Background—Chronic kidney disease is associated with the incidence of cardiovascular disease. Chronic kidney disease may also increase the risk of atrial fibrillation (AF), but existing studies have reported inconsistent results.

Methods and Results—We estimated cystatin C–based glomerular filtration rate (eGFR<sub>cys</sub>) and measured urinary albumin-to-creatinine ratio (ACR) in 10 328 men and women free of AF from the Atherosclerosis Risk in Communities (ARIC) Study in 1996 to 1998. Incidence of AF was ascertained through the end of 2007. During a median follow-up of 10.1 years, we identified 788 incident AF cases. Compared with individuals with eGFR<sub>cys</sub> ≥90 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>, multivariable hazard ratios and 95% confidence intervals (CIs) of AF were 1.3 (95% CI, 1.1 to 1.6), 1.6 (95% CI, 1.3 to 2.1), and 3.2 (95% CI, 2.0 to 5.0; P for trend <0.0001) in those with eGFR<sub>cys</sub> of 60 to 89, 30 to 59, and 15 to 29 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>, respectively. Similarly, the presence of macroalbuminuria (ACR ≥300 mg/g; hazard ratio, 3.2; 95% CI, 2.3 to 4.5) and microalbuminuria (ACR, 30 to 299 mg/g; hazard ratio, 2.0; 95% CI, 1.6 to 2.4) was associated with higher AF risk compared with those with ACR <30 mg/g. Risk of AF was particularly elevated in those with both low eGFR<sub>cys</sub> and macroalbuminuria (hazard ratio, 13.1; 95% CI, 6.0 to 28.6, comparing individuals with ACR ≥300 mg/g and eGFR<sub>cys</sub> of 15 to 29 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup> and those with ACR <30 mg/g and eGFR<sub>cys</sub> ≥90 mL·min<sup>-1</sup>·1.73 m<sup>-2</sup>.

Conclusion—In this large population-based study, reduced kidney function and presence of albuminuria were strongly associated with the incidence of AF independently of other risk factors. (Circulation. 2011;123:2946-2953.)

Key Words: atrial fibrillation ▪ epidemiology ▪ kidney

Clinical Perspective on p 2953

Evidence shows that patients with end-stage renal disease on hemodialysis are more likely to develop AF than the general population.10 Similarly, cross-sectional studies have found a higher prevalence of AF in individuals with non-dialysis-dependent CKD.11–13 To date, 3 prospective population-based studies have evaluated the association of kidney function with AF, reporting conflicting results.14–16 Additionally, none of these studies explored whether this association might differ by race, sex, or presence of cardiovascular disease and risk factors.

Therefore, we examined the association of kidney function and urinary albumin excretion with the incidence of AF in the Atherosclerosis Risk in Communities (ARIC) cohort, a community-based study of cardiovascular disease in the United States. We hypothesized that individuals with worse kidney function and more severe albuminuria would have an increased risk of AF independently of other cardiovascular risk factors.
Methods

Study Population
In 1987 to 1989, the ARIC Study recruited 15,792 men and women 45 to 64 years of age from 4 communities in the United States (Washington County, Maryland; suburbs of Minneapolis, MN; Jackson, MS, and Forsyth County, North Carolina).17 Participants were mostly white in the Minneapolis and Washington County field centers and white and black in Forsyth County, whereas only blacks were recruited in the Jackson field center. Study participants had 3 additional exams, each approximately 3 years apart (the last in 1996 to 1998). Response rates among survivors for the successive examinations were 93%, 86%, and 80%. In addition, ARIC participants have received annual follow-up calls since the first visit (>90% response rate). Because cystatin C and urinary albumin were measured in samples collected during the 1996 to 1998 examination (ARIC visit 4), we considered that visit as baseline. Institutional review boards at participating institutions approved the study protocol. All study participants provided written informed consent.

