ARIC Manuscript Proposal #2271

PC Reviewed: 12/10/13 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: **A combined measure for the evaluation of prevalent microvascular brain disease as a risk factor for stroke incidence in the ARIC study**

b. Abbreviated Title (Length 26 characters): Microvascular brain disease and stroke

2. Writing Group:
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- Others welcome

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

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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).

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3. Timeline: Starting immediately, to be completed by March 2014

4. Rationale:
Microvascular brain disease may manifest as asymptomatic ischemic lesions readily identified on CT and MRI scans. Diffuse lesions are usually referred to as white matter hyperintensities or leukoaraiosis; while isolated lesions are generally categorized as lacunar brain infarct. Both are likely due, at least in part, to arteriolar disease. White matter hyperintensities are associated with

vascular risk factors, particularly age and hypertension, and have been related to increased risk of stroke in several studies[1-2] including ARIC[3]. In elderly populations, leukoaraiosis has been associated with global or selective cognitive deficits, changes in mood, decreased motor function and urinary disturbances, all contributing to increased disability in the elderly [4-5]. In patients with acute ischemic stroke, leukoaraiosis volume has been reported an independent predictor of infarct growth[6] and associated with poor outcome including reduced physical functioning, decreased quality of life and low community integration[7], stroke recurrence[8], and mortality[9]. Subclinical infarctions, most characterized as lacunes, are defined as "imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion"[10]. They are present in 8%-28% of participants in population-based studies, and up to 50% of patients with acute stroke [11]. They share risk factors with white matter hyperintensities and have been associated with physical functional decline[12], frailty[13], impaired cognition and visual field deficits[14]. In population-based studies, increased risks of stroke [2, 15] and dementia[16] have been reported for participants with evidence of subclinical infarctions. Post-stroke disabilities for patients with prior subclinical stroke are similar to those of patients with prior overt stroke (Koton, in press). Despite the similar pathophysiology, risk factors, and outcomes, and frequent co-occurrence of both white matter hyperintensities and subclinical infarcts, and the difficulty in clearly distinguishing between them in some cases[11], there are few reports on the clinical profile of the two entities in a single study[17], and their combined significance for the prediction of overt stroke has not been reported. A recent study on retinal microvascular abnormalities as predictor of progression of brain microvascular disease in ARIC (Hanff et al, submitted) used volumetric measures of progression of leukoaraiosis- calculated as the difference in volume at follow-up Brain MRI visit (2004-06) and initial MRI at visit 3 (1993-95) - in combination with a dichotomous characterization of incident lacunes (absent at visit 3 and then present at the Brain MRI visit) as the study outcome. We propose assessing the validity of a measure using not only presence of lacunes, but a quantitative measure of progression of lacunes (i.e. change in number of identified lacunes or progression in lacunar volume between visit 3 and follow-up MRI visit) combined with volumetric measures of progression of leukoaraiosis for the prediction of incident overt stroke in ARIC participants.

5. Main Hypothesis/Study Questions:

1. The association between a combined measure of lacunes and leukoaraiosis and risk of stroke is stronger than associations between separate measures of lacunes and leukoaraiosis and risk of stroke.
2. Progression of lacunes and leukoaraiosis is associated with increased risk of overt clinical stroke.

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).

Validated data on stroke (total, although will analyze ischemic stroke separately) collected for all participants in the ARIC Cohort will be used.

Main Outcome Variables:

- Prevalence of lacunes, leukoaraiosis and a combined measure of them in ARIC.
- Rate of definite/probable incident stroke after visit 3.
- Risk of stroke associated with lacunes, leukoaraiosis and a combined measure of them.
- Risk of stroke associated with progression of lacunes, leukoaraiosis and a combined measure of them.

Incidence rate and risk associated with lacunes, leukoaraiosis and a combined measure of them will be studied for total stroke and separately for all ischemic strokes and lacunar ischemic stroke.

Study population:

The study population includes white and African-American ARIC participants who underwent a brain MRI both at Visit 3 (1993-1995) and follow-up Brain MRI visit (2004-2006), n=1134. Participants with missing data on main covariates in the planned statistical models will be excluded.

Summary of Data Analysis:

1. Leukoaraiosis and lacunes will be analyzed both as binary categorical (presence (above a certain volume of leukoaraiosis or presence for lacunes)/absence) and continuous variables (using estimated volume of lesions).
2. Two combined scores for microvascular brain disease will be created: a. using the categorical classification of leukoaraiosis and lacunes, 3 levels of a combined variable will be categorized (0 for absence of evidence of leukoaraiosis or lacune, 1 for presence of either leukoaraiosis or lacune and 2 for presence of both. B. using a combination of volume of lesions. The predictive value of different combinations will be assessed.
3. Microvascular brain disease as a risk factor for stroke incidence will be studied with Cox proportional hazard models, adjusting for other risk factors including age, gender, race, study center, hypertension, diabetes, cholesterol (total and HDL), smoking, BMI, prevalent heart disease.
4. Risk for stroke will be assessed for total stroke and separately for ischemic stroke. An exploratory analysis will evaluate lacunar stroke.

In addition, we will evaluate CHS white matter hyperintensities scale category change.

Anticipated challenges/limitations:

1. There might not be enough power for the assessment of associations between progression of lacunes, leukoaraiosis and their combined measure and stroke incidence.
2. Although the strongest associations are expected for incidence of lacunar stroke, we anticipate that numbers are not large enough to show significant associations

7.a. Will the data be used for non-CVD analysis in this manuscript? __Yes _X_No

8.a. Will the DNA data be used in this manuscript? ___Yes _X_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)?

- Wong TY, Klein R, Sharrett AR, Couper DJ, Klein BE, Liao DP, Hubbard LD, Mosley TH .Cerebral white matter lesions, retinopathy, and incident clinical stroke. *JAMA*. 2002;288:67-74.
- Hanff TC, Sharrett AR, Mosley TH, Shibata D, Knopman DS, Klein R, Klein B, Gottesman RF. Retinal microvacular abnormalities predict progression of brain microvascular disease: An ARIC MRI study (submitted manuscript).
- Windham G et al. Cerebral MRI Changes in mid-life to older age and incident stroke: the Atherosclerosis Risk in Communities Study (manuscript proposal #2081).

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _X_ Yes

11.b. If yes, is the proposal

_X_ A. primarily the result of the ARIC Brain MRI ancillary study, # 1999.01

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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