ARIC Manuscript Proposal # 1856

1.a. Full Title: Cardiac Troponin T Measured by Highly Sensitive Assay and MRI-Defined Small Vessel Disease of the Brain in the Atherosclerosis Risk in Community Study

   b. Abbreviated Title (Length 26 characters): **HS-Troponin and CVD in ARIC**

2.   Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. RTD

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3. Timeline: All brain MRI imaging on the ARIC Visit 3 cohort has been completed as well as the follow up MRI and data was submitted to the ARIC coordinating center. Analysis will start as soon as the manuscript proposal has been approved. We anticipate journal submission of the completed manuscript within 1 year after manuscript proposal approval.

4. Rationale:

Small vessel disease (SVD) of the brain is the third leading cause of death and the leading cause of severe long-term disability in the United States.(1) White matter lesions (WML) and brain infarcts (BI) are extremely common in the elderly.(2, 3, 4, 5) Most of these MRI-detectable abnormalities do not produce acute clinical symptoms, however they are associated with an increased risk for cognitive deficits motor function impairment, and future stroke.(6, 7, 8, 9). SVD of the brain is strongly associated with age, the presence of diabetes and hypertension which are also common risk factors for heart disease. Recently, it has been shown that chronically elevated cardiac troponin T (cTnT) measured with a highly sensitive assay is markers of end organ damage of the heart (10). The same patients who have end organ damage of the heart might have end organ damage in the brain expressed by the small vessel disease of the brain. In addition it is also possible that cardiac injury, measured by cTnT level, directly leads to cerebral injury which may manifest itself as WML or BI. In this study we will analyze the association of highly sensitive cTnT with the baseline volume of MRI-determined WML and with the 9 year volume change in the WML. We will also analyze the association of highly sensitive cTnT with the prevalent brain infarcts on the baseline and follow up MRI in the ARIC study.

Background:

BI and WML are the MRI markers of small vessel disease (SVD) of the brain and they contribute to the increased risk of stroke and vascular dementia in older adults (11, 12, 13, 14, 15). Aging, hypertension, diabetes mellitus, and cardiac diseases are common risk factors for SVD of the brain, with the most important one being the aging (16, 17).

The pathogenesis of SVD is thought to reflect ischemic damage resulting from arteriolosclerosis of the deep penetrating vessels of the white matter (18). Aging, chronic hypertension, and diabetes induce the same changes in small penetrating arteries and arterioles of the white matter. It is assumed that underlying generalized SVD is responsible for this association. This observation is supported by the observation that similar pathological changes (eg, hyaline arteriolosclerosis) are found in kidneys of patients with hypertensive nephropathy and in brains of patients with cerebral SVD (19) These changes include replacement of the smooth muscle cells by fibro-hyaline material with thickening of the wall and narrowing of the vascular lumen (arteriolosclerosis) (20) Arteriolosclerosis, almost always detected within areas of WML and LI, may be one of the reasons the blood supply to the white matter is altered, and this vascular alteration

may lead to either localized ischemic areas of necrosis and cavitations or diffuse rarefaction (21).

Multiple interactions exist between the various forms of cardiovascular and cerebrovascular diseases, and risk factors for the development of stroke and major cardiovascular events are similar. There are three potential reasons for an association between an elevated cardiac biomarker, such as cTnT, and stroke or SVD: 1) they both share risk factors, and are both markers of some system arteriosclerosis; 2) reduced cardiac function or cardiac injury (detected by elevation in cTnT) might lead to stroke (such as through embolization from an akinetic heart segment or in the setting of atrial fibrillation) or decreased blood flow to the brain (perhaps via reduced cardiac output, which could in turn cause stroke or perhaps white matter ischemia); or 3) stroke itself causing myocardial injury and an elevation in cTnT. Increases in cTnT have been reported in all types of stroke (ischemic, intracerebral hemorrhage, and subarachnoid hemorrhage) (22). In a recent meta-analysis of 15 studies including 2901 patients with acute stroke, the prevalence of elevated cTnT above a clinically significant cut point, varied from 0 to 35% most likely due to different exclusion criteria and different cTnT cut-offs and assays. In the meta-analyses made by Kerr et al., acute stroke patients with elevated troponin levels were more likely to have features suggestive of myocardial ischemia on the ECG and had a greater risk of death than those without a troponin rise. (23) Several studies have reported a strong positive correlation between the rise in cTnT and the severity of the stroke. (24, 25) In a recent study, patients with acute ischemic stroke and high cTnT did not have more perfusion abnormalities on myocardial perfusion scintigraphy when compared with acute stroke patients with normal cTnT (26)

