ARIC Manuscript Proposal # 3182

PC Reviewed: 6/12/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Migraine and Venous Thromboembolism (VTE)

b. Abbreviated Title (Length 26 characters): Migraine and VTE

2. Writing Group:
Writing group members: Aaron Folsom, Pam Lutsey, Mary Cushman

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

First author: Aaron Folsom or TBN student
Address:

Phone: Fax:
E-mail: folso001@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name:
Address:

Phone: Fax:
E-mail:

3. Timeline: Fall 2018

4. Rationale:

A recent, large, record-based prospective study (Adelborg K et al. BMJ 2018;360:k96) showed positive associations of migraine with multiple cardiovascular outcomes, including venous thromboembolism (VTE) (RR=1.59). A Chinese prospective clinical study found an increased risk of VTE for migraine with aura but not without aura (Peng KP et al. Headache 2016;56:1290-9). A cross-sectional German Study showed a 2-fold higher history of VTE in migraineurs than

in non-migraineurs (Schwaiger J et al. Neurology 2008;71:937-43). In a large, population based sample of pregnant women, VTE discharge codes during pregnancy were 3 fold more common in those with peripartum migraine vs. no migraine (Bushnell CD et al. BMJ. 2009;338:b664).

Although many reports relate cerebral venous thrombosis with migraine-like headaches, the relation of migraine with deep vein thrombosis and pulmonary embolism seems surprising and unexplained. Of course, an association of migraine with stroke is well established (PMIDs 24057117, 28885052, 8864251).

Migraine was self-reported in ARIC by questionnaire at visit 3, which included information on aura. Additionally, the LITE study has validated VTE events, and recently updated VTE occurrence in ARIC through 2015. Therefore using LITE data we can examine the association of migraine with VTE prospectively with better outcome validation than most previous studies on this topic.

5. Main Hypothesis/Study Questions:

Main hypothesis: compared with those free of migraine, participants with migraine have greater VTE incidence in ARIC.

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).

Main design: Prospective
Exposure: migraine assessed at Visit 3; migraine with and without aura
Outcome: time to VTE occurrence
Exclusions: VTE and anticoagulant use
Potential confounders: sex, race, age, BMI, CKD, cancer diagnosis
Analysis: Calculate age and sex-adjusted incidence rates using Poisson and multivariably adjusted HRs for migraine diagnosis (yes, no) and Cox models. Similar analyses will be done looking at a 3 level exposure (migraine with aura, migraine without aura, no migraine). Subgroup analyses will examine PE/DVT and provoked/unprovoked VTE individually.

If we find an association, in secondary analyses we will try to understand possible explanations by exploring whether biomarkers related to VTE are related to migraine

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _xx___ 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 ICTDER 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 __xx__ 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"? ____ 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

___xx___ 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)?

None

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

11.b. If yes, is the proposal

_xx__ A. primarily the result of an ancillary study (list number* ___2001.16 LITE__)

___ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.