ARIC Manuscript Proposal #2549

PC Reviewed: 5/12/15 Status: A Priority: A
SC Reviewed: ________ Status: _____ Priority: ____

1.a. Full Title:

b. Abbreviated Title (Length 26 characters): Stroke risk scores and white matter hyperintensity progression: The Atherosclerosis Risk in Communities Study

2. Writing Group:
Writing group members: Rebecca Gottesman (first author), Michael Griswold, Samantha Seals, Ralph Sacco, Shyam Prabhakaran, Clinton Wright, Natalia Rost, Melinda Power, David Knopman, Dean Shibata, Thomas Mosley

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: 6 months

4. Rationale: Pathologic and neuroimaging studies have identified varying subtypes of brain microvascular disease, including not only silent infarcts but also leukoaraiosis, or white matter hyperintensities (as well as a number of other subtypes of brain
microvascular disease not relevant to this proposal, as recently outlined in the STRIVE consortium publication\(^1\). Evidence supporting a vascular etiology of these white matter hyperintensities includes their strong relationships with vascular risk factors, particularly hypertension,\(^2\)\(^-\)\(^4\) especially when measured in midlife. In ARIC we have similarly found strong associations between hypertension and white matter hyperintensities, using ARIC Brain MRI data, as well as between blood pressure,\(^5\) fasting glucose,\(^6\) retinal microvascular changes,\(^7\) and smoking,\(^8\) each, and progression of white matter hyperintensities.

Progression of white matter hyperintensities appears even more clinically relevant than a single measurement: although presence and degree of white matter hyperintensities are known to be associated with worse outcomes at the time of stroke,\(^9\)\(^,\)\(^10\) higher risk of stroke\(^11\) (including in ARIC\(^12\)), and greater odds of cognitive impairment\(^13\) and dementia,\(^14\) it has also been reported that progression of white matter hyperintensities over time is associated with steeper worsening of cognition.\(^15\)

Although hypertension is a prominent risk factor for white matter hyperintensities and their progression, the association with other vascular risk factors with these brain microvascular changes supports the importance of looking at a composite of vascular risk factors to better understand vascular risk. In the Framingham Offspring cohort, the Framingham stroke risk profile was strongly associated with white matter hyperintensities.\(^16\) However, it has not been clearly established: 1) whether this risk score would also be associated with progression of white matter lesions; and 2) whether this score or another risk score, including the ARIC stroke risk score, would be more pertinent in cohorts including minority participants, such as ARIC.

The ARIC stroke risk score\(^17\) includes, in its primary form, race, smoking status, age, prior CHD, hypertension medication use, left ventricular hypertrophy, diabetes status, systolic BP, and sex; the Framingham stroke risk score\(^18\) does not include race but also includes atrial fibrillation (otherwise the components are the same, although the weighting of different components differs). The initial Framingham CVD risk score included age, sex, LDL and HDL cholesterols, systolic blood pressure, current smoking status, and diabetes;\(^19\) an updated score was published in 2008 and included dyslipidemia, age range, blood pressure and its treatment, smoking, and total cholesterol, but not diabetes.\(^20\) Finally, the pooled cohorts equation recommended by the AHA/ACC in 2013, for calculated cardiovascular disease risk, includes race- and sex-specific equations, including information about age, total cholesterol, HDL, treated (or untreated) systolic blood pressure, current smoking status, and diabetes.\(^21\)

These scores were both created to evaluate risk of clinical ischemic stroke or cardiovascular disease, but given shared risk factors between clinical stroke and subclinical changes such as white matter hyperintensities, we anticipate similar associations between these risk scores and progression of brain white matter hyperintensities. These results could also lead future interventional studies aimed at minimizing progression of white matter hyperintensities, by identifying a means by which those individuals at highest risk of progression might be identified.
5. **Main Hypothesis/Study Questions:**

1. The ARIC stroke risk score, Framingham CVD risk score(s) (FRS), Framingham stroke risk score (FSRS), and AHA/ACC pooled cohort equations for CVD will each be associated with risk of white matter hyperintensity (WMH), and WMH progression (with greater progression among persons with higher risk scores).

2. Newly generated risk scores, specifically focusing on WMH and WMH progression, using ARIC data, will have better discriminating ability than the ARIC stroke risk score, FRS, FSRS, and/or ACC/AHA pooled equation in identifying persons with WMH and progression of WMH.

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).**

*Inclusion criteria:* Participants with two brain MRI scans (visit 3, Brain MRI ancillary study visit, so restricted to the Forsyth Co., NC and Jackson, MS sites).

*Exclusion criteria:* Prior clinical stroke.

