ARIC Manuscript Proposal # 1627

PC Reviewed: 4/13/10	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Chronic kidney disease and the incidence of atrial fibrillation: the ARIC Study

b. Abbreviated Title (Length 26 characters):
CKD and AF in ARIC

2. Writing Group:
Alvaro Alonso, Brad Astor, Lin Chen, Elsayed Soliman, Laura Loehr, Sunil Agarwal, Kunihiro Matsushita, Josef Coresh

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

First author: Alvaro Alonso
Address: 1300 S 2nd St, Suite 300
University of Minnesota
Minneapolis, MN 55454
Phone: 612 626 8597 Fax: 612 624 0315
E-mail: alonso@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Josef Coresh
Address: 2024 E Monument St, Suite 2-600
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD 21287
Phone: 410 955 0495 Fax: 410 955 0476
E-mail: coresh@jhu.edu

3. Timeline:
Data analysis will start upon manuscript approval. We expect to submit preliminary results in abstract form to the American Heart Association Scientific Sessions 2010 (deadline June 2nd). We would expect to have a final draft of the manuscript by the abstract presentation at the Scientific Sessions.

4. Rationale:

Individuals with chronic kidney disease (CKD) are at higher risk of coronary heart disease, heart failure, peripheral artery disease, or venous thromboembolism, independently of other risk factors.[1-4] CKD might be also a risk factor of AF, a common cardiac arrhythmia associated with increased morbidity and mortality.[5-7] CKD leads to hypertension, left ventricular hypertrophy, inflammation, and increases the risk of heart failure and coronary artery disease.[8] All these factors are potentially associated with a higher risk of AF.[7] In addition, CKD can lead to alterations in the renin-angiotensin-aldosterone (RAA) system which, as recent evidence suggests, might increase atrial fibrosis and increase the risk of AF.[9] Finally, CKD causes sympathetic activation, a potential trigger of AF.[10, 11]

Existing evidence suggests that patients with end-stage renal disease in dialysis are more likely to develop AF.[12] Similarly, cross-sectional studies have found a higher prevalence of AF in individuals with non-dialysis-dependent CKD.[13, 14] Only two prospective studies have evaluated the association of kidney function with AF incidence in the general population, providing conflicting results. The first one, conducted in the context of the Niigata Preventive Medicine Study (Niiagata, Japan), found that lower estimated glomerular filtration rate (eGFR), using the MDRD study equation for Japanese population, was associated with an increased risk of AF (multivariable HR 1.4, 95% CI 1.1-1.7 comparing those with eGFR<60 mL/min per 1.73 m^2 to those with eGFR≥60 mL/min per 1.73 m^2).[15] More recently, an analysis of 2673 participants of the Framingham Offspring Study examined the association of urinary albumin-to-creatinine ratio (ACR) with AF incidence. The multivariable HR (95% CI) of AF associated with a 1-standard deviation increase in log-transformed ACR was 1.1 (0.9-1.3).[16] This study only included 166 AF events. In summary, though previous evidence strongly supports a higher risk of AF among individuals with chronic kidney disease, this association has been seldom studied in prospective populations. Moreover, previous studies have not explored whether this association is potentially different by race, gender or risk factor profile.

Therefore, we propose to examine the association of kidney function and kidney disease, evaluated with serum creatinine, cystatin C, and albumin-creatinine ratio, with the incidence of AF in the ARIC study, independently of established cardiovascular risk factors. We will also evaluate whether this association is mediated through an increased risk of heart disease.

5. Main Hypothesis/Study Questions:

We hypothesize that individuals with worse kidney function will have an increased risk of AF, independently of other cardiovascular risk factors, and that the association will be non-linear for estimated glomerular filtration rate (eGFR) and log-linear for urinary albumin-creatinine ratio.

In addition, we hypothesize, that this association will be present in white and black individuals, and also in individuals without history of cardiovascular disease (CVD).

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).

Study design

We will conduct a follow-up analysis of the ARIC cohort, using visit 4 as baseline.

Inclusion/exclusion criteria

Whites and African-Americans who attended visit 4, were free of prevalent AF (defined by ECG at visits 1-4 or AF hospitalization before visit 4), and have measurements of kidney function will be included. Individuals with severely decreased kidney function (eGFR<15 ml/min/1.73 m^2) will be excluded from the analysis.

