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

2. Writing Group:
Coordinating center contact to be determined.

3. Timeline:
The data for these analyses are already available as part of ARIC visits 1 & 2. We project that the decline in renal function using the visit 1 and 2 plasma creatinine measures adjusted for lean body mass (more detailed rationale in manuscript proposal #223).

The proposed study will be divided into two analyses. A cross-sectional analysis of risk factors for elevated creatinine at baseline and a prospective analysis of risk factors for a rise in plasma creatinine during the 3 years of follow-up. In each analysis an estimated creatinine clearance will be constructed after accounting for the estimated lean body mass. This estimated creatinine clearance will be used as the dependent variable in the regression analysis. Each analysis will also be done using logistic regression with binary definition (yes/no) of decreased renal function (elevated creatinine) or declining renal function (rise in serum creatinine larger than the expected laboratory plus physiologic variation). These parallel analytic approaches will ensure that results are robust to the specific statistical model used.

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 sclerosis. 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 supported by the observation that heparin or warfarin reduced glomerulosclerosis in rats subjected to subtotal 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 thrombocytopenic purpura, and hemolytic-uremic syndrome have all been associated with platelet aggregation as well as renal damage. Because of these observations it would be worth while 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 e 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 take 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 performed by Dr. J. Coresh at Johns Hopkins School of Hygiene & Public Health in collaboration with Drs. 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).