ARIC Manuscript Proposal #3653

PC Reviewed: 6/9/20 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Silent small vessel cerebrovascular disease in individuals with a family history of coronary artery disease: The ARIC Study

b. Abbreviated Title (Length 26 characters): WMH and Family History of CAD

2. Writing Group:

Writing group members: Michelle C. Johansen M.D., Ph.D, (first author), Paul Nyquist M.D., Myriam Fornage Ph.D., M.P.H., Rebecca F. Gottesman M.D., Ph.D, Diane M. Becker M.P.H., ScD. (last author) with others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __MCJ___ **[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: 1 year, data acquisition and statistical analysis first few months, planned interim abstract submission fall 2020, final manuscript submission planned mid 2021

4. Rationale:

Family history (FH) of early onset coronary artery disease (CAD) has been found to have a strong association with multiple measures of atherosclerotic vascular disease in the heart in the absence of manifest disease in healthy persons, independent of known risk factors. There is evidence of a marked excess risk of clinically manifest coronary artery disease (CAD) events, independent of cardiovascular risk factors, in originally healthy biological relatives of probands with a CAD event prior to 60 years of age.[1] Preclinical CAD was found to be highly prevalent in these families using CT imaging and SPECT techniques.[2-4]

It is possible that early coronary atherosclerosis may be associated with other vascular disease, including cerebral arteriosclerosis, which manifest itself in the brain as silent small vessel cerebrovascular disease (SVCVD). Other research efforts have supported a high prevalence of ischemic white matter hyperintensities (WMH) in those with coronary atherosclerosis and a significant relationship between measures of preclinical CAD and WMH volumes.[6-8] What remains to be determined is if FH of CAD conveys an excess risk of larger, preclinical WMH volumes. To date, the effect of FH of early vascular disease on preclinical SVCVD has not been examined and ARIC provides a unique cohort in which to answer this question. We thus have posited that the high prevalence of preclinical SVCVD, independent of traditional risk factors, is associated with a FH of early-onset CAD.

5. Main Hypothesis/Study Questions:

Our objective with this project would be: To determine whether FH of CAD conveys an excess risk of SVCVD independent of traditional risk factors (low density lipoprotein, systolic blood pressure, diabetes mellitus, smoking, age, sex, race etc.)

To do this, we propose comparing markers of SVCVD, specifically WMH volumes, lacunar infarcts and subcortical microbleeds, in persons with a FH, as defined by presence of a sibling or parent with CAD, to those without a FH.

We propose three aims:

A. To compare the presence of markers of SVCVD (lacunar infarcts, subcortical microbleeds, WMH, WMH volumes and % WMH) between the cohort with any level of FH of CAD (parent or sibling) to individuals without a FH of CAD in ARIC.

Hypothesis: Those participants with a FH of CAD will have lacunar infarcts, subcortical microbleeds, larger volumes of WMH and total % WMH compared to those participants without a FH of CAD, independent of traditional vascular risk factors.

B. To compare the presence of markers of SVCVD (lacunar infarcts, subcortical microbleeds, WMH, WMH volumes and % WMH) between the ARIC cohort with a "stronger" FH of CAD, defined as those with two or more family members with CAD, to those with only one relative with CAD, and to those without a family history of CAD (to evaluate for a dose response relationship).

Hypothesis: Those participants with two or more relatives with a history of CAD will have lacunar infarcts, subcortical microbleeds, larger volumes of WMH and total % WMH compared to those participants with only one relative with a history of CAD or those without a family history of CAD. Those participants with one relative with CAD will have lacunar infarcts,

subcortical microbleeds, larger volumes of WMH and total % WMH compared to those with no family history of CAD.

C. (Secondary analysis) To compare markers of SVCVD between the ARIC cohort with a FH of premature CAD (less than age 55 males, less than age 60 females) in any relative (≥1), to those with a family history of CAD, but without a premature family history (≥1), and to those without a family history of CAD.

Hypothesis: Those participants with at least one relative with a premature family history of CAD will have lacunar infarcts, subcortical microbleeds, larger volumes of WMH and total % WMH compared to those participants with only one relative with a history of CAD that is not premature as defined by age, or those without a family history of CAD.

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:
All participants in the ARIC study who have completed a brain MRI at visit 5 will be eligible for inclusion. Those who are demented will be included, but a sensitivity analysis will be performed excluding those with dementia. Those participants with incomplete demographic/covariate information will be excluded (see below).

