ARIC Manuscript Proposal #2087

PC Reviewed: 3/12/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cardiac structure and function of elderly African-Americans carrying the amyloidogenic V122I transthyretin mutation.

b. Abbreviated Title (Length 26 characters): Cardiac profile of TTR V122I.

2. Writing Group:

Writing group members: C. Cristina Quarta, Joel Buxbaum, Rodney H. Falk, Amil Shah, Dalane Kitzmann, Tom Mosely, Ervin Fox, Ken Butler (suggested by Ervin Fox so you should check with him and Tom Mosley), OTHERS WELCOME, Scott D. Solomon.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **CCQ [please confirm with your initials electronically or in writing]**

First author: **Candida Cristina Quarta**
Address: 75 Francis street, 02115 Boston, MA

Phone: 617-732-2733 Fax: Fax: 617-582-6027
E-mail: cquarta@partners.org

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).

Name: **Scott D. Solomon**
Address:
Brigham and Women's Hospital
Cardiovascular Division
75 Francis Street
Boston, MA 02115

Phone: 857-307-1960 Fax: 857-307-1944
E-mail: ssolomon@rics.bwh.harvard.edu

3. Timeline: Once the proposal is approved, analysis will begin following the completion of echocardiography of the ARIC visit 5 cohort in 2013. Anticipate a manuscript will be completed within 6 months of that date.

4. Rationale:

Hereditary transthyretin-related amyloidosis (ATTR) is the most common cause of familial amyloidosis, a group of rare dominantly inherited diseases characterized by variable degrees of neurological, cardiological and visceral involvement.[1] ATTR is due to over 100 point mutations in the transthyretin (TTR) gene.

Pathogenic mutations in the TTR protein lead to destabilization of its tetrameric structure and dissociation into monomers that misfold and assemble into toxic oligomers, then protofibrils and amyloid fibrils that deposit in tissues ultimately causing tissue compromise.[1]

Its clinical spectrum varies widely from almost exclusively neurological involvement to predominantly cardiac manifestations.[2] This heterogeneity is linked to several factors including specific TTR mutations, patient gender, geographical distribution, and endemic/non-endemic aggregation.[2] V122I is the most frequent TTR variant, being reported in ~3-4% of African-Americans.[3] It is usually associated with a restrictive cardiomyopathy with a hypertrophic phenotype that manifests over the age of 65 years in the absence of —or with only mild— neuropathy.[3] The absence of clear signs of systemic involvement makes the diagnosis of ATTR in African-Americans caused by this TTR variant a challenge.[2]

The Atherosclerosis Risk in Communities (ARIC) study began in 1987 and enrolled over 15000 individuals aged 45-64 years in four communities in the U.S., approximately 30% of whom are African-American. In an ancillary ARIC study, African-American participants were genotyped for the amyloidogenic transthyretin allele V122I. Among the 3712 patients genotyped, mainly from the Jackson community (3592 successfully genotyped patients), 119 (117 heterozygotes and 2 homozygotes) were found to carry the TTR V122I variant with a prevalence between 3.2% (when considering the overall African-American population of ARIC) and 3.45% (when considering only the Jackson community).[4] At the time of the third visit (1993-95) the electrocardiographic and echocardiographic profile of these subjects did not differ from of that of subjects with the non-mutant alleles.[4]

ARIC participants are now more than 70 years old, a period of life during which the manifestations of TTR V122I amyloid disease appear, although the exact penetrance of the allele has not yet been established. In a recent case-control study of African Americans men aged ≥ 60 years who were referred for echocardiography for a variety of reasons (although none with a diagnosis of cardiac amyloidosis), those carrying the V122I variant were more likely to show heart failure symptoms and echocardiographic features of myocardial infiltration (80% of cases), suggesting a high clinical penetrance of the disease.[5]

Furthermore, the impact of the V122I variant on the survival of carriers vs. non carriers requires more study: data from the Cardiovascular Health Study indicate that male V122I carriers fared significantly worse than non-carriers, losing as much of 2 years of life after age 65, while females did not.[4] No differences in survival between V122I variant carriers and non-carriers from ARIC (when they were all under 65 years old) were apparent, supporting the notion that the amyloidogenic allele behaved as an autosomal dominant with age dependent penetrance .[4]

From 2011, as part of the currently funded ARIC study, the cohort survivors are undergoing a new full clinical and instrumental assessment, which includes serum and

urine collection, ECG and echocardiographic evaluations. Furthermore, in recent years, newer echocardiographic and imaging techniques, which allow better assessments of the structure and function of the myocardium have been validated also in cardiac amyloidosis.[6,7]
ARIC therefore presents a unique opportunity to investigate the cardiac structure and function in V122I variant carriers and to assess the penetrance, and mortality, of amyloid heart disease in patients over the age of 70 years.

