ARIC Manuscript Proposal # 3212

PC Reviewed: 8/14/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Long-term consequences of VTE on physical functioning and quality of life.

b. Abbreviated Title (Length 26 characters):

2. Writing Group: Pamela L. Lutsey, B. Gwen Windham, Jeff Misialek, Mary Cushman, Anna Kucharska-Newton, Saonli Basu, Aaron R. Folsom

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __PLL___

First author: Pamela L. Lutsey
Address: 1300 South 2nd St.; Suite 300
Minneapolis, MN 55454

Phone: (612) 624-5812
E-mail: Lutsey@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: Aaron R. Folsom
Address: 1300 South 2nd St.; Suite 300
Minneapolis, MN 55454

Phone: (612) 626-8862
E-mail: folso001@umn.edu

3. Timeline: Analyses will begin immediately; anticipated completion summer 2018.

4. Rationale: Nearly half of DVT patients develop post-thrombotic syndrome, characterized by leg pain, swelling, edema, skin discoloration/dryness and ulcers.[1,2] Limited evidence suggests that, in addition to reduced mobility, patients with post-thrombotic syndrome have diminished health-related quality of life.[3,4] Similarly, PE survivors appear to have diminished quality of life.[5] Venous thromboembolism (VTE) patients, in addition, often experience anxiety and depression.[5,6] Most of this evidence on long-term outcomes of VTE is from countries other than the U.S., not population-based, and often without appropriate control groups for comparison.

Therefore, we will take advantage of the considerable information obtained in ARIC visit

5 (2011-13) and visit 6 (2016-17) to assess long term functional outcomes and quality of life in participants who had or did not have VTE, adjusted for relevant confounders. Specifically, we propose to evaluate physical function and quality of life among participants with prior VTE. Comparators will be ARIC participants without VTE, ARIC participants with prior myocardial infarction (MI), and ARIC participants with prior stroke. The rationale for using prevalent MI as a comparator is that, similar to VTE, it is an acute event and comparison of long-term consequences of VTE versus MI may be interesting. Stroke is also in interesting comparator, as it is known to have long-term adverse consenequences. Previous work in ARIC has found that functional status post-MI declined relative to pre-event levels, but improved to close to pre-MI levels within 3 years.[7] Conversely, decline in functional status following stroke remained over time.

The present proposed analyses will be cross-sectional, and will enhance understanding of the long-term prognosis of VTE patients.

5. Main Hypothesis/Study Questions:

We will study the long-term consequences of VTE on quality of life, frailty, and physical function (Short Physical Performance Battery [SPPB] and separately, gait speed, endurance), frailty. Outcomes measures will predominantly come from visit 5 (2011-2003) though as the 2-minute walk test was not conducted at visit 5 these data will come from visit 6 (2016-17).

Hypothesis: Participants who developed VTE have poorer subsequent quality of life, frailty and physical function than those who remain free of VTE, those who experienced MI, or those who experienced stroke.

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).

Study design: Data from visit 5 (and in some instances visit 6) will be analyzed in a cross-sectional manner.

Inclusion/exclusion: We will exclude participants who are not black or white, and blacks from MN and MD, VT from sites other than leg, possibly cancer related VTE or all cancer patients

Outcomes:

- Quality of life: a modified version of the SF-12v2 was used. Summary scores will be calculated overall, and separately for physical components and mental components, and modeled continuously.
- Frailty: Operationalized using the CHS criteria, which has been previously implemented in ARIC.[8] Briefly, this definition incorporates measures of weight loss, exhaustion, slow walking speed, low physical activity and low grip strength. As has been done previously, frailty will be categorized as frail, pre-frail, or not frail.
- Short Physical Performance Battery (SPPB):[9,10] composed of three tests, namely 4 meter walking speed, standing balance, chair stands. The SPPB composite score will be categorized as low (0-6), fair (7-9) and good (10-12).

- Gait speed (mobility): 4 meter walking speed. Although gait speed is a component of the SPPB, it is being included as a separate outcome as of the components of SPPB it may be most likely to be impacted by VTE.
- Endurance: 2 minute "as fast as you can" walk, recommended in the NIH toolkit, was conducted at visit 6. Specifically it was offered to all participants who completed the 4-minute walk without a walking aid. Although adding a single measure from visit 6 complicates the analysis, this measure may be more sensitive as other measures do have ceiling effects. And, it is a different but relevant construct.

Covariates (and potential effect modifiers): Age, race-site, sex, BMI, physical activity, smoking, diabetes, SBP, DBP, hypertension medications, COPD, HF, PAD.

