ARIC Manuscript Proposal #2248

PC Reviewed: 10/8/11          Status: A          Priority: 2
SC Reviewed: __________  Status: _____  Priority: _____

1.a. Full Title: Peripheral Arterial Disease as an Indicator of Enlarged Abdominal Aorta Diameters

b. Abbreviated Title (Length 26 characters): PAD and AAD

2. Writing Group: Ada Al-Qunaibet, Weihong Tang, Aaron Folsom, Hirofumi Tanaka, Jacqueline Wright, Thomas Mosley, Lynne Wagenknecht

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

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3. Timeline: Work will begin upon approval, and will produce a manuscript within 8 months.

4. Rationale: Ankle brachial index (ABI) is a non-invasive tool used to assess peripheral arterial occlusive disease. Large cohort studies have reported an association of lower levels of ABI and central atherosclerotic changes, including subclinical atherosclerosis, clinical coronary artery disease, incident ischemic strokes, and recurrent
strokes[1-8]. Furthermore, ABI has been shown to aid in identifying persons with moderate to high cardiovascular risk, and as a predictor of cardiovascular morbidity and mortality[2, 4, 6]. While ABI has been associated with atherosclerotic occlusive disease in the coronary, carotid and peripheral arteries, the abdominal aorta is also a site of predilection and of early onset of atherosclerosis that may lead to abdominal aortic dilatation and loss of the tapered cylindrical shape of this segment of the aorta. Low ABI levels indicative of coronary artery disease, carotid artery stenosis, and/or peripheral artery disease have been shown to coexist in AAA persons[9]. While ABI is an established marker of peripheral arterial occlusive disease due to atherosclerotic changes, abdominal aortic ultrasound is used to assess morphologic characteristics and diameters of the abdominal aorta that may be indicative of underlying atherosclerosis.

The relationship between abdominal aorta diameter and peripheral occlusive disease measured by ABI are of interest. A limited number of studies have examined the relationship between AAA and peripheral arterial disease [10, 11]. Insights into the strength of association between ABI and abdominal aortic ultrasound measures will allow us to determine the inferences that can be concluded about abdominal aorta diameter using ABI as a proxy measure.

The relationship between ABI and AAD has not been characterized in a community-based population of older adults, and to our knowledge the cross-sectional association between the abdominal aorta diameters and ABI have not been examined. The purpose of the analyses proposed here is to examine hypothesized direct (positive) association between ABI and the diameters of the abdominal aorta at pre-specified sites, and to estimate the ability of ABI in predicting enlarged abdominal aorta diameters in a population based, bi-ethnic cohort of men and women ages 70-89 years.

5. **Main Hypothesis/Study Questions:**

   *Our goal is to characterize the relation between peripheral artery disease measured by ankle-brachial index (ABI) and diameters of the abdominal aorta at a proximal, mid-aorta and distal locations in a population based, bi-ethnic cohort of men and women ages 70-89 years.*

**Aims**

1. Describe the distribution of abdominal aorta diameters at proximal, mid, and distal locations by levels of peripheral artery disease measured by ABI at the cohort Visit 5 examination.
   
   - Describe the strength and shape of the association between ABI and abdominal aorta diameters at proximal, mid, and distal locations, and across the range of ABI values.
     
     i. We hypothesize that decreasing levels of ABI will be associated with wider abdominal aorta diameters.
     
     ii. We hypothesize that the strength of association will increase from proximal to distal levels of the abdominal aorta.
II. Examine the role of cumulative exposure to cigarette smoking, elevated blood pressure, blood lipids and excess weight on the association between ABI and AAD, as covariates and potential effect modifiers.

- Examine whether the cumulative exposure to cigarette smoking, elevated blood pressure, blood lipids and excess weight modifies the strength of association between ABI and AAD.
  
  i. We hypothesize that cumulative exposure to cigarette smoking, elevated blood pressure, blood lipids and excess weight will increase the magnitude of the association between ABBI and AAD on a multiplicative scale.

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).

Study design
Cross-sectional analysis of participants at ARIC visit 5 for Aim 1, and estimation of cumulative exposure for Aim 2, for consideration of effect modification of the association(s) observed in Aim 1.

