ARIC Manuscript Proposal # 1327

PC Reviewed: 01/15/08	**Status: _A___**	**Priority: _2__**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between initial etiological stroke subtype and recurrent etiological stroke subtype and vascular event type.

b. Abbreviated Title (Length 26 characters): **Etiological stroke subtype**

2. Writing Group:

Writing group members: Sen, Rosamond, Beck, Offenbacher, Folsom, Shahar, Suri, others welcome.

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

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3. Timeline: Begin analysis by January 1, 2008, first draft by March 30, 2008.

4. Rationale: Stroke recurrence is an important public health concern.[1] Among the estimated 700,000 people with stroke in the United States each year, 200,000 of them are among persons with a recurrent stroke. The number of people with TIA, and therefore at risk for stroke, is estimated to be much greater. Additionally,decline in stroke mortality and the increase in life expectancy of the US population will undoubtedly increase the number of persons at risk for recurrent stroke, stroke-related disability, and the cost of

medical care. The long-term stroke recurrence rates range from 4% to 14% annually. In the Framingham Study,[2] the 5-year cumulative recurrence rate for athero thrombotic brain infarction was 42% for men and 24% for women. In Rochester, Minnesota, the 5-year cumulative recurrence rate was 29%, with no sex difference.[3] Recurrences were generally of the same type as the initial stroke. In the Northern Manhattan Stroke Study,[4] the 5-year stroke recurrence rate was 25%. Overall, stroke recurrence is highest in the first 30 days after the initial event; 30% of recurrences occur within this time frame.[5] However, there may be differences in recurrence rates by stroke subtype.

It is controversial whether the subtype of the index stroke predicts the type of subsequent strokes. Two population-based studies found that recurrences were of the same subtype in almost 90% of cases.[6,7] However, this high level of agreement could have been due to the crude classification used, which differentiated only between ischemic and hemorrhagic strokes. A retrospective hospital-based study with a more detailed categorization of stroke subtypes suggested that stroke recurrences in lacunar and hemorrhagic index strokes are often of a different type.[8] A recent population based study relying solely on clinical presentation to classify stroke, reported a multifactorial origin of stroke recurrence.[9]

Another controversy shrouding the literature relates to the type of vascular events (stroke, MI or death) in stroke patients. Meta-analysis of several antiplatelet therapy trials [10, 11] as well as one population based longitudinal study suggests that the recurrence rate of stroke is higher than the rate of incident MI in stroke patients.[3] However, population-based longitudinal study of stroke patients relate a higher rate of cardiovascular event related mortality including those related to MI compared to stroke related mortality. [12] However these differences in recurrence pattern may be related to a difference in stroke subtypes. For example lacunar stroke may be prone to stroke recurrence, whereas cardioembolic strokes may have a high rate of MI and death.

Although various stroke etiological subtypes have common vascular risk factors, the presumed pathogenesis is variable. Lacunar strokes are believed to arise from microatheroma affecting small penetrating vessels 40-200 μm causing small infarcts ≤1.5 cm in the deep gray matter or subcortical white matter. Large artery atherothrombosis shares the mechanisms that lead to atherothrombosis in other vascular tree (CAD, PAD, etc), is initiated as a inflammatory mediated endothelial injury and progresses to lipid deposition and thrombosis. Cardioembolism on the otherhand originates from cardiac abnormality (example atrial fibrillation) that predisposes to a clot formation that embolizes to the brain vessel. Based on the specific mechanism stroke of a particular stroke subtype should lead to recurrence of the same stroke subtype. This may be modified by risk factors and concomitant stroke prevention medicines such as antiplatelet agents and statins.