5. Main Hypothesis/Study Questions:

The primary objective of this study is to assess the cardiac structure and function and its impact on the outcome in African-Americans carrying the TTR V122I mutation after the age of 70 and compare their profiles with those of a subset of age- and gender-matched African-Americans without the TTR gene abnormality. To meet this goal, we have the following specific aims:

1. To analyze cardiologic data from the ARIC database in order to determine if the African-Americans previously identified as carriers of the amyloidogenic TTR V122I allele differ from those individuals carrying only the wild type allele with respect to the incidence of clinical and laboratory features of cardiac amyloidosis and mortality;
2. Using the results from specific aim 1, to define the role of the TTR V122I allele in the development of clinical (including electrocardiographic and echocardiographic) manifestations of cardiac amyloidosis in aging African-Americans with the analysis of the mutant allele carriers and matched non-carriers participating in the ARIC genotyped before age 65 who have now passed their 70th birthday.
3. To define if clinical, echocardiographic, electrocardiographic and biomarker (NT-proBNP, high sensitivity troponin) parameters correlate with carrying the TTR V122I allele and to assess the role of gender (along with age) in these correlations.
4. To assess, in the sera of V122I variant carriers, the presence of TTR oligomers, which might be useful as biomarkers of the amyloidogenic process and how their presence correlates with cardiac (both clinical and instrumental) features.
5. To compare the outcome between the V122I variant carriers and the matched non-carriers over the age of 70.

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 methodologic limitations or challenges if present).

This study will include a cross sectional analysis of ARIC cohort African Americans carrying the TTR Val122Ile mutation at the time of visit 5 (2011-2013) as well as a longitudinal analysis of their outcome. The study will include all African-Americans that have been genotyped at the time of their entry in the ARIC study and have survived. We will examine the clinical and laboratory data, echocardiograms and ECGs of the carriers of the amyloidogenic mutation and of a group of matched carriers of

the normal TTR gene. We will exclude from the analysis all patients (both V122I carriers and non-carriers) with evidence of abnormal serum and/or urine immunofixation compatible with monoclonal gammopathy, as well as those with an already diagnosed light-chain-related amyloidosis (which is the most frequent cause of systemic and cardiac amyloidosis worldwide).[8]

Clinical variables (collected at visit 5) to be evaluated include:
Age, gender, height, weight, body mass index, body surface area, creatinine, brain natriuretic peptide, high sensitivity troponin T cardiac and HF risk factors, prevalence of hypertension, diabetes mellitus, obesity, coronary artery disease, stroke/TIA, atrial fibrillation/flutter, chronic kidney disease. The sera of V122I variant carriers will be analyzed for the presence of TTR oligomers.

Electrocardiographic variables (collected at visit 5) to be evaluated include:
Heart rate, left ventricular hypertrophy, QRS duration, QT duration, QRS axis deviation, peripheral and total QRS amplitude, Sokolow index, atrioventricular and ventricular conduction defects, low QRS amplitude, pseudoinfarction pattern (Q waves or QS complexes in the absence of coronary artery disease).

Echocardiographic variables (collected at visit 5) to be evaluated include:
Those from standard 2D evaluation (left ventricular size (LV), wall thickness and mass, LV geometry, left atrial size and volumes, aortic root dimension, pericardial effusion, interatrial septum thickness, right ventricular free wall thickness, valvular disease, LV ejection fraction, cardiac output and index, doppler mitral inflow), from tissue Doppler imaging at septal and lateral wall levels (E', A' and S waves) and from the speckle tracking imaging (longitudinal, circumferential and radial strain and strain rate).

