

## ARIC Manuscript Proposal #2266

PC Reviewed: 12/10/13  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Associations between brain vascular imaging features and regional volumetrics

**b. Abbreviated Title (Length 26 characters):**

**2. Writing Group:** Knopman, J Graff-Radford, Jack, Kantarci

Writing group members: D Knopman, C Jack, J Graff-Radford, Kantarci, T Mosley, R Gottesman, M Griswold, AR Sharrett, G Windham, M Albert, L Coker

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

**First author: Jonathan Graff Radford / David Knopman**

Address: Neurology, Mayo Clinic

Phone: 507 5381038

Fax: 507 538 6012

E-mail: [grafradford.jonathan@mayo.edu](mailto:grafradford.jonathan@mayo.edu)

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: **David Knopman**

Address: Neurology, Mayo Clinic

Phone: *same as above*

Fax:

E-mail: knopman@mayo.edu

**3. Timeline:** Complete manuscript by March 31, 2014

**4. Rationale:**

Cerebrovascular disease contributes to late life cognitive impairment, but relationship between cerebrovascular disease and neurodegeneration (using the term broadly to indicate neuronal and synaptic loss) has been very difficult to understand. Features that serve as proxies for cerebrovascular disease, including white matter hyperintensities, small infarcts (lacunar infarcts), large infarcts (major vessel distribution infarcts), and more recently microbleeds, have modest relationships with cognitive decline and incident cognitive impairment. There is much work on the quantitative relationships between cerebrovascular imaging lesions and brain volume loss, but mainly using whole brain or ventricular volume: for WMH (DeBette Neurology 77:461; Silbert Neurology 71:108; Barnes Neurobiol Aging 2013; Godin, Cerebrovasc Dis 28:177; Wen, Neuroimage 29:1031; Kloppenborg, Neurology 70:2029). (For the record, an association of

WMH and brain volume seems to occur only in cognitively normal persons). A few articles report associations between infarcts and brain volume (Appelman, *Cerebrovasc Dis* 29:28; Thong *JNNP* 83:1291; Kloppenborg, *Neurology* 70:2029). The most recent study by Thong et al is the only one to report regional volumetrics. And, I am not aware of any studies reporting associations between microbleeds and brain volume loss. To the extent that microbleeds represent vascular amyloid, and vascular amyloid is at least weakly related to parenchymal amyloid and AD pathological changes, it is possible that microbleeds could share variance with AD-pathophysiology based brain volume loss. With the new imaging approach taken in ARIC NCS, we have the capability of looking at regional volumetrics both for white matter changes and cortical volumes.

## **5. Main Hypothesis/Study Questions:**

- (1) Increasing burdens of WMH, INF and MB are individually associated with greater global brain volume loss.
- (2) Each vascular lesion type has a regionally specific anatomic predilection for brain atrophy (exclusive of actual infarcts themselves). That is, WMH and small (lacunar) infarcts in deeper brain structures are presumed to be proxies for microvascular disease, and it is the latter that exerts an impact on cortical volume. WMH and INF, because they are typically associated with “frontal-type” cognitive changes will be more associated with smaller frontal lobe cortical volume. MB, on the other hand, because they are associated with parenchymal AD changes, will be associated with reduced volumes in areas typically affected in AD, such as lateral and medial parietal, lateral and medial temporal regions.
- (3) WMH location varies between persons with predominantly athero- or arteriolo-sclerotic disease versus persons with amyloid angiopathy. The former could be identified by medical history (eg, diabetes, hypertension, myocardial infarctions, abnormal carotid IMT) while the latter could be identified by the presence of MBs, abnormal levels of plasma beta-amyloid, and the absence of an atherosclerotic history.

## **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).**

Subjects: Study includes all non-demented participants with MR scans at ARIC NCS.

Outcome measures: regional brain volumes as determined by Freesurfer analysis of cortical volumes; ventricular volume, whole brain volume, ROI

Predictors: White matter hyperintensity burden as percent of total white matter volume, small infarcts, microbleeds as counted on gradient echo imaging.

Covariates: age, sex, race, education level, APOE e4 carriage.

Analytic methods: For hypotheses 1 and 2: (1) Regression of WMH, INF, MBs on regional and global brain volumes. (2) Divide distribution of WMH, INF, MB into tertiles or quartiles and compare brain volumes across groups. For hypothesis 3: select subgroups that are ‘atherosclerotic’ versus “amyloidogenic” and compare WMH, infarcts, volumetrics.

7.a. Will the data be used for non-CVD analysis\* in this manuscript?\_\_ Yes  
\_X\_ No x

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? \_\_\_\_\_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.cscce.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)?

This type of analysis has never been done before in ARIC because we have never had brain regional volumetrics available from brain MR scans until ARIC NCS

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\* \_\_\_\_\_)  
\_\_\_\_ 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.cscce.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.csc.unc.edu/aric/index.php>, under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit\\_process\\_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.