ARIC Manuscript Proposal # 1285

1.a. Full Title: Vascular risk factors are associated with carotid calcium in the ARIC population

b. Abbreviated Title (Length 26 characters): Carotid Calcification and Vascular Risk Factors

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

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3. **Timeline:** Data analysis: 3 months.
   Paper composition, discussion and review: 3 months.

4. **Rationale:**

   The development of non-invasive methods for quantifying atherosclerosis has resulted in a paradigm shift in the assessment and treatment of cardiovascular disease. Whereas previously investigators relied on cardiac catheterization or autopsy to provide information about atherosclerosis, more recently B-mode ultrasound of the extracranial carotids and computed tomography quantification of coronary calcification have been used to identify new risk factors, to estimate the risk of coronary disease and ischemic stroke and as outcome variables for clinical trials.

   IMT of the carotid artery is a well established surrogate measure of atherosclerosis that has been in use since the mid 1980s (1,2). This technology takes advantage of the increase in wall thickness rather than stenosis that is an early manifestation of atherosclerosis and has been shown to relate to risk factors, clinical outcome, and treatment benefit in clinical trials. Non-invasive CT imaging of coronary calcium has also been extensively studied as a marker of atherosclerosis with variable results (3-5). In view of the demonstrated association between extracranial carotid atherosclerosis and coronary artery disease (6-8), carotid calcium should also be a valid index of atherosclerosis, but has not been widely evaluated for associations with risk factors or clinical abnormalities. In addition, carotid calcium could be directly related to carotid IMT (9-12). This study explores the relationship of carotid calcium with coronary calcium, carotid IMT and vascular risk factors in a subgroup of the ARIC study population. Although often clinically unapparent, carotid calcification occurs in stages of advanced atherosclerosis and may therefore be a marker for vascular risk factors and concomitant pathology in other vascular beds.

   Ischemic stroke results from a multitude of causes, but more than 30% are due to atherosclerosis of arteries providing blood to the brain. More than 67% of all atherosclerotic carotid lesions are located in the extracranial cerebral circulation and
38% percent of those are found in the region of the carotid bifurcation (13,14). Atheromatous plaques in the bifurcation occur frequently as flow characteristics of blood are altered at arterial branching points causing turbulence and shear stress (15).

Plaque composition seems to define the risk for embolization and rapid lesion progression better than the degree of carotid artery stenosis. Characterization of plaque may therefore aid in decision making whether to manage patients medically or by intervention including carotid endarterectomy or carotid stenting. Low echogenicity of plaque detected by B-mode ultrasound is a reflection of increased lipid content and/or thrombus formation. Calcified plaque is hyperechoic and typically causes acoustic shadowing on B-mode imaging. Carotid calcification is associated with traditional risk factors such as male gender, increased and total cholesterol, smoking and hypertension as well as von Willebrand factor (16,17). The association with markers of inflammation on the other hand remains less well established (17). Highly echogenic plaque on the other hand suggests the presence of calcium and fibrous tissue and seems to be associated with a decreased risk for ipsilateral ischemic stroke and TIA (18,19). Therefore calcified atheromas may be best treated medically even in the presence of a > 60% asymptomatic internal carotid stenosis. Calcification may thus on one hand indicate stable plaque causing stiffening of the plaque and protection from shear stress and embolization (20,21), but on the other hand could be a marker of advanced atherosclerosis associated with the presence of vascular risk factors and concomitant cardiovascular disease requiring aggressive medical treatment and risk factor modification (22).

5. Main Hypothesis/Study Questions:

Carotid Calcification often represents a subclinical stage of advanced atherosclerosis. We hypothesize that there are associations between the various means of quantifying subclinical disease: calcified carotid plaque is associated with coronary artery calcification (CAC) and increased IMT. Additionally we plan to study whether different vascular risk factors relate in a different way with calcification of the coronaries compared to the carotid arteries. Finally, we will determine whether risk factors that relate to CAC are independent of or dependent on the association between calcified carotid plaque indicated by echogenic plaque and acoustic shadowing on B-mode and CAC by entering first risk factors only and then both risk factors and calcified carotid plaque into a multivariable model with CAC as outcome variable. Depending on the strength of these associations we may be able to draw conclusions about the differential importance of risk factors per se and individual responsivity to risk factors for determining risk of CAC.

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).
This is a cross sectional study that will analyze a subpopulation of the Atherosclerosis Risk in Communities Study (ARIC) in Forsyth County, NC who underwent an additional CT examination of the carotid arteries. Carotid Calcium was measured in 168 study subjects, ages 45-65 years, between 1999-2000 (after visit#4) using fast helical computed tomography (HCT) to assess prevalence and distribution of plaque within the carotid system. IMT measurements were performed by high resolution B-mode ultrasonography of the carotid bifurcation bilaterally using a 7.5 MHz transducer and a Biosound ESOTE ultrasound machine. Coronary calcium was measured by a GE fast helical CT using 2.5 mm slice thickness with data acquisition during suspended respiration and electrocardiogram gating at 50% above the RR interval. The study included participants (45% women and 89% Caucasians) eligible for study enrollment according to inclusion criteria of the parent ARIC study. B-mode and risk factor data will be taken from the last visit where B-mode measurements were collected for each participant. We expect approximately a 50/50 mix of visit 3 and visit 4 data. The study population is not representative for the community at large as only asymptomatic middle aged adults were examined who agreed to undergo additional CT imaging of their coronary arteries. Demographic characteristics of the study population in comparison to the entire ARIC cohort and to Forsyth county will be presented in table 1.

The data analysis plan for this study includes:

1. Description of severity and distribution of carotid calcification measured by CT within different vascular segments of the carotid system and for each side individually.
2. Analysis of the possible association between carotid plaque on CT with coronary calcium scores on CT and IMT (mean max) and traditional risk factors. For initial data analysis we will explore different modeling approaches:
   2a. We will use ln-transformed carotid calcium scores measured by CT (ln[score+1], including individuals without calcium in Agatston units) and will transform those scores into quartiles (no calcium present, minimal, moderate and severe amount of calcium with meaningful cutoff scores to be determined). We will then use logistic regression models of CT carotid plaque predicted by first continuous crude IMT and then crude dichotomous IMT (cutoff>75%). Subsequently both models will be adjusted for gender, age, and plaque calcification on B-mode ultrasound. As the study population consists predominantly of whites (90% Caucasian, 10% Afro-American) we will not stratify the data by race.
   2b. In a second approach we will then perform logistic regression analysis of CT-carotid plaque predicted first by continuous crude CAC (coronary calcium scores measured by CT (ln[score+1], including individuals without calcium in Agatston units) and then crude dichotomous CAC. Both models will then be adjusted as under 2a.
3. We will test the relative contribution of other subclinical disease markers including CAC and IMT to independently predict carotid plaque. As under (2) we will examine continuous and dichotomous outcome models for CAC and IMT as independent predictors with age and gender being covariates using linear and repression analysis, respectively. We will then adjust for covariates (traditional vascular risk factors) including LDL -and HDL-cholesterol, creatinine, BMI, waist/hip ratio, tobacco use, and presence of diabetes and hypertension.
4. Finally we will analyze the possible association between carotid plaque appearance on B-mode ultrasound with coronary calcium scores on CT and IMT (mean max). We will explore whether acoustic shadowing on B-mode ultrasound indicating stable plaque has a different relation to coronary calcium scores and IMT and traditional risk factors compared to echolucent plaque.

REFERENCES:


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? ____ 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 ICTDER02 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.csec.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
   _X_ 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/](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.