ARIC MANUSCRIPT PROPOSAL FORM

Manuscript #504

1. Title: Does a low ankle-brachial index predict the development of renal insufficiency?

2. Working group:
Abhijit V. Kshirsagar, Herman A. Tyroler, Susan L. Hogan, Ronald J. Falk, Romulo E. Colindres, Frederick L. Brancati, Joseph Coresh, Daniel Jones.

3. Timeline:
Data analysis to begin August 1997 and continue through Fall 1997. Writing will begin in Fall 1997 and end by December of the same calendar year.

4. Rationale:
Atherosclerosis is a systemic disease. Hyperlipidemia predisposes to cholesterol deposition in arterial walls which leads to progressive narrowing of vessels throughout the body. This process can lead to tissue ischemia, and thus to the clinically recognized entities of myocardial infarction, peripheral vascular disease (PVD), and stroke. Researchers have long believed that atherosclerosis should also affect the kidney and thereby contribute to renal insufficiency and end-stage renal disease (ESRD). Now, mounting evidence suggests that lipids may contribute to renal disease. Noninvasive measures of atherosclerosis in non-renal organ systems could help delineate the role of lipids in renal disease.

Atherosclerosis of the renal vessels is a common finding of middle-aged adults. Usually, there is radiographic evidence of slow, progressive stenosis (Wollenweber 1968, Tollefson 1991). Most authorities agree that vessel narrowing contributes to the development of, or worsening of hypertension. It is controversial whether the stenosis leads to progressive loss of renal function, an entity referred to as ischemic nephropathy. Studies implicating atherosclerotic narrowing as a cause of renal insufficiency have been small prospective cohorts or retrospective case series (Dean 1981, Hansen 1993).
On a cellular level, there appears to be a relationship between serum cholesterol and glomerular damage in the rat model (Van Goor 1991). Furthermore, lowering blood cholesterol levels slows the progression of renal disease in rats (Kasiske 1987). Finally, in one human autopsy study, atherosclerotic renal artery disease predicts the occurrence of a particular glomerular kidney lesion (Kasiske 1988).

Large prospective cohort studies seem to validate the results seen in animal and small human studies. In one study, serum cholesterol was shown to be a strong risk factor for the development of ESRD in a cohort of over 330,000 men followed for 16 years (Klag 1995). From a subset of the Helsirdci Heart Study cohort, another study demonstrated that low HDL level accelerates the decline in renal function in dyslipidemic men with

hypertension (Manttari 1995). Finally, a secondary analysis of a randomized controlled trial showed that treatment with a lipid-lowering medication improves renal function compared to treatment with placebo in a cohort of hypercholesterolemic men (Hogan 1996).

As a systemic disease, atherosclerosis often occurs simultaneously in two or more vascular beds (Friedman l973, Choudhri 1990, Harding 1993). Individuals with clinical evidence of atherosclerosis in one organ system are at increased risk for clinical evidence of atherosclerosis in another organ system (McKenna 1991, Criqui 1992, Webb 1993).

Therefore, measures of atherosclerosis in a non-renal organ system may be predictive of renal insufficiency, and would help screen individuals at risk. Possible measures include the ankle-brachial index (ABI) and carotid artery ultrasound; the focus of this study will be ABI for the reasons outlined in the design section.

5. Main Hypothesis:
Low ABI, a measure of atherosclerosis, increases the risk of developing renal insufficiency as compared to normal ABI.

6. Design:

The Atherosclerosis Risk in Communities (ARIC) study provides a cohort of 15,800 men and women between 45 and 64 years followed in four US communities (The ARIC Investigators 1989). Two important noninvasive measures of atherosclerosis are recorded for all individuals at visit 1: carotid artery ultrasound, and ankle and arm blood pressure (used to generate ABI). Serum creatinine, a commonly used measure of renal function, is also recorded at visits l, 2, and 4 for all participants. Currently, ARIC is in the middle of data collection for visit 4; as such, data on 3665 individuals, 1/3 of the original cohort, is available. Of these 3665 individuals, only 927 have carotid ultrasound scans at visit 1; 3536 individuals have ankle brachial measurements. Because of these limitations, the proposed analysis will focus on ABI alone.

The main exposure variable will be ABI at visit 1. It will be analyzed as both a continuous and categorical variable. Use as a continuous exposure variable will be advantageous for statistical power. Use as a multi-level exposure will help establish a dose-response effect. Clinically accepted values of ABI, normal 0.85-1.5, low 0.84-0.55, and very low < 0.54 categories (Bernstein 1982, Moneta 1994), may not be suited for the ARIC cohort. These cutpoints have been validated in groups of individuals with existing peripheral vascular disease, and not in the general population. Therefore, it will be necessary to use cutpoints developed in an another study: < 0.8, 2 0 8 to < 0.9, > 0.9 to < 1.0, and 21.0 to < 1.5 (Newman 1993). Individuals with ABI values > 1.5 will not be used in the analysis; the high ABI indicates increased rigidity of vessels, usually due to calcification, and does not confer the expected protection from atherosclerotic ischemia
The main outcome variable of interest will be change in renal function. The change will be estimated by the slope of the reciprocal serum creatinine (Mitch 1976). The slope will

be obtained from the serum creatinine measures at visit 1, 2, and 4. Of note, the technique of measuring serum creatinine in the ARIC cohort changed during follow-up; an adjustment factor has been developed to account for this change, and can be used in the proposed analysis.

The proposed study would consist of two phases. The first phase will be a cross sectional analysis of the association of ABI with renal function, as assessed by serum creatinine level, at visit 1. The purpose of the cross-sectional study is for descriptive analysis of baseline characteristics. The second phase will take advantage of the 9 years of follow-up. Regression modeling will be used to generate the slope of reciprocal serum creatinine for each individual. The integrated slope of all participants will indicate the overall change in renal function per unit change in ABI over time. The mean slopes of the three exposure categories will be compared by analysis of variance. The potential for obtaining well-accepted clinical outcomes, such as development of ESRD or doubling of serum creatinine, will be low; nevertheless, it will be attempted as nephrologists have a particular interest in them. The use of a continuous outcome such as slope of serum creatinine will increase the power to the study to detect a difference between exposure groups. Important covariates of the main exposure and outcome relationship include: race, smoking status, obesity, hypertension, diabetes mellitus, socioeconomic status, and age. These covariates will be a priori assessed in the model for confounding, effect modification, or intervening variable status in multivariate models.

7. Data Requirements:

The data analysis will be performed by Abhijit Kshirsagar at UNC-CH as part of his Master's Thesis. Information on the main exposure variable and covariates will be needed from visit 1. Information on the outcome, serum creatinine will be needed from visits 1, 2, and 4.

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