

ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #346

1. Title: Apolipoprotein E Genetic Polymorphism Predicts Incident Coronary Heart Disease

2. Writing Group: Darrell Ellsworth, Michael Hallman, Gerardo Heiss, Ed Davis, Richey Sharrett, Louis Smith, and Eric Boerwinkle

3. Timeline:

Clinical and biochemical data collection is complete. Measurement of the apo E polymorphism is ongoing.

4. Rationale:

A positive family history of heart disease is a significant risk factor for coronary heart disease (CHD) and genes are known to contribute to interindividual variation in plasma lipid, lipoprotein, and apolipoprotein levels. However, little is known about the ability of individual genes to predict disease beyond that afforded by traditional risk factors such as gender, plasma cholesterol levels, weight, and smoking.

Allelic variation at the apolipoprotein E (apo E) gene locus is common and its impact on plasma lipid transport has been extensively studied. Apo E is a structural component of circulating chylomicrons, very low density lipoproteins, and high density lipoproteins, and is a ligand for several classes of lipoprotein receptors. Human apo E is polymorphic with three common alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. Numerous studies have shown that the average effect of the $\epsilon 2$ allele is to lower total serum cholesterol and the average effect of the $\epsilon 4$ allele is to raise total cholesterol levels. Most previous studies have reported a positive association between the $\epsilon 4$ allele and clinically recognized CHD. Unexpectedly, we have previously found in the ARIC study that the $\epsilon 2$ allele is positively associated with carotid artery wall thickness in a sample which excluded subjects with diagnosed CHD. In this proposed study, we will define the role of the apo E polymorphism in predicting incident CHD in the ARIC cohort, and ask whether this role is different than that for carotid artery atherosclerosis.

5. Main Issues:

- (1) Ability of the apo E polymorphism to predict incident CHD case/control status.
- (2) Ability of the apo E polymorphism to predict incident CHD case/control status after considering the predictive ability of other (traditional) risk factors.
- (3) Comparison of the ability of the apo E polymorphism to predict incident CHD case/control status versus carotid artery disease case/control status.

6. Data Requirements:

Data analyses will be carried out under the supervision of Dr. Eric Boerwinkle in the Human Genetics Center at the University of Texas Health Science Center. Dr. Boerwinkle will consult regularly with Dr. Davis at the coordinating center throughout the analysis stages. Interpretation of the results of these statistical analyses will be shared jointly by Drs. Smith, Sharrett, and Boerwinkle.

The three groups study sample will be used for these analyses. The primary dependent variable is the incident CHD case/control status. However, the results from incident CHD status will be compared to those

obtained from the analysis of carotid artery wall thickness. Independent variables include, but are not limited to, the apo E polymorphism and the vector of traditional risk factors, such as age, BMI, plasma lipids, hypertension status, etc.