ARIC Manuscript Proposal #3232

PC Reviewed: 9/11/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Heart Failure Risk Based on 2017 High Blood Pressure Guidelines and Implications of Serum Biomarkers: Pooled Analysis of the Dallas Heart Study, Atherosclerosis Risk in Community Study, Jackson Heart Study, and Multi-Ethnic Study of Atherosclerosis

b. Abbreviated Title (Length 26 characters): Risk with high BP and biomarkers

2. Writing Group: Ambarish Pandey, Kershaw Patel, Colby Ayers, Muthiah Vaduganathan, Jarett Berry, Michael Blaha, John W. McEvoy, Wanpen Vongpatanasin, Stephen Seliger, Adolfo Correa, Javed Butler, Daichi Shimbo, Paul Muntner, Robert Mentz, Vijay Nambi, Christie Ballantyne, Christopher DeFilippi, James De Lemos, Parag Joshi

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

First author:
Ambarish Pandey, MD
Address: 5323 Harry Hines Boulevard, Dallas, TX 75390
Phone: 617-869-8957
Fax: 214-645-2480
E-mail: ambarish.pandey@utsouthwestern.edu

Corresponding Author:
Parag Joshi, MD
Address: 5323 Harry Hines Boulevard, Dallas, TX 75390-8830
Phone: 214-645-2395
Fax: 214-645-2480
Email: parag.joshi@utsouthwestern.edu

ARIC authors 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).
Name: Vijay Nambi, MD; Christie Ballantyne, MD
Address: 6565 Fannin Street, Suite B157, Houston, Texas 77030
Phone: 713-798-5800
E-mail: vnambi@bcm.edu; cmb@bcm.edu

3. Timeline: 8/2018 – 08/2019

4. Rationale:

The 2017 ACC/AHA guidelines on high blood pressure have revised the definition of hypertension in the United States, and the decision to treat is based on both blood pressure level and cardiovascular risk (1). Individuals with stage 1 hypertension (BP 130-139/80-89) are recommended BP-lowering medication based on estimated 10-year ASCVD risk ≥ 10% (from ACC/AHA Pooled Cohort Equations), a strategy that has not been examined rigorously in a clinical trial and does not account for heart failure risk.

Hypertension is considered one of the most important modifiable risk factors for the development of heart failure (HF) (2,3). Additionally, most incident cardiovascular disease occurs in adults with blood pressure less than 140/90 mmHg in the US, suggesting a role for additional risk stratification in this population (4). Individuals with risk factors, like hypertension, develop intermediate cardiac phenotypes that can progress to HF (5,6). Several prior studies have demonstrated that individuals with chronic myocardial injury measured by high sensitivity troponin and hemodynamic stress measured by N-terminal pro-B-type natriuretic peptide have elevated risk of incident heart failure and cardiovascular death (5,7). In an analysis of asymptomatic individuals without cardiovascular disease in the Atherosclerosis Risk in Communities Study (ARIC), troponin T was associated with increased risk of heart failure among individuals categorized with normal and elevated systolic blood pressure level ranges (8). In a longitudinal, observational cohort study, higher B-type natriuretic peptide predicted increases in systolic and diastolic blood pressures as well as progression of BP stage (9).

In the Systolic Blood Pressure Intervention Trial (SPRINT), participants randomized to intensive treatment with a target SBP of less than 120 mmHg had lower incident heart failure events (HR 0.62; 95% CI 0.45-0.85) leading to lower target blood pressure level recommendations in HF (1,10,11). However, the evidence base for current recommended target of 130/80 is unclear and falls in between the prior treatment goal of 140/90 and the target BP levels achieved in the intensive treatment group in SPRINT. Taken together, we plan to evaluate atherosclerotic vascular disease and HF risk based on the 2017 ACC/AHA Adult High Blood Pressure Guidelines and assess whether chronic myocardial injury, based on high sensitivity cardiac troponin, and hemodynamic stress, based on B-type natriuretic peptide, modify risk assessment in individuals not prescribed BP-lowering medications.

