ARIC Manuscript Proposal #2063

PC Reviewed: 1/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: LpPLA2 and venous thromboembolism

b. Abbreviated Title (Length 26 characters): LpPLA2 and VTE

2. Writing Group:

Writing group members: Aaron Folsom, Pam Lutsey, Nick Roetker, Christie Ballantyne, Ron Hoogeveen, Wayne Rosamond, Mary Cushman

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]**

F**irst author**:

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3. Timeline: start immediately

4. Rationale:

Inflammation is generally not believed to be important in the etiology of venous thromboembolism (VTE). For example, most (1-3) but not all studies (4,5) have found no independent association of VTE with CRP. Yet, certain rheumatologic diseases are associated with increased risk of VTE.

Lipoprotein associated phospholipase A2 (LpPLA2) is another biomarker related to thrombosis and inflammation status. LpPLA2 has been associated positively with CHD and stroke incidence in ARIC (6,7). However, we found no relation of LpPLA2 and VTE in the Cardiovascular Health Study (8). This association has not been explored in ARIC.

If, as in CHS, we observe no association, we anticipate submitting our findings as a brief report or letter.

5. Main Hypothesis/Study Questions:

LpPLA2 at visit 4 is associated positively with incidence of 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: cohort
Endpoint: VTE incidence
Exposure: visit 4 LpPLA2 activity
Exclusions: VTE prior to visit 4, anticoagulant use, missing LpPLA2
Main covariates: visit 4 age, race, sex, HRT, BMI, diabetes, eGFR, CRP; visit 1 factor VIII and aPTT
Analysis: Cox proportional hazards, with LpPLA2 modeled as a continuous variable and as quartiles. LpPLA2 differs considerably by race and sex, so quartiles may have to be sex/race specific.

REFERENCES

1: Fox EA, Kahn SR. The relationship between inflammation and venous thrombosis. A systematic review of clinical studies. Thromb Haemost. 2005 Aug;94(2):362-5. Review.

2: Vormittag R, Vukovich T, Schönauer V, Lehr S, Minar E, Bialonczyk C, Hirschl M, Pabinger I. Basal high-sensitivity-C-reactive protein levels in patients with Spontaneous venous thromboembolism. Thromb Haemost. 2005 Mar;93(3):488-93.

3: Kamphuisen PW, Eikenboom JC, Vos HL, Pablo R, Sturk A, Bertina RM, Rosendaal FR. Increased levels of factor VIII and fibrinogen in patients with venous Thrombosis are not caused by acute phase reactions. Thromb Haemost. 1999 May;81(5):680-3.

4. Ridker PM et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973-9.

5. Folsom AR, Lutsey PL, Astor BC, Cushman M. C-reactive protein and venous thromboembolism. A prospective investigation in the ARIC cohort. Thromb Haemost. 2009 Oct;102(4):615-9.

6. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Chambless LE, Myerson M, Wu KK, Sharrett AR, Boerwinkle E. Lipoprotein-associated phospholipase

A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med. 2005 Nov 28;165(21):2479-84.

7. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Heiss G, Sharrett AR.Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2004 Feb 24;109(7):837-42

8. Olson N, O'Meara ES, Jenny NS, Folsom AR, Bovill EG, Furberg CD, Heckbert SR, Psaty BM, Cushman M. Lipoprotein-associated phospholipase A2 and risk of venous thrombosis in older adults. Am J Hematol. 2008 Jul;83(7):524-7.

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.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)?

1. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Chambless LE, Myerson M, Wu KK, Sharrett AR, Boerwinkle E. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Arch Intern Med. 2005 Nov 28;165(21):2479-84.

2. Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Heiss G, Sharrett AR.Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2004 Feb 24;109(7):837-42

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.