ARIC Manuscript Proposal #3801

PC Reviewed: 3/9/21 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: **The Association between Ischemic Stroke Subtype and Stroke Severity: The ARIC Study**

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Michelle C. Johansen (1st Author and Corresponding), Josef Coresh, David Knopman, Andrea L. C. Schneider, Julia Carlson, Taylor Haight, Kamakshi Lakshminarayan, Shalom Patole, Rebecca F Gottesman, Silvia Koton (Last and Sr. Author)

Writing group members: Others welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. **_MCJ____**

First author: **Michelle C. Johansen**
Address: 600 N Wolfe Street
Phipps 4-446
Baltimore, MD 21287

Phone: 410-955-2228 Fax: 410-614-9807
E-mail: mjohans3@jhmi.edu

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).

Name: **Rebecca F. Gottesman**
Phipps 446; 600 North Wolfe Street; Baltimore, MD 21287
Phone: 410-614-2381 Fax: 410-955-0672
E-mail: rgottesm@jhmi.edu

3. Timeline: Analysis to begin as soon as proposal is approved, planned abstract submission fall of 2021 with manuscript submission for ARIC review beginning of 2022.

4. Rationale:

Ischemic stroke is associated with disability after it occurs. Disability post-stroke can be captured by the NIHSS, a standardized algorithm by which physical deficits are enumerated, as well as by the modified Rankin Scale, a way to define functional deficits post-stroke. While disability can and does occur across ischemic stroke subtypes, there is literature to suggest that

some specific stroke mechanisms are associated with more severe deficits post-stroke than other stroke mechanisms.

Cardioembolic stroke (CS), or where the thrombus arises from the heart and travels to the brain resulting in stroke, is financially[1] and socially costly to patients and their families due to high rates of recurrence and the highest rate of mortality compared to other stroke sub-types.[2] Hospital readmission is common for CS, with estimates ranging from 20-27% in the first year[3,4] and CS readmission rates are 40% higher than thrombotic stroke.[5] The prevalence of CS is increasing in the elderly, who represent a growing population at the highest risk for incident CS.[6] Atrial fibrillation (AF) is the most common cause of CS, and it has been suggested that AF associated CS is associated with worse 90-day outcomes and represents the most severe ischemic stroke mechanism.[7] Finally, CS more frequently occurs in the anterior circulation, where strokes are known to adversely impact cerebral structures that are of the utmost importance to both cognition and self-care.

While CS is known to be severe, and devastating, an important remaining question is whether the more direct measures of physical and functional outcome, such as the NIHSS and mRS, would differ between strokes of other subtypes. Specifically, do patients with CS and similar demographics and vascular risk profiles, have more severe strokes and worse functional outcome, to include mortality, than strokes of other subtypes? Clarifying this question will aid to better define any discrepancies in stroke care, and will represent a first step in defining the pathophysiologic link between stroke mechanism and patient outcome.

Another important step in understanding the relationship between CS and stroke outcomes compared to other stroke subtypes is the interaction with race and sex. Both sex and race are known to differentially impact both cardiovascular disease, and cerebrovascular disease. Women have been shown in some studies to have worse outcomes after stroke than men, despite adjusting for age. Additionally, adjusting for covariates such as pre-stroke function, while reducing these discrepancies, did not account for the differences in other work.[8] The interaction with race and stroke subtype is also not well understood. Black patients do not have as high a prevalence of AF compared to white patients, and among older individuals with AF, the risk of death and stroke was higher in black patients, but this was eliminated when adjusting for co-morbidities.[9]

The main aim of this study is to determine if there is a difference in the severity of stroke on admission based on stroke subtype with the specific hypothesis being that embolic strokes, as adjudicated and defined in ARIC, will be significantly associated with more severe stroke, characterized by a worse NIHSS on admission and a poorer mRS at discharge, or death, compared to strokes of all other subtypes, and that this association will differ by race and sex.

5. Main Hypothesis/Study Questions:

Study Aim 1: To determine if there is a difference in stroke severity on admission among ARIC participants with non-hemorrhagic strokes by stroke subtype.
Hypotheses:

1. Participants with an embolic stroke (definite and probable embolic stroke, ARIC adjudicated and defined) will have a higher NIHSS on admission compared to participants with non-hemorrhagic strokes of all other subtypes, independent of demographics and vascular risk factors.

