB, Majoie CB, Hamon M, Piek JJ and Delewi R. Silent cerebral infarcts associated with cardiac disease and procedures. *Nat Rev Cardiol*. 2013;10:696-706.

5. Dichgans M and Leys D. Vascular Cognitive Impairment. *Circulation research*. 2017;120:573-591.

6. Hu X, De Silva TM, Chen J and Faraci FM. Cerebral Vascular Disease and Neurovascular Injury in Ischemic Stroke. *Circulation research*. 2017;120:449-471.

7. Bogousslavsky J, Cachin C, Regli F, Despland PA, Van Melle G and Kappenberger L. Cardiac sources of embolism and cerebral infarction--clinical consequences and vascular concomitants: the Lausanne Stroke Registry. *Neurology*. 1991;41:855-9.

8. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. *Ann Intern Med*. 1998;128:639-47.

9. Barnes ME, Miyasaka Y, Seward JB, Gersh BJ, Rosales AG, Bailey KR, Petty GW, Wiebers DO and Tsang TS. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. *Mayo Clin Proc*. 2004;79:1008-14.

10. Russo C, Jin Z, Liu R, Iwata S, Tugcu A, Yoshita M, Homma S, Elkind MS, Rundek T, Decarli C, Wright CB, Sacco RL and Di Tullio MR. LA volumes and reservoir function are associated with subclinical cerebrovascular disease: the CABL (Cardiovascular Abnormalities and Brain Lesions) study. *JACC Cardiovasc Imaging*. 2013;6:313-23.

11. Cogswell RJ, Norby FL, Gottesman RF, Chen LY, Solomon S, Shah A and Alonso A. High prevalence of subclinical cerebral infarction in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2017;19:1303-1309.

12. Gupta S, Matulevicius SA, Ayers CR, Berry JD, Patel PC, Markham DW, Levine BD, Chin KM, de Lemos JA, Peshock RM and Drazner MH. Left atrial structure and function and clinical outcomes in the general population. *Eur Heart J*. 2013;34:278-85.

13. Boyd AC, Richards DA, Marwick T and Thomas L. Atrial strain rate is a sensitive measure of alterations in atrial phasic function in healthy ageing. *Heart*. 2011;97:1513-9.

14. Dadu RT, Fornage M, Virani SS, Nambi V, Hoogeveen RC, Boerwinkle E, Alonso A, Gottesman RF, Mosley TH and Ballantyne CM. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. *Stroke*. 2013;44:1803-8.

15. Qiu C and Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. *Nat Rev Cardiol*. 2015;12:267-77.

16. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol*. 1989;129:687-702.

17. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR, Jr., Graff-Radford J, Schneider AL, Windham BG, Coker LH, Albert MS, Mosley TH, Jr. and Investigators AN. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. *Stroke*. 2015;46:433-40.

18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W and Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1-39 e14.