ARIC Manuscript Proposal #2679

PC Reviewed: 12/8/15   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Neurocognitive function and quality of life in heart failure: the ARIC study.

  b. Abbreviated Title (Length 26 characters): Cognition, QOL & heart failure

2.   Writing Group:

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

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3. **Timeline**: Analysis to begin January 2015 with possible submission January 2016.

4. **Rationale**:

Approximately 25-50% of patients with heart failure (HF) have cognitive impairment (1). Decreased attention and decreased executive function, along with reduced processing speed and memory loss are the most frequent deficits (1-3). Cerebral hypoperfusion and cardioembolism have been suggested as physiological mechanisms linking heart failure to impaired cognitive function (4). Cognitive function is also affected by atherosclerotic vascular disease, whether from the cumulative exposure to cardiovascular risk factors (elevated glucose and blood pressure) or subclinical atherosclerosis (5-9). In patients with coronary artery disease, low left ventricular ejection fraction may be associated with worse cognitive performance, particularly in the presence of lower mean arterial pressure and the decompensated HF state (10-12). The ARIC cohort provides an opportunity to further elucidate these relationships.

Similarly to neurocognitive decline, heart failure is known to reduce quality of life (13). The exact mechanism of this relationship, however, has not been fully detailed. Previous studies examining elderly patients with multiple co-morbidities have shown a clear relationship between worse cognition and a decreased quality of life (14, 15). Exercise intolerance and reduced physical independence are important parts of reduced quality of life, therefore it is likely that co-morbidities such as severity of heart failure (preserved or reduced ejection fraction), hypertension, diabetes, and depression would contribute to a patient's happiness and abilities (16). Using a cross sectional analysis of ARIC participants, this analysis will further describe the associations between quality of life, cognition, medical co-morbidities, and heart failure.

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

1. Differences in Neurocognitive Function
   a. How does cognitive function differ in participants with heart failure (HF) compared to participants without HF?
   b. In participants with HF, does the degree of neurocognitive function differ between those with reduced (HFrEF) v. preserved (HFpEF) ejection fraction? Does it differ by concomitant presence of coronary heart disease (CHD), hypertension, diabetes, chronic kidney disease, history of stroke, and/or depression?
2. Differences in Quality of Life
   a. Does quality of life (QOL) differ between those with and without HF?
   b. In participants with HF, does the quality of life differ by HF type (HFrEF v. HFpEF)
   c. In participants with HF does quality of life differ by level of cognitive function?
   d. In participants with HF does change in quality of life over time differ between those with HFrEF v. HFpEF?

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).

Design

Study population: ARIC cohort members with non-missing cognitive status assessments who have completed Visit 5.

Study design: We will run cross- sectional multivariate analyses to assess the association of heart failure with neurocognitive function and quality of life using Visit 5 data. We will use logistic regression, multinomial logit, and OLS regression to model binary, categorical, and continuous dependent variables, respectively.

We will apply inverse probability of response weighting (IPRW) to allow extrapoloation of results to the entire living cohort at the time of Visit 5, while accounting for differences between the regression sample and those participants who did not attend the fifth ARIC visit. Specifically, we will construct weights for IPRW using data collected on the entire living cohort: demographics, education, hospitalization data based on ARIC surveillance and CMS claims, data collected during semi-annual follow-up calls and dementia assessments completed at Visit 5 and in participants who did not attend the visit.

Propensity score methods may also be considered to identify a matched comparison group for participants with heart failure.

A secondary analysis will assess changes in quality of life assessed at two different time points (SF-12 measures at Visit 5 and the subsequent AFU questionnaire in 2014) relative to having HF at Visit 5. If we are able to determine that a sufficient number of cohort members have onset of HF between Visit 5 and the 2014 AFU, we will consider a panel data analysis.

Outcome Variables: (Assessed at Visit 5)
Neurocognitive Function:
> Neurocognitive function will be assessed using the following variables:
> 1. Factor scores developed by Alden Gross (17) to capture 3 cognitive domains, memory, language and executive function as well as a global cognitive function score.
> 2. COGDIAG51 combines MCI/dementia diagnoses at Visit 5 based on algorithmic diagnosis and reviewer diagnosis
> 3. DEMDXL2_51 and DEMDXL3_51 combine dementia diagnoses at Visit 5 with data collected for participants who did not attend the visit (TICSm, informant interviews and discharge/death codes). These variables may be used for IPRW analysis.

Quality of Life:

   Health-related quality of life will be measured using data from the SF12 questionnaire. The SFI-12 is a questionnaire employed to assess different domains (physical and mental) of health-related quality of life. The SF-12 questionnaire was administered at Visit 5 (between 2011 and 2013) and repeated via telephone in 2014, which enables an assessment of changes over time in the health-related quality of life for those participants who completed both questionnaires. This questionnaire assesses participants' limitations due to pain, their energy level, and their ability to perform everyday tasks such as climbing stairs (18). We will use the Z transformations of the separate function scales (e.g., SF12PFZ51 for physical functioning) as a dependent variable. Other domains of SF-12 will be further analyzed to assess the association of heart failure with specific mental or physical domains.

