

ARIC Manuscript Proposal # 3078

PC Reviewed: 11/14/17
SC Reviewed: _____

Status: _____
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Plasma biomarker changes and incidence of venous thromboembolism (VTE)

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

2. Writing Group:

Writing group members: Aaron Folsom, Saonli Basu, Susan Heckbert, Pam Lutsey, Ron Hoogeveen, Mary Cushman, Christie Ballantyne

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: Aaron Folsom or TBN student
Address:

Phone: _____ Fax: _____
E-mail: _____

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: _____
Address: _____

Phone: _____ Fax: _____
E-mail: _____

3. Timeline: Spring 2018

4. Rationale:

Inflammatory diseases increase the risk of VTE.¹²⁹ Our Longitudinal Investigation of Thromboembolism Etiology (LITE, including ARIC and CHS) and others also have shown in the general population that higher levels of the inflammatory marker, CRP, are associated with

increased risk of VTE.¹³⁰ The adjusted hazard ratio of VTE was 1.76 (95% CI 1.23, 2.52) for CRP above versus below the 90th percentile in ARIC. In addition, LITE reported that troponin T, a cardiac myonecrosis marker, and NT-proBNP, a marker of myocardial stretch and volume overload, were also positively and moderately strongly associated with VTE incidence.⁵⁷ Age, race, and sex-adjusted hazard ratios for total VTE were 1.00, 0.85, 1.36, 1.51, and 1.98 (p-trend <0.0001) across five categories of troponin T. The association of NT-proBNP with VTE was positive in ARIC (hazard ratios approximately 2.5-fold for the highest versus lowest NT-proBNP quintiles), but null in CHS.

We now propose to study 6-year changes in NT-proBNP, troponin T, and CRP with incidence of VTE in ARIC. In addition, CHS measured NT-proBNP and CRP over time (see table below) and will be used as a validation sample. This will be the first study to examine whether rising levels of these biomarkers are associated with greater VTE risk. Of note and by analogy, changes in inflammatory markers are associated positively with risk of the post-thrombotic syndrome.¹²⁸

Intended phenotype to match w ARIC	Description	Calendar years	N of ppts w data
NT-proBNP* (6-yr change)	BL for both cohorts (Y2, Y5) and f/u at Y5 (old) and Y7 (new) Y9 (separate Anc Study, but harmonized)	1989-90 1992-93 1992-93 1994-95 1996-97	Y2: n=4148 (old) Y5: n=3608 (old) Y5: n=547 (new) Y7: n=473 (new) Y9: n=3307 (both)
hs-troponin T (6-yr change)	BL for both cohorts (Y2, Y5) and f/u at Y5 (old) and Y7 (new)	1989-90 1992-93 1994-95	Y2: n=3886 (old) Y5: n=4146 (both) Y7: n=473 (new)
CRP (6-yr change)	Y2 (baseline), Y5, Y9, Y18	1989-90 1992-93 1996-97 2005-2006	nearly all who attended these visits

*For NT-proBNP, CHS has 3-yr change and 7-yr change in the original cohort, and has 2-yr change and 4-yr change in the new cohort. We may want to go with short intervals in CHS because of shorter follow-up time after the later measurements.

(Citations not provided but available on request.)

5. Main Hypothesis/Study Questions: 6-year change in plasma NT-proBNP, troponin T, and CRP from 1990-92 to 1996-98 in ARIC is associated positively with VTE incidence after 1998 (and in CHS as a validation study).

Although these biomarkers are available at later visits, we probably will not use them because of concerns about reverse causality, as the later visits would have occurred after VTE in many instances.

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).

The ARIC atherosclerosis laboratory (Baylor College of Medicine) measured a number of analytes using state of the art methods in stored plasma on the entire ARIC cohort examined in Visit 4 (1996-98). We estimated that measurements would be available on approximately 11,097 of the 15,792 original ARIC participants for CRP (immunoturbidimetric assay on a Beckman Olympus AU400); NT-proBNP and troponin T (Roche chemiluminescent assays). These three biomarkers were measured by identical methods in ARIC Visit 2 (1990-92), allowing the study of incident VTE in relation to 6-year changes in them. Although the primary analysis will involve ARIC, CHS has baseline and 5 year change in NT-proBNP and CRP in over 3000 participants, and can serve as a replication of any associations identified in ARIC. We will use CHS to replicate, rather than pool both cohorts, because lab methods were different and the time interval for change in biomarkers is somewhat different.

We will primarily employ Cox proportional hazards regression to investigate the associations of VTE with change in these novel risk factors. In the regression model, the dependent variable will be the time to first VTE event with predictors as individual risk factors and potential confounders measured. We will assess the proportional hazards assumption by testing for interaction of each risk factor with survival time. In the event of violations, time-dependent Cox regression models will be used.

The prospective analysis of change in biomarkers between visit 2 and 4 will involve roughly 11,097 ARIC participants and approximately 743 VTE events from 1996-98 through 2015. At $\alpha = 0.05$, in ARIC alone we should have 80% power to detect HRs of 1.11 per SD of baseline levels of biomarkers or per SD of change in biomarkers.

If there is no association in ARIC, we will not pursue analyses in CHS. If there is an association for one or more factors in ARIC, we will try to replicate in CHS.

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.csc.unc.edu/ARIC/search.php>

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)?

They are all our own proposals.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* 2001.16)**
 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.csc.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.csc.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 No.