ARIC Manuscript Proposal #3645

PC Reviewed: 6/9/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Left atrial structure and function of the amyloidogenic allele V122I transthyretin variant in elderly African-Americans

b. Abbreviated Title (Length 26 characters): LA assessment in V122I variant

2. Writing Group: Writing group members: Masatoshi Minamisawa, Riccardo M. Inciardi, Brian Claggett, Sarah Cuddy, Candida Cristina Quarta, Amil M. Shah, Sharmila Dorbala, MD, Rodney H. Falk, Kunihiro Matsushita, Dalane W. Kitzman, Lin Yee Chen, and Scott D. Solomon.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **_MM_ [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:

Amyloidosis is a clinical disorder caused by the extracellular deposition of insoluble abnormal fibrillar proteins in organs and tissues. Amyloid infiltration of the heart typically leads to an increase in wall thickness, greater left ventricular (LV) stiffness resulting in diastolic dysfunction, and progressive congestive heart failure. Cardiac amyloidosis (CA) is primarily encountered in immunoglobulin light-chain amyloidosis (AL) and transthyretin (TTR)-associated (senile and hereditary/familial) amyloidosis. CA usually portends a dismal prognosis, and the early diagnosis is crucial for successful management.[1, 2] The association between low voltage on the electrocardiogram (ECG) and LV thickness on echocardiogram is suggestive of CA. However, the early diagnosis of CA is still challenging and relies on a high degree of clinical suspicion, a combination of imaging techniques and often an endomyocardial biopsy. The problem of differentiating CA from cardiomyopathies due to other causes is common, such as hypertrophic cardiomyopathy (HCM), or advanced LV hypertrophy attributable to other causes (e.g. hypertension, diabetes, chronic kidney disease). Misdiagnosis can lead to the use of certain cardiac medications that may be harmful in CA patients.[3]

While cardiac biopsy remains the reference standard for diagnosing CA, recent advances in multimodality imaging have allowed for a non-invasive approach. The detection of subendocardial late gadolinium enhancement on cardiac magnetic resonance imaging can also assist with making the diagnosis, as can cardiac uptake on ^{99m}Tc-pyrophosphate scintigraphy, which is able to distinguish TTR from AL amyloid and HCM.[4-7] More contemporary echocardiographic techniques play an adjunctive role in the diagnosis of CA.[8] Conventional echocardiographic patterns of LV wall thickness, diastolic dysfunction, speckled appearance of the LV myocardium have been used to raise suspicion for CA; however, these methods are not sensitive or specific enough to make a definitive diagnosis.[9] Amyloid can infiltrate virtually all cardiac chambers and cardiac amyloidosis is characterized by significant left atrial (LA) dilatation and dysfunction. Two-dimensional (2D) speckle tracking imaging (STI) technique a robust and sensitive echocardiographic technique for the LV and LA assessment and has proven to play a crucial role in the diagnosis and prognostic stratification of CA. In the previous studies,

LA structure and function were assessed with algorithms designed for LV analysis since dedicated software for LA strain had not been released.[10-12] Recently, dedicated software for LA strain analysis has been released, but the performance of LA assessment to identify and discriminate CA from other cardiovascular diseases has not been confirmed.

The Atherosclerosis Risk in Communities (ARIC) study began in 1987 and enrolled over 15,000 individuals aged 45-64 years in four communities in the U.S., approximately 30 % of whom are African-Americans. In an ancillary ARIC study, African-American participants were genotyped not only for the amyloidogenic transthyretin allele V122I, which is most frequent TTR variant among world, but also for the other potential TTR variants. Regarding the V122I variant study in the ARIC, 124 (3%) were carriers and 3,732 were noncarrier. Although the prevalence of overt LV abnormalities among V122I TTR carriers was low (7%),[13] it is well-suited to investigate the LA deformation using a software dedicated for LA strain analysis.

The purpose of this study is to compare the LA structure and function between V122I TTR variant carriers and noncarriers in elderly African-Americans using 2D-STI dedicated for LA strain analysis and evaluate the proportions of abnormalities in LA structure and function between the carriers and noncarriers.

5. Main Hypothesis/Study Questions:

LA enlargement and dysfunction will be more prominent 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 a cross-sectional analysis of ARIC cohort African-Americans who have been genotyped for any of the TTR variants known to be amyloidogenic at the time of visit 5 (2011-2013) and undergone echocardiography. We will examine the clinical and laboratory data, ECGs, and echocardiograms.

