ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #583

1. Full Title: Echocardiographic Correlates of Prevalent Stroke in African Americans
   Abbreviated Title: Echo Correlates of Stroke

2. Writing Group:
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3. Timeline:
   Analyses will begin after a statistician has been assigned.

4. Rationale:
   Echocardiographic predictors of incident stroke have been examined in the largely
   Caucasian Framingham Heart Study. Adjusting for traditional clinical stroke risk factors
   mitral annular calcification (1), left ventricular mass (2), and left atrial size (3) have all
   been demonstrated to be predictive of incident stroke. However, the relations of
   echocardiographic findings and stroke are largely unexplored in the African American
   population. Ideally we would like to examine the relation of echocardiographic features
   to incident stroke. However, such a project undoubtedly will require the availability of
   longer follow-up. Given the burden of stroke in the African American Community,
   identification of echocardiographic features associated with increased risk of prevalent
   stroke may provide insights into the pathogenesis and prevention of stroke.

5. Main Hypothesis:
   a) Left ventricular mass, mitral annular calcification and left atrial size will be associated
      with prevalent clinical infarcts and transient ischemic attacks and
      infarcts on magnetic resonance imaging in African Americans.
b) The relation of echocardiographic features to stroke and TIA will be independent of traditional clinical stroke risk factors.

6. Data:
Study Population:
- ARIC Jackson subjects who received echocardiograms on examination cycle 3.
Exclusions:
- Mitral stenosis, prosthetic mitral or aortic valve
- Echocardiogram not performed
- MRI not performed (an exclusion only for the analysis of the relation to MRI findings; one analysis will look (#1 the relation to prevalent clinical stroke)
- Missing echocardiographic variable (missing data will vary by analysis)
Outcomes:
- For clinical strokes we will use ARIC validated stroke. By validated strokes we mean both ARIC algorithm and ARIC physician diagnosed strokes - as opposed to patient report of stroke or TIA which has questionable validity.
- Primary analyses will examine the relation of the echocardiographic variables to:
  - Prevalent stroke at examination 3 by clinical history
  - Prevalent cerebral infarct (> and < 3 mm) by MRI
- Secondary analyses will look at:
  - Prevalent stroke or transient ischemic attack by clinical history
  - Combined prevalent stroke or transient ischemic attack or MRI cerebral infarct, if the risk factors seem similar

Clinical Variables:
- age
- sex
- blood pressure
- hypertension treatment
- cholesterol/HDL
- diabetes
- smoking
- myocardial infarction
- atrial fibrillation by EKG at clinic exam 1, 2 or 3
- body mass index (BMI)
- fibrinogen

Echocardiographic Variables:
- LV mass
- mitral annular calcification
- left atrial size
- LV internal diameter
- relative wall thickness
- regional wall motion abnormality
- LV = left ventricular
- LV ejection fraction (qualitative)
- LV fractional shortening*
- LV midwall fractional shortening*
- sum of the LV wall thickness
- mitral inflow Doppler A>E [1.2] or E>A [2.0]
- mitral or aortic regurgitation > 2+
*use if no significant regional wall motion abnormalities

7. Analyses:
At Jackson Cohort Visit 3 - 2621 individuals 49-73 years old attended (64% female, 36%
male). Of these 1908 had M-mode LV mass. At Jackson Cohort Visit 3 - 536 men and
307 women had MRI examinations. 15.6% men and 17.4% of women had cerebral
infarcts (> 3 mm)
Initial analyses will examine the number of subjects who:
- were alive at examination 3 with prevalent stroke
- the number of subjects who had Jackson examination 3
- the number of subjects who received an echocardiogram; the number who received an
MRI.

- We will look at the characteristics of subjects missing echocardiogram, and subjects
missing MRI to see how they differ from subjects receiving both.
  Univariate analyses will examine the relations between the designated echo variables
  and transient ischemic attack or stroke defined clinically, and defined by
  MRI.
- Bivariate analysis will then adjust for age.
- Multivariate modeling will then adjust for the clinical covariates and each echo
covariable separately.
- Stepwise modeling will force in the key clinical variables and then examine which, if
  any, of the echo variables remain related to TIA/stroke.
- We might also examine a model that gives us insight into the incremental value of echo
  in the prediction of stroke.

