ARIC Manuscript Proposal #2633

PC Reviewed: 9/8/15   Status: <u>A</u>   Priority: <u>2</u>
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Associations between Novel Biomarkers and Risk of Abdominal Aortic Aneurysm

  b. Abbreviated Title (Length 26 characters): Novel Biomarkers and AAA

2.   Writing Group:

Writing group members: Weihong Tang, Lu Yao, Ron Hoogeveen, Alvaro Alonso, Richard Maclehose, Pamela L. Lutsey, Aaron Folsom; others welcome

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

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3.   Timeline: Finish by March 2016

4.   Rationale:

Abdominal aortic aneurysms (AAA) are an important manifestation of vascular disease in older age. It is estimated that 5%-9% individuals in the US over the age of 65 years are affected by this condition. [1-3] Rupture of an AAA is a life threatening

condition, and a lot of research has been put into clinical guidelines for screening and revascularization of AAAs.

The etiology of AAA is complex and not well understood. Traditional atherosclerotic disease risk factors, particularly age, male sex, smoking and hypertension, contribute to the etiology of AAA.[4-7] Novel etiopathogenic mechanisms, including extracellular matrix remodeling and degradation, inflammation, and thrombosis, have been hypothesized but their roles are not appropriately determined.[8-11] Most evidence for the novel biomarkers as AAA risk factors, including MMPs, PIIINP, IL-1β and IL-6, and osteopontin, come from cross-sectional studies,[12] which do not provide information on the time sequence between the rising of the biomarkers and disease occurrence.

Dr. Tang's ancillary study has identified hospitalized AAAs through ARIC cohort surveillance and Medicare data, outpatient AAAs through Medicare data, and silent/asymptomatic AAAs through visit 5 ultrasound screening. A total of 680 AAAs have been identified in the ARIC cohort. As one of its two major Aims, Dr. Tang's ancillary study measured seven novel biomarkers for AAA in ARIC participants using a nested case-cohort design. The novel biomarkers include MMP-2, MMP-3, MMP-9, PIIINP, IL-6, IL-1β, and osteopontin. A total of 765 subcohort members were selected randomly from ARIC at baseline without regard to their AAA status during follow-up. The subcohort members were drawn within strata defined by race, gender, and baseline age (>55 vs. ≤ 55 years) so that the distributions of these variables are comparable between AAA cases and the subcohort comparison group. Blood samples for the 680 AAAs and 765 subcohort members at Visit 1 or Visit 2 (if Visit 1 samples were depleted) were used to measure those novel biomarkers. These data offer an excellent opportunity to examine the association of the novel biomarkers with AAA in this biracial community-based cohort.

5.   Main Hypothesis/Study Questions:

Novel biomarkers measured in middle age will be associated with risk of AAA over the next 20 years.

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: Nested case-cohort study with the ARIC prospective cohort from Visits 1 or 2 through the 2011 event follow-up and the abdominal aortic ultrasound exam at Visit 5.

Endpoint: clinical/hospital AAAs and ultrasound AAAs as defined below.
   1. Hospital AAAs ascertained through hospital discharge diagnoses and death certificates from Visit 1 to 2011 events follow-up. Hospital AAAs were defined using the definite ICD diagnostic codes 441.3, 441.4, 441.02, 38.44 and 39.71, and mortality code

I71.02, I71.3, I71.4, 441.3 and 441.4. Other diagnostic codes that indicate probable diagnosis of AAA will be investigated case-by-case to clarify or rule out AAA diagnosis.

2. Asymptomatic AAAs ascertained based on the Visit 5 abdominal aortic ultrasound exam. We will use a widely used definition for asymptomatic AAA, which is infrarenal abdominal aortic diameter ≥ 30 mm.

Overlap between the hospital and asymptomatic ultrasound AAAs: we expect a small overlap between the two groups because 1) a majority of clinical AAAs were asymptomatic but detected by participants' clinicians, or they had symptoms, surgical repair or rupture, 2) clinical AAAs who had a history of rupture or surgical repair have been excluded from the abdominal ultrasound exam.

