ARIC Manuscript Proposal #2882

PC Reviewed: 11/08/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Galectin-3 and Venous Thromboembolism Incidence

b. Abbreviated Title (Length 26 characters): Galectin-3 and VTE

2. Writing Group:

Writing group members: Aaron Folsom, David Aguilar, Christie Ballantyne, Ron Hoogeveen, Mary Cushman, Susan Heckbert

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, although likely this manuscript will be given to an interested student

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3. Timeline: Begin fall 2016

4. Rationale:

Galectin-3 (Gal3) is a beta-galactoside binding lecitin involved in important regulatory roles in adhesion, inflammation, immunity, and fibrosis. Recent epidemiologic studies have shown Gal3 is positively associated with incident heart failure and CHD.

Inflammatory diseases and higher levels of inflammation markers, such as CRP and interleukin-6, are associated with increased risk of VTE. Galectin-3–binding protein (Gal3bp) and Gal3 are secreted proteins that can interact with each other to promote cell-to-cell adhesion and initiate pathologic, proinflammatory signaling cascades [PMCID: PMC4357586]. Gal3bp and Gal3 play important roles in a number of pathologic conditions, such as cancer, diabetes, atherosclerosis, heart failure, and rheumatoid arthritis, and some evidence suggests a role in VTE. A recent study showed that Gal3 and Gal3bp are associated with murine thrombogenesis, that Gal3 and Gal3bp interact at the thrombus–vein wall interface, and that Gal3 may be contributing to thrombosis through proinflammatory, interleukin-6–dependent mechanisms [PMCID: PMC4357586]. Gal3bp is up-regulated in microparticles from DVT patients compared to control patients [PMCID: PMC2860062].

Gal3 measurements at ARIC visit 4 offer an opportunity to test the following hypothesis:

5. Main Hypothesis/Study Questions:
Plasma galectin-3 concentration is associated positively with incidence of VTE.

Secondary: a *LGALS3* (galectin-3 structural gene) locus associated with plasma galectin-3 levels is also associated 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: prospective with visit 4 (1996-98) as baseline, with galectin-3 as the exposure (*LGALS3* SNP as secondary). We also have access to galactin-3 in CHS (1992-93), and this will serve as a replication sample.

Outcome: time to incident VTE as validated by the LITE ancillary

Exclusions: prevalent VTE or use of anticoagulants at analysis baseline; missing galectin-3

Primary Covariates: Main VTE risk factors as published by LITE (age, race, sex, , BMI, diabetes, eGFR). Cancer is a potential confounder; we will run a sensitivity analysis excluding those with baseline cancer and cancer related VTEs.

Analysis: Examine association of galectin-3 with covariates. Linear splines to examine association with VTE incidence. Main analysis—Cox proportional hazards models. A first model will test race interactions (stratify by race if indicated) and adjust for the main VTE risk factors. A second model will adjust further for NT-proBNP, CRP, and troponin T.

The SNP analysis will be conducted assuming an additive genetic model, with and without plasma galectin-3 in the model.

A similar analysis will be conducted in CHS and potentially results will be pooled.

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? __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 ICTDER03 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)?**
    Galectin-3 and Cardiovascular Outcomes (submitted by David Aguilar)

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* ___2006.16_____)

___ 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.cscc.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, 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 ___x_ No.