Inclusion Criteria:

Key inclusion criteria are the following:

1. Sinus rhythm

Exclusion Criteria:

Participants with suboptimal 2D image quality or missing data for key echocardiographic data (LVEF, LV wall thickness, LV diameters, LV volumes, and LV longitudinal strain) will be excluded.

Exposure variables:

Categorize participants into 2 groups.

1. Subjects with V122I TTR variant carriers
2. Subjects with V122I TTR variant noncarriers

Clinical variables (collected at visit 5 in the ARIC) to be evaluated include:

Age, sex, height, weight, body mass index, body surface area, blood pressure, and heart rate.

Electrocardiographic variables (collected at visit 5 in the ARIC) to be evaluated include:

Heart rate, low QRS amplitude (was defined as a QRS amplitude of ≤ 0.5 mV in all limb leads or ≤ 1mV in all precordial leads), Sokolow index (sum of S wave in lead V1 and R wave in lead V5 or V6), Voltage/mass index (Sokolow index divided by the cross-sectional area of the LV wall).[14]

Echocardiographic variables (collected at visit 5 in the ARIC) to be evaluated include:

Those from standard 2D evaluation (LV size, LV wall thickness, LV mass, LV systolic and diastolic diameters and volumes, left atrial size and volumes, LVEF, cardiac output and index, Doppler mitral inflow), from tissue Doppler imaging at septal and lateral wall levels (E' and A'), and from the speckle tracking imaging (longitudinal, circumferential, and radial strain). For LV deformation, global longitudinal strain (GLS) will be calculated as the average LV longitudinal strain (LS) across the 12 segments obtained using 4- and 2-chmaber views as previously described.[15] Relative regional strain ratio, a measure of the degree of apical sparing of longitudinal

strain, is calculated by dividing the sum of apical LS by the sum of basal and mid LS values.[16] As for LA assessment, we will evaluate LA maximum/minimum volume index and LA peak (reservoir, conduit, and contractile) LS using apical 4-chamber views.

Outcomes:

The primary outcome of interest is to compare the LA structure and function between V122I TTR variant carriers and noncarriers using dedicated software for LA strain analysis. The second outcome of interest is to investigate the proportions of abnormalities between the two groups by referring echocardiographic values based on 95th percentile limits derived from ARIC healthy subjects.[17]

Potential covariates: Demographic characteristics (age, race, sex, body mass index), blood pressure, heart rate, echocardiographic parameters (LV wall thickness, LV mass index, LA volume index, LVEF, Doppler mitral inflow, and tissue Doppler images).

Analytical approach:

Reproducibility for LA stain analysis

We will randomly select up to 40 studies of at lease adequate or good image quality to evaluate intra-observer and inter-observer reproducibility of LA peak LS measurements performed blinded to participant demographic and clinical information. Reproducibility of measures will be assessed using Bland-Altman plots, coefficients of variation, and intra-class correlation coefficients.

Clinical and echocardiographic comparisons

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. Continuous data will be compared by Wilcoxon rank sum test, t test, Kruskall-Wallis test and 1-way ANOVA followed by Bonferroni test as appropriate. We will compare the differences in LA strain data and RRSR as continuous measure between categories. We will compare the LA volume index and strain values after adjustment for demographic variables (age,

sex, and body mass index). All analyses will be performed using STATA version 14.1 (Stata Corp., College Station, TX, USA).

Limitations:

First, the LA strain analysis will be performed using 2D speckle tracking imaging obtained using 4-chamber view alone, and hence the findings may not be generalizable to all methods of longitudinal strain. Second, we will not investigate the difference of LA strain in the other TTR mutations. The aim of this study is mainly to compare V122I TTR noncarriers with carriers, which may lead to late-onset amyloid cardiomyopathy.

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)?

a. MS# 1107r - (Buxbaum J et al) Cardiac parameters in African-Americans carrying the amyloidogenic transthyretin V122I allele.
b. 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.
c. MS#2087 – (Quarta C et al) Cardiac structure and function of elderly African-Americans carrying the amyloidognic V122I transthyretin mutation.
d. 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 **)**

___ 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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