1.a. **Full Title**: Associations of Prior Stroke and Traumatic Brain Injury with Subclinical Myocardial Damage

b. **Abbreviated Title (Length 26 characters)**: Stroke, TBI, and Troponin

2. **Writing Group**:

   Writing group members:

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Others Welcome

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

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3. **Timeline:**
Visits 4 and 5 data are currently available; visit 6 data collection is underway. We will perform analyses within 6-12 months of manuscript proposal approval with a goal to submit an abstract to a conference within this time period. We anticipate submitting the manuscript for publication within 1-2 years of manuscript proposal approval.

4. **Rationale:**
Processes that cause brain injury, such as stroke and traumatic brain injury, have been associated with elevated troponin levels in the acute setting\(^1\)\(^-\)\(^8\). Several studies have hypothesized that elevated troponin is seen in the acute stroke setting, for example, as a result of sympathoadrenal activation secondary to cerebral stress, particularly in the insular cortex (which is the origin of autonomic control; right side: parasympathetic and left side: sympathetic)\(^9\). However, many studies acknowledge that troponinemia is more likely in acute stroke patients in the setting of QTc-prolongation and a hypertrophic myocardium\(^10\),\(^11\). There is evidence from animal studies showing that sympathoadrenal activation is associated with insular cortex damage leading to a loss of central inhibitory control of sympathetic activity\(^12\),\(^13\). Beyond ischemic stroke, the concept of a “neurogenic stunned myocardium” as a result of sympathoadrenal activation has been well described following subarachnoid hemorrhage and is comprised of left ventricular dysfunction, electrocardiogram changes (QTc prolongation, ST-T wave changes), and elevations in cardiac enzymes (troponin) - all occurring as a result of catecholamine excess\(^9\). It reasons that any type of brain injury, whether subarachnoid hemorrhage, stroke, or traumatic brain injury, may be associated with subclinical myocardial damage via similar mechanisms in the acute setting.

However, the long-term effects on the myocardium in relationship to prior brain injuries is less clear. Prior studies have suggested that individuals with a history of stroke\(^14\) and traumatic brain injury\(^15\) may be at increased risk for subsequent incident cardiovascular disease. Most likely, stroke would be associated with subsequent incident cardiovascular disease via common atherosclerotic pathways, but it is possible that subsequent incident cardiovascular disease among those with a prior traumatic brain injury may be via non-atherosclerotic pathways (e.g., cardiac stunning). Additionally, in a recent analysis of Veteran Health Administration data, Ahmadi et al\(^15\) reported an increased risk of both subclinical (coronary artery calcification) and clinical cardiovascular disease among those with mild/moderate traumatic brain injury over a median of 4-years follow-up. It remains unknown if persons with prior brain injury, such as stroke or traumatic brain injury, are at increased risk for future subclinical myocardial damage (as assessed by elevated high-sensitivity cardiac troponin T (hs-cTnT)). The ARIC Study offers a unique opportunity to examine the relationship between prior stroke and traumatic brain injury with long-term subclinical myocardial damage, as assessed by hs-cTnT.

5. **Main Hypothesis/Study Questions:**
   - **Main Study Questions:**
     - Is a history of ischemic or hemorrhagic stroke associated with the presence of subclinical myocardial damage?
     - Is a history of traumatic brain injury associated with the presence of subclinical myocardial damage?
   - **Hypotheses:**
A history of ischemic and hemorrhagic stroke will be associated with higher baseline hs-cTnT levels and a greater incidence of elevated hs-cTnT over time.

A history of traumatic brain injury will be associated with higher baseline hs-cTnT levels and a greater incidence of elevated hs-cTnT over time.

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 using ARIC visit 4 (1996-1998), visit 5 (2011-2013), and ARIC visit 6 (2015-2017) data. Both baseline cross-sectional and prospective analyses will be performed.

Of note, we will investigate using either visit 4 or visit 5 as baseline – our decision of which visit to use as baseline will most likely be dependent on our assessment of study attrition (for example, if attrition is less of an issue between visits 5 and 6 than between visits 4 and 5, we may opt to present analyses looking only at visit 5 and 6 data in the final manuscript).

**Inclusion/Exclusion Criteria:**
The eligible population for our analyses will include all ARIC participants who attended the baseline visit for this analysis (ARIC visit 4 or 5). Participants will be excluded from our analyses for the following reasons: non-white or non-black race or black race in Minnesota or Maryland field centers, missing hs-cTnT at baseline, or missing covariates of interest.

**Exposures:**
- **Stroke:** Stroke events in ARIC are identified by self-report at study visits or during annual or semi-annual telephone calls or by active surveillance of hospitals within study communities (data available for 1987-2015). Hospital records for all possible stroke-related hospitalizations are obtained (International Classification of Diseases, Ninth Revision [ICD-9] codes 430-438 until 1997 and then 430-436 afterwards) and reviewed by physician adjudicators. Stroke events are classified as ischemic or hemorrhagic events.16,17

- **Traumatic Brain Injury:** Traumatic brain injury will be defined using a combination of self-reported questions and hospitalization/Centers for Medicare/Medicaid ICD-9 data.

