ARIC Manuscript Proposal # 1118

PC Reviewed: _11/22/05	**Status: __A__**	**Priority: __2_**
SC Reviewed: __11/23/05	**Status: __A__**	**Priority: __2_**

1.a. Full Title: Kidney Function as a Risk Factor for Heart Failure Hospitalization: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Kidney Function Heart Failure

2. Writing Group:

Writing group members: Anna Kottgen, Stuart Russell, Wayne Rosamond, Lloyd Chambless, Josef Coresh, Others welcome.

Invited: Patricia Chang

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __X___ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Analysis to start immediately, first draft by May 2006

4. Rationale:

Heart failure has a prevalence of almost 5 million among the U.S. population and a yearly incidence rate of more than 500,000. Data from the Framingham Study suggests that the lifetime risk of heart failure is 1 out of 5 for both genders (1). A growing appreciation that a kidney dysfunction is common among older adults, approximately 8 million have moderately or severely reduced kidney function (2), and the interplay between kidney disease and heart failure make examination of this question of interest. The relationship is complex with kidney disease aggravating heart failure and causing poor outcomes as well as decreased cardiac output in heart failure causing renal hypoperfusion. It is also clear that lower kidney function as marked by either an elevated serum creatinine or a rise in serum creatinine during a heart failure hospitalization is a very strong predictor of outcomes among patients with heart failure(3). Finally, experimental animal models show that nephrectomy worsens cardiac outcomes(4).
Recently, there has been evidence from the Cardiovascular Health Study and other studies suggesting that reduced kidney function might be a risk factor for incident heart failure (5-7). Lower kidney function is an independent risk factor for coronary heart disease, especially in patients with cardiovascular disease, in the ARIC Study and elsewhere (8-11). However, studies of the relationship between kidney function and heart failure incidence are very limited and the question has not been examined in ARIC.

A better understanding of the relationship between decreased kidney function and risk of heart failure will help inform risk stratification and the management of patients at risk. In addition, examination of changes in serum creatinine and estimated GFR between ARIC visits which precede and follow the first heart failure hospitalization will allow for a characterization of the time course relating change in kidney function to the onset of heart failure.

The ARIC Study as a large community based study provides an excellent opportunity to investigate a possible relationship between reduced kidney function and heart failure, two highly prevalent conditions among the adult US population.

5. Main Hypothesis/Study Questions:

1. Reduced kidney function will predict a higher incidence of hospitalized heart failure.

2. The relationship above will be independent of other risk factors for heart failure including existing coronary heart disease, demographics, and coronary heart disease risk factors.

3. Estimated kidney function will show a greater deterioration among participants who develop heart failure. The primary contrast will be the change in kidney function between consecutive visits where kidney function was estimated comparing participants who had heart failure during the interval to participants who did not.

6. Data (variables, time window, source, inclusions/exclusions):

We will strive to keep the definition of the patient population and outcome of hospitalized heart failure consistent with manuscript proposal 927 where 1,382 cases of hospitalized heart failure were found. Kidney function will be estimated from serum creatinine using the simplified MDRD equation which incorporates the participant's age, sex and race(12,13).

Patients with prevalent heart failure at visit 1 will be excluded. The primary analysis will include individuals with a history of coronary heart disease at baseline. However, given the critical importance of myocardial infarction in the development of heart failure, analyses will also be stratified by history of CHD at baseline (absent vs. present). Patients at all levels of estimated kidney function will be included but analyses will also be stratified by presence of decreased kidney function at baseline (GFR < 60 ml/min/1.73m^2).

Incident hospitalized heart failure will be assessed based on hospitalization records (hospital discharge diagnosis during follow-up period). Data to be used include hospital discharge diagnosis from cohort eligibility (CEL) forms. Pre-existing cases of heart failure will be excluded based on self reported use of heart failure medications at visit 1. Heart failure incidence rates will be calculated using person time methods and modeled using a Cox Proportional Hazards model.

Kidney function will be estimated using the MDRD equation incorporating data of serum creatinine concentration, age, gender, and race from visit 1, 2, and 4 and measured in ml/min/1.73m^2. Kidney function will be categorized using national guidelines as normal (90+), mildly decreased (60-89), and moderately or severely decreased (15-59). Kidney function will also be modeled continuously and models will explore for deviations from linearity using splines.

Variables that might be potential confounders of an association of kidney function and heart failure will also be taken from visit 1. These include participant demographics (age, sex, and race-center), pre-existing disease (history of coronary heart disease and stroke, left ventricular hypertrophy), coronary heart disease risk factors (diabetes, blood pressure level and medications, cholesterol level and medications, smoking) and education. Use of cardiac medications before and after the onset of heart failure will be tabulated but is not the primary focus of this paper.

Change in kidney function between consecutive visits will be explored by examining the full distribution in the difference between estimated kidney function in visit 2 minus visit 1 and visit 4 minus visit 2. The distribution will be plotted using Epanechnikov kernel density smoothing and compare between individuals who did and did not develop heart failure between visits. Since kidney function estimates are more precise at the lower range we will also calculate the percent change in kidney function as well as conduct a categorical analysis (>30% decline in kidney function and incidence of GFR<60). To the extent changes in kidney function are correlated with baseline kidney function (very weak correlation in previous papers) we will need to take into account baseline kidney function and measurement error in estimating kidney function. For participants who

develop their first heart failure hospitalization between visit 2 and visit 4 it will be possible to compare the decline in kidney function prior to heart failure (visit 1 to visit 2) to the decline from before hospitalization to after hospitalization (visit 2 to visit 4). Percentage rates of decline per year will help in making comparisons but the unequal interval and variable timing to hospitalization is a recognized limitation.

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 ICTDER02 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 ICTDER02 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

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
____ Yes ____ No

9.The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

_X_____ Yes _____ No

Three proposals use HF as the primary outcome but neither looks at kidney function:
MP#927 – Heart Failure Incidence and Survival: 13 Year Follow up of the ARIC Cohort
MP#922 - Alcohol consumption and risk of congestive heart failure
MP#855 - Retinal Microvascular Abnormalities and Congestive Heart Failure

Other proposals with some heart failure focus include:
MP#617 - Evaluation of International Classification of Diseases Codes to Identify Hospitalized Heart Attack Patients with Acute Congestive Heart Failure: The Atherosclerosis Risk in Communities Study
MP#328 - Analysis of the relationship between potassium and incidence of cardiovascular diseases
MP#1049 - Prevalence and Prognosis of Asymptomatic Left Ventricular Systolic Dysfunction (ALVSD) in African Americans: the ARIC study

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Manuscript proposal #927 to investigate heart failure incidence and survival at 13 year follow up. We have contacted Drs. Chang, Folsom and Rosamond

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X__ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primiarly based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

References:

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11. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial. Mann,J.F.; Gerstein,H.C.; Pogue,J.; Bosch,J.; Yusuf,S. Ann.Intern.Med., 2001, 134, 8, 629-636

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