ARIC Manuscript Proposal #2905

PC Reviewed: 12/13/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Platelet activity measured by P-Selectin, CD40 Ligand, and β-thromboglobulin and cardiovascular disease risk in the general population: the Atherosclerotic Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Platelet activity and CVD

2. Writing Group:

Writing group members: Yasuhiko Kubota, Ron Hoogeveen, Christie Ballantyne, Aaron Folsom, others welcome

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

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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).
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3. Timeline:

Data analysis: 1-2 months from manuscript approval date.
First draft of the manuscript: 2-3 months from manuscript approval date.

4. Rationale:

Platelets are essential to atherothrombosis and thromboembolic events (1, 2). Platelets may be activated by impaired endothelial antithrombotic properties, reactive oxygen species deriving from cardiovascular risk factors such as smoking and diabetes, and increased prothrombotic and pro-inflammatory mediators (3). Activated platelets adhere

to the vessel wall, accelerate the inflammatory process by releasing their granules, contributing to atherosclerosis, and also play a key role in thrombus formation on erosion or rupture of an atherosclerotic plaque (3). Abundant previous reports have suggested that increased levels of activated platelets are associated with increased risks of cardiovascular morbidity and mortality among patients with cardiovascular disease (CVD) (4-7).

However, there is limited evidence on the association between platelet activity and CVD risk in populations without clinical CVD (7). Some studies have reported P-Selectin and CD40 Ligand, which can be considered to be markers for activated platelets are associated with CVD risk in general populations (8-10); other population studies have found no association between these markers and CVD (11, 12). Thus, those associations need further exploration. Other platelet function tests such as aggregometry, mean platelet volume, platelet count, bleeding time and thromboxane appear to have no associations with incident CVD risk (7).

In ARIC, β-thromboglobulin, which is a well-established marker for activated platelet, as well as P-Selectin and CD40 Ligand, were measured on blood stored from ARIC clinic examinations in nested case-cohort studies. Therefore, we sought to test the hypothesis that activated platelet, measured by higher levels of P-Selectin, CD40 Ligand, and β-thromboglobulin, are associated with increased risk of incident CVD.

5. Main Study Questions:
Activated platelet functions measured by P-Selectin, CD40 Ligand, and β-thromboglobulin are associated with increased risks of incident CVD.

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 cohort

Inclusion/exclusion criteria
Inclusion: Cohort random sample who provided blood samples for P-Selectin and β-thromboglobulin at visit 1 (n=about 1,000) and for CD40 Ligand at visit 2 (n=about 900). These were measured in nested case-cohort studies of CVD cases.

Exclusion: Those who had prevalent CVD (coronary heart disease, heart failure and stroke) at each baseline.

Main exposure
Plasma P-Selectin, CD40 Ligand, and β-thromboglobulin levels.

Covariates
Age, sex, race/ARIC field center, body mass index, hypertension, diabetes mellitus, HDL, LDL, triglyceride, estimated GFR, antiplatelet therapy, smoking status, alcohol drinking, alcohol amount, and educational attainment.

Endpoints
Incident coronary heart disease, heart failure and stroke from baseline through 2,013.

Statistical analysis
Firstly, covariates first will be presented according to quartiles of plasma platelet activation markers.

Secondly, hazard ratios and their 95% confidence intervals for incident CVD will be calculated using a weighted Cox proportional hazard models in relation to quartiles of platelet activity marker levels and 1-SD increment for natural log-transformed or $\log_2$-transformed plasma platelet activation markers if we find they are left or right skewed.

- Model 1: adjustment for age, sex, race, and ARIC study site.

- Model 2: Model 1 + adjustment for body mass index, hypertension, diabetes mellitus, HDL, LDL, triglyceride, estimated GFR, antiplatelet therapy, smoking status, alcohol drinking, alcohol amount, and educational attainment.

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)?

Multiple ARIC papers on individual outcomes. For example:

#597: Association of beta-thromboglobulin levels with coronary heart disease
#941: Circulating levels of CD40 ligand (CD154) and ICAM-1 and Incident Coronary Heart Disease in Middle-Aged Men and Women: The ARIC Study
#1205: Association of platelet markers with peripheral arterial disease (PAD) (PMID: 21406422)

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

11.b. If yes, is the proposal

___ 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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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.

References:

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2. Vorchheimer DA, Becker R. Platelets in atherothrombosis. Mayo Clin Proc. 2006 Jan;81(1):59-68.
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12. Jefferis BJ, Whincup PH, Welsh P, Wannamethee SG, Rumley A, Lawlor DA, Ebrahim S, Lowe GD. Prospective study of circulating soluble CD40 ligand concentrations and the incidence of cardiovascular disease in a nested prospective case-control study of older men and women. J Thromb Haemost. 2011 Aug;9(8):1452-9.