Inclusion criteria: All participants who completed Visit 5. (Full surviving cohort will be used to obtain the IPRW.)

Exposure variables: Prevalent HF at Visit 5 will be measured based on the variable approved by the Heart Failure Research Committee and to be programmed by the CC.

Covariates: Include but are not limited to: age, sex, race, field center, education level, marital status, depression, hypertension, diabetes, stroke, ejection fraction, coronary heart disease, chronic kidney disease, alcohol usage, tobacco usage, and ApoE genotype.

Analytical considerations

   Over 6400 participants completed the neurocognitive assessments at Visit 5, among whom approximately 15% have reported having heart failure. Analyses will be done with all Visit 5 participants when possible.

Below is an explanation of the analysis by question.

Question 1a: How does cognitive function differ in participants with heart failure (HF) compared to participants without HF?

   Cognitive domain factor scores and the global cognitive function factor score will be modeled using OLS with heart failure as the main exposure adjusted for possible confounders (see covariates). We will conduct multinomial logit regression models adjusting for possible confounders (see covariates) to compare the categorical domains of neurocognitive function (normal, MCI and dementia) using the summary variable COGDIAG51.

Question 1b: In participants with HF, does the degree of neurocognitive function differ between those with reduced (HFrEF) v. preserved (HFpEF) ejection fraction? Does it differ by concomitant presence of coronary heart disease (CHD), hypertension, diabetes, chronic kidney disease, history of stroke, and/or depression?

Comparisons between participants will be made using methods similar to Q1a if the sample provides sufficient observations with HFrEF and HFpEF (as otherwise the analysis will be under-powered if the differences between these groups are small). A propensity score approach will be used if there are significant differences between groups with regard to specific comorbidities or other demographics.

Questions 2a: Does quality of life (QOL) differ between those with and without HF?

The continuous variable of quality of life will be assessed using regression analysis to identify differences between those persons with and without heart failure. Further analysis will include examining individual domains of quality of life including mental and physical self-reported health.

Question 2b: In participants with HF, does the quality of life differ by HF type (reduced v. preserved EF)

Comparisons between participants will be made using methods similar to Q2a but comparing those with HFrEF v. HFpEF if the sample size is sufficient.

Question 2c: In participants with HF does quality of life differ by level of cognitive function?

ANOVA will be used when comparing quality of life scores between non-dichotomous categories such as neurocognitive function.

Question 2d: In patients with HF does change in quality of life over time differ between those with HFrEF v. HFpEF?

Differences in the mean change in reported quality of life (between Visit 5 and subsequent follow-up visit) will be analyzed using a t-test to compare those with preserved and reduced ejection fraction.

All analyses will be completed using SAS.

Limitations

Cross-sectional analyses are inherently limited due to their inability to determine causation. All proposed analyses are cross-sectional, though Q2c does use a measure of change in the SF-12 scores over time as the dependent variable of interest. Of all Visit 5 participants, approximately 1,100 participants were identified as having prevalent heart failure; therefore, the analyses comparing HFpEF and HFrEF groups may be underpowered. The variable used to define heart failure in this analysis will be PREVFHF51, a prevalent HF definition that includes participants with hospitalization with ICD code 428.x in the first position, physician reported HF or cardiomyopathy (CM), or prior hospitalization before Visit 5 during which the patient was classified as definite, probable or chronic HF. This variable is a closed definition and its lag time ends

two years after surveillance was initiated. This may lead to under-diagnosis of heart failure and an underestimation of HF prevalence. If this variable significantly under-classifies participants as having heart failure, it will bias our analysis towards the null.

The variable SF12, used to assess quality of life was administered at varying times during the Visit 5 survey period. This means that some participants will describe changes over months while others will detail changes over years. This may limit the interpretation of this data.

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?
_____ 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.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)?

MP 1707, Incident heart failure and cognitive decline: The Atherosclerosis Risk in Communities (ARIC) study, J Bressler et al (Drs. Bressler and Gottesman are members of the writing group).

MP 2334, Troponin T and N-terminal pro-B-type Natriuretic Peptide and Cognitive Decline and Dementia in the ARIC study, Y Pokharel et al (Dr. Gottesman is a member of the writing group).

MP2288 Associations of Brain Imaging with Cognitive Change over 20 years/ K Knopman, et al.

MP1121 Cognitive change over 12 years and its relationship to cardiovascular risk factors: ARIC MR Study. D Knopman et al.

MS2175 Midlife blood pressure and 20-year cognitive change: The ARIC-Neurocognitive Study. R. Gottesman et. al

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.

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.

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