Measurements
Ankle brachial index is the ratio of systolic blood pressure at the ankle by that in the arm, and it is measured at visit 5 with the OMRON VP-1000 plus system (Colin Co., Ltd., Komaki, Japan). A Gulick II anthropometric tape is used to measure the circumference of the arm and ankle to select the correct cuff size. Three arm cuff sizes are available; small (upper arm circumference 16-25 cm), medium (upper arm circumference 20-32 cm), and large (upper arm circumference 30-38 cm). Two cuff sizes are available for the ankle; medium (ankle circumference 16-33 cm), and large (ankle circumference 30-38 cm). The device used measures pulse wave velocity and ABI simultaneously.

In the clinical setting and in population-based studies ABI was traditionally measured using handheld Doppler probes, a validated approach of high sensitivity which is however observer dependent, and time consuming. To reduce observer-dependent variability and time, oscillometric devices are more widely used today, such as the one used in ARIC Visit 5. A number of calibration studies of oscillometric devices vs. conventional ABI measurement protocols have been published. The OMRON VP-1000 device selected for use in ARIC was favorably ranked in its performance relative to the reference method [12]. It has been established that oscillometric devices tend to overestimate the ABI value [12], a property amenable to correction if reliance on cut points is required; completeness, reliability and quality of the ABI data are enhanced on the other hand by simultaneously measuring blood pressure at the arm and ankle and by eliminating observer variability[13].
**Dependent Variable(s)**
Abdominal aorta diameters (AAD) were measured by high resolution, real time duplex ultrasound (Philips IE33) by trained and certified sonographers. Transverse images at five different segments of the abdominal aorta were taken to identify the anterior-posterior and transverse diameters.

**Covariates**
Covariates of interest include; gender, race, age, smoking status, systolic blood pressure, diastolic blood pressure, lipid levels, body mass index (BMI), and blood pressure-lowering treatments.

**Eligible Observations/Sample**
All participants with ABI values and abdominal aorta diameter values obtained at visit five will be included. An ultrasound examination of the aorta was not performed on participants with a history of previous abdominal aortic aneurysm repair or previous aortic bypass surgery for occlusive atherosclerotic disease. Since the excluded participants may have lower ABI readings compared to their counterparts with enlarged abdominal aorta diameters, selection bias toward the null is likely.

**Analyses**
The AAD as well as peripheral artery disease measured by ABI will be analyzed on a continuous scale. Aortic diameter measurements will be retrieved from the radiology over-read AAO files (giving precedence to the last reading for a participant in that file), and from the AAT files for those not over-read by radiology.

Bivariable comparisons of each independent variable to the abdominal aorta diameters will be explored and summary statistics will be estimated. We expect an inverse non-monotonic relationship between ABI and AAD. To avoid making assumptions we will allow for non linear relationship and we will characterize it in the course of model fitting.

To address aim two we will employ regression analysis to estimate the cumulative effect of elevated blood pressure, blood lipids and excess weight on the strength of association between ABI and AAD. The values of the aforementioned possible modifiers from cohort visit one through five will be included as multiplicative effects in the analysis. Cumulative exposures will be estimated as ‘time-in-risk’ constructs, i.e., products of the intensity of exposure in the ith year, summed over the years of follow-up.

**Attrition/Informative loss to follow-up**
Attrition and selective loss to follow-up over the prolonged follow-up period for data analyses will be quantified, and the degree to which it is selective according to the exposures considered here will be examined. Inverse weighing according to probability of attrition will be applied if warranted according to the quantification of selective loss to follow-up.
Limitations
The ARIC Visit 5 examinees represent a selected subset of this closed cohort. Achieving internal validity/unbiased estimates despite selective loss of follow-up will be our target; caution will be exercised in generalizing the results to other populations of older adults. Ultrasound scans of the abdominal aorta were not performed on participants with a history of abdominal aortic aneurysm repair or previous aortic bypass surgery for occlusive atherosclerotic disease, thus introducing informative censoring. Sensitivity analyses will be used to estimate the magnitude of this concern and its potential impact. As is known, adjusting for confounding covariates will not rule out residual confounding. Finally, causality will not be inferred from these cross-sectional data.

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.csc.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)?

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* AS 2009.18: “Identifying Genetic and Epidemiological Risk Factors for Abdominal Aortic Aneurysm”, R01HL103695)

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.
References:


