ARIC Manuscript Proposal #2598

PC Reviewed: 8/11/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Stroke and Risk of Subsequent Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Stroke and Risk of Hospitalization

2. Writing Group:
Writing group members:

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

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3. Timeline:

We anticipate that data analysis and manuscript preparation will be complete in 6-12 months.

4. Rationale:

The burden of stroke in the United States is high. Stroke is the 5th leading cause of death and the leading cause of disability in the United States[1]. Approximately 795,000 strokes are diagnosed in the United States every year and more than 125,000 of these result in death[1]. Stroke represents a significant proportion of United States healthcare costs (approximately $35 billion per year)[1]. Overall, inpatient hospitalizations account for the majority of all medical expenditures[2]. Indeed, a significant proportion of stroke-related medical expenditures are related to inpatient hospital care for acute stroke events, which comprised approximately 25% of the total estimated cost[3]. However, this estimate only includes the cost of hospitalization for an acute stroke event and does not include the cost of hospitalizations occurring after a stroke event. Prior studies have suggested that hospitalizations among stroke survivors are common[4,5]. However, the magnitude of risk of cause-specific hospitalization by stroke subtype (ischemic [thrombotic, cardioembolic, lacunar] and hemorrhagic [intracerebral, subarachnoid]) occurring within 30-days, 1-year, and long-term after an incident stroke event are not well characterized. Further, trends in all-cause and cause-specific hospitalization occurring after stroke over time have not been previously described.

Few studies have investigated causes for hospitalization occurring after an incident stroke event. Two studies (one Taiwanese and one European) reported that the most common reasons for subsequent hospitalizations after an incident stroke event (combined ischemic and hemorrhagic strokes for the Taiwan study and ischemic stroke for the European study) include infection, recurrent stroke, and cardiovascular disease[4,6]. However, these studies did not investigate cause-specific hospitalization risk by stroke type or by stroke subtype. Reasons for hospitalization after stroke may vary by stroke type and stroke sub-type. Indeed, prior studies have reported higher risk of all-cause hospitalization after ischemic strokes compared to hemorrhagic strokes[7,8]. In contrast, another study reported no difference in risk of hospitalization after ischemic versus hemorrhagic stroke[4].

To our knowledge, no study has reported risk of cause-specific hospitalization by subtypes of ischemic (thrombotic, cardioembolic, lacunar) and hemorrhagic (intracerebral, subarachnoid) stroke. Prior work in ARIC[5] suggests that the risk of long-term all-cause hospitalization after an incident stroke event was highest for cardioembolic ischemic strokes compared to thrombotic ischemic stroke (HR 1.4 [95% CI: 1.1-1.7]). Those with cardioembolic ischemic strokes also had higher incidence of cardiovascular-disease related hospitalizations[5]. In contrast, lacunar ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage did not have significantly different risks of all-cause and cardiovascular-disease related hospitalization compared to thrombotic ischemic stroke[5]. We propose to add to this body of literature by investigating relationships between stroke types (ischemic and hemorrhagic) and stroke sub-types (ischemic [thrombotic, cardioembolic, lacunar] and hemorrhagic [intracerebral, subarachnoid]) with cause-specific hospitalizations occurring within 30-days, 1-year, and long-term after an incident stroke. We also propose to investigate trends in all-cause and cause-specific hospitalization occurring after incident all-cause stroke events over time follow-up (1987-2012).

5. Main Hypothesis/Study Questions/Objectives:

Objective:

- To assess the association of stroke types (ischemic and hemorrhagic) and stroke sub-types (ischemic [thrombotic, cardioembolic, lacunar] and hemorrhagic [intracerebral, subarachnoid]) with cause-specific hospitalizations occurring within 30-days, 1-year, and long-term after an incident stroke event among community dwelling adults.
- To investigate trends in all-cause and cause-specific hospitalization occurring after incident all-cause stroke events over time following incident stroke diagnosis (1987-2012).

