ARIC Manuscript Proposal # 3267

PC Reviewed: 11/13/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. **Full Title**: Malignant Left Ventricular Hypertrophy and Heart Failure Risk in African Americans: A Multi-Cohort Study
b. **Abbreviated Title (Length 26 characters)**: Malignant LVH and HF Risk

2. **Writing Group**: Alana A. Lewis, MD; Colby Ayers, MS, Christie Ballantyne, MD, Vijay Nambi, MD, Elizabeth Selvin, PhD, MPH, Chris DeFilippi, MD, Stephen Seliger, MD, Ian Neeland, MD, Mercedes Carnethon, MD, Ambarish Pandey, MD, Tiffany Powell-Wiley, MD, Jarett Barry, MD, James de Lemos, MD

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]
A.A.L.

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3. **Timeline**: 9/1/2018 to 8/31/2020

4. **Rationale**:
Heart failure (HF) affects over 5 million people and accounts for more than $35 billion in annual health care costs in the United States.[1] Despite significant therapeutic advances in HF management, hospital admissions rates remain high, and overall outcomes remain poor.[2,3] Heart failure has been shown to disproportionately affect black individuals, with risk factors such as hypertension and obesity contributing to early onset incident heart failure in this population.[4] Given that blacks shoulder a higher burden of HF than any other racial/ethnic group, a focus on preventive interventions in this population should be prioritized.

Previous studies have demonstrated that a series of intermediate subclinical cardiac phenotypes characterized by left ventricular (LV) hypertrophy (LVH) or LV dysfunction and adverse remodeling lead to progression from at-risk to symptomatic HF.[5-10] In addition, chronic, subclinical myocardial injury, now detectable using high sensitivity assays for cardiac troponin (cTn), and neurohormonal activation (defined

by higher levels of NT-proBNP) are strongly associated with structural heart disease and with future HF risk.[11-13]

In our prior work, we have demonstrated that HF develops via progression through a series of subclinical cardiac phenotypes, which can be characterized by ECG or imaging measures of left ventricular hypertrophy (LVH) and plasma biomarkers reflecting cardiac injury or neurohormonal activation. We have identified a malignant subphenotype of LVH, characterized by elevated cardiac troponin and/or N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, that appears to be more common among blacks than other racial/ethnic groups, and is an ominous marker of HF risk. In the Jackson Heart Study (manuscript under review), black individuals without existing cardiovascular disease who had malignant LVH were found to have a remarkable 35-40% risk for HF over 10 years.

Although these epidemiological data are compelling, important knowledge gaps remain. First it is not known whether race/ethnic differences in malignant LVH prevalence may contribute to higher risk of HF in blacks. More importantly, little is known about the factors that lead to the development of this phenotype, and without this knowledge, precision-medicine strategies for prevention and treatment cannot be developed. The primary objective of our proposal is to fully characterize the malignant LVH subphenotype and to assess to what extent this phenotype contributes to racial disparities in HF. We also aim to delve deeper into some of the clinical and socioeconomic factors that may correspond to an increased risk for development of the malignant LVH subphenotype, to inform approaches to improving clinical outcomes in individuals with this predisposition. This latter aim will be the focus of a second manuscript using this pooled dataset, for which we will submit a separate proposal.

5. Main Hypothesis/Study Questions:

Data from multiple cohort studies will be pooled to create a sample with sufficient statistical power to compare prevalence of malignant LVH and associated HF outcomes across race/ethnic groups. Successful completion of the aims of this study will result in characterization of a novel and important intermediate phenotype in the pathway to HF, which may play a key role in the excess burden of HF among AA.

Aim: Determine whether differences in the prevalence of malignant LVH contribute to racial disparities in HF risk.

Hypothesis: Malignant LVH will contribute to racial disparities in HF, through higher risk associated with malignant LVH in blacks, higher prevalence in blacks, or both.

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).

CONCISE SUMMARY OF PROJECT: The team of collaborative investigators will pool data from multiple existing cohort studies to determine whether differences in the prevalence of malignant LVH contribute to racial disparities in HF risk. These cohort studies include the Atherosclerosis Risk in Communities Study (ARIC), the Multi-Ethnic Study of Atherosclerosis (MESA), and the Dallas Heart Study (DHS). Given the relatively low prevalence of malignant LVH (<5% in the population) the individual studies performed to date have had insufficient sample size to determine whether the prevalence and incidence of malignant LVH differs by race/ethnicity, and insufficient power to test for interaction of malignant LVH and race/ethnicity with HF risk. No new data will be collected for the current study, as this will represent a pooling project of existing data across different cohorts. All data are currently available through our NASA grant proposal. In the pooled dataset, we will define the prevalence of malignant LVH at baseline and incidence over long-term follow up. The primary outcome

