ARIC Manuscript Proposal # 3216

PC Reviewed: 8/14/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Incidence and risk factors associated with carotid endarterectomy in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Carotid endarterectomy in ARIC

2. Writing Group:
Writing group members: Caitlin W. Hicks, Natalie Daya, James Black III, Gerardo Heiss, Kunihiro Matsushita, Elizabeth Selvin; others welcome

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

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3. Timeline: Data to be used in this proposal are available. Analyses and manuscript preparation will be performed over the next 12 months.

4. Rationale:

The prevalence of carotid artery stenosis (CAS) is estimated to be approximately 4% in the United States [1]. The risk of CAS has been shown to be significantly higher for persons with hypertension, smoking history, hyperlipidemia, coronary heart disease (CHD), diabetes, and chronic kidney disease (CKD) [1,2]. As a result, the American Heart Association (AHA) recommends intensive medical therapy to control hypertension, hyperlipidemia, diabetes, obesity, and encourage smoking cessation among patients with atherosclerotic disease of the extracranial carotid arteries [3].

For patients with moderate- or severe CAS, carotid revascularization is recommended. The Society for Vascular Surgery recommends carotid endarterectomy (CEA) for symptomatic patients with 50-99% stenosis and asymptomatic patients with 60-99% stenosis [4]. Similarly, the AHA recommends CEA for patients with symptomatic patients with 50-99% stenosis and asymptomatic patients with 70-99% stenosis [3]. Based on these guidelines, nearly 50,000 carotid revascularization procedures are performed in the United States annually [5].

Despite numerous clinical trials designed to define the indications for and risks associated with CEA [6-8], there are significant sex- and race-based disparities in the management of CAS. Black patients have been shown to undergo less CAS screening than white patients [9,10], and present more frequently with disabling ischemic stroke events [11]. Similarly, women are less frequently offered CEA for CAS than men [12,13], despite data showing equivalent periprocedural outcomes [14]. The aim of the current study is to describe risk factors associated with the incidence of CEA among a community-based population without prevalent CAS. Specifically, we are interested in exploring race- and sex-based disparities in the incidence of CEA after adjusting for traditional CAS risk factors.

5. Main Hypothesis/Study Questions:

The aim of this study is to describe the incidence of and risk factors associated with CEA among participants in the ARIC study without prevalent carotid artery stenosis at visit 1. We hypothesize that there will be significant variation in the incidence of CEA based on sex, race, and center that is independent of traditional CAS risk factors.

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/Exclusion

We will include all black or white ARIC participants who did not have prevalent carotid artery stenosis at visit 1. Participants with self-reported ethnicities other than black or white will be excluded.

Exposures of Interest:

Exposures of interest for this study will include the following variables: sociodemographics (age, race-center, sex, education, income), physical information (blood pressure, weight, body mass index [BMI]), lifestyle (smoking status, alcohol consumption), comorbidities (diabetes, dyslipidemia, hypertension, CHD, CKD, stroke), and clinical variables (LDL-c, HDL-c, triglycerides, systolic blood pressure). We will collect data on the presence of

symptomatic and asymptomatic carotid artery disease ICD-9 diagnosis codes through linkage with CMS data.

Outcomes:

The primary outcome of interest is hospitalization for carotid endarterectomy after visit 1. Carotid endarterectomy procedures were identified using the CCS-Procedures Category 51 (endarterectomy; vessel of the head and neck).

Analysis Plan:

We will conduct a prospective cohort analysis of existing data from the ARIC Study. For the first stage of the analysis, we will estimate cumulative incidence of CEA overall as well as for clinical subgroups of interest (male vs. female, white vs. black, and also by race-center) using the Kaplan-Meier method.

For the second stage of the analysis, we will construct a series of multivariable Cox proportional hazards models to describe risk factors associated with undergoing carotid endarterectomy. Model 1 will be an unadjusted model. Model 2 will include age, sex, race-center, education level, and income level. Model 3 will further adjust for potential atherosclerotic risk factors, including dyslipidemia, smoking, BMI, hypertension, diabetes, CHD, CKD, stroke, and symptomatic status.

Limitations:

The main limitation of this study is the lack information regarding indication for surgery in affected participants. We will include stroke as a covariate in the analysis to represent symptomatic status, and we will link to CMS data to extract data on the presence of symptomatic or asymptomatic carotid artery disease based on ICD-9 diagnosis code. However, data on transient ischemic attacks, amarousis fugax, and other symptoms possibly attributable to carotid artery disease are limited. We also cannot account for degree of carotid artery stenosis or the distribution of disease, which may differ between races and by sex. Carotid intima-media thickness is available for the early ARIC visits, but not the later visits. Similarly the carotid MRI study provides data on a subset of patients, but not all patients. Based on preliminary analysis we estimate that there are 357 CEA events between ARIC visit 1 and visit 6; given this small number, we do not want to limit our analysis to a smaller subset of patients. An additional limitation is the race-site aliasing inherent in the ARIC Study design. We can conduct exploratory analyses comparing black and white participants at the Forsyth Field Center, but ultimately we will not be able to separate out any "effects" of race from geography given the ARIC Study design.

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)?

There are currently no manuscript proposals in ARIC that evaluate carotid endarterectomy as an outcome. Manuscript proposal #591 (Risk for carotid artery stenosis in the Washington county ARIC cohort) and manuscript proposal #379 (Prevalence and risk factors of clinically significant carotid artery narrowing), and manuscript proposal #261 (The relationship of carotid artery atherosclerosis to family history of coronary heart disease in African-Americans and whites) are the most related proposals in ARIC. The senior authors on each of these manuscript proposals will be invited to collaborate on this study so that we can benefit from their experience and expertise on this topic.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ 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.

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 __X__ Yes ____ No.

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