ARIC Manuscript Proposal # 1294r

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 case-cohort studies are available for common hypercoagulable conditions, only a few retrospective case-control studies have investigated coagulation factor levels in patients with ischemic stroke compared to control patients. The ARIC cohort provides a unique opportunity to examine this hypothesis using the blood samples collected in 1992 in a case-cohort 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: case-cohort.
Inclusion criteria:
1. In case-cohort sample, with coagulation factors clotting levels available (ARIC Table 4). 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARIC variable</th>
<th>Visit</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Factor-II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Factor-V</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Factor-X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Factor-IX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Factor-XI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Factor-XII</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Plasminogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Alpha-2 antiplasmin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>ARIC variable</th>
<th>Visit</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Age</td>
<td>GENDER</td>
<td>1</td>
<td>Continuous</td>
</tr>
<tr>
<td>10. Gender</td>
<td>RACEGRP</td>
<td>1</td>
<td>Dichotomous</td>
</tr>
<tr>
<td>11. Race</td>
<td></td>
<td>1</td>
<td>Categorical: White, African American, Others</td>
</tr>
<tr>
<td>12. Hypertension</td>
<td>HYPERT05</td>
<td>1</td>
<td>Dichotomous</td>
</tr>
<tr>
<td>13. Diabetes</td>
<td>DIABTS02</td>
<td>1</td>
<td>Dichotomous</td>
</tr>
<tr>
<td>14. Body Mass Index</td>
<td>BMI01</td>
<td>1</td>
<td>Continuous</td>
</tr>
</tbody>
</table>
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 defined 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 case-cohort design using Barlow’s method

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

    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.csec.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.