ARIC Manuscript Proposal # 1107r

PC Reviewed: _01/24/06	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Cardiac parameters in African-Americans carrying the amyloidogenic transthyretin V122I allele.

b. Abbreviated Title (Length 26 characters):
TTR V122I and the aging heart

2. Writing Group:
Writing group members:
Joel Buxbaum, Mike McMullen, Alice Alexander, Daniel Jacobson, Jim Koziol

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

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3. Timeline: Analysis of echocardiographic, electrocardiographic and clinical cardiac data of all ARIC African-American participants that have been genotyped for the amyloidogenic transthyretin allele V122I at time of entry to ARIC will take 1 year. Identification of TTR V122I ARIC participants and four times as many controls being followed in the Jackson Heart Study in whom baseline data are available from ARIC: 6 months. Analysis of echocardiographic, electrocardiographic, clinical cardiac data and

ARIC/JHS participants obtained after passing age 65 and comparison with data from that obtained at time of entry 12-18 months.

4. Rationale: Autopsy data indicate that TTR V122I carriers all develop some degree of cardiac amyloid deposition after age 65. A recently completed case control study (presently being prepared for publication) indicates that carriers of the amyloidogenic allele over age 65 have echocardiographic and electrocardiographic changes consistent with cardiac amyloid deposition. An analysis of the African-American participants in the Beta-blocker effect on survival trial (BEST), all of whom had NYHA grade III and IV heart failure indicated that in the over age 60 cohort, 10% carried the amyloidogenic allele, 5 times as many as in the community based CHS cohort (in press JACC). We wish to test the hypothesis that by examining individuals who were genotyped prior to age 65 and have been followed regularly we will be able to determine both the degree and rate of the clinical penetrance, i.e. is it 100% as it appears to be anatomically?

5. Main Hypothesis/Study Questions: Are the electro and echocardiographic parameters (see below) that are usually associated with cardiac amyloidosis normal in TTR V122I carriers prior to age 65? This is the only question that can be answered solely with the data from ARIC. Our hypothesis, based on previous data, is that the frequencies of amyloid-associated abnormalities will not differ significantly between the gene carriers and the age, gender, and ethnically matched non-allele carriers. The subsequent questions: Do all TTR V122I carriers develop cardiac disease? Do all the carriers that develop disease do so at the same rate can only be answered in examining those individuals being followed in the Jackson Heart Study. Follow-up echocardiographic and electrocardiographic findings in ARIC participants who are TTR V122I positive and age and gender matched controls and are being followed in JHS will be compared with those obtained at baseline to determine if the parameters (see below) that are consistent with cardiac amyloidosis have appeared with a greater frequency in allele carriers than in the controls. Since we can only depend on having two data points, for each individual, the first of which will be at some age between 44 and 65, it may not be possible to determine a true rate. We should be able to determine the proportion of (allele positive and allele negative) individuals developing such changes. Since there is a 20 year age range (44-65) for the time of first evaluation and it may be possible relate the development of amyloid-associated changes to either their absolute age or to the number of years between determinations. The validity of such estimates will depend upon the number of allele positive individuals being followed in JHS. **If the number is large enough** and we determine that at any age there are allele positive individuals who have positive cardiac findings and a cohort who do not we can compare their genotypes at markers that we have already established to have an influence on the age of onset of another amyloidogenic mutation in the same gene (Soares ML, Coelho T, Sousa A, Batalov S, Conceição I, Sales Luís MD, Ritchie MD, Williams SM, Saraiva MJ, Buxbaum JN. Susceptibility and modifier genes in Portuguese Transthyretin V30M amyloid polyneuropathy: complexity in a single gene disease Hum. Mol. Gen. 14(4):543-553, 2005.)

Data (variables, time window, source, inclusions /exclusions): From the ARIC data set we will examine the echo, ekg and clinical cardiac variables in the allele carriers and controls at the time of entry into ARIC. These include the echocardiographic parameters interventricular septal thickness, posterior left ventricular wall end-diastolic thickness,

left atrial end systolic diameter, right ventricular free wall dimension, left ventricular end-diastolic dimension, left ventricular end systolic dimension and the presence of a pericardial effusion. We will calculate the LV mass. From Doppler analyses we would like to know data for the E peak, A peak, E/A, and mitral deceleration time. From the electrocardiograms we would like to know rate and rhythm, presence of premature atrial and ventricular contractions, overall ventricular voltage and obtain measurements of Sv1 and Rv5 and Rv6 to be able to calculate the voltage mass ratio. **We expect that in the baseline ARIC data set there will be no significant differences in the occurrence of abnormalities associated with cardiac amyloidosis in the allele carriers and the controls, or be found only in individuals who were over 60 at the time of their ARIC echo and electrocardiograms.**
In a recently completed case-control study we have already established that a majority of these parameters are significantly different in allele carriers over age 65 from controls matched for age, gender, ethnicity, socioeconomic status, presence of hypertension, and ejection fraction (Buxbaum in preparation). In addition we have already seen a trend in that direction in a comparison of the 10 identified allele carriers with 90 age, gender and ethnically matched controls in a much smaller sample obtained from the Cardiovascular Health Study. Comparisons for categorical variables will utilize the Fisher Exact Test while for continuous variables we will use Wilcoxon (nonparametric) tests. Clinical cardiac variables will include clinical report of myocardial infarction or congestive heart failure. We will be measuring 12 different cardiac parameters, which can be grouped as seven independent variables (some such as (E/A) and mitral deceleration time are not truly independent, similarly the voltage/mass relationship is not independent of either the voltage measurements or the calculated ventricular mass). We will use the Bonferroni method for controlling the overall Type I error rate with multiple testing.

We have proposed an analysis of the same variables in those African-American participants in ARIC who are being followed in JHS to attempt to define the kinetics and sequence of appearance of the changes in those measured cardiac-amyloid associated parameters we have enumerated above. It is this comparison that will ultimately provide the clinically relevant information.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

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/

12. 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.