ARIC Manuscript Proposal #2130

**PC Reviewed:** 5/14/13  
**Status:** A  
**Priority:** 2

**SC Reviewed:** _________  
**Status:** _____  
**Priority:** ____

1.a. **Full Title:** Left Ventricular Hypertrophy, Biomarkers of Subclinical Myocardial Injury and Hemodynamic Stress, and the Risk of Heart Failure: Results from the ARIC Study

b. **Abbreviated Title (Length 26 characters):** LVH, Cardiac Biomarkers, and Heart Failure

2. **Writing Group:**
   Writing group members: Ian Neeland MD, James de Lemos MD, Christie Ballantyne MD, Vijay Nambi MD PhD, Mark Drazner MD MSc, Jarett Berry MD MS, Ron C. Hoogeveen, PhD, and Wensheng Sun

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

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Review by study groups July 1 - August 1. Submit August 15.
4. **Rationale:**

Although left ventricular hypertrophy (LVH) is an important risk factor for heart failure (HF) and death, its natural history is heterogeneous, with a progressive course in some individuals but an uncomplicated course in many others. Identification of biological pathways that contribute to the transition from LVH to clinical HF, and biomarkers that accurately represent these pathways, may help to identify individuals at high risk for adverse outcomes and to develop therapeutic targets to prevent subclinical disease transition. Biomarkers of myocardial injury and neurohormonal activation due to hemodynamic stress may therefore play key roles in defining the transition from asymptomatic LVH to clinical HF\(^1-^3\).

Cardiac troponin T (cTnT) and the N-terminal fragment of the prohormone of B-type natriuretic peptide (NT-proBNP) are released from cardiac myocytes in response to a variety of pathologic stimuli including increased LV wall stress and hypertrophy, and are markers of cardiac injury and ventricular wall stress\(^4,^5\). Both biomarkers have been shown to associate strongly with incident HF and mortality in the general ARIC cohort\(^6-^8\).

Recently, working in collaboration with ARIC investigators, we published an analysis among participants in the Dallas Heart Study without clinical heart failure or LV dysfunction in which LVH was characterized by MRI and ECG, and highly sensitive cTnT (hs-cTnT) and NT-proBNP were measured by state-of-the-art assays\(^9\). Participants with LVH and concomitant elevation in troponin or NT-proBNP demonstrated a highly “malignant” LVH phenotype. Subgroups with LVH and either detectable troponin or elevated NT-proBNP had a > 20% risk for heart failure or death over a median 8 years of follow-up vs. only 6% in those with LVH alone. Among those with LVH and elevation in both biomarkers the risk increased to 30%. This preliminary analysis suggests that hs-cTnT and NT-proBNP are powerful prognostic markers in asymptomatic individuals with LVH, and more importantly may identify a disease phenotype that has both biological and clinical relevance. However, our study was limited by low numbers of events, particularly among individuals who were not African-American. In light of these limitations, we feel that this study was hypothesis-generating but requires validation in a more robust cohort with larger numbers of heart failure events, longer term follow-up, and more non-African-American participants in order to truly translate the findings to clinical relevance.

In addition, by virtue of collection of data at visits prior to the Visit 4 measurements of hs-cTnT and NT-proBNP, ARIC offers the opportunity to evaluate factors that may have influenced the development of the “malignant” LVH phenotype. This strategy was used effectively in a prior ARIC publication to demonstrate associations between remote glycemic control and prevalent cardiac injury\(^10,^11\). Exploration of factors associated with the development of “malignant” LVH may help to identify potential strategies to prevent this high risk phenotype.

5. **Main Hypothesis/Study Questions:**
Our hypothesis is that biomarker evidence of subclinical myocardial injury (reflected by detectable hs-cTnT ≥3 pg/mL) or hemodynamic stress (defined as NT-proBNP > age-and-sex specific 75th percentile of the population) will identify asymptomatic individuals with LVH at higher risk for transition to heart failure and cardiovascular death compared with those with LVH alone.

