ARIC Manuscript Proposal # 1894

PC Reviewed: 1/10/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Retinal Microvascular Abnormalities predict Progression of White Matter Disease and Incident Lacunar Infarcts: The ARIC MRI study

b. Abbreviated Title (Length 26 characters): Small vessel disease, eye and brain

2. Writing Group:

Writing group members:

Thomas Hanff, Rebecca Gottesman, A. Richey Sharrett, Thomas Mosley, Dean Shibata, Ron Klein, Barbara Klein, Others welcome

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

First author: **Thomas Hanff, BS**

Address: 600 North Wolfe Street
Johns Hopkins University School of Medicine
Baltimore, MD 21287
Phone: 818-640-0726 Fax: 410-955-0672
E-mail: thanff1@jhmi.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: **Rebecca Gottesman, MD, PhD**

Address: Meyer 6-113
600 North Wolfe Street
Johns Hopkins University School of Medicine
Baltimore, MD 21287
Phone: 410-614-2381 Fax: 410-955-0672
E-mail: rgottesm@jhmi.edu

3. Timeline: Analyses to begin as soon as manuscript proposal is approved.
Goal is for abstract submission March 2012.

4. Rationale:

Early detection of cerebral small vessel disease is critical for the primary prevention of cerebrovascular injury. However, it is possible that microvascular pathology in the brain precedes detectable changes in brain MRI. Therefore, it is important to identify any pre-clinical variables that could predict the development of cerebral small vessel disease prior to the detection of abnormalities on MRI. The retina offers a unique opportunity to

achieve this goal because the retinal microvascular bed mirrors the cerebral small vessels in embryologic origin, anatomic features, and physiologic properties[1,2]. Hypertensive and diabetic retinal signs are associated with incident stroke and stroke mortality, independent of blood pressure and other cardiovascular risk factors[3]. Likewise, retinal signs are associated with[4,5] and may also predict subclinical brain microvascular pathology as an intermediary step towards clinical cerebrovascular disease.

White matter disease and silent lacunar infarcts are two variations of subclinical brain microvascular pathology that share numerous pathological features and risk factors[1]. Moreover, both also predict similar outcomes, increasing a patient's risk for clinical stroke and dementia while predicting a worse prognosis from cerebral infarction[6]. Many studies seeking to elaborate risk factors for these phenomena separate these outcomes during the analysis. This is problematic for two reasons. First, the two are not always easily distinguished, particularly when the white matter disease is found in areas typical of lacunar infarcts such as the basal ganglia and thalamus[7]. Secondly, separate analysis of white matter disease and lacunar infarcts limits a study's power to detect statistically significant odds ratios for exposure-outcome relationships in brain microvascular disease.

In contrast, if we were to combine the effects of white-matter disease and silent lacunar infarcts into one score, we would achieve a global assessment of brain microvascular disease reflecting shared pathophysiology between these two MRI-detected phenomena. As an outcome, the score would be more likely to detect true risk factors for brain microvascular disease than when the risk factors are evaluated in association with lacunar infarcts or white matter disease alone. Similarly, if the score is a more sensitive measure of microvascular disease as an exposure, it would have greater predictive value as a risk factor for cognitive decline, incident stroke, and stroke prognosis.

Before using the score to identify new risk factors, however, we would need to first test the validity of the score. This could be done by demonstrating an association between the score and known risk factors for white matter disease or with an already validated risk score for stroke[8]. In particular, hypertension is known to associate well with white matter volume progression in multiple ethnicities[9], and in theory, white matter progression might associate even more strongly with the stroke risk score shown in ARIC to strongly predict ischemic strokes. In blacks, blood pressures elevated earlier in life predict white-matter disease progression more strongly than blood pressures elevated later in life. In both whites and blacks, cumulative blood pressure is a stronger predictor of white matter disease progression than individual blood pressure values. We would expect to observe similar trends, perhaps more reliably assessed using as the endpoint a score reflecting global cerebral microvascular disease burden.

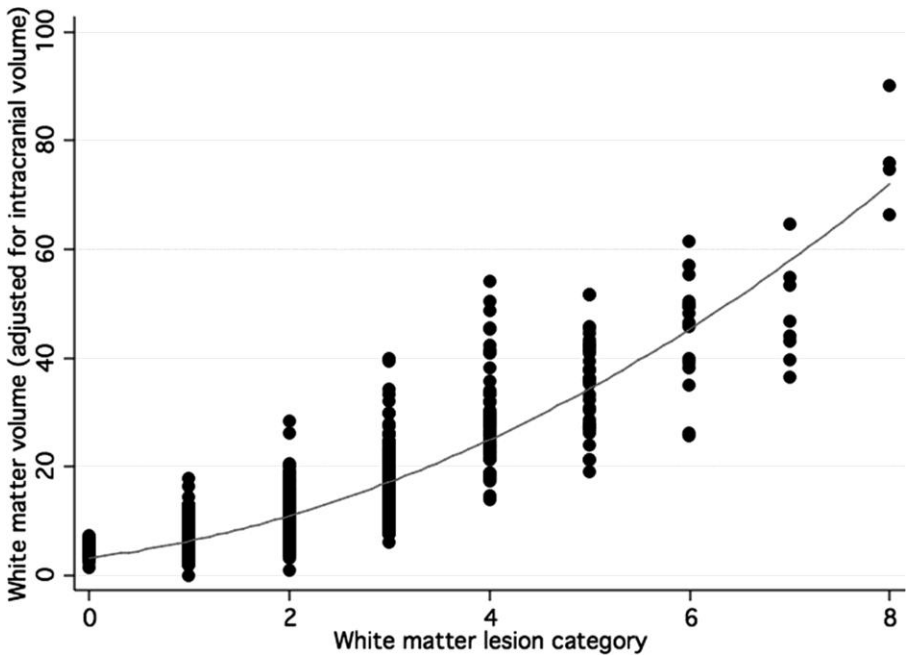
In a previous ARIC MRI study, Cheung et al. tested the association between retinal microvascular pathology as an exposure and silent cerebral infarct, silent lacunar infarcts, incident white matter lesions, and white matter lesion grade progression as separate outcomes[7]. Of the 810 participants, 164 had silent cortical infarcts, 131 had silent lacunar infarcts, and 182 had incident white-matter disease. However, only 49 had progression of white matter disease, when this was defined using a categorical white matter disease

rating scale from 0-9, with progression defined as at least a 2 step increase in score at follow up visit. For retinal findings, 28 had microaneurysms, 21 had retinal hemorrhage, 88 had arteriovenous nicking, and 96 had focal narrowing. The relatively low number of participants with white matter disease progression coupled with the infrequency of retinal signs limited the power to find associations between retinal disease and this outcome. Of the 6 categories of retinal pathology assessed, only arteriovenous nicking had significant association with white-matter disease progression with an odds ratio of 2.22 (1.00,5.88). In contrast, lacunar infarcts had significantly increased odds for microaneurysms, retinal hemorrhage, arteriovenous nicking, and any retinopathy but were not significantly associated with cotton wool spots or focal narrowing. It is possible that by 1) using volumetric measurements instead of a categorical rating of white matter disease as a more precise measure of white matter disease progression, and by 2) combining incident lacunar infarct with this measure of white matter disease progression, we would be able to detect associations between the retinal variables and the combined score that were missed by treating them separately.

Additionally, although baseline white-matter disease is an important risk factor for clinical stroke and dementia[10], progression of white-matter disease has been shown to be more strongly associated with subsequent cognitive decline[11]. In the study by Cheung et al, as described above, progression of white matter disease was assessed using a global score from 0 to 9 assigned by two independent MRI readers with a kappa of 0.48[7]. This relatively low kappa reflects the limited inter-rater reliability associated with this qualitative score.

