

**ARIC Manuscript Proposal # 3020**

**PC Reviewed:** 7/11/17  
**SC Reviewed:** \_\_\_\_\_

**Status:** \_\_\_\_\_  
**Status:** \_\_\_\_\_

**Priority:** 2  
**Priority:** \_\_\_\_\_

**1.a. Full Title:**

Troponin, NTproBNP, galectin and Cardiovascular events across systolic and diastolic blood pressure categories

**b. Abbreviated Title (Length 26 characters):**

NTproBNP, galectin, BP categories and CVD

**2. Writing Group:**

Writing group members:

Vijay Nambi MD,PhD, Wensheng Sun, PhD, Anita Deswal MD MPH, James DeLemos MD, John W. McEvoy MB, BCh MHS, Ron C Hoogeveen PhD, David Aguilar MD, Salim S Virani MD PhD,Amil M. Shah MD MPH, Elizabeth Selvin PhD, Chiadi Ndumule MD, Aaron Folsom MD, Christie M. Ballantyne, MD

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

The analysis will start immediately after approval with a plan to publish after analysis is complete (~1 year)

**4. Rationale:** We have shown in previous analyses that troponin T (tnt) measured with a higher sensitivity assay is strongly associated with the future risk of cardiovascular diseases (CVD) (coronary heart disease, stroke and heart failure) and improves the prediction of these CVD (Saunders J, Circulation 2011 Apr 5;123(13):1367-76). Additionally, we have shown that when participants in the ARIC study were grouped/categorized by systolic blood pressure (SBP) and diastolic blood pressure (DBP), it was those individuals with elevated tnt that had increased risk for incident events including heart failure hospitalization (HF) (Pokharel Y, Hypertension 2015 Jan;65(1):78-84, McEvoy J J Am Coll Cardiol. 2016 Oct 18;68(16):1713-1722). In fact, individuals with SBP that were not well controlled (example 150-159 mmHg) but had undetectable tnt had better outcomes than those with SBP that was well controlled but with detectable/elevated tnt. With DBP, a J/U shaped relationship emerged with those having a low DBP (<60 mmHG) and those having DBP >90 mmHg having an increased myocardial injury as evidenced by tnt levels.

In some ways, one can postulate that cTnT identifies and documents the cumulative adverse CV consequence of hypertension better than single SBP or DBP measurements which have been well noted to vary over time and in response to treatment.

We wish to extend this assessment by studying other biomarkers associated with HF including troponin I (tni) measured with a high sensitivity assay, NT-pro B type Natriuretic Peptide (NT-proBNP) and galectin individually. Biomarkers will be assessed individually and together with tnt/tni

### **5. Main Hypothesis/Study Questions:**

- a. Troponin I identifies individuals at higher CVD risk across BP categories
- b. NTproBNP identifies individuals at higher CVD risk across BP categories
- c. Galectin identifies individuals at higher CVD risk across BP categories

- d. Biomarkers (NTproBNP, galectin and tni) identify individuals at highest CVD risk across BP categories

Questions

- a. Are NTproBNP/galectin/troponin I levels associated with incident CVD across SBP, DBP and pulse pressure categories?
- b. Do NTproBNP/galectin/troponin I levels have a stronger association with incident CVD compared with SBP/DBP/pulse pressure categories?
- c. Can a biomarker score identify the higher and lower risk individuals across SBP, DBP and pulse pressure categories

**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:**

ARIC visit 4 will serve as the baseline for this analysis.

**Inclusion/Exclusion:**

From the individuals participating in ARIC visit 4 we will exclude individuals

- missing information on biomarkers of interest (galectin, NTproBNP, tni and tnt). Note individuals will be excluded only for the pertaining analysis (example missing galectin will be excluded only for the galectin analysis and so on)
- missing SBP/ DBP values
- missing information on traditional CHD risk factors (TRF) including blood pressure information (including use of medications), tobacco use, lipid information (total cholesterol, HDL-c) and diabetes information for the CVD analysis and additional factors used in the stroke, HF and atrial fibrillation (afib) prediction score for the stroke, HF and afib analysis respectively
- races other than black or white, and black participants from the Minnesota or Washington field center.
- Individuals with prevalent CHD, stroke or HF

**Outcome:**

The outcome of interest will include incident CHD (definite or probable MI, CHD death or revascularization), ischemic stroke, HF hospitalization, atrial fibrillation For the combined analysis CHD+ischemic stroke +HF+Afib will be the outcome of interest.

**Summary of Data Analysis:**

Sex stratified analyses will be performed. Systolic blood pressure (mean of second/third measurement) will be categorized as <120, 120-129, 130-139, 140-149, 150-159 and  $\geq$  160 mmHg. If adequate numbers (especially when events are considered) are not available in some of the bins they may be combined. Diastolic blood pressure will similarly be categorized into <70, 70-79, 80-89, 90-99 and  $\geq$  100 mmHg. Finally pulse pressure categories will be described as well (<30, 30-39, 40-49, 50-59 and  $\geq$  60 mmHg).

Distribution of the biomarkers in these various blood pressure categories will be described with and without stratification by anti-hypertensive medication use and CVD status. Linear splines will be used to further evaluate the relationship of the blood pressure categories with the biomarkers. Biomarkers will be categorized by tertiles or quartiles and used for the analyses.

Using Cox-proportional hazards models, the association between the biomarkers and adverse cardiovascular events (defined as myocardial infarction (definite or probable), death from coronary heart disease, revascularization), stroke (all types), heart failure hospitalization, afib and death from cardiovascular causes) will be reported initially using minimally adjusted models (age/ race/ center in gender specific models) and then after adjustment for other variables such as anti-hypertensive medication use, kidney function (eGFR), diabetes, fasting glucose, total/HDL cholesterol, BMI, cigarette and smoking for the various blood pressure groups/ categories.

Stratified analysis will be pursued by anti-hypertensive medication use status.

Additional analysis will be pursued modeling blood pressure as a continuous variable adjusting for anti-hypertensive medication use.

We will then examine and compare individuals (with respect to clinical outcomes) with clinically controlled BP values (example SBP 120-139 mmHG, DBP70-90 mmHg) who have biomarker levels in the highest tertile/quartile with clinically poorly controlled BP (example 150-159 mmHg) who have biomarkers in the lowest tertile/quartile.

Finally, we will develop a composite biomarker score. The score will be developed by first evaluating the results of the individual biomarkers and for those strongly associated with events we will identify subjects with at least 2 biomarkers in the highest tertile and similarly identify individuals with all biomarkers in the lowest tertile and compares across various SBP, DBP and pulse pressure categories as above.

**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.csc.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)?

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

\_\_\_ 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 <http://www.csc.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](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](mailto:pingping_wu@unc.edu). I will be using CMS data in my manuscript \_\_\_\_ Yes  No.