ARIC Manuscript Proposal #3542

PC Reviewed: 1/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of cardiac troponin T and N-terminal pro-B-type Natriuretic Peptide with longitudinal changes in left ventricular structure and function: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): cTnT, NT-proBNP and LV remodeling

2. Writing Group:

Writing group members: Peder Langeland Myhre, Brian Claggett, Christie Ballantyne, Liz Selvin, Kunihiro Matsushita, Dalane Kitzman, Suma Konety, Thomas Mosley, Amil Shah; others welcome

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

We will begin work on the analysis immediately after obtaining approval and data. We estimate the time to journal submission will be less than 6 months from data acquisition

4. Rationale:

Cardiac troponin measured by a high-sensitivity assay (hs-cTn) detects low-grade cardiomyocyte damage, and is prognostic of incident heart failure (HF) and mortality in community-based

studies [1-3]. Moreover, higher hs-cTn concentrations are associated with greater left ventricular (LV) hypertrophy and diastolic dysfunction in the general population, and the presence of both elevated hs-cTn and LV hypertrophy or diastolic dysfunction seems to reflect a particularly malignant phenotype [1, 4, 5]. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is released by ventricular myocytes in the response to increased ventricular wall stress, and is an established prognostic biomarker in HF in both acute and stable settings. [6, 7] Circulating NT-proBNP concentrations associate with several measures of cardiac structure and function, and most prominent is the correlation with LV wall stress.[8] In general population studies, higher concentrations of NT-proBNP are associated with heightened risk of incident HF and cardiovascular (CV) death. [9, 10] Pooled data from FHS, CHS, PREVEND and MESA suggest that cardiac troponin and NT-proBNP are predictive of both incident HFpEF and HFrEF, with a stronger association to HFrEF for both biomarkers.[11] While the cross-sectional associations of hs-cTnT and NT-proBNP with cardiac structure and function has been well described in the general population, the extent to which circulating NT-proBNP and hs-cTnT concentrations predict longitudinal *changes* in cardiac function is not known. In a previous analysis from the MESA study assessing serial CMR among persons primarily in mid-life, higher hs-cTn concentrations at baseline (Visit 1) were associated with a higher likelihood of increasing LV mass and greater extent of late gadolinium enhancement 10 years later (Visit 5).[12] However, data on LV diastolic function, systolic deformation, left atrial size, and pulmonary pressure – all prognostically important in HFpEF – were not available. Furthermore, little data exist regarding the correlation of longitudinal changes in cardiac biomarkers with concomitant changes in cardiac structure and function. Evaluating the association of cardiac biomarkers at Visit 5, and changes from Visit 5 to 7, with longitudinal changes in echocardiographic measures from Visits 5 to 7 in ARIC will help disentangle the temporal relationship between abnormalities of circulating biomarkers and alterations in cardiac structure and function predisposing the HF development.

5. Main Hypothesis/Study Questions:

We hypothesize that, among HF-free community-based older adults, higher baseline concentrations, and greater increases over ~5 years, of hs-cTnT and NT-proBNP are associated with (a) longitudinal increase in LV mass and worsening of LV systolic and diastolic function over ~5 years, and (b) heightened risk of both incident HFpEF and HFrEF. We will assess each biomarker individually and in combination with respect to longitudinal changes in cardiac structure and function, and to risk of incident HFpEF and HFrEF to address the following aims:

1. Determine the associations of Visit 5 concentrations of hs-cTnT and NT-proBNP with longitudinal changes in echocardiographic measures of LV structure, systolic function, and diastolic function between Visits 5 and 7. This analysis will be stratified by HF status (no HF V5/no HF V7, no HF V5/HF V7, HF V5).
2. Determine the associations of changes in concentration from V5 to V7 of hs-cTnT and NT-proBNP with longitudinal changes in echocardiographic measures of LV structure, systolic function, and diastolic function between Visits 5 and 7. This analysis will also be stratified by HF status (no HF V5/no HF V7, no HF V5/HF V7, HF V5).
3. Among persons free of HF at Visit 5, determine the association of concentrations of hs-cTnT and NT-proBNP assessed at ARIC Visit 5 with incident HFpEF and incident

HFrEF post-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 methodologic limitations or challenges if present).

Study design:
We will relate hs-cTnT and/or NT-proBNP concentrations at Visit 5 (primary exposure variables for analysis #1 and #3) and changes from Visit 5 to 7 (primary exposure variables for analysis # #2) to (a) changes in echocardiographic measures from Visit 5 to Visit 7 (primary outcome variables for analysis #1), and (b) incident HFpEF and HFrEF post-Visit 5 (primary outcome variables for analysis #2). The associations with longitudinal changes in echo measures will be assessed in the total sample of participants with echocardiographic data at Visits 5 and 7, and stratified into 4 categories: 1) Established HF at Visit 5; 2) No HF at Visit 5, with incident HFpEF during follow-up; 3) No HF at Visit 5, with incident HFrEF during follow-up; 4) No HF at Visit 5 and no incident HF during follow-up.

Inclusion/exclusion criteria:
For Analysis #1, completion of echocardiogram at Visit 7 will also be required. We will stratify the analysis by known HF status at Visit 5.

