

ARIC Manuscript Proposal #2391

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1.a. Full Title:

Hospitalized infection as a trigger for acute ischemic stroke in the ARIC study

b. Abbreviated Title (Length 26 characters):

Infection and stroke risk

2. Writing Group:

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

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3. Timeline:

Obtain data set: Summer 2014

Begin statistical analysis: Fall 2014

Complete statistical analysis: Winter 2014

Complete manuscript: Spring 2015

4. Rationale:

Stroke is the 4th leading cause of death in the United States,¹ with 795,000 cases in the U.S. each year.² Ischemic strokes account for approximately 85% of all strokes in the U.S. and hemorrhagic strokes explain the remaining 15%.² Population-based cohort studies such as the Atherosclerosis Risk in Communities Study (ARIC) have identified many long-term risk factors for incident stroke.³⁻⁵ However, relatively little is known about the short-term triggers of acute ischemic stroke.

Identification of stroke triggers offers potential strategies for stroke prevention during periods of vulnerability. One hypothesized stroke trigger is infection. Multiple case-control studies have identified an association between infection and ischemic stroke.⁶⁻¹¹ Using a case series study design, another study showed that recent upper respiratory and urinary tract infections were associated with a three-fold increased risk of ischemic stroke up to three months following infection.¹² Using a clever case-crossover design, the Cardiovascular Health Study identified an association between hospitalization for infection and short-term risk of ischemic stroke (14-day OR = 8.0, 30-day OR = 7.3, 90-day OR = 3.4).¹³ Given these findings, assessing the association between infection and stroke using a large prospective cohort study like ARIC is warranted. An improved understanding of post-infection stroke risk could help patients with recent infections and their clinicians take steps to reduce their otherwise elevated stroke risk.

Studies have shown that stroke risk after acute infection is greater in those with fewer vascular risk factors.^{13, 14} One study found that atherosclerotic carotid disease modified the relationship between infection and short-term stroke risk with lower observed risk among those with advanced atherosclerosis compared to those with low atherosclerosis.¹³ The authors hypothesized that acute triggers (such as infection) were less significant in people with more advanced atherosclerosis since they are already at elevated stroke risk. Thus, infection may present greater risk for stroke among those with few vascular risk factors in the general population.

As an extension of this hypothesis, we intend to examine the hypothesis that infection is a trigger for acute stroke and explore potential effect modification by atherosclerosis and atrial fibrillation (AF) using data from the ARIC study. Specifically, the ARIC study used high-resolution B-mode ultrasonography to measure atherosclerosis on the left and right sides of the common and internal carotid arteries, and at the carotid bifurcation,¹⁵ as reflected by the overall mean intima-medial thickness (IMT) based on the six-measured sites.¹⁶

To our knowledge, AF has only been identified as an independent risk factor of stroke but not as an effect modifier between infection and stroke.¹⁷ Since studies^{13,14} suggest that the risk of stroke after acute infection appears to be greater in those with lower vascular burden, we will evaluate AF as an effect modifier. AF in ARIC is assessed using ECG readings at cohort visits, ICD-9 hospital discharge codes (427.31) from the patient medical record, or follow-up survey results.

Data on IMT and AF were ascertained at baseline (visit 1) and again during annual follow-up calls and follow-up visits. The baseline data are the most complete while the later visits are likely more reflective of risk status most proximal to the outcome. We will compare risk factor status as ascertained at baseline to those assessed at later time points prior to the control periods to examine any changes in the magnitude of the associations of interest. The objectives of this study are to (1) corroborate the finding that infection is a trigger of stroke using the ARIC study sample and (2) examine potential effect modification by carotid atherosclerosis and AF.

5. Main Hypothesis/Study Questions:

(1) - Is infection a trigger of acute ischemic stroke?

We hypothesize that there is an association between infection hospitalization and subsequent short-term stroke risk: specifically, we anticipate finding higher odds of an infection hospitalization prior to an ischemic stroke compared to periods without an ischemic stroke.

