ARIC Manuscript Proposal # 1056r

PC Reviewed: __02/11/05	**Status: _____**	**Priority: _____**
SC Reviewed: _____	**Status: _____**	**Priority: _____**

1.a. Full Title: Hemoglobin A_{1c} (HbA_{1c}) and Peripheral Arterial Disease in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): HbA_{1c} and Peripheral Arterial Disease

2. Writing Group:

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Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Same as lead author.

3. Timeline: Data have already been collected; we expect to complete the manuscript by June 2005.

4. Rationale:

Chronic hyperglycemia may contribute to the development of atherosclerosis and subsequent macrovascular events in persons with diabetes, but this relation is controversial. Hemoglobin A_{1c} (HbA_{1c}), a measure of long-term glycemic control, is used to monitor and guide clinical treatment in persons with diabetes. Chronic hyperglycemia, as measured by HbA_{1c}, is an established risk factor for diabetes-associated microvascular disease (1;2). Recent studies have also suggested that HbA_{1c} may be associated with incident large-vessel disease (coronary heart disease, stroke, and peripheral arterial disease (PAD)) in persons with diabetes (3).

We have previously demonstrated using data from the ARIC Study, that HbA_{1c} is associated with incident coronary heart disease independent of other heart disease risk

factors in persons with diabetes [ARIC MS #1024]. There have been few prospective studies that have examined the association between HbA_{1c} and PAD in persons with diabetes (4-6). The few previous studies in the literature have shown a positive association between HbA_{1c} and incident PAD, however these studies have not consistently adjusted for known heart disease risk factors, including smoking, lipids, and adiposity (3). There is currently no consensus regarding a standard definition for PAD and prevalence estimates and risk factors associations may differ depending on the definition used. Previous studies have not separately examined the association between HbA_{1c} and different measures of peripheral arterial disease such as low ABI and intermittent claudication (which are related primarily to stenoses between the aortic bifurcation and the arteries around the knee), or re-vascularization procedures and amputation (which may also have a component of inadequate microvascular supply to the skin and peripheral nerves). This study will assess the association between HbA_{1c} and incident PAD in a community-based cohort of persons with diabetes. We will also investigate whether this association is robust across different manifestations of PAD.

5. Main Hypothesis/Study Questions:

H_1: HbA_{1c} is positively associated with incident PAD (combined definition, see below) in persons with diabetes in the ARIC study independently of other known risk factors.

H_{1A}: HbA_{1c} is associated with incident PAD as defined by an ankle-brachial index (ABI) < 0.90.

H_{1B}: HbA_{1c} is associated with incident PAD as defined by intermittent claudication as determined from ARIC annual surveillance.

H_{1D}: HbA_{1c} is associated with incident PAD as defined by hospital discharge codes for symptomatic PAD.

H_{1C}: HbA_{1c} is associated with incident PAD as defined by lower extremity amputation or leg revascularization procedure by hospital discharge codes.

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

Exposure: Hemglobin A_{1c} (HbA_{1c})

We measured HbA_{1c} from stored whole blood specimens in ARIC as part of ARIC Ancillary Study #2003.5, "Glycemic Control (HbA_{1c}) at Visit 2 as a Predictor of Stroke, Coronary Heart Disease, Kidney Disease and Incident Diabetes." HbA_{1c} data are available on all participants with diabetes at ARIC Visit 2, which will be the baseline visit for the present study.

Outcome: Incident Peripheral Arterial Disease

Incident PAD (combined definition) will be defined by any one of the following:

(1) Low ankle brachial index (ABI)

Defined as ABI < 0.9 in one leg at either Visit 3 or Visit 4

(2) Intermittent claudication from ARIC annual surveillance
Intermittent claudication based Rose Questionnaire administered annually to ARIC participants by telephone.

(3) Symptomatic PAD by ICD-9 Code
Defined as a hospital discharge ICD-9 code of 443.9 (intermittent claudication, peripheral vascular disease NOS, peripheral angiopathy NOS, spasm of artery)

(4) Lower extremity amputation or revascularization procedure by ICD-9 code
Defined as hospital discharge ICD-9 code of 84.11 (toe amputation), 84.12 (foot amputation), 84.15 (below knee amputation), 38.18 (leg endarterectomy), and 39.29 (leg bypass surgery).

Sample-size permitting, we will also examine the HbA_{1c}-PAD association separately for each of these groups (1-4).

