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:
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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]**

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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

1.   Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J.* 2006;151:492-500.

2.   Kottgen A, Russell SD, Loehr LR, et al. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol.* 2007;18:1307-1315.

3.   Wattanakit K, Folsom AR, Selvin E, Coresh J, Hirsch AT, Weatherley BD. Kidney function and risk of peripheral arterial disease: results from the Atherosclerosis Risk in Communities (ARIC) Study. *J Am Soc Nephrol.* 2007;18:629-636.

4.   Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol.* 2008;19:135-140.

5.   Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults. National implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA.* 2001;285:2370-2375.

6.   Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation.* 1998;98:946-952.

7.   Benjamin EJ, Chen P-S, Bild DE, et al. Prevention of atrial fibrillation: report from an NHLBI workshop. *Circulation.* 2009;119:606-618.

8.   Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation.* 2003;108:2154-2169.

9.   Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence. *Eur Heart J.* 2006;27:512-518.

10. Schlaich MP, Socratous F, Hennebry S, et al. Sympathetic activation in chronic renal failure. *J Am Soc Nephrol.* 2009;20:933-939.

11. Chen P-S, Tan AY. Autonomic nerve activity and atrial fibrillation. *Heart Rhythm.* 2007;4:S61-S64.

12. Korantzopoulos PG, Goudevenos JA. Atrial fibrillation in end-stage renal disease: an emerging problem. *Kidney Int.* 2009;76:247-249.

13. Iguchi Y, Kimura K, Kobayashi K, et al. Relation of atrial fibrillation to glomerular filtration rate. *Am J Cardiol.* 2008;102:1056-1059.

14. McManus DD, Corteville DCM, Shlipak MG, Whooley MA, Ix JH. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). *Am J Cardiol.* 2009;104:1551-1555.

15. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa Y. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: The Niigata preventive medicine study. *Am Heart J.* 2009;158:629-636.

16. Schnabel RB, Larson MG, Yamamoto JF, et al. Relations of biomarkers of distinct pathophysiological pathways and atrial fibrillation incidence in the community. *Circulation.* 2010;121:200-207.

17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612.

18.   Stevens LA, Coresh J, Schmid CH, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis.* 2008;51:395-406.
19.   Alonso A, Agarwal SK, Soliman EZ, et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* 2009;158:111-117.