For Analysis #2: ARIC participants who were HF-free at Visit 5 and have available hs-cTnT and/or NT-proBNP and echocardiographic data at Visit 5.

Variables of interest:
1. Cardiac biomarkers (Visit 5 and 7): NT-proBNP, hs-cTnT
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, TDI E', E/e' ratio, LAVi, and LA diameter); (3) LV systolic function (LVEF, global longitudinal strain, global circumferential strain); (4) pulmonary hemodynamics (estimated PASP based on TR jet velocity) and right ventricular function (RV fractional area change, TDI tricuspid annular s')
3. Clinical covariates (Visits 5 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 A1C, fasting glucose
4. Outcome variable: Adjudicated incident HF post Visit 5. [13] For the HF events with available information on LVEF or with LVEF measurements in the nearest 6 months, we will categorize as incident HFpEF or HFrEF. We will also analyze with the combined endpoint incident HF or death to account for competing risk in sensitivity analyses.

Data analysis
hs-cTnT, NT-proBNP and the ratio between the two will be modeled as both an ordered categorical (quintiles) and continuous variable. Clinical covariates, laboratory variables and

echocardiographic parameters of structure and function at Visit 5 will be described for each category. For the continuous analysis, hs-cTnT and NT-proBNP will be log transformed, with undetectable levels assigned a value half of the limit of detection for the assay. Changes in hs-cTnT and NT-proBNP will be determined by calculating the ratio of V7:V5 concentrations. The biomarker concentrations and the ratio of change will be log transformed to account for the right-skewed distribution in regression analysis. Cox proportional hazard models adjusting for age, gender, race, comorbidities and eGFR will be applied to assess the association between hs-cTnT and NT-proBNP at Visit 5 with time to incident HFrEF and HFpEF post Visit 5. For time to event analyses with incident HFpEF as an outcome, participants with incident HFrEF will be censored at the time of HF, and vice versa for incident HFrEF. Associations between the biomarkers – and their changes – and changes in echocardiographic measurements from Visit 5 to Visit 7 will be assessed by univariable linear regression analysis and multivariable regression analysis adjusting for age, sex, race, blood pressure, history of hypertension, diabetes, coronary artery disease and eGFR. Additional models with interaction terms for gender and race will be generated to assess for effect modification of the relationship by sex and race. To account for the potential impact of regression to the mean, additional models will also adjust for the baseline echocardiography and biomarker measurement from Visit 5. Analyses will be performed for the total population and stratified in 4 categories: 1) Established HF at Visit 5; 2) No HF at Visit 5, with incident HFpEF during follow-up; 3) No HF at Visit 5, with incident HFrEF during follow-up; 4) No HF at Visit 5 and no incident HF during follow-up. All analyses will be performed using STATA version 14 (StataCorp LLC; College Station, TX, USA), and a two-sided p-value < 0.05 will be considered statistically significant.

Limitations: The major limitations relate to survival bias, as only participants who survived to Visit 7 will be investigated, and to attendance bias, as only participants alive and attending both Visits 5 and 7 will be included. We plan to perform supplemental analyses implementing inverse probability of attrition weights to try to account for the potential impact of attendance bias.

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/mantrack/maintain/search/dtSearch.html

____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)?

MPF#2775 (Ballantyne et al) High-sensitivity troponin I and incident heart failure hospitalization, myocardial infarction, stroke and cardiovascular disease mortality in ARIC
MPF#1808 (Nambi et al) The utility high sensitivity cardiac troponin t in the prediction of heart failure risk
MPF#1917 (Shah et al) Association of diastolic dysfunction with high sensitivity troponin T and NT-proBNP across left ventricular geometries in the community: A preliminary analysis from the ARIC study
MPF#2128 (McEvoy et al) Patterns and determinants of temporal change in high-sensitivity cardiac troponin-T: The Atherosclerosis Risk in Communities Cohort Study
MPF#2269A (McEvoy et al) Six-year change in high-sensitivity cardiac troponin T and risk of subsequent coronary heart disease, heart failure, and death
MS#1917 (Myhre et al) Association Between Circulating Troponin Concentrations, Left Ventricular Systolic and Diastolic Functions, and Incident Heart Failure in Older Adults
MS#1811- (Oluleye et al) Association of high sensitive Troponin T (hs-cTnT),N- Terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study
MS#1808- (Nambi et al) The utility high sensitivity cardiac troponin t in the prediction of heart failure risk
MS#1757 (Nambi et al) The association of high sensitivity troponin with heart failure, mortality and recurrent coronary heart disease (CHD) in individuals with prevalent CHD
MS#1564 (Saunders et al) Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events
MS#1172 (Nambi et al) Lp-PLA2 and hs-CRP as Predictors of Ischemic Stroke
MS#940 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high sensititivity c-reactive protein, and risk for ischemic stroke
MS#934 (Folsom et al) An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers
MS#889 (Ballantyne et al) Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein and risk for incident coronary heart disease in middle-aged men and women in Atherosclerosis Risk in Communities Study
MS#606 (Folsom et al) C-reactive protein and incident cornary heart disease in the Atherosclerosis Risk in Communities (ARIC) 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 (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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies

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.

We aim to submit the manuscript for ARIC review within 6 months of obtaining data.

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.
The authors are aware of this policy.

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