ARIC Manuscript Proposal #2227

PC Reviewed: 9/10/13  Status: A  Priority: 2
SC Reviewed: _________  Status: _____  Priority: ____

1.a. Full Title: Relationship of cardiac structure and function with cognitive performance: as study of the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): Echo and cognition

2. Writing Group:
   Writing group members: Pardeep Jhund, Deepak Gupta, Brian Claggett, Josef Coresh, Tom Mosley, Scott Solomon, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. PSJ [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 and availability of the visit 5 data. Anticipating completion of echocardiography of the ARIC Visit 5 cohort in 2013, a manuscript will be completed within 6 months of that date.
4. **Rationale:**

As the population ages the prevalence of cognitive impairment rises as does the prevalence of cardiovascular disease. However, little is known about the association between cardiac structure and function and cognitive impairment. Left ventricular (LV) ejection fraction and LV mass have been linked to cognitive impairment 1-8. The relationship between ventricular function and cognitive impairment has been most commonly examined in heart failure though in small studies with limited assessment of cardiac structure and function and using disparate measures of cognitive function.9-12 Little is known about the association of cognitive impairment with chamber volume, function as measured by strain analysis and diastolic function. Understanding the cardiac structural and functional correlates of cognitive impairment is an important step towards preventing or treating cognitive impairment. For example in a small study of 27 patients with heart failure improving cardiac function, through cardiac resynchronization therapy, led to an improvement in cognitive function.13

The ARIC cohort provides a unique opportunity to study the echocardiographic correlates of cognitive impairment. We will assess the association between test scores on the neuropsychological battery and echocardiographic structure and function.

5. **Main Hypothesis/Study Questions:**

We hypothesize that severity of cognitive impairment will be associated with an abnormalities of cardiac structure and function and that the severity of cognitive impairment is proportional to severity of alterations in cardiac structure and function.

Specific Aims:

1. To assess the relationship between cognitive impairment at Visits 5 and cardiac structure and function as measured by echocardiography at Visit 5 including strain analysis and 3D imaging.
2. To assess the relationship between performance in specific cognitive domains (memory, language, visuospatial, attention and executive function) at Visits 5 and cardiac structure and function as measured by echocardiography at Visit 5 including strain analysis and 3D imaging.
3. To assess whether race, age or sex modifies the relationship between cardiac structure and function and cognitive impairment.

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 will be a cross sectional study of ARIC cohort participants during visit 5 (2011-2012) who have acceptable image quality for analysis. We will exclude those with a prior
history of stroke defined by adjudicated events. Myocardial infarction will be defined using ARIC definitions of adjudicated events and heart failure will be defined as either participant reported medication use for heart failure or Gothenberg score=3 or hospitalization for HF.

In people with and without cognitive impairment at Visit 5 we will assess cardiac structure and function using the following echocardiographic measures:

1) LV mass (primary measure of LV structure), LV volume (2D and 3D volumes)
2) tissue Doppler imaging E prime (primary measure of LV diastolic function),
3) speckle-tracking based longitudinal strain (primary measure of LV systolic function).

We will also examine the following measures of LV structure and function:
LV relative wall thickness, left atrial volume, E/A ratio, deceleration time, LV ejection fraction, circumferential strain, and radial strain. We will also examine the association with right ventricular size and volumes (2D and 3D volumes), aortic root dimension, valvular disease and regional wall motion abnormalities. Noninvasive hemodynamic parameters including stroke volume, cardiac output, LV filling pressures, pulmonary vascular resistance, and pulmonary artery pressures will also be analyzed.

We will assess cognition using the scores from the neuropsychological battery and will include the following measures:
Mini-Mental State Examination (MMSE)
Wide Range Achievement Test (WRAT-3)
Delayed Word Recall Test (DWRT)
Digit Symbol Substitution test (DSST)
Incidental Learning
Word Fluency (FAS)
Animal Naming
Logical Memory I and II
Digit Span Backwards
Trail Making Test (TMT) A & B
Finger Tapping
Boston Naming Test (BNT)
Clock Perception Test
Smell Test

To assess the impact of depression we will use the score from the Center for Epidemiologic Studies Depression Scale (CESD) Short Form & Hopelessness test.

Statistical methods:
Continuous normally distributed data will be displayed as mean and standard deviation and continuous non-normally distributed data will be displayed as median and interquartile range. Categorical data will be shown as a total sample and proportion. Associations of cognitive function and primary echocardiographic outcomes will be evaluated first using logistic regression (with cognitive impairment categorized as present or not) and then scores for each of the tests of cognitive function examined using linear
regression. Each of the domains of cognitive function (memory, language, visuospatial, attention and executive function) will be examined separately.

We will perform multivariable regression analyses adjusting for the following covariates: age, sex, heart rate, height, weight, smoking, alcohol, blood pressure, body mass index, diabetes, atrial fibrillation, heart failure, myocardial infarction, history of coronary artery bypass grafting, depression, eGFR and total/HDL cholesterol. In further models we will assess the additional effect of adjusting for c-reactive protein, high-sensitivity troponin, and b-type natriuretic peptide. We will test for interaction among LV structure and systolic/diastolic function and age. A P value of <0.05 will be considered significant.

Limitations
- The neuropsychological tests performed during Visit 5 may not accurately capture cognitive function in individuals with structural heart disease.
- Prior studies of cognitive function in cardiovascular disease have used different methods of assessment making cross comparison with prior studies difficult.
- Unknown confounders may exist that are not accounted for in analysis models
- Only those individuals surviving to visit 5 and attending for echocardiography can be assessed introducing a survivor bias.

References


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? ___Yes__ X_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”?
   ___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.cscce.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 closely related manuscript proposals are:
# 1701 Incident heart failure and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study  
#1739 Atrial Fibrillation is Associated with Cognitive Decline and Brain MRI abnormalities: The ARIC Study  
#2002 Association of High-Sensitivity Cardiac Troponin T (hs-cTnT) with Cognitive Function: the Atherosclerosis Risk in Communities 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/](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.