1. **Full Title:** Association of cardiac biomarkers (high-sensitivity cardiac troponin T, NT-proBNP, and galectin-3) with mild cognitive impairment, dementia, and findings on MRI in older adults

2. **Abbreviated Title (Length 26 characters):** cardiac markers and brain MRI at visit 5

3. **Timeline:** All data is currently available, we plan to submit for publication within 12 months of approval of the manuscript proposal.
4. Rationale:
The prevalence of dementia among persons aged 70 and above is estimated to be 14%, and another 22% are estimated to have cognitive impairment without dementia. Clinical cardiac diseases, including ischemic heart disease, coronary artery disease, and heart failure, are common in older adults and have been associated with the development of cognitive impairment and dementia. Identifying whether markers of early cardiac dysfunction are associated with cognitive function may improve the possibility for timely intervention; however, the association between subclinical cardiac disease in older adults and subclinical brain disease has been less studied. Risk factors for cardiovascular disease are similar to those of cerebrovascular disease, and the two are hypothesized to share pathogenic mechanisms. Therefore, our overarching aim is to examine markers of subclinical cardiac disease, including hs-cTnT, NT-proBNP, and galectin-3, with cognition, including 1) expert-committee defined MCI and dementia, including etiologic subtypes and 2) measures of subclinical cerebrovascular disease on brain MRI.

High-sensitivity cardiac troponin T (hs-cTnT) assays have recently been approved for clinical use in the diagnosis of myocardial infarction in the US (MI), and are considered a biomarker of chronic subclinical cardiac damage in the general population. Studies have shown that, in persons without overt cardiovascular disease, hs-cTnT improves prediction of cardiovascular disease and all-cause mortality in community-based populations. We have previously shown in ARIC that hs-cTnT measured in late middle-age (1996-1998, mean age 65 years) was associated with lower cognitive function in cross-sectional analyses, and with higher risk dementia (identified using ICD-9 codes on hospitalization) over a median follow-up of 13 years. Analyses in ARIC have also found associations between hs-cTnT and vascular findings on brain MRI, including brain infarcts, white matter lesions (WMLs), and progression of WMLs in a subset of participants who underwent a subsequent MRI exam.

NT-proBNP is also considered a biomarker of subclinical cardiac injury, representing ventricular wall stress. Prospective analyses in ARIC and other studies have found associations suggesting NT-proBNP may be useful in identifying subclinical small vessel disease in the brain. Finally, galectin-3 is another biomarker that has been implicated in the pathophysiology of heart failure and is associated with higher risk of cardiovascular mortality, independent of other risk factors, but we found only one study that examined associations with dementia.

At the fifth ARIC exam (2011-2013), participants underwent a comprehensive assessment of their cognitive function, including brain MRI and etiologic dementia diagnosis, and had three biomarkers (hs-cTnT, NT-proBNP, galectin-3) that can be used to assess subclinical cardiac function. Our aims are to characterize the association between cardiac markers and 1) MCI/dementia and etiologic diagnosis and 2) evidence of small vessel disease on brain MRI, including white matter hyperintensities, the presence of cortical and lacunar infarcts, and the presence of microhemorrhages, and 3) overall and regional brain volumes. Lastly, we will examine the prognostic performance of hs-cTnT in predicting short-term mortality in persons with MCI and dementia.
5. Main Study Questions:

Aim 1
To examine the association between cardiac biomarkers and measures of cerebrovascular disease including presence of cortical and lacunar infarcts, white matter hyperintensity volume, and the presence of microhemorrhages.

Aim 2
To examine the association between cardiac biomarkers and total and regional brain volumes.

Aim 3
To examine the association between cardiac biomarkers and expert-committee defined MCI and dementia, including etiologic subtypes.

Aim 4
To examine the association between cardiac biomarkers with 3-year mortality in persons with MCI and dementia.

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
- Aims 1-3: Cross-sectional using data from visit 5
- Aim 4: Prospective from visit 5 to the end of available data on death (expected through the end of 2015 or 2016)

Exclusions
We will exclude participants who meet any of the following criteria:
- Have prevalent cardiovascular disease at visit 5 (based on CHD, MI, stroke, HF) – in secondary analyses, we will examine associations separately by CVD status to potentially improve generalizability of our study results. These analyses will mirror those described below, but done stratified by CVD status
- Did not undergo MRI at visit 5 (or MRI of poor quality)
- Race other than black or white, and blacks from Minneapolis or Washington County field centers
- Have a history of multiple sclerosis, surgery or radiation to the skull or brain, or brain tumor
- Missing covariates (described below)
Exposures – hs-cTnT, NT-proBNP, galectin-3
- hs-cTnT will be examined continuously (linearly and using splines) and categorically using 1) sex-specific cut-points, 2) cut-points used previously in ARIC: <5 ng/L, 6-8 ng/L, 9-13 ng/L, and >14 ng/L, and 3) quartiles.
- NT-proBNP and galectin-3 will be examined continuously (linearly and using splines) and categorically using quartiles

We will examine associations among each exposure individually and will also examine their associations independently of each other (that is, will be included in models simultaneously).

