

ARIC Manuscript Proposal #2297

PC Reviewed: 1/14/13
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: The association of diabetes, impaired glucose tolerance, and chronic hyperglycemia with pulse wave velocity: the ARIC study

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

2. Writing Group:

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

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3. Timeline: Manuscript to begin immediately

4. Rationale:

Pulse wave velocity (PWV) is a valid and reliable measure of arterial stiffness known to predict mortality and cardiovascular events in clinical and community based studies [1]. PWV has also been predictive of mortality among individuals with diabetes [2]. Prior studies of the association of diabetes and impaired fasting glucose with PWV have been in selected clinical populations or in subsets from community cohorts, of which the majority of these studies are in populations outside of the US.

In a 2004 study of aortic PWV measured using applanation tonometry, 186 British patients with and without diabetes with mean age of 55 years were consecutively recruited from diabetic and hypertension clinics [3]. They observed that PWV increased more with age in women with diabetes than in women without diabetes, whereas they found a similar increase in PWV for men with and without diabetes. From the Asklepios study of 2,368 community-dwelling healthy Belgian volunteers aged 35-55, aortic root PWV and carotid femoral PWV were higher in those with type 2 diabetes compared to those without diabetes [4]. They did not find significant differences for those with impaired fasting glucose. The Bogalusa Heart Study, a cohort study in the US, measured aortic-femoral pulse wave velocity (af-PWV) in 518 adults aged 27-43 years [5]. In this population of asymptomatic young adults, the correlation for homeostasis model assessment of insulin resistance (HOMA-IR) with af-PWV was 0.2, and HOMA-IR was observed to be a significant predictor of af-PWV.

The American Diabetes Association (ADA) has published guidelines in which hemoglobin A1C (HbA1c), a measure of blood glucose levels over several months, is a recommended diagnostic test for diabetes [6]. A prior study found that greater hemoglobin A1c was associated with a higher carotid-femoral (cfPWV), a measure of central arterial stiffness, in a Chinese population of 5,098 men and women (mean age: 50 years) without a prior history of diabetes [7]. In this same study, fasting glucose was not associated with cfPWV.

No prior studies have evaluated PWV in a population-based US cohort of older adults with detailed measures of diabetes. Previous studies are largely in populations younger than the ARIC population at the time of Visit 5. We propose to study both peripheral (brachial ankle (aPWV)) and central measures of PWV (carotid-femoral (cfPWV)) and their association with diabetes and impaired fasting glucose using distribution-based and clinically defined cut points for fasting glucose and HbA1c, in a population-based cohort of older adults [6, 8].

5. Main Hypothesis/Study Questions:

We aim to assess whether impaired insulin/glucose metabolism and diabetes and impaired fasting glucose are associated with peripheral and central arterial stiffness measured by baPWV and cfPWV, and to assess age, race, coronary artery disease, and gender as modifiers.

Assess whether severity of diabetes, as defined by presence of end organ damage (retinopathy, microalbuminuria), is associated with arterial stiffness.

Assess whether chronic hyperglycemia, as defined by level of hgbA1C, is associated with arterial stiffness.

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: Cross-sectional analysis of participants at V5 with PWV measures

Exposure:

We plan to define diabetes, impaired fasting glucose and chronic hyperglycemia by fasting glucose measures and/or the use of hypoglycemic medication and by HbA1c measures, as described below.

Definition 1:

- 1) Diabetes will be defined as (1) fasting glucose >126 mg/dL or (2) diabetes medication use.
- 2) Impaired fasting glucose (IFG) will be defined among those without diabetes (as defined in #1) and with fasting glucose 100-125 mg/dL.
- 3) The group without 'diabetes' will include everyone without IFG or DM, and with fasting glucose measures.

Definitions 2-3 for hyperglycemia using clinical categories for Hgb A1c that vary depending on the presence of diabetes.

(1) For those without known diabetes:

- a. Hgb A1c < 5.7%
- b. Hgb A1c 5.7-6.5%
- c. With Hgb A1c >6.5% considered undiagnosed diabetes

(2) For those with known diabetes by self-report or currently on medications for diabetes we will stratify by Hgb A1c <8% or \geq 8%, and in sensitivity analyses by a cutpoint of 7% HgbA1c.