2. The relative increase in stroke severity, measured by NIHSS, in the participants with embolic stroke versus other stroke subtypes will be greater in Black participants compared to white participants, independent of demographics and vascular risk factors.

3. The relative increase in stroke severity, measured by NIHSS, in the participants with embolic stroke versus other stroke subtypes will be greater in female participants compared to male participants, independent of demographics and vascular risk factors.

Study Aim 2: To determine if there is a difference in functional outcome after stroke, measured by the mRS and mortality, among ARIC participants with non-hemorrhagic strokes by stroke subtype.

Hypotheses:

1. Participants with an embolic stroke (definite and probable embolic stroke, ARIC adjudicated and defined) will have a poorer mRS at discharge compared to participants with non-hemorrhagic strokes of all other subtypes, independent of demographics and vascular risk factors.

2. Participants with an embolic stroke are more likely to dead during study follow up after the incident stroke event, than participants with other stroke subtypes, independent of demographic and vascular risk factors. We also hypothesize that this difference in mortality between stroke subtypes will be mediated by stroke severity.

3. The relative increase in mRS in the participants with embolic stroke versus other stroke subtypes will be greater in Black participants compared to white participants, independent of demographics and vascular risk factors.

4. The relative increase in mRS in the participants with embolic stroke versus other stroke subtypes will be greater in female participants compared to male participants, independent of demographics and vascular 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).

Study cohort:

The inclusion criteria will be participants in the ARIC study, across all study visits, with non-hemorrhagic strokes (ischemic strokes), stroke severity data and complete demographic and vascular risk factor data. Participants will be excluded if they have had a previous stroke prior to the baseline visit as we are interested in associations with incident, not recurrent stroke. This will be a non-concurrent, cross-sectional analysis in the sense that the vascular risk profile will be obtained from the ARIC study visit that immediately preceded the stroke event. Demographics will be obtained from ARIC baseline.

Stroke Subtype:

Stroke is classified in ARIC according to established adjudication guidelines and ischemic strokes will be considered in this analysis. The primary classification will consider non-carotid embolic brain infarction (definite and probable) versus strokes of all other subtypes. In the first sensitivity analysis, we will consider each stroke subtype individually, recognizing that this is likely to be underpowered. In a second sensitivity analysis, will we exclude participants with possible stroke of undetermined type from the comparator group in our binary analysis (embolic

stroke vs other) to see how this changes effect estimates as it has been hypothesized that some of the stroke of undetermined type actually represent an embolic mechanism not currently captured.

Statistical Analysis:

Ordinal logistic regression will be used to determine if there is association between NIHSS category (minor, moderate and severe as defined below) and stroke subtype, adjusting for demographic and vascular risk factors. If the hazards are not proportional between the categories of NIHSS, multinomial logistic regression will instead be used. Ordinal logistic regression will also be used to determine if there is an association between categories of discharge mRS (0-2, 3-5, 6) and stroke subtype, adjusting for demographic and vascular risk factors.

A cox proportional hazards model will be used to determine if stroke subtype (embolic versus others) is associated with mortality (through December 31, 2019) after incident stroke, accounting for demographics and vascular risk factors, and if the effect of stroke subtype on mortality is mediated through stroke severity on admission (NIHSS).

Ordinal (or multinomial) logistic regression with interaction terms, for race and sex, each in separate models, will be used to determine if there is a difference across race or sex in the association between stroke severity (NIHSS) and stroke subtype with adjustment for demographics and vascular risk factors. Multivariable logistic regression with interaction terms for race and sex, in separate models, will be used to determine if there is a difference in the association between dichotomized mRS and stroke subtype.

Study Outcomes:

NIHSS on admission will be described continuously in the cohort (0-42), but will be categorized into minor stroke (NIHSS$\leq$5), moderate severity stroke (NIHSS 6-10) and severe stroke (NIHSS $\geq$11) for formal analysis. mRS at discharge will be categorized (0-2, 3-5, 6). Mortality will be defined as per ARIC, and all-cause mortality will be considered. In a sensitivity analysis, cardiovascular causes of mortality will be considered.

Study Covariates:

We will include race*center, sex, age, education, prevalent CHD and AF information from ARIC baseline. The other covariates will be obtained from the study visit that immediately preceded the incident stroke event. Specifically, these will be hypertension, diabetes, total cholesterol, body mass index and smoking.

