1.a. Full Title: Genome wide association(GWAS) to identify relationship between SNP’s and arterial stiffness measurements in the ARIC study.

b. Abbreviated Title (Length 26 characters): GWAS and Arterial stiffness

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. **Timeline:** Analysis is to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We hope that the manuscript will be prepared within one year from approval of the analysis.

4. **Rationale:**

Arterial stiffness measured by pulse wave velocity (PWV) has been shown to be an independent risk factor for both stroke and CHD (Circulation 2005;111(25):3384-3390; Circulation. 2006;113:657-663). Recent analysis in the ARIC population demonstrated association between arterial stiffness, measured by carotid ultrasound, and incident CHD and stroke events (MP#1461). One of the approaches taken to identify genetic variants that are associated with arterial stiffness is the GWAS approach (BMC Med Genet. 2007 Sep 19;8). However, most of the studies examining genetic variants associated with arterial stiffness had limited success. A recent GWAS study conducted on a Sardinian cohort with both internal and external validation, identified a few loci including a consistent association of a SNP in the COL4A1 gene (Circulation: Cardiovascular Genetics. 2009;2:151-158). We propose to perform a GWAS to identify novel genetic variants that are associated with arterial stiffness and in particular examine weather SNP’s identified in GWAS with the phenotype of PWV would be associated with arterial stiffness measured with carotid ultrasound in the ARIC study as well. Implementing the idea of mendelian randomization, SNP’s associated with arterial stiffness will be tested for association with CVD.

5. **Main Hypothesis/Study Questions:**
1. Gene variants can be identified that are associated with arterial stiffness when measured by carotid ultrasound in the white and black population in ARIC.
2. Gene variants that were previously identified in GWAS with PWV would be associated with carotid stiffness measured by carotid ultrasound as well.
3. Gene variants associated with arterial stiffness in ARIC are associated with CVD events.

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).**

1. Two cross sectional analyses (at visit 1 and 2 where stiffness data is available) would be done.
2. Analysis will be done for whites and blacks separately
3. Exclusion criteria will include individuals without arterial stiffness measurement information, Affi 6.0 data, and individuals that did not consent for genetic analysis.
4. Outcome variable will consist of arterial stiffness measures (arterial strain, arterial distensibility, arterial compliance, stiffness index, pressure-strain elastic modulus, and Young’s elastic modulus) as a continuous variables.
5. Analysis will be done first with age and sex as covariates. A second analysis will include age, sex, blood pressure, pulse pressure, blood glucose, total, HDL-c, LDL-c and triglycerides as covariates.

6. Significant SNP’s associated with arterial stiffness will be tested for association with prevalent CHD, stroke, and total CV events (ischemic strokes, coronary heart disease). The same SNP’s will be tested for incident coronary heart disease, ischemic strokes and total CV events with and without adjustment for age, sex, blood pressure, HDL-C, LDL-C.

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 ICTDER03 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?  ___X___ 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”?  ___X___ Yes  ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?  ___X___ 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)?

   MP#1291 – The clinical utility of genetic risk score in reclassifying risk for incident CHD in the ARIC study

   MP#1461 – The association of arterial stiffness with incident cardiovascular disease
11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  

_____ Yes  ___X___ 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/

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.