ARIC Manuscript Proposal #3822

PC Reviewed: 4/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association of a Polygenic Risk Score for Coronary Artery Disease with Venous Thromboembolism Incidence

b. Abbreviated Title (Length 26 characters): CAD polygenic risk score & VTE

2. Writing Group:
Writing group members: Aaron Folsom, Paul de Vries, 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]**

First author: Aaron Folsom (folso001@umn.edu)

3. Timeline: this is to be a letter to Thromb Haemost, so will be finished almost immediately

4. Rationale:

Medical literature is inconsistent about whether chronic coronary artery disease (CAD) or generalized atherosclerosis is a causal risk factor for venous thromboembolism (VTE).[1-3] Acute myocardial infarction increases risk of VTE for a few months but is explained by concomitant conditions such as immobilization and infection.[4,5]

Some CAD risk factors, in particular obesity and to a lesser degree smoking, appear to increase VTE risk; however, hyperlipidemia, hypertension, and diabetes do not.[6,7] We recently reported that the ACC/AHA cardiovascular disease summary risk equation[8] does not readily predict VTE, especially after also adjusting for obesity.[7]

A family history of myocardial infarction is associated with a modestly elevated VTE risk.[9] Yet, a large Swedish family study concluded that the familial background for CAD is different from VTE.[10] Important individual genetic variants related to CAD (e.g., influencing LDL levels) are different from genetic variants associated with VTE occurrence.[11] Vice-versa, factor V Leiden and other mutations of the hemostatic system that increase the risk of VTE are not generally associated with CAD occurrence.

Recently large-scale prospective studies have created polygenetic risk scores (PRS) that are highly predictive of CAD, for example that by Khera et al.[11] If CAD predisposes to VTE, then one would expect a higher PRS for CAD would be associated with increased risk of VTE. We will test this hypothesis ARIC.

5. Main Hypothesis/Study Questions:

Higher PRS for CAD will not be associated with increased risk of VTE

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 from baseline

Exposure: CAD PRS (derived variable provided to ARIC by Dr. de Vries and colleagues), originally developed and validated by Khera et al.[11]

Outcome: VTE from the LITE project through 2015

Exclusions: non-Whites, missing PRS, baseline anticoagulant use

Analysis: categorize the CAD PRS into quintiles and calculate crude incidence rates of VTE and hazard ratios. No adjustments will be made for other VTE risk factors, as they should not be associated with the PRS and thus would not be confounding variables.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _xx___ 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? _xx___ 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"? __xx__ 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

___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? _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.

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