will be incident heart failure up to 10 years, and the secondary outcome will be CV death + heart failure. Malignant LVH will be defined as the presence of LVH, with evidence of hscTn+ (defined as ≥ 6 ng/L) and/or NT-proBNP+ (defined as ≥ 100 pg/mL). Next we will determine the absolute risk for HF in the three subsets: 1) LVH-, 2) LVH+, hs-cTn- and NT-proBNP-, and 3) LVH+, hscTn+ and/or NT-proBNP+ (malignant LVH), adjusting for traditional cardiovascular risk factors and estimated GFR. Interactions by race/ethnicity, sex and age will be tested and analyses will be stratified by race and sex. With a sample size of >15,000, including nearly 1000 malignant LVH cases (over 500 in blacks), we have >90% power to detect a race x malignant LVH interaction for the outcome of incident HF. We will also calculate the population attributable risk for development of HF for individuals with the malignant LVH phenotype, stratified by race/ethnicity.

CRITERIA FOR INCLUSION OF SUBJECTS: The study will include all asymptomatic individuals with ECG and biomarker data available from ARIC visit 2.

CRITERIA FOR EXCLUSION OF SUBJECTS: Participants with prevalent cardiovascular disease (prior MI, stroke, coronary or extra-coronary revascularization, or heart failure) will be excluded. Participants with race/ethnicity other than black or white will be excluded.

SOURCES OF RESEARCH MATERIAL: Data already present in the ARIC Database.

RECRUITMENT OF SUBJECTS: Not applicable, no subject recruitment will be required.

PROCEDURES TO MAINTAIN CONFIDENTIALITY: All information will be kept electronically, and password protected. Only members of the research team will have access to the data.

POTENTIAL BENEFITS: By combining data from multiple well defined cohort studies with diverse racial/ethnic backgrounds, we may determine whether differences in the prevalence of malignant LVH contribute to racial disparities in HF risk. By further establishing the significance of the malignant LVH phenotype, we aim to identify potential target areas for preventive interventions, in an attempt to modify clinical outcomes in individuals with this predisposition in the future.

FUNDING: Investigator and statistical support is provided by Dr. de Lemos' research funds.

DATA REQUESTED: No new data transfer is needed as we have the existing data pooled from our approved NASA grant proposal

Demographics and Risk Factors: Age, sex, race/ethnicity; hypertension, diabetes, smoking status, history of CAD, HF, family history of CAD; continuous measures of total, HDL, LDL cholesterol and triglycerides, systolic and diastolic BP, eGFR estimated from serum creatinine, BMI, HgbA1c, statin prescription, education and income.

ECG LVH by Cornell and Sokolow-Lyon criteria

Biomarkers: hs-cTnT, hs-CRP, NT-proBNP (Roche Diagnostics platform)

Echo: Categorical LVH; concentric LVH, eccentric LVH, Continuous measures of LV diameter, LV mass, LV mass index, LVEF, LV posterior wall thickness, relative wall thickness, mean mid-wall circumferential strain, E/A ratio

Cardiovascular Endpoints (with dates): All-cause mortality, CV and CHD death, HF, MI, PCI or CABG, stroke, heart failure hospitalization, atrial fibrillation.

STATISTICAL APPROACH:
Hs-cTnT+ will be defined as hs-cTnT ≥ 6 ng/L. NT-proBNP+ will be defined as NT-proBNP ≥ 100 pg/mL. ECG LVH will be defined using Sokolow-Lyon criteria. Secondary analyses will focus on echo LVH. Primary participant level data for demographic information, risk factors, biomarkers, LVH, imaging data, and CV outcomes will be obtained from the individual studies and the data will be pooled. Data harmonization has already been performed through our NASA grant. The first step will be to compare demographics across the three study populations. Next, the prevalence of the three phenotypes of interest: 1) ECG LVH-, 2) ECG LVH+, hs-cTnT- and NT-proBNP-, 3) ECG LVH+, hs-cTnT+ and/or NT-proBNP+ (malignant LVH), will be determined, stratified by sex and race. Cox proportional hazard models will be created to estimate the risk of HF and CV death + HF events with standard traditional risk factors included as independent variables (age, sex, total and HDL cholesterol, current smoking, systolic blood pressure, and antihypertensive therapy), as well as creatinine and BMI, as these are important predictors of HF. Cox PH models will be used with different baseline hazards for each study and via robust standard errors to account for patients clustered within studies. Interactions of malignant LVH with race will be evaluated and analyses will be stratified by race and sex. We will calculate the population attributable risk for development of HF for the malignant LVH phenotype, stratified by race/ethnicity. SAS (SAS Institute, Cary, NC) software will be used for all analyses. In exploratory analyses we will evaluate dose effects of the biomarkers by analyzing separately participants with LVH and elevations in one or both of the two biomarkers.