References:

1. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2017.
2. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA 1996;275:1557-62.
3. Writing Committee M, Yancy CW, Jessup M 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:e240-327.
4. Tajeu GS, Booth JN, 3rd, Colantonio LD et al. Incident Cardiovascular Disease Among Adults With Blood Pressure <140/90 mm Hg. Circulation 2017;136:798-812.
5. Neeland IJ, Drazner MH, Berry JD et al. Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. J Am Coll Cardiol 2013;61:187-95.
6. Drazner MH. The progression of hypertensive heart disease. Circulation 2011;123:327-34.
7. Peters MN, Seliger SL, Christenson RH et al. "Malignant" Left Ventricular Hypertrophy Identifies Subjects at High Risk for Progression to Asymptomatic Left Ventricular Dysfunction, Heart Failure, and Death: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Heart Assoc 2018;7.
8. Pokharel Y, Sun W, de Lemos JA et al. High-sensitivity troponin T and cardiovascular events in systolic blood pressure categories: atherosclerosis risk in communities study. Hypertension 2015;65:78-84.
9. Fox ER, Musani SK, Singh P et al. Association of plasma B-type natriuretic peptide concentrations with longitudinal blood pressure tracking in African Americans: findings from the Jackson Heart Study. Hypertension 2013;61:48-54.
10. Group SR, Wright JT, Jr., Williamson JD et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373:2103-16.
11. Yancy CW, Jessup M, Bozkurt B et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136:e137-e161.

5. Main Hypothesis/Study Questions:

We hypothesize that biomarkers of chronic myocardial injury, such as high sensitivity cardiac troponin, and hemodynamic stress, such as B-type natriuretic peptide, will re-classify the risk of atherosclerotic vascular disease and heart failure associated with new BP-treatment thresholds recommended in the current guidelines. Thus, presence of elevated high sensitivity troponin and B-type natriuretic peptide levels will identify individuals at high risk for adverse cardiovascular events, particularly heart failure, among participants with elevated blood pressure or stage I hypertension who do not qualify for BP-lowering medication based on current 2017 ACC/AHA recommendations. Furthermore, among participants with stage I hypertension who qualify for pharmacotherapy based on current BP guidelines, normal high sensitivity troponin and B-type natriuretic peptide levels will identify low risk individuals who may receive only a small benefit from BP-lowering medication.

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:
Prospective cohort study

Inclusion criteria:
Participants of DHS, MESA, ARIC and JHS without prevalent CVD or HF and who are not taking BP-lowering medications with available high sensitivity cardiac troponin and B-type natriuretic peptide levels at baseline.

Exclusion criteria:
Participants with missing information on CVD status, clinic blood pressure, troponin levels, B-type natriuretic peptide levels, or pooled cohort equation variables. Participants with established CVD (or PAD or HF) at baseline. Participants taking BP-lowering medications.

Outcomes:

Primary outcome of interest:

- Composite of incident HF or CV death

Secondary outcomes of interest:

- Incident HF
- Incident CV death
- Incident ASCVD (as defined in the ACC/AHA pooled cohort equation)
- Composite of incident ASCVD and incident HF

Data analysis:
Covariates of Interest:
Age, sex, ethnicity, body mass index, baseline clinic systolic and diastolic blood pressure, history of hypertension, diabetes, family history of CAD, smoking, socioeconomic status, education level, alcohol use, troponin levels, B-type natriuretic levels, estimated glomerular filtration rate

Defining abnormal elevation in biomarkers of Interest:
Dallas Heart Study and the Multi-Ethnic Study of Atherosclerosis measure high sensitivity cardiac troponin T; Jackson Heart Study measures high sensitivity cardiac troponin I, and elevated levels are $\geq$ 6 ng/L, and ARIC study has both high sensitivity cardiac troponin T and I levels assessed. Owing to differences in the platforms used from high sensitivity cardiac troponin assessment, we will use multiple approaches to define normal vs. abnormal troponin levels. First, we will use previously defined cohort-specific cut-offs for troponin elevation: > 3 for high sensitivity troponin T in MESA and DHS, > 5 ng/L for high sensitivity Troponin T in ARIC, and > 6 ng/L for high sensitivity troponin I in JHS. Second, the previously described approach of natural log transformation and direct standardization will be be used for lab values from each cohort (center mean = 0, each unit change = 1 standard deviation) to account for cohort-specific and inter-assay factors (12). Using this approach, a Z-score above the 90^{th} percentile in the overall pooled cohort will be defined as abnormal elevation in high-sensitivity cardiac troponin. Sensitivity analysis will also be conducted using sex-specific cut-offs (90^{th} percentile for men and women). Third, separate pooled analysis will also be performed for cohorts with available high sensitivity cardiac troponin T levels (ARIC, MESA, and DHS) and high sensitivity cardiac troponin I levels (ARIC and JHS).