AF will be considered in the adjustment model as AF confounds the relationship between stroke subtype and stroke severity. However, we acknowledge that AF is one of the reasons that a patient may be adjudicated as having an embolic stroke. Characteristics of patients with and without AF and incident ischemic stroke subtype will be described in the manuscript and AF will be also added to the final adjustment model in a sensitivity analysis.

Additionally age at the time of stroke, which will be considered continuously in the primary model, will be dichotomized into old $\leq$75yo vs. older >76, and the characteristics of participants with each stroke subtype, and stroke severity based on these age categories will be described.

Limitations:

We recognize that there are limitations in defining study covariates based on the study visit that is closest in time (preceded) the onset of the acute ischemic stroke. We will state this as a limitation in the manuscript, but anticipate that the trajectory of these vascular risk factors would not have changed dramatically in the years that may have passed prior to the stroke event and would still account for some degree of confounding. We will not consider covariates that are collected after the incident stroke, as these may have changed as a result of initiation of therapies as a result of the ischemic stroke. We recognize that when considering mortality, it may be that covariates collected after the stroke event might reflect factors that could impact the relationship between stroke subtype and mortality. In order to be consistent across analyses, and recognizing that the covariates will not be at the same time of the stroke event, we have chosen to consider those immediately prior to the stroke event as most reflective of vascular risk at the time of the stroke.

We also recognize that there may be changes in stroke care across the time in which the ARIC study was performed that would independently affect the participant outcome, such as the advent of thrombectomy in stroke care circa 2015. The majority of the adjudicated stroke cases from ARIC with severity data pre-date this change, and additional manuscripts will address the impact of acute interventional therapies on stroke severity. Additionally, intravenous tissue plasminogen activator was approved in 1999, and therefore we do not anticipate that this therapy would have changed dramatically over the six study visits. There would not be an anticipated difference in administration of IV tPA based on stroke subtype alone, apart from severity, so we would anticipate administration to affect all stroke subtypes equally.

We recognize that there may be cases in which stroke severity data is not available. We could consider using multiple imputation, or worst case scenario in which the participants without stroke severity data are considered in the severe stroke category (NIHSS ≥11). We anticipate this to be a small proportion of cases.

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/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)?

#3672- Stroke Incidence and Severity as Risk Factors for Dementia and MCI in the ARIC cohort Study
#3490- Thirty-year trends in stroke severity on admission in the Atherosclerosis Risk in Communities (ARIC) 1987-2017

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 https://www2.cscc.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.

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.

References:

1. Winter Y, Wolfram C, Schaeg M, et al. Evaluation of costs and outcome in cardioembolic stroke or TIA. *J Neurol*. 2009;256(6):954-963.

2. Redfors P, Jood K, Holmegaard L, Rosengren A, Blomstrand C, Jern C. Stroke subtype predicts outcome in young and middle-aged stroke sufferers. *Acta Neurol Scand*. 2012;126(5):329-335.

3. Thorngren M, Westling B, Norrving B. Outcome after stroke in patients discharged to independent living. *Stroke*. 1990;21(2):236-240.

4. Sacco RL, Hauser WA, Mohr JP. Hospitalized stroke in blacks and hispanics in northern manhattan. *Stroke*. 1991;22(12):1491-1496.

5. Jones SB, Sen S, Lakshminarayan K, Rosamond WD. Poststroke outcomes vary by pathogenic stroke subtype in the atherosclerosis risk in communities study. *Stroke*. 2013;44(8):2307-2310.

6. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. *Heart Rhythm*. 2019.

7. Henninger N, Goddeau RP,Jr, Karmarkar A, Helenius J, McManus DD. Atrial fibrillation is associated with a worse 90-day outcome than other cardioembolic stroke subtypes. *Stroke*. 2016;47(6):1486-1492.

8. Gall S, Phan H, Madsen TE, et al. Focused update of sex differences in patient reported outcome measures after stroke. *Stroke*. 2018;49(3):531-535.

9. Kabra R, Cram P, Girotra S, Vaughan Sarrazin M. Effect of race on outcomes (stroke and death) in patients >65 years with atrial fibrillation. *Am J Cardiol*. 2015;116(2):230-235.