1.a. Full Title: Common Carotid Diameter, Wall Area, and CCA Ratio measures as Indicators of Prevalent and Incident CHD

b. Abbreviated Title (Length 26 characters): CCA area CHD Prediction by CCA measures

2. Writing Group (list individual with lead responsibility first):

   Lead: Marsha L. Eigenbrodt
   Address: Department of Epidemiology
            UAMS College of Public Health
            4301 West Markham, #820
            Little Rock, AR 72205
   Phone: (501) 526-6610    Fax: (501) 526-6750    E-mail: eigenbrodtmarshal@uams.edu

Writing group members: proposed: Zoran Bursac, David Couper, Jawahar Mehta, Kathy Rose, Richard Tracy, Fred Brancati, Greg Evans

3. Timeline:

4. Rationale:

   Intima medial thickness (IMT) of the common carotid artery (CCA) has been associated with atherosclerosis risk factors and vascular events in epidemiologic and clinical studies, as has CCA diameter and other arterial wall characteristics. Theoretically, arterial remodeling could impact statistical models' predictiveness if IMT is used alone instead of in conjunction with diameter. At least two studies have suggested that incorporating plaque dimensions may improve a statistical model's ability to identify persons with clinical cardiovascular disease. While the ARIC study does not have measurements specifically related to plaque size, including both wall thickness and diameter (or wall area estimated from IMT and diameter) might improve model prediction since diameter enlarges in response to plaques. By calculating arterial wall volume from the entire 1 cm segment of the CCA, an even better estimate of the extent of CCA wall involvement with plaque might be provided. Thus, it is possible that including diameter in addition to IMT (or wall area, or volume calculated from IMT and diameter) would improve models predicting outcomes caused by atherosclerotic plaques.

   Ratio measures, such as CCA IMT/diameter ratio or CCA lumen area/CCA artery area, could provide an alternative measure that would control for some of the measurement error and for the size of the individual as well.

   The ability to identify persons at risk of CHD by using large artery measures is likely to be limited however since studies of microvascular damage is associated with CHD as well. Also, coronary thrombosis depends not only on the coronary artery characteristics but also on patient
vulnerability such as hypercoagulable and inflammatory states.\textsuperscript{19} Therefore, adjustment for CCA IMT and diameter (or other CCA measures) may improve model prediction only modestly.

The artery characteristics that we propose to investigate are likely to reflect an intermediate step between the risk factors and the outcome. Studies have shown associations between risk factors and CCA wall thickness and diameter.\textsuperscript{8,10,20} In models predicting CHD as the outcome, changes in risk factor betas after adjusting for specific artery characteristics can potentially suggest the arterial characteristics intermediate between the risk factor and CHD. For instance, if inclusion of IMT results in reduction in the betas for risk factors in models predicting CHD, then this would suggest that arterial wall thickening is an intermediate step between the risk factor and CHD. Similarly, reduction in risk factor betas when diameter is included would suggest that diameter is in the causal pathway. Because diameter and wall thickness are related by La Place’s Law in physiologic conditions, their relationships with risk factors is likely to be complex and require evaluation of models including individual CCA characteristic as well as their combined effect (or wall area). These studies could provide hypotheses to be evaluated further in other studies.

5. Main Hypothesis/Study Questions:

We hypothesize that a statistical model including both CCA diameter and IMT (or wall area or CCA segment volume, or CCA ratio measures) will improve models predicting both the prevalence and incidence of CHD compared to models with IMT or diameter alone, but that the difference in the models’ prediction will be reduced by atherosclerosis risk factor adjustment.

In models predicting prevalent and incident CHD, we hypothesize that adjusting individually for CCA diameter or CCA IMT will not impact all risk factors in the same way and so will provide information regarding which arterial characteristics may be the causal pathway leading to CHD.

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

Variables: Baseline age, race, sex, center, standing height at baseline, prevalent coronary heart disease (CHD), stroke, diabetes, blood glucose, fasting information, hypertension, anti-hypertensive medication use, systolic and diastolic blood pressure, body mass index, smoking status, years of cigarette smoking, drinking status, ethanol consumption, LDL and HDL cholesterol, cholesterol medication use, plaques or shadowing in any carotid site, WBC, fibrinogen, von Willebrand factor, plaques/shadowing in right or left common carotid artery, mean and ten individual CCA diameter and far wall measurements for each view: optimal, anterior, and posterior views.

CHD disease from baseline to exam 4.

CCA diameter and IMT will be adjusted for reader differences and for drift associated with time during the first year as we have specified in earlier proposals.

Developmental and test data sets: From baseline data, a random sample of 10,000 participants who have B-mode ultrasound measurements of the right common carotid artery (CCA) will be selected as the developmental sample and the remaining sample will be used for model testing/validation.

Statistical analyses:

1) A. Logistic regression analyses will be used to evaluate models predicting prevalent CHD at baseline and incident CHD events from baseline forward to exam 4 (or latest data available). For incidence of events, we can test both logistic regression analyses and proportional hazards analyses. The main exposure of interest would be CCA measures (IMT, diameter,
ratio of CCA IMT to diameter, ratio of CCA lumen to artery areas). For identifying improvement in model predictivity, models containing two CCA measures (or measures developed from both IMT and diameter) will be compared to models containing CCA IMT. Models containing CCA IMT will be considered the reference model. The area under the receiver operating characteristic (ROC) curve will be compared to identify improvement in model prediction and the deviance test using the -2Loglikelihood will be compared for determining improvement in model fit. A method similar to that reported for ARIC in the investigation of prediction of stroke will be used.21

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B. Repeat analyses using a prospective design for incident disease.
C. Repeat analyses analyzing period prevalence data.

2) For models predicting CHD, models with CCA IMT, diameter or both will be evaluated to identify changes in the betas for the risk factors after CCA measures are included.

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

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  Kathy Rose has reviewed the proposals and has identified the following potentially related proposals. However, none of the proposals have proposed using the combined diameter and IMT to determine risk.

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)?

| Popliteal vs. carotid thickness and clinical disease (A) | MS 122 – withdrawn |
| Atherosclerosis risk profile in low-risk subjects (M) | MS 115 – withdrawn |
| Levels of CHD risk factors, arterial wall thickness, and MI attack rates in the ARIC communities, 1987-89 (M) | MS 128 – withdrawn |
Both of these were published – author Robin Crouse:

MS 132: Lumen compensation to arterial wall thickening (A) Crouse R 11/05/91 Apprd 1 11/20/91 Apprd 1 01/28/94 1994

132A (A) Risk factors and arterial enlargement Crouse R 06/02/94 Apprd 2 07/25/94 Apprd 2 08/21/95 1996

174 Incident CHD and wall thickness (D) Chambless LE 11/24/92 Apprd 3 01/23/93 Apprd 3 02/18/97 1997 PDF

500A (J) Carotid artery plaque with and without acoustic shadowing as a predictor of incident CHD and stroke Hunt KJ 09/26/97 Apprd 2 09/29/97 Apprd 2 09/05/00 2001 PDF

611 (J) ARIC CHD risk prediction Chambless LE 09/11/98 Apprd K 09/15/98 Apprd K 12/16/02 2003 PDF

801 Risk factors for peripheral arterial disease (PAD), CHD, and carotid atherosclerosis Sharrett AR 06/05/01 ----- - --/--/-- ----- - 09/22/03 2004 PDF

818 Carotid artery atherosclerosis, coronary heart disease and stroke incidence and mortality from cardiovascular disease in type 2 diabetic and nondiabetic men and women with and without history of myocardial infarction: ARIC Lee CD 08/23/01 Apprd 2 09/06/01 Apprd 2 11/21/03 2004 PDF

11. 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.

Selected References