Definition of amyloid heart disease
As a general rule, histological evidence of amyloid deposits is essential for a final diagnosis of amyloidosis. However, if a molecularly proven diagnosis of ATTR has already been made, ECG and echocardiography generally provide all the necessary diagnostic information. In particular, an echocardiographic diagnosis of amyloidotic cardiomyopathy requires an end-diastolic thickness of the interventricular septum >1.2 in the absence of any other plausible cause of left ventricular hypertrophy. Other echocardiographic findings potentially suggesting amyloid heart disease include: a) homogeneous atrioventricular valve thickening, b) atrial septum thickening, c) increased thickness of right ventricular free wall, d) sparkling/granular appearance of the ventricular septum, and e) pericardial effusion.[2,9]

Categorical variables will be expressed as numbers and percentages. Continuous variables will be expressed as mean (standard deviation) or median (interquartile range) when appropriate. Categorical variables will be compared via $\chi 2$ or Fischer exact test, while continuous data will be compared via Student's t-test or Mann Whitney U-test. P values < 0.05 will be considered significant.
V122I mutation carriers will be matched with a group of non carriers by age, gender and other major clinical conditions (i.e. presence/absence of hypertension).

Univariate and multivariate models will be constructed to study the association of clinical, ECG and echocardiographic variables to a diagnosis of TTR V122I-related amyloidotic cardiomyopathy.

Kaplan-Meier curves will be constructed to describe the survival of the study population according to the mutation carrier status and other possible determinants (such as gender).

Limitations will include the absolute small number of individuals carrying the TTR V122I mutation enrolled in the analysis that can limit the statistical power. However, the inclusion of accurately selected matched patients for comparison can overcome the sample size issues. Echocardiogram and ECG cannot provide a 100% accurate diagnosis of amyloidotic cardiomyopathy in the absence of a histological confirmation of amyloid infiltration. However, clinical, ECG and echocardiographic data can be appropriately interpreted in the context of a genetically based diagnosis of ATTR and the analysis of carriers'sera for TTR oligomers might be useful.[2,9]

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 _ X _ 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

8.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)?

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

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

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* 1995.05)

___ 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. Planté-Bordeneuve V, Said G. Familial amyloid polyneuropathy. Lancet Neurol 2011;10:1086-97.
2. Rapezzi C, Quarta CC, Riva L, Longhi S, Gallelli I, Lorenzini M, Ciliberti P, Biagini E, Salvi F, Branzi A Transthyretin-related amyloidoses and the heart: a clinical overview. Nat Rev Cardiol 2010;7:398-408.
3. Jacobson DR, Pastore RD, Yaghoubian R, et al. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. N Engl J Med 1997;336:466-73.
4. Buxbaum J, Alexander A, Koziol J, Tagoe C, Fox E, Kitzman D. Significance of the amyloidogenic transthyretin Val 122 Ile allele in African Americans in the Arteriosclerosis Risk in Communities (ARIC) and Cardiovascular Health (CHS) Studies. Am Heart J 2010;159:864-70.
5. Jacobson D, Tagoe C, Schwartzbard A, Shah A, Koziol J, Buxbaum J. Relation of clinical, echocardiographic and electrocardiographic features of cardiac amyloidosis

to the presence of the transthyretin V122I allele in older African-American men. Am J Cardiol 2011;108:440-4.
6. Bellavia D, Abraham TP, Pellikka PA, Al-Zahrani GB, Dispenzieri A, Oh JK, Bailey KR, Wood CM, Novo S, Miyazaki C, Miller FA Jr. Detection of left ventricular systolic dysfunction in cardiac amyloidosis with strain rate echocardiography. J Am Soc Echocardiogr 2007;20:1194-202.
7. Sun JP, Stewart WJ, Yang XS, Donnell RO, Leon AR, Felner JM, Thomas JD, Merlino JD. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of ventricular wall thickening by two-dimensional strain imaging echocardiography. Am J Cardiol. 2009;103:411-5.
8. Gertz MA. Immunoglobulin light chain amyloidosis: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol. 2011;86:180-6.
9. Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, Merlini G, Moreau P, Ronco P, Sanchorawala V, Sezer O, Solomon A, Grateau G. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. Am J Hematol. 2005;79:319-28.