Outcomes: Carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV) PWV was measured by the Omron VP-1000 plus system (Omron Co., Ltd., Komaki, Japan) and the path length was calculated using the following formula: path length (cm) = carotid-femoral distance (cm) – (suprasternal notch – carotid distance (cm)). A minimum of two measurements were taken per participant and the last two usable measurements (i.e. non-zero values) were averaged. baPWV was similarly measured.

Covariates of interest: study site, race, age, gender, heart rate, hypertension, medications for hypertension, blood pressure, GFR, smoking status, BMI, microalbuminuria, diabetic retinopathy, medication type for diabetics, insulin levels, glucose levels, and height.

Inclusions: All ARIC participants with PWV measures from V5.

Exclusions:

- 1) Race not white or African-American due to limited numbers and African Americans not from Forsyth or Jackson
- 2) BMI \geq 40
- 3) Not fasting 8 hours
- 4) Outliers for PWV defined as >3 SD from the mean

Statistical Analysis:

We will present the distribution of the two PWV measures by diabetes status as means, standard deviations, medians and inter-quartile ranges (IQR). If normality is a concern we will use non-parametric methods. We will graphically display the relationship between PWV and diabetes status (DM, IFG, and neither DM or IFG) with cumulative frequency plots and make statistical comparisons using the Kolmogorov-Smirnov test. We will do the same for the hyperglycemia categories as defined by HgbA1c.

We will examine associations between diabetes status and cfPWV and baPWV using multivariable linear regression analysis adjusting for study site, race, age, gender and heart rate. In addition, we will have models adjusting for hypertension, smoking status, and BMI. Variables with skewed distribution will be naturally log transformed for analysis. We will report betas and r^2 values that represent the amount of variability in cfPWV and baPWV accounted for by the model. We will also evaluate whether there is effect modification by gender by including an interaction terms for diabetes status and gender in the model along with the main effects ($P < 0.1$ threshold for significance of interaction). Similarly, we will test for effect modification by age and race. All analyses will be stratified as necessary.

In secondary analysis, we will re-run this analysis after excluding those with known coronary artery disease. In addition, we will further stratify the diabetics into those with and without end organ damage as defined by microalbuminuria, and retinopathy. We will then evaluate PWV for diabetics with end organ damage and then diabetics without end organ damage to the same referent group (discussed above) of non-diabetics with normal fasting glucose. In additional analysis, we will compare diabetes with chronic hyperglycemia (as defined by Hgb A1C) to those without chronic hyperglycemia.

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 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 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.csc.unc.edu/ARIC/search.php>

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)?

#1970 Descriptive Epidemiology of Pulse Wave Velocity in the Atherosclerosis

#2246 Risk in Communities (ARIC) Study Pulse Wave Velocity and Retinal Microvascular Characteristics: the Atherosclerosis Risk in Communities (ARIC) Study-Neurocognitive Study (NCS)

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.csc.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.csc.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.

1. Vlachopoulos, C., K. Aznaouridis, and C. Stefanadis, *Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis*. J Am Coll Cardiol, 2010. **55**(13): p. 1318-27.
2. Cruickshank, K., et al., *Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function?* Circulation, 2002. **106**(16): p. 2085-90.
3. De Angelis, L., et al., *Sex differences in age-related stiffening of the aorta in subjects with type 2 diabetes*. Hypertension, 2004. **44**(1): p. 67-71.
4. Chirinos, J.A., et al., *Central pulse pressure and its hemodynamic determinants in middle-aged adults with impaired fasting glucose and diabetes: the Asklepios study*. Diabetes Care, 2013. **36**(8): p. 2359-65.
5. Bhuiyan, A.R., et al., *Correlates of vascular structure and function measures in asymptomatic young adults: the Bogalusa Heart Study*. Atherosclerosis, 2006. **189**(1): p. 1-7.
6. American Diabetes, A., *Diagnosis and classification of diabetes mellitus*. Diabetes Care, 2010. **33** **Suppl 1**: p. S62-9.
7. Liang, J., et al., *Hemoglobin A1c levels and aortic arterial stiffness: the Cardiometabolic Risk in Chinese (CRC) study*. PLoS One, 2012. **7**(8): p. e38485.
8. International Expert, C., *International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes*. Diabetes Care, 2009. **32**(7): p. 1327-34.