Assessment of Kidney Function
Serum creatinine was measured in samples collected during visit 4 with a modified kinetic Jaffé reaction. The reliability coefficient for 439 blinded quality-control replicates was 0.95. Creatinine values were calibrated to the Cleveland Clinic Laboratory.18 Serum cystatin C was measured in 2008 from stored frozen samples collected in visit 4 by a particle-enhanced immunophelometric assay (N Latex Cystatin C, Siemens Healthcare Diagnostics, Deerfield, IL) with a BNII nephelometer (Siemens Healthcare Diagnostics). The reliability coefficient for 421 blinded quality-control replicates of cystatin C was 0.65, but it was 0.94 after the removal of 10 pair outliers (>3 SDs). Cystatin C was calibrated to the Cleveland Clinic after a relatively constant difference of 16% was found between ARIC and Cleveland Clinic values (Cleveland Clinic = 1.16 × ARIC). Estimated glomerular filtration rate (eGFR) based on creatinine (eGFRcrea) was calculated from the CKD Epidemiology Collaboration equation for creatinine;20 and eGFR by cystatin C (eGFRcys) was estimated with the CKD Epidemiology Collaboration equation for cystatin C.21,22 The final sample included 10,328 participants (8143 whites and 2185 blacks).

Urinary albumin was measured by a nephelometric method on either the Dade Behring BN100 (assay sensitivity, 2.0 mg/L) or the Beckman Image Nephelometer, and urinary creatinine was measured either the Dade Behring BN100 (assay sensitivity, 2.0 mg/L) or the Siemens Healthcare Diagnostics). The reliability coefficient for 421 blinded quality-control replicates of cystatin C was 0.65, but it was 0.94 after the removal of 10 pair outliers (>3 SDs). Cystatin C was calibrated to the Cleveland Clinic after a relatively constant difference of 16% was found between ARIC and Cleveland Clinic values (Cleveland Clinic = 1.16 × ARIC). Estimated glomerular filtration rate (eGFR) based on creatinine (eGFRcrea) was calculated from the CKD Epidemiology Collaboration equation for creatinine;20 and eGFR by cystatin C (eGFRcys) was estimated with the CKD Epidemiology Collaboration equation for cystatin C.21,22 The final sample included 10,328 participants (8143 whites and 2185 blacks).

Urinary albumin was measured by a nephelometric method on either the Dade Behring BN100 (assay sensitivity, 2.0 mg/L) or the Beckman Image Nephelometer, and urinary creatinine was measured with the Jaffé method to determine the albumin-to-creatinine ratio (ACR; mg/g). Blinded samples (n = 516) analyzed for quality assurance showed the correlation coefficient of the loge-transformed ACR to be 0.95.

Ascertainment of Atrial Fibrillation
For the main analysis, we used visit 4 (1996 to 1998) as the baseline visit and considered only incident AF events occurring after that time. Individuals with AF identified at visit 4 or before were considered to have prevalent AF and were therefore excluded from this analysis.

Identification of AF events after visit 4 was done through hospital discharge codes and death certificates.22,23 Hospitalizations in ARIC participants were identified through annual follow-up calls and review of local hospital discharges through the end of 2007.24 Atrial fibrillation was identified when International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) code 427.31 or 427.32 was listed as a discharge diagnostic code. Atrial fibrillation events identified during hospitalizations for cardiac surgery were excluded. We confirmed ~90% of the cases in a physician review of discharge summaries from 125 possible AF cases. Finally, an AF diagnosis was assigned if AF was listed as a cause of death (ICD-9 427.3 or ICD-10 I48). Most incident AF cases (>99%) in the present analysis were identified from hospital discharge codes.

