

ARIC Manuscript Proposal # 1007

PC Reviewed: 04/08/04
SC Reviewed: 04/13/04

Status: A
Status: A

Priority: 2
Priority: 2

1.a. Full Title: Risk Factor Profile and Subclinical Measures in Individuals with a High vs Normal Ankle-Brachial Index: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group (list individual with lead responsibility first):

Lead: Keattiyot Wattanakit
Address:

Phone: (612) 626-8873 Fax:
E-mail: wattanakit@epi.umn.edu

Writing group members: Alan T. Hirsch, Aaron Folsom, Daniel Duprez, and Elizabeth Weatherly

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

4. Rationale:

An ankle-brachial index (ABI) less than 0.9 serves as the international definition of peripheral arterial disease (PAD), and PAD is increasingly recognized as an important marker of generalized atherosclerosis and is a predictor of both cardiovascular ischemic events (myocardial infarction and stroke) and mortality.¹⁻⁴ ABI values also predict rates of amputation and the need for lower extremity revascularization. Individuals with lower ABI values have a higher prevalence of subclinical and clinical coronary heart disease (CHD), higher carotid intima-media thickness, and atherosclerosis risk factors.^{1,2} Individuals with low ABI values, even in the absence of classic symptoms of PAD (e.g. claudication), are known to have worsened lower extremity physical function, including poor standing balance, walking distance, and walking velocity.⁵ The clinical value of a low ABI has, therefore, led to increasing efforts to disseminate its use into routine clinical practice.^{6,7}

In contrast, the clinical significance of a high ABI, often arbitrarily defined as greater than 1.3,⁸ has not been completely evaluated. Past investigations, usually derived from clinical populations with overt PAD, have suggested that a high ABI is associated with arterial rigidity⁹ and medial arterial calcification¹⁰. These data have led to a widely held belief that individuals with a high ABI have PAD, but that the ABI test is “not diagnostic” due to the presence of non-

compressible ankle arteries. As well, with little data, the prognosis of individuals with a high ABI is often considered to be less favorable than those with a “normal” ABI. To our knowledge, the risk factor profile and arterial structure of individuals with high versus normal ABI values have been characterized in only the American Indian population¹¹, which known to have high rates of both type 2 diabetes and cardiovascular disease. However, a similar investigation in the general population has never been evaluated. We hypothesize that in a non-referral, community-derived population, a high ABI is not associated with elevated risk factors or subclinical CVD markers. If this is correct, these data will improve the interpretation of ABI data as this test is increasingly performed in the years ahead.

In the ARIC study, participants had measurements of traditional atherosclerosis risk factors, the ABI, and carotid and popliteal intima-medial thickness at baseline. Within the population of 15,792 ARIC participants, 14,063 participants had a “normal” ABI between 0.9-1.3, and 813 had ABI values greater than 1.3. We propose to analyze these data to compare risk factor profiles and subclinical measures in these two groups.

5. Main Hypothesis/Study Questions:

The risk factor profile and subclinical CVD measures in the high ABI (>1.3) cohort are not different from the “normal” ABI (0.9-1.3) cohort.

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

Design: Cross-sectional analysis using baseline data.

Exclusion: ABI < 0.9

Groups: High and normal ABI

Independent variables: traditional atherosclerosis risk factors (smoking, diabetes, systolic blood pressure, diastolic pressure, LDL and HDL cholesterol), nontraditional risk factors (fibrinogen, factor VII, factor VIII, von Willebrand factor, Lp(a), white blood cell count, albumin), left ventricular hypertrophy on ECG, prevalent CHD, prevalent intermittent claudication, carotid and popliteal intima-media thickness, and serum creatinine.

Covariates: age, race, sex, center, and use of medication for hypertension or hyperlipidemia:

Statistical Analysis:

The primary sample of this analysis will be categorized into 2 groups based on ABI level. For categorical variables, the proportions will be calculated and compared between the two groups using the Chi-square. For continuous variables, the sample means and standard errors adjusted for covariates will be calculated using an analysis of variance and compare using a 2-sample t-test. Plots of ABI by ankle pressure and by arm pressure will be created to better understand the contribution of each pressure to the “high ABI” calculation.

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 there is an unpublished manuscript by J.J. Nelson entitled "Lower Extremity Arterial Disease as a Predictor of Coronary Heart Disease and Mortality: the Atherosclerosis Risk in Communities (ARIC) Study". This manuscript is now in inactive status. Although baseline major risk factors across ABI categories were examined, it did not specifically focus on the risk factor profile of the high ABI group. In addition, nontraditional risk factors and subclinical measures, including carotid and popliteal intima-media thickness, were not examined.

References:

1. Zheng ZJ, Sharrett AR, Chambless LE, Rosamond WD, Nieto FJ, Sheps DS, Dobs A, Evans GW, Heiss G. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis*. 1997;131:115-25.
2. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol*. 1999;19:538-45.
3. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *Bmj*. 1996;313:1440-4.
4. Tsai AW, Folsom AR, Rosamond WD, Jones DW. Ankle-brachial index and 7-year ischemic stroke incidence: the ARIC study. *Stroke*. 2001;32:1721-4.
5. McDermott MM, Fried L, Simonsick E, Ling S, Guralnik JM. Asymptomatic peripheral arterial disease is independently associated with impaired lower extremity functioning: the women's health and aging study. *Circulation*. 2000;101:1007-12.
6. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, Creager MA, Easton JD, Gavin JR, 3rd, Greenland P, Hankey G, Hanrath P, Hirsch AT, Meyer J, Smith SC, Sullivan F, Weber MA. Critical issues in peripheral arterial disease detection and management: a call to action. *Arch Intern Med*. 2003;163:884-92.
7. Peripheral arterial disease in people with diabetes. *Diabetes Care*. 2003;26:3333-41.
8. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;344:1608-21.
9. Young MJ, Adams JE, Anderson GF, Boulton AJ, Cavanagh PR. Medial arterial calcification in the feet of diabetic patients and matched non-diabetic control subjects. *Diabetologia*. 1993;36:615-21.
10. Everhart JE, Pettitt DJ, Knowler WC, Rose FA, Bennett PH. Medial arterial calcification and its association with mortality and complications of diabetes. *Diabetologia*. 1988;31:16-23.
11. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, Howard BV. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the Strong Heart Study. *Circulation*. 2004;109:733-9.