ARIC Manuscript Proposal # 1244

1.a. Full Title: Kidney Dysfunction and Sudden Cardiac Death among Participants in the ARIC study

b. Abbreviated Title (Length 26 characters): Kidney Dysfunction and Sudden Cardiac Death

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___x (I confirm that all coauthors have provided their approval - RD)___ [please confirm with your initials electronically or in writing]

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3. Timeline:
   Analysis to be completed in 2 months – May 2007
   Manuscript draft – June 2007
4. **Rationale:**

Sudden cardiac (SCD) is an important clinical and public health problem: over 450,000 Americans died in 1998 from SCD, which is usually defined as death with minimal premonitory symptoms, attributed to cardiovascular disease.\(^1\) The presence and severity of underlying heart disease including coronary heart disease and chronic heart failure is the most predictive risk factor for the future occurrence of SCD.\(^2,4\) Another population at high risk for SCD are persons with ESRD.\(^5\) According to the United States Renal Data System (USRDS) approximately 22% of all deaths are sudden and the incidence increases with age: 20 per 1000 patient years for ages 20-44, 37 for ages 45-64 and 70 for ages 65 and older.\(^5,6\) Unfortunately, no other risk factors have been established as an independent predictor for SCD among patients without advanced cardiovascular or kidney disease or an inheritable disorder predisposing one to arrhythmias.

Despite the high risk for SCD in patients with ESRD, few studies have evaluated the association between less severe reductions in kidney function and SCD risk. Two recent studies found that impaired kidney function was associated with an increased risk for SCD among subjects with advanced heart failure who were enrolled in clinical trials involving ICDs.\(^7,8\) In this setting, however, it might be difficult to discern whether CKD was merely a marker of heart failure severity or an independent predictor of SCD risk.

References:


5. **Main Hypothesis/Study Questions:**

We hypothesize that chronic kidney disease (CKD) is associated with an increased incidence of SCD independent of other comorbidities. We will evaluate the association of impaired kidney function, as measured by elevated creatinine and reduced estimated glomerular filtration rate (GFR) with sudden cardiac death.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

We propose to study the association between impaired kidney function and sudden cardiac death among participants in the Atherosclerosis Risk in Communities study.

A. Study population

All ARIC individuals with measured serum creatinine, age, sex and race allowing for estimation of GFR.

Outcome: Sudden cardiac death events adjudicated as part of the Reynolds ancillary study.

B. Key Predictor Variables

Estimated GFR: GFR will be estimated using the abbreviated MDRD study equation. Calculated values will be based on creatinine measurements from visit 1. Estimated GFR will be categorized at <60, 60-89, and 90+ ml/min/1.73 m². These cutpoints follow clinical guidelines and include approximately 3%, 49% and 48% of ARIC participants. In addition, we will explore the association continuously. In particular this will allow us to explore the relationship below 60 ml/min/1.73m² as well as above 120 ml/min/1.73m². There is concern that risk will rise in the latter category since it reflects muscle wasting and not merely high kidney function.

C. Outcome Variable: sudden cardiac death

To identify cases of sudden cardiac death (SCD) in the ARIC study, all cases of fatal CHD (definite fatal MI, definite fatal CHD, or possible fatal CHD, in- and out-of-hospital deaths) were reviewed and adjudicated by a committee of physicians, funded through the Johns Hopkins University Donald W. Reynolds Cardiovascular Research Center. SCD was defined as a sudden
pulseless condition from a cardiac origin in a previously stable individual. After review of data available from death certificates, informant interviews, physician questionnaires, coroner reports, and hospital discharge summaries, the reviewers completed the Reynolds sudden death event classification form. From this form a classification of definite sudden arrhythmic death, possible sudden arrhythmic death, not sudden arrhythmic death, or unclassifiable was obtained. Cases were identified as either in or out of hospital deaths.

The cutoff dates for adjudication for SCD was December 31, 2002. Fatal CHD deaths occurring after that date will be censored since they were not evaluated for SCD.

In addition, we will compare the risk of SCD with the risk of “fatal but not sudden” coronary heart disease events. We hypothesize that the adjusted relative risk will be higher for SCD than for fatal but not sudden CHD. We further hypothesize that the risk will be lower for the combined end-point of non-fatal and fatal but non-sudden CHD than for SCD.

D. Confounding Variables
Demographics – age, sex, race
Lifestyle – smoking, alcohol use, BMI, family history of CHD or sudden death
Comorbid conditions: diabetes, hypertension, CHF, MI, atrial fibrillation
Cardiac Parameters: JT/QT interval, interventricular conduction delay, LVH, HR, PR interval, QRS axis, presence of extrasystoles (esp PVCs), presence of AV block
Lab results: Serum magnesium, potassium, and calcium from the visit 1 chemistry panel.
Medications: use of ACE inhibitors, ARBs, beta blockers, calcium channel blockers, digoxin, diuretics, amiodarone, aspirin, statins will be considered as time dependent covariates.

Statistical Analysis
The primary analysis will use Cox proportional hazards models to estimate the association between kidney dysfunction and risk of sudden cardiac death (SCD). We will then adjust for the covariates listed above. The primary analysis will be categorical with the excess risk expected in the eGFR<60 group. The relative hazard of SCD will then be compared qualitatively to the relative hazard of fatal CHD which is not defined as SCD (non-sudden fatal CHD) and combined CHD incidence and mortality excluding SCD. Since these events are mutually exclusive we anticipate being able to test whether the relative risks are statistically different. This will likely require a survival analysis which allows for two outcomes. In addition to evaluating this technique we will consult with the coordinating center about using bootstrap estimation to address the comparison. We recognize that the power to detect these differences may be limited but a presentation of the differences is of substantial interest. The ARIC study is large and contains a substantial number of SCD events.

In addition, we will evaluate for potential confounders from other clinical characteristics, such as the presence or absence of baseline coronary heart disease or congestive heart failure in the incidence of sudden cardiac death. We will also adjust for coronary heart disease and congestive heart failure as time dependent covariates to determine whether incident cardiovascular disease affects the association between impaired kidney function and SCD.
7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes ___ 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 ___ 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

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)?

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

11.b. If yes, is the proposal ____x_ A. primarily the result of an ancillary study (list number* 2004.03 ________) ____ B. primarily 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.