Recently cTnT concentrations as measured with a highly sensitive assay were found to be significantly associated with the incidence of cardiovascular death and heart failure in patients with stable coronary artery disease (27) cTnT, measured with the novel highly sensitive assay, was also detectable in the majority of middle-aged individuals without prevalent cardiovascular disease. Small elevations were strongly associated with death, especially CHD death, and HF hospitalization and myocardial infarction (10). Since diabetes age and hypertension have adverse effects not only on the heart but on the brain and kidney as well, chronically elevated cTnT might be a marker not only for cardiac damage in these patients but also a marker for the brain end organ damage illustrated by the SVD. Up to date there is no study that investigated the association of cTnT measured by a highly sensitive assay and the MRI detected WML and brain infarcts in patients without acute stroke. If an association is found between cTnT and the progression of WML and prevalent BI at the follow up MRI, and this association is independent of carefully measured shared risk factors, this would support the idea that there might be some direct consequence of cardiac dysfunction or cardiac injury leading to brain changes.

5.   Main Hypothesis/Study Questions:

Hypothesis:

Elevated levels of cTnT measured with a highly sensitive assay at ARIC Visit 4 are associated with: the WML volume at the baseline MRI performed at ARIC Visit 3 and with 9 year change in the WML at the follow up MRI. Elevated levels of cTnT are associated with the prevalent BI at baseline and with the prevalent BI at the 9 year follow up MRI.

Study questions:

1. Are cTnT levels associated with the volume of MRI defined WML and prevalent BI at the baseline MRI visit?

2. Are cTnT levels associated with 9 year change in the volume of WML and with the prevalent BI at the follow up MRI?

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).

Overview: To test our hypotheses, we will utilize plasma samples collected at Visit 4 ARIC for the individuals who had a brain MRI performed on ARIC Visit 3.

Plasma levels of cTnT have been measured in the entire ARIC Visit 4 cohort. Brain MRI was performed in about 2000 patients at the ARIC visit 3 and most of them have a 9 year follow up brain MRI. The reproducibility of visual scoring of WMH is good, with inter- and intra-reader agreement within 1 grade of 92% and 94.5%, and relaxed kappas of 0.81 and 0.93, respectively (28). The mean absolute error and test-retest coefficient of variation for the volumetric method (2nd MRI exam) are 6.6% and 1.4%, respectively (29). We request access to the ARIC data analysis files, and their periodic updates, for cohort data collected by the ARIC study on risk factors and baseline and 9 year follow up head MRI results.

We are interested in the following variables in the ARIC database measured at ARIC visit 3: age, gender, race, body mass index, smoking status, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, troponins, hs-CRP, NT-proBNP, creatinine, estimated glomerular filtration rate, the presence of left ventricular hypertrophy (calculated by ECG with the Cornell criteria), systolic blood pressure, presence of diabetes (fasting blood sugar ≥ 126 mg/dl or use of diabetes medication), use of antihypertensive medications, use of diabetes medications, use of aspirin, incident cases of coronary heart disease (CHD) events (fatal coronary heart disease, definite or probable myocardial infarction, and coronary revascularizations), strokes (ischemic and hemorrhagic), and all cause

mortality, occurring after ARIC V4, baseline brain MRI results on ARIC V3 and their 9 year follow up MRI, cognitive function status

For analysis of the association between cTnT and the volume of the WML at baseline MRI as well as the change of WML we will use linear regression models. For the association between cTnT and the prevalent BI at baseline and at the follow up MRI, we will use the logistic regression analysis. We will model cTnT as both categorical and a continuous variable. Depending on the distribution of the cTnT, for the categorical analysis and we will do stratified analysis bi quintiles or quartiles.
We will create 3 models:

- Model 1 will be a basic model adjusted for age gender, race

- Model 2 will be adjusted for: all variables in Model 1 plus total cholesterol, high density lipoprotein cholesterol, systolic blood pressure, antihypertensive medication use, smoking status and the presence of diabetes mellitus (fasting blood glucose> 126 mg/dl or diabetes medication use), BMI, history of stroke before ARIC visit 3

- Model 3 will be adjusted for all the factors included in model 2 plus hs-CRP, NT-pro-BNP and estimated GFR, left ventricular hypertrophy (calculated by ECG with the Cornell criteria)

Depending on the strength of the associations found in the primary analysis we will perform stratified analysis by other variables such as: age, presence of hypertension and the presence of diabetes.

Inclusion criteria:
Patients with a baseline MRI performed at Visit 3 ARIC and measured cTnT at VISIT 4.

Exclusion criteria
Patients who have missing covariate data.
Patients with history of coronary heart disease and heart failure at the time of cTnT measurement.

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.cscc.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? ___ Yes __X_ No

11.b. If yes, is the proposal
__ **A. primarily the result of an ancillary study ()**
___ **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.

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