ARIC Manuscript Proposal # 3094

PC Reviewed: 1/9/2018 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Mitigation of Venous Thromboembolism Risk through Favorable Lifestyle: the LITE Study

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

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

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3. Timeline: A manuscript draft will be completed by spring 2018 and anticipate publication submission. I will be presenting the findings of this report at the 2018 Thrombosis and Hemostasis Societies of North America Summit as the proposal received a NASTH student research fellowship.

4. Rationale:

Venous thromboembolism (VTE), a public health burden, is the third most common cardiovascular disease.[1] Estimates suggest 1 to 2 per 1,000 individuals are affected by VTE each year in the United States, and once VTE has occurred, the recurrence risk is about 30% over 8 years.[1, 2] Thus, the US Surgeon General issued a "Call to Action" to prevent deep vein thrombosis and pulmonary embolism.[3] Genetic predisposition and lifestyle factors are key drivers of cardiovascular health.[4] Although individually researched, there are few studies assessing both genetics and lifestyle in relation to VTE risk. We reported that the American Heart Association's Life's Simple 7, a cardiovascular health metric, has been associated with lower VTE risk.[5, 6] Life's Simple 7 is based on favorable levels of smoking status, body mass index (BMI), physical activity, healthy diet score, total cholesterol, blood pressure and fasting glucose. Using a genetic risk score (GRS) composed of single-nucleotide polymorphisms (SNPs), genetically high risk individuals for cardiovascular disease were identified in previous studies, and it was recently reported that adhering to a healthy lifestyle was associated with a lower relative risk of coronary artery disease in individuals at high genetic risk.[7-9] Availability of a GRS for VTE risk, which we previously validated, also allows us to determine whether healthy lifestyle lowers the genetic risk of VTE.[10] Additionally, little is known about lifestyle mediators of recurrent VTE, a topic of high clinical interest currently given trends for usage of long term anticoagulation after a single VTE.

5. Main Hypothesis/Study Questions:

1. Determine if a composite score for Life's Simple 7 reduces the VTE risk in individuals with high genetic risk score
2. Determine which components of American Heart Association's Life's Simple 7 attenuate genetic risk
3. Determine if favorable Life's Simple 7 score is associated with reduced risk of recurrent VTE, and which components of Life's Simple 7 are most important.

We hypothesize that favorable health factors assessed as Life's Simple 7 can reduce VTE occurrence in high GRS individuals. We anticipate BMI and physical activity metrics of Life's Simple 7 will attenuate GRS risk for VTE greater than other metrics. Further, among those at highest risk of VTE, people who have already had VTE, favorable Life's Simple 7 factors, especially BMI and physical activity, will attenuate recurrence risk. This study will have immediate clinical relevance on the potential for lifestyle intervention to reduce VTE, both first and recurrent events. In addition, the results could generate hypotheses for future studies aimed to reduce genetic predisposition.

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).

Methods:

Subjects

Participants are from the Longitudinal Investigation of Thromboembolism Etiology (LITE) study, a prospective 21,680 participant combined cohort of VTE occurrence from the Atherosclerosis Risk in Communities (ARIC) Study and the Cardiovascular Health Study (CHS).[11, 12] Cases are adjudicated for all definite and probable VTE events using established criteria of this longtime Ancillary Study.[13, 14]
Baseline data on Life's Simple 7 and the GRS are available for analysis. We will use the most up to date LITE database at the time of analysis, which we anticipate will include ~1300 VTE cases. Each metric of Life's Simple 7 is given a point score of 0, 1 or 2, as outlined in Table 1. The points are added to give a 14 point summary score, which is divided into three categories, using a 14 point summary score, into inadequate (0 to 4 points), average (5 to 9 points), and optimal (10 to 14 points) health l.[5, 15] The GRS includes data on five SNPs (*F5* Leiden rs6025, *F2* rs1799963, *ABO* rs8176719 (O vs. non-O groups), *FGG* rs2066865, and *F11* rs2036914) associated with VTE. Risk alleles for each SNP were assigned literature established weights based on average odds ratio for each SNP. The total GRS ranges from 0 to 10.[10]
We will exclude participants with missing or Life's Simple 7 or GRS data, or who were on anticoagulation at baseline. Demographic data should include age, sex, race, education, and income.

Statistical Analysis
For Aims 1 and 2, characteristics of participants who developed VTE, or did not, will be tabulated for descriptive purposes. Primary analysis of the GRS will include white participants since the GRS was not related to VTE risk in LITE African-Americans (but we will confirm this given we have longer follow up now). Excluding those with prebaseline VTE, Kaplan-Meier probabilities will be used to show the time to VTE by GRS classification and time to VTE by Life's Simple 7 categories. We will evaluate the association of VTE with Life's Simple 7 and GRS using Cox proportional hazard models. Hazard ratios (HRs) and 95% confidence intervals of VTE by Life's Simple 7 categories (inadequate, average, optimal) and GRS (low, intermediate, high) will be calculated. A second model will adjust for age, sex, race, education and study (ARIC/CHS). To examine Aim 2, we will evaluate whether adding Life's Simple 7 score to the model for GRS as the main independent variable, will lower the HR of GRS for VTE. This analysis will be done with and without adjustment for age, sex, education and study. The individual metrics of Life's Simple 7 will also be examined separately as attenuating factors for the GRS to determine which factors in Life's Simple 7 are important clinically.
For Aim 3, similar methods as above will be used for recurrent VTE as the endpoint. The primary goal will be to assess the relationship of Life's Simple 7 with recurrent VTE since we believe the GRS will not be an important determinant of this (although this will be confirmed). This analysis will include those without prebaseline VTE and who have at least two VTE during follow up. Data for Life's Simple 7 and covariates above will come from the study visit closest in time to the first VTE occurring during follow up.

