ARIC Manuscript Proposal # 1230

1.a. Full Title: Does a genetic risk score and single nucleotide polymorphisms associated with cardiovascular disease predict abnormal carotid-intima media thickness (c-IMT) and ankle brachial index (ABI): the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): genetic risk score, c-IMT, ABI

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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 to be done by June 2007. Manuscript to be written after the same

4. **Rationale:** Recently single nucleotide polymorphisms associated with incident coronary artery disease have been aggregated to develop a genetic risk score for the prediction of incident coronary events (Bare L et al). This risk score that has been developed most likely include genes and pathways that are important in the development of clinical “atherothrombotic” events. Although clinical events are crucial, they are related to several factors such as burden of atherosclerosis, inflammation, plaque instability and thrombosis. Identification of genes and pathways associated with the burden of atherosclerosis would provide for more focused information on genes important for both susceptibility and possibly resistance to atherosclerosis. Carotid ultrasound provides noninvasive quantitative assessment for the thickness of the intima-media (thickness and the presence or absence of atherosclerotic plaque). Similarly ankle brachial indices provide a non-invasive method to evaluate for the presence of lower extremity arterial disease. Identifying whether genetic risk scores associated with incident cardiovascular events are also associated with carotid atherosclerosis and/or lower extremity arterial disease will provide further crucial insights into the genetic contribution to atherosclerosis. Further we will be able to examine if the genetic risk scores and SNP’s associated with incident CVD events are also associated with presence of atherosclerosis. The hypotheses and aims listed below will delineate a plan to do the same.

5. **Main Hypothesis/Study Questions:**

**Hypothesis:** Single nucleotide polymorphisms and genetic risk score associated with incident CVD (that have already been developed) will be associated with carotid intima media thickness and lower extremity arterial disease (as evidenced by an ABI <0.9). For the current proposal, we will use age, gender and race adjusted c-IMT. Patients with an ankle brachial index <0.9 at any visit (baseline, visit 3 or 4) will be considered to have lower extremity arterial disease.

The individual SNP’s and the genetic risk score for this study are those that were used in a prior study (Bare L et al) that evaluated the value of these in predicting incident CHD in ARIC. In order to generate a genetic risk score (GRS) for CHD in ARIC, Bare et al examined an initial set of 51 putative functional SNPs that were genotyped as a part of Ancillary Study 2004.11. Only SNPs that had a risk allele that could be specified based on association with CHD in at least two antecedent (i.e., before testing in ARIC) association studies were chosen. The risk alleles for 49 of these SNPs were specified based on two antecedent case–control studies of MI: the Cleveland Clinic Foundation (CCF) study and the University of California, San Francisco (UCSF) study. The risk alleles for the 2 additional SNPs were specified based on their association with CHD in the placebo arms of two CHD prevention trials: the Cholesterol and Recurrent Events (CARE) study and the West of Scotland Coronary Prevention study (WOSCOPS). Of these 51 SNPs, 5 were associated with incident CHD and formed the risk score.(p<0.10)
Aim 1: Use the already described genetic risk score (Bare L et al) for incident coronary heart disease risk prediction and examine if the risk score predicts c-IMT, ABI over and above traditional risk factors.

Aim 2: Using the single nucleotide polymorphisms that have been already been associated with CHD examine if they are associated with age, sex and gender adjusted c-IMT and ABI.

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).

Aim 1 will be tested using the already developed genetic risk score for CHD. Using the genetic risk score we will evaluate if the score is associated with c-IMT and ABI. Genetic risk scores will be calculated for all the ARIC participants with a baseline c-IMT and ABI. The ability of the genetic risk score to predict c-IMT thickness will then be examined by linear regression after initially adjusting for age, sex and race and subsequently for traditional risk factors for atherosclerosis. Similarly the genetic risk score will be used to test if they can predict abnormal ABI. Lower extremity atherosclerosis will be defined by any ABI (at any visit) which is less than 0.9 (i.e. abnormal). After this persons with ABI >1.3 will be excluded and the analysis repeated. Although ABI >1.3 has not been associated with adverse outcomes in the ARIC study, there has been data from other studies to suggest the contrary. Hence we will also perform the analysis of the association with ABI after excluding those patients with ABI>1.3. If the risk score is associated with c-IMT and/or ABI, an AUC of a ROC will be generated to evaluate how much the genetic risk score adds to the AUC of a ROC over and above traditional risk factors. Similarly analysis will be carried out by IMT quartiles to evaluate if the risk score can differentiate the upper and lower age, sex and gender adjusted quartiles using logistic regression. Similar analysis will be performed for ABI using ABI ranges of <0.9, 0.9-1.0, 1.0-1.1, 1.1-1.3 and >1.3.

Aim 2 will be tested in all ARIC participants who had a c-IMT at baseline and similarly ABI at baseline. We will evaluate 51 SNPs that have already been identified to be associated with CHD (myocardial infarction) and has been evaluated for incident CHD events (please see above for details). The association of these SNP,s with c-IMT and ABI will be tested by linear regression after adjustment for age, gender and race. All c-IMT will be age, sex and race adjusted.

Limitation: Since the SNP,s selected were used for the development of a GRS for incident CHD and since in ARIC there is a correlation between baseline IMT and incident CHD, this will likely lead to a correlation between the GRS and the baseline IMT which we acknowledge.

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? _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 ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”? __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)?

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

11.b. If yes, is the proposal ___ A. primarily the result of an ancillary study (list number* __________) _x__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ___2004.11__________ ____________)

*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.