

ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #447

1. a. Full Title: Lipoprotein[a] and incident ischemic stroke

b. Abbreviated Title: Lp[a] & incident stroke

2. Writing Group:

Lead: Pamela J. Schreiner, Ph.D.

Address: Division of Epidemiology, University of Minnesota, 1300 S. 2nd Street,
Suite 300, Minneapolis, MN 55454

Phone: (612) 626-9097

Fax: (612) 624-0315

E-mail: Schreiner@epivax.epi.umn.edu

A. Folsom

L. Cooper

J. Morrisett

L.E. Chambless

W. Rosamond

3. Timeline:

Analyses to begin during Fall 1996 or with the arrival of the most recent endpoint data, but will be dependent on adequate number of events to detect associations.

4. Rationale:

We have previously shown that lipoprotein[a] (Lp[a]) is positively and statistically significantly associated with self-reported stroke/transient ischemic attack using data from the first ARIC visit (MS#091). The only study that has examined the association prospectively, the Physicians' Health Study, found no evidence of an association between baseline Lp[a] and either incident total or thromboembolic stroke. However, there is sufficient biologically plausible evidence to warrant examination of this association in a more generalized population rather than a predominantly white male cohort from a middle-to-upper socioeconomic group. Lp[a] may be causally related to ischemic stroke via both chronic, atherogenic mechanisms, and acute thrombogenic mechanisms—investigation of these associations require prospective data in individuals free of prevalent disease at initiation of followup. Although the prevalence of stroke has been low relative to CHD in the ARIC cohort because of differences in average age of presentation, surveillance for incident CHD and cerebrovascular disease among the

cohort has now reached a point where sufficient stroke cases are available to provide adequate power to detect an association between Lp[a] and incident stroke. Further, the careful validation of these events and the length of followup will strengthen the credibility of this association beyond our self-reported findings.

5. Main Hypothesis:

For individuals who do not self-report a history of stroke or transient ischemic attack at Visit 1, Lp[a] is positively associated with incidence of ischemic stroke. This association (hazard rate ratio) does not vary by race or gender despite markedly higher mean Lp[a] levels in African-Americans (examination of this research hypothesis is dependent on adequate power). Racial differences in population attributable risk will also be examined although sample size constraints apply for this analysis as well.

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

Proportional hazards (Cox) regression will be used to examine both the univariate and multivariable-adjusted association between Lp[a] levels at baseline and time to incident stroke. We will evaluate both the association between Lp[a] and all strokes, and Lp[a] and ischemic stroke. Race interactions will be tested, and, if statistically significant, race-specific models will be run [sample size calculations suggest that final models will involve the entire stroke-free baseline cohort, adjusted for race and gender]. The other relative interaction that will be tested will be the Lp[a]-by-time-to-event interaction as a test of the proportional hazards assumption. Covariates that will be adjusted for in multivariable models include: age, gender, center, education, LDL-cholesterol, fasting triglycerides, hypertension, diabetes, fibrinogen, hormone replacement therapy (women), antihyperlipidemic medication usage, smoking, physical activity, and ethanol consumption. These covariates have all been inconsistently reported to affect Lp[a] levels. Because Lp[a] is thought to be a largely genetically determined lipoprotein, we believe that most of these covariates will not be substantial confounding variables to the Lp[a]/stroke relationship.