ARIC Manuscript Proposal #1529

PC Reviewed: 07/14/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: *Race and Venous Thromboembolism: The Longitudinal Investigation of Thromboembolism Etiology*

New Title: Racial Differences in Venous Thrombosis in Three Cohorts

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

2. Writing Group:

Writing group members:

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

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3. Timeline: From approval of the manuscript proposal and release of the dataset, a manuscript will be drafted within 1 year.

4. Rationale:

Venous thromboembolism (VTE) is a common disease affecting between 350,000 and 600,000 Americans each year and is related to over 100,000 deaths each year[1, 2]. VTE occurs due to interrelationships of both genetic and environmental risk factors, with the incidence increasing dramatically with age and a substantially higher incidence among African-Americans as compared to European-Americans[2]. The US Surgeon General's Call to Action in 2008 highlighted both the need for more research on the epidemiology of VTE and the need to address racial differences in incidence[1].

Multiple studies have observed that African-American have a 30% to 60% higher incidence of VTE compared to their European-American counterparts[3-5]. The reasons for this are not well understood. The most common genetic variants associated with VTE in Caucasian populations (factor V Leiden and the prothrombin gene G20210A variant) are disorders of European origin and are rare in African-Americans[5], while the prevalence of abnormal biomarkers of VTE risk such as elevated D-dimer, elevated factor VIII, shorter aPTT and elevated C-reactive protein (CRP) is higher in African-Americans[6-10]. Further, VTE risk factors such as obesity and diabetes are more common in African-Americans[11].

For this analysis, we will use data from the Longitudinal Investigation of Thromboembolism Etiology (LITE), an ancillary study capturing VTE events in both the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study and data from REGARDS-VTE, an ancillary study in REGARDS capturing VTE events. **Table 1** presents the number of VTE in LITE to date subdivided by race and whether the event was idiopathic or provoked.

Table 1: Documented VTE in LITE to Date.

		LITE		
		ARIC	CHS	Total
Cohort	African-American	4,266	923	5,189
	European-American	11,526	4,965	16,491
	Total	15,792	5,888	21,680
Total VTE		516	210	726
Site	DVT	405	174	579
	PE	183	67	250
Race	European-American	340	162	502
	African-American	176	48	224
VTE Type	Idiopathic	196	89	285
	Secondary	320	121	441

We hypothesize that differences in known risk VTE factors and that a higher incidence of provoked (and potentially preventable) VTE explain part of the disparity in VTE risk. Specifically, the increased burden of VTE in African-Americans will be related to differences in (1) the incidence of provoked versus unprovoked VTE (2) the prevalence of medical conditions that are risk factors for VTE, such as obesity, kidney disease and diabetes; (3) differences in biomarkers of risk (factors VIII, XI, D-dimer, vWF, and protein

C) and elevated CRP. Given known differences in health care by race, we additional hypothesize that medical conditions may be stronger VTE risk factors in blacks compared to whites. Analyses will be stratified by cohort by biomarker availability.

5. Main Hypothesis/Study Questions:

1. African-Americans will have a higher incidence of VTE and of potentially preventable VTE (provoked by surgery and hospitalizations) than European-Americans.
2. A higher prevalence of obesity and diabetes, and a procoagulant state as assessed by coagulation factor levels in African-Americans will mediate part of the increased risk of VTE observed in African-Americans.
3. Diabetes, kidney disease, and obesity will be more strongly associated with VTE in African-Americans than in European-Americans while coagulation biomarkers will have an equal association.

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).

Data [Variables to be used, sample inclusions/exclusions]:

As this is an analysis of 3 cohorts (REGARDS, CHS, and ARIC), some information will be available only in 1 or 2 cohorts,or in the case of LITE, in a nested case control study of biomarkers. Participants who are not African-American or European-American will be excluded. . Analyses including genetic information will exclude individuals not consenting to use of genetic information.

Outcome Variable: VTE (provoked and idiopathic), DVT, and PE

Covariates:

Baseline: Age, gender, race, body mass index, diabetes, hypertension, kidney disease (estimated GFR, creatinine, cystatin c), income, education (Available in each cohort).

