ARIC Manuscript Proposal # 1832

PC Reviewed: 8/9/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: A risk prediction model for incident PAD in the ARIC cohort

b. Abbreviated Title (Length 26 characters): PAD risk prediction model

2. Writing Group:
Writing group members: Laura Loehr, MD, PhD, Anna Kucharska-Newton, PhD, MPH, Elizabeth Selvin, PhD, MPH, Aaron R. Folsom, MD, MPH, Lloyd E. Chambless, PhD, Miguel Quibrera, PhD, Gerardo Heiss, MD, PhD; Lisa Wruck, PhD, others welcome

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

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3. Timeline: Data analysis to begin upon approval of proposal. Abstract submission to EPI/NPAM by October 2011.

4. Rationale:

Peripheral arterial disease (PAD) is a term given to a series of conditions caused by atherosclerotic lesions in the lower extremity arteries. PAD most commonly manifests as lifestyle-limiting claudication, a condition that causes leg cramping/pain during exercise. PAD can also present more severely and be classified as critical limb ischemia or limb threatening ischemia. Presentation of this type of PAD may include ischemic rest pain (IRP), or pain in the forefoot and toes that occurs at night, and various forms of tissue loss including non-healing wounds, ulcerations, and gangrene (1). The most common risk factors for PAD include diabetes and smoking and to a lesser extent comorbidities such as hypertension, hyperlipidemia, end-stage renal disease, and obesity (2). To date there is no widely accepted risk prediction model for PAD. This is important because it is estimated that prevalence of PAD among older adults (>65 years) can be as high as 20%. Furthermore, PAD is estimated to affect approximately 8 million individuals in the U.S. (3), with blacks reportedly having a higher prevalence than whites (4). As PAD increases with age, it follows that the prevalence of PAD will only increase in the upcoming years as the population ages (5,6).

Identifying those at risk for PAD is a serious public health challenge. PAD-related CVD mortality has been estimated to be 12.8% at 3 years (7). PAD often remains asymptomatic yet the disease continues to progress leading eventually to significant functional limitation and an increased risk of cardiovascular events (3). PAD is indicative of increased systemic atherosclerotic burden and those with atherosclerosis in their lower extremity arteries often have more proximal disease in their coronary and carotid arteries. Improving clinicians' capacity to predict those at risk for PAD could therefore have benefits in delaying or preventing myocardial infarction, stroke, and other major circulatory system disorders.

The most prominent PAD risk assessment to date is the Framingham Heart Study risk profile (8). Notably, this profile was created strictly for identifying those at risk for lifestyle-limiting claudication. The FHS identified 381 Caucasian men and women with claudication and used the follow-up data from the original Framingham cohort to create a risk profile for predicting subsequent claudication-related events (8). The final score included age, sex, serum cholesterol, hypertension, cigarette use, diabetes, and coronary heart disease. This score has been challenged as having limited accuracy and misclassifying risk in low- and high-risk populations (9, 10). Additionally, this risk assessment neglects other forms of PAD, such as those classified as critical limb ischemia.

Other attempts at determining risk for incident PAD hospitalizations in observational cohort studies are sparse. The PREVALENT study, conducted in general practices in the Netherlands, examined 7,454 patients aged $\geq$ 55 years with at least one vascular risk factor. The resulting prediction model included points for age, smoking, and hypertension (11). This group concluded that the PREVALENT prediction model allows practitioners the ability to identify the group at highest risk for future PAD events using ABI measurement (11).

While these risk profiles exist we believe the ARIC cohort provides a unique opportunity to improve on these models. Importantly, the ARIC cohort is larger, geographically diverse and multi-ethnic. Additionally, the participants have developed a significant number of PAD-related hospitalizations and a significant number of cohort members have been identified as having asymptomatic PAD.

The ARIC study will also allow us to add race (black/white) to the risk equation. This is particularly important given a recent report indicating that blacks have a higher prevalence of PAD than whites (4). Furthermore, whereas existing risk profiles are limited to identification of intermittent claudication, an ARIC-based risk profile will include all PAD-related hospital admissions between 1987 and 2008, and symptomatic PAD (claudication, ischemic rest pain, tissue loss/gangrene) will be considered as an additional outcome. This data will be collected via ICD-9 codes as well as information from the cohort exam visits and annual follow-up interviews. Finally, the ARIC cohort has a breadth of laboratory, hemostatic, and biomarker measurements that will be tested for their putative value as additions to the risk profile.

5. Main Hypothesis/Study Questions:

Aim 1: Estimate the incidence and life-time risk of PAD in the ARIC cohort (1987-2008), overall and stratified by race, age, and gender.

Aim 2: Develop a risk prediction score for incident PAD in the ARIC cohort. We hypothesize that smoking, diabetes, male gender, hypertension, age, chronic kidney disease, and increased BMI will optimally predict incident PAD.