Self-report questions have been shown to be reliable in assessing a history of remote traumatic brain injury.18 Self-report questions were asked to all participants at ARIC visit 3 (1993-1995) and visit 4 (1996-1998) and to a subset of participants selected for further cognitive testing and brain MRI at ARIC visit 5 (2011-2013). Self-report questions inquired about prior head injury requiring physician/hospital care, loss of consciousness, number of prior head injuries, and year of most recent head injury. Specifically, participants were asked the following questions:

  - At ARIC visit 3:
- **amha5**: Have you ever had a head injury which led you to see a physician or seek hospital care?
- **amha5a**: How many times has this happened?
- **amha5b**: How many of these head injuries resulted in your losing consciousness, no matter how briefly?
- **amha5c**: In what year was your last head injury for which you sought medical care?

  - At ARIC visit 4:
    - **hhxd10**: Have you ever had a major head injury? That is, one that resulted in your losing consciousness, no matter how briefly, or that led you to see a physician or seek hospital care?
    - **hhxd10a**: How many times has this happened?
    - **hhxd10b**: How many head injuries resulted in your losing consciousness, no matter how briefly?
    - **hhxd10c**: In what year was your last head injury for which you lost consciousness sought medical care?

  - At ARIC visit 5:
    - **nhx2**: Have you ever had a head injury that resulted in loss of consciousness?
    - **nhx2a**: Have you had a head injury with extended loss of consciousness (>5 minutes)?
    - **nhx2b**: Have you had a head injury that resulted in long-term problems or dysfunction?

Hospitalization surveillance data is available over the entire duration of the ARIC study (currently data available through the end of 2015) and Centers for Medicare/Medicaid surveillance data was available for participants aged ≥65 years between the years of 1991 and 2013. The following previously validated ICD-9 codes\textsuperscript{19,20} will be used to identify hospitalizations with traumatic brain injury:

- 800.xx (fracture of vault of skull)
- 801.xx (fracture of base of skull)
- 803.xx (other and unqualified skull fractures)
- 804.xx (multiple fractures involving skull or face with other bones)
- 850.xx (concussion)
- 851.xx (cerebral laceration and contusion)
- 852.xx (subarachnoid subdural and extradural hemorrhage following injury)
- 853.xx (other and unspecified intracranial hemorrhage following injury)
- 854.xx (intracranial injury of other and unspecified nature)
- 959.01 (head injury, unspecified).

**Outcome:**
- **High-Sensitivity Cardiac Troponin-T (hs-cTnT)**: Measurement of hs-cTnT occurred at visit 2 (1990-1992), visit 4 (1996-1998), visit 5 (2011-2013), and visit 6 (2015-2017). For purposes of this analysis, data from visits 4, 5, and 6 will be used. hs-cTnT ≥14 ng/L
represent the 90th percentile in the ARIC sample and the 99th percentile value for a “healthy” reference population of individuals aged 20 to 70 years (defined by the assay manufacturer)\textsuperscript{21}. However, there is growing evidence for the use of age-specific (and possibly sex-specific) cut-points to define elevations; this is particularly important in elderly populations where the use of a cut-point of 14 ng/L may over-diagnose myocardial damage\textsuperscript{22,23}. To this end, we will model hs-cTnT both continuously and using age and sex-specific cut-points (e.g., 99th percentile reference values for adults >65 years of age: >31ng/L for men and >17 ng/L for women)\textsuperscript{22,23}.

Visit 4 hs-cTnT was measured from stored plasma samples at Baylor College of Medicine in 2010 using an electrochemiluminescence immunoassay implemented on a Roche Cobas e411 analyzer. Intra-assay coefficients of variation (CVs) were 2.1\% at a mean hs-cTnT concentration of 29ng/L and 0.76\% at 2378ng/L. Inter-assay CVs were 6.9\% and 2.6\% at mean cTnT concentrations of 29 ng/L and 2378 ng/L. Visit 5 hs-cTnT was measured from stored plasma samples at Baylor College of Medicine in 2013 using an electrochemiluminescence immunoassay implemented on a Roche Cobas e411 analyzer. Intra-assay coefficients of variation (CVs) were 1.8\% at a mean hs-cTnT concentration of 29 ng/L and 1.9\% at 2227 ng/L. Inter-assay CVs were 6.4\% and 5.6\% at mean cTnT concentrations of 29 ng/L and 2227 ng/L. Visit 6 hs-cTnT measurements are currently underway.