Atrial fibrillation events before ARIC visit 4 were identified from ECGs done at study visits, in addition to hospitalizations and death certificates. Specifically, at each study visit, a 10-second 12-lead ECG was done with a MAC PC cardiograph (Marquette Electronics Inc, Milwaukee, WI) and transmitted to the ARIC ECG Reading Center for coding and interpretation. ECGs automatically coded as AF were visually checked by a trained cardiologist to confirm the diagnosis.23 Atrial fibrillation events before visit 4 were not included in the main analysis, but were considered in sensitivity analyses with visit 1 as baseline (see below).

Measurement of Other Covariates
At each study visit, participants reported information on smoking and alcohol intake, underwent a physical examination, and provided blood samples. For the present analysis, we used covariates measured at visit 4. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured with a random-zero sphygmomanometer after 5 minutes of rest in the sitting position and was defined as the average of 2 measurements taken. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL, nonfasting glucose ≥200 mg/dL, treatment for diabetes mellitus, or a self-reported diagnosis of diabetes mellitus. High-sensitivity C-reactive protein was measured with an immunonephelometric assay (Siemens Healthcare Diagnostics). Heart failure at baseline was defined as the reported use of heart failure medications in the previous 2 weeks or the presence of heart failure according to Gothenburg criteria; incident heart failure was defined as the presence of ICD-9-CM code 428 in any hospitalization or death certificate during follow-up.26 Similarly, prevalent CHD was defined as physician-diagnosed CHD or the presence of a previous myocardial infarction by ECG, and incident CHD was adjudicated by the ARIC Morbidity and Mortality Classification Committee using information obtained from follow-up calls, hospitalization records, and death certificates, as previously described.24 Prevalent heart failure and CHD for this study were defined as prevalent disease at baseline plus incident events before visit 4.

Statistical Analysis
Of 11,656 individuals who attended ARIC visit 4, we excluded individuals who were of a racial/ethnic group other than white or black and nonwhites in the Minneapolis and Washington County field centers (n = 69); those with prevalent AF at visit 4 (n = 304), unreadable ECG (n = 202), or prevalent stroke (n = 226); those with missing eGFRcrea, eGFRcys, or ACR (n = 420) or other missing covariates (n = 92); and those with eGFRcrea < 15 mL·min⁻¹·1.73 m⁻² (n = 15). The final sample included 10,328 participants (8143 whites and 2185 blacks).

Initially, we explored the association between measures of kidney function and AF risk by modeling eGFR and ACR using restricted cubic splines. Then, we categorized individuals according to their eGFR following the National Kidney Foundation guidelines: ≥90 mL·min⁻¹·1.73 m⁻² (normal), 60 to 89 mL·min⁻¹·1.73 m⁻² (mildly decreased kidney function), 30 to 59 mL·min⁻¹·1.73 m⁻² (CKD stage 3), and 15 to 29 mL·min⁻¹·1.73 m⁻² (CKD stage 4).27 Separate categorization was done with eGFRcrea and eGFRcys. The ARIC participants were also categorized according to their ACR levels: normal (<30 mg/g), microalbuminuria (30 to 299 mg/g), and macroalbuminuria (≥300 mg/g). P values for trend were calculated including measures of kidney function or albuminuria as continuous variables in the models.

We estimated the association of eGFR and ACR levels with the incidence of AF using Cox proportional hazards models with time to AF as the main outcome variable. Follow-up time was defined as the time elapsed between visit 4 and the date of AF incidence, death, loss to follow-up, or December 31, 2007, whichever came first. Initial models were adjusted for age, sex, and race. In a second model, we additionally adjusted for study site, education (did not complete high school, high school diploma, at least some college), income
Table 1. Baseline Characteristics by Cystatin C–Based Estimated Glomerular Filtration Rate and Albumin-to-Creatinine Ratio, Atherosclerosis Risk in Communities, 1996 to 1998

