ARIC Manuscript Proposal #3669

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

1.a. Full Title: Causes of Death after Venous Thromboembolism

b. Abbreviated Title (Length 26 characters): Causes of Death after VTE

2. Writing Group:
Writing group members: Mary Cushman, Pamela Lutsey, Neil Zakai, Aaron Folsom

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

First author: Mary Cushman
Address: University of Vermont
360 South Park Dr
Colchester, VT 05446
Phone: 802-656-8968 Fax: 802-656-8965
E-mail: mary.cushman@uvm.edu

3. Timeline: Fall-Winter 2019-20

4. Rationale:
Venous thromboembolism (VTE) is the 4th leading vascular diagnosis, affecting up to 1 million Americans annually and 700,000 Europeans [1]. It's impact on lifelong health beyond a few years after an event is little understood. The LITE study (including ARIC) and others have identified numerous risk factors for VTE, ranging from abnormal levels of coagulation and inflammation factors to acute and chronic medical conditions such as cancer, lung disease and heart failure. The short- and long-survival probabilities after VTE have also been examined [2, 3]. For example, recent data from Alberta Canada reported 1-year and 5-year survival probabilities of 60% (95% CI: 57–64%) and 39% (95% CI: 36–43%) in patients with cancer-associated PE, 93% (95% CI: 92–94%) and 80% (95% CI: 78–81%) in provoked PE, and 94% (95% CI: 93–95%) and 85% (95% CI: 83–87%) in unprovoked PE [3]. One report detailed the adjudicated causes of death among 991 Swiss VTE patients aged ≥65 with median follow up of only 30 months (maximum 36 months)[4]. Of those who died within 3 years of a diagnosis, cancer was the most likely cause (34%), PE remained a substantial cause (18%), and infection as a cause rose over time (12% in first year and 22% after the first year). Other studies have used death certificate-defined causes of death. In 30-year national data from Denmark, VTE was the cause of death for 12% of

patients, cancer for 7%, and respiratory diseases for 15%. Among 4,965 patients treated in anticoagulation clinics in the Netherlands followed for 5.5 years after VTE, 12% died; 65% of these from cancer, 1% from PE and 6% from respiratory diseases [5]. We are not aware of studies of long term survival and causes of death in a general US population with VTE, or of studies addressing causes of death by presentation of VTE.

As VTE treatments have improved in the past decade, with recommendations for longer term duration of anticoagulation after unprovoked events leading to reduced rates of recurrent VTE, it becomes important to understand health status of those surviving after VTE. In this work, we will report the underlying causes of death after VTE in ARIC participants to gain clues on chronic disease prevention after VTE. We will define distinct patterns of causes of death among VTE patients by type of presenting VTE.

5. Main Hypothesis/Study Questions:

1. Determine the cumulative incidence of death from all cause and specific underlying causes for first-time VTE.
2. Underlying causes of death in ARIC participants experiencing VTE will be reported descriptively.
3. Underlying causes of death after PE will be different than after DVT.
4. Underlying cause of death will also differ in those with unprovoked VTE, provoked non-cancer related VTE, and other provoked VTE
5. The crude cumulative incidence and the age, race, sex adjusted hazard of death in ARIC participants will be higher for those with VTE during follow up than other participants.

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).

Exclusions. We will exclude participants self-reporting prebaseline VTE.

Exposure. Incident (first) VTE, characterized as deep vein thrombosis (DVT) of the leg or inferior vena cava and pulmonary embolism (PE). Upper extremity DVT will not be considered VTE, as it was nearly always central venous catheter related in ARIC and the treatment is different. VTE will be categorized into three groups: unprovoked, cancer-related provoked, and other provoked VTE.

To address the long-term consequences of VTE, a separate analysis will exclude those with death within 90 days of their VTE.

Analysis in VTE cases only (Questions 1-4)**.** We will tabulate the cumulative incidence of death from all cause and specific underlying causes for overall first-time VTE, and separately for the three groups: cancer-provoked events, other provoked events and unprovoked events. Results will be shown with Kaplan-Meier curves. We will tabulate the underlying causes of death in groups defined by ICD9/10 and compare them by VTE groups using Chi Squared tests. A second analysis will describe death in the first 90 days, and death after 90 days in order to address long

term consequences of VTE survival. If the distribution of causes of death is similar in the three groups, the groups will be combined to repeat the same analysis for DVT vs PE +/- DVT. Otherwise these analyses will be reported separately by provoked/unprovoked status. We will also consider whether causes of death differ by age at the time of VTE, sex and race (black, non-black).

Analyses in the Whole Cohort. For question 5, we will calculate age- race and sex- and prebaseline cancer-adjusted hazard ratios of death for the different types of VTE cases compared to the rest of the cohort. This would be done by considering VTE as a time-varying exposure in survival models. For each of the three VTE types we will censor participants from analysis when they develop one of the other two VTE types. Finally, we will contrast the crude underlying causes of death after VTE to the causes of death in the overall ARIC cohort using Chi Squared tests.

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

___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? _xx___ Yes ____ No

11.b. If yes, is the proposal

_xx__ A. primarily the result of an ancillary study (list number* ___2001.16 LITE__)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation 2018;137:e67-e492.
2. Cushman M, Tsai AW, White RH, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. Am J Med 2004;117:19-25.
3. Alotaibi G, Wu C, Senthilselvan A, McMurtry MS. Short- and long-term mortality after pulmonary embolism in patients with and without cancer. Vasc Med 2018;23:261-266.
4. Faller N, Limacher A, Mean M, et al. Predictors and Causes of Long-Term Mortality in Elderly Patients with Acute Venous Thromboembolism: A Prospective Cohort Study. Am J Med 2017;130:198-206.
5. Flinterman LE, van Hylckama Vlieg A, Cannegieter SC, Rosendaal FR. Long-term survival in a large cohort of patients with venous thrombosis: incidence and predictors. PLoS Med 2012;9:e1001155.