ARIC Manuscript Proposal # 1090

PC Reviewed: _07/26/05	**Status: _A__**	**Priority: _2_**
SC Reviewed: _07/28/05_	**Status: _A__**	**Priority: _2__**

1.a. Full Title: Risk Factors for Ischemic Stroke Subtypes. The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Risk for Stroke Subtypes

2. Writing Group:

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3. Timeline: We expect to complete the manuscript by October 2005.

4. Rationale:

A number of epidemiological studies have reported that several factors such as hypertension, smoking, diabetes mellitus, and hemostatic factors predict future ischemic stroke events (1, 2), but few prospective studies have demonstrated associations of these risk factors with subtypes of ischemic stroke (3, 4). Since pathogenesis, prognosis, and

treatment are different among ischemic stroke subtypes, risk factor assessment for each subtype should be performed separately.

A previous prospective study of 4,736 older US, predominantly white, women and men showed that current smoking and history of diabetes were independently associated with increased risk of lacunar stroke but not both atherosclerotic and embolic strokes (3). Another prospective study of 1,621 Japanese men and women observed significant positive associations between current smoking, glucose intolerance and lacunar stroke incidence in women but not in men (4). Since the number of ischemic stroke events in the previous prospective studies was relatively small, it is necessary to examine the differences in risk factors among stroke subtypes using large cohort samples. Furthermore, no prospective study has examined the relationships of nontraditional risk factors such as hemostatic factors and Lp(a) with ischemic stroke subtypes.

On the other hand, the ARIC study reported that African Americans had a 2.4 fold higher age-adjusted relative risk of stroke incidence compared with whites (5) which could be partially explained by higher prevalence of stroke risk factors such as hypertension, diabetes, and current smoking among African Americans than among whites (6). Therefore, the higher prevalence of stroke risk factors among African Americans may contribute to a predominance of a particular stroke subtype among African Americans.

5. **Main Hypothesis/Study Questions**:

1) Associations of hypertension, smoking, and diabetes mellitus with lacunar stroke incidence are stronger than those with nonlacunar and embolic stroke incidence.
2) Associations of hemostatic factors with emobolic stroke incidence are stronger than those with lacunar and nonlacunar stroke incidence.
3) Associations of cholesterol and Lp(a) levels with nonlacunar stroke incidence are stronger than those with lacunar and embolic stroke incidence.
4) The relative rate of lacunar stroke in African Americans compared with whites is higher than that of nonlacunar stroke and embolic stroke.

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

Dependent variables: Ischemic stroke subtypes incidence (up to 2002)

Independent variables: systolic blood pressure, hypertensive medication, diabetes mellitus, smoking, total & HDL cholesterol, fibrinogen, von Willebrand factor, white cell count, lipoprotein(a), left ventricular hypertrophy, history of CHD, body mass index, and alcohol consumption.

Adjustment for age, gender, race-field center, education level, cholesterol-lowering medication, and postmenopausal hormone therapy.

Exclusion: history of stroke, no independent variable.

Proportional hazards (Cox) regression will be used to examine both the univariate and multivariable-adjusted associations between independent variables and time to incidence of lacunar, nonlacunar, and embolic stroke.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __×__ 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 __×__ 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)?

Manuscript ARIC #442: Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __×__ No

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ B. primiarly 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. Folsom AR, Rosamond WD, Shahar E, Cooper LS, Aleksic N, Nieto FJ, Rasmussen ML, Wu KK. Prospective study of markers of hemostatic function with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Circulation*. 1999;100:736-42.
2. Chambless LE, Heiss G, Shahar E, Earp MJ, Toole J. Prediction of ischemic stroke risk in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 2004;160:259-69.
3. Davis BR, Vogt T, Frost PH, Burlando A, Cohen J, Wilson A, Brass LM, Frishman W, Price T, Stamler J. Risk factors for stroke and type of stroke in persons with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *Stroke*. 1998;29:1333-40.
4. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, Arima H, Tanaka K, Ibayashi S, Fujishima M. Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama study. *Stroke*. 2000;31:2616-22.
5. Rosamond WD, Folsom AR, Chambless LE, Wang CH, McGovern PG, Howard G, Copper LS, Shahar E. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. *Stroke*. 1999;30:736-43.
6. Schreiner PJ, Chambless LE, Brown SA, Watson RL, Toole J, Heiss G. Lipoprotein(a) as a correlate of stroke and transient ischemic attack prevalence in a biracial cohort: the ARIC Study. Atherosclerosis Risk in Communities. *Ann Epidemiol*. 1994;4:351-9.