ARIC Manuscript Proposal # 3024

PC Reviewed: 7/10/2017	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Intracranial atherosclerotic disease and brain amyloid deposition: The ARIC Study

b. Abbreviated Title (Length 26 characters): ICAD and brain amyloid

2. Writing Group:

Writing group members: Rebecca Gottesman (first and corresponding author); Thomas Mosley; David Knopman; Qing Hao; Dean Wong; Yun Zhou; Lynne Wagenknecht; Ye Qiao; Jennifer Dearborn; Bruce Wasserman (last author); Others welcome.

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

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3. Timeline: 3-6 months; planned abstract submission August 2017 for International Stroke Conference; manuscript submission soon after.

4. Rationale:

Intracranial atherosclerosis is increasingly identified as a cause of stroke, but its role as a marker or even potential risk factor for cognitive impairment and dementia is less well

established. Although autopsy series have demonstrated associations between Circle of Willis atherosclerosis and dementia, including neuropathologic changes specific for Alzheimer's disease,[1] the ability to evaluate intracranial plaque in vivo, before death, has been limited until recent years. Evaluation of calcification in vessels, particularly in the carotid arteries, has been associated with dementia and cognitive decline,[2] but this neither identifies mechanism nor whether the association is specific to the vessels involved (as opposed to their calcification being a marker of general systemic vascular disease). Several methods exist to evaluate the health of the intracranial vessels themselves in more detail, which further support an association between intracranial atherosclerosis and dementia. In ARIC-NCS, presence and location of intracranial plaque was associated with adjudicated mild cognitive impairment (MCI) and dementia, using high-resolution vessel wall imaging with black-blood MRI.[3] Studies of intracranial plaque in ARIC-NCS included high-resolution vessel wall MRI images, which offer unprecedented measures of plaque presence and burden even in the absence of luminal narrowing. In fact, data from the ARIC-NCS vessel wall MRI study revealed nearly 11% of participants with intracranial plaque had lesions that were not detectable by luminal narrowing (i.e., angiography).

These data thus support the growing body of literature pointing to a vascular contribution to cognitive impairment and dementia, but do not provide information about Alzheimer's disease specifically, or whether intracranial vascular disease is at all causative in the development of dementia. In the ARIC-PET study, a subset of nondemented ARIC participants underwent amyloid PET imaging with florbetapir. According to current leading hypotheses, amyloid deposition in the brain is a primary factor leading to the development of Alzheimer's Disease. In ARIC-PET, amyloid deposition was greater in African-American participants than in whites,[4] and was greater in individuals with a larger number of vascular risk factors in midlife,[5] further supporting a potential direct effect of vascular disease on Alzheimer's neuropathology.

Beyond traditional risk factors, intracranial atherosclerosis provides evidence of specific vascular damage. Evidence of an association between intracranial atherosclerotic markers and brain amyloid might point to a more specific mechanism by which vascular risk factors might act, and could point to a potentially modifiable risk factor for amyloid deposition and Alzheimer's disease, if intracranial plaque were found to develop prior to the development of amyloid (this question cannot be addressed in this cross-sectional proposal, but with the future availability of followup PET data on ARIC-PET participants, would ultimately be testable). In addition to the importance of studying intracranial atherosclerosis and brain amyloid more broadly, the study of intracranial atherosclerosis in this setting may represent another way to evaluate the observed racial differences in amyloid deposition. Both in ARIC[6] and in clinical populations,[7] intracranial atherosclerosis is observed at higher frequencies in blacks than in whites. Thus, it represents a potential mechanism for the observed racial disparities in amyloid rates, and perhaps even ultimately in dementia rates (observed in our own study[8] as well as elsewhere).

5. Main Hypothesis/Study Questions:

1. Global cortical Aβ deposition by PET will be associated with plaque presence in intracranial vessels; plaque presence will be considered as a binary global variable (any plaque), as well as regionally (in separate vessels).

2. Global cortical Aβ deposition by PET will be associated with a higher number of intracranial plaques, globally, as well as number of vessels in which plaque is noted.
3. Associations observed in #1, and 2, above, will be stronger in blacks compared to white participants, and will be independent of other vascular risk factors including hypertension, diabetes, hyperlipidemia, and smoking.
4. Associations observed in #1 and 2, above, will be stronger in carriers of an APOE ε4 allele than in noncarriers.
5. We will find similar associations with amyloid deposition and vessel wall thickness, plaque thickness, and normalized wall index.
6. Global cortical Aβ deposition by PET will be associated with presence of intracranial stenosis (defined by any vessels with >70%, or >50%, stenosis).

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).

Analysis of all participants in completed ARIC-PET study (N= 346 completed scans (one additional person was not able to complete the scan so her data are not usable). All analyses will be cross-sectional, using vessel wall imaging MRI data from ARIC visit 5 and PET data from ARIC-PET.

Inclusion criteria (for inclusion in ARIC-PET; all of these persons will be included in analysis): persons with a CDR of 3 or lower, and also with a FAQ of 5 or lower, and with a brain MRI (from ARIC-NCS) within 12 months of recruitment. MMSE cannot be "low" (<19 for African-Americans and <21 for Caucasians) at the time of visit 5/ NCS. All participants were required to be able to give their own consent.
Exclusion criteria for involvement in ARIC-PET: We excluded individuals with history of: (1) radiation therapy, chemotherapy, or surgery in the 6 weeks preceding the ARIC-PET visit; or (2) clinically significant liver or renal dysfunction; (3) prolonged QT interval; (4) drug or alcohol abuse. We will allow use of anticholinergic medications or memantine if the dose has been stable for ≥3 months preceding the PET scan.

Outcome: Standardized Uptake Volume Ratio (SUVR) of florbetapir (amyloid) by ARIC-PET, in prespecified regions of interest. Global mean cortical SUVR, which is a weighted average (based on region-of-interest (ROI) volumes) of regions known to be typically impacted in AD. The SUVR's will be evaluated at a cutpoint of 1.2, with values >1.2 considered positive. Other cutpoints in the literature, including 1.1 and 1.11, will also be explored in sensitivity analyses.

MRI variables to include: plaque presence (overall); plaque presence within particular vessels; plaque number (overall); number of territories or vessels including plaques; vessel wall thickness; plaque wall thickness; normalized wall index. Also, presence of vascular stenosis: defined primarily as any vessel with >70% stenosis, but we will also examine presence of any stenoses>50%.

For hypothesis 1-2, and 5 and 6, the various intracranial vessel markers will be evaluated separately as independent variables, with elevated SUVR as the dependent binary variable. For hypothesis 3, we will repeat analyses stratified by race, and stratified

by APOE for hypothesis 4. Formal interaction terms will also be tested. All models will be adjusted for potential confounders as described below.

Other variables: We will include race, center, sex, and age information from ARIC baseline (race, center, sex) and visit 5 (age), as well as APOE genotype from prior ARIC measurement. In addition, hypertension and systolic and diastolic blood pressures, diabetes, hypercholesterolemia, statin use, and smoking status will all be assessed from ARIC-NCS. Level of educational attainment as a covariate will be included in models. Cognitive status (MCI versus normal cognition, since no participants with dementia were included in the cohort), defined based on the ARIC-NCS expert classification, will also be considered in later models as a covariate and/or an effect modifier.

In later models we will also consider small vessel disease (defined by brain MRI; white matter hyperintensities and silent infarcts, from the ARIC-NCS MRI) as effect modifiers; these do not clearly represent confounders.

Data analysis: Our primary analysis will consider logistic regression models with evaluation of elevated SUVR as a binary dependent variable; the SUVR data are highly skewed, not easily handled with transformation, so we will not plan to use the continuous SUVR data at this point. Models will include adjustment for demographics (model 1); other covariates (model 2), with addition of APOE and cognitive status in model 3. The same sequential covariate adjustment will be made for all of the ICAD markers.

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 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.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)?

2544. Arterial stiffness and beta-amyloid deposition in the ARIC-PET study. Hughes et al.
2511. Vascular risk factors and brain amyloid deposition: The ARIC-PET Study. Gottesman et al.
2673. Intracranial atherosclerosis and cognitive function and impairment across domains. Dearborn et al.
2488. Prevalence and risk factors for intracranial atherosclerosis in the ARIC cohort. Qiao et al.

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* _2009.29, 2009.27, 2009.28**___)**

___ 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.
Understood.

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.

Bibliography and References Cited

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5. Gottesman RF, Schneider ALC, Zhou Y, et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA*. 2017;317(14):1443-1450.
6. Qiao Y, Guallar E, Suri FK, et al. MR Imaging measures of intracranial atherosclerosis in a population-based study. *Radiology*. 2016;280(3):860-868.
7. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. *Stroke*. 1995;26:14-20.
8. Gottesman RF, Albert MS, Alonso A, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. *JAMA Neurology*. 2017;in press.