1. Full Title:
The association of cardiac troponin T measured by a highly sensitive assay and arterial stiffness

b. Abbreviated Title (Length 26 characters):
hs-cTnT and arterial stiffness

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. SPW [please confirm with your initials electronically or in writing]

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3. Timeline:
Data to be used in this proposal will be available within the next few months. Analyses and manuscript preparation will be performed over the next six months.

4. Rationale:
Increased arterial stiffness has been suggested as an early marker of adverse vascular structural changes and is linked to aging and other cardiovascular risk factors for atherosclerosis. It is associated with an increased pulse pressure and the elevation in
systolic blood pressure can lead to cardiac myocyte hypertrophy, while the decrease in diastolic blood pressure can result in decreased coronary artery perfusion.\textsuperscript{2, 3} Changes in vascular stiffness are also associated with a delay in cardiac relaxation and stiffening of the left ventricle.\textsuperscript{4} Moreover, individuals with stiffer arteries have been demonstrated to be at an increased risk for the development of heart failure, myocardial infarction, stroke, and cardiovascular mortality.\textsuperscript{5-7} Therefore, there is reason to believe that the adverse cardiovascular outcomes associated with arterial stiffness may be related to subclinical myocardial damage.

Cardiac troponin is a highly specific marker of myocardial damage and a key component in the diagnosis of myocardial infarction.\textsuperscript{8} A recently developed highly sensitive cardiac troponin assay (hs-cTnT) can detect cardiac troponin at levels approximately 10 times lower than traditional assays and in the general population an elevated level of hs-cTnT is associated with an increased risk of incident cardiovascular disease.\textsuperscript{9, 10} Hs-cTnT has also been associated with transient myocardial ischemia and has been suggested as a marker of subclinical myocardial injury.\textsuperscript{11, 12}

A cross sectional study Bai et al investigated the relationship of arterial stiffness as measured by pulse wave velocity and hs-cTnT in 1,479 Chinese participants. They found a significant association between central, but not peripheral, stiffness. In addition, when they stratified by age (<60, ≥60) the results were significant only for older participants. However, all of the participants resided within Beijng, 55% had a detectable hs-cTnT (compared to about 67% at ARIC Visit 4), and the median age was 62. This cross sectional study was also unable to examine change in hs-cTnT.

At ARIC Visit 2 arterial stiffness was measured using a B-mode ultrasound of the carotid artery and calculated using Peterson’s Elastic Modulus and Young’s Elastic Modulus in approximately 13,400 participants, which will allow for the comparison between different measurements of arterial stiffness at the same site. Hs-cTnT was measured at Visit 2 and Visit 4. Therefore, we propose to examine the association between arterial stiffness as measured by B-mode ultrasound at Visit 2 and the change in hs-cTnT between Visits 2 and 4.

5. Main Hypothesis/Study Questions:

Hypothesis:

1) Arterial stiffness will be associated with the change in hs-cTnT levels, both 1) progression of hs-cTnT among those with a detectable level at Visit 2 and 2) the incident development of a detectable hs-cTnT at Visit 4

2) This association will be present among both measurements of arterial stiffness (Young’s Elastic Modulus and Peterson’s Elastic Modulus).

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 analysis of the change in hs-cTnT: 1) progression of hs-cTnT in those with a detectable level at Visit 2 and 2) incident development of detectable hs-cTnT.

Inclusion criteria:
- Participants who have measurements of arterial stiffness at Visit 2 and hs-cTnT at Visits 2 and 4.

Exclusion criteria:
- Participants without a Visit 2 measurement of arterial stiffness, without hs-cTnT at Visit 2 or 4, who are missing important covariates, participants with known coronary artery disease (history, EKG evidence of angina or myocardial infarction), persons whose race was reported to be other than white or black, and blacks in the Minneapolis and Washington County cohorts.

- Sensitivity analyses will include analyses excluding participants with heart failure and an eGFR <60

Main Variables:
- Change in hs-cTnT, continuous and categorical
- Measures of arterial stiffness (Young’s Elastic Modulus and Peterson’s Elastic Modulus) will be divided into quartiles and modeled continuously.