Exposures: MMP-2, MMP-3, MMP-9, PIIINP, IL-6, IL-1β, and osteopontin.

Data Analysis: Cox proportional hazards models for clinical/hospital AAA nested case-cohort analysis, and logistic regression for ultrasound AAA analysis.

1) Analysis of Clinical AAAs

The time-to-event data in the case-cohort study will be analyzed using the Cox proportional hazard model with weighting to adjust for the varying sampling fractions of cases and controls across strata. The ARIC Study has typically applied the weighting method proposed by Barlow, where the subcohort of controls are weighted by the inverse of the sampling fraction and case weights are always one.[13, 14] In addition, variance estimation in Cox regression needs to be adjusted in the analysis of case-cohort data. We will use the robust variance estimation proposed by Barlow et al that uses an efficient jackknife approach for variance estimation in case-cohort studies. Recently, Breslow et al have reanalyzed data from an ARIC Study of CHD and have found that their proposed method for adjustment can dramatically improve the precision of HRs relative to Barlow case-cohort weighting.[15] They have also found the properties of their weighting procedure to be good when partially missing baseline covariates are imputed. We will further investigate the properties of this adjustment technique and will use it over the Barlow method if the claims of enhancing precision are confirmed. The techniques will be implemented in SAS.

As a first step, we will explore the shape of the association between the biomarkers and AAA risk using restricted cubic splines. The values of biomarkers will be log-transformed if necessary. If the association is approximately linear, then we will use continuous measures of the biomarkers and report that as the primary analysis. If not linear, the measures for the biomarkers will be categorized into quartiles or tertiles in the Cox regression analysis. The analysis will first be adjusted for age, race, and gender. Other potential confounding variables will be additionally adjusted for in a multivariable adjustment model. We will identify potential confounders based on our prior knowledge on AAA risk factors and test them in the initial analysis in the subcohort. We will consider adjust for the following risk factors that have been established in the literature: age, race, gender, height, smoking status and pack-years, alcohol consumption,

hypertension, peripheral artery disease, total, LDL, and HDL cholesterols, and diabetes. The following new biomarkers have recently been reported to predict AAA in our study[16] and will also be considered as potential confounders: white blood cell count, fibrinogen, D-dimer, troponin T, N-terminal pro-brain natriuretic peptide, and high sensitivity C-reactive protein. We will assess the proportional hazards assumption by testing for interaction between each risk factor (biomarkers and covariates) and survival time; time-dependent Cox regression models will be used if the assumption is violated.

2) Analysis of Ultrasound AAAs

People with known clinical AAA will not be included. We will use logistic regression to estimate the odds ratios (OR) and 95% CI for the association of each biomarker with asymptomatic AAA. For case-cohort data, the sample OR can be used to estimate the relative risk (RR) but the variance estimate for the log(OR) needs to be adjusted to take into account the possibility of having selected cases among the subcohort of controls. We will use the Schouten *et al.* sandwich estimator of the covariance matrix for log(OR) to adjust for the overlap in their logistic regression analysis of case-cohort data.[17] This estimator is equivalent to the robust variance estimator of Zeger and Liang[18] that was proposed for the analysis of longitudinal data. Adjustment for potential confounders will follow the approach described above. Because this analysis only includes ARIC participants returning for Visit 5 exam, there is potential for selection bias if the loss to follow-up is differential with regard to exposure and AAA outcome.[19] We will attempt to limit this potential bias by adjusting for all variables potentially related both to the outcome and the probability of being censored. In addition, we will perform sensitivity analyses that apply the inverse-probability-weighting method where the observed responses are weighted by the inverse of the probability of participating in Visit 5 given their covariates at baseline.[20]

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 ICTDER03 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

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
　　　　　＿＿＿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)?

1505. Risk Factors for Abdominal Aortic Aneurysm (Tang)
1505A. Hemostatic Factors and Aortic Aneurysm Incidence (Folsom)

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 (AS 2009.18: "Identifying Genetic and Epidemiological Risk Factors for Abdominal Aortic Aneurysm", R01HL103695, PI Weihong Tang)
　　　___ 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/

12. 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.

References:

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