ARIC Manuscript Proposal # 1241

PC Reviewed: __4_/_10/07	**Status: _A___**	**Priority: __2_**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Design and Validation of a Multicenter Study to Characterize Carotid Artery Atherosclerotic Plaque**

b. Abbreviated Title (Length 26 characters): **Carotid MRI Design and Methods**

2. Writing Group: Diane Catellier, Bruce Wasserman, Richey Sharrett, Brad Astor, Cory Swingen, and others

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

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3. Timeline: Completion of data analysis expected by May, 2007 and completion of manuscript preparation is expected by August, 2007.

4. Rationale: The purpose of this paper is to describe the methodology of the MRI exam and report on the reliability of MRI variables in a multicenter study designed to characterize carotid atherosclerotic plaque.

The MRI exam has two main objectives: (1) To determine the composition of carotid atherosclerosis, in particular the presence and size of the lipid core, calcification, hemorrhage, and the overlying fibrous cap; (2) To provide reliable measurements of these components using MRI equipment at multiple sites. We will describe the methodology of this exam designed to achieve these objectives.

We can think of an individual's measurement as being made up of two components, the true value and random error. Reliability is the proportion of "truth" in the measurement, or the ratio of the true score variance to the observed score variance. Reliability can be estimated by taking repeated

measurements of the same group of people to determine how much their measurements fluctuate. Fluctuations from one person's measurements are attributed to error. If reliability is low, the ability to differentiate between the subjects with different risk factors or disease states decreases. The ARIC Carotid MRI quality control program was designed to monitor the reliability of MRI measurements over time, and to identify factors that might affect reliability.

Potential sources of error in measurement include variability in scan quality, variation in protocol adherence, variation between readers performing the image analyses, and variation over time within an individual. Two sub-studies were designed to evaluate additional sources of variation. The first study has fewer sources of variation. A sample of approximately 100 participants were selected at the MRI reading center for replicate analysis. The MRI scan was sent to the same or a different reader for analysis and measures obtained from independent analyses were compared. Measurement error variation estimated from this data cannot be attributed to variation in scan quality, protocol adherence, or within-subject variation over time. In the second study, a random sample of 60 subjects was selected to have undergo a second MRI scan within 4 to 8 weeks of the first exam. These additional QC scans were labeled with a *phantom* participant ID that is indistinguishable from other ID numbers, so that the MRI reading center laboratory was blinded to the QC process. Measurement error variation estimated from this second study includes the sources of error present in Study 1 and variation in scan quality, protocol adherence, or within-subject variation over time.

5. Main Hypothesis/Study Questions:
1) What is the reliability of MRI variables in a large multicenter study? Are there factors that are associated with reliability (e.g., quality of the scan)? Using results from both sub-studies, estimate the component of variation that is attributable to reader error, image acquisition, and short-term within-subject.

2) What is the prevalence of the lipid core, intraplaque hemorrhage and calcification in carotid atherosclerosis in the ARIC population? What is the average maximum and mean wall thicknesses of the carotid wall in the general population? What is the mean cap thickness for carotid plaques at the slice showing the largest lipid core?

6. Data (variables, time window, source, inclusions/exclusions): Internal QC pool: 100 replicates selected at random at the MRI Reading Center. Repeatability study data: repeated MRI one month apart on 60 participants selected (non-randomly) at the field centers, and blinded to Reading Center staff.

Exclusions/Inclusions: none

For each of the sub-studies, we will compute standard indices of reliability including: (1) mean, standard deviation of paired measurements; (2) the mean difference, and associated confidence interval, between paired measurements on the same subject; (3) variances (within- and between-subject); (4) proportion of total variance attributable to measurement error (e.g., reliability).

We will estimate reliability (R) from a one way analysis of variance with subject as the only factor. That is, $R = (MS_b - MS_w)/ (MS_b + MS_w)$, where using the MS_b and MS_w are the between

and within-subject mean square values, respectively. We can also estimate reliability by treating subject as a random effect in a mixed model. Using this model, the total variance is partitioned between the variance of the random effect parameter (within-subject) and residual components of variation. Using this modeling framework, we will also examine the effect of various factors on reliability. In particular, we will examine whether inclusion of fixed effects such as field center, technician, scan quality score, time trends significantly reduces or "explains" the within-subject component of variance.

Some of the variables can only be estimated for patients who have a lipid core present (approximately 30% of the sample). For these variables, we will test for differences between reliability estimates obtained for Study 1 and Study 2 – in the absence of significant differences we will combine the data for both studies for these variables.

Prevalence and mean values of MRI variables will be estimated, using sample weights, to represent the entire ARIC eligible population and separately its black women, black men, white women and white men.

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.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)?
none

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* _1997.02_)

___ 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.