Outcome:
Lacunar infarcts (presence and frequency of lacunes), subcortical microbleeds (presence), WMH, volume of WMH and % total WMH will be used from ARIC visit 5. Specifically the variables LAC15PRES51-Presence of lacunes, LAC20FREQ51-Frequency of lacunes, SUBCORTICALCMHPRES51-Presence of subcortical microhemorrhages, WMHPCT51-Percentage of white matter hyperintensities, WMHPRES51-White matter hyperintensity presence, WMHVOL51-Volume of white matter hyperintensities, will be used.

Exposure:
The exposure of interest is a family history of CAD as well as premature CAD, defined by age. Parental data was collected at visit 1 and Sibling data was collected at visit 2 in ARIC. The variables that will be used for the family history analysis will be: MOMHISTORYCHD -New Maternal History of CHD, DADHISTORYCAD-Paternal history of CAD, MOMPRECHD-Maternal history of premature CAD (before age 60), DADPRECHD-Paternal history of premature CAD (before age 55), FHXA12/21/30/39/48-Did your sibling ever have a heart attack?, FHXA13/22/31/40/49- If so, age at time of heart attack?

In the event that the data is unavailable, or the information is unknown, it will be assumed that a family history did not exist. A sensitivity analysis will be conducted to see if the associations change when only complete cases are considered.

Other variables:
We will include age, sex, race, and center (combined variable, race*center). In addition systolic blood pressure, diabetes, low density lipoprotein, smoking status, education and total intracranial volume will be included in the adjustment models. Cognitive status, defined based on the ARIC-

NCS expert classification, will be used to exclude participants with a history of dementia in the sensitivity analysis.

Specifically the variables used in the adjustment models will be either baseline variables, or those collected at visit 5. They are as follows: V5AGE51-Visit 5 age, GENDER-Sex, RACEGRP-Race, V5CENTER-Visit 5 Field Center, HYPERT55-V5 HTN definition 5 (SYSTOLIC51 GE 140 or DIASTOLIC51 GE 90 or HTN medication), LDLSIU51-v5 ldl Cholesterol in SI Units, DIABTS56-V5 Diabetes - Hemoglobin A1C, cutpoint 6.5%, EVRSMK52-V5 ever smoked cigarettes, DEMDXL1-Dementia diagnosis level 1, ETIV51-Estimated total intracranial volume (eTIV; mm3), ELEVEL01-highest education completed (continuous, number)

Analytic plan:
Multivariable regression models will be used to determine the association of WMH (linear regression for volume of WMH and % total WMH; logistic regression for presence of WMH) with a family history of CAD, first adjusting for demographics and then successively for the possible confounding risk factors and eTIV. WMH volumes will be log-transformed due to skewed nature of the data. FH will be defined per the levels above.

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? ____ 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"? ____ 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) Family history of stroke and MRI abnormalities-Rich et al.
2) Family history of coronary heart disease predicts incident coronary heart disease-Tyroler 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* ___ARIC NCS_____)

___ 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.
Yes, we understand this provision.

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x___ No.

Bibliography:

1. Vaidya D, Yanek LR, Moy TF, Pearson TA, Becker LC, Becker DM. Incidence of coronary artery disease in siblings of patients with premature coronary artery disease: 10 years of follow-up. Am J Cardiol 2007;100:1410-1415.

2. Kral M, Skoloudik D, Sanak D, et al. Assessment of relationship between acute ischemic stroke and heart disease--protocol of a prospective observational trial. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2012;156:284-289.

3. Kral BG, Becker LC, Vaidya D, et al. Noncalcified coronary plaque volumes in healthy people with a family history of early onset coronary artery disease. Circ Cardiovasc Imaging 2014;7:446-453.

4. Kral BG, Nyquist P, Vaidya D, et al. Relation of subclinical coronary artery atherosclerosis to cerebral white matter disease in healthy subjects from families with early-onset coronary artery disease. Am J Cardiol 2013;112:747-752.

5. Nyquist PA, Wityk R, Yanek LR, Vaidya D, Yousem DM, Becker LC, Becker DM. Silent small-vessel cerebrovascular disease and silent myocardial ischemia in families with premature coronary disease. Neuroepidemiology 2009;33:66-67.

6. Nyquist PA, Bilgel M, Gottesman R, et al. Age differences in periventricular and deep white matter lesions. Neurobiol Aging 2015;36:1653-1658.

7. Nyquist PA, Yanek LR, Bilgel M, et al. Effect of white matter lesions on manual dexterity in healthy middle-aged persons. Neurology 2015;84:1920-1926.

8. Nyquist PA, Yanek LR, Kral BG, Becker LC, Vaidya D, Becker DM. White matter lesion progression and cognitive function over 5 years in a young susceptible population. Neuroepidemiology 2017;49:62-63.