Variables of interest

Renal function

The main independent variable, kidney function, will be defined in three ways:

- eGFR based on recalibrated creatinine levels at visit 4. eGFRcreat will be estimated using the CKD-EPI equation.[17]
- eGFRcys calculated using cystatin C and the CKD-EPI equation.[18]
- Albumin-creatinine ratio (ACR).

Both eGFR and ACR will be categorized using clinical cutoff points (<60 ml/min/1.73 m^2, 60-90, and >90 for eGFR; normoalbuminaria: <30 mg/g, microalbuminuria: 30-300 mg/g, macroalbuminuria >300 mg/g for ACR) and will be also considered as continuous variables.

Atrial fibrillation incidence

AF in ARIC is ascertained from three different sources: (1) 12-lead ECGs done in study exams, (2) ICD-9 codes from hospitalization discharges (427.31, 427.32), and (3) death certificates including AF as any cause of death (427.3 or I48).[19] More than 90% of AF cases have been identified from hospital discharges. For the present proposal, we will consider incident AF as any first occurrence of AF between visit 4 and December 31, 2007.

Other variables

For the analysis, we will include covariate information obtained in visit 4, including sociodemographic factors (age, gender, race, education, income), anthropometric measures (height, body mass index), cardiovascular risk factors (diabetes, systolic blood pressure, use of antihypertensive medication, smoking, alcohol intake, C-reactive protein [hsCRP]), and history of heart failure, coronary artery disease, or stroke. Additionally, we will use incident CVD occurring during the follow-up in some analyses.

Statistical analysis

We will use Cox proportional hazards models to estimate the association of kidney function with the new-onset of AF. Separate analyses will be run for each measure of kidney function. We will use restricted cubic splines to explore the shape of the association between kidney function measures and risk of AF. In the survival analysis, we will categorize them based on the spline analysis and usual clinical categories.

For each measure of kidney function, we will run a series of nested models:

- Model 1: age, gender, race-adjusted
- Model 2: Model 1 + adjustment for study site, education, income, and height
- Model 3: Model 2 + diabetes, systolic blood pressure, use of antihypertensive meds (ACE inhibitors and ARBs, other antihypertensive medications), smoking, alcohol intake, body mass index, hsCRP
- Model 4: Model 3 + history of heart failure, CAD, and stroke
- Model 5: Model 4 + incidence of heart failure, CAD, and stroke as time-dependent covariates

We will study effect modification by age, gender, race, hypertension, and history of CVD.

In sensitivity analysis, we will exclude AF cases identified in the first 2 years after exam 4 (to avoid reverse causation).

Power calculations

After applying exclusion criteria, 11,111 ARIC participants will be eligible. Of these, 9.4% have eGFRcreat<60 ml/min/1.73 m^2, 61.3% 60-90 ml/min/1.73 m^2, and 29.3% >90 ml/min/1.73 m^2. Prevalence of microalbuminuria and macroalbuminuria are 6.3% and 1.6% respectively. During an average 7.9 years of follow-up, we have identified 584 cases of AF among eligible participants (through 2005). Assuming a two-tailed alpha error of 0.05, we will have 90% statistical power to detect a hazard ratio of 1.5 or larger comparing those with eGFR<60 vs. >90, and a hazard ratio of 1.3 or larger comparing eGFR 60-90 vs. >90. Similarly, we expect to have 90% statistical power to detect a hazard ratio of 1.5 or larger comparing those with ACR>30 mg/g to those with ACR≤30 mg/g. Statistical power will be larger to detect linear trends.

Strengths and limitations

The main strengths of this study include: the assessment of kidney function using different measures, the large sample size, with an adequate number of AF cases, and the biracial composition of the sample. Our proposal, however, has two important limitations. First, the ascertainment of AF is based mostly on hospital discharges. Even though we have shown previously an adequate validity of hospital discharge codes for the ascertainment of AF,[19] we will most likely miss cases of AF diagnosed and treated in outpatient settings. Second, we will not have updated information on covariates and kidney function during the follow-up, which could lead to misclassification of the exposure.

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 ICTDER03 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 ICTDER03 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 ICTDER03 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)?
No previous proposal in ARIC focus specifically on the association of kidney function and atrial fibrillation.

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* 2002.02, 2006.16, 2008.12**)**
___ 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.

References

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