ARIC Manuscript Proposal #2328

PC Reviewed: 3/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
The association between ankle-brachial index and incident diabetes mellitus: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): ABI and incident diabetes

2. Writing Group:
Writing group members:
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. S.H. **[please confirm with your initials electronically or in writing]**

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3. Timeline:
We will use existing ARIC data to perform the analysis and prepare the manuscript in the following 12 months.

4. Rationale:

Lower extremity peripheral arterial disease (PAD), characterized by atherosclerotic stenosis or occlusion of leg arteries and typically diagnosed by ankle-brachial index (ABI) <0.9 [1], affects approximately 8 million people in the United States [2]. PAD increases the risk of cardiovascular disease and reduces quality of life due to ischemic leg pain and intermittent claudication [1][3]-[5].

Regardless of leg symptoms, patients with PAD experience functional decline and impairment [6]-[9], which can result in reduced level of physical activity [10][11]. As physical inactivity is a well-known risk factor for diabetes [12], it is possible that low ABI is associated with the development of diabetes. However, to the best of our knowledge, this association has not been studied, although the opposite direction (i.e., diabetes as a risk factor of PAD) is well-known [1][2]. Therefore, the aim of this study is to investigate the association of ABI and incident diabetes in a community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study. Shared pathophysiology between atherosclerosis and insulin resistance, such as the involvement of inflammation, may also contribute to the link of ABI to diabetes risk [13][14][15].

5. Main Hypothesis/Study Questions:

1. Low ABI will be independently associated with increased risk of incident diabetes.
2. High ABI, a condition seen in some individuals with PAD and vascular calcification, can be also associated with increased risk of incident diabetes.

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: prospective cohort study

Inclusion criteria

All black and white ARIC study participants free from diabetes at baseline examination (visit 1) with data of ankle-brachial index.

Exclusion criteria

Participants who identified themselves as non-white/non-black.

Participants with diabetes at baseline defined by self-reported physician diagnosis or treatment of diabetes, fasting blood glucose ≥126 mg/dl or random blood glucose ≥200 mg/dl [16].

Participants with missing variables of interest.

Exposure

ABI at visit 1: defined as a ratio of systolic blood pressure (SBP) of ankle to that of arm [17]. The blood pressure of the upper extremity and lower extremity were measured by automated oscillometric device Dinamap Model 1846 SX as a part of ARIC Ultrasound Assessment of carotid and popliteal arteries [18]. Ankle SBP was measured four times in a randomly selected leg and the last non-missing value was used as numerator of ABI and brachial SBP was measured twice in the right arm and the first non-missing value was used as denominator of ABI [19]. ABI was also assessed at visits 3 and 4 in subsample, which will be used for sensitivity analysis.

Outcome

Incident diabetes: We will test a visit-based definition and an interview-based definition, as previously done in ARIC [20]. Visit-based diabetes cases will be defined as newly identified diabetes at follow-up visit 2 to 5 based on glucose measurements, self-reported diagnosis by physicians or diabetes medication use. Given a long elapsed time between visits 4 and 5 (~15 years), we will also investigate visit-based diabetes cases restricted to visits 2, 3 and 4. Interview-based cases are defined as newly identified diabetes based on self-reported diagnosis or diabetes medication use at annual phone interview during ~20 years of follow-up.

Other variable of interest:

(1) Age, gender, race
(2) Body mass index, sitting blood pressure, total cholesterol level, low-density and high-density lipoprotein cholesterol level, triglyceride level, fasting glucose level.
(3) Lifestyle: cigarette smoking and alcohol drinking habits.
(4) Physical activity/physical function: At visit 1, visit 3 and during annual phone interview, ARIC has collected various information on physical activity/function such as Baecke physical activity questionnaire, which recorded the duration, intensity and frequency of physical activity at work, in leisure time and during sports and produced an index score to represent level of physical activity [21]. We will treat physical activity/function as a time-fixed and time-varying covariate.
(5) Family history of diabetes.
(6) Medical history: hypertension, cardiovascular diseases.
(7) Inflammatory markers: white blood count, fibrinogen at visit 1 and hs-CRP at visit 2.

Data Analysis Plan

Primary analysis will use Cox proportional hazards models to examine the association between ABI with its spline terms (knots at thresholds of subsequent categories) and incident diabetes (visit-based diagnosis and interview based diagnosis separately). We will also treat ABI as a categorical variables using its quintiles as well as the following categories of ABI [22]: <0.5, 0.5~0.7, 0.7~0.9, 0.9~1.1, 1.1~1.3, and 1.3+.We will construct four models: Model 1 will only adjust for age, sex and race; Model 2 will include additional covariates mentioned above except for physical activity/physical function and inflammatory markers; Models 3 will further adjust for inflammatory markers. Model 4 will add physical activity/physical function as a potential mediator. For all four models, we will test models both with and without adjustment for baseline fasting glucose levels.