**Covariates:**

All covariates will be assessed at baseline (visit 4 or visit 5), unless otherwise indicated. All models will be adjusted for the following covariates: age (continuous; years), sex (male; female), race/field center (suburbs of Minneapolis, Minnesota whites; Washington County, Maryland whites; Forsyth County, North Carolina whites; Forsyth County, North Carolina blacks; Jackson, Mississippi blacks), education (<high school; high school, GED, or vocational school; college, graduate, or professional school; assessed at visit 1), body-mass index (continuous; kg/m\textsuperscript{2}), cigarette smoking (never; former; current), hypertension (yes; no; defined as systolic blood pressure >140 mmHg, diastolic blood pressure > 90 mmHg, or medication use), diabetes (yes; no; defined as fasting glucose >126 mg/dL, non-fasting glucose >200 mg/dL, or medication use), estimated glomerular filtration rate (<60 mL/min/1.73m\textsuperscript{2}; ≥60 mL/min/1.73m\textsuperscript{2}), and history of atrial fibrillation.

**Statistical Analysis:**

Baseline characteristics (visit 4 or visit 5) of the study population will be stratified by stroke status (no history of stroke; ischemic stroke; hemorrhagic stroke [intraparenchymal hemorrhage and subarachoid hemorrhage]) and separately by traumatic brain injury status (no history of traumatic brain injury; yes history of traumatic brain injury) using means and proportions. Characteristics will be compared between groups using t-tests and chi-square tests.

Cross-sectional associations (baseline: visit 4 or visit 5) of stroke and traumatic brain injury with hs-cTnT will be evaluated using adjusted linear (outcome: continuous hs-cTnT) and logistic regression models (outcome: hs-cTnT ≥ age- and sex-specific 99\textsuperscript{th} percentile reference values).
Prospective associations of stroke and traumatic brain injury with change in hs-cTnT from either visit 4 to visit 5 or visit 5 to visit 6 (most likely will not do change from visit 4 to visit 6 due to significant attrition) will be evaluated using adjusted logistic regression models (outcome: incident elevated hs-cTnT ≥ age- and sex-specific 99th percentile reference values) among participants without prior elevation in hs-cTnT.

For all analyses, we will perform three sequential statistical models:
- Model 1: adjusted for demographic variables: age, sex, and race/field center.
- Model 2: adjusted for Model 1 + education, smoking status, and body-mass index.
- Model 3: adjusted for Models 1 and 2 + hypertension, diabetes, and estimated glomerular filtration rate

We will consider a mediation analysis by carotid intimal medial thickness (measure of subclinical atherosclerosis). In sensitivity analyses, we will evaluate for possible interaction by heart failure, coronary heart disease, prolonged QTc, and by left ventricular hypertrophy. We will perform stratified analyses and/or exclude those with heart failure and coronary heart disease from analyses. We will also investigate using a time-varying exposure for stroke and traumatic brain injury in our prospective associations as well as censoring interim cardiovascular disease events. In other sensitivity analyses we will also examine the impact of number of prior traumatic brain injuries and strokes and time from most recent traumatic brain injury and stroke on hs-cTnT concentrations. We will also consider methods to account for participant attrition (e.g., inverse probability of attrition weighting).

Limitations:
A limitation of this study is the use of self-reported and hospitalization ICD-9 codes to define head injury. However, the CDC has previously used defined head injury using ICD-9 codes\textsuperscript{19,20}. We do not have details regarding the type of injury that occurred or details on treatment received. Another limitation of this study is participant attrition – we will investigate attrition between visit 4 and visit 5 as well as between visit 5 and visit 6 and look into methods to account for attrition. Additionally, as with any observational study, we will not be able to rule out the possibility of residual confounding in our analyses.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ___ Yes  ___ No

\textbf{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  ___ No

\textbf{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

Yes X 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)?

- MSP 2769: The Association of Head Injury with Risk of Stroke, Cardiovascular Disease, and Mortality in the ARIC Study – Andrea Schneider
- MSP 2767: The Association of Head Injury with Brain MR and Brain PET Amyloid Imaging in the ARIC Study – Andrea Schneider
- MSP 2768: The Association of Head Injury and Cognition, Mild Cognitive Impairment, and Dementia in the ARIC Study – Andrea Schneider
- MSP 1856: Cardiac Troponin T Measured by Highly Sensitive Assay and MRI- Defined Small Vessel Disease of the Brain in the Atherosclerosis Risk in Community Study – Razvan Dadu
- MSP 1899: Troponin T, NT-proBNP and stroke incidence – Aaron Folsom
- MSP 2099: Utility of biomarker panel, hsTnT, NT-proBNP, and cystatin C to prediction of ischemic stroke, and mortality in AF patients: the ARIC Study – Sunil Agarwal
- MSP 2707: Hypoglycemia and Subclinical Myocardial Damage in Older Adults with Diabetes – Alexandra Lee

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* 2009.16, 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/

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.
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1448.

and Elevated High-Sensitivity Cardiac Troponin T in Older Adults With Diabetes: The