Co-variates:
- Age, sex, race, cholesterol levels (total, LDL, HDL), blood pressure (Visit 2 measurement and at the time of carotid examination), pulse pressure, heart rate, hypertension, hypertension medication use, heart rate, body mass index (height, weight), eGFR, smoking (current, former, never)

Analysis plan and methods:
Aim 1 - Statistical analyses: We will conduct analyses of the association between carotid stiffness at Visit 2 and 6-year change in hs-cTnT (from visit 2 to visit 4) using linear and logistic regression models. Among persons with no detectable levels of hs-cTnT at visit 2, we will examine the association with carotid stiffness for incident detectable hs-cTnT at visit 4 (binary variable). We will consider the following core models:

- Adjusted for age, gender, and race-center
- Adjusted for above + BMI, SBP, DBP, anti-hypertensive use, heart rate, pulse pressure, smoking, LDL-C, HDL-C, triglycerides, lipid-lowering use, hs-CRP, and family history of CHD

Aim 2 - We will categorize individuals as having undetectable and detectable levels of hs-cTnT at visit 2 and visit 4. Among persons with detectable levels of hs-cTnT, we split the population into approximate thirds as per previous analyses of hs-cTnT in ARIC. We will characterize change across these categories (i.e., movement from undetectable at
visit 2 to detectable at visit 4 and, among persons with detectable levels of hs-cTnT at visit 2, movement across thirds of hs-cTnT from visit 2 to visit 4).

We will conduct analyses with and without adjustment for baseline (visit 2) levels. In secondary analyses we will conduct analyses of past change— to answer the question of whether past levels and changes from visit 2 to visit 4 add prognostic value to current (visit 4) levels.\(^\text{13}\) It is possible that adjustment for baseline (visit 2) hs-cTnT levels may be biased due to regression to the mean. In contrast, adjustment for follow-up (visit 4) hs-cTnT may also be problematic since adjustment for baseline in the presence of measurement error can inflate regression the coefficients\(^\text{14}\). Thus, we will also look at percent change without adjustment for hs-cTnT at either visit.

For comparability to previous epidemiologic studies with serial measurements of hs-cTnT, we will compare the risk of being in the most stiff carotid artery quintile between persons with and without detectable hs-cTnT levels at follow-up before and after adjustment for confounding factors. Among participants with detectable hs-cTnT at visit 2, we will categorize the population by categories of relative change in hs-cTnT level, i.e. greater than 50% increase, greater than 50% decrease, and change of 50% or less (reference group). We will compare risk of being in the most stiff carotid artery quintile across these categories. The 50% change cut-point was previously used in an analysis of hs-cTnT and cardiovascular events and death in the Cardiovascular Health Study\(^\text{15}\). Due to limitations of the above—described (but previously used) approach we will also conduct analyses with three categories at each visit (undetectable, detectable, elevated). We will cross-classify these categories at the two visits to create a 3x3 grid (9 groups) and compare risk across these groups. If there is sufficient sample size (precision within cells), we will also examine tertiles within the detectable groups at visit 2 and visit 4 and generate a 4x4 grid (undetectable, detectable tertile 1, detectable tertile 2, detectable tertile 3) and compare risk across these 16 groups.

To characterize the continuous associations, we will generate piece-wise linear splines with knots corresponding to the cutoffs for the quartiles and we will also implement restricted cubic splines to obtain a smoother fit to the data.

**Sensitivity analyses:**

We will conduct analyses of the association between carotid stiffness at Visit 2 and 6-year change in hs-cTnT (from visit 2 to visit 4) using linear and logistic regression models stratified by:

- age (<65, ≥65)
- gender
- race
- hypertension
- diabetes
- smoking
- CHF
- eGRR <60
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.c.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)?

MP# 1811 Association of high sensitive Troponin T (hs-cTnT),N-terminal pro-brain natriuretic peptide (NT-proBNP) and high sensitivity C-reactive protein (hs-CRP) with cause-specific mortality: ARIC study

MP#1758 Chronic Hyperglycemia and Arterial Stiffness: the Atherosclerosis Risk in the Communities Study

MP# 1734 Biomarker, anthropometric parameters associated with highly sensitive cardiac troponin T

MP# 1563: Novel highly sensitive cardiac Troponin-T (hs-cTnT) assay, mortality, and major adverse cardiovascular events in the ARIC Study

MP#3C Hypertension and arterial stiffness: The Atherosclerosis Risk in Communities Study
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*  _2009.16 and 2008.10)_

   ___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.cscc.unc.edu/aric/forms/

12. 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.

References


