ARIC Manuscript Proposal # 1003

PC Reviewed: 04/08/04	**Status: A**	**Priority: 2**
SC Reviewed: 04/13/04	**Status: A**	**Priority: 2**

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

b. Abbreviated Title (Length 26 characters): **Hemorrhagic Stroke in CHS and ARIC**

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:
April 2004-October 2004

4. Rationale:
Hemorrhagic stoke accounts for approximately 20% of all stroke and has a high 30 day mortality rate [1]. Hemorrhagic stroke 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 hemorrhagic stroke identified the major risk factors as age, male sex, hypertension, and high alcohol intake [3]. Additionally, others have proposed low serum cholesterol, smoking, lack of exercise, diabetes, lipoprotein lipase polymorphism, parity, blood transfusions, apolipoprotein E ε4, and low protein in the diet [3, 4, 5, 6, 7, 8, 9, 10, 13]. There remains a high degree of uncertainty about novel risk factors due to the methodology of the studies reporting results and the rarity of hemorrhagic stroke [11].

Neither CHS nor ARIC have enough hemorrhagic cases to analyze their data separately, but the two studies share a wealth of data that could potentially reveal several of these novel risk factors and add new data to solidify the major risk factors. The combined ARIC and CHS studies would have at least 195 cases of intracerebral hemorrhage (CHS: 72 IPH, 18 SAH, 6 undetermined as of 2/26/04; ARIC: 58 IPH, 34 SAH). A 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.

ARIC and CHS were previously successfully pooled in our collaboration on the L.I.T.E. study.

References:
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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. Kurth T, Kase CS, Berger K, et al. Smoking and the Risk of Hemorrhagic Stroke in Men. Stroke. 2003; 34:1151-1155.
5. Kurth T, Kase CS, Berger K, et al. Smoking and the Risk of Hemorrhagic Stroke in Women. Stroke. 2003; 34:2792-275
6. Iso H, Sato S, Kitamura A, et al. Fat and Protein Intakes and Risk of Intraparenchymal Hemorrhage among Middle-aged Japanese. Am J Epidemiol 2003; 157:32-39.
7. Morrison AC, Ballantyne CM, Bray M, et al: LPL polymorphism predicts stroke risk in men. Genet Epidemiol 2002;22:233-42.
8. Rosand J, Greenberg SM. Editorial Comment- Beyond Hypertension: Unraveling the Causes of Intracerebral Hemorrhage. Stroke. 2002; 33: 1195-1196.
9. McCarron M O, Muir K W, et al. The Apolipoprotein E e4 Allele and Outcome in Cerebrovascular Disease. Stroke. 1998;29:1882-1887
10. Yamada S, Koizumi A, et al. Risk Factors for Fatal Subarachnoid Hemorrhage: The Japan Collaborative Cohort Study. Stroke. 2003; 34:2781-2787
11. Thrift AG. Editorial Comment- Minor Risk Factors for Intracerebral hemorrhage: The Jury is Still Out. Stroke. 2003; 34:2065-2066.
12. Broderick, J P. William M. Feinberg Lecture: Stroke Therapy in the Year 2025: Burden, Breakthroughs, and Barriers to Progress. Stroke. 2004: 35:205-211.
13. Woo D, Sauerbeck LR, Kissela BM, et al. Genetic and Environmental Risk Factors for intracerebral Hemorrhage: Preliminary Results of a population Based Study. Stroke. 2002; 33:1190-1196.

5. Main Hypothesis/Study Questions:

Hemorrhagic stroke is associated positively with established risk factors (age, male sex, hypertension, alcohol) and with novel risk factors (eg, fibrinogen, Lp(a), CRP, and WBC). We also hypothesize an inverse relationship with total cholesterol.

6. Data (variables, time window, source, inclusions/exclusions):

Inclusions: ARIC and CHS cohorts.
Exclusions: Prior stroke; baseline warfarin, heparin, or other anticoagulant use (but not aspirin).
Dependent variables: Hemorrhagic stroke through most recent closure date (subtypes SAH and ICH, but subtype specific analysis has limited power).
Independent variables:

Established: Blood pressure, alcohol intake, smoking status.
Novel: Fibrinogen, factors VII and VIII, Lp(a), apolipoprotein E genotype, lipids (total and HDL cholesterol, triglycerides), parity, CRP (CHS only), WBC, and platelets.

Other Covariates: Age, sex, race, anthropometrics, diabetes, blood glucose, insulin, medications, hormone replacement therapy status, prior CHD.
Analysis Plan: We plan on conducting a retrospective cohort analysis examining hemorrhagic stroke and both traditional risk factors and potential risk factors. The independent and dependant variables are listed above. Independent categorical variables will be analyzed using their natural categories (ex: male and female for gender) and continuous variables will be analyzed as both continuous (blood pressure measure) and discrete (blood pressure divided into 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 itinerative steps beginning with the complete model and then selectively adding and removing variables and observing the impact on

the model. We anticipate including confounders such as age and sex in our model. We plan on looking at total hemorrhagic stroke, but will look at ICH and SAH separately to determine if any differences can be detected. The small sizes will prevent the reporting of different outcomes by race, but we should be able to construct strata specific estimates by gender. ARIC and CHS have some measure that were taken at baseline and throughout the time of the cohort, while some were only taken at baseline. We may use time-dependant covariates to account for this data, but are waiting until analysis to determine the best approach. 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 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? __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 ICTDER02 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)? Although there are many ARIC manuscripts on total and ischemic stroke risk factors, we know of only one that has analyzed hemorrhagic stroke (904H Henderson: Alchohol and Stroke Incidence).

11. 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.