ARIC Manuscript Proposal # 1294

PC Reviewed: 10/09/07	**Status: __A__**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Coagulation factor levels and risk of ischemic stroke

b. Abbreviated Title (Length 26 characters): Coag. factors and stroke

2. Writing Group:

Writing group members: F Suri, K Yamagishi, N Matijevic, P Hannan, A Folsom, I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _MFKS____ **[please confirm with your initials electronically or in writing]**

First author: **M. Fareed K. Suri**
Address: 420 Delaware Ave,
MMC 295
Department of Neurology
Phone: 612-626-8221 Fax: 612-626-9464
E-mail: fareedsuri@gmail.com (preferred), suri002@umn.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address:

Phone: Fax:
E-mail:

3. Timeline:

Three months

4. Rationale:

The pathophysiology for the majority of ischemic strokes can be identified as cardioembolic, large vessel thromboembolism, small vessel occlusive disease or other unusual mechanisms. However, for 30-40% of patients, the pathophysiology remains undetermined.[1-3] Among the multiple possible pathologies that have been considered as an explanation for cryptogenic stroke, hypercoagulability either alone or in combination with other risk factors is the prime suspect. Multiple acquired or hereditary hypercoagulabilities have been identified in patients with cryptogenic stroke in case

studies but because of the rarity of these conditions the causal relationship is still unproven.

Furthermore, usual levels of hemostatic factors even if not in the hypercoagulable range, may contribute to increased cerebral thrombosis. Although some large trials or nested case-control studies are available for common hypercoagulable conditions,[4, 5] only a few retrospective case-control studies have investigated coagulation factor levels in patients with ischemic stroke compared to control patients.[6, 7] The ARIC cohort provides a unique opportunity to examine this hypothesis using the blood samples collected in 1992 in a nested case-control design. We propose to study the association of levels of coagulation factors with risk of stroke.

5. Main Hypothesis/Study Questions:

Primary: Increased levels of natural procoagulant factors is associated with increased risk of ischemic stroke

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: Nested case-cohort.

Inclusion criteria:

1. In nested case-cohort sample, with coagulation factors clotting levels available. This includes factor II, V, X, IX, XI, XII, and plasminogen

Exclusion criteria:

1. Previous history of stroke on baseline examination
2. History of stroke before the collection of samples for clotting factor levels

Outcome:

1. Ischemic stroke defined as definite or probable ischemic stroke

Independent Variables of Interest

	Variable
1.	Factor-II
2.	Factor-V
3.	Factor-X
4.	Factor-IX
5.	Factor-XI
6.	Factor-XII
7.	Plasminogen
8.	Alpha-2 antiplasmin

Other Variables

	Variable	ARIC variable	Visit	Usage
9.	Age		1	Continuous
10.	Gender	GENDER	1	Dichotomous
11.	Race	RACEGRP	1	Categorical: White, African American, Others
12.	Hypertension	HYPERT05	1	Dichotomous
13.	Diabetes	DIABTS02	1	Dichotomous
14.	Body Mass Index	BMI01	1	Continuous

15.	Smoking status	CIGT01	1	Categorical: Current, Former, Never ('never' to include unknown or missing)
16.	LDL cholesterol	LDL02	1	Categorical (<100, 100-129, 130+)

Analysis

1. If normal values for the pro-coagulant factor levels are not well define in literature then quartiles or quintiles will be used for categorization
2. Univariate analysis between clotting factors (variables of interest 1-15) and cardiovascular risk factors will be performed
3. Cox-regression analysis for each independent variable in relation to outcome
    a. adjusted for age, gender, race, hypertension, diabetes, body mass index, smoking status and LDL cholesterol and
    b. weighted for sampling fractions and accounting for the nested case-cohort design using Barlow's method

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

_____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)?

Ms 777 Activity of coagulation and fibronolytic factors and inhibitors in coronary heart disease. (The current proposal could be considered ms 777B).
Ms 446 Prospective study of markers of hemostatic function with risk of ischemic stroke.

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.

1. Schneider AT, Kissela B, Woo D, et al. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. *Stroke.* 2004;35:1552-1556.
2. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke.* 2001;32:2735-2740.
3. Sacco RL, Ellenberg JH, Mohr JP, et al. Infarcts of undetermined cause: the NINCDS Stroke Data Bank. *Ann Neurol.* 1989;25:382-390.
4. Brey RL, Stallworth CL, McGlasson DL, et al. Antiphospholipid antibodies and stroke in young women. *Stroke.* 2002;33:2396-2400.
5. Levine SR, Brey RL, Tilley BC, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *Jama.* 2004;291:576-584.
6. Demarmels Biasiutti F, Berger D, Mattle HP, Lammle B, Wuillemin WA. Hemostatic risk factors in ischemic stroke. *Thromb Haemost.* 2003;90:1094-1099.
7. Austin H, Chimowitz MI, Hill HA, et al. Cryptogenic stroke in relation to genetic variation in clotting factors and other genetic polymorphisms among young men and women. *Stroke.* 2002;33:2762-2768.