

ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #350

1. Title: Circulating adhesion molecules predict atherosclerosis and incident CHD in the ARIC study.
2. Writing Group: Eric Boerwinkle (lead), A. Richey Sharrett, Christie Ballantyne, C. Edward Davis, Antonio Gotto, Jr, and Louis Smith.
3. Timeline: Data collection is ongoing and should be completed by November.

4. Rationale:

Atherosclerosis and CHD are the result of life-long interactions among multiple metabolic and cellular processes. Adhesion and integration of circulating white cells and platelets onto and into active vascular endothelium is an early and continuous process in atherogenesis - the leading cause of most CHD. This manuscript will test the ability of the adhesion molecules VCAM, ICAM, and E-selectin to predict carotid artery atherosclerosis and CHD cases status. VCAM and ICAM are inducible immunoglobulin-like membrane bound proteins which are expressed at sites of inflammation and immune reactivity. E-selectin is another inducible protein expressed at sites of inflammation, and is involved in the recruitment of white cells into the affected area. This study will further define the importance of chronic inflammation and cellular adhesion in atherogenesis and CHD.

5. Primary Null Hypotheses:

- (1) The distribution of plasma levels of VCAM, ICAM, and E-selectin are not significantly different between incident CHD cases and controls.
- (2) The distribution of plasma levels of VCAM, ICAM, and E-selectin are not significantly different between carotid artery atherosclerosis cases and controls.
- (3) The distribution of plasma levels of VCAM, ICAM, and E-selectin are not significantly different between incident CHD cases and carotid artery atherosclerosis cases.
- (4) The ability of plasma levels of VCAM, ICAM, and E-selectin to predict case-control status is statistically independent of the effects of established risk factors such as BMI, plasma lipids, and hypertension status.
- (5) The ability of plasma levels of VCAM, ICAM, and E-selectin to predict incident CHD case-control status is statistically independent of carotid artery wall thickness.

6. We will use the tripartite case-control design including incident CHD cases (n=313), carotid artery atherosclerosis (CAA) cases (n=553), and matched healthy controls (n=502) to determine the ability of the adhesion/inflammation molecules, VCAM, ICAM, and E-selectin, to predict the occurrence of atherosclerosis and/or the onset of CHD.

7. Data, requirements:

ARIC visit one data will be used. The dependent variable of primary interest is case/control status. The independent variables of primary interest are the levels of VCAM, ICAM, and E-selectin in plasma. The list of other predictor variables includes: age, BMI, lipids (LDL cholesterol, lipoprotein(a), HDL cholesterol, triglyceride), fasting glucose, fasting insulin, nutrient intake (keys score), hemostatic factors (APTT, factor VIII:C, fibrinogen, factor VII, antithrombin III, protein C), life style (cigarette smoking, alcohol intake), physical activity, presence of hypertension, and derived carotid artery wall thickness.