1. Title (length 26):

Lp[a] and incident angina

Full Title: Lipoprotein[a] as a risk factor for incident angina

2. Writing Group:

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3. Timeline: Analyses will be initiated during Fall 1992 and manuscript preparation completed during Spring 1993.

4. Rationale:

High levels of lipoprotein[a] are associated with angiographically-assessed coronary heart disease (CHD), myocardial infarction (MI), and a family history of MI in asymptomatic individuals. In vitro, Lp[a] has been shown to interfere with fibrinolysis due to the high degree of homology between apo[a] and plasminogen. Other investigators have suggested that Lp[a] may be an acute phase reactant that is elevated following an MI. Recently, several studies (Oshmia et al., 1991; Qui et al.) have found that among individuals presenting with unstable angina pectoris; Lp[a] is transiently elevated. While Lp[a] levels are similar between males and premenopausal females or postmenopausal females on hormone replacement therapy, the prevalence of angina is generally higher in women than in men. Finally, reports of Lp[a] as a risk factor for incident CHD are equivocal.

We therefore propose to investigate whether Lp[a] is associated with incident angina, which may be a marker for early CHD and/or an acute phase response. Further, the gender difference in this association will be examined. Incident angina is assessed with the validated Rose instrument in the context of a yearly questionnaire among the ARIC cohort, ages 45-64. By choosing participants without a history of prevalent CHD at baseline from an ambulatory population
sample, the newly reported angina events are likely to be the first manifestations of CHD.

5. Main Hypothesis:

1) Elevated levels of Lp[a] associated with increased incidence of angina
2) This association does not vary by gender

6. Data

Black and white participants in the cohort component of the ARIC study who were free of prevalent CHD (MI diagnosed either by ECG or by physician, angina, or prior coronary revascularization) at the baseline visit will be included in this study. Incidence of angina will be determined via standardized Rose angina algorithm, administered at each annual followup contact.

At the time of analysis, at least 3 years of reasonably complete followup data are available for the visit 1 cohort (year 4 or potentially year 5 of the study). Sample size estimates – based on alpha = 0.05 and beta = 0.20 for a one-tailed test, using an effect size for Lp[a] protein of 33 ug/ml (comparable to a 10 mg/dl difference in total plasma Lp[a] levels), and assuming a 2% annual incidence of angina – have determined that a total sample size of 4268, with 85 angina events, is required to detect the anticipated effect size at these levels of significance. During contact years 2, 3, and 4, 393 positive Rose angina events were reported among individuals 1) without prevalent CHD at baseline and 2) without multiple reports of angina (each event representing a unique participant), implying sufficient power to stratify analyses into gender-specific models.

Lp[a] measured as its apolipoprotein will be the main exposure (independent) variable. Other covariates that will be considered as potential confounders or effect modifiers include age, race, fibrinogen, hematocrit, LDL- and HDL-cholesterol, hypertension status, amount of cigarette smoking, diabetic status, and menopausal status in female participants – all collected at baseline. The association of Lp[a] and these risk factors with newly-reported angina will be assessed in gender-specific models using Cox proportional hazard modeling (although, because of the short followup period, logistic regression modeling should yield equivalent results).

References:
