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

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

2. Writing Group:
   Writing group members: Yasuhiko Kubota, Alvaro Alonso, 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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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:
   There is growing evidence on the association between atherosclerosis and atrial fibrillation (AF) (1). Recent studies have suggested that even subclinical atherosclerosis, in addition to heart failure and coronary heart disease, may be a risk marker for AF (1-5). Although AF and atherosclerosis share several risk factors such as smoking and
hypertension (1), other risk factors for atherosclerosis and its clinical manifestations may be also associated with increased risk of AF.

Platelets are essential to atherothrombosis and thromboembolic events (6, 7). 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 (8). Thus, activated platelet may be also a risk factor for AF. Although abundant previous studies have reported that patients with AF have higher levels of platelet activation markers than people without AF, which is considered as one reason why patients with AF have a higher risk of thromboembolic events than those without AF (9-13), to the best of our knowledge, there is no study prospectively investigating the association between platelet activation and AF risk in the general population.

In ARIC, β-thromboglobulin, P-Selectin and CD40 Ligand, which are considered to be platelet activation markers, were measured on blood stored from ARIC clinic examinations in nested case-cohort studies. Therefore, we sought to test the hypothesis that activated platelets, measured by higher levels of β-thromboglobulin, P-Selectin and CD40 Ligand are associated with increased risk of incident AF.

5. Main Study Questions:
Activated platelets, measured by higher levels of β-thromboglobulin, P-Selectin and CD40 Ligand are associated with increased risk of incident AF.

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: Participants who provided blood samples for P-Selectin and β-thromboglobulin at visit 1 (n=about 1,500) and for CD40 Ligand at visit 2 (n=about 1,700). These were measured in nested case-cohort studies of CVD cases in visits 1-3, so the analysis must take into account the original sampling strata.

Exclusion: Those who had prevalent atrial fibrillation at each baseline.

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

Covariates
Age, sex, race/ARIC field center, body mass index, systolic and diastolic blood pressure, anti-hypertension medication, diabetes mellitus, estimated GFR, smoking status, alcohol drinking, alcohol amount, educational attainment, antiplatelet therapy, left ventricular hypertrophy, prevalent heart failure at visit 1, as well as time-varying coronary heart disease and heart failure.
Endpoints
Incident atrial fibrillation from baseline through 2,013.

Statistical analysis
Firstly, covariates first will be presented according to tertiles (or quartiles) of plasma β-thromboglobulin levels.

Secondly, hazard ratios and their 95% confidence intervals for incident AF will be calculated using a weighted Cox proportional hazard models in relation to tertiles of platelet activity marker levels and 1-SD increment for natural log-transformed or log2-transformed biomarkers if we find biomarkers are left or right skewed, for early coronary heart disease cases and a cohort random sample, respectively.

- Model 1: adjustment for age, sex, race, and ARIC study site.
- Model 2: Model 1 + adjustment for baseline body mass index, systolic and diastolic blood pressure, anti-hypertension medication, diabetes mellitus, estimated GFR, smoking status, alcohol drinking, alcohol amount, educational attainment, antiplatelet therapy, left ventricular hypertrophy, carotid intima-media thickness and prevalent heart failure.
- Model 3: Model 2 + adjustment for time-varying incident coronary heart disease and time-varying incident heart failure.

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.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? __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 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: