1. Full Title: Common Carotid Artery (CCA) Diameter, Wall Area, and Ratio Measures: Indicators of Incident Atherosclerotic Plaques/Shadowing

b. Abbreviated Title (Length 26 characters):
Incident Plaques/CCA measures

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

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

3. Timeline:
We can begin analyses as soon as we receive the full ARIC data.

4. Rationale:
Intima medial thickness (IMT) has been associated with atherosclerosis risk factors and vascular events in epidemiologic and clinical studies.1-8 Common carotid artery (CCA) diameters have also been associated with a number of atherosclerosis risk factors8-10 and arterial wall characteristics9,11-13 including vulnerable plaques.14 La Place’s Law suggests there should be a relatively constant relationship between diameter and wall thickness under normal physiologic situations. Animal studies demonstrate that diameter changes may occur in response to hemodynamic changes prior to arterial wall thickening.15 Remodeling in response to atherosclerotic plaques, however, may not follow the same relationship since studies indicate that remodeling may result in overcompensation with lumens larger than in normal arteries.9,16,17 Some human studies indicate positive remodeling occurs even in early atherosclerosis.18 It is possible that either wall thickening or diameter enlargement, or both contribute to plaque formation. Also, remodeling may have an impact on wall thickness by thinning of the wall underneath the atherosclerotic plaque.14 So, wall area may be the best predictor of incident plaque formation. Also, since La Place’s Law suggests diameter and IMT should be related, the ratio of IMT to diameter could indicate the lack of a physiologic state and be a useful predictor of plaque formation. For some of the ratio measures that are proposed, such as CCA IMT/CCA diameter, the ratio would potentially correct for part of the measurement errors since the error would be in both the numerator and denominator of the ratio. Similarly, the CCA lumen/CCA area could correct for some of the measurement error and also be important as an indicator of area available for normal blood flow.
June 29, 2005

Since both diameter and IMT may contribute to the development of plaques and interact with risk factors differently, we will evaluate whether IMT and/or diameter (and wall area) predict the incidence of plaque in unadjusted models and models adjusted for other risk factors.

5. **Main Hypothesis/Study Questions:**

We hypothesize that including CCA diameter (or wall area or ratio measures) in addition to CCA IMT will improve models predicting incident plaques/shadowing at follow-up compared to models with IMT alone, but that the difference in the models' prediction will be reduced by atherosclerosis risk factor adjustment.

We hypothesize that both IMT and diameter will be significantly associated with incident atherosclerotic plaques even after adjustment for baseline atherosclerotic risk factors.

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

Variables: Baseline age, race, sex, center, standing height at baseline, prevalent coronary heart disease, 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, plaques or shadowing in any carotid, 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.

Exams 2, 3 or 4: plaques and shadowing in the right or left CCA.

**Reader/Trend adjustment:**

Reader trend adjustment for baseline CCA measures will be performed as described in the cross-sectional proposal. Once the baseline adjustment has been performed, it is unlikely that the equipment change that occurred between exams 1 and 3 or 4 will have much impact on this study since only plaque/shadowing will be needed from exams 3 and 4.

**Data sets:**

Developmental and test data sets will be selected: From baseline data, a random sample of 10,000 participants who have B-mode ultrasound measurements of the right common carotid artery (CCA) or left common carotid artery will be used as the developmental sample and the remaining sample will be used for model testing/validation. The developmental data set will be restricted to persons who have data on plaques/shadowing at exams, 2, 3 or 4 and who do not have prevalent plaques at baseline.

**Analytic models:**

1) Logistic regression (or proportional hazard) analyses will be used to evaluate models predicting incident plaques/shadowing at follow-up (exams 3 or 4) with the main exposure of interest being baseline CCA measures (IMT, diameter, ratio of IMT to diameter, ratio of lumen to artery areas). For identifying improvement in model predictivity, models adding a CCA measure will be compared to models including only IMT (reference model). To identify the impact of risk factors on beta changes, models with the CCA measures only will be compared to models including basic adjustment (race, sex, and height) and with models adjusting for additional atherosclerosis risk factors. Models with IMT, diameter or both will be evaluated to identify changes imposed by risk adjustment. Betas for standardized, ranked, and absolute values of variables will be evaluated. The areas under the receiver operating characteristic (ROC) curves will be compared to identify improvement in model prediction and -2Loglikelihoods will be compared for determining improvement in model fit for the logistic models. Time to event analyses may need to be performed instead of logistic regression modeling.
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Vascular measures:
- CCA IMT
- CCA diameter
- CCA wall area
- CCA IMT/CCA diameter ratio
- CCA lumen area/CCA artery area
- Baseline volume of the 1 cm CCA wall segment (in the future)

A method similar to that reported for ARIC in the investigation of prediction of stroke will be used.19

2) Models will evaluate the magnitude of the betas for IMT and diameter to identify their potential contribution to the development of plaques in models with and without risk factor adjustment.

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  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)?

<table>
<thead>
<tr>
<th>Proposal Title</th>
<th>MS Number</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>Popliteal vs. carotid thickness and clinical disease</td>
<td>122</td>
<td>withdrawn</td>
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<tr>
<td>Atherosclerosis risk profile in low-risk subjects</td>
<td>115</td>
<td>withdrawn</td>
</tr>
<tr>
<td>Levels of CHD risk factors, arterial wall thickness, and MI attack rates in the ARIC communities, 1987-89</td>
<td>128</td>
<td>withdrawn</td>
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</tbody>
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Both of these were published – author Robin Crouse:
These proposals do not overlap with the fundamental goals of our study.

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