<table>
<thead>
<tr>
<th>eGFRcys, mL·min⁻¹·1.73 m⁻²</th>
<th>ACR, mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90 (n=3014)</td>
<td>&lt;30 (n=9546)</td>
</tr>
<tr>
<td>60–89 (n=6051)</td>
<td>30–299 (n=633)</td>
</tr>
<tr>
<td>30–59 (n=1114)</td>
<td></td>
</tr>
<tr>
<td>15–29 (n=149)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
</tr>
<tr>
<td>Blacks, %</td>
</tr>
<tr>
<td>High school degree, %</td>
</tr>
<tr>
<td>Current smoker, %</td>
</tr>
<tr>
<td>Current alcohol use, %</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
</tr>
<tr>
<td>Hypertension, %</td>
</tr>
<tr>
<td>Use of ACEIs/ARBs, %</td>
</tr>
<tr>
<td>Use of other antihypertensive medications, %</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
</tr>
<tr>
<td>Coronary heart disease, %</td>
</tr>
<tr>
<td>Heart failure, %</td>
</tr>
</tbody>
</table>

- eGFRcys indicates cystatin C–based estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and hsCRP, high-sensitivity C-reactive protein. Values are mean (SD) when appropriate.

During a median follow-up of 10.1 years, we identified 788 incident cases of AF. Lower levels of eGFRcys were associated with a higher risk of AF, even after adjustment for multiple potential confounders (Table 2). The incidence of AF in individuals with eGFRcys 15 to 29 mL·min⁻¹·1.73 m⁻² was 3 times higher compared with that in individuals with eGFRcys in the optimal range (hazard ratio [HR], 3.2; 95% confidence interval [CI], 2.0 to 5.0) after adjustment for potential confounders and history of cardiovascular disease. The association of eGFRcys and AF incidence was J shaped, with the lowest risk in individuals with eGFRcys of 60 to 89 mL·min⁻¹·1.73 m⁻² (Table 2). Multivariable HRs of AF associated with 10-mL·min⁻¹·1.73 m⁻²—lower eGFRcys or eGFRcys were 1.06 (95% CI, 1.01 to 1.12) and 1.16 (95% CI, 1.11 to 1.21), respectively. Results were only slightly attenuated after adjustment for incident CHD and heart failure. Atrial fibrillation–free survival curves in whites and blacks by eGFRcys categories are shown in Figure 1.

Similarly, the presence of microalbuminuria or macroalbuminuria was associated with a higher risk of AF (Table 3). Compared with those with ACR <30 mg/g, the HR of AF was 2.0 (95% CI, 1.6 to 2.4) in those with an ACR of 30 to 299 mg/g and 3.2 (95% CI, 2.3 to 4.5) in those with ACR of ≥300 mg/g after adjustment for multiple potential confounders and history of cardiovascular disease. Multivariable HR associated with 100-mg/g-higher ACR was 1.04 (95% CI, 1.03 to 1.05). The higher risk of AF with higher ACR and lower eGFRcys levels was cumulative, with the highest risk among study participants with low eGFRcys (15 to 29 mL·min⁻¹·1.73 m⁻²) and macroalbuminuria (ACR ≥300 mg/g).
mg/g; Figure 2). The HR in these individuals compared with those with ACR 30 mg/g and optimal eGFRcys was 13.1 (95% CI, 6.0 to 28.6). Figure 2 also shows higher AF risk with higher ACR across all categories of eGFRcys and higher risk with lower eGFRcys across all categories of albuminuria. No evidence of multiplicative interaction between ACR and eGFRcys was present (P for interaction 0.35).

Although lower eGFRcys and higher ACR levels were associated with a higher risk of hospitalization (P for trend <0.0001), adjustment for incident hospitalizations before AF incidence or censoring did not materially change the associations (Tables 2 and 3, model 4b). Similarly, results did not appreciably change after additional adjustment for maximum P-wave duration, ECG-defined left ventricular hypertrophy, and fasting blood glucose. Model 4d: model 3 excluding AF events occurring in the first 2 years of follow-up.

*Per 1000 person-years. Adjusted for age, sex, and race.