The ideal measure for white-matter disease progression would be direct volumetric measurement[9]. However, the image resolution from the initial MRI acquisitions in ARIC (from visit 3) is not adequate for volumetric analysis. Fortunately, images taken one decade later at the second MRI acquisition were assessed with both MRI white matter disease score (using the same 0-9 Cardiovascular Health Study (CHS) rating scale) and white matter hyperintensity volumetric analysis. Gottesman et. al used these data to generate a prediction equation (R^2=0.80) for imputing white-matter volume from reader scores (Figure 1)[9]. Subtracting the MRI volume of the first acquisition from the second generates a quantifiable continuous measure of white-matter disease progression which may prove to be more strongly associated with hypertension and other predictors.

Figure 1.



A better understanding of the temporal relationship between retinal microvascular pathology and brain microvascular pathology might eventually allow earlier and more accurate prediction of subsequent cognitive decline and risk of stroke. Importantly, given limitations in the precision of current MRI technology, our ability to detect retinal disease may precede our ability to detect brain microvascular pathology directly[3].

5. Main Hypothesis/Study Questions:

1. White matter disease volume progression, assessed using a continuous measure, will be associated with presence of retinal microvascular signs (defined below).
2. A new score combining white matter disease volume progression and incident lacunar infarct will be highly associated with hypertension and with the ARIC stroke risk score. This hypothesis has the goal of validating and optimizing the new composite cerebral microvascular score.
3. Retinal microvascular signs detected with retinal photography at visit 3 will predict worse cerebral microvascular disease, measured as higher values on the new score described in hypothesis #2.

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 data collection of risk factors with longitudinal definition of white matter disease progression based on change between the visit 3 brain MRI and the ARIC Brain MRI in 2004-2006. Lacunar infarct incidence based on development of new lacunar infarcts from the visit 3 Brain MRI to the ARIC Brain MRI in 2004-2006.
Inclusion: All individuals in the ARIC Brain MRI cohort (N=1034).
Exclusion: Missing Brain MRI data; Missing blood pressure data at over 50% of the visits; Missing interpretable retinal photographs (except for hypothesis 2). History of stroke or transient ischemic attack before ARIC Brain MRI visit. Those with large cerebral infarct on MRI at visit 3 (for hypothesis 3).

Hypothesis 1: White matter disease volume progression defined as volume change (Brain MRI visit volume – interpolated visit 3 volume) or alternatively as top quintile of volume of change. Linear regression for volume change, logistic regression for quintile change, with white matter disease progression as dependent variable and retinal microvascular changes, including retinopathy and its major components (microaneurysms and hemorrhages), arteriovenous nicking, retinal arteriolar narrowing measured by the central retinal arteriolar equivalent (CRAE), and retinal venular widening as measured by the central retinal venular equivalent (CRVE), as independent variables. Adjust for age, gender, race, study center, total cholesterol, HDL cholesterol, BMI, and smoking status, blood pressure, and blood glucose using visit 3 status. Stratify analysis by hypertension and diabetes status.

Hypothesis 2: Ordinal logistic regression with microvascular disease score (dependent variable) and blood pressure or ARIC stroke risk score (as independent variables). We will evaluate various combinations of points for white matter disease volume progression and presence of incident lacunar infarcts to construct a score (for instance, trying if 1 point is added whether there are either incident radiographic lacunar infarcts or if white matter disease volume progression is in the top quintile, with 2 points if both of these are present, and so on). In addition, we will evaluate the role of including in this microvascular disease score the very small infarct-like lesions (< 3 mm in size) that are typically excluded from analysis as "lacunes" in previous ARIC studies, but which, in a recent ARIC publication, are shown to be highly associated with certain vascular risk factors[12]. The current goal is to have between 3 and 5 possible points for the score- we will select the best score based on what scale is most strongly predicted by cumulative systolic blood pressure (time-averaged SBP; we have previously shown (Gottesman et al) that a cumulative measure of SBP is a stronger predictor of white matter disease progression than is an individual value from a single visit.

An alternative approach to optimize the score could be considered in which we use the MRI variables (white matter disease progression and incident lacunes) as independent variables and BP or ARIC stroke risk score as a dependent variable in a multivariable linear analysis. The coefficients for the MRI variables would then used to create the optimal new composite score.