We will repeat the analysis in several key subgroups according to age, sex, race, smoking status, and history of cardiovascular disease. When visit 5 data are included for visit-based definition, we will conduct a sensitivity analysis with inverse probability of attrition weighting to account for participants who died before visit 5 or were alive at the initiation of visit 5 but did not attend. For this sensitivity analysis, we will use key demographic and clinical prognostic variables obtained at visit 4 or after that during

follow-up before visit 5 (e.g., incidence of cardiac disease). To explore the possibility of reverse causation, we will exclude incident diabetes that occurred in the first three years of baseline and also explore the association between ABI and development of impaired fasting glucose (IFG) (≥100 mg/dL) among those with normal fasting glucose (<100 mg/dL) at baseline.

Limitations and challenges

Although we will rigorously adjust for covariates in our models, we still could not rule out the possibility of residual confounding. In addition, diabetes is based on self-report during 15 years between visit 4 and 5, particularly for those who did not attend visit 5. However, we will test the impact of limiting to visit-based definition at visit 2 through 4 and also conduct inverse probability attrition weighting approach. ABI was measured at a randomly selected leg, which may affect the validity of exposure measurement. However, the effect size of ABI on cardiovascular risk in ARIC is similar to that from other cohorts [3]. Finally, the physical activity is predominantly based on self-report, which usually leads to an overestimate of actual physical activity [23].

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.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)?

There are no proposals investigating the association of ABI and future risk of diabetes.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes ____ 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/

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

[1] Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113:e463-654.

[2] Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics--2012 update: a report from the American Heart Association. Circulation 2012;125:e2-220.

[3] Fowkes FG, Murray GD, Butcher I, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA 2008;300:197-208.

[4] O'Hare AM, Katz R, Shlipak MG, et al. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation

2006;113:388-93.
[5] Weatherley BD, Nelson JJ, Heiss G, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. BMC Cardiovasc Disord 2007;7:3.
[6] McDermott MM, Liu K, Greenland P, et al. Functional decline in peripheral arterial disease: associations with the ankle brachial index and leg symptoms. JAMA 2004;292:453-61.
[7] Nitta A, Hozawa A, Kuriyama S, et al. Relationship between peripheral arterial disease and incident disability among elderly Japanese: the Tsurugaya project. J Atheroscler Thromb 2010;17:1290-6.
[8] Widener JM. Peripheral arterial disease and disability from NHANES 2001-2004 data. J Vasc Nurs 2011;29:104-12.
[9] Selvin E, Hirsch AT. Contemporary risk factor control and walking dysfunction in individuals with peripheral arterial disease: NHANES 1999-2004. Atherosclerosis 2008;201:425-33.
[10] McDermott MM, Greenland P, Ferrucci L, et al. Lower extremity performance is associated with daily life physical activity in individuals with and without peripheral arterial disease. J Am Geriatr Soc 2002;50:247-55.
[11] Hawkins MS, Gabriel KP, Conroy MB, et al. Physical activity intensity and cardiovascular risk by ankle-brachial index. Vasc Med 2013;18:79-84.
[12] Gill JM, Cooper AR. Physical activity and prevention of type 2 diabetes mellitus. Sports Med 2008;38:807-24.
[13] Ertek S, Cicero A. Impact of physical activity on inflammation: effects on cardiovascular disease risk and other inflammatory conditions. Arch Med Sci 2012;8:794-804.
[14] Stohr R, Federici M. Insulin resistance and atherosclerosis: convergence between metabolic pathways and inflammatory nodes. Biochem J 2013;454:1-11.
[15] Rocha VZ, Libby P. Obesity, inflammation, and atherosclerosis. Nat Rev Cardiol 2009;6:399-409.
[16] American Diabetes Association. Diagnostic and classification of diabetes mellitus. Diabetes Care 2013; 36:S67-S74.
[17] Murphy TP, Dhangana R, Pencina MJ, et al. Ankle-brachial index and cardiovascular risk prediction: an analysis of 11,594 individuals with 10-year follow-up. Atherosclerosis 2012;220:160-7.
[18] ARIC Manual 6A Ultrasound scanning. http://www2.cscc.unc.edu/aric.
[19] ARIC Data Book: Ankle Brachial Index Data. http://www2.cscc.unc.edu/aric.
[20] Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362:800-11.
[21] Pols MA, Peeters PH, Bueno-De-Mesquita HB, et al. Validity and repeatability of a modified Baecke questionnaire on physical activity. Int J Epidemiol 1995;24:381-8.
[22] McDermott MM, Greenland P, Liu K, et al. The ankle brachial index is associated with leg function and physical activity: the Walking and Leg Circulation Study. Ann Intern Med 2002;136:873-83.
[23] Prince SA, Adamo KB, Hamel ME, et al. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act 2008;5:56.