ARIC Manuscript Proposal #3525

PC Reviewed: 12/10/19	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Polymorphism in ApoE, Echocardiographic Remodeling, and Risk of Heart Failure

b. Abbreviated Title (Length 26 characters): **ApoE and Heart Failure**

2. Writing Group:
Writing group members:

Senthil Selvaraj, Amil Shah, Eric Boerwinkle, Rebecca F. Gottesman, Scott 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: 6-9 months from data acquisition

4. Rationale:

It has been recently demonstrated that Aβ amyloid deposits, which are critical in the pathogenesis in Alzheimer's dementia (AD), not only in the brain, but also in the myocardium.[1] Most amyloid in the heart has been generally thought to be related to TTR and light chain deposition. Thus, our burgeoning understanding of the neuro-cardiac axis is expanding. In this

seminal study, AD was linked to greater left ventricular wall thickness as well as worsening diastolic function compared to a matched cohort. However, such an association is possibly confounded by greater comorbidity burden in those with AD (as vascular risk factors are associated with AD as well), rather than representing amyloid infiltration and subject diastolic dysfunction.[2]

One important genetic determinant of AD is variation in ApoE. In particular, the ApoE4 isoform has been linked to increased risk and earlier disease onset of AD.[3] The ApoE gene exists on chromosome 19 and has 3 codominant alleles (E2, E3, and E4). Frequency of ApoE4 varies by race – it is roughly 15% in Caucasians individuals and 25% in African Americans.[4] Further, there is a dose response relationship between ApoE and risk for AD, and heterozygotes have a 2-3x increased risk of AD, where the risk is significantly higher among homozygotes (up to 30x).[5] However, the risk has significant effect modification by gender and race, with the effect greater in women and Caucasians.[6]

Thus, whether genetic risk for AD is associated with left ventricular remodeling, diastolic dysfunction, and heart failure is unknown. Such a mendelian randomization allows greater ability to parse out the effects of an Aβ cardiac deposition and subsequent echocardiographic infiltration and HF risk. Since ApoE is also a lipoprotein involved in cholesterol homeostasis and has been implicated in atherosclerotic cardiovascular disease (but does not appear related to hypertension),[2] our analysis of the risk of ApoE and heart failure will address the modestly increased risk of coronary heart disease.[7]

5. Main Hypothesis/Study Questions:

The two main study questions are:

1.) Is genetic variation in the gene encoding ApoE associated with adverse cardiac structure and function as assessed by echocardiography?
2.) Are individuals with certain polymorphisms in ApoE (E4) at increased risk of incident heart failure?

We hypothesized that genetic variation in ApoE is associated with alterations incardiac structure, function, and risk of incident heart failure.

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).

Study design and inclusion/exclusion criteria: We will prospectively study ARIC participants starting with Visit 1 data and with available genetic data to determine risk of incident heart failure. Since echocardiographic data was collected from Visit 5 (2011-2013) and thus includes only surviving and participating ARIC study patients, a separate cross-sectional analysis will be performed for those individuals to relate genetic variation in apoE to cardiac structure/function.

Cross-sectional outcome: Echocardiographic correlates of ApoE4 variants, in particular left ventricular wall thickness, diastolic function, left atrial size, and pulmonary artery systolic pressure.

Longitudinal outcome: Time to incident heart failure hospitalization or death, as well as time to incident heart failure hospitalization and time to death.

Variables of interest: Baseline demographic, comorbidities, medication, and laboratory values (including troponin and BNP) will be compared by presence of ApoE4 (no alleles, 1 allele, or 2 alleles). Echocardiographic data at visit 5 will be compared by ApoE4 status.

Genetic Analysis
Genotyping of APOE polymorphisms coding for ε4 was detected using the TaqMan assay (Applied Biosystems, Foster City, Calif) and completed in 2004 for the entire cohort.[8] We will stratify by self-reported ethnicity and perform genetic association analyses within each ethnicity for each of our phenotypes of interest. For our longitudinal analyses, we will adjust for age, sex, systolic blood pressure, and LDL and HDL cholesterol, and history of coronary heart disease.

Limitations: The major limitations of the study are dropout before the echocardiographic study at Visit 5 (which will bias potentially toward less severe manifestations of the genetic risk) as well as influence of atherosclerotic risk on HF risk. For the latter, our analysis will therefore adjust for standard cholesterol values (LDL, HDL) as well as history of coronary heart disease.

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 ICTDER 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)?

The most related proposal is the following below, for which Scott Solomon (senior author of this proposal) is also a co-author on this manuscript. While this substudy assessed echocardiographic correlates of cerebral amyloid on PET imaging, our analysis focuses on genetic risk using ApoE polymorphism in the entire ARIC cohort for the longitudinal analysis.
The Associations between Left Ventricular structure, function, and Cerebral Amyloid: The ARIC-PET 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.

This is understood.

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.

This is understood.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.

References

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