(2) - Is carotid atherosclerosis or AF an effect modifier of the relationship between infection and ischemic stroke?

We hypothesize that infection will be a weaker stroke trigger among patients with other vascular risk factors including carotid atherosclerosis and AF. We anticipate finding higher odds of infection hospitalization prior to an ischemic stroke in patients without AF or lower burden of carotid atherosclerosis compared to patients with AF or higher burden of carotid atherosclerosis.

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:

Since we are interested in ischemic stroke triggers, we are going to evaluate within-person exposures (what makes a person more likely to have a stroke at a particular point in time). We will use a case-crossover study design in which ARIC participants with ischemic stroke will serve as their own controls. The occurrence of hospitalization for infection immediately prior to stroke will be compared with preceding time intervals 1 year and 2 years prior to the stroke.

Inclusion/Exclusion:

All study participants who suffered an ischemic stroke while enrolled in the study will be included. Cases whose control periods occurred prior to study enrollment will be excluded.

Exposure/Outcome:

The exposure of interest is infection hospitalization up to 90 days before ischemic stroke for the case period and equivalent 90-day periods exactly 1 and 2 years before the ischemic stroke for the control periods due to the seasonality of infection rates. The first day of hospitalization will be considered the first day of infection. Infection will be assessed using hospital discharge ICD-9 codes. The following ICD-9 codes for infection hospitalizations will be included:

Respiratory - 460-466,480-487

Assorted - 001-134

Urinary tract - 599.0, 595, 590

Skin and subcutaneous tissue - 680-686

Bacteremia - 790.7

Osteomyelitis - 730.0-730.2

Codes in any position will be counted. The infection date must precede the stroke hospitalization date. Infections within a hospital within 4 days of a stroke will be excluded to avoid infections diagnosed secondarily during hospitalization for stroke. The outcome of interest is ischemic stroke as defined for ARIC (n = 1,062). Like infection, the hospital admission date abstracted from the patient medical record will be considered the stroke date. Additionally, we will perform sensitivity analysis using CMS data for people over 65 and enrolled in Medicare.

Justification:

Several studies have examined the relationship between infections and ischemic stroke. While involvement of cerebral vasculature through septic embolic (endocarditis) or direct vascular compromise (cryptococcal meningitis, herpes zoster vasculitis) is well known, an association between other infections without direct involvement of the CNS (such as respiratory infections) and ischemic stroke has also been demonstrated. Some proposed mechanisms include a pro-coagulant state triggered by the inflammatory response to infections including increased levels of clotting factors such as fibrinogen, inhibition of natural anticoagulants such as protein C/S, increased production of cytokines which may alter properties of the vascular endothelium and increased expression of the thromboplastin by activated monocytes and macrophages. There are no clear biological pathways mediating hemorrhagic stroke risk and infection and hence we do not intend to examine this relationship in this study.

Analysis:

The prevalence of exposure 14, 30, and 90-days prior to ischemic stroke will be compared to the corresponding time periods exactly 1 and 2 years prior to the stroke. Conditional logistic regression will be used to estimate exposure odds ratios (ORs) and

95% confidence intervals (CIs) for each time period (14, 30, and 90 days). Most fixed stroke risk factors should not be confounders in the case crossover design though some risk factors could change status – e.g. smoking cessation could occur or patients could start antihypertensive medications. Since the risk and control periods are 90 days long, we do not anticipate that there will be changes in these risk factors within this time period. We will control for potential confounders that may vary between risk and control periods (e.g. medication use, smoking status) based on annual follow up and updated visit data. AF will be analyzed as a dichotomous (yes/no) variable. IMT will be operationalized separately for men and women using two relative cut points (75th and 95th percentiles) and analyzed using the three severity groups, <75th percentile, 75th-95th percentiles, and >95th percentile. Effect modification will be assessed using a two-step process. Interaction terms for atherosclerosis and AF will be added to models and the significance of the regression coefficients will be assessed using p-values. When significant interactions are identified, stratified results will be reported.

Limitations:

Confounding by age is possible because as participants age their stroke risk and hospitalization for infection increase. To reduce potential confounding, only time periods proximal to stroke (1 and 2 years previous) will be included. The validity of ICD codes for hospitalized infection is unknown. Some confounders that vary over the exposure and control periods assessed (e.g. air pollution, flu shots) are not measured. Since we are using the hospital admission as the stroke date, stroke dates for patients who do not seek immediate medical attention may be inaccurate but we believe that this is rare. We could be under-ascertaining infection because we are only looking at hospitalized infections. There could well be infections that did not require hospitalization.

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 X 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

References:

1. Miniño AM, Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2008. National vital statistics reports : from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2011;59(10):1–126.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):e6–e245.
3. Arnold AM, Psaty BM, Kuller LH, et al. Incidence of cardiovascular disease in older Americans: the cardiovascular health study. *Journal of the American Geriatrics Society*. 2005;53(2):211–8.
4. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke; a journal of cerebral circulation*. 2009;40(4):1032–7.
5. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke; a journal of cerebral circulation*. 1999;30(4):736–43.
6. Syrjanen J, Valtonen VV, Iivanainen M, Kaste M, Huttunen JK. Preceding infection as an important risk factor for ischaemic brain infarction in young and middle aged patients. *BMJ*. 1988;296:1156–1160.
7. Grau AJ, Bugge F, Heindl S, Steichen-Wiehn C, Banerjee T, Maiwald M, Rohlf M, Suhr H, Fiehn W, Becher H, et al. Recent infection as a risk factor for cerebrovascular ischemia. *Stroke*. 1995;26:373–379.
8. Bova IY, Bornstein NM, Korczyn AD. Acute infection as a risk factor for ischemic stroke. *Stroke*. 1996;27:2204–2206.
9. Grau AJ, Bugge F, Becher H, Zimmermann E, Spiel M, Fent T, Maiwald M, Werle E, Zorn M, Hengel H, Hacke W. Recent bacterial and viral infection is a risk factor for cerebrovascular ischemia. *Neurology*. 1998; 50:196–203.
10. Macko RF, Ameriso SF, Gruber FA, Griffin JH, Fernandez JA, Barndt R, et al. Impairment of the protein C system and fibrinolysis in infection-associated stroke. *Stroke*. 1996;27:2005.
11. Grau AJ, Preusch MR, Palm F, Lichy C, Becher H, Bugge F. Association of symptoms of chronic bronchitis and frequent flu-like illnesses with stroke. *Stroke*. 2009; 40:3206–3210.
12. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med*. 2004; 351:2611–2618.

13. Elkind, MSV, Carty CL, O'Meara ES, et al. Hospitalization for infection and risk of acute ischemic stroke: the cardiovascular health study. *Stroke*. 2011; 42(7): 1851–1856
14. Paganini-Hill A, Lozano E, Fischberg G, et al. Infection and risk of ischemic stroke: differences among stroke subtypes. *Stroke*. 2003; 34: 452-457.
15. Duncan BB, Metcalf P, Crouse JR 3rd, et al. Risk factors differ for carotid artery plaque with and without acoustic shadowing. Atherosclerosis Risk in Communities Study Investigators. *Journal of Neuroimaging*. 1997; 7(1) :28-34.
16. Chambless LE, Folsom AR, Clegg LX, et al. Carotid wall thickness is predictive of incident clinical stroke: the Atherosclerosis Risk in Communities (ARIC) study. *American Journal of Epidemiology*. 2000; 151(5): 478-87.
17. Levine DA, Langa KM, Rogers, MAM. Acute infection contributes to racial disparities in stroke mortality. *Neurology*. 2014; 82(11): 914-21.