Coagulation Factors: aPTT, D-dimer, factors VIII, IX, XI, fibrinogen, protein C, vWF (Available in LITE only)

Genetic Markers: prothrombin G20210A, factor V Leiden, ABO blood group (Available in LITE only)

Inflammation Markers: CRP (Available in REGARDS and CHS)

Brief analysis plan and methods:

a. African-Americans will have a higher incidence of VTE and of potentially preventable VTE (provoked by surgery and hospitalizations) than European-Americans.

We will compare the age and gender normalized incidence of VTE per 1000 person years in each cohort as well as for African-Americans and European-Americans separately for all VTE, idiopathic VTE, provoked VTE, pulmonary embolism (with or without deep venous thrombosis) and deep venous thrombosis alone using a z-test.

b. A higher prevalence of obesity and diabetes, and a procoagulant state as assessed by coagulation factor levels in African-Americans will mediate part of the increased risk of VTE observed in African-Americans.

We will compare the prevalence of VTE risk factors between African-Americans and European-Americans using t-tests or Wilcoxon Rank Sum tests for continuous risk factors as appropriate and χ^2 analyses for dichotomous risk factors. For each cohort, we will run separate analyses. We will use Cox proportional hazard models for data available in the entire cohort and logistic regression models for data available only as case-control data. In age-, sex-, and race-adjusted models we will evaluate the impact that individually adding risk factors for VTE (i.e. obesity, diabetes, factor VIII etc.) has on the race coefficient. In addition to individual risk factors, we will enter groups of risk factors such as coagulation factors etc. We will assess the impact of the addition of variables on the race-coefficient. We will not do a traditional mediation analysis but perform bootstrap estimates for promising covariates such as body mass index (see power section).

c. Diabetes, kidney disease, and obesity will be more strongly associated with VTE in African-Americans than in European-Americans while coagulation biomarkers will have an equal association.

In age-, sex-, and race-adjusted models (either Cox proportional hazard models or logistic regression as appropriate) we will assess for a significant interaction term between the race term and the risk factor (race*risk factor). We will also look at additive interactions between race and categorical variables by calculating the relative excess risk percent. Where appropriate we will add additional covariates (such as body mass index when assessing coagulation factors). We will present stratified models for all interaction terms ≤ 0.1.

Combining Data Among Cohorts

The cohorts have different recruitment strategies, time periods, follow-up, and ascertainment of events. Due to hypothesized heterogeneity between studies, data will be combined using a random effects meta-analysis for survival data, or presented stratified depending on the results of the analyses[12].

Power Considerations

There is already a known difference in the incidence of VTE in African-Americans and European-Americans in LITE[11]. For sub-group analyses without significant results we will report the potentially detectable difference based on the person-years of follow-up and the observed rates. In some analyses we may lack power to detect clinically meaningful differences while in others clinically meaningful differences may be ruled out.

For Aim B, we will look at the change in the race coefficient within a clinical context and not perform a traditional mediation analysis, for which we potentially lack power to detect moderate effect sizes. If the mediation effect size appears large or clinically relevant, we will consider performing bootstrap estimates of the change in hazard ratio.

For Aim C Table 2 presents the potentially detectable OR in stratified analyses (250 cases represents an estimation for the number of African-American VTE and 500 cases represents an estimation for the number of European-Americans with VTE). We assumed a power of 80% and an alpha of 0.05 and a case to control ratio of 1:2. This is our most restricted analysis; other analyses will have more power.

Table 2: Detectable Odds Ratios for Logistic Regression Models (Power = 80%, $\alpha < 0.05$, case:control = 1:2)

	Risk Factor Prevalence					
Number of Cases	**5%**	**10%**	**20%**	**30%**	**40%**	**50%**

250	2.35	1.93	1.68	1.59	1.57	1.57
500	1.88	1.61	1.45	1.39	1.37	1.37

Summary/conclusion:
By accomplishing our aims we will characterize racial differences in VTE, evaluate the impact of VTE risk factors in African-Americans and European-Americans, and begin to understand what risk factors may mediate the difference.

The reasons for racial differences in VTE are poorly understood with available prospective data limited by small numbers of African-American participants. REGARDS and LITE offers the opportunity to study racial differences in VTE, and more importantly can provide the opportunity for hypothesis generation for potential future studies addressing the racial differences in VTE.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

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

1998.03)

___ B. primiarly 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/

12. 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.

References:

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