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?
_X___ 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)?
The related proposals and papers include those reporting associations of hs-cTn, NT-proBNP and presence of LVH with outcomes. James de Lemos (the PI on this paper request) was a coauthor on many of these papers. Thus, ARIC investigators who contributed the data are represented in this writing group.

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 (list number* ____2009.16_____)

___ 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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6. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. *J Am Coll Cardiol.* 2009;54(5):410-418.
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10. Zile MR, Gaasch WH, Patel K, Aban IB, Ahmed A. Adverse left ventricular remodeling in community-dwelling older adults predicts incident heart failure and mortality. *JACC Heart failure.* 2014;2(5):512-522.

11. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation.* 2011;123(13):1367-1376.
12. Seliger SL, Hong SN, Christenson RH, et al. High-Sensitive Cardiac Troponin T as an Early Biochemical Signature for Clinical and Subclinical Heart Failure: MESA (Multi-Ethnic Study of Atherosclerosis). *Circulation.* 2017;135(16):1494-1505.
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Table 1. Baseline characteristics of DHS, MESA and ARIC participants.

	Atherosclerosis Risk in Communities Study (ARIC) (N=)	**Dallas Heart Study (DHS) (N=)**	**Multi-Ethnic Study of Atherosclerosis (MESA) (N=)**
Age – years			
Men – n (%)			
Race/Ethnicity **Black – n (%)** **White – n (%)**			
Hypertension – n (%)			
Systolic BP (mm Hg)			
Diastolic BP (mm Hg)			
Diabetes – n (%)			
Current Smoker – n (%)			
Estimated GFR ml/min/1.73 m^2			
Glucose, mmol/L			
Total chol, mg/dL			
LDL, mg/dL			
HDL, mg/dL			
Triglycerides, mg/dL			
Statin Prescription – n(%)			
BMI, kg/m^2			
Waist-hip ratio			
10-year PCE Risk Score			
LV mass, gm			
LV mass/BSA (g/m^2)			
LV wall thickness (mm)			
LV ejection fraction (%)			
ECG with LVH – n (%)			
Hs-c-Tn-T ≥ 6 ng/l - n(%)			
NT-proBNP ≥ 100 pg/ml - n(%)			
CRP, mg/L			
CAC score			
Carotid IMT			
Family History CVD / Premature CVD			
Exercise variables, Fitness assessment			

Table 2. Baseline characteristics of all study participants stratified by presence of LVH, chronic myocardial injury (hs-cTnT ≥ 6), and neurohormonal activation (NT-proBNP ≥ 100).

Characteristics	**LVH (-) (N =)**	**LVH (+) hs-cTnT (-) and NT-proBNP (-) (N =)**	**LVH (+) hs-cTnT (+) and/or NT-proBNP (+) (N =)**	**P value**
Age – years				
Men – n (%)				
Race/Ethnicity **Black – n (%)** **White – n (%)**				
Hypertension – n (%)				
Systolic BP (mm Hg)				
Diastolic BP (mm Hg)				
Diabetes – n (%)				
Current Smoker – n (%)				
Estimated GFR ml/min/1.73 m^2				
Glucose, mmol/L				
Total chol, mg/dL				
LDL, mg/dL				
HDL, mg/dL				
Triglycerides, mg/dL				
Statin Prescription – n(%)				
BMI, kg/m^2				
Waist-hip ratio				
10-year PCE Risk Score				
LV mass, gm				
LV mass/BSA (g/m^2)				
LV wall thickness (mm)				
LV ejection fraction (%)				
ECG with LVH – n (%)				
Hs-c-Tn-T ≥ 6 ng/l - n(%)				
NT-proBNP ≥ 100 pg/ml - n(%)				
CRP, mg/L				
CAC score				
Carotid IMT				
Family History CVD / Premature CVD				
Exercise variables, Fitness assessment				

Table 3. Prevalence of baseline LVH, chronic myocardial injury (hs-cTnT ≥ 6), and neurohormonal activation (NT-proBNP ≥ 100) among men and women stratified by race/ethnicity.

	Men			**Women**		
	Black (N=)	**White (N=)**	**P value**	**Black (N=)**	**White (N=)**	**P value**
LVH (+) hs-cTnT (+) and/or NT-proBNP (+) ***n (%)***						
LVH (+) hs-cTnT (-) and NT-proBNP (-) ***n (%)***						
LVH (-) ***n (%)***						