ARIC Manuscript Proposal #4236

PC Reviewed: 5/09/23_	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cardiovascular disease risk in individuals with elevated NT-proBNP but no cardiovascular risk factors - the Atherosclerosis Risk in Communities Study

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

2. Writing Group:(alphabetical):

Mahmoud Al Rifai
Christie M. Ballantyne
Biykem Bozkurt
Ron Hoogeveen
Xiaoming Jia
Vijay Nambi
Chiadi Ndumle
Amil Shah
Elizabeth Selvin
Justin Echouffo Tcheugui
Salim Virani
Jeremy Van't Hof
(Others welcome)

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]**

First author:
Xiaoming Jia, MD
Baylor College of Medicine
Department of Medicine
One Baylor Plaza,
Houston TX 77030
Email: xiaoming.jia@bcm.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Vijay Nambi, MD, PhD
Baylor College of Medicine
1 Baylor Plaza, 521D, MS 285, Houston, Texas 77030 AND
Michael E DeBakey Veterans Affairs Hospital
2002 Holcombe Blvd., Houston, Texas 77030
vnambi@bcm.edu

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:

The recently published 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure outlined 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 diagnosis, prognostic assessment and management of HF. Based on the current guideline, HF stages are defined as: Stage A – at high risk for HF but without structural heart disease, elevated biomarkers or symptoms of HF; Stage B – structural heart disease but without signs or symptoms of HF or elevated cardiac biomarkers in the presence of cardiovascular risk factors; Stage C – structural heart disease with prior or current symptoms of HF; Stage D – refractory HF requiring specialized interventions (2). One important update within the current guidelines from prior documents is the inclusion of natriuretic peptides and cardiac troponin in defining stage B HF. The guidelines now recommend that an individual who have cardiovascular risk factors and with a B-type natriuretic peptide ≥ 35pg/mL or N-terminal pro-BNP (NT-proBNP) ≥125pg/mL in an ambulatory setting, or with persistently elevated levels of high-sensitivity cardiac troponins (hs-cTn) should be considered as having stage B HF. Previously, we found that a significant number of older adults from the ARIC population at visit 5 were re-classified to Stage B HF based on the new guideline definition and that participants with both elevated biomarkers and cardiac structural/functional abnormalities on echocardiography had the highest risk of cardiovascular events compared to elevated biomarkers or abnormal echocardiography alone (ARIC MS 3827) (3). This current analysis is an extension of our prior manuscript proposal. One group of individuals who are not clearly defined in the guidelines are those with elevated cardiac biomarkers only but without clinical HF (CVD), cardiac structural abnormalities or cardiovascular risk factors. Data is limited on whether these individuals have elevated risk for incident HF and mortality.

The aim of our study is to leverage data from the Atherosclerosis Risk in Communities (ARIC) study to better define risk for incident HF and mortality among these individuals with elevated cardiac biomarkers alone but without cardiovascular risk factors, cardiac structural abnormalities or clinical HF.

5. Study Aims:

To assess association between elevated NT-proBNP, hs-TnT and hs-TnI with risk for incident heart failure events and death among patients without baseline clinical CVD, cardiac structural abnormalities or cardiovascular risk factors.

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).

Study Design:

Participants at ARIC visit 5 will be used as the index visits as this visit is the earliest visit where echocardiography in defining cardiac structure/function is available. Participants with prevalent HF; those with cardiac structural/functional abnormalities on echocardiography; those with cardiovascular risk factors AND elevated NT-proBNP or hs-Tn; and those without NT-proBNP or hs-Tn measurements 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:

The primary comparators will be individuals with elevated cardiac biomarkers but no cardiovascular risk factors, echocardiography abnormalities or clinical HF, individuals with cardiovascular risk factors but no biomarker elevation, cardiac structural/functional abnormalities by echocardiography or clinical HF (defined as Stage A HF by current guidelines) and individuals without cardiovascular risk factors or elevated biomarkers (reference group). Elevated biomarkers will be defined as a NTproBNP level ≥125pg/mL or hs-cTnT level ≥14ng/L. Cardiovascular risk factors will be defined as hypertension, diabetes, metabolic syndrome, obesity, prevalent coronary heart disease, prevalent atrial fibrillation. Cardiac structural/functional abnormalities by echocardiography will be defined as: left ventricular ejection fraction (LVEF) <50%, global longitudinal strain <16%, regional wall motion abnormality, left ventricular mass index >116g/m^2 in men and >95 g/m^2 in women, left ventricular end diastolic volume index ≥75ml/m^2 in men and ≥62ml/m^2 in women, left atrial volume index ≥29ml/m^2, average E/e' ≥15, tricuspid regurgitant velocity >280cm/s, or having a valvular abnormality (1). In our study, we defined valvular abnormality as peak aortic valve velocity ≥300cm/s, mitral regurgitation jet area ≥4cm^2, presence of moderate or greater aortic insufficiency and presence of moderate or greater mitral stenosis.

Outcome Variables:

Incident HF hospitalization, cardiovascular death and all-cause death after visit 5. HF events further analyzed by HF subtypes: preserved ejection fraction (HFpEF: LVEF ≥50%) or HF with reduced ejection fraction (HFrEF: LVEF <50%) if LVEF information was available at or around time of hospitalization (4).

Statistical Analysis:

Cox regression analysis assessing association between individuals with elevated biomarkers but no cardiovascular risk factor and individuals with stage A HF compared with those without cardiovascular risk factors or elevated biomarkers (reference group) with respect to incident HF events, cardiovascular death and all-cause death. Adjustment model 1: age, sex and race-center.

- Adjustment model 2: model 1 plus eGFR, systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, high-density lipoprotein cholesterol, cholesterol lowering medication use, BMI, prevalent smoking.
- To account for higher rate of death in an older population at visit 5, we will perform competing risk of death for the overall HF outcome using the Fine and Gray method (5). For analysis of the HF subtypes, we performed competing risk analysis accounting for death, the other HF subtype and unclassified HF (due to lack of data of ejection fraction).
- Subgroup analysis will be performed stratified by age, sex, race, eGFR.
- We will also evaluate how many patients with elevated cardiac biomarkers at visit 5 also had elevated cardiac biomarkers at visit 4 and/or visit 6. We will then perform stratified analysis by elevated vs not elevated biomarker status at visit 4/visit 6.

To assess whether cardiovascular risk factor is an effect modifier of the association between NT-proBNP and hs-cTnT with cardiovascular risk, we will perform Cox regression analysis using NT-proBNP and hs-cTnT as linear variables (log-transformed) and stratify by 0 vs >0 risk factors as well as by 0, 1, 2-3, >3 risk factors.

In exploratory analysis, we will repeat Cox regression analysis comparing participants with elevated biomarkers but no cardiovascular risk factor, individuals with risk factors but no elevated biomarkers and those without cardiovascular risk factors or elevated biomarkers (reference group) with respect to incident HF events, cardiovascular death and all-cause death using Visit 4 as baseline.
We will further use logistic regression analysis to compare between participants with elevated biomarkers but no cardiovascular risk factor and those without cardiovascular risk factors or elevated biomarkers (reference group) at Visit 4 with respect to development of future hypertension, diabetes, and obesity at Visit 5 as well as development of abnormal echocardiography parameters at visit 5 defined as: left ventricular ejection fraction (LVEF) <50%, global longitudinal strain <16%, left ventricular mass index >116g/m^2 in men and >95 g/m^2 in women, left ventricular end diastolic volume index $\geq$75ml/m^2 in men and $\geq$62ml/m^2 in women, left atrial volume index $\geq$29ml/m^2, average E/e' $\geq$15. We acknowledge that at visit 4, there is no echocardiography data available, thus there will be some individuals included who may have abnormal echo findings at baseline at visit 4.

Limitations:

1. Echo data was not available prior to ARIC visit 5, thus our analysis is focused on older adults. We acknowledge that at visit 5, there is a limited number of participants with risk factors but without elevated biomarkers. We attempt to address this by also assessing participants at visit 4. However, as stated above, there is no echocardiography data available, thus there will be some individuals included who may have abnormal echo findings at baseline at visit 4.
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)?
ARIC Proposal #3827. 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.

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 *
___ 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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2. Writing Committee M, Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128(16):e240-327.
3. Jia X, Al Rifai M, Ndumele CE, Virani SS, de Lemos JA, Lee E, et al. Reclassification of Pre-Heart Failure Stages Using Cardiac Biomarkers: Atherosclerosis Risk in Communities (ARIC) Study. JACC Heart Fail. 2023.
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5. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509.