

ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #499

1. a. Full Title: Oxidative stress and the development of carotid artery plaque with and without acoustic shadowing.

b. Abbreviated Title: Calcified plaque V1-3

2. Writing Group:

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3. Timeline:

Analysis to begin following Publications Committee approval. MS anticipated in July, 1998.

4. Rationale:

Until recently, vascular mineralization was seen as a late (or secondary) development in the process of complicated atherosclerotic plaque formation. Recent evidence suggests that mineralization not only occurs early in the development of atherosclerotic plaques, but is a regulated process similar to bone growth. While mineralization is seen in complicated plaques and is a marker of advanced atherosclerosis, it is unclear whether it plays a protective or deleterious role. Further, the risk factors associated with the development of mineralization are not understood.

While coronary calcification has been associated with an increased CHD risk profile in cross sectional studies, prospective studies have not been completed. Duncan et al. examined baseline characteristics of the ARIC cohort associated with plaque with and without acoustic shadowing, and found that fibrinogen levels, smoking status and hypertensive status were associated not only with the presence of plaque, but an increased likelihood of acoustic shadowing. Further, recent evidence suggests that mineralization

is associated with exposures which represent oxidative pressure.

The second and third ARIC exams allow us to address in a prospective manner the associations reported earlier by Duncan et al. In addition, the ARIC cohort provides the opportunity to relate information on oxidative pressure (derived from dietary antioxidant levels, vitamin and supplement intake, and cigarette smoking status) to (1) the development of shadowing in individuals who have plaque without shadowing at baseline as well as (2) the development of carotid plaque with and without acoustic shadowing in individuals free of plaque at baseline.

To date no one has addressed specifically the repeatability of measuring plaque with shadowing, the repeatability of measuring plaque without shadowing, or the repeatability of measuring shadowing. Because acoustic shadowing may draw attention to a plaque, plaques with and without shadowing may be recognized differentially.

Using ARIC quality assurance data, Li et al. examined the combined reproducibility of carotid atherosclerotic lesions with and without plaque during the first and second ARIC examinations; however, the reproducibility of measuring shadowing was not addressed. This will be done in the companion manuscript proposal submitted to the Publications Committee.

5. Main Hypothesis:

- a) Development of acoustic shadowing is associated with exposures that represent oxidation pressures.
 - Acoustic shadowing is associated inversely with dietary antioxidant levels and reported consumption of vitamins and dietary supplements.
 - The effect of cigarette smoking on plaque with acoustic shadowing is modified by antioxidant levels (reported consumption of vitamins and dietary supplements).
- b) Development of acoustic shadowing is associated with increased fibrinogen levels.
- c) Development of acoustic shadowing is associated with hypertensive status.

6. Data (variables, time window, source, inclusions/exclusions):

outcome: carotid artery plaque with and without shadowing

time window: ARIC visits one, two and three.

descriptive: baseline IMT, LDL, HDL, total cholesterol, smoking, hypertension, fibrinogen, age, gender, race, center, antioxidants in diet, vitamins and dietary supplements

References:

Duncan BB, Metcalf P, Crouse III JR, Li R, Sharrett AR, Tegeler C, Tyroler HA, Heiss G: 1997. Risk factors differ for carotid artery plaque with and without acoustic shadowing. *Journal of Neuroimaging* 7(1):28-34.

Parhami F, Morrow AD, Balucan J, Leitinger N, Watson AD, Tintut Y, Berliner JA, Demer LL: 1997. Lipid oxidation products have opposite effects on calcifying vascular cell and bone cell differentiation: a possible explanation for the paradox of arterial calcification in osteoporotic patients. *Arterioscler Thromb Vasc Biol.* 17:680-687.

Sarig S, Weiss TA, Katz I, Kahana F, Azoury R, Okon E, Kruth HS: 1994. Detection of cholesterol associated with calcium mineral using confocal fluorescence microscopy. *Laboratory Investigation* 71(5):782-787.