Table 2. Hazard Ratio (95% Confidence Interval) of Atrial Fibrillation by Categories of Estimated Glomerular Filtration Rate Calculated From Blood Creatinine or Cystatin C Levels, Atherosclerosis Risk in Communities, 1996 to 2007

<table>
<thead>
<tr>
<th>eGFRcys, mL·min⁻¹·1.73 m⁻²</th>
<th>AF cases</th>
<th>60–89</th>
<th>30–59</th>
<th>15–29</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>132</td>
<td>473</td>
<td>159</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>29,825</td>
<td>58,163</td>
<td>97,80</td>
<td>1143</td>
<td></td>
</tr>
<tr>
<td>AF incidence*</td>
<td>4.1</td>
<td>6.1</td>
<td>10.2</td>
<td>15.2</td>
<td></td>
</tr>
</tbody>
</table>

- eGFRcys indicates cystatin C–based estimated glomerular filtration rate; eGFRcreat, creatinine-based estimated glomerular filtration rate; and AF, atrial fibrillation.
- Model 1: Cox proportional hazards model adjusted for age, sex, and race. Model 2: model 1 with additional adjustment for study site, education, income, height, smoking, drinking status, diabetes mellitus, systolic blood pressure, use of antihypertensive medication, body mass index, and high-sensitivity C-reactive protein.
- Model 3: model 2 with additional adjustment for prevalent coronary heart disease and prevalent heart failure.
- Model 4a: model 3 with additional adjustment for incident heart failure or myocardial infarction during follow-up.
- Model 4b: model 3 with additional adjustment for incident heart failure or myocardial infarction or any hospitalization before end of follow-up.
- Model 4c: model 3 with additional adjustment for maximum P-wave duration, ECG-defined left ventricular hypertrophy, and fasting blood glucose.
- Model 4d: model 3 excluding AF events occurring in the first 2 years of follow-up.

Figure 1. Cumulative incidence of atrial fibrillation (AF) by categories of estimated cystatin C–based glomerular filtration rate (≥90, 60 to 89, ≤60 mL·min⁻¹·1.73 m⁻²) in whites (top) and blacks (bottom), Atherosclerosis Risk in Communities (ARIC), 1996 to 2007. Cox proportional hazards model adjusted for age, sex, study site, education, height, high-sensitivity C-reactive protein, body mass index, systolic blood pressure, prevalent cardiovascular disease, smoking, alcohol intake, and use of antihypertensive medication.
of interaction was present in analyses stratified by age, sex, race, history of cardiovascular disease, use of antihypertensive medication, or history of hypertension (Figures I and II in the online-only Data Supplement).

We conducted an additional sensitivity analysis using eGFR\textsubscript{creat} measured at the first ARIC visit (1987 to 1989) as the main exposure and incident AF identified from ECGs done in the 3 ARIC follow-up visits (1990 to 1992, 1993 to 1995, and 1996 to 1998) as the outcome. Among 14 839 eligible ARIC participants, 119 cases of AF were observed in follow-up ECGs. Multivariable HRs of ECG-defined AF were 2.3 (95% CI, 0.9 to 6.0) and 1.5 (95% CI, 1.0 to 2.2) in those with eGFR\textsubscript{creat} of 15 to 60 mL·min\textsuperscript{-1}·1.73 m\textsuperscript{2} and 60 to <90 mL·min\textsuperscript{-1}·1.73 m\textsuperscript{2}, respectively, compared with those with eGFR\textsubscript{creat} >90 mL·min\textsuperscript{-1}·1.73 m\textsuperscript{2} (P for trend=0.01; Table I in the online-only Data Supplement). Corresponding HRs including the 1544 cases of incident AF identified through study ECGs or hospitalization and death certificate surveillance from visit 1 through the end of 2007 were 1.7 (95% CI, 1.3 to 2.3) and 1.1 (95% CI, 1.0 to 1.2; P for trend=0.003; Table II in the online-only Data Supplement).

**Discussion**

In this population-based prospective study, we found that kidney damage, manifested as microalbuminuria or macroalbuminuria, and decreased kidney function were associated with a higher AF risk. An elevated risk of AF was observed even among individuals with mildly decreased kidney function measured by eGFR\textsubscript{cyt}. These associations were independent of lifestyles, clinical factors, and cardiovascular disease and were similar in men, women, whites, and blacks; in individuals with or without a history of cardiovascular disease or hypertension; and among those taking antihypertensive medications. The somewhat different results with eGFR\textsubscript{cyt} and eGFR\textsubscript{creat} are consistent with previous data suggesting that the former presents a more linear association

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**Table 3. Hazard Ratio (95% Confidence Interval) of Atrial Fibrillation According to Urinary Albumin-to-Creatinine Ratio, Atherosclerosis Risk in Communities, 1996 to 2007**

<table>
<thead>
<tr>
<th>ACR (mg/g)</th>
<th>AF cases, n</th>
<th>Person-years</th>
<th>AF incidence*</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4a</th>
<th>Model 4b</th>
<th>Model 4c</th>
<th>Model 4d</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>645</td>
<td>92 353</td>
<td>5.8</td>
<td>1 (Referent)</td>
<td>2.59 (2.10–3.20)</td>
<td>2.02 (1.62–2.52)</td>
<td>1.97 (1.57–2.46)</td>
<td>1.91 (1.53–2.39)</td>
<td>1.93 (1.54–2.41)</td>
<td>1.89 (1.49–2.41)</td>
</tr>
<tr>
<td>30–299</td>
<td>103</td>
<td>5447</td>
<td>14.6</td>
<td>4.83 (3.50–6.67)</td>
<td>3.15 (2.25–4.40)</td>
<td>3.08 (2.20–4.32)</td>
<td>2.90 (2.07–4.06)</td>
<td>3.08 (2.18–4.36)</td>
<td>2.69 (1.82–4.00)</td>
<td></td>
</tr>
<tr>
<td>≥300</td>
<td>40</td>
<td>1111</td>
<td>26.3</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

ACR indicates albumin-to-creatinine ratio; AF, atrial fibrillation. Model 1: Cox proportional hazards model adjusted for age, sex, and race. Model 2: model 1 with additional adjustment for study site, education, income, height, smoking, drinking status, diabetes mellitus, systolic blood pressure, use of antihypertensive medication, body mass index, and high-sensitivity C-reactive protein. Model 3: model 2 with additional adjustment for prevalent coronary heart disease and prevalent heart failure. Model 4a: model 3 with additional adjustment for incident heart failure or myocardial infarction during follow-up. Model 4b: model 3 with additional adjustment for prevalent coronary heart disease and prevalent heart failure. Model 4c: model 3 with additional adjustment for prevalent coronary heart disease and prevalent heart failure. Model 4d: model 3 excluding AF events occurring in the first 2 years of follow-up.

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![Figure 2. Hazard ratios (HR) and 95% confidence intervals (CI) of atrial fibrillation (AF) according to urinary albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate from blood cystatin C (eGFR\textsubscript{cyt}). Atherosclerosis Risk in Communities (ARIC), 1996 to 2007. Cox proportional hazard model adjusted for age, sex, race, study site, education, income, height, smoking, drinking status, diabetes mellitus, systolic blood pressure, use of antihypertensive medication, body mass index, high-sensitivity C-reactive protein, prevalent coronary heart disease, and prevalent heart failure.](image-url)
with mortality, probably because creatinine is lowered by muscle loss.30