*Outcome:* The primary variable of interest for hypothesis 1 will be quantitative change in WMH progression from visit 3 through the 2004-2006 Brain MRI visit, calculated using methods previously published in ARIC, as well as exploring new methods given concern for differential measurement error with respect to vascular risk factors in WMH volumes. We will use multiple imputation chained equations to multiply impute WMH volumes at visit 3, which will incorporate the strong quadratic association previously observed between the qualitative scores and actual volumes from the Brain MRI visit, but will also avoid introducing bias. We will also examine additional measures of progression such as change in the 0-9 CHS category across visits, percentile change scores, and the potential for a calibrated absolute change. WMH levels will also be examined. For categorical progression, we will initially focus on change in CHS category by at least one category (requiring at least a one category increase to be defined as a “progressor”), with alternative WMH progression and WMH level/volume outcomes detailed following initial data explorations; for our prior analyses on smoking and WMH we found that a two category change was most meaningful.

*Other variables of interest:* The stroke risk profiles will be defined using visit 1 race and additional variables from visit 3, (including, as appropriate for each risk score): smoking status (current vs not current, as used in both prior models), age, prevalent CHD, hypertension medication use (at the time of the visit, so defined as a binary yes/no variable), left ventricular hypertrophy (by EKG), diabetes status (defined in the Chambless ARIC paper as fasting glucose 126 mg/dl or higher, nonfasting glucose of 200 mg /dl or higher, self-reported physician diagnosis or on pharmacologic treatment, to be used for both stroke risk scores), fasting lipid levels, systolic BP (the mean of the 2nd
and 3rd measurements at study visit 3), and sex. Atrial fibrillation, for the FSRS, will use data from the incident atrial fibrillation dataset available in ARIC, to define a binary ever/never history of a. fibr.

In addition, for hypothesis 2, we will evaluate other possible predictors of WMH progression specifically, such as subclinical disease markers (including but not limited to CIMT), inflammatory markers (CRP/IL6/ESR) and medication use (including statin use at visit 3 and the Brain MRI visits (anticipated to be very low at visit 3)/aspirin use/etc.)

**Planned data analysis:** Hypothesis one will include general linear regression models with appropriate link and distributional functions for estimated WMH volumes and for a binary WMH progression indicator, using separate models for each of the stroke risk scores. Risk prediction metrics (sensitivities, specificities, AUC’s, reclassification tables and reclassification statistics (NRI/IDI) will be compared overall, and also separately by race.

Creation of new WMH and WMH progression risk scores will follow standardized multivariate risk score development frameworks (TRIPOD)\(^2\) with internal validation components using cross-validation and bootstrap architectures; external validation may be pursued if appropriate alternative data sources become available (such as through collaborations with CHS). We plan to develop two scores for each of the WMH and WMH progression outcomes: (1) using a multifaceted model with many contributing predictors which optimizes precision at the expense of being more challenging to implement broadly (given the larger number of variables) and (2) a simpler, shorter version of the WMH progression risk score that optimizes broad applicability at the expense of potentially lower predictive utility. Risk prediction metrics will be similar as above. To summarize, we intend to develop new risk scores for WMH disease and disease progression using ARIC data:

1) WMH long form – many useful variables for predicting
   a. concurrent WMH level/volume
   b. future (10 year) WMH level/volume
2) WMH short form – a few commonly available and useful variables for predicting
   a. concurrent WMH level/volume
   b. future (10 year) WMH level/volume
3) WMH progression long form – many useful variables for predicting progression of WMH disease over 10 years
4) WMH progression short form – a few commonly available and useful variables for predicting progression of WMH disease over 10 years

**Limitations:** More recent ARIC MRI data is available; however, because these visit 5/ARIC-NCS scans were completed on a 3T MRI, progression from earlier MRI visits is not easily calculated. In addition, for the purposes of this proposal, we are interested in WMH progression at a slightly younger age (ages for visit 3 through Brain MRI visit), since this might be a group for whom interventions aimed at decreasing progression would be most important.
7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes  
   ____ 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?  
    ____ 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”?  
     ____ 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/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)?

    MP 2351: Power, Gottesman; Association of BP with neurodegenerative and  
            cerebrovascular changes on brain MRI

    MP 2244: Power, Gottesman; Smoking and progression of white matter hyperintensities:  
            The ARIC-MRI Study

    MP 1902: Dearborn, Gottesman: The metabolic syndrome, MRI volumetrics and  
            cognitive outcomes: Brain structure and function in the ARIC cohort

    MP 2315: Schneider, Gottesman; Association of diabetes with brain magnetic resonance  
            imaging

    MP 2179: Wruck; Ischemic stroke risk score at baseline and 20-year cognitive decline:  
            The Atherosclerosis Risk in Communities Study
MP 824: Chambless; Ischemic stroke risk prediction (referenced)

MP 1387: Gottesman; Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI study

MP 1961: Variability of BP and its impact on CHD, Stroke, and Heart Failure risk prediction in the ARIC 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* 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/

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