Data analysis:

For the primary analysis visit 5 data will be used cross-sectionally. At visit 5, ARIC measured the outcomes noted above (except endurance) on approximately 6,500 participants using standardized methods. Descriptive characteristics will be provided according to four categories: prevalent VTE, no prevalent VTE, prevalent MI, and prevalent stroke. These categoires are not mutually exclusive; the "no prevalent VTE category" will include people with prevalent stroke and MI.

For the main analysis, comparisons will be made between prevalent VTE and #1: no prevalent VTE, #2 prevalent MI (for this analsis indivdiuals with both VTE and MI will be excluded) and #3 prevalent stroke (for this analysis indivdiuals with both VTE and stroke will be excluded). The outcomes will include both categorical and continuous variables. Linear regression will be used for the continuous physical function outcomes. For multilevel categorical outcomes we will conduct analyses using a) polytomous regression or b) prevalence ratios[11] when outcome variables are categorized dichotomously. Regardless of outcome type the models will be as follows:

- Model 1: Adjusted for age (visit 5), sex, race-site, BMI.
- Model 2: Adjusted for model 1 + physical activity, smoking status, and comorbidities (diabetes, SBP, hypertension medications, COPD, HF, PAD)

Time since the event is also a critical consideration.

- Figures will be used to display visit 5 physical functioning and quality of life according to time since the event (prevalent VTE, MI, stroke, in mutually exclusive categories).
- Sensitivity analyses will also stratify on time since VTE (categories will be based on number of events available).

Several sensitivity analsyes will be conducted, including:

- Excluding cancer associated VTE
- Restricting to unprovoked VTE as the exposure, as it is likely less confounded by disease status than provoked VTE.
- Excluding individuals with stroke at visit 5 (or visit 6 for the endurance analyses).
- Effect modification will be explored by age at VTE, sex and race.

Visit 6 analyses the 2-minute walk test will be conducted in a similar manner to the visit 5 analyses. In secondary analyses, if the number of VTE events are sufficient, we will also evaluate whether patterns observed with prevalent VTE cases at visit 5 are also present for newly prevalent VTE cases at visit 6.

Anticipated methodological limitations: As with all observational analyses residual confounding is a concern. Though ARIC contains rich information on comorbidities and treatments, the counterfactual is (of course) unknown.

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? ____ Yes __X__ 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

___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)?

Below are some of the physical function proposals. Authors from these papers, and from ARIC VTE work, are represented on this proposal.

MP 2077. Windham BG B. Gwen Windham, Michael E. Griswold, Seth Lirette, Anna Kucharska-Newton, Randi Foraker, Wayne Rosamond, Thomas H Mosley, Jr., PhD. Functional Status Moderates Mortality Risk Associated with Blood Pressure: the Atherosclerosis Risk in Communities Study

MP 2383. Windham BG, Harrison K, Wang W, Lirette S, Wilkinson M, Popeii L, Gabriel K, Koton S, Steffen L, Griswold M, Mosley T.

MP. 1697. Functional status and cardiovascular disease. Anna Kucharska-Newton, Randi Foraker, Kathryn Rose, Wayne Rosamond, Beverley Gwen Windham, Corey Kalbaugh

MP 3092. Associations of Subclinical vascular burden among Middle-Aged Adults with Change in Functional Status Later in Life. Chenkai Wu, B. Gwen Windham, Anna Kucharska-Newton, Priya Palta, Michelle C. Odden, Kunihiro Matsushita, Rebecca Gottesman

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

___ A. primarily the result of an ancillary study (list number* 2001.16 LITE; 2008.06 ARIC NCS for V6 function/TMW)

___ 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.

References

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6. Chida Y, Steptoe A. Positive Psychological Well-Being and Mortality: A Quantitative Review of Prospective Observational Studies. *Psychosomatic Medicine.* 2008;70(7):741-756.
7. Kucharska-Newton A, Griswold M, Yao ZH, et al. Cardiovascular Disease and Patterns of Change in Functional Status Over 15 Years: Findings From the Atherosclerosis Risk in Communities (ARIC) Study.

Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease. 2017;6(3):e004144.
8. Kucharska-Newton AM, Palta P, Burgard S, et al. Operationalizing Frailty in the Atherosclerosis Risk in Communities Study Cohort. *The Journals of Gerontology: Series A.* 2017;72(3):382-388.
9. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-Extremity Function in Persons over the Age of 70 Years as a Predictor of Subsequent Disability. *New England Journal of Medicine.* 1995;332(9):556-562.
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11. Spiegelman D HE. Easy SAS calculations for risk or prevalence ratios and differences. *Am J Epidemiol.* 2005;162(03):199-200.