Both coronary artery disease and various stroke subtypes have common vascular risk factors. However among the stroke subtypes, only large artery atherothrombosis shares the pathophysiological conditions that lead to atherothrombosis in other vascular tree (CAD, PAD, etc). Hence it is possible that strokes secondary to atherothrombosis are

likely to have cardiac event as the recurrent vascular event, whereas lacunar strokes may have stroke or TIA as the recurrent event. This pattern of recurrent vascular event may be modified by risk factors and concomitant stroke prevention medicines such as antiplatelet agents and statins.

The stroke etiological subtypes are known to have different rate of recurrence. While large artery thrombosis has the highest annual rate of recurrence, lacunar strokes have the lowest rate. It is possible that large artery atherothrombosis has the shortest time to event recurrence and lacunar strokes has the longest. Time to event may be modified by coexistence of vascular risk factors or concommitant medications such as antiplatelet agents and statins.

5. Main Hypothesis/Study Questions:

1. Is the specific initial ischemic stroke etiological subtype associated with specific ischemic recurrent stroke etiological subtype?
2. Is the specific ischemic stroke etiological subtype associated with specific type of vascular events (stroke, MI and death)?
3. Is the initial ischemic stroke etiological subtype associated with a different time to recurrent vascular event?

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).

This is an analysis of recurrent vascular events among the ARIC cohort members through 2005. The analysis includes both cross-sectional and longitudinal elements. All participants with initial stroke will be assessed for stroke subtype and follow-up data on stroke recurrence will be included in the analysis. Through 2004, approximately 800 initial strokes have experienced 229 recurrent strokes. For purposes of question 1 a table will be constructed with primary stroke subtypes (R) and recurrent stroke subtypes (C) and R x C χ^2 test used to detect any association between the two. Similarly for question 2 a table will be constructed with primary vascular event subtypes—stroke, MI, PAD (R) and recurrent vascular subtype subtypes (C) and R x C χ^2 test used to detect any association between the two. In both cases odds ratio will be computed overall and stratified by risk factors and medication (antiplatelet, lipid lowering and antihypertensive meds) to assess for effect measure modification. For purposes of question 3 time to recurrent event will be compared between the groups (stroke subtype) by Kaplan Meier curve and log-rank analysis. Hazards ratio will be assessed to determine the risk of recurrence of stroke or composite vascular events in patients stratified by stroke subtypes.

Limitations: 1. RECURRENT STROKE: All recurrent strokes may not be captured in the ARIC cohort. The severe strokes may have missed follow-up on account of their disability. Also minor and silent strokes may have not been detected due to lack of specific clinical signs or symptoms.

2. MISCLASSIFICATION OF STROKE SUBTYPE: In the ARIC study, "cardioembolic stroke" is not based on scientifically rigorous definition. According to the algorithm, it requires the presence of a possible cardio-embolic source. Presence of a possible cardioembolic source may not necessarily mean cardioembolism as the etiology of the ischemic stroke. Also, artery-to-artery embolic stroke (e.g., dislodged carotid plaque) is classified in ARIC as "atherothrombotic". Lacunar stroke in ARIC is based on some imaging features, regardless of the presence or absence of a "lacunar stroke syndrome". The definition may miss lacunar strokes with negative scans. Also some lacunar strokes may be cardioembolic in etiology. Current methodology do not allow the clear distinction between these subtypes within a stroke etiological type.

Despite the limitations this will be the first look at recurrent stroke etiological subtype in the US population. The South London Stroke register investigate the syndrome subtype (Oxfordshire classification), the Framingham and NOMAS studies have investigated the association between stroke subtype and recurrent stroke (ischemic or hemorhagic), but not the specific recurrent etiological stroke subtype. The proposal has important clinical implications. The initial stroke subtype may correlate with recurrent stroke subtype due to shared stroke risk factors. Alternately, it might not correlate because of treatment effect. Example: A subject with initial cardioembolic stroke from atrial fibrillation and treatment with oral anticoagulation may have a recurrent stroke of the lacunar type. The result will help refine stroke prevention strategy instituted by the clinician.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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

_____ 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)?

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/

12. 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

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