

ARIC Manuscript Proposal #3691

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1.a. Full Title: Cerebral microhemorrhages and cortical amyloid: The ARIC-PET study

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

2. Writing Group:

Writing group members: Rebecca Gottesman (first/ lead); Jonathan Graff-Radford; David Knopman; Thomas Mosley; Dean Wong; Michelle Johansen; Keenan Walker; Cliff Jack; James Pike; 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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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: Abstract to be submitted late August 2020 for International Stroke Conference; manuscript prepared and submitted in ~6 months.

4. Rationale: The diagnostic criteria for cerebral amyloid angiopathy (CAA), a condition in which amyloid deposits in the arterial walls and leads to cerebral macro- and microhemorrhage, include distribution of the hemorrhages, with an emphasis on lobar/ cortical, or corticosubcortical regions,¹ and requires either full postmortem neuropathology examination for a definite CAA diagnosis, or inclusion of appropriate clinical criteria for a probable or possible CAA diagnosis. Thus, the relevance of similar microhemorrhage distributions in the general

population, without a clear appropriate clinical history, is less clear. Furthermore, the definition of “probable” CAA requires multiple lobar hemorrhages, with “possible” CAA being reported with single lobar hemorrhages; both of these are in the background of an appropriate clinical setting (usually intracerebral hemorrhage). Finally, lobar hemorrhages often co-occur with non-lobar, or deep microhemorrhages, and although it has been speculated that a higher ratio of lobar: subcortical microhemorrhages is more consistent with CAA² than other etiologies of hemorrhage (such as hypertension), the importance of this pattern in non-clinical populations is unclear.

Florbetapir PET, which binds to cortical amyloid (which accumulates in Alzheimer’s disease) has provided an opportunity to differentiate CAA-related microhemorrhage from non-CAA microhemorrhage, even though CAA distribution of amyloid is in the vessel wall as opposed to cortical tissue. Patients with intracerebral hemorrhage who met criteria for CAA had higher global cortical amyloid (as well as occipital cortical amyloid, specifically) using florbetapir PET than did patients with ICH felt to be from a hypertensive etiology (standardized uptake value ratios of 1.41 vs 1.15, $p=0.001$), and in this sample of 19 adults, florbetapir PET had a 100% sensitivity and 89% specificity for probable CAA among ICH patients with normal cognition.³ Other authors have reported elevated global cortical florbetapir uptake in CAA vs hypertensive ICH patients but with lower sensitivities.⁴ The combination of both lobar and deep microhemorrhages, however, is less clearly associated with amyloid imaging markers by PET; individuals with mixed ICH (lobar and deep) vs hypertensive hemorrhage had similar Pittsburgh compound B amyloid imaging results.⁵ In the Mayo Clinic Study of Aging, lobar microbleeds were associated with elevated PET Pittsburgh compound B measured amyloid deposition, but subcortical microbleeds were not, and mixed microbleeds were relatively infrequent in this population.⁶

The presence of microbleeds in non-clinical (community-based) populations, in the absence of formal diagnoses of CAA, is uniformly associated with poor clinical outcomes. The META-MICROBLEEDS Initiative published a meta-analysis of 31 cohorts, each with at least 100 participants, which evaluated microbleeds on MRI. Although only 5 of these cohorts were community-based (contributing 11,722 participants, of a total of 20,368), this meta-analysis demonstrated associations between microbleeds and subsequent risk of stroke (and especially intracerebral hemorrhage), all-cause mortality, and incident dementia.⁷ It is not clear if these associations exist because they represent CAA, or simply because they are a marker of other risk factors, such as hypertension. The ability to separate out location of microbleeds (lobar vs deep) allows consideration of these distinct mechanisms. In ARIC, lobar microbleeds were more frequently associated with APOE e4, as well as smaller Alzheimer’s Disease signature regions, both of which are more likely to be markers of CAA, whereas deep microbleeds more frequently co-occurred with lacunar infarcts and white matter hyperintensities, both markers of (frequently hypertensive) small vessel disease.⁸ In this study, we propose to test the association between microbleeds in patients *without a history of intracerebral hemorrhage* and brain florbetapir (amyloid) PET, to further explore the potential clinical relevance of these imaging findings, and understand a potential mechanism of their link to dementia, in a community-based population.

5. Main Hypothesis/Study Questions:

1. Cerebral microbleeds are associated with elevated global cortical brain amyloid by PET, in ARIC-PET participants (all who are without dementia) without prior history of intracerebral hemorrhage.
2. Lobar microbleeds (presence and frequency) are associated with elevated brain amyloid by PET in the same population as #1, but deep (subcortical) microbleeds are not. Individuals with a mixed pattern of microbleeds have a weaker association with brain amyloid than those with only lobar-distribution microbleeds.
3. The associations described above are stronger in participants with MCI than those with normal cognition. We will also evaluate effect modification by sex, race, and APOE status.

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).

Design: cross-sectional

Participant inclusion: All ARIC-PET participants will be eligible for inclusion. *Exclusion:* history of adjudicated intracerebral hemorrhage in ARIC, or visit 5 diagnosis of dementia (ARIC-PET excluded dementia but complete adjudication was not finished, so one ARIC-PET participant was recruited who ultimately was given a research diagnosis of dementia).

Outcome: Flortbetapir PET global cortical SUVR (other regions, especially occipital lobes, as have been identified in other literature as important in CAA, will also be evaluated), from ARIC-PET scan #1. This will be dichotomized at the study median of 1.2, as we have evaluated before. Other cutpoints will also be considered, as will transformation of the data for more continuous evaluation of the outcome.

Other variables: The primary independent variable will be microbleeds, from the visit 5 MRI. These are already rated by presence (overall); presence by location (lobar y/n; subcortical or deep y/n); and number overall and within each location. Covariates to be considered as adjustment covariates or effect modifiers (see analysis plan) will include visit 5 measures of: age, hypertension (measured blood pressure and antihypertensive use also to be considered), diabetes, body mass index, smoking status, and MCI status, and v1 measures of educational level, sex, race (numbers too small in ARIC-PET for race-center delineation), and APOE genotype.

Data analysis: The primary analysis will construct logistic regression models with global cortical SUVR (dichotomized at 1.2) as the dependent variable, and each microbleed measure in separate models (as a binary variable and in frequency categories). A composite variable for ratio of number of lobar to deep microbleeds will be calculated, as will another composite variable considering presence/ absence of lobar vs deep microbleeds (none; deep only; deep + lobar; lobar only). Models will include the covariates listed above (an initial model incorporating demographic adjustment (age, sex, race, educational attainment) + APOE only, with a second model adding vascular risk factors and MCI status); interaction terms and, when appropriate, stratified models will be evaluated considering effect modification by MCI, sex, race, and APOE status. We will use MICE when appropriate to impute missing covariate information.

Limitations: The sample size for ARIC-PET is small (346 total participants), although microbleeds are fairly common (present in 25% of the ARIC-PET sample). Power may be limited, and the distribution of number of microbleeds as highly right-skewed.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ___ Yes ___X___ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = “ARIC only” and/or “Not for Profit” ? ___ Yes ___ No

(The 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 current derived consent file ICTDER05 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.csc.unc.edu/aric/mantrack/maintain/search/dtSearch.html>

___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)?

MP #2288. Knopman et al., Associations of brain imaging with cognitive change over 20 years

MP #2266. Graff-Radford/ Knopman et al., Associations between brain vascular imaging features and regional volumetrics

MP # 2822. Gottesman et al., Subclinical cerebrovascular disease and brain amyloid deposition: The ARIC-PET study

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)**

___ **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 <https://sites.csc.unc.edu/aric/approved-ancillary-studies>

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.csc.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.

CITED REFERENCES

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3. Guroi ME, Becker JA, Fotiadis P, et al. Florbetapir-PET to diagnose cerebral amyloid angiopathy: a prospective study. *Neurology* 2016 87:2043-2049.
4. Raposo N, Planton M, Peran P, et al. Florbetapir imaging in cerebral amyloid angiopathy-related hemorrhages. *Neurology* 2017;89:697-704.
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7. Charidimou A, Shams S, Romero JR, et al. Clinical significance of cerebral microbleeds on MRI: a comprehensive meta-analysis of risk of intracerebral hemorrhage, ischemic stroke, mortality, and dementia in cohort studies. *International Journal of Stroke* 2018;13:454-468.
8. Graff-Radford J, Simino J, Kantarci K, et al. Neuroimaging correlates of cerebral microbleeds: The ARIC Study (Atherosclerosis Risk in Communities). *Stroke* 2017;48:2964-2972.