ARIC Manuscript Proposal # 1037D

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

b. Abbreviated Title (Length 26 characters): CCA area

Stroke Prediction by CCA measures

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

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3. Timeline:
Analyses with the LAD for the cross-sectional study have been mostly completed without adjustment for the reader or time trend.

4. Rationale:
Stroke may be caused by both large and small artery damage.1-3 Common carotid artery (CCA) intima medial thickness is frequently used as a risk indicator for the occurrence of clinical cardiovascular events since CCA IMT has been associated with atherosclerosis risk factors and vascular events in numerous epidemiologic and clinical studies.4-11 Common carotid artery (CCA) diameters have also been associated with a number of atherosclerosis risk factors11-13 and arterial wall characteristics.12,14-16 CCA atherosclerosis is particularly relevant for stroke since carotid thrombi can embolize to the brain and atherosclerotic narrowing of the carotids can result in reduced cerebral perfusion during periods of hypotension.17 Carotid plaques may be particularly relevant to atherothrombotic infarction.18 Because remodeling may impact wall thickness, arterial remodeling could therefore, at least theoretically, impact statistical models’ predictiveness if IMT is used alone instead of in conjunction with diameter19 and studies have used plaque dimensions to improve the prediction of stroke.20,21 While ARIC does not have plaque dimensions, it is possible that including diameter in addition to IMT (or wall area calculated from IMT and diameter) would improve models predicting strokes, especially atherothrombotic strokes. It is also possible that the CCA IMT/diameter ratio (or CCA lumen area/CCA artery area) would provide better prediction since the ratio 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 stroke by using large artery measures alone is likely to be limited however since strokes occur because of both large and small artery damage.1 Also, thrombosis of atherosclerotic plaques depends not only on the plaque characteristics but on other patient
factors such as coagulability of their blood and inflammatory activation.\textsuperscript{22} 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 atheroembolic strokes. Changes in risk factor betas after adjusting for the artery characteristics can potentially suggest the arterial change intermediate between the risk factor and stroke. For instance, if inclusion of IMT results in reduction in the betas for risk factors in models predicting stroke, then this would suggest that arterial wall thickening is an intermediate step between the risk factor and stroke. Similarly, reduction in risk factor betas when diameter is included would suggest that diameter is in the causal pathway. However, a simple, direct relationship is unlikely and investigation into intermediate steps may be required. For instance, because diameter and wall thickness are related by La Place’s Law in physiologic conditions, their relationships with risk factors could overlap. Also, micro- and macro-vascular disease may be related,\textsuperscript{23} and so may add additional complexity. This proposal is to identify the CCA measure that has the strongest relationship with stroke (especially of larger atheroembolic stroke). We have a separate manuscript proposal for evaluating the effects of both macro- and micro-vascular disease.

Since CHD is a risk factor for stroke, this will be an additional step that we will need to evaluate.

**Main Hypothesis/Study Questions:**
We hypothesize that a statistical model including both CCA diameter and IMT (or wall area or CCA segment volume, calculated from diameter and IMT measures) will improve models predicting both the prevalence and incidence of atheroembolic stroke compared to models with IMT or diameter alone, but that the difference in the models’ prediction will be reduced by atherosclerosis risk factor adjustment or adjustment for prevalent CHD.

In models predicting prevalent and incident stroke, we hypothesize that adjusting individually for CCA diameter or CCA IMT will not impact all risk factors to the same extent and so will provide information regarding which arterial characteristic may be the intermediate step leading to stroke. Adjustment for CHD can suggest whether the risk factors contribute via CHD or more directly.

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 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.
Overall and specific stroke subtype (lacunar and atheroembolic) incidence after baseline 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. For analyses of incident stroke, persons with stroke at baseline will be excluded.

Statistical analyses:
1) A. Logistic regression analyses will be used to evaluate models predicting prevalent stroke at baseline and incident stroke during follow-up (latest data available). For incidence of events, we can use proportional hazards analyses to evaluate whether the time to event has an impact on the relationship. The main exposure of interest would be CCA measures (IMT, diameter, wall areas, 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. 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 where basic and sequentially adjusted models are evaluated.24

Traditional cardiovascular risk factors (systolic and diastolic BP, BP medication, current smoking, diabetes mellitus, drinker status, previous CAD, previous stroke, BMI, HDL and LDL cholesterol) as well as other risk factors (fibrinogen, WBC, pack years of smoking, grams of alcohol consumption, LVH by Cornell voltage criteria, presence or absence of plaques and/or shadowing) and finally carotid plaques, age and race will be tested.
B. Repeat analyses using a prospective design for incident disease.
C. Repeat analyses with a period prevalence design.

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

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

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)?

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]

443 (A) IMT is predictive of incident clinical stroke Chambless LE 12/11/96 Apprd 2 01/22/97
Apprd 2 11/11/98 [2000 PDF]

513 (J) Association of arterial stiffness and cerebrovascular diseases Chambless LE 08/27/97
Apprd 2 09/03/97 Apprd 2 --/--/-- ---- [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