Limitations
Given the years during which the study took place, we will assume that most patients after a first VTE were treated with a time-limited duration of anticoagulation for their first VTE. We do not have specific information on duration of anticoagulation and will acknowledge this as as weakness, although we believe it is a minor issue. To assure this we will exclude the last 5 years

of follow up and repeat the analysis to account for trends in patient care favoring long term anticoagulation for unprovoked VTE. We do not have information on family history of VTE for correlation to the GRS, or to address the importance of lifestyle factors in reducing risk in those with a positive family history.

Table 1. Definitions of Life's Simple 7 Categories

Metric	**Inadequate**	**Average**	**Optimal**
Current smoking	Yes	Former ≤12 months	Never or quit >12 months
Body mass index	≥30 km/m2	25 to 29.9 km/m2	<25 km/m2
Physical activity	None	1 to 3 times per week	≥4 times per week
Healthy diet	0 to 1 components	2 to 3 components	4 to 5 components
Total cholesterol	≥240 mg/dL	200 to 239 mg/dL or treated to goal	<200 mg/dL (not on treatment)
Blood pressure	SBP ≥ 140 mmHg or DBP ≥90 mmHg	SBP 120 to 130 mmHg or DBP 80 to 89 mmHg or treated to goal	SBP <120 mmHG and DBP <80 mmHG (not on treatment)
Fasting plasma glucose	≥126 mg/dL	100 to 125 mg/dL or treated to goal	<100 mg/dl (not on treatment)

Citations

1. Benjamin, E.J., et al., *Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association.* Circulation, 2017. **135**(10): p. e146-e603.
2. Heit, J.A., *Epidemiology of venous thromboembolism.* Nat Rev Cardiol, 2015. **12**(8): p. 464-74.
3. Office of the Surgeon, G., L. National Heart, and I. Blood, *Publications and Reports of the Surgeon General*, in *The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism*. 2008, Office of the Surgeon General (US): Rockville (MD).
4. Piazza, G. and S.Z. Goldhaber, *Venous thromboembolism and atherothrombosis: an integrated approach.* Circulation, 2010. **121**(19): p. 2146-50.
5. Olson, N.C., et al., *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): p. e001494.
6. Lindqvist, P.G., E. Epstein, and H. Olsson, *The relationship between lifestyle factors and venous thromboembolism among women: a report from the MISS study.* Br J Haematol, 2009. **144**(2): p. 234-40.
7. Deloukas, P., et al., *Large-scale association analysis identifies new risk loci for coronary artery disease.* Nat Genet, 2013. **45**(1): p. 25-33.

8. Khera, A.V., et al., *Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease.* N Engl J Med, 2016. **375**(24): p. 2349-2358.
9. Nikpay, M., et al., *A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease.* Nat Genet, 2015. **47**(10): p. 1121-30.
10. Folsom, A.R., et al., *Replication of a genetic risk score for venous thromboembolism in whites but not in African Americans.* J Thromb Haemost, 2016. **14**(1): p. 83-8.
11. Cushman, M., et al., *Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology.* Am J Med, 2004. **117**(1): p. 19-25.
12. Tsai, A.W., et al., *Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology.* Arch Intern Med, 2002. **162**(10): p. 1182-9.
13. Bell, E.J., et al., *Lifetime Risk of Venous Thromboembolism in Two Cohort Studies.* Am J Med, 2016. **129**(3): p. 339.e19-26.
14. Folsom, A.R., et al., *C-reactive protein and venous thromboembolism. A prospective investigation in the ARIC cohort.* Thromb Haemost, 2009. **102**(4): p. 615-9.
15. Lloyd-Jones, D.M., et al., *Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond.* Circulation, 2010. **121**(4): p. 586-613.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ Yes ____ 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? __X__ 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)?

Cushman M, O'Meara ES, Heckbert SR, Zakai NA, Rosamond W, Folsom AR. 2016. Body size measures, hemostatic and inflammatory markers and risk of venous thrombosis: The Longitudinal Investigation of Thromboembolism Etiology.. Thromb Res. 144:127-32.

Rebholz CM, Anderson CAM, Grams ME, Bazzano LA, Crews DC, Chang AR, Coresh J, Appel LJ. 2016. Relationship of the American Heart Association's Impact Goals (Life's Simple 7) With Risk of Chronic Kidney Disease: Results From the Atherosclerosis Risk in Communities (ARIC) Cohort Study.. J Am Heart Assoc. 5(4):e003192.

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/

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.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.