

ARIC Manuscript Proposal # 2293 addendum

PC Reviewed: 3/9/21

Status: _____

Priority: 2

SC Reviewed: _____

Status: _____

Priority: _____

1.a. Full Title: Outcomes and Healthcare Utilization of Heart Failure Stages in the ARIC Cohort

b. Abbreviated Title (Length 26 characters): Heart Failure Stages Outcomes

2. Writing Group: Lena Mathews, Ning Ding, Carla A. Sueta, Anna Kucharska-Newton, Amil Shah, Kunihiro Matsushita, Chiadi Ndumele, Patricia P. Chang

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

Once the data is obtained, data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

Background:

Heart failure (HF) currently afflicts 5.1 million Americans with an estimated increase to 8.1 million by 2030. (1,2) Morbidity and mortality are high and HF is the number one reason that

people aged 65 and older are hospitalized. (2) The elderly are projected to have the highest increase in HF prevalence – 66% by 2030. (1) The AHA/ACC 2013 Heart Failure guideline (3) defines stages of heart failure and recommended management. The stages include individuals having other diseases such as hypertension that put them at risk for the development of heart failure (Stage A), having structural heart disease but no symptoms (Stage B), having structural heart disease with prior or current symptoms (Stage C), and individuals with structural heart disease and refractory symptoms (Stage D).

Given the projected significant increase in the prevalence of heart failure and the concomitant increase in health care dollars spent – \$34 billion in 2013 projected to \$70 billion in 2030, it is important to determine the outcomes and healthcare utilization of participants by heart failure stage as well as predictors of disease progression. The majority of previous echocardiographic cohort studies have recruited patients prior to 2000, enrolled primarily Caucasian populations, or have not identified participants by HF stage. (4-8) Healthcare utilization and medications were usually not reported. There is little data on predictors of disease progression. Elevated biomarkers and worsening diastolic function have been associated with progression of Stage A and B to symptomatic HF in Caucasian populations. (9,10)

During the Visit 5 clinical examination, participants of the ARIC Study cohort underwent a detailed echocardiographic examination. These data constitute a unique opportunity to identify HF stage in a racially diverse cohort of elderly men and women. Furthermore, the ARIC cohort participants represent a contemporary population with detailed characteristics not commonly reported, including evidence-based medication utilization.

We will describe outcomes, healthcare utilization, and predictors of disease progression at year 1 and 5 following HF stage assessment during Visit 5 in this ethnically diverse population. Three subgroups will be examined specifically: women, African Americans, and those aged ≥ 80 yrs who are less well studied. The 2013 ACC/AHA guideline defines HFrEF as $LVEF \leq 40\%$, HFpEF as $\geq 50\%$, and borderline HFpEF as 41-49%. (2) There are scant data published on this intermediate group. We will also compare outcomes stratified by left ejection fraction (LVEF).

Determination of healthcare utilization and predictors of disease progression will facilitate the development of diagnostic and treatment strategies that will prevent progression and reduce the epidemic of heart failure.

5. Main Hypothesis/Study Questions:

1. To describe the 1 and 5 year outcomes and healthcare utilization of the ARIC cohort according to HF stage ascertained at Visit 5 using AFU questionnaires and Medicare claims. Analyses will be stratified by gender, race, and age 80+ years. *Hypothesis: HF stage will be associated with worse outcomes at 1 and 5 years but this will differ by gender, race and age.*
2. To compare the outcomes of participants stratified by baseline left ventricular ejection fraction: $\leq 40\%$, 41-49%, $\geq 50\%$ and whether they differ by gender, race, and age. *Hypothesis: Baseline LVEF will be associated with worse outcomes at 1 and 5 years, but this will differ by gender, race and age.*

3. To examine predictors of HF stage progression over 5 years from Stage A and B to Stage C and D. *Hypothesis: Guideline-directed medical therapies, and echocardiographic features of structure and function at V5 will influence HF stage progression.*

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 methodological limitations or challenges if present).

This will be a longitudinal primarily descriptive analysis of ARIC cohort participants who have completed Visit 5. Participants with a technically acceptable baseline echocardiogram performed during Visit 5 will be included. Participants will have been previously classified by HF stage by Visit 5 in manuscript 1921 (Frequency and Correlates of Heart Failure Stages in the Community).

Briefly, Stage A patients will be defined by the presence of hypertension, hyperlipidemia, smoking, diabetes, coronary heart disease (excluding myocardial infarction), stroke/TIA, peripheral artery disease, obesity (BMI > 30), lack of symptoms and a normal echo. Participants classified as Stage B will be asymptomatic and have an abnormal echo (left ventricular hypertrophy, ejection fraction $\leq 50\%$, moderate to severe diastolic dysfunction, moderate to severe valvular disease). Stage C and D will include patients with prevalent HF at visit 1 and incident HF by visit 5. Symptoms recorded in the Respiratory Questionnaire at Visit 5 will help distinguish between Stages C and D. Participants will be further classified as HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and borderline HFpEF. Normals will be defined as having no risk factors and a normal echocardiogram.

Kaplan-Meier survival and composite outcome curves will be generated for each heart failure stage determined at Visit 5. The curves will be compared using the log-rank test. Depending on sample size, subgroups (gender, ethnicity, age ≥ 80) will be compared to normals by Cox proportional hazard analysis.

We will also explore predictors of disease progression with a focus on medications, biomarkers, and echocardiographic characteristics. Progression of Stage A and B patients to Stage C or D will be defined as HF hospitalization, incident HF. Incident HF will be determined from the AFU questionnaire (have you been diagnosed with HF or do you take medications for heart failure, with physician confirmation) or from Medicare claims data. This analysis will be contingent on a sufficient sample size of participants in Stage A or B progressing to Stage C or D. Categorical variables will be compared via χ^2 or Fisher exact test, while continuous data will be compared between groups via Wilcoxon Rank Sum or Kruskal-Wallis tests. P values < 0.05 will be considered significant. Multivariable logistic regression analysis will be used to determine predictors of progression from asymptomatic Stages A and B to symptomatic Stage C or D.

Limitations: The sickest participants may not attend Visit 5, which may limit our evaluation of Stage C and D participants. Therefore, we may group Stage C and D participants together. The sample size of disease progression of Stage A and B participants over a 1-yr period may be small and limit analysis of associations with disease progression. Furthermore, if the sample size is sufficient, we would estimate more extensive outcomes models. For example, we would consider

multivariable linear modeling of continuous outcomes such as total Medicare payments. However, we have not described these models and some of the issues in estimating such models because of concerns that the sample size will be insufficient to support such modeling.

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 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 ☒ 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.csc.c.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)?

ARIC is #1921 Frequency and Correlates of Heart Failure Stages in the Community which will classify visit 5 participants into heart failure stage published in 2017 (11 Shah et al 2017). Here the authors found that worse HF stage was associated with higher risk of incident hospitalization and mortality. MP2293 will additionally examine other CVD outcomes including other CVD events, and health utilization using CMS data, and assess predictors of disease progression.

ARIC MP #3537 Association of Glycemic Status and Progression of Cardiac Dysfunction among Older Adults (Echouffo-Tcheugui, Selvin et al 2020) examines that association of prevalent and worsening hyperglycemia with HF stage progression. MP2293 will focus on mediations, biomarkers and echo characteristics.

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* _____)**

____ **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/>

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.csc.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.

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 ____ No.

References:

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11. Shah AM, Claggett B, Loehr LR, et al. Heart Failure Stages Among Older Adults in the Community: The Atherosclerosis Risk in Communities Study. *Circulation.* 2017;135(3):224-240.