Outcome – MCI/dementia and etiologic diagnosis
MCI and dementia will be defined using information from the full Visit 5 examination with expert committee diagnosis and information captured in annual follow-up (AFU) interviews and proxy report. Cognitive function was categorized as normal, mild cognitive impairment (MCI), or dementia. We will examine MCI/dementia etiology as 1) MCI/dementia without CVD (primary or secondary) and 2) MCI/dementia with CV (primary or secondary). In this analysis, persons with a primary or secondary diagnosis of “other” (non-AD or CVD), will be excluded due to small sample sizes.

Outcome – measures from brain MRI
MRI data at visit 5 including:
- Measures of subclinical cerebrovascular disease:
  o Number and presence of cortical and lacunar infarcts
  o Number and presence of microbleeds, divided into subcortical and lobar
  o White matter hyperintensity (WMH) volume
- Volumes:
  o Total brain volume
  o Regional brain volumes (temporal, parietal, occipital, and frontal)
  o Hippocampal
  o Alzheimer’s signature region (inferior parietal, hippocampus, precuneus, and cuneus)
  o Deep gray matter (thalamus, putamen, caudate, globus pallidus)

To allow comparisons across regions, volumes will be standardized to Z scores by subtracting the mean and dividing by the standard deviation for each volume (total and regional). Because of its skewed distribution, WMH volume will be first log transformed then standardized.

Outcome – death
For Aim 4, evaluating the prognostic performance of these markers among persons with cognitive impairments, we will use death after visit 5. We anticipate have data on mortality through 2015 or 2016.

Covariates
We will evaluate the following variables as covariates: age, sex, race-center, body mass index, education, hypertension, hypertension medication use, apoE genotype, smoking, alcohol use, diabetes, diabetes duration and medication use, physical activity, and atrial fibrillation. Intracranial volume will be used as a covariate in all analyses of brain volumes except for WMH.

**Statistical Analysis**
We will characterize our analytic population using means/standard deviations or percent for all covariates. For MCI and dementia and subtypes (Aim 1), we will use multinomial logistic regression (outcome: normal cognition, MCI, or dementia). For analyses of volumes (Aim 2), we will use linear regression with adjustment for covariates described above. For analyses of infarcts and microbleeds (Aim 3), we will use logistic regression, but we will also consider negative binomial and Poisson regression where the proportion with infarcts/microbleeds exceeds 10%.

To examine prognostic performance of the cardiac biomarkers in predicting mortality in persons with MCI and dementia (Aim 4), we will use Cox regression using visit 5 as baseline.

**Effect Modification**
We will examine possible effect modification by age, race, and sex.

**Sensitivity analyses**
- Persons who underwent MRI may be healthier than those who did not and compared to those who did not attend visit 5. We will consider the use of inverse probability weighting\(^\text{26}\) or other methods to account for selection bias (e.g. Heckman correction\(^\text{27}\)).
- Instead of adjusting for afib, we will examine the impact on associations of excluding these persons from analyses

**Challenges/Limitations**
- Single measurement of hs-cTnT, NT-proBNP, and galectin-3
- We may have limited power in some analyses
- Selection bias of who ends up with an MRI is of concern and may limit generalizability of our study
- We will not be able to rule out the possibility of residual confounding

**7.a. Will the data be used for non-CVD analysis in this manuscript?**
- Yes    _ 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_DÑA = “CVD Research” would be used?**
- x 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?  x_ Yes   ___ 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”?  __x__ 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.cscf.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 #1553: Associations between vascular risk factors and longitudinal changes in ventricular size: a 14-Year longitudinal study (Knopman)
MP #1771: Cognitive, Vascular Risk Factors, and APOE Genotype Predictors of Hippocampal Volume (Knopman)
MP #1899: Troponin T, NT-proBNP and stroke incidence (Folsom)
MP #2288: Associations of brain imaging with cognitive change over 20 years (Knopman)
MP #2002: Association of High-Sensitivity Cardiac Troponin T (hs-cTnT) with Cognitive Function: the Atherosclerosis Risk in Communities Study (Schneider/Rawlings)
MP #2227: Relationship of cardiac structure and function with cognitive performance: a study of the Atherosclerosis Risk in Communities (ARIC) study (Jhund)
MP #2315: Association of diabetes with brain magnetic resonance imaging (Schneider)
MP #2334: Troponin T and N-terminal pro-B-type Natriuretic Peptide and Cognitive Decline and Dementia in the ARIC study (Pokharel)
MP #2351: Association of blood pressure with neurodegenerative and cerebrovascular changes on brain MRI (Power)
MP #3018: Evaluation of novel circulating biomarkers in the prediction of adverse cardiovascular events including heart failure (Nambi)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  _x_ Yes   _____ No

ARIC NCS

11.b. If yes, is the proposal  

x   A. primarily the result of an ancillary study (list number* 2008.06)  

___ 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


