ARIC Manuscript Proposal #3819

PC Reviewed: 4/13/21	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. **a. Full Title:**

Bidirectional Association Between Frailty and Heart Failure: The ARIC Study

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

2. Writing Group:

Writing group members: Diego Ramonfaur, Amil Shah, Brian Claggett, Hicham Skali, Dalane Kitzman, Beverly Gwen Windham, Priya Palta, Suma Konety, Chiadi Nduleme, others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. DRG

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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:

We will begin analysis once the proposal is approved and anticipate manuscript completion in approximately 6 months following proposal approval.

4. **Rationale:**

Frailty is a clinical syndrome predominantly found in elderly people. It is characterized mainly by slow gait speed, poor grip strength and weight loss. (1) Known risk factors for developing frailty include, but are not limited to: low physical activity, dietary quality, alcohol intake, smoking and low education. (2–4) It has been established that frailty is associated with different outcomes such as cardiovascular disease, falls, fractures, depression and mortality. (5,6) Frailty is known to be highly associated with heart failure (HF) and to predict mortality or hospitalization in patients with cardiovascular disease. (7–9) Moreover, frailty has been associated with poor hemodynamic and echocardiographic parameters. (10,11) However, few studies have looked at a longitudinal association between frailty or pre-frailty and HF, and the results are somewhat conflicting. HF is a well-studied entity. While the diagnosis is merely clinical, echocardiography plays a major role in its characterization by measuring left ventricular systolic and diastolic function. Additionally, echocardiography may be used as a follow-up and prognostic tool in these patients. Many authors have described a strong cross-sectional association between frailty and HF. A bidirectional relationship between frailty and HF has been proposed, but data is lacking. (12) While this association has been clear, few data exists regarding the longitudinal risk of frail patients to develop future HF, and vice versa. Our analysis aims to define the risk of HF (with preserved or reduced ejection fraction) among frail participants in the ARIC study.

5. **Main Hypothesis/Study Questions:**
   We hypothesize that participants with frailty or pre-frailty at visit 5 will have more incident HF at visit 7, compared to non-frail controls.

   Specifically, we aim to:
   1. Estimate the extent to which frailty or prefrailty increases the risk of HF
   2. Describe a temporal and bidirectional association between frailty and heart failure
   3. Compare diastolic dysfunction between frail and non-frail participants.

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:
   This is a longitudinal analysis using data from visits 5, 6 and 7, including clinical and echocardiographic data.

   Inclusion/Exclusion criteria:

We will include ARIC participants who underwent frailty and echocardiographic assessment at visit 5, 6 and 7.
We will exclude participants congenital heart disease.

Key variables of interest:

1. Clinical covariates (Visits 5, 6, and 7): Age, gender, race/ethnicity, height, weight, blood pressure, heart rate, history of hypertension, diabetes, dyslipidemia, coronary artery disease, prior MI or revascularization procedure, atrial fibrillation, prior stroke or TIA, heart failure, eGFR, serum creatinine, hemoglobin, hematocrit, hemoglobin HbA1c, fasting glucose, frailty measures (grip strength, self-reported exhaustion, unintentional weight, walking speed, physical activity), incident or previous heart failure (HFpEF or HFrEF).
2. Echocardiographic variables (Visits 5 and 7): (1) LV structure (LV end-diastolic and end-systolic volumes and dimensions), wall thickness, relative wall thickness, and mass); (2) LV diastolic function (E wave, A wave, E', E/e' ratio, LAVi, and LA diameter); (3) LV systolic function (LVEF, global longitudinal strain, global circumferential strain)
3. Cardiac biomarkers (Visit 5 and 7): NT-proBNP, hs-cTnT, CRP.

Data Analysis:

Aim 1: Among a sub-group of ARIC participants free of HF, we will use logistic regression (Stata "logistic") to estimate the risk of developing HF at visit 6 and 7 given a diagnosis of frailty at visit 5.

- Primary predictor: Frailty (Fried ≥3 criteria)
- Primary outcome: Incident Heart Failure
- Statistical approach: Time-event analysis (Cox proportional hazard model)
    - Demographic and covariate adjusted models

Aim 2: Among a sub-group of ARIC participants free of frailty/pre-frailty, we will use logistic regression (Stata "logistic") to estimate the risk of developing frailty at visit 6 and 7 given a diagnosis of HF at visit 5.

- Primary predictor: HF (clinical diagnosis)
- Primary outcome: Frailty (Fried ≥3)
    - Secondary outcome: Pre-frailty (Fried ≤2)
- Statistical approach: Logistic regression.
    - Inverse probability of attrition weights.

Analyses will be performed with Stata IC-16.

Anticipated methodologic limitations

- Attendance bias may impact our findings. We will attempt to mitigate the impact of these biases by performing sensitivity analyses incorporating inverse probability weighting. Probability weights will be based on clinical, characteristics at visit 5. Death between Visits 5, 6 and 7 will introduce survival bias, which we expect to bias us toward underestimating incident HF and incident frailty correspondingly to each aim, and the associations of predictors with this change.
- Unintentional weight loss is a criterion for frailty by the Freid criteria. Unintentional weight loss was not ascertained at Visit 5 so weight loss was defined as V5 weight -V4 weight and BMI <18.5 (assumed to be unintentional). This variable does not discriminate between intentional and unintentional weight loss at Visit 5, and may overestimate the proportion of frail individuals. Our primary analysis will employ consistent definitions at Visits 6 and 7 (frail61a, frail71a). We will perform a sensitivity analyses incorporating data on unintentional weight loss which was assessed at Visit 6 and 7. Additional sensitivity analyses will be performed assuming a frequency of intentional weight loss at Visit 5 that is proportional to that at visit 6.

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

8. **a. Will the DNA data be used in this manuscript? ____ Yes __x__ No**

   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)?

ARIC Manuscript Proposal #3314 Impact of left ventricular diastolic function on association between systemic arterial stiffening and elevated pulmonary pressure

ARIC Manuscript Proposal # 1158 Prevalence and correlates of mitral, tricuspid, and aortic regurgitation in middle-aged and elderly African-Americans: the ARIC study

ARIC Manuscript Proposal #0452 The longitudinal relationship between diastolic and isolated systolic hypertension

ARIC Manuscript Proposal #0633 Pulmonary function and left ventricular mass in African Americans: the Atherosclerosis Risk in Communities (ARIC) study

ARIC Manuscript Proposal #XXXX Physical Activity Trajectories from Midlife to Older Adulthood and their Associations with Older Adulthood to Later Life Physical Function and Frailty: The Atherosclerosis Risk in Communities (ARIC) Study.

ARIC Manuscript Proposal #XXXX Systemic inflammation in midlife as a predictor of frailty in late-life: The ARIC Study

ARIC Manuscript Proposal #XXXX Comparison of cardiac and clinical characteristics between frailty and heart failure in the elderly: The ARIC Study (Nadruz)

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __x__ No

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/

12. a. 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.

b. 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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