ARIC Manuscript Proposal #3714

PC Reviewed: 9/8/20 **Status: _____** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Risk of Atrial Fibrillation and Stroke with the Amyloidogenic V122I Transthyretin variant among Black Americans

b. Abbreviated Title (Length 26 characters): Atrial fibrillation and stroke in V122I variant

2. Writing Group: Writing group members: Senthil Selvaraj, Masatoshi Minamisawa, B. Gwen Windham, Joel Buxbaum, Brian Claggett, Lin Yee Chen, Thomas Mosley, Amil Shah, Riccardo Inciardi, and Scott D. Solomon. Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **_SS_ [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 with the aim of completing analysis and a manuscript within 6 months.

4. Rationale:

Cardiac amyloidosis results from extracellular deposition of insoluble abnormal

fibrillar proteins in the cardiac chambers, including transthyretin (TTR). This cardiac infiltration typically leads to an increase in wall thickness, greater left ventricular (LV) stiffness resulting in diastolic dysfunction, atrial enlargement, and heart failure (HF). However, cardiac amyloid can also lead to atrial enlargement through infiltration of the atrial chambers themselves.[1, 2] The amyloidogenic V122I variant is relatively common in African Americans (3%, N=124 in ARIC, 3.43% in U.S. African-Americans), and previous ARIC analysis has shown this variant increases the risk of heart failure (HF).[3] However, atrial arrhythmias are common among patients with diagnosed TTR cardiac amyloidosis as well, and one case-control study noted that 22% of V122I carriers had AF compared with 9% of controls.[4] Further, atrial fibrillation (AF) in cardiac amyloid is a particularly thrombogenic state associated with left atrial appendage thrombi.[2, 5, 6] In fact, any atrial fibrillation in cardiac amyloid is an indication for anticoagulation irrespective of CHADS2-VASC score.[2, 7] However, little is known regarding the risk of the V122I variant and atrial fibrillation and stroke.

Our team has recently found that the V122I variant is associated with significant atrial remodeling and dysfunction as characterized by speckle tracking analysis among ARIC participants in late life (proposal #3645, manuscript in preparation). Further, atrial abnormalities were more abundant than ventricular abnormalities, and atrial remodeling is likely a more sensitive marker of cardiac disease. Thus, the cardiac substrate for atrial fibrillation (atrial remodeling and dysfunction) is significantly altered among individuals with the V122I variant, which sets the framework for exploring the risk of atrial fibrillation and stroke.

Thus, we seek to explore whether the V122I variant is associated with AF and stroke in ARIC. We will also analyze whether the variant is associated with both subclinical AF and cerebral infarcts which has been performed via sub-studies investigating ambulatory electrocardiographic monitoring and brain MRI.

5. Main Hypothesis/Study Questions:

Incident AF and stroke will be more frequent in subjects with V122I carriers compared with those in noncarriers.

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).

Study Design:

The study sample will include ARIC cohort African-Americans who have been genotyped for the V122I variant.

Inclusion Criteria:

We will include those with

1. Available genotyping for V122I

Exclusion Criteria:

We will exclude non-Black participants given the very infrequent rate of V122I in this population.

Exposure variables:

V122I carrier status

Clinical variables (collected at visit 1 in ARIC) to be evaluated include:

Age, sex, body mass index, blood pressure, heart rate, atrial fibrillation, comorbidities (hypertension, diabetes, coronary heart disease, HF, stroke, smoking, related medications, LDL cholesterol), which will allow us to calculate components of the CHADS2VASC score (a scoring system for stroke risk among those with atrial fibrillation).

Primary Outcomes:

The primary outcomes are incidence of AF and ischemic stroke. We will also assess total strokes. In cross-sectional analysis, we will assess prevalence of AF, stroke, and HF at subsequent visits.

Secondary outcomes:

We will assess the prevalence of cerebral infarcts on brain MRI obtained at visit 3, 2004-2006, and visit 5[8] as well as subclinical atrial fibrillation (obtained at visit 6 via Ziopatch monitoring), premature atrial contractions, and average heart rate.[9] Infarcts have been previously defined as

focal, non-mass lesions ≥ 3 mm that were bright on T2 and proton density and dark on T1 images.[10] If there are enough participants with the V122I, we will also assess those who underwent repeat Ziopatch monitoring.

Potential covariates: We will adjust analyses for age and sex.

Analytical approach:

Continuous normally distributed data will be showed as mean and standard deviation and continuous non-normally distributed data will be showed as median and interquartile range. Categorical data will be reported as percent frequencies and compared by chi-squared or Fischer exact tests. We will use Cox regression (minimally adjusted for age, sex) to assess for incident AF and stroke (with baseline study visit as visit 1). Logistic regression will be used for cross-sectional analysis of prevalent cerebral infarcts (visit 5) and subclinical AF (visit 6) with V122I carrier status. For stroke and cerebral infarct analyses, we will assess if the association between V122I and these outcomes are modified by CHADS2VASC. All analyses will be performed using STATA version 14.1 (Stata Corp., College Station, TX, USA).

Limitations:

We may be limited in power to detect a difference in AF and strokes. If this is the case, we may pool data from clinical and subclinical AF (as well as strokes) to improve power.

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?

__ X __ 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"? _ X ___ 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)?**

Dr. Minamisawa is a collaborator for the present analysis and is firth author of MS 3645.

a. MS 3645 - Left atrial structure and function of the amyloidogenic allele V122I transthyretin variant in elderly African-Americans
b. MS# 1107r - (Buxbaum J et al) Cardiac parameters in African-Americans carrying the amyloidogenic transthyretin V122I allele.
c. MS#1108 – (Buxbaum J et al) The Frequency of an Amyloidogenic Allele of Transthyretin (V122I) Decreases with Increasing Age in Community Samples of African-Americans.
d. MS#2087 – (Quarta C et al) Cardiac structure and function of elderly African-Americans carrying the amyloidognic V122I transthyretin mutation.

e. MS#2368 – (Quarta C et al) The Frequency and Clinical Significance of Amyloidogenic Transthyretin (TTR) Variants in a Sample representative of the US Community: data from the Atherosclerosis Risk In Communities (ARIC) study.

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* MS#2368. As a subanalysis we may use the MRI data from 1999.01**)**

___ 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.

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