1.a. Full Title: Associations of carotid plaque characteristics with remodeling and stenosis

b. Abbreviated Title (Length 26 characters): Plaques which remodel

2. Writing Group:
   Writing group members: Astor B, Coresh J, Sanhueza A, Sharrett AR

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

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3. Timeline: Analysis to begin with currently interpreted carotid MRI scans and be completed by Dec06

4. Rationale: Arterial compensatory remodeling, specifically outer wall expansion accommodating a normal lumen size, was originally studied by pathologic examination of the left main coronary artery by Glagov¹. In ARIC, remodeling will be evaluated using MRI measurements of carotid arteries as described in the ARIC manuscript proposal entitled “wall size and stenosis”. Its occurrence and extent will be related in the current proposal to specific plaque characteristics such as lipid core and cap thickness,
and calcium or hemorrhage in the arterial wall. Remodeling has not been studied non-invasively in population-based studies using techniques capable of distinguishing these characteristics.

Because of the popularity of coronary screening by EBCT, there is great current interest in the clinical implications of arterial calcification. It is not known whether calcification is associated with plaque stability or vulnerability to rupture, but fibrocalcific lesions found in CHD decedents appear to be associated with greater coronary stenosis. Fibrocalcific lesions studied with intravascular ultrasound had less outer wall expansion than those with “soft” echolucent walls. Autopsy investigations led Stary to speculate that the occurrence of atheroma in younger children is associated with outward arterial expansion, but that evolution to fibroatheroma limits that expansion, leading then to stenosis. Studies primarily based on atheroma specimens suggest that intraplaque hemorrhage also leads to plaque expansion.

The associations of plaque characteristics with remodeling or stenosis have not been studied in representative asymptomatic populations.

5. Main Hypothesis/Study Questions:

1. There will be less compensatory remodeling (maintenance of the lumen with expansion of the wall) in arteries with calcium, hemorrhage or thick fibrous cap than in arteries of comparable total wall area lacking these features.

2. We do not know whether lipid core presence or size will be associated with greater stenosis or with more compensatory remodeling. This too will be examined.

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).

All ARIC MRI participants with the needed wall and lumen area measurements will be included. No exclusions are expected on the basis of participant characteristics.

Outer wall area, lumen area, and (by subtraction) wall area will be assessed at the flow divider and at a location seen 3 MRI slices above the flow divider. Plaque characteristics of interest include arterial calcium, hemorrhage and lipid core, and the size of the core and thickness of the cap. Walls with these plaque characteristics will be compared with walls of similar area lacking the same characteristics. Quantitative characteristics (core area, cap thickness) will be studied in models adjusting for arterial wall area. The extent of compensatory remodeling and the existence and location of lumen-reduction thresholds will be studied in relation to the presence and size of these plaque characteristics. The specific analytical methods to be used will be determined at the completion of the “wall size and stenosis” manuscript, which will determine whether the
wall-lumen associations in the ARIC population can be described in simple linear or more complex models.

For example, if the association between wall and lumen areas can be described in a simple linear model, we may compare slopes in persons with or without calcification. If there is a non-linear association with a clear threshold, we may determine whether persons with arterial calcification have a shifted threshold: e.g. they begin to lose lumen area at a smaller wall area compared with persons without calcification.

Analyses will generally be adjusted for age, sex, race, and height. Though this manuscript will be based on incomplete recruitment available at the time of the analysis, an attempt will be made to better represent the ARIC population eligible for the MRI study by applying the sample weights used for the earlier phases of selection.

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 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  ____ No

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)?

ARIC ms# 132 and 132A (Crouse et al.), relating lumen and interavdentitial diameters, are published 7,8
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.

References


