**ARIC Manuscript Proposal #3827**

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

**1.a. Full Title**: Reclassification of Heart Failure Stages in the Community based on the HFSA/ESC(HFA)/JHFS Universal Definition and Classification of Heart Failure: Insight from the Atherosclerosis Risk in Communities Study

**b. Abbreviated Title (Length 26 characters)**: Reclassification of Heart Failure Stages in the Community

**2. Writing Group**:(alphabetical):

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

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**3. Timeline**: Analysis is anticipated to begin as soon as approval is obtained. The manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation is anticipated to take place within one year of approval of the proposal.

**4. Rationale**:

There is currently significant variation on the definition of heart failure (HF). The lack of standardization creates potential uncertainty for clinicians when implementing guideline-directed medical therapy and confusion for patients in their understanding of HF. The recently published consensus document by the Heart Failure Society of America (HFSA)/Heart Failure Association of the European Society of Cardiology (ESC[HFA])/Japanese Heart Failure Society (JHFS) propose a more standardized classification of HF (1). This approach aims to improve provider and patient understanding of the disease as well as facilitate adoption of guideline-directed prognostication, diagnosis and management of HF. One important aspect of definition of HF is staging, which describes the development and progression of the disease.

The stages of HF from the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines defines the spectrum of the disease as: A – at high risk for HF but without structural heart disease or symptoms of HF; B – structural heart disease but without signs or symptoms of HF; C – structural heart disease with prior or current symptoms of HF; D – refractory HF requiring specialized interventions (2). One important proposed revision to this classification of HF stages in the consensus document involves the inclusion of cardiac biomarkers namely natriuretic peptides and troponin in defining stage B HF. In the consensus document, B-type natriuretic peptide (BNP) ≥ 35pg/mL or N-terminal pro-BNP (NT-proBNP) ≥125pg/mL in an ambulatory setting would meet criteria as stage B disease. With respect to cardiac troponins (cTn), levels >99$^{th}$ percentile in a normal reference population would be classified to the stage B category.

The use of biomarkers to define stage B HF has important clinical implications given likely identification of more individuals in the community who may be at higher risk for progression to clinical HF and future adverse cardiovascular events (3, 4). Importantly, these individuals could benefit from early implementation of aggressive risk modification including more intensive blood pressure control and possibly, initiation of agents such as sodium-glucose cotransporter 2 inhibitors (SGLT2i). The aim of our study is to leverage data from the Atherosclerosis Risk in Communities (ARIC) study to assess the number of individuals from a community-dwelling population who will be identified as stage B HF based on the addition of biomarker (NT-proBNP and/or cTn) diagnosis as well as to explore how the use of biomarker cutpoints from the consensus document compare with stage A risk factors and structural cardiac abnormalities with respect to association with future HF events.

**5. Study Aims:**

1. Assess the number of participants in a community-dwelling population who will be newly identified as stage B HF by adding the new biomarker criteria (NT-proBNP ≥125pg/mL OR hs-TnT ≥14ng/L) from the HFSA/ESC(HFA)/JHFS consensus document and characterize these participants based on demographic and clinical factors. Assess the percentage of participants categorized as stage A HF at the index visit who progress to stage B or stage C at the subsequent visit and percentage of participants categorized as stage B HF that progress to stage C.

2. Assess the association of risk factors (example HTN, DM) that constitute stage A HF group and NT-proBNP and hs-TnT with incident HF. Evaluate biomarker cut points with comparable relative and absolute risk to traditional stage A risk factors. Explore potential differences in risk for incident HF events based on using NT-proBNP, hs-TnT or both (with or without traditional risk factors) in the context of stage B HF.

3. Assess and describe number of individuals who will have concordant and discordant classification of being in "Stage B" HF when echo and biomarker data are compared. Assess potential differences in risk for incident HF events based on structural abnormalities by echocardiography (stage B HF defined by imaging) as compared with cardiac biomarkers (stage B HF defined by biomarkers) in older adults (ARIC visit 5).

**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).**

**<u>Aim 1:</u>**

**Study Design:**

Participants at ARIC visit 2 (middle age adults) and visit 5 (older adults) will be used as the index visits. Participants with prevalent HF, those without NT-proBNP or hs-TnT measurements at visit 2 or visit 5 will be excluded. Individuals other than White or Black and non-Whites from the Minneapolis and Washington county field center will also be excluded due to small numbers.

Of note, we are pursuing analysis at both visit 2 and visit 5 because echo parameters were not available prior to ARIC visit 5. Thus, determination of cardiac structural abnormalities at visit 2 was limited to ECG evidence of LVH. The reason we did not exclusively use only visit 5 data as participants are older at this point. As NT-proBNP is

known to increase with age, we felt that the cutoff of ≥125pg/mL for NT-proBNP may not be as applicable in a study population of older adults.

**Exposure Variables:**

Baseline characteristics at ARIC visit 2 or visit 5 including age, sex, race, hypertension status, hypertensive medication use, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure, diabetes status, fasting blood glucose, hemoglobin A1c (A1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride, estimated glomerular filtration rate (eGFR), body mass index (BMI), prevalent coronary heart disease (CHD).

**Outcome Variables:**

HF status:

1. Group 1 – no risk factors for HF, no structural abnormalities and cardiac biomarkers not elevated (stage 0)
2. Group 2 – presence of HF risk factors (stage A) defined as any of the following: hypertension, diabetes, obesity, metabolic syndrome.
3. Group 3 – Stage B HF by structural abnormalities (defined as ECG evidence of left ventricular hypertrophy [LVH] or having prevalent CHD for visit 2 analysis and echo evidence of structural abnormalities or having prevalent CHD for visit 5 analysis) (5). Structural abnormalities by echo are defined as having LVEF <50%, LVH, or severe grade valvular heart disease including severe aortic stenosis/regurgitation, severe mitral stenosis/regurgitation, severe tricuspid stenosis/regurgitation and severe pulmonic stenosis/regurgitation.
4. Group 4 – Stage B HF by cardiac biomarkers defined as having either a plasma concentration of NT-proBNP ≥125pg/mL OR hs-TnT ≥14ng/L but without cardiac structural abnormalities.

