

ARIC Manuscript Proposal #4048

PC Reviewed: 5/17/22 Status: _____ Priority: 2
SC Reviewed: ___/___/___ Status: _____ Priority: _____

1.a. Full Title: Risk of Heart Failure by Heart Failure Subtypes in Late Life with the Amyloidogenic V122I Transthyretin variant among Black Americans

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

2. Writing Group:

Writing group members: Senthil Selvaraj, Joel Buxbaum, Brian Claggett, Thomas Mosley, Amil Shah, Riccardo M. 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). 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).¹

However, both amyloid and HF are diseases associated with aging. Cardiac amyloidosis has age-dependent penetrance.² Therefore, the risk of amyloid for HF may be particularly marked in late life. The previous ARIC analysis did not analyze post visit 5 outcomes, which may significantly increase the risk for HF at the point in life. In addition, the adjudication of HF events as HF with reduced ejection fraction (HFrEF) and HF with preserved EF (HFpEF) as not been reported with the V122I variant. Amyloid has historically been considered the great “HFpEF masquerader”,³ 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.⁴ In addition, in a clinical trial of tafamidis (a protein stabilizer) in cardiac amyloidosis, the average EF was mildly reduced (~48%).⁵

Thus, we seek to explore using post visit-5 data whether the V122I variant is associated with HF hospitalization, with specific attention to HF subtypes as well, in late life in ARIC. In addition, we will assess the risk of prevalent HF at ARIC visits in late life, which includes outpatient diagnoses of HF.

5. Main Hypothesis/Study Questions:

HF risk will be particularly heightened in late life (post visit 5) with the V122I variant, and this will increase both risk for HFpEF and HFrEF hospitalizations.

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 and attending visit 5.

Inclusion Criteria:

We will include those with

1. Available genotyping for V122I and attending visit 5.

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 5 in ARIC) to be evaluated include:

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

Primary Outcomes:

The primary outcome is incidence of HF hospitalization post visit 5. We will also analyze the risk for death, HF hospitalization or death, and phenotype specific (HFpEF and HFrEF) hospitalization.

Secondary outcomes:

In cross-sectional analysis, we will assess prevalence of HF at visits 5 and 6.

Potential covariates: We will adjust analyses for age, sex, and covariates imbalanced at visit 5, similar to previous ARIC analyses and other analyses of V122I in other cohorts.^{1, 2, 6}

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 (adjusted for age, sex, and covariates imbalanced at visit 5) to assess for incident HF hospitalization (baseline = visit 5), death, and the combined outcome.

We will test the interaction of the variant * prevalent HF at visit 5 for the risk of HF hospitalization. Logistic regression will be used for cross-sectional analysis of prevalent HF with V122I carrier status with similar adjustment performed. 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 HF subtypes since not all HF hospitalizations have a determined subtype (HFpEF or HFrEF). Regardless, this is a secondary aim of the study, and the findings will be unique and still of interest to the cardiovascular community.

7.a. Will the data be used for non-CVD analysis in this manuscript?

Yes 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 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.csc.unc.edu/ARIC/search.php>

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 amyloidogenic 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?

Yes 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.csc.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.csc.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. Quarta CC, Buxbaum JN, Shah AM, Falk RH, Claggett B, Kitzman DW, Mosley TH, Butler KR, Boerwinkle E, Solomon SD. The amyloidogenic V122I transthyretin variant in elderly black Americans. *N Engl J Med* 2015;**372**(1):21-9.
2. Parcha V, Malla G, Ivin MR, Armstrong ND, Judd SE, Lange LA, Maurer MS, Levitan EB, Goyal P, Arora G, Arora P. Association of Transthyretin Val122Ile Variant With Incident Heart Failure Among Black Individuals. *JAMA* 2022.
3. Hahn VS, Yanek LR, Vaishnav J, Ying W, Vaidya D, Lee YZJ, Riley SJ, Subramanya V, Brown EE, Hopkins CD, Ononogbu S, Perzel Mandell K, Halushka MK, Steenbergen C, Jr., Rosenberg AZ, Tedford RJ, Judge DP, Shah SJ, Russell SD, Kass DA, Sharma K. Endomyocardial Biopsy Characterization of Heart Failure With Preserved Ejection Fraction and Prevalence of Cardiac Amyloidosis. *JACC Heart Fail* 2020;**8**(9):712-724.
4. Ruberg FL, Maurer MS, Judge DP, Zeldenrust S, Skinner M, Kim AY, Falk RH, Cheung KN, Patel AR, Pano A, Packman J, Grogan DR. 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**(2):222-228 e1.
5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, Drachman BM, Shah SJ, Hanna M, Judge DP, Barsdorf AI, Huber P, Patterson TA, Riley S, Schumacher J, Stewart M, Sultan MB, Rapezzi C, Investigators A-AS. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018;**379**(11):1007-1016.
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**(1):89-91.