ARIC Manuscript Proposal # 1188

PC Reviewed: _9__/_29__/06	**Status: __A__**	**Priority: _2__**
SC Reviewed: _9__/_29__/06	**Status: __A__**	**Priority: _2__**

1.a. Full Title: Carotid Wall Thickness and Risk of Ischemic Stroke Subtypes. The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): IMT and Stroke Subtypes

2. Writing Group:

Writing group members: Tetsuya Ohira, MD; Aaron R. Folsom, MD; Eyal Shahar, MD; Wayne D. Rosamond, PhD; A. Richey Sharrett, MD; Lloyd E. Chambless, PhD.

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3. Timeline: We expect to complete the manuscript by December 2006.

4. Rationale:

Carotid artery intima-media thickness (IMT) and carotid plaques are markers of subclinical atherosclerosis and help in the early identification of presymptomatic individuals. Previous epidemiological studies have reported that carotid IMT thickness predicts future stroke events (1, 2), but few studies have demonstrated associations of

IMT with subtypes of ischemic stroke (3-5) and these results are inconsistent. Since the pathogenesis, prognosis, and treatment differ among subtypes, to evaluate a predictive value of IMT for individual subtypes may contribute to more effective primary and secondary prevention of ischemic stroke.

A cross-sectional case-control study of 470 case and 463 controls in French men and women showed that an increased common carotid artery (CCA)-IMT was associated with all ischemic stroke subtypes, such as atherothrombotic, lacunar, and cardioembolic strokes even after adjustment for cardiovascular risk factors, and the association between ischemic stroke and CCA-IMT was stronger in the atherothrombotic stroke than in other subtypes (3). The adjusted odds ratios, associated with an increase in CCA-IMT of 1 SD, were 2.19 (95%CI, 1.45, 3.31) for atherothrombotic stroke, 1.58 (95%CI, 1.11, 2.25) for lacunar stroke, and 1.60 (95%CI, 1.03, 2.70) for cardioembolic stroke. Another cross-sectional case-control study of 311 case and 792 controls in Japanese men and women observed that CCA-IMT and plaque score were significantly associated with atherothrombotic and lacunar strokes but not cardioembolic stroke (5). Further, a cross-sectional case-control study of 292 case and 129 controls in Italian men and women reported that CCA-IMT values were significantly higher in subjects with nonlacunar stroke versus both those with lacunar stroke and control subjects (4). Since these studies reported using a cross-sectional case-control study, the association of carotid IMT and plaques with ischemic stroke subtypes should be confirmed prospectively.

On the other hand, the ARIC study reported that African Americans had a 2.4 fold higher age-adjusted relative risk of stroke incidence compared with whites (6) which could be partially explained by higher prevalence of stroke risk factors such as hypertension, diabetes, and current smoking among African Americans than among whites (7). Further, a recent ARIC study showed that while African Americans had a 3-fold multivariable-adjusted risk ratio of lacunar stroke compared with whites, there was no racial difference for nonlacunar and cardioembolic strokes after adjustment for traditional and nontraditional cardiovascular risk factors (8). Mean CCA-IMT was higher among African Americans than among whites (9) and carotid stenosis may have an important role in the development of lacunar stroke (10). Therefore, the higher prevalence of carotid stenosis among African Americans may contribute to a predominance of a lacunar stroke among African Americans.

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

1) CCA and internal carotid artery (ICA)-IMT is positively associated with all ischemic stroke subtypes: lacunar, nonlacunar, and cardioembolic strokes.
2) Associations (hazard ratios) of CCA and ICA-IMT with nonlacunar stroke incidence are stronger than those with lacunar and cardioembolic stroke incidence.
3) Associations (hazard ratios) of CCA and ICA-IMT with lacunar stroke incidence are stronger among African American than whites.

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

Dependent variables: Ischemic stroke subtypes incidence (up to 2002)

Independent variables: CCA-IMT, ICA-IMT, carotid bifurcation-IMT, all-site mean IMT, and plaques

Adjustment for age, gender, and race-field center. (2) Adjustment for age, gender, race-field center, systolic blood pressure, hypertensive medication, diabetes mellitus, smoking, total & HDL cholesterol, fibrinogen, von Willebrand factor, white cell count, lipoprotein(a), left ventricular hypertrophy, body mass index, and education level.

Exclusion: history of stroke, no baseline IMT measured.

Proportional hazards (Cox) regression will be used to examine both the univariate and multivariable-adjusted associations between independent variables and time to incidence of lacunar, nonlacunar, and cardioembolic stroke.

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

___×___ 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)?

Manuscript ARIC #443: IMT is predictive of incident clinical stroke
#1190: Risk factors for ischemic stroke subtypes: the Atherosclerosis Risk in Communities (ARIC) Study

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __×__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primiarly 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.

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