

## ARIC Manuscript Proposal # 997 Revised

PC Reviewed: 04/08/04  
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Status: A  
Status: A

Priority: 2  
Priority: 2

**1.a. Full Title:** Risk Factors for Peripheral Arterial Disease Incidence in Persons with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study

**b. Abbreviated Title (Length 26 characters):**

**2. Writing Group (list individual with lead responsibility first):** Keattiyot Wattanakit,

**Lead:** Keattiyot Wattanakit  
Address: University of Minnesota  
School of Public Health  
1300 South Second St, Suite 300  
Minneapolis, MN 55454

Phone: (612) 626-8873

Fax:

E-mail: [Wattanakit@epi.umn.edu](mailto:Wattanakit@epi.umn.edu)

Writing group members: Aaron Folsom, Elizabeth Selvin, Elizabeth Weatherly, Jim Pankow, Fred Brancati, Alan Hirsch

**3. Timeline:** Analysis will begin following approval; a manuscript is expected to be completed in June 2004.

#### **4. Rationale:**

It is well recognized that diabetes mellitus magnifies the risk of morbidity and mortality from cardiovascular disease. In the Multiple Risk Factor Intervention Trial, diabetic men were 3 times more likely to die of cardiovascular disease (CVD) than nondiabetic men, independent of age, ethnicity, tobacco use, cholesterol level, and blood pressure.<sup>1</sup> Diabetic people also have a 2- to 4-fold increased risk of developing peripheral arterial disease (PAD) and leg claudication.<sup>2</sup>

Many prospective studies have shown that traditional risk factors are important predictors of coronary heart disease in persons with diabetes.<sup>3-5</sup> The ARIC study has also measured nontraditional risk factors, including albumin, fibrinogen, von Willebrand factor, factor VIII activity, and white blood cell, and found them significantly associated with incident coronary heart disease in people with diabetes.<sup>6</sup>

In contrast, few studies have examined the association of traditional and nontraditional risk factors with PAD in the diabetic population. Some studies suggest that risk factors such as

increased age, LDL and HDL cholesterol, smoking, and long duration of diabetes are independent predictors for incidence and progression of PAD.<sup>7-10</sup> To our knowledge, there is no epidemiologic study that has examined the role of nontraditional risk factors as predictors for incident PAD.

In the ARIC study, participants had measurements of traditional and nontraditional factors and ankle-brachial index (ABI) at initial and subsequent visits. ICD codes for hospitalizations with PAD and annual surveillance for intermittent claudication based on the Rose Questionnaire have also been identified. Out of the 15,792 ARIC participants, 1651 participants had diabetes and were free of PAD ( $ABI \geq 0.9$ ) at baseline. We propose to use data from this subset of the cohort to investigate predictors of incident PAD.

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

The main hypothesis to be tested is that in the diabetic population high levels of traditional and nontraditional risk factors will be related independently to incident PAD, defined by  $ABI < 0.9$ , hospital PAD discharge diagnosis, amputation, or leg revascularization procedures, and intermittent claudication.

## **6. Data (variables, time window, source, inclusions/exclusions):**

Predictor variables: traditional risk factors (age, hypertension, smoking, body mass index, sport index score, LDL and HDL cholesterol) and nontraditional risk factors (lipoprotein(a), fibrinogen, factor VII, factor VIII, von Willebrand factor, white blood cell count, antithrombin III, protein C, creatinine, magnesium, and albumin)

Outcome variables: incident PAD ( $ABI < 0.9$ ) in either visit 3 or 4, hospital discharge diagnosis of PAD, amputation, revascularization procedures (leg endarterectomy, aorto-iliac-femoral bypass surgery, leg bypass surgery), or intermittent claudication from the ARIC annual surveillance. [Note: there are some drawbacks to this definition: ABI in only 1 leg and not every visit; outpatient PAD diagnosis not captured; undocumented validity of hospital discharge PAD codes.]

## **Statistical Analysis:**

The primary sample of this analysis includes a total of 1651 participants who had baseline diabetes and no history of PAD. Of these, 238 participants had incident PAD by December 31, 2000, characterized by one of these criteria: 1)  $ABI < 0.9$  in either visit 3 or 4; 2) hospital discharge ICD-9 code of 443.9 (claudication, peripheral arterial disease NOS, peripheral angiopathy NOS, spasm of artery), 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below knee amputation), 84.17 (above knee amputation); 3) revascularization procedures [38.18 (leg endarterectomy), 39.25 (aorto-iliac-femoral bypass), 39.29 (leg bypass surgery)]; 4) intermittent claudication from the ARIC annual surveillance.

We will categorize and compare risk factors of participants who had incident PAD with those who did not. The prevalence of baseline traditional and nontraditional risk factors will be

analyzed using the Chi-square for categorical variables and analysis of variance for continuous variables. To examine associations of these risk factors with incident PAD, we will divide these risk factors into quartiles using the percentile distribution in the sample and dummy code quartiles using indicator variables. The lowest quartile will serve as a reference group.

ABI was done on subsets of participants in exams 3 and 4. We will take an abnormal ABI at whichever exams were done as PAD. Because of length of follow-up from the baseline examination to time of PAD diagnosis in the ABI group is unknown, we assign the exam date when ABI was first abnormal as the endpoint date. For the hospital PAD and intermittent claudication groups, discharge date and the date when intermittent claudication first reported will be used as the diagnosis date, respectively. Because of these design issues, we will analyze the ABI group separately from the hospital PAD and intermittent claudication groups. To determine the robustness of results, both odds ratios and rate ratios will be computed against a reference group using logistic regression and Cox regression, respectively. If the results from these analyses differ, we may have to analyze the association for low ABI using logistic regression and Cox regression for the latter hospitalized PAD and intermittent claudication groups.

For the univariate analysis, the rate ratios, adjusted for age, sex, race-center, and baseline ABI, will be calculated. To determine which risk factors are predictive of PAD incidence, a forward regression approach will be used. Independent variables will be chosen to form a core model on the basis of known or suspected associations from previous research. Based on the univariate associations, nontraditional risk factors will be added to a core model one at a time to identify important predictors at p-value < 0.05.

When Drs. Weatherly and Chambless finish developing the strategy for adjustment for ABI unreliability, we hope to incorporate it here.

**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 ICTDER02 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 ICTDER02 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 ICTDER02 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://bios.unc.edu/units/csc/ARIC/stdy/studymem.html>**

Yes     No

We are aware that Dr. Heiss and Beth Weatherly are working in a similar area. I had contacted Beth Weatherly to clarify any potential areas of overlap. It appears that the two proposals minimally overlap. Her work is focused on traditional risk factors in predicting incident PAD, defined by only  $ABI < 0.9$ , in the original cohort. On the other hand, this proposal is emphasized non-traditional risk factors in predicting incident PAD, defined by a composite endpoint of  $ABI < 0.9$ , intermittent claudication, or revascularization procedures, in the diabetic subcohort. Beth Weatherly has been added as a coauthor to this proposal.

## References

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