Hypotheses:

- The most common primary system-based cause for hospitalization after any stroke event will be infection-related, with aspiration pneumonia and urinary tract infections being the most common disease-specific causes.
- Ischemic strokes will have higher risk of hospitalization for cardiovascular disease related causes compared to hemorrhagic stroke.
- Cardioembolic ischemic strokes will have higher risk of atrial fibrillation and systolic heart failure related hospitalizations compared to other stroke sub-types whereas lacunar ischemic strokes and intracerebral hemorrhages will have higher risk of hypertension related hospitalizations compared to other stroke sub-types.
- Reasons for hospitalization for any stroke will vary by time frame analyzed, with infection related hospitalization being more common earlier (e.g., within 30-days) and cardiovascular causes being more common over time (e.g., 1-year and long-term follow-up).
- Rates of all-cause and cause-specific hospitalizations occurring after incident stroke events will decrease over study follow-up (1987-2012).
- Rates of all-cause and cause-specific hospitalizations will be higher among those with longer incident-stroke-related hospitalizations.

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).

Study Design:
Prospective cohort study (1987-2012).

Inclusion/Exclusion Criteria:
Main Analysis: Using ARIC hospitalization data 1987-2012

- Inclusion Criteria: All participants who experienced an incident definite/probable stroke (as defined by ARIC adjudication) and who survived to hospital discharge between the years of 1987 to 2011 (to allow at least 1-year of follow-up time for hospitalization events).
- Exclusion Criteria:
    - Participants with stroke occurring prior to 1987 (prevalent stroke)

- Non-white race, non-black race, or black race at the Minnesota or Maryland field centers

Sensitivity Analysis: Using ARIC and CMS hospitalization data 1999-2012
Analyses will utilize the combined ARIC CEL/CHI/CMS hospitalization file, which contains hospitalization information obtained from ARIC medical records and from the CMS Medicare Provider Analysis and Review (MedPAR) file. The CMS Medicare hospitalizations records in the combined file are not limited to records for participants enrolled in Medicare fee-for-service programs. Inclusion of managed care records in CMS inpatient claims was not required until 2008, therefore to avoid bias in the ascertainment of hospitalizations based on CMS Medicare data, we will limit analyses to hospitalizations that are within windows of participants' fee-for-service enrollment.

- Inclusion Criteria: All participants who experienced an incident definite/probable stroke (as defined by ARIC adjudication) and who survived to hospital discharge between the years of 1999 to 2011 (to allow at least 1-year of follow-up time for hospitalization events).
- Exclusion Criteria:
  - Age <65 years at time of stroke
  - Persons with stroke occurring prior to 1999 (prevalent stroke)
  - Missing CMS data (will exclude non-fee-for-service hospitalizations)
  - Non-white race, non-black race, or black race at the Minnesota or Maryland field centers

For the main analysis, we estimate that there are approximately 1,200 incident strokes that occurred between the years of 1987 to 2011 among ARIC participants[9]. For the sensitivity analysis, we estimate that there are approximately 600 incident stroke cases that occurred between the years of 1999 to 2011 among ARIC participants who were aged 65 years or older at the time of stroke[9].

Exposure(s):
Definite/probable incident stroke (as defined by ARIC adjudication) classified by stroke types (ischemic and hemorrhagic) and stroke subtypes (ischemic [thrombotic, cardioembolic, lacunar] and hemorrhagic [intracerebral, subarachnoid]).

Outcome(s):
We will use data ascertained through hospitalization reports from annual telephone contact with study participants and active surveillance of hospitalizations occurring in the study community hospitals. Follow-up is currently available from baseline through December 31, 2012. In sensitivity analyses, we will add CMS fee-for-service hospitalization data (available only on a subset of ARIC participants aged 65 years or older starting in 1999). The first ICD-9 code listed in the hospital discharge documentation will define the primary cause for hospitalization.

Our main outcome will be cause-specific hospitalizations. We will categorize the primary cause of each hospitalization using the Clinical Classification Software developed by the Agency for Healthcare Quality and Research[10]. According to this categorization, the primary cause of each hospitalization will be classified into 18 systems-based categories and then sub-classified into

285 disease-based categories[10]. In our analyses looking at trends in hospitalization over time, we will look at both all-cause and cause-specific hospitalizations.

Covariates:
Covariates included in the main statistical model will include: age at time of stroke (continuous; years), sex (male; female), and race/center (Minnesota whites; Maryland whites; North Carolina whites; North Carolina blacks; Mississippi blacks).

Supplemental statistical models will add the following covariates (assessed at visit occurring prior to stroke event or as time-varying over follow-up): education (<high school; high school or equivalent; college, graduate or professional school), family income (<$35,000/year; ≥$35,000/year; not reported), health insurance (yes; no), body mass index (BMI, continuous; weight [kg]/height [m^2]), cigarette smoking (current; former; never), systolic and diastolic blood pressure (continuous; mmHg), hypertension medication use (yes; no), coronary heart disease (yes; no), total and high-density lipoprotein (HDL) cholesterol (continuous; mg/dl), and cholesterol medication use (yes; no).

