

## ARIC Manuscript Proposal #2149

PC Reviewed: 6/11/13  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Liver dysfunction and venous thromboembolism

**b. Abbreviated Title (Length 26 characters):** Liver dysfunction-VTE

**2. Writing Group:**

Writing group members: Aaron Folsom, Pam Lutsey, Saonli Basu, Wayne Rosamond, Mariana Lazo, Susan Heckbert, Mary Cushman, Elizabeth Selvin

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

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**3. Timeline:** start Summer 2013

**4. Rationale:**

Clinical dogma suggests chronic liver disease carries a high risk of hemorrhage. However, recent evidence suggests that decreased plasma coagulation factors are balanced by decreased anticoagulant factors to offset bleeding.<sup>1</sup> In fact, case reports indicate that cirrhosis patients often get VTE and therefore have a thrombogenic diathesis,<sup>2,3</sup> and a large case-control administrative database study in Denmark showed a 2-fold elevated VTE risk for both cirrhosis and non-cirrhotic liver disease.<sup>4</sup> Another recent BMI-matched clinical case-control study linked nonalcoholic fatty liver disease with 2-fold odds of VTE.<sup>5</sup> NHANES indicates that elevated liver enzymes are highly prevalent [ALT, 10%; AST, 16%; GGT, 9%].<sup>6</sup> Thus, liver dysfunction could be a VTE risk factor in the general population, but solid epidemiologic data are lacking.

In February 2012, the ARIC chemistry laboratory (University of Minnesota) began measuring liver enzymes in stored serum on the entire ARIC cohort examined in Visit 2 (1990-92). Thus, Visit 2 measurements on approximately 14,000 of the 15,792 original ARIC participants will be available for serum GGT, ALT, AST.

**5. Main Hypothesis/Study Questions:**

Liver markers are associated positively with VTE incidence.

**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: cohort

Endpoint: VTE incidence

Exposure: visit 2 Measures of liver dysfunction (serum GGT, ALT, AST)

Exclusions: VTE prior to visit 2, anticoagulant use, missing liver enzymes. For analyses using thrombophilia SNPs, we will also exclude on no DNA use or missing data.

Main covariates: visit 2 age, race, sex, HRT, BMI, diabetes, eGFR.

Analysis: The prospective cohort analysis for liver markers will involve 14,000 ARIC participants followed from 1990-92 through 2011 and approximately 622 VTE events. Expected variances are 10-15% for elevated liver enzymes, but these markers will also be analyzed as continuous variables. Analyses will be performed using proportional hazards modeling as in previous LITE publications. Most relevant confounding variables have been measured. At  $\alpha = 0.05$ , in ARIC alone we should have 80% power to detect HRs of 3.06, 2.23, 1.67, 1.45, 1.32, and 1.26 for prevalences of 1%, 2%, 5%, 10%, 20%, and 38%, respectively. Thus, we can reasonably detect moderate associations for liver dysfunction.

A supplemental analysis will look at liver dysfunction associations with VTE in relation to people with thrombophilia SNPs or not.

Another supplemental analysis may examine coagulation factors as mediators, using LITE's previous nested case-control sample. However, the visit dates for liver enzymes and coagulation factors do not match exactly.

## REFERENCES

1. Tripodi A, Mannucci PM: The coagulopathy of chronic liver disease. *N Engl J Med* 2011;365:147-56.
2. Lippi G, Targher G, Favaloro EJ, Franchini M. Venous thromboembolism in chronic liver disease. *Semin Thromb Hemost* 2011;37:66-76.
3. Ali M, Ananthkrishnan AN, McGinley EL, Saeian K. Deep vein thrombosis and pulmonary embolism in hospitalized patients with cirrhosis: a nationwide analysis. *Dig Dis Sci* 2011;56:2152-9.
4. Søgaard KK, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based

case-control study. *Am J Gastroenterol* 2009;104:96-101.

5. Di Minno MND, Tufano A, Rusolillo A, Di Minno G, Tarantino G. High prevalence of nonalcoholic fatty liver in patients with idiopathic venous thromboembolism. *World J Gastroenterol* 2010;16:6119-22. [PMCID: PMC3012581]
6. Tsai J, Ford ES, Li C, Zhao G. Past and current alcohol consumption patterns and elevations in serum hepatic enzymes among US adults. *Addict Behav* 2012;37(1):78-84.

**7.a. Will the data be used for non-CVD analysis in this manuscript?**

Yes  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  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)?**

None.

**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 (\* 2006.16 and 2009.16)

\_\_\_ **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](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.