Hypothesis 3: Ordinal logistic regression of microvascular disease score vs retinal microvascular changes, as defined above. Adjust for age, gender, race, study center, total cholesterol, HDL cholesterol, BMI, and smoking status, systolic and diastolic blood pressure, and blood glucose, and HbA1c using visit 3 status. Stratify analysis by hypertension and diabetes status.

Outcome:

1. White matter lesions: Volume (measured volumetrically) and white matter grade.
2. Composite score, including both incident lacunar stroke and white matter disease progression.

Variables of interest: Blood pressure: visits 1, 2, 3, 4, Brain MRI visit

White matter disease volume: Brain MRI visit #2 (2004-2006); categorical rating of white matter disease (visits 3 and Brain MRI visit)

Blood glucose measurements, diabetes

Other potential confounders: Weight loss (from visit 1 to ARIC Brain MRI visit), history of CABG surgery, new use of hemodialysis, prevalent CHD, body-mass index, history of tobacco use.

Limitations: Of the 1684 study participants with an initial MRI and retinal assessment, the 1034 participants that returned for a second MRI generally had a healthier cardiovascular risk profile than those that did not return. This may confound any odds ratios between retinal disease and brain microvascular disease, shifting the odds ratio towards the null. However, given that Cheung et. al only found 131 patients with incident lacunes and 49 with white matter progression defined categorically, our combined score that includes both of these variables as well as smaller (<3mm) lacunes should have a greater power to overcome this limitation.

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? _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? ____ 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"?
__X__ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?

__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.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)? 1. Cheung et al. **"**Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study" 2. Gottesman et al. "Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study" 3. Wong et al. "Cerebral white matter lesions, retinopathy, and incident clinical stroke."

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

_X A. primarily the result of an ancillary study (list number* ARIC Brain MRI:__1999.01_____)

___ 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

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol. 2010 Jul;9(7):689-701
2. Patton N, Aslam T, Macgillivray T, Pattie A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat* 2005;206(4):319-348. Ref ID: 2553
3. Baker ML, Hand PJ, Wang JJ, Wong TY. Retinal signs and stroke: revisit- ing the link between eye and brain. Stroke 2007; 39: 1371–9.

4. Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, Hubbard LD, Mosley TH; ARIC Investigators. Atheroslerosis Risk in Communities Study. Cerebral white matter lesions, retinopathy, and incident clinical stroke. JAMA. 2002 Jul 3;288(1):67-74.
5. Cooper LS, Wong TY, Klein R, Sharrett AR, Bryan RN, Hubbard LD, Couper DJ, Heiss G, Sorlie PD. Retinal Microvascular Abnormalities and MRI-Defined Subclinical Cerebral Infarction: The Atherosclerosis Risk in Communities Study. *Stroke* 2006;37:82-86. Ref ID: 2172
6. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: a systematic review. Lancet Neurol 2007; 6: 611–9
7. Cheung N, Mosley T, Islam A, Kawasaki R, Sharrett AR, Klein R, Coker LH, Knopman DS, Shibata DK, Catellier D, Wong TY. Retinal microvascular abnormalities and subclinical magnetic resonance imaging brain infarct: a prospective study. Brain. 2010 Jul;133(Pt 7):1987-93
8. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* 2004;160(3):259-269. Ref ID: 2994
9. Gottesman RF, Coresh J, Catellier DJ, Sharrett AR, Rose KM, Coker LH, Shibata DK, Knopman DS, Jack CR, Mosley TH Jr. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2010 Jan;41(1):3-8.
10. Smith EE. Leukoaraiosis and stroke. Stroke. 2010 Oct;41(10 Suppl):S139-43
11. Silbert LC, Howieson DB, Dodge H, Kaye JA. Cognitive impairment risk: white matter hyperintensity progression matters. Neurology. 2009; 73:120–125.
12. Bezerra DC, Sharrett AR, Matsushita K, Gottesman RF, Shibata D, Mosley TH Jr, Coresh J, Szklo M, Carvalho MS, Selvin E. Risk factors for lacune subtypes in the Atherosclerosis Risk in Communities (ARIC) Study. Neurology. 2011 Dec 14