The ARIC manuscript proposal #172 published only one-half of the original proposal and the writing group does not wish to write a manuscript on the remaining topic; thus, there is no overlap.

ARIC Manuscript Proposal #758

PC Reviewed: 01/16/01  Status: A  Priority: 
SC Reviewed: 01/30/01  Status: A  Priority: ____

1. a. Full Title: Serum creatinine and risk of CVD: Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Serum creatinine and CVD

2. Writing Group (list individual with lead responsibility first):

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   First draft: May 2001

4. Rationale: A number of reports indicate that elevated serum creatinine may be an independent predictor of all cause and of cardiovascular disease mortality (1-7). These studies, however, have focused on specific groups such as hypertensive individuals (1), elderly (2), patients with recent stroke (3), survivors of myocardial infarction (4), patients undergoing carotid end arterectomy (5), patients undergoing elective cardiac valve surgery (6) and patients with left ventricular systolic dysfunction (7). In the Hypertension Detection and Follow up Program (HDFP) study, for example, the 8 year mortality risk increased progressively with increasing concentration of serum creatinine from low levels (1). The risk of cardiovascular disease was two folds higher in those who had serum creatinine at or above the 97th percentile, relative to those with creatinine below this level (1).

   Recent reports addressing the relationship between serum creatinine concentration and risk of cardiovascular disease have also become available (8). The British Regional Heart Study is a large perspective study of cardiovascular disease comprising 7735 men aged 40-59 years selected from the age-sex registers of one group general practice in each of the 24 towns in England, Wales and Scotland (8). All men were followed up for all cause mortality and incident cardiovascular disease (fatal and non-fatal). After an average follow up period of 15 years, it was
The ARIC manuscript proposal #172 published only one-half of the original proposal and the writing group does not wish to write a manuscript on the remaining topic; thus, there is no overlap. Noted, that stroke incidence was significantly increased at levels of serum creatinine that were above the 90 percentile relative to the rest of distribution of serum creatinine even after adjustment for a wide range of cardiovascular risk factors. Major ischemic heart disease events were also significantly increased at or above the 97.5 percentile of serum creatinine relative to the rest of the distribution. It is of note, however, that risk was attenuated after adjustment for other risk factors. More recently, serum creatinine was measured in over 6,000 adults participants in the Framingham Heart Study. Mild renal insufficiency, defined as serum creatinine between 1.5 – 3.0 mg/dL was prevalent at baseline in roughly 8% of male and female participants (9). In women, mild renal insufficiency was not associated with increased risk of cardiovascular disease incidence or all-cause mortality. In men, mild renal insufficiency showed no significant association with CVD incidence, either, but it was associated positively with all-cause mortality in age-adjusted and multivariate analysis. The evidence linking serum creatinine concentration to cardiovascular events is not limited to the observational reports cited above. Data from over 24,000 hypertensive participants who constituted the control groups from 8 controlled trials (HDFP, MRFIT, SHEP, among others) clearly shows that a lower level of glomerular filtration rate was associated with increased risk of fatal strokes, fatal coronary events and cardiovascular mortality (10). The strength of this association was similar to that of blood pressure and total cholesterol (10).

Death from cardiovascular disease continues to be a major problem in patients with end stage renal disease. It accounts for 50% of all deaths in patients on dialysis and renal transplants (11). This excess risk is due in part to renal patients’ older age, hypertension, diabetes, hyperlipidemia and physical inactivity (12-14). Other factors including elevated serum homocysteine level and higher prevalence of coronary artery calcifications even in younger patients also have received attention lately (15-16) Whether early stages of renal insufficiency predisposes to cardiovascular events in the general population is not well established and will be the focus of this proposal. The reason why the relationship of serum creatinine to CVD differs among these studies is not entirely clear. Different populations may behave differently. Of importance, is the fact that some studies used serum creatinine and others used the Cockroft-Gault equation for estimation of glomerular filtration rate. This difference in measurement method maybe, at least partially, responsible for some of the different conclusions from these studies. 5. Main Hypothesis/Study Questions: The aim of this proposal is to address whether serum creatinine at baseline can predict cardiovascular events in the Atherosclerosis Risk In Communities study (ARIC). Also GFR will be estimated by applying the Cockroft-Gault equation and a newly introduced formula (17) so the association, if any, will not be dependent on how kidney function is assessed.

6. Data (variables, time window, source, inclusions/exclusions):
   1. Exclusion: Prevalent CVD.
   2. Independent variable: Serum creatinine @ visit 1 and 2.
   3. Dependent variable: CHD and stroke incidence through 1997
   4. Covariates: age, race, ARIC field center, baseline smoking status and amount, systolic and diastolic blood pressures, use of antihypertensives, LDL cholesterol, total cholesterol, HDL cholesterol, BMI, diabetes, fibrinogen, von Willebrand factor,waist/hip ratio, baseline serum
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albumin and white blood cells count, LVH by ECG.

5. Main analysis: Cox proportional hazard regression model will be used to calculate the multivariable adjusted relative risk of incident CHD in relation to categorical (sex and race specific quintiles) or continuous serum creatinine concentration.

7. a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes _X_ No

b. If Yes, is the author aware that the file ICTDER01 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ___ Yes ___ No

(This file ICTDER01 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8. a. Will the DNA data be used in this manuscript? ___ Yes _X_ No

b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER01 must be used to exclude those with value RES_DNA = “No use/storage DNA”? ___ Yes ___ No

References


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