For NT-ProBNP levels, we will use similar approaches (previously described categorical cut-off of 100 pg/ml and standardized Z-score cut off of 90th percentile) to define abnormal elevation in NT-ProBNP levels.

Brief analysis plan and methods:

- Our study is focused on determining how available biomarkers of chronic myocardial injury and hemodynamic stress can inform us about risk of HF and other adverse cardiovascular events among individuals with elevated blood pressure or hypertension based on the 2017 High Blood Pressure Guidelines. Accordingly, study participants (participants of DHS, JHS, and MESA without history of CVD) will be categorized into 4 groups:

    1. Participants without hypertension (mean clinic BP < 120/80 mmHg) who do not qualify for BP-lowering medication
    2. Participants with elevated blood pressure (mean clinic BP 120-129/<80 mmHg) or stage 1 hypertension (mean clinic BP 130-139/80-89 mmHg) who do not qualify for BP-lowering medication
    3. Participants with stage 1 hypertension (mean BP 130-139/80-89 mmHg) who qualify for BP-lowering medication
    4. Participants with stage 2 hypertension (mean clinic BP ≥140/90 mmHg) who qualify for BP-lowering medication

- The cumulative incidence of clinical outcome events of interest will be assessed and compared across the 4 groups
- Participants in the elevated blood pressure or stage 1 hypertension group who do not qualify for BP-lowering medication and in the stage 1 hypertension group who do quality for BP-lowering medication (groups 2, 3) will be further sub-classified based on presence of chronic myocardial injury (+high sensitivity troponin) and/or hemodynamic stress (+B-type natriuretic peptide) and the incidence of clinical outcome events will be compared across the groups, first stratified by high sensitivity troponin only, then B-type natriuretic peptide only, and then both together. For these groups, the cumulative incidence rate for adverse clinical events in the group 1 and group 4 will be considered as reference to identify lower and upper cutoffs of risk for considering BP management among group 2 and 3 participants.
- Multivariable adjusted Cox models will be constructed to evaluate the association of the BP based groups with group 1 as reference. Separate models will be constructed using the 4-group (as recommended by current ACC/AHA guidelines) and biomarker-based approach (including further stratification of elevated BP and stage 1 hypertension groups by presence of chronic myocardial injury and hemodynamic stress: first stratified by high sensitivity troponin only, then B-type natriuretic peptide only, and then both together) with adjustment for relevant confounders as described previously.
- Sensitivity analysis will be conducted using alternative approaches to define elevation in high sensitivity cardiac troponin levels and NT-ProBNP levels as discussed above.
- Sensitivity analysis will also be conducted to assess the association of continuous measure of high sensitivity troponin, NT-ProBNP (standardized Z-scores) and risk of

adverse outcomes among participants with elevated blood pressure or stage1 hypertension.

- Sensitivity analysis will also be conducted within each cohort separately and pooling cohort-specific hazard ratios using random effect modeling.
- Sensitivity analysis will also be conducted to assess the effect of statins on 10-year ASCVD risk by the following: 1) exclusion of individuals on statins and 2) estimated 10-year ASCVD risk prior to initiating statin therapy based on statin intensity and expected cholesterol levels.
- Sensitivity analysis will also be conducted to assess the effect of initiation of BP-lowering therapy on follow up by excluding individuals started on BP-lowering medications.
- Race stratified analysis (black vs. non-black; black Hispanic vs. non-black Hispanic; white Hispanic vs. non-white Hispanic) will also be conducted as sensitivity analysis.
- Gender stratified analysis (females vs. males) will also be conducted as sensitivity analysis.
- Age stratified analysis by decade of life will also be conducted as sensitivity analysis.

References:

12. de Boer RA, Nayor M, deFilippi CR et al. Association of Cardiovascular Biomarkers With Incident Heart Failure With Preserved and Reduced Ejection Fraction. JAMA Cardiol 2018.

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/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)?

1) Pokharel Y, Sun W, de Lemos JA et al. High-sensitivity troponin T and cardiovascular events in systolic blood pressure categories: atherosclerosis risk in communities study. Hypertension 2015;65:78-84.

2) Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. 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;123:1367-1376.

We are including Dr. Nambi and Dr. Ballantyne in our present project.

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*_Carotid MRI 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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __x__ No.