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

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

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

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

3. Timeline:
Initial analyses have been completed using the ARIC LAD without reader trend adjustment. Complete analyses within 3 months of receiving full data set with draft manuscript to co-authors within one month following completion of data analysis.

4. Rationale:
Intima medial thickness (IMT) has been associated with atherosclerosis risk factors, atherosclerotic plaques, 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 characteristics.9,11-13 The axial resolution of the Biosound 2000IIS (0.1 mm14) and the pixel resolution (0.067 mm) would comprise a larger proportion of the CCA IMT (CCA mean from 0.58 to 0.86 mm14) than of CCA diameter (mean 7.18 to 8.3 mm10). Theoretically, remodeling could impact statistical models predictiveness of plaques if IMT is used alone instead of in conjunction with diameter.15 Also, several studies have evaluated plaque areas and found improved associations with clinical outcomes.16,17 While ARIC does not have plaque dimensions available, it is possible that including diameter in addition to IMT (or wall area calculated from IMT and diameter) would improve statistical models predicting the prevalence of plaque. It is also possible that the ratio measures that compare wall thickness to diameter or lumen area to artery area would improve prediction since the ratios would potentially control for some of the measurement error as well as control for differences in individual body size and for gender differences.

One method to evaluate whether diameter contributes to the development of plaque or whether diameter is the result of remodeling after plaques develop (reverse causality) is to evaluate the betas in sequential statistical models. If sequential statistical models are compared, beginning
with CCA measures of IMT and diameter and then adding major atherosclerosis risk factors, there should be little reduction in the betas for the CCA measures which are intermediate in the causal pathway. However, if diameter enlargement is predominantly the result of plaque remodeling, then one would anticipate less reduction in the beta for the diameter variable since it would be a result of plaque formation. Other sequential models could examine how adding the CCA measures impacted the risk factor betas to estimate how the risk factor is contributing to the development of plaques. While the relationships are likely to be complex, the associations could provide hypothesis generating information.

5. Main Hypothesis/Study Questions:
We hypothesize that a statistical model including CCA diameter (or wall area) in addition to CCA IMT will improve models predicting the prevalence of plaques/shadowing 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 a statistical model including a CCA ratio measure will improve models predicting the prevalence of plaques/shadowing compared to models with IMT alone, but that the difference in the models’ prediction will be reduced by atherosclerosis risk factor adjustment.

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, cholesterol medication use, plaques or shadowing in any carotid, WBC, fibrinogen, von Willebrand factor, right CCA plaques/shadowing, left CCA plaques/shadowing, means and ten individual CCA diameters and far wall measurements for each view: optimal, anterior, and posterior views.

Reader/Trend adjustment:
While IMT has had reader trend adjustment performed, CCA diameter has not been corrected. We therefore propose to perform adjustment for both CCA diameter and IMT for reader differences and for drift associated with time during the baseline study. This will assure adjustments are performed in the same way for both CCA variables. We will limit analyses initially to a low risk subset of the ARIC study so that differences in diameters or IMT will not be the result of major differences in atherosclerosis severity at different time points at baseline. We will test for trend and reader differences by race and gender to determine whether we need to run race/gender specific adjustments. The low risk subset will be defined by the absence at baseline of prevalent stroke, CHD, plaques or shadowing, diabetes (self-reported physician diagnosis, medication within 2 weeks, or fasting blood glucose ≥ 126 mg/dL, or non-fasting blood glucose ≥ 200 mg/dL); hypertension (anti-hypertensive medication within 2 weeks or BP>140/90); obesity (body mass index (BMI) ≥ 30, computed as weight in kg divided by height in meters²); current cigarette smoking; hyperlipidemia (LDL cholesterol ≥160 mg/dL and/or use of cholesterol lowering medication). Linear regression analyses will be run with CCA diameter and CCA IMT as separate outcomes. Variables for time and reader will be included as variables to test whether there is a significant difference in these nuisance variables after we adjust for race, sex, age, and height. Analyses will be first run for participants whose exam was after the first 5 month period as was previously done for the IMT adjustment. Since the presence of plaques/shadowing could contribute to differences in readings of IMT over time and by reader, analyses evaluating the need to adjust diameter and IMT will also be evaluated for a subset limited to participants with plaques/shadowing.
Data sets:
Developmental and test data sets will be selected from baseline data: a random sample of 10,000 participants will be selected and limited to persons who have B-mode ultrasound measurements of the right common carotid artery (CCA) and plaques at any carotid site. This will be used as the developmental sample and the remaining sample with the necessary information will be used for model testing/validation.

Analytic models:
1) Several logistic regression models predicting prevalent plaques/shadowing at baseline will be evaluated. For identifying improvement in model predictivity, models adding a CCA measure will be compared to models including only IMT (as 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 will be used to compare improvement in model fit.
2) To identify the potential pathway from risk factors to plaques (i.e. anatomic factors that are intermediate between the risk factor and plaques) we will evaluate the changes in the betas of the risk factors after including different CCA measures. A reduction in the risk factor would suggest the risk factor contributes to plaques by contributing to the CCA characteristic that resulted in the beta reduction. Betas for ranked variables, and betas for absolute and standardized CCA measures will be evaluated. Because of the relationship between IMT and diameter, models with only one measure and both measures will need to be evaluated in determining the potential pathway. These analyses will at least provide information for hypothesis generation.

Vascular measures:
a. CCA IMT  
b. CCA diameter  
c. CCA wall area  
d. CCA IMT/CCA diameter ratio  
e. CCA lumen area/CCA artery area  
f. 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.18

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)?

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 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

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