Previous studies addressing the relationship of kidney function with AF risk have provided inconsistent results. Lower eGFRcreat was associated with a higher risk of AF in 2 studies in Japan.14,31 However, reduced kidney function as measured by both higher cystatin C levels and reduced eGFRcreat was not associated with AF risk in the Cardiovascular Health Study, a population-based study of elderly individuals in the United States.16 Potential explanations for the discrepancy with our results include the older age in the Cardiovascular Health Study (average, 75 versus 63 years in the ARIC study), differences in the classification of kidney dysfunction (cystatin C quartiles in the Cardiovascular Health Study versus clinical categories of eGFRcys in our analysis), and differences in AF ascertainment.19 In a subset of participants in the prospective Framingham Heart Study, ACR was not associated with AF incidence; however, that analysis had limited statistical power in that it included only 135 AF events.15 In contrast, cross-sectional analyses have consistently shown a higher prevalence of AF among individuals with CKD.11–13 Our study compares favorably with previous reports in its large sample size, extended follow-up, and well-characterized information on potential confounders.

Chronic kidney disease may increase the risk of AF through several mechanisms. Individuals with kidney dysfunction are more likely to develop hypertension and to have poorer control of their blood pressure.32 The resulting expansion of the extracellular fluid might lead to left ventricular hypertrophy, poor ventricular compliance, and eventually atrial stretch and fibrosis, established predictors of AF.5,33 In addition, CKD leads to pathological activation of the intrarenal renin-angiotensin-aldosterone system.34 Compelling evidence suggests that an upregulated renin-angiotensin-aldosterone system causes atrial fibrosis and electric remodeling, creating the required substrate for the development of AF.35 This effect might be partly mediated through increased secretion of transforming growth factor-β1, which is profibrotic.36 Moreover, involvement of the renin-angiotensin-aldosterone system in AF pathogenesis is also suggested by the potential reduced risk of AF after the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers,35,37 although this has not been observed in all studies.38 Whether CKD affects AF risk through this mechanism merits further inquiry. Finally, CKD might cause AF through an increased risk of cardiovascular disease, including heart failure and CHD,1,2,5 or through sympathetic overactivity.8 Our observation that both low eGFRcys and the presence of albuminuria independently increased the risk of AF hints that a variety of mechanisms underlie these associations.

Some study limitations should be noted. In our primary analysis, incident AF was identified mostly from hospitalization discharges; therefore, we could not include asymptomatic AF and AF managed exclusively in an outpatient setting. However, an analysis including only AF events identified from systematic study of ECGs found an association between CKD and AF risk of similar magnitude. Moreover, we and others have previously shown that the validity of AF ascertainment using hospitalizations is acceptable,22,30 that incidence rates of AF in the ARIC Study are consistent with other population-based studies,22 and that the associations between variants in the chromosome 4q25—extremely specific for AF risk—and AF incidence in ARIC are similar to those in other studies with a more intensive ascertainment of AF.40 Still, individuals with reduced renal function may have been more likely to have their AF detected by hospitalization than those with normal function, potentially creating ascertainment bias. Other important limitations include the absence of echocardiographic data; the potential for residual confounding by some CKD risk factors (eg, hypertension, diabetes mellitus); the availability of only 1 measurement of ACR and cystatin C, which could lead to measurement bias; and the lack of standardization of cystatin C assays and equation. Despite some limitations, our study has important strengths: a large sample size, the elevated number of AF events, the long follow-up, the diversity of the study population, and the quality and extent of measured covariates.

Conclusions

We have found that kidney damage and impaired kidney function are associated with an increased risk of AF independently of other risk factors. Given the growing burden of CKD in the general population and the potential for its prevention,41 future studies should focus on understanding the specific mechanisms underlying this association. Furthermore, strategies for the prevention of AF will have to consider CKD as a preventable risk factor for AF in addition to other well-established risk factors.6

Acknowledgments

We thank the staff and participants of the ARIC study for their important contributions.

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Disclosures

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2. Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PF, Chambless LE, Coresh J. Reduced kidney function as a risk


CLINICAL PERSPECTIVE

Previous research has shown that individuals with end-stage renal disease have a higher risk of developing atrial fibrillation, