1.a. Full Title: Cardiac Biomarkers and Risk of Hypertension in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Cardiac biomarkers and hypertension

2. Writing Group:
   Writing group members: Julie K. Bower, Jonathan Rubin, Mariana Lazo, Kunihiro Matsushita; Ron Hoogeveen; Christie Ballantyne; Elizabeth Selvin, others welcome.

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

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3. Timeline: We aim to complete this manuscript within one year of approval.

4. Rationale:
Less than 20% of hypertension cases occur in isolation; a majority of individuals with new diagnoses present with other cardiovascular risk factors such as diabetes that may result in myocardial damage. Changes in cardiac structure—often a consequence of increased pressure on the blood vessels and sometimes present even in normotensive individuals—may occur prior to and accelerate the development of hypertension.

Various measures of subclinical cardiovascular disease have been previously shown to be associated with incident hypertension. For example, population-based studies have documented a positive association between carotid intima-media thickness and incident hypertension. Additionally, coronary artery calcification has been cross-sectionally associated with blood pressure and prospectively associated with incident hypertension.

Newly developed tests detect subclinical myocardial damage in asymptomatic individuals by measuring minute elevations in circulating concentrations of troponin in the blood. Indeed, a recently developed highly sensitive assay for cardiac troponin T (hs-cTnT) can detect approximately ten-fold lower concentrations than the previous generation assays. Troponin T measured with this new, ultra-high sensitivity assay has utility in acute settings for ruling out myocardial infarction but also improves the prediction of cardiovascular disease and mortality in asymptomatic individuals. In the ARIC cohort, 66% of participants without a history of coronary heart disease at the fourth visit (1996-1998) demonstrated detectable levels of hs-cTnT; 7% had elevated levels (≥14 ng/L). The presence of detectable troponin below the clinical threshold is predictive of future risk for cardiovascular events and death. Subtle elevations of hs-cTnT among normotensive individuals may be an indicator of very early vascular damage and a marker of subsequent risk of hypertension.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a second commonly used cardiac biomarker indicative of ventricular overload and cardiovascular disease risk. Often used to detect, diagnose, and evaluate the severity of heart failure, NT-proBNP is tied closely with left ventricular mass and is associated with cardiovascular mortality. NT-proBNP exhibits direct effects on blood vessels (vasodilatation) and diuresis and thus hypothetically could lead to decreased blood pressure. However, it has been recently demonstrated that NT-proBNP promotes the release of norepinephrine that may counteract the overall hemodynamic effects of NT-proBNP.

Previous studies have found cross-sectional associations of elevated hs-cTnT and NT-pro-BNP with hypertension. In the ARIC study, hs-cTnT and NT-proBNP were measured at Visit 4 (1996-1998) and information about new diagnoses of hypertension are ascertained prospectively during the post-visit 4 annual telephone calls to all participants. This allows for an investigation of hs-cTnT, NT-proBNP, and risk of self-reported incident hypertension (report of physician diagnosis or medication use) in a community-based general population.

5. Main Hypothesis/Study Questions:
The aim of this study is to evaluate the associations of hs-cTnT and NT-proBNP, two markers of subclinical myocardial damage, with incident hypertension.

**Hypothesis 1:** Baseline hs-cTnT levels will be positively associated with incident hypertension in the ARIC cohort.

**Hypothesis 2:** Baseline NT-proBNP levels will be positively associated with incident hypertension in the ARIC cohort.

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.** A prospective study design will be used to evaluate the association of hs-cTnT and NT-proBNP with incident hypertension. Because hs-cTnT and NT-proBNP were measured at Visit 4, this examination will serve as the baseline for all analyses.

**Inclusion/Exclusion Criteria.** We will exclude participants with prevalent hypertension at baseline; individuals with prevalent CHD, prevalent congestive heart failure, and history of stroke; and those with missing data for variables of interest.

**Outcome.** Incident hypertension will be defined using information collected during the annual follow-up (AFU) telephone calls occurring after the date of ARIC Visit 4. Hypertension cases will be defined as the first positive response to one or both of the following questions:

1) “Since we last contacted you has a doctor said you had high blood pressure?” (through AFU form version H) or “Has a doctor ever said you had high blood pressure?” (AFU form version I and later)

2) “Did you take any medications during the past two weeks for high blood pressure?”

**Covariates of Interest.** Adjustment variables (at visit 4 unless stated otherwise) will include age, sex, race/center, educational attainment (visit 1), body mass index (BMI), waist circumference, smoking status, alcohol use, Baecke physical activity score (visit 3), lipids, diabetes status, estimated glomerular filtration rate (eGFR, using the CKD-Epi equation), systolic blood pressure, and diastolic blood pressure.

**Potential Effect Modifiers.** We will formally test for effect modification by age, sex, and race/ethnicity.

**Data Analysis.** Cox proportional hazards models will be used to quantify the associations of hs-cTnT and NT-proBNP with incident hypertension after adjustment for potentially confounding factors. The primary measures of association that will be reported will be hazard ratios and 95% confidence intervals, adjusted for potential confounding variables listed above. Participants that develop incident coronary heart disease, congestive heart
failure, or stroke will be censored in the main analysis. We will conduct sensitivity analyses excluding individuals with diabetes or eGFR < 60 mL/min/1.73 m².

To address the concern that the association of the cardiac biomarkers with incident hypertension might be influenced by baseline blood pressure, we will conduct sensitivity analyses stratifying by measured blood pressure level at baseline (normotensive, prehypertensive, and undiagnosed hypertension), excluding those with undiagnosed hypertension at baseline, and adjusting for baseline blood pressure. Additionally, we will conduct a sensitivity analysis using the CAMRI subsample, for whom blood pressure was measured in 2005-2006. For this group, we will evaluate the following: (1) the effect of including undiagnosed hypertension the outcome definition, and (2) the association of cardiac biomarkers with change in blood pressure from visit 4 (stratifying by hypertension treatment status as well as excluding those on blood pressure lowering medication).

Limitations. Only single measures of hs-cTnT and NT-proBNP are currently available for analysis and therefore we cannot examine the impact of changes in levels over time. Additionally, there are currently no established clinical cut points for the interpretation of detectable levels below diagnostic cut points. Therefore, we will consider our exposures modeled several ways (continuous, detectable versus undetectable, and categorical based on the distribution of values within the ARIC cohort).

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 ICTDER03 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)?

MP1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study

MP 1759: Associations of traditional cardiovascular risk factors and high-sensitivity cardiac troponin T

MP1846: Subclinical cardiac damage explains the changing association between blood pressure and coronary heart disease events with age

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* ARIC Ancillary Study #2008.10, “Measurement of NT-pro-BNP and troponin T at visit 4 for the full ARIC cohort”)

___   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


