1.a. Full Title: Associations between chromosome 9p21 and arterial stiffness

b. Abbreviated Title (Length 26 characters): Art stiffness and 9p21

2. Writing Group:
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   Others are welcome.

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

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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:**

Several studies including the ARIC study have documented a clear association between a single nucleotide polymorphism in chromosome 9p21 and coronary heart disease but the mechanism by which the risk of CHD is increased is still unclear. A recent study has revealed a possible association of the chromosome 9p21 coding region with excess vascular cell proliferation using an orthologous mouse model (Visel A, Zhu Y, May D, et al. Targeted deletion of the 9p21 non-coding coronary artery disease risk interval in mice. *Nature.* Feb 21 2010). Small studies in older individuals (n=400, age 70-88) have shown that aortic distensibility and compliance may be associated with the SNPs associated with CAD in the 9p21 region (Björck HM, Association of genetic variation on chromosome 9p21.3 and arterial stiffness. *Intern Med.* 2009 Mar;265(3):373-81. Epub 2008 Oct 25).

We have recently shown that arterial stiffness measures obtained from carotid ultrasound examination are associated with incident CV events in ARIC (MP#1461). Therefore we propose to examine the association between the SNP in 9p21 and parameters of arterial stiffness obtained on carotid ultrasound examination (visit 1 or visit 2) in the ARIC study.

5. **Main Hypothesis/Study Questions:**
   a) The 9p21 SNP linked with increased CHD risk will be associated with increased arterial stiffness and reduced compliance (determined on ultrasound)
   b) This relationship will persist after adjustment for age, blood pressure, adjusted mean carotid IMT, other traditional CHD risk factors and anthropometric measurements.
   c) The strength of associations between 9p21 and incident CHD, stroke and cardiovascular events will be reduced after adjustment for the arterial stiffness or compliance measures.

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. After standard ARIC exclusions, subjects from ARIC visit 1 and 2 with prevalent cardiovascular disease (strokes, coronary heart disease) at the time of carotid ultrasonography, absent strain data, and absent rs10757274 (9p21 SNP) genotype information will be excluded. All others will be eligible.
   2. Arterial stiffness measures (arterial strain, arterial distensibility, arterial compliance, stiffness index, pressure-strain elastic modulus, and Young’s elastic modulus) will be described and compared among the 9p21 genotypes. The
association between the various parameters of arterial stiffness and 9p21
genotypes will be examined before and after adjustment for other traditional
cardiovascular risk factors and adjusted mean carotid IMT. Arterial stiffness
measures will be considered as continuous variables, transformed as necessary to
satisfy model normality assumptions. We will also consider separately 9p21
genotype associations with extreme stiffness values (e.g. the 10%ile of stiffest or
least compliant values).

3. Associations of arterial stiffness parameters and 9p21 genotypes with incidence of
coronary heart disease, ischemic strokes and cardiovascular events (ischemic
strokes, coronary heart disease) will be described before and after adjustment for
traditional risk factors. Covariates we will adjust for includes age, sex, blood
pressure, pulse pressure, blood glucose, total, HDL-c, LDL-c and triglycerides.

4. Associations of 9p21 genotypes with incidence of coronary heart disease,
ischemic strokes and cardiovascular events will then be described in models
including (one at a time) the predictive arterial stiffness parameters.

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 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? ___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

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?
___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.csec.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)?

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

MP#1421 – The clinical utility of carotid intimal medial thickness (CIMT) and a single nucleotide polymorphism on chromosome 9p21 in reclassifying risk for incident CHD and stroke 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  ____ 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.