Aim 3: Examine differences in risk prediction according to manifest CHD at baseline, and account for competing risk from other atherosclerotic disease manifestations.

Aim 4: Establish collaboration(s) with one or more pertinent study for external validation and calibration of the ARIC PAD risk score.

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 methodological limitations or challenges if present).

Study population
ARIC cohort study participants with follow-up from 1987 through 2008.

Study Covariates (using Visit 1 data)
(1) Demographic: age, gender, race

(2) Comorbidities: diabetes mellitus (including severity based on prior history vs. newly acquired), cholesterol levels, blood pressure, hypertension, BMI, smoking (pack years), coronary heart disease (CHD), stroke, waist-to-hip ratio

(3) Lab data: hemostatic markers including factor VIIIc, VWF, factor VII; inflammatory markers including WBC, albumin, fibrinogen; HDL-C, creatinine-derived eGFR

(4) Medication use: blood pressure medication use, lipid medication use, aspirin use, diabetes medication use

(5) Prevalent CHD at baseline

(6) Markers of subclinical disease: carotid IMT

(7) 10 year predicted probability of CVD

Hospitalized Events

This definition will be a modified version of the definition proposed by Dr. Keattiyoat Wattanakit, MD, MPH, in MS #731 (Ref #12) Dr. Elizabeth Selvin in MS #1056r (Ref #13) to be discharge codes for symptomatic PAD and discharge codes for relevant procedures.

(1) ICD-9 diagnosis codes for symptomatic PAD: 443.9 (intermittent claudication, peripheral vascular disease not otherwise specified), 707.1-707.19 (lower extremity ulcers), 785.4 (gangrene)
(2) ICD-9 procedure codes for symptomatic PAD: 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below knee amputation), 84.17 (above knee amputation), 38.18 (leg endarterectomy), 39.29 (leg bypass), 39.50 (leg angioplasty).

Non-Hospitalized Events

While reliance on clinically manifest / diagnosed PAD represents a strength in the context of risk prediction, an exclusive reliance on hospital discharge codes is a potential limitation. Calibration and sensitivity analyses will be performed to estimate – and potentially correct for – losses/mis-classification due to non-hospitalized events, drawing on two sources: (a) CMS claims data linked to the ARIC cohort (2003-2007), for outpatient as well as for inpatient codes, and (b) self-reported PAD diagnoses ascertained as part of the annual follow-up interviews. Also available for this purpose, although of limited sensitivity and restricted to the initial 9-12 years of cohort follow-up, are ABI measurements and the Rose claudication questionnaire.

Exclusions

Those with prevalent PAD at visit 1 (ABI <0.90), self-reported peripheral revascularization, amputation or PAD, those with missing covariates of interest, and non-black and non-white racial groups.

Statistical Methods

The association of the above mentioned characteristics and measurements of interest at baseline with incident PAD will be estimated. Best fitting Cox proportional hazards models will be developed and model performance measures calculated. These will include model goodness-of-fit statistics, area under the receiver operating characteristic curve (AUROC) and net reclassification improvement (NRI), which will both be estimated for discrimination and Gronnesby-Borgan statistics (GBS) for model fit (14).

Because of its clinical applicability, NRI cut-off points for 10 year risk will be calculated. These will be cross-tabulated to determine how many observations belong in each risk level classification (e.g. low, medium, high).

Limitations

PAD is not a validated endpoint in ARIC, thus hospitalizations here are only identified with ICD codes without further validation.

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

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)?

Manuscript #611 (Chambless, LE): Coronary heart disease risk prediction in the ARIC Study

Manuscript #731 (Wattanakit, K): Risk factors for cardiovascular event recurrence in the Atherosclerosis Risk in Communities (ARIC) study

Manuscript #824 (Chambless, LE): Ischemic stroke risk prediction in the Atherosclerosis Risk in Communities study

Manuscript #1056r (Elizabeth Selvin): Hemoglobin A1c (HbA1c) and Peripheral Arterial Disease in Diabetes: The Atherosclerosis Risk in Communities (ARIC) study

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* _____)

___ 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.

Reference List

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4. Allison MA, Ho E, Denenberg JO, Langer RD, Newman AB, Fabsitz RR, Criqui MH. Ethnic-specific prevalence of peripheral arterial disease in the United States. *Am J Prev Med*. 2007;32:328 –333.
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Mortality. *Journal of the American College of Cardiology* 2008; 52(21): 1736-1742.
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12. Wattanakita K, Folsom AR, Selvin E, Weatherley BD, Pankowa JS, Brancatib FL, Hirsch AT. Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis 2005; 180(2): 389-397.
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14. Gronnesby JK and Borgan O. Method for Checking Regression Models in Survival Analysis Based on the Risk Score. *Lifetime Data Analysis* 1996; 2: 315-328.