8. Issues to be resolved by the writing group:
- Outcome.
- Primary analyses will be to look at clinical and MRI cerebral infarcts. Per Dr.
  Hutchinson, the writing group will discuss further whether to include MRIs that
  were done in the first 6 months of exam 4, and whether to include cerebral infarcts < 3
  mm on MRI. The writing group will discuss further but is inclined to
  examine as a secondary analysis the relation of echocardiographic findings to MRI
  white matter disease (WMD). Advantages include that our power will
  increase with more events [e.g. in CHS 196/2516 participants without MRI infarcts > 3
  mm, had white matter infarct like lesions](4). Further, WMD have
  similar risk factors to strokes (5,6). However, the etiology and clinical significance of
  WMD is still ambiguous. In addition, CHS data has suggested that
  echocardiographic findings including LV ejection fraction, LV wall motion
  abnormalities, left atrial size and LV internal diameter end-diastole were not
  related to WMLs. While LVM had a partial correlation 0.67 (p<0.01), LVM was not
  independently related to white matter lesions(7).
- Initially we will not combine clinical stroke/TIA with stroke on MRI unless they have
  similar risk factors.
- Clinical variables.
- Because of limited power it is desirable to be parsimonious in the number of variables
• Data on participant attendance, the availability of echo LVM, and the prevalence of MRI findings on Jackson

* ARIC visit 3 is from the booklet distributed at the Jackson Heart Study Symposium, 11/97(6,7)

We include in the models:
• Which blood pressure measure to adjust for has not been established clearly by ARIC precedent. Dr. Cooper suggests that we look at both SBP (systolic blood pressure) and MAP (mean arterial pressure: 1/3 SBP + 2/3 DBP) to see which is best to use as a covariate. Because of prior work relating blood pressure with intimal medial thickness, Dr. Arnett favors including MAP and pulse pressure (versus SBP)
• Although cholesterol has not been related to incident stroke in a number of epidemiologic investigations, given recent statin trials demonstrating reduced stroke risk with cholesterol lowering, we will adjust for total cholesterol/HDL.
• Atrial fibrillation may not be defined by ARIC on ECG.
• CHF is not clinically validated in ARIC, but we might do an analysis including CHF diagnoses abstracted from the hospital record onto the HRA form.
• We will examine whether there are sex interactions and decide whether to adjust or stratify by sex.
• Echocardiographic variables.

Other potential echocardiographic variables to be included in the analyses will be discussed by the writing group. For instance, one might want to analyze mitral valve prolapse and mitral stenosis. We initially didn't include these variables because their low prevalence will greatly diminish our power to describe a relation with stroke.
• Many of the echo variables are co-linear (e.g. LV internal diameter and LVM and LV ejection fraction). We will discuss how to handle co-linearity.
• How do we index echo measurements? By BSA or BMI [potentially 'forgiving' for obesity] or by height. Initially, in the clinical covariates we will adjust for BMI, we will index echo measurements by height. Many subjects are missing M-mode data. For instance, per Dr. Arnett, 383 women and 210 men (out of a total of 1575 women and 870 men) are missing m-mode LV mass (ECHA32). To boost our power, we believe that it is reasonable to use a regression equations to relate 2-D to M-mode measurements and substitute the 2-D echo variables when the M-Mode is missing.
• Initially we will analyze echo variables as continuous variables. We may explore analyzing variables that appear predictive in a categorical fashion (quintiles or a threshold approach).

9. Limitations:
• Missing data
• Missing data may limit the proposed investigation's power to describe the relations of echo features and prevalent stroke.
• The missing data will undoubtedly not be randomly distributed. For example,
technically limited echocardiograms are associated with obesity, age and lung disease.

- An unavoidable limitation is that analyzing prevalent stroke censors the subjects with the most severe strokes. Prior severe strokes may have died or been institutionalized, and hence been unavailable for MRI and echo f/u at exam 3. Survivor bias may limit our power to describe the relation between echo features and stroke.

Regardless, the availability of population-based routinely ascertained echocardiograms on a large well characterized cohort represent a unique opportunity to address risk factors for stroke in the African-American community.

10. Bibliography: