ARIC Manuscript Proposal #2150

PC Reviewed: 6/11/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Sickle trait and venous thromboembolism

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

2. Writing Group:
Writing group members: Aaron Folsom, Weihong Tang, Saonli Basu, James Pankow, Pam Lutsey, Mary Cushman, and TBN from sickle trait ancillary

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

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3. Timeline: start immediately

4. Rationale:

Carriers of sickle cell trait have a hemoglobin genotype AS, rather than a normal AA. Sickle cell trait is considered generally benign. However, Austin reported in a 2007 case-control study of VTE that sickle cell trait carried a 1.8 (95% CI 1.2-2.9) fold risk of VTE and 3.9 (2.2-6.9) for PE.[1] Austin and colleagues had asked us several times to attempt to replicate this finding, but the number of VTEs in LITE African Americans was limited and we did not have specific funding to measure sickle cell genotypes. An ancillary study measuring sickle trait in the ARIC cohort gives us the opportunity to now test this hypothesis.

Hemoglobin S and C genotypes are measured by TaqMan and these provide the basis for defining sickle cell trait (HbAS).

5. Main Hypothesis/Study Questions:

Sickle cell trait is a risk factor for VTE in African Americans 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).

Design: cohort
Endpoint: VTE incidence
Exposure: sickle trait

Exclusions: VTE prior to visit 1, anticoagulant use, exclusion from DNA use, missing sickle trait, homozygous for sickle cell disease.

Main covariates (though none are expected to confound): visit 1 age, principal components of ancestry, sex, HRT, BMI, diabetes, eGFR, CRP, factor VIII and aPTT.

Analysis: Cox proportional hazards, as in other LITE papers. This will include all ARIC African Americans who have provided consent for genotyping (n = 3809), in whom there will be approximately 208 VTE events through 2011. The expected prevalence of sickle cell trait (HbAS) is 8%. At alpha = 0.05, we should have 80% power to detect a HR of 2.05, which is only slightly greater than the value of 1.8 reported by Austin.[1]

REFERENCES

1. Austin H, Key NS, Benson JM, Lally C, Dowling NF, Whitsett C, Hooper WC: Sickle cell trait and the risk of venous thromboembolism among blacks. *Blood* 2007;110(3):908-12.

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 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?
__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 ICTDER03 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)?**

    None

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

11.b. If yes, is the proposal
__x__ A. primarily the result of an ancillary study (* 2006.16)
_____ 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.