Diabetes Status
We will compare the HbA_{1c}-PAD association in persons with undiagnosed (unreported) diabetes (by glucose level only) and persons with diagnosed diabetes (reported history). We will examine the effects of different types of medication use in persons with diagnosed diabetes. Because the inclusion of all persons with diabetes at Visit 2 will result in a population with mix of different diabetes duration and severity of disease, we will conduct sensitivity analyses looking at the HbA_{1c}-PAD association in diabetic adults using different definitions of diabetes, including comparing fasting glucose cut-points of 126 mg/dl and 140 mg/dl. We will also conduct separate analyses using the following definitions of diabetes: (1) diabetes by glucose/history at either Visit 1 or Visit 2; and (2) diabetes diagnosis by glucose/history at both Visit 1 and Visit 2. Furthermore, we will also evaluate the effect of diabetes duration (available from Visit 3 data) on the sub-sample of individuals for which this information is available.

Covariates
Other variables of interest include age, race, sex, HDL- and LDL-cholesterol, blood pressure, hypertension medication, diabetes medication use, body mass index, waist-hip ratio, education level, smoking. Final analyses may also consider a broader range of confounders including family history, intima-medial thickness, kidney function, insulin/HOMA index (Visit 1 only), and fibrinogen (Visit 1 only).

Inclusions/Exclusions
Inclusions: all persons with diabetes at Visit 2.
Exclusions: persons with prevalent PAD (excludes all PAD cases occurring on or before or Visit 2) or missing covariates of interest.

Statistical Analysis

We will use Cox proportional hazards models to generate relative risk estimates for PAD by quartiles of HbA_{1c} and modeling HbA_{1c} continuously (if relation appears linear). Separate models will be constructed to examine whether the HbA_{1c}-PAD association persists using different definitions of diabetes, in persons with undiagnosed diabetes, and using different PAD definitions.

Limitations

There are no ABI data at Visit 2 (our baseline in this study) when HbA1c is measured. As a result, exclusion of prevalent disease is limited to prevalent cases at Visit 1 and clinical cases occurring by Visit 2. Additionally, previous studies of incident PAD have adjusted for baseline ABI, however these data are unavailable in this manuscript. In previous analyses of incident PAD using Visit 1 as baseline we found that adjusting for baseline ABI did not appreciably alter our results. Nonetheless, we will explore controlling for Visit 1 ABI (since Visit 2 ABI is not available) and evaluate the effect of measurement error in the multivariable models (e.g., using Stata *eivreg* commands). While we will use all incident PAD cases occurring during post-Visit 2 follow-up to maximize power in this study, we will have limited power to detect moderate associations for those outcome definitions with small numbers of events, such as revascularization/amputation. Previous analyses indicate, however, that the associations for these more severe, but smaller, sub-groups may actually be stronger than for PAD defined based on ABI alone. Loss to follow-up is also a potential concern in cohort studies. To address this, we will examine whether people who are loss-to-follow up differ according to baseline characteristics, including HbA_{1c} level. However, because loss-to-follow-up in ARIC is very low, we do not expect selection bias to pose a major problem in this study.

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 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 __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 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://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)?

Selvin E, et al. Long-term stability of hemoglobin A_{1c} (HbA_{1c}) measurements from frozen whole blood samples stored over a decade, under review. [MS #1011]

Selvin E, et al. Glycemic control (HbA_{1c}) and coronary heart disease risk in persons with and without diabetes: The Atherosclerosis Risk in Communities Study, submitted. [MS #1024]

Sharrett AR, et al. Smoking and diabetes differ in their associations with subclinical atherosclerosis and coronary heart disease—the ARIC Study. Atherosclerosis, 172(1);2004:143-149.

Wattanakit K, Folsom et al. Risk Factors for Peripheral Arterial Disease Incidence in Persons with Diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. Atherosclerosis (in press). [MS # 997]

Zheng ZJ, et al. 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 May;131(1):115-25.

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

ARIC Ancillary Study #2003.5, "Glycemic Control (HbA_{1c}) at Visit 2 as a Predictor of Stroke, Coronary Heart Disease, Kidney Disease and Incident Diabetes."

11.b. If yes, is the proposal

__X_ A. primarily the result of an ancillary study (list number* _#2003.5_)

___ 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

(1) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352(9131):837-853.

(2) The Diabetes Control and Complications Trial Research Group. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med* 1993; 329(14):977-986.

(3) Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; 141(6):421-431.

(4) Lehto S, Ronnemaa T, Pyorala K, Laakso M. Risk factors predicting lower extremity amputations in patients with NIDDM. *Diabetes Care* 1996; 19(6):607-612.

(5) Adler AI, Stevens RJ, Neil A, Stratton IM, Boulton AJ, Holman RR. UKPDS 59: hyperglycemia and other potentially modifiable risk factors for peripheral vascular disease in type 2 diabetes. *Diabetes Care* 2002; 25(5):894-899.

(6) Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 1999; 22(6):951-959.