1. Title:
Lp(a) and fibrinolytic activity.

2. Writing Group:
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3. Timeline:
Analysis can begin upon completion of the 300 case control pairs for which fibrinolytic variables are currently being determined.

4. Rationale:
The well-known similarity in the structure of the apo(a) moiety of Lp(a) and plasminogen, and the rather consistent relationship of elevated plasma Lp(a) with CHD, have stimulated investigation as to the possible mechanisms by which Lp(a) may exert an effect. In particular, laboratory studies have focused on exploring the effects of Lp(a) on fibrinolytic activity and also on incorporation of Lp(a) into macrophages and into the vessel wall. Inhibition of fibrinolysis by Lp(a) has not been demonstrated in vivo.

The ARIC ultrasound case-control study, for which variables pertinent to fibrinolysis (tPA, PAI-1, and D-dimer) are measured, can serve as a substantive population group that permits investigation of the association of Lp(a) with these components of the fibrinolytic system.

The limitation of the ARIC case-control approach lies in the selective criteria applied for choosing the cases and their matched controls resulting in a study group that may be non-representative of the ARIC cohort. While this probably is an important drawback for studies of the prevalence of a measure, associations between variables are in the main less susceptible to such bias.

5. Main Hypothesis:
The association between Lp(a) and fibrinolytic activity is complex. A simplistic hypothesis may be that elevated Lp(a) inhibits plasminogen activation to plasmin or blocks plasmin receptor sites and hence results in reduced or slower breakdown of fibrin. This may be reflected in lower levels of D-dimer, a breakdown product. It is difficult to predict the effect, if any, on tPA and PAI-1 concentrations in a free-living population; fibrinolysis is driven by activation of coagulation, and measures relating to the flux through the coagulation cascade, such as the activation peptide F1+2, could improve the informativeness of such an analysis.

6. Data:
The fibrinolytic variables (tPA, PAI-1, D-dimer) and measures reflecting platelet activation (PF4 and BTG) determined in the case-control pairs and fibrinogen, factor VII, measures of adiposity, time of day, triglycerides, LDL-C, HDL-C, smoking, physical activity and social class all collected at Visit 1. Exclusions: use of anticoagulation medication (n=3) and systemic hemostatic meds (n=3).
7. Analysis:
Nonparametric analyses of the association between Lp(a) and the fibrinolytic variables, as well as analyses of the appropriate transformations of these variables, are contemplated separately for cases and controls. Subsequently, weighting techniques will be applied to permit a combined analysis. Race specific or race restricted analyses may be undertaken because of the very different Lp(a) distribution and level between blacks and whites. Possible effect modification by important variables that may modulate fibrinolytic activity (TG, insulin, smoking and BHI) will be considered. Analysis will also be designed to consider the possible episodic nature of fibrinolysis.