ARIC Manuscript Proposal # 1663

PC Reviewed: 6/8/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Risk Factors for Hemorrhagic Stroke II: A pooled study of CHS and ARIC

b. Abbreviated Title (Length 26 characters):
Hemorrhagic Stroke

2. Writing Group:
Writing group members:
Aaron Folsom, Will Longstreth, Hiroshi Yatsuya, Bruce Psaty

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

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3. Timeline: Work to be done summer 2010

4. Rationale:
Intraparenchymal hemorrhage (IPH) accounts for approximately 20% of all strokes and has a high 30-day mortality rate [1]. IPH also causes significant morbidity in the form of both physical and cognitive disability [2]. Current treatment is mostly palliative, so searching for risk factors that may identify high-risk patients and modifiable risk factors is still of critical importance. Unfortunately the search for risk factors has been hampered due to the relative rarity of the disease. A recent review of literature on IPH identified the major risk factors as age, male sex, hypertension, and high alcohol intake [3]. There remains a high degree of uncertainty about novel risk factors due to the methodology of the studies reporting results and the rarity of IPH [4].

Neither CHS nor ARIC have enough IPH cases to analyze their data separately, but the

two studies share a wealth of data that permit the study of established and novel risk factors. In fact, Jared Sturgeon, under the leadership of Aaron Folsom, Will Longstreth and colleagues, published two PhD dissertation papers on the combined ARIC and CHS IPH data [5,6]. Based on 135 incident IPH events through 2002, their main conclusions were that risk factors for IPH were older age, African-American ethnicity, hypertension, lower LDL-C, lower triglycerides, and higher fibrinogen and von Willebrand factor. Many other traditional or hemostatic CVD risk factors were not statistically significantly associated with IPH risk.

With extension through 2007, we hope expect there to be about 190 incident IPH events. This pooled analysis would be larger than all but two recently reviewed studies [3]. We anticipate this sample size would allow us to detect relative risks for typical dichotomous risk factors on the order of RR = 2 with power = 0.8.

This proposal takes advantage of the fact that Aaron Folsom is in Seattle and can work directly with CHS investigators. Our aim is to study novel risk factors not previously examined in the Sturgeon et. al. papers.

5. Main Hypothesis/Study Questions:

IPH is associated positively with several novel risk factors (listed below).

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).

Inclusions: ARIC and CHS cohorts.

Exclusions: Prior stroke; baseline warfarin, heparin, or other anticoagulant use (but not aspirin). For ABO or any future genetic analysis, we will exclude those who did not provide genetic consent.

Dependent variables: IPH stroke through 2007

Independent variables (baseline unless unavailable): eGFR (CKD), metabolic syndrome and insulin, some chemistries not examined before (uric acid, albumin, total protein, magnesium, phosphorus), orthostatic hypotension, pulse pressure, cIMT, ABI, LVH by ECG, white matter grade, aPTT (ARIC), platelet count, ABO blood type, and APOE genotype.

NOTE: IT IS NOT CLEAR WHETHER BOTH COHORTS HAVE ALL OF THESE VARIABLES OR WHETHER THEY ARE COMPARABLE. THIS WILL BE EXPLORED BEFORE BEGINNING ANALYSIS. SOME ANALYSES MAY HAVE TO BE COHORT SPECIFIC OR DROPPED TO DUE LIMITED POWER.

Other Covariates (baseline): Age, sex, race, SBP and antihypertensives, LDL-C, triglycerides, fibrinogen, von Willebrand factor, diabetes, smoking, alcohol, prior CHD.

Brief analysis plan and methods:

We plan on conducting a prospective analysis examining IPH and several potential risk factors. The independent and dependent variables are listed above. Independent categorical variables will be analyzed using their natural categories, and continuous variables will be analyzed as both continuous and discrete (quartiles, etc). We plan to report incidence rates and relative risks for the outcome variables for levels of our independent variables. We will also report relative risks created using Cox proportional hazard regression models. We will produce our model through iterative steps beginning with the basic model developed by Sturgeon and then selectively adding and removing variables and observing the impact on the model. The small sizes will prevent the reporting of different outcomes by
race, but when necessary we will stratify by parent study (ARIC and CHS). We will be using SAS for our analysis.

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 ICTDER03 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? ___x_ Yes ____ 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"?
___x_ 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)?

#1003 Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007 Oct;38(10):2718-25

#1009 Sturgeon JD, Folsom AR, Bray MS, Boerwinkle E, Ballantyne CM. Apolipoprotein E Genotype and Incident Ischemic Stroke; The Atherosclerosis Risk in Communities (ARIC) Study. Stroke. 2005 Nov;36(11):2484-6.

Previously Jared Sturgeon worked on hemorrhagic stroke with Dr. Folsom. He is no longer in epidemiology.

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.

References:

1. Gebel JM, Broderick, JP. Intracerebral hemorrhage. Neurol Clin. 2000; 18:419-428.
2. Hanel RA, Xavier AR, et al. Outcome following intracerebral hemorrhage and subarachnoid Hemorrhage. Neurol Res. 2002; 24 Suppl 1: S58-62.
3. Ariesen MJ, Claus SP, et al. Risk Factors for Intracerebral Hemorrhage in the General Population: A Systematic Review. Stroke. 2003; 34:2060-2066.
4. Thrift AG. Editorial Comment- Minor Risk Factors for Intracerebral hemorrhage: The Jury is Still Out.
Stroke. 2003; 34:2065-2066.
5. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Hemostatic and inflammatory risk factors for intracerebral hemorrhage in a pooled cohort. Stroke. 2008 Aug;39(8):2268-73. PMID: 18535282.
6. Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007 Oct;38(10):2718-25. PubMed PMID: 17761915.