We propose a paper that will validate our preliminary findings and extend the implications of these findings into practical clinical use. We plan to use ECG definitions of LVH given their widespread availability in ARIC and clinical practice. The larger sample size will also allow us to test alternative thresholds for the hs-cTnT and NT-proBNP assays to define an optimal cut-point for heart failure prediction. In addition, the larger sample size will permit assessment of effect modification by key demographic and clinical factors such as age, sex, race, hypertension, diabetes, and chronic kidney disease.

As an exploratory analysis, we plan to identify factors associated with the “malignant” LVH phenotype by examining the relationship between LVH with biomarker elevation (at visit 4) with factors measured in earlier visits. This analysis may inform us as to what clinical factors are associated with future development of malignant LVH. ARIC is uniquely suited to this analysis given 3 ARIC visits occurred prior to the measurements of hs-cTnT and NT-proBNP.

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).

Exclusion:
2. History of prior myocardial infarction.
3. Estimated glomerular filtration rate (based on MDRD) < 60 mL/min/1.73 m²
4. Missing ECG, hs-cTnT, or NT-proBNP data.

Exposure variables:
1. Left ventricular hypertrophy by ECG criteria (Sokolow-Lyon criteria used in prior study)
2. hs-cTnT
3. NT-proBNP

Outcome variables:
1. Primary: Composite of incident heart failure and cardiovascular mortality
2. Secondary: Incident heart failure
3. Secondary: Cardiovascular mortality
Analysis:
1. Participants categorized into groups based on the presence (+) or absence (-) of LVH and biomarker levels above (+) or below (-) the pre-defined threshold.
2. Baseline characteristics compared between those without LVH, those with LVH but without elevated biomarkers, and those with LVH and elevated biomarkers using chi-square tests for dichotomous variables and Wilcoxon rank-sum tests for continuous variables.
3. Cumulative incidence of the primary outcome among groups with LVH-biomarker-, LVH- biomarker+, LVH+ biomarker-, and LVH+ biomarker+ estimated using time-to-event analysis. Kaplan-Meier curves constructed and compared using the log-rank test. Separate analyses will be performed for cTnT and NT-proBNP.
4. Cox proportional hazards models used to calculate the hazard ratios and 95% confidence limits for the primary outcome among each group.
5. Interaction terms included in the unadjusted models to determine if qualitative, multiplicative interactions between LVH, cTnT, and NT-proBNP are present.
6. Stratified analyses by age, sex, race/ethnicity, hypertension, and diabetes.
7. Cox proportional hazards models used to adjust for age, sex, race, diabetes, hypertension, CVD, smoking, body mass index, and eGFR.
8. Sensitivity analyses performed using a 5 pg/mL threshold to define detectable cTnT and defining LVH using various other ECG criteria (e.g. Cornell).
9. Exploratory analyses performed comparing outcomes among those with LVH and 0, 1, or 2 elevated biomarkers.
10. Exploratory analyses to evaluate remote exposure variables and LVH phenotypes at visit 4. Exposure variables to be tested from prior ARIC visits include hypertension, number of hypertension medications, systolic and diastolic blood pressure, diabetes, hemoglobin A1C, eGFR, and family history of hypertension, heart failure, cardiomyopathy, or LVH.
11. Power calculation: Assuming a 5% prevalence of LVH by ECG in the study population, we should have 90% power to detect an absolute 10% difference in incident heart failure rates between the LVH+biomarker+ and LVH+biomarker- groups.

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  ___X__ 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.cscce.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)?

This proposal is related to two published studies.6, 8

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

   2008.10 Measurement of NT-pro-BNP and troponin T at visit 4 for the full ARIC cohort

11.b. If yes, is the proposal
   ___ X___ A. primarily the result of an ancillary study (list number* _2009.10_)  
   ___ 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.cscce.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.cscce.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:


