ARIC Manuscript Proposal # 1149

PC Reviewed: _04/_18_/06 Status: __A__   Priority: _2__
SC Reviewed: __04/19/06_   Status: ___A__   Priority: __2__

1.a. Full Title: **Echocardiographic Predictors for Incident Stroke in African Americans: the Atherosclerotic Risks in the Communities Study**
  b. Abbreviated Title (Length 26 characters): **Echo and Stroke in ARIC**
2. Writing Group:

Writing group members: Tom Mosley, Kenneth Butler, Alan Penman, Herman Taylor, Tandaw Samdarshi

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __*EF*___ **[please confirm with your initials electronically or in writing]**
First author: Ervin Fox, MD, MPH
Address: University of Mississippi Medical Center, Cardiology Division
         2500 N. State Street
 Jackson, MS 39216
                Phone: (601) 984-5635   Fax: (601) 984-5630
                E-mail: efox@medicine.umsmed.edu
       Corresponding/senior author (if different from first author correspondence will be
       sent to both the first author & the corresponding author):
Ervin Fox, MD, MPH
Address: University of Mississippi Medical Center, Cardiology Division
       2500 N. State Street
          Jackson, MS 39216

          Phone: (601) 984-5635   Fax: (601) 984-5630
          E-mail: efox@medicine.umsmed.edu

3. Timeline:
    Complete Analysis   August 2006
    Submit first draft to publications committee   November 2006
4. Rationale:
The age-adjusted incidence rates (per 100,000) for first-ever strokes are 167 for white males, 138 for white females, 323 for black males and 260 for black females. Blacks have almost twice the risk of first-ever stroke compared with whites (1).
Several echocardiographic parameters and findings have been associated with incident stroke including left ventricular mass and structure, left ventricular function, left atrial size, aortic valve calcification (AVC) and mitral annular calcification (MAC). Despite the potential link between these echocardiographic parameters and atherosclerosis, there are limited data regarding the relationship between echocardiographic-derived measures and incident stroke in African Americans. Though the mechanism is not well understood, each of these parameters has been shown to be a potential marker for atherosclerosis and cardiovascular events. Recently, Fox et al. and Taylor et al. have reported that in the ARIC Jackson cohort, the presence of MAC and AVC respectively

incur a significant risk for coronary events (2,3). Left ventricular mass index and left ventricular diastolic function based on echocardiographic early-to-late mitral velocity ratio have also been shown to be risks for all-cause mortality in the ARIC cohort (4,5). Additionally, Framingham and other investigators have found that valvular calcification and left ventricular mass are significantly associated with incident stroke (6). Similarly, MAC and other forms of cardiac calcification have been associated with an increased risk of stroke and congestive heart failure in other, predominantly white non-Hispanic, populations (7-12). To the best of our knowledge, however, there very limited if any existing data on how each of these echocardiographic parameters relate to incident stroke in a population-based cohort of African Americans.

REFERENCES

1. American Heart Association. *Heart Disease and Stroke Statistics — 2004 Update*. Dallas, Tex.: American Heart Association; 2003.

2. Fox ER, Taylor HA, Harkins D, McMullan M, Han H, Samdarshi T, Garrison RJ, Skelton TN. Epidemiology of mitral annular calcification and its predictive value for coronary events in African American: the Jackson cohort of the ARIC Study. American Heart Journal 2005 148(6): 979-984.

3. Taylor HA, Clark BL, Garrison RJ, Andrew ME, Han H, Fox ER, Arnett D, Jones DW. Aortic valve sclerosis and risk of coronary heart disease in African Americans. American Journal of Cardiology 2005;95:401-404.

4. Nunez D, Arnett DK, Benjamin EJ, Liebson PR, Skelton TN, Taylor H, Andrew M. Optimal threshold valvue for left ventricular hypertrophy in blacks: the atherosclerotic risk in communities study .

5. Han H, Taylor HA, Walls UC, Fox ER. The predictive value of early to late mitral diastolic filling ratio for incident cardiovascular events in African Americans: the atherosclerotic risk in communities study. (Abstract present at American Society Echocardiography Annual Scientific Sessions, 2005)

6. Benjamin EJ, Plehn JF, D'Agostino RB, *et al*. Mitral annular calcification and the risk of stroke in an elderly cohort. N Engl J Med 1992; 327:374-9.

7. Roberts WC. The senile cardiac calcification syndrome. Am J Cardiol 1986; 58:572-4.

8. Adler Y, Herz I, Vaturi M, *et al.* Mitral annular calcium detected by transthoracic echocardiography is a marker for high prevalence and severity of coronary artery disease in patients undergoing coronary angiography. Am J Cardiol 1998; 82:1183-6.

9. Petty GW, Khandheria BK, Whisnant JP, *et. al.* Predictors of cerebrovascular events and death among patients with valvular heart disease. A population-based study: Stroke 2003; 31:2628-35.

10. D'Cruz IA, Cohen HC, Prabhu R, *et al.* Clinical manifestations of mitral annulus calcification with emphasis on its echocardiographic features. Am Heart J 1977; 94:367-77.

11. Mellino M, Salcedo EE, Lever HM, *et al.* Echocardiographic-quantified severity of mitral annular calcification: prognostic correlation to related hemodynamic, valvular, rhythm, and conduction abnormalities. Am Heart J 1982; 103:222-5.

12. Pomerance A. Pathology of the heart with and without cardiac failure in the aged. Br Heart J 1965; 27:697-710.

5. Main Hypothesis/Study Questions:

Are echocardographic derived left ventricular mass and structure, systolic/diastolic function, left atrial size and valvular calcification independent predictors for incident stroke in African Americans?

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study population will include African-American participants of the ARIC Jackson cohort who have undergone 2D and M-mode echocardiographic exams (N=2,445) at visit 3. Exclusions: subjects with severe valvular disease on echocardiography, poor quality echocardiograms, or missing LV measurements, and subjects with prevalent CHD and TIA/stroke (history of TIA/stroke prior to visit 3).

Demographic variables will include age and gender.

Clinical variables that will need to be adjusted for in the Cox proportional hazard model include HDL/total cholesterol, LDL, smoking status, systolic and diastolic blood pressures measured over multiple visits, hypertension status (including use of hypertensive medications), diabetes status, and BMI.

Echocardiographic variables that will be measured (or calculated) include LV internal diameter, interventricular septal thickness, posterior wall thickness, left atrial diameter, relative wall thickness, LVMI, aortic valve calcification, and mitral annular calcification. Systolic function will be obtained based on estimated ejection fraction and diastolic function will be obtained based on the diastolic mitral early and late velocity ratio.

We will calculate the crude and adjusted stroke incidence rates and hazard ratios in those with the echocardiographic variables described, adjusting for clinical and echocardiographic risk factors for stroke; we will evaluate the predictive value of MAC for incident stroke.

7.a. Will the data be used for non-CVD analysis in this manuscript?
____ **Yes**   __✓_ **No**

> **7b. 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)?

MS 845/846 Fox et al. Mitral Annular Calcification
Predictive Value for Coronary Events in ARIC

MS 948 Han, Taylor, Fox, et al.
Mitral E/A ratio Predictive Value for All-Cause Mortality
and Incident Cardiovascular Events

MS 583 Fox et al. Left Ventricular Mass Index and
Prevalent MRI Cerebrovascular Disease

MS 790 Taylor et al. Relation of Aortic Valve Sclerosis to Incident Coronary
Heart Disease in African Americans

Lead authors from both proposals/manuscripts are on this proposal.

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.