ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #349

1. Title: Association of coagulation Factors with 9-year incidence of decreased renal function in the ARIC Study.

2. Writing Group:

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Coordinating center contact to be detemined.

3. Timeline:

The data for these analyses wil be available as part of ARIC visits 4. We project that the analyses and writing will take place over in the year after the data is available.

4. Rationale:

ARIC provides an excellent opportunity to study risk factors for the early stages of the decline in renal function. Serum creatinine data from visit 1 and visit 2 will allow for a study of factors associated with prevalence and short term incidence of renal insufficiency (MSP# 223, 224, 225). The current proposed manuscript will focus on the 9-year incidence of renal dysfunction. This analysis will benefit from having longer follow-up and therefore will be have more power to study the relationships initially tested in the visit 1 & 2 data.

The main endpoint in the proposed study will be incidence of hypercreatnemia defined as in subjects with a "Normal" plasm creatanine in visit 1 (see Table 1)* who developed definite or severe hypercreatinemia by visit 4. Table 2* shows the number of prevalent cases of hypercreatinemia in visit 1 as the number of incident cases by visit 2 and the projected number by visit 4. In addition, the power implications of these numbers for analysis of continuous and categorical variables are shown. This table is limited to the non-diabetic members of the cohort since the analysis will be stratified on diabetes. This stratification will account for the potential for heterogeneity in the etiology of diabetic and non-diabetic renal disease.

Coagulation Factors: The kidney is particularly susceptible to the action of platelets and clotting because of its large endothelial capillary surface. Intraglomerular coagulation has been implicated as a possible contributor to the progression of glomerular scleroris. Intraglomerular thrombosis may occur as the result of the activation of the coagulation cascade due to complement activation; platelet activation; or local procoagulant activity. These suggested mechanisms are supoorted by the observation that heparin or warfarin reduced glomerulosclerosis in rats subjected to sutotal nephrectomy. Platelets can release substances that affect glomerular structure and function. Platelet factor 4, which is highly cationic, binds avidly to the glomerular polyanions and could induce sustained proteinuria. Platelet-derived growth factor, when consistently present, can induce the proliferation of mesangial cells. In addition, intravascular coagulation, thrombotic thromocytopenic prupura, and hemolytic-uremic syndrome have all been associated with platelet aggregation as well as renal damage. Because of these observations it would be worthwhile to test whether abnormalities of the coagulation factors exist early in the progression of renal disease. We realize that the platelet hypothesis can't be effectively addressed since the platelet activation measures are only available on a small subsample of atherosclerosis cases and controls. In addition, careful attention will

be paid to the possibility that some hemostatic abnormalities may be the consequence of rather than the precursors for renal disease.

Potential confounding by age, gender, race & socioeconomic factors, blood pressure, hypertension, diabetes, and lipids will be controlled for. All analyses will be done stratified on diabetes, gender, hypertension, and race to avoid overlooking potential interactions.

Subjects who have taken medications which alter blood coagulation will be excluded from these analyses.

5. Main Hypothesis/Issues to be Addressed:

Abnormalities of the coagulation factors exist early in the progression of renal disease.

6. Data Requirements:

Data analysis will be performeed by Dr. J. Coresh at Johns Hopkins School of Hygiene & Public Health in collaboration with Dr. J. Nieto.

Variables needed: plasma creatinine and time of collection, coagulation factors, center, age, gender, race, blood pressure, anthropometric data, dietary data, lipids, lipoproteins and apolipoproteins, medical history data (diabetes), risk factor questions (smoking, alcohol consumption).

Visit 4 Variables (not yet available): plasma creatinine & anthropometric data.

*Note: For a copy of the manuscript with the tables, please contact the ARIC Student Assistant at Collaborative Studies Coordinating Center, Department of Biostatistics, UNC-Chapel Hill. Contact by phone: (919) 962-3268 or fax: (919) 962-3265.