ARIC Manuscript Proposal #3660

PC Reviewed: 7/14/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Risk Scores for Incident Venous Thromboembolism

b. Abbreviated Title (Length 26 characters): VTE risk scores

2. Writing Group: Aaron Folsom, Nathan Pankratz, Weihong Tang, Wayne Rosamond, Mary Cushman

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: 2020

4. Rationale:

Clinically useful risk scores already exist to estimate either risk of provoked VTE in a medical setting or recurrent VTE.

On the other hand, there are few published risk scores—polygenic or clinical—for incident unprovoked VTE. From the Leiden case-control study, de Haan et al. published a 5-variant genetic risk score (GRS) and showed the GRS contributed to VTE prediction beyond a clinical risk score (1). We replicated an association of the GRS in ARIC whites but not blacks (2). We and others also have shown that Life's Simple 7 (LS7) is associated with incident VTE (3-5). Moreover, LS7 and the deHaan GRS seem to contribute independently to prediction of VTE (ARIC MS 3094, submitted). Recently, Klarin et al. reported a large prospective study associating VTE with a GRS nearly 300 variants (6).

We now would like to examine the risk scores further, namely the large Klarin GRS compared with deHaan's GRS, as well as develop a combination risk score to try to predict incident total and unprovoked VTE.

5. Main Hypothesis/Study Questions:

- Does the Klarin GRS predict total and unprovoked VTE better than the deHaan 5-SNP score?

- How well can the combination of best GRS, lifestyle (LS7), and other VTE risk factors, put into a global risk score. "predict" VTE in whites and blacks of 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: prospective using V1 exposures

Exclusions: baseline VTE history, use of anticoagulants, no permission to use genetic info, missing data on exposures

Outcome: validated VTE (total and unprovoked) through 2015

Exposures: age, race, sex, history of cancer, LS7 components, principal components for ancestry, all genetic variants (to create the de Haan and Klarin risk scores), possibly some other clinical variables

Main analysis method: Cox models relating total and unprovoked VTE to listed exposures (including GRSs). Testing of goodness of fit, discrimination, calibration by standard methods. Focus first on whether we can replicate the Klarin findings in whites and blacks separately; then, compare the two GRS; then, development of combined clinical and GRS risk score.

Supplementary analysis: In passing, we will also see if the Klarin GRS also predicts cancer related VTE.

References

1. de Haan HG, Bezemer ID, Doggen CJ, Le Cessie S, Reitsma PH, Arellano AR, Tong CH, Devlin JJ, Bare LA, Rosendaal FR, Vossen CY. Multiple SNP testing improves risk prediction of first venous thrombosis. Blood 2012;120(3):656-63.

2. Folsom AR, Tang W, Weng LC, Roetker NS, Cushman M, Basu S, Pankow JS. Replication of a genetic risk score for venous thromboembolism in whites but not in African Americans. J Thromb Haemost 2016;14(1):83-8.

3. Olson NC, Cushman M, Judd SE, McClure LA, Lakoski SG, Folsom AR, Safford MM, Zakai NA. American Heart Association's Life's Simple 7 and risk of venous thromboembolism: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. J Am Heart Assoc 2015;4(3):e001494.

4. Folsom AR, Olson NC, Lutsey PL, Roetker NS, Cushman M. American Heart Association's Life's Simple 7 and incidence of venous thromboembolism. Am J Hematol 2015;90(5):E92.

5. Ogunmoroti O, Allen NB, Cushman M, Michos ED, Rundek T, Rana JS, Blankstein R, Blumenthal RS, Blaha MJ, Veledar E, Nasir K. Association Between Life's Simple 7 and Noncardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc 2016;5(10):e003954.

6. Klarin D, et al. Genome-wide association analysis of venous thromboembolism identifies new risk loci and genetic overlap with arterial vascular disease. Nat Genet 2019;51(11):1574-1579

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _x___ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

__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)?
Those cited above, which we wrote.

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 (list number* __1998.03_)
___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.