Data Analysis:
Baseline characteristics (defined at time of stroke or visit just prior to stroke) will be shown overall and by stroke subtype (ischemic [thrombotic, cardioembolic, lacunar] and hemorrhagic [intracerebral, subarachnoid]). T-tests will be used to compare means for continuous variables and chi-square tests will be used to compare proportions for categorical variables. Numbers of cause-specific hospitalizations will be tabulated overall, by stroke type (ischemic and hemorrhagic), and by subtype (ischemic [thrombotic, cardioembolic, lacunar] and hemorrhagic [intracerebral, subarachnoid]).

We will calculate adjusted rates of cause-specific hospitalization per 1,000 person-years (95% confidence intervals) overall, by stroke type (ischemic and hemorrhagic), and by subtype (ischemic [thrombotic, cardioembolic, lacunar] and hemorrhagic [intracerebral, subarachnoid]) using Poisson or negative binomial regression models. We will determine if negative binomial regression models are preferred over Poisson models for our data by assessing for over-dispersion (likelihood-ratio test of alpha=0). We will also determine if zero-inflated Poisson or negative binomial regression models are necessary (depending on how many participants were never hospitalized during follow-up). We will use Akaike information criterion and the Vuong test will be used to assess goodness-of-fit for our models.

We will evaluate hospitalization rates and causes during three time periods: 1) from stroke until death, loss to follow-up or administrative censoring whichever came first, 2) 30-days post-stroke and 3) 1-year post-stroke. .

In our trends analyses looking at trends in all-cause and cause-specific hospitalization occurring after any stroke event (and depending on power, by ischemic versus hemorrhagic stroke separately), we will divide follow-up time (1987-2012) into time periods (number of periods will depend on power) and compare rates of all-cause and cause-specific hospitalizations over time.

Our main statistical model will be adjusted for the demographic variables of: age at time of stroke, sex, and race/center. We will also consider a supplemental statistical model further

adjusted for the socioeconomic and cardiovascular disease risk factors of: education, family income, health insurance status, body mass index, cigarette smoking status, systolic blood pressure, diastolic blood pressure, hypertension medication use, coronary heart disease, total cholesterol, HDL cholesterol, and cholesterol medication use. In analyses limited to CMS Medicare data we will include as a covariate use of post-discharge rehabilitation services.

We will formally test for multiplicative interaction by age, race, and sex in our main statistical models and if there is evidence for interaction, we will present stratified analyses.

Limitations:
Although the ARIC study ascertained hospitalization data via both annual telephone contact with study participants and active surveillance of hospitalizations occurring in all study communities, some hospitalizations occurring among ARIC participants (e.g., hospitalizations outside of the surveillance areas that are not reported during follow-up) are likely not captured in our data used in the main analysis. Therefore, our results from main analysis will likely underestimate the true rates of hospitalization in our population. However, we will perform a sensitivity analysis adding CMS hospitalization data as a way to assess and estimate the amount of underestimation. The sensitivity analysis adding CMS data will have its own limitations, including being restricted to the years of 1999 to 2011, to participants aged 65 years or older at the time of stroke, and to fee-for-service hospitalizations. Our analyses by stroke subtypes (thrombotic, cardioembolic, lacunar, intracerebral hemorrhage, subarachnoid hemorrhage) may be limited by low power for certain subtypes of stroke, especially in the analyses limited to CMS Medicare data .

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)?

MSP 1264: Stroke Survival and Weekend Admission (Emily O'Brien)

MSP 1327: Association Between Initial Etiological Stroke Subtype and Recurrent Etiological Stroke Subtype and Vascular Event Type (Souvik Sen)

MSP 2030: Twenty-five Year Trends in Stroke Incidence and Mortality in the Atherosclerosis risk in Communities (ARIC) Study (Silvia Koton)

MSP 2102: Validity of Hospital Discharge Diagnosis Codes for Stroke in Four US Communities (Sydney Jones)

MSP 2277: Burden of Stroke in the US: Data from the National Inpatient Sample and the Atherosclerosis risk in Communities (ARIC) Study (Silvia Koton)

MSP 2391: Hospitalized Infection as a Trigger for Acute Ischemic Stroke in the ARIC Study (Logan Cowan)

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.

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