ARIC Manuscript Proposal #4343

PC Reviewed: 10/10/23 **Status: _____** **Priority: 2**

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

1.a. Full Title: Longitudinal Echocardiographic Changes in Late Life with the Amyloidogenic V142I Transthyretin variant among Black Americans

b. Abbreviated Title (Length 26 characters): Echo changes with V122I variant in late life

2. Writing Group: Writing group members: Senthil Selvaraj, Brian Claggett, Riccardo Inciardi, Amil Shah, 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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3. Timeline: Analysis will begin following proposal approval with the aim of completing analysis and a manuscript within 6-12 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). The amyloidogenic V142I (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).[1] Additionally, subtle echocardiographic changes in carriers compared with non-carriers were noted at visit 5, including greater wall thickness, E/A ratio, global longitudinal strain (characteristic of amyloid changes).[1]

However, amyloid penetrance appears to increase with markedly aging. We have recently shown, for example, that cardiovascular outcome risk rises steeply with age.[2] Therefore, the risk of amyloid phenotype on echocardiography may be particularly marked in late life, and notably echocardiography at V7 has now been performed.[3] No studies to date (to our knowledge) have systematically evaluated echocardiographic changes in very late life or the longitudinal changes in echocardiographic parameters with the variant (average age at V7 is 81, with an average of 6-7 years between visits 5-7). Indeed, amyloid has historically been considered the great "HFpEF masquerader",[4] yet cardiac amyloid can present with systolic dysfunction in more advanced cases. In fact, the EF in cardiac amyloid decreases 3.2% every 6 months of follow-up.[5] Therefore, understanding the natural history of changes in echocardiographic parameters will further inform if/when treatment with amyloid specific therapies may be warranted among carriers. Given the recent surge in therapies for transthyretin amyloid, understanding the echocardiographic progression among carriers compared with non-carriers will be relevant.

Thus, we seek to explore echocardiographic differences with the V142I variant compared with non-carriers in late life (visit 7) as well as the longitudinal changes in these parameters between visits 5-7.

5. Main Hypothesis/Study Questions:

At visit 7, there will be greater progression of cardiac remodeling among carriers compared with non-carriers.

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 V142I variant and attending 7 with echocardiographic data.

Inclusion Criteria:

We will include those with

1. Available genotyping for V122I
2. Available echocardiographic data at visit 7. For analyses assessing longitudinal change, we will also require echocardiogram at visit 5 (there were 1240 Black participants with echo at visit 5 and there were ~665 Black participants with echo at visit 7).

Exclusion Criteria:

We will exclude non-Black participants given the very infrequent rate of V142I in this population.

Exposure variables:

V142I carrier status

Clinical variables (collected at visit 5 and 7 in ARIC) to be evaluated include:

Age, sex, body mass index, blood pressure, heart rate, atrial fibrillation, comorbidities, hs-troponin, nt-probnp.

Primary Outcomes:

Visit 7 echocardiographic parameters (carriers vs. non-carriers), additionally adjusted for visit 5 echocardiographic parameters. We will assess comprehensive echocardiographic metrics as done previously, including LV structure/function, RV structure/function, and LA/LV strain.[1]

Potential covariates: We will adjust analyses for age, sex, and covariates imbalanced at visit 7. For analyses analyzing the change from visit 5 and 7, we will adjusted for imbalanced covariates at visit 5, similar to previous ARIC analyses and other analyses of V142I in other cohorts.[1,6,7]

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 linear and/or logistic regression to assess the relationships between carrier status and echocardiographic parameters both as a cross-sectional analysis (at visit 7) as well as the change in echocardiographic parameters (from visits 5 to 7), adjusting for parameters and other covariates identified above. Among echo parameters differentially associated with carrier status, we will perform further analysis to understand whether log-transformed NT-proBNP and hs-TnT (V5) predict the change in these echocardiographic parameters, combined and stratified by carrier status, using linear or logistic regression as appropriate. An interaction between carrier status and NT-proBNP and hs-TnT will be tested for echocardiographic outcomes. All analyses will be performed using STATA version 17.1 (Stata Corp., College Station, TX, USA).

Limitations:

We may be limited in power to detect differences in echocardiographic parameters at visit 7 given the modest sample size (expected ~25 carriers at visit 7 and 640 non-carriers). Regardless, these are unique data and will still be of interest to the community, particularly given the recent surge in interest in cardiac amyloid and novel treatments. We will consider multiple imputation techniques, as done in the previous ARIC analysis,[1] to include Black participants who attended visit 7 but did not undergo echocardiography, thereby increasing sample size (there were 429 Black and White participants who did not undergo echo despite attending Visit 7).[1,3] We will also consider performing an interaction analysis to understand whether the change in echo parameter between visit 5 and 7 vary by carrier status, thereby pooling the data, and using an interaction p-value<0.10 to define statistical significance.

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# 1107 - (Buxbaum J et al) Cardiac parameters in African-Americans carrying the amyloidogenic transthyretin V122I allele.

b. MS#2087 – (Quarta C et al) Cardiac structure and function of elderly African-Americans carrying the amyloidognic V122I transthyretin mutation.
c. 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?

_ ___ 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:

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2. Selvaraj S, Claggett BL, Quarta CC, Yu B, Inciardi RM, Buxbaum JN, Mosley TH, Shah AM, Dorbala S, Falk RH, et al. Age Dependency of Cardiovascular Outcomes With the Amyloidogenic pV142I Transthyretin Variant Among Black Individuals in the US. *JAMA Cardiol*. 2023. doi: 10.1001/jamacardio.2023.1525
3. Shelbaya K, Claggett B, Dorbala P, Skali H, Solomon SD, Matsushita K, Konety S, Mosley TH, Shah AM. Stages of Valvular Heart Disease Among Older Adults in the Community: The Atherosclerosis Risk in Communities Study. *Circulation*. 2023;147:638-649. doi: 10.1161/CIRCULATIONAHA.122.061396
4. Hahn VS, Yanek LR, Vaishnav J, Ying W, Vaidya D, Lee YZJ, Riley SJ, Subramanya V, Brown EE, Hopkins CD, et al. Endomyocardial Biopsy Characterization of Heart Failure With Preserved Ejection Fraction and Prevalence of Cardiac Amyloidosis. *JACC Heart Fail*. 2020;8:712-724. doi: 10.1016/j.jchf.2020.04.007
5. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, Falk RH, Cheung KN, Patel AR, Pano A, et al. Prospective evaluation of the morbidity and mortality of wild-type and V122I mutant transthyretin amyloid cardiomyopathy: the Transthyretin Amyloidosis Cardiac Study (TRACS). *Am Heart J*. 2012;164:222-228 e221. doi: 10.1016/j.ahj.2012.04.015
6. Selvaraj S, Claggett B, Minamisawa M, Windham BG, Chen LY, Inciardi RM, Buxbaum JN, Mosley TH, Shah AM, Solomon SD. Atrial Fibrillation and Ischemic Stroke With the Amyloidogenic V122I Transthyretin Variant Among Black Americans. *J Am Coll Cardiol*. 2021;78:89-91. doi: 10.1016/j.jacc.2021.04.042
7. Parcha V, Malla G, Ivin MR, Armstrong ND, Judd SE, Lange LA, Maurer MS, Levitan EB, Goyal P, Arora G, et al. Association of Transthyretin Val122Ile Variant With Incident Heart Failure Among Black Individuals. *JAMA*. 2022. doi: 10.1001/jama.2022.2896