**Statistical Analysis:**

1. Categorize participants from ARIC visit 2 (or visit 5) who are included in the study into group 1 through 4 as above.
2. Tabulate baseline characteristics by groups 1 through 4. Compare mean ± standard deviation (SD) by ANOVA and percentages by chi-square test.
3. Perform multivariate multinomial logistic regression analysis to assess variables that are independently associated between groups.
4. Describe how many additional subjects identified as stage B using the new biomarker-based definition. Also describe number of individuals who would have been missed as being identified as stage B due to the lack of biomarkers (i.e. no risk factors that classifies individual as stage A but with elevated biomarkers).

5. Describe the percentage of participants who were classified as stage A HF at ARIC visit 2 who progressed to stage B or stage C HF at visit 4 (~6 years apart) and those were classified as stage B HF who progressed to stage C HF during this time frame. Similarly, describe the percentage of participants who were classified as stage A HF at ARIC visit 5 who progressed to stage B or stage C HF at visit 6 (~5 years apart) and those were classified as stage B HF who progressed to stage C HF during this time frame. Imputation using inverse probability weighting will be used to address missingness between index and subsequent visits.

**Aim 2:**

**Study Design:**

Participants at ARIC visit 2 will be included. Participants with prevalent HF and those without NT-proBNP or hs-TnT measurements at visit 2 will be excluded. Individuals other than White or Black and non-Whites from the Minneapolis and Washington county field center will also be excluded due to small numbers.

**Exposure Variables:**

Stage A HF risk factors ARIC visit 2:
- Hypertension status (yes vs no)
- Diabetes status (yes vs no)
- Obesity status (BMI ≥30 vs BMI <30)
- Metabolic syndrome status (yes vs no)
- Prevalent CHD status (yes vs no)
- Stage A HF status (if participants meets any of the criteria above)

NT-proBNP cutpoints: <100pg/mL, 101-125pg/mL, 126-150pg/mL, 151-200, >200pg/mL

hs-TnT cutpoints: <3 ng/L, 3-6 ng/L, 6-9ng/L, 9-14ng/L, >14ng/L

**Outcome Variables:**

Incident HF hospitalization after visit 2.

**Statistical Analysis:**

1. Determine rates of incident HF events for participants with stage A HF risk factors without elevated biomarkers and for participants with NT-proBNP and hs-TnT at or above each of the pre-determined cutpoints.
2. Construct Cox proportional hazard models to estimate association between each stage A risk factors for incident HF hospitalization first using unadjusted an unadjusted model and then as a multivariable model including each of the risk

factors (exposure variable) as well as adjusting for age, sex, race, SBP, DBP, LDL-C, eGFR, smoking, alcohol use.

3. Construct Cox proportional hazard models assessing the association between categories of NT-proBNP or hs-TnT with incident HF hospitalization first as an unadjusted model and then adjusting for stage A HF risk factors plus age, sex, race, SBP, DBP, LDL-C, eGFR, smoking, alcohol use.

**Aim 3:**

**Study Design:**

Participants at ARIC visit 5 will be included. Participants with prevalent HF, those without the echo parameters of interest (LVEF, LVH, severe valvular heart disease) and those without NT-proBNP or hs-TnT measurements at visit 5 will be excluded. Individuals other than White or Black and non-Whites from the Minneapolis and Washington county field center will also be excluded due to small numbers.

**Exposure Variables:**

- Stage B HF by cardiac structure (LVEF ≥ 50% vs <50% or LVH status (yes vs no) or severe valvular heart disease (yes vs no). Severe valvular heart disease includes severe stenosis or regurgitation of the aortic, mitral, tricuspid or pulmonic valves.
- Stage B HF by cardiac biomarkers (NT-proBNP≥125pg/mL or hs-TnT ≥14ng/L)

**Outcome Variables:**

Incident HF hospitalization after visit 5.

**Statistical Analysis:**

1. Identify individuals classified as Stage B by echo with NT-proBNP <125 pg/ml and hs-TnT <14 ng/L. Identify individuals classified as Stage B by biomarkers who had no echo characteristics of Stage B HF. Identify individuals classified as Stage B HF by both biomarkers and echo characteristics. Describe risk for incident HF of above categories (with specific focus on those with discordant stage B classification) using Cox proportional hazard models.
2. **Stratify analysis of Cox regression analysis assessing association between Stage B HF as defined only by echo with incident HF by** NT-proBNP≥125pg/mL vs <125pg/mL and hs-TnT ≥14ng/L vs hs-TnT <14ng/L.
3. Describe ranges of NT-proBNP/ hs-TnT levels in individuals with prevalence of stage B HF identified by echocardiography.

**Limitations:**

1. As described above, echo data was not available prior to ARIC visit 5, thus for visit 2 analysis we were limited in determination of structural cardiac abnormalities to ECG evidence of LVH. However, given that this is a population of community dwelling adults free from CVD at baseline, the number of participants with significant structural abnormalities at ARIC visit 2 is likely low.
2. Though we will adjust for multiple co-variables, we cannot completely exclude residual confounding in this observational study.

**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 __X_ 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)?**

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

**11.b. If yes, is the proposal**
**_X__ A. primarily the result of an ancillary study ***
**___ 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.

**References**


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