

ARIC Manuscript Proposal #1701

PC Reviewed: 10/8/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Incident heart failure and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study

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

2. Writing Group:

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

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3. Timeline: Statistical analyses: September 2013 – November 2013
Manuscript preparation: December 2013 – February 2014
Manuscript revision: March 2014
Manuscript submission: April 2014

4. Rationale:

Heart failure (HF) is a major cause of both hospitalization and mortality in the United States, and was estimated to affect 6,600,000 adults 20 years or older in 2010.¹ The incidence of heart failure in individuals older than 65 years was reported to be approximately 10 in 1,000 in the Framingham Heart Study. For adults 40 years of age, the lifetime risk of developing HF for both men and women is one in five, with this risk reported to double for subjects with blood pressure greater than 160/90 when compared to those with blood pressure less than 140/90.² Major risk factors for heart failure include coronary heart disease, hypertension, left ventricular hypertrophy, abnormal heart valves diabetes, cigarette smoking, obesity, and lack of physical activity.^{3,4}

In a systematic review of studies published between 2002 and 2007, Pressler reported that approximately 25-50% of patients with heart failure had cognitive impairment, with decreased attention and executive function, reduced processing speed, and memory loss as the most frequent deficits.⁵⁻⁷ Similarly, in a pooled analysis of 2,937 heart failure patients and 14,848 controls, the odds ratio for cognitive impairment was 1.62 ($p < 0.0001$) for subjects with heart failure.⁸ A comparable estimate of a 1.96-fold greater risk of cognitive impairment in patients with HF was obtained in a population-based study of 1,075 Italian individuals 65 years and older ($p < 0.028$).⁹ Cerebral hypoperfusion secondary to reduction in cerebral blood flow has been suggested as a physiological mechanism linking heart failure to impaired cognitive function.¹⁰

However, an association between cognitive deficits and heart failure has not been observed in all studies. For example, a recent report in which the impact of cardiovascular risk factors including heart failure was examined in 3,336 participants 80 years or older in the Hypertension in the Very Elderly Trial found no association with cognitive decline.¹¹ In another large study, the relationship between heart failure and cognitive impairment was attenuated if depression was added to logistic regression models where cognitive impairment was defined by scores on the Six-item Screener in 14,080 participants in the Reasons for Geographic and Racial Differences in Stroke cohort.¹²

In an earlier study, Elkins et al. tested the hypothesis that impaired cognitive function in early middle age is likely to be attributed to subclinical vascular injury.¹³ Since cardiovascular disease and cognitive decline share a common set of vascular risk factors including diabetes and hypertension,¹⁴ the authors speculated that poor cognitive function may be used to identify individuals who are particularly susceptible to developing myocardial infarction and stroke and found that lower cognitive scores were associated with a greater risk of cardiovascular events over a 6.4-year period in the ARIC study. Similar results were recently reported for 5,292 participants in the Whitehall II study where lower scores on the general cognitive factor (g) and

tests of vocabulary and verbal and mathematical reasoning were associated with an increased incidence of coronary heart disease during 6 years of follow-up.¹⁵

The aim of this proposal is to evaluate whether scores on three neurocognitive tests administered at the second clinical examination, or decline in cognitive function are associated with incident heart failure in Caucasian and African-American participants in the ARIC study. Cognitive data from a 6-year follow-up period for the entire cohort and from a 14-year follow-up period for 1,134 subjects participating in the ARIC Brain MRI study (2004-2006) are available for this study.

References

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11. Peters, R. *et al.* Cardiovascular and biochemical risk factors for incident dementia in the Hypertension in the Very Elderly Trial. *J Hypertens* 27, 2055-62 (2009).
12. Pullicino, P.M. *et al.* Factors contributing to global cognitive impairment in heart failure: results from a population-based cohort. *J Card Fail* 14, 290-5 (2008).
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5. Main Hypothesis/Study Questions:

The aims of the study are:

Aim 1: To estimate the frequency distributions of the test scores for three neurocognitive tests (DWR, DSS, and WF) administered at Visit 2 in incident heart failure cases and in non-cases who will serve as the comparison group.

Aim 2: To estimate the frequency distributions of the change in test scores for three neurocognitive assessments between Visits 2 and 4 (6-year change), or between Visits 2 and the ARIC Brain MRI visit (14-year change) in incident heart failure cases and in non-cases who will serve as the comparison group.

Aim 3: To determine if cognitive status at baseline is associated with incident heart failure. Cognitive status will be defined by cognitive test scores (DWR, DSS, and WF) at Visit 2. Incident heart failure will be assessed after the date of Visit 4 for each study participant.

Aim 4: To determine if change in cognitive function over a 6 or 14-year follow-up period for the DWR, DSS, and WF tests is associated with incident heart failure after Visit 4 or after the ARIC Brain MRI visit, respectively.

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).

Independent variable/Cognitive variables:

The Delayed Word Recall Test (DWR), Digit Symbol Substitution Test (DSS), and Word Fluency Test (WF) are available from Visit 2 (1990-1992, whole cohort), Visit 4 (1996-1998, whole cohort), and in participants in the ARIC Brain MRI study (2004-2006, Forsyth and Jackson Brain MRI study subset).

Dependent Variable:

The incidence of hospitalization for heart failure has been assessed in the entire ARIC cohort. In a preliminary data analysis of the race-specific incidence between Visit 4 (1996-1998) and 2008, there were 632 cases in whites and 196 cases in African-Americans.

Data Analytic Plan:

Caucasian and African-Americans will be evaluated separately by self-reported racial groups. Cox proportional hazards models will be used to test the hypothesis that the incidence of heart failure is not associated with cognitive status as measured by individual test scores at Visit 2 and at the ARIC Brain MRI visit. A categorical measurement of cognitive impairment, defined as those falling below the 20th percentile of scores for each of the cognitive tests, will also be analyzed in these models. Hazard ratios (HRs) based on the regression coefficients from Cox proportional hazards modeling will be reported.

Cox proportional hazards models will be also be applied to examine the association between mean change in cognitive function between Visit 2 and Visit 4 (6-year change) and incident heart failure for the entire ARIC cohort. Cognitive change will be defined as the Visit 4 test score minus the Visit 2 test score for each of the three cognitive tests. Likewise, we will examine mean change in cognitive function between Visit 2 and the ARIC Brain MRI visit (14-year change) for participants in the ARIC Brain MRI study.

Incident cardiovascular events will be ascertained by annual telephone contact and surveillance of hospital and death records. Heart failure will be defined as the first HF hospitalization (ICD-9 code 428 in any position), or any deaths where the death certificate included an HF code (code 428, ICD-9 or 150, ICD-10, in any position). Exclusion for HF will be based on reported current medication use for HF, or having manifest HF as defined by Gothenburg criteria stage 3. The follow-up data in this study used to determine incident heart failure will include events after Visit 4 through December 31, 2008 for the analyses of 6-year cognitive change, and after the ARIC Brain MRI visit for the analyses of 14-year cognitive change (variable INCHF08).

Inclusion/Exclusion:

We will exclude by ethnic group (as appropriate to each field center) and missing data. Other exclusion criteria will include history of stroke or TIA prior to Visit 2, prevalent HF at Visit 1, incident heart failure between Visit 1 and Visit 2, incident stroke and heart failure between Visit 2 and Visit 4, and incident stroke after Visit 4.

Other variables of interest:

In both aims 3 and 4 above, we will determine whether any observed relationships are independent of cardiovascular risk factors and potential confounding factors. These factors will include but are not limited to:

Visit 1- Education, gender, exam center.

Visit 2- Age, *APOE* genotype, history of diabetes, fasting glucose, smoking pack years, hypertension status, antihypertensive medications, systolic blood pressure and diastolic blood pressure, BMI, carotid IMT (right and left sides), alcohol consumption, total cholesterol, LDL-c, HDL-c, and triglycerides.

Depression as assessed as Vital Exhaustion at Visit 2 and the CES-D score at the ARIC Brain MRI visit. CNS medications (antidepressants, neuroleptics, antianxiolytics, benzodiazepines, antiepileptics) at each visit (Visit 2, Visit 4 and the ARIC Brain MRI visit).

Limitations of study:

A limitation of the study is the possibility of selection bias introduced because of differences between those subjects who did and did not participate in the Brain MRI study. To address this issue, baseline characteristics and clinical outcomes will be compared for the two groups.

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 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? 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"? Yes No

10. 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)?

#314 Cerebral abnormalities identified on magnetic resonance imaging and cognitive functioning: the ARIC study (Lead author: Thomas Mosley, University of Mississippi, Jackson, MS)

#410 Longitudinal association of alcohol consumption and cognition (Lead author: M Eigenbrodt, University of Mississippi, Jackson, MS)

#672 Changes in cognitive test scores in the ARIC cohort over a 6-year period (Visit 2 to Visit 4) and their correlation with vascular risk factors (Lead author: David Knopman, Mayo Clinic, Rochester, MN)

#924 Apolipoprotein E genotype, cardiovascular risk factors, and cognitive decline in a middle-aged cohort: the Atherosclerosis Risk in Communities Study (Lead author: Cindy K. Blair, University of Minnesota, Minneapolis, MN)

#1010 Omega-3 fatty acids, hypertension, and risk of cognitive decline among older adults: The Atherosclerosis Risk in Communities (ARIC) study (Lead author: May A. Beydoun, University of North Carolina, Chapel Hill NC)

#1018r Physical activity and cognitive decline (Lead author: Patricia M. Dubbert, VA Medical Center, Jackson, MS)

#1066 Metabolic syndrome, diabetes and decline in cognitive function (Lead author: Annie McNeill, GlaxoSmithKline, Research Triangle Park, NC)

#1121 Cognitive change over 12 years and its relationship to cardiovascular risk factors: ARIC-MRI Study (Lead author: David Knopman, Mayo Clinic, Rochester, MN)

#1125 Diabetes, obesity and insulin resistance as risk factors for incident heart failure: The Atherosclerosis Risk in Communities (ARIC) Study (Lead author: Laura Loehr, University of North Carolina School of Medicine, Chapel Hill, North Carolina)

#1363 *PCSK9* sequence variation and cognitive decline (Lead author: Jan Bressler, University of Texas Health Science Center at Houston, Houston, TX)

#1153 Association between vascular risk factors and longitudinal changes in ventricular size: a 14 year longitudinal study (Lead author: David Knopman, Mayo Clinic, Rochester, MN)

#1222 The association of microvascular abnormalities with cognitive decline and cognitive status after 10 years (Lead author: Suzanne Lesage, University of Maryland Medical Center, Baltimore, MD)

#1418 Glycemic control (hemoglobin A1c), cognitive decline, and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study (Lead author: Elizabeth Selvin, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD)

1475 Hypertension, left ventricular hypertrophy, and risk of incident hospitalized heart failure: The ARIC study (Lead author: Patricia Chang, University of North Carolina School of Medicine, Chapel Hill, North Carolina)

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* AS#_1999.01)

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/>

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. Agree.