ARIC Manuscript Proposal #2612

1.a. Full Title: Associations of Age, Sex, and Race with Unprovoked and Cancer-Associated Venous Thromboembolism in two Cohorts

b. Abbreviated Title (Length 26 characters): Race and Cancer Associated VTE

2. Writing Group: Daniel Douce, Nels Olson, Mary Cushman, Pamela L. Lutsey, Suzanne Judd, Kristen George, Neil Zakai.

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

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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).

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3. Timeline: Data analyses will begin immediately after approval by the ARIC supervising committee. Goal completion will be by November 2015.

4. Rationale:
   Venous thromboembolism (VTE) is classified as provoked (associated with surgery, hospitalization, trauma, or cancer) and unprovoked events. Whether provoked, unprovoked or cancer-associated VTE differs by age, sex or race, in the United States is poorly understood. Administrative data based on hospital admissions found a higher incidence of both idiopathic and secondary VTE in blacks compared to whites¹, however data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort found a similar overall incidence of VTE between races². Women were noted in one study to have a higher incidence of VTE than men, as well as a greater proportion of VTE being idiopathic,
before adjusting for hormone therapy and pregnancy\textsuperscript{3}. One-fourth to one-half of VTE are initially diagnosed as being unprovoked\textsuperscript{4,5}, having none of the typically recognized triggers, and 15-25\% of all VTE are associated with cancer\textsuperscript{5}.

After analyzing data from the REGARDS cohort, we found that blacks had a significantly lower risk of developing Cancer-Associated VTE than whites (hazard ratio = 0.38, 95\% confidence interval 0.18-0.77). We also found that the percentage of unprovoked VTE did not differ by age, sex, or race even though the total VTE incidence increased significantly with advanced age and male sex.

We were surprised by the racial disparity we found, as this has not been documented in the literature. We plan to analyze the associations of age, sex, and race with VTE in the ARIC cohort to see if these findings are replicated. With its inclusion of African-Americans, longer follow up times, and thorough ascertainment of VTE events, ARIC is a very useful cohort for confirming or contradicting our findings in REGARDS.

5. Main Hypothesis/Study Questions:

**Study Question 1:** Do VTE categories (unprovoked, provoked non-cancer, and cancer-associated) differ significantly with age, or by race or sex?

**Hypothesis 1:** Blacks will have significantly fewer cancer-associated VTE than whites. The ratio of unprovoked to provoked (both cancer associated and non-cancer associated) VTE will otherwise be similar across age, sex, and racial groups.

**Study Question 2:** Does the risk of developing unprovoked VTE, provoked non-cancer associated VTE, or cancer-associated VTE differ by age, race or sex?

**Hypothesis 2:** The risk of developing all types of VTE will increase with age. Blacks will have a lower risk of developing a Cancer Associated VTE than whites. Compared to women, men will have a higher risk of developing Unprovoked and Provoked, Non-Cancer Associated VTE, but not Cancer-Associated 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 cohort data from ARIC will be used. Age, sex and race reported at the initiation of the study will be used as well as VTE event data which were obtained through 2005 using previously published methods of event ascertainment\textsuperscript{6}.

**Exclusions:** Exclusion criteria will include self-reported race other than black or white, VTE patients with incomplete records (who cannot be assessed as having provoked, unprovoked or cancer associated VTE).
**Exposures:**
All ARIC participants with VTE with available records

**Outcome:** The primary outcome will be VTE during follow-up. VTE subtypes will be analyzed as unprovoked, provoked, and cancer or non-cancer-associated events

**Covariates:** The study will focus primarily on covariates of age, sex, and self-reported race. Other covariates will include body mass index, hypertension, diabetes, kidney disease, anticoagulant use, education and income.

**Data analysis:**
Variables will include: sex (male versus female), and race (black versus white).

For Study Question 1, we will compare means or frequencies of demographic characteristics (sex, and race) by case status (idiopathic VTE, provoked, non-cancer associated VTE, and cancer associated VTE) using chi square analysis. We will then use logistic regression to assess whether age, sex, and race are independently associated with idiopathic VTE, provoked VTE, and with cancer-associated VTE. Models will be adjusted for age, sex, and race (as appropriate) as well as body mass index, hypertension, diabetes mellitus, kidney disease, baseline anticoagulant use, education, and income. We will also model age as a continuous variable (per standard deviation increment).

For Study Question 2, we will evaluate the prospective associations of age, sex, and race, with provoked versus unprovoked VTE and in cancer-associated versus non-cancer-associated VTE in the entire ARIC cohort of participants using Cox proportional hazard models (mean follow-up ~ 15 years). Idiopathic VTE, provoked VTE and cancer associated VTE will be analyzed as the outcome variables, with adjustment for the variables listed in study question 1. We will compare the age, sex, and race hazard ratios (HRs) for VTE for unprovoked versus provoked VTE and cancer associated VTE vs non-cancer associated VTE. If the HRs differ by more than 10% between variables, we will use bootstrapping with replacement (1,000 replicates) to determine whether the HRs are significantly different.

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.csecc.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)? No overlapping manuscripts. Drs. Lutsey and George are participating from the Longitudinal Investigation of Thromboembolism Etiology (Dr. Folsom does not want to participate but has agreed for us to do this analysis).

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) LITE (PI Folsom)

   ___      B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s))* 1998.03

*ancillary studies are listed by number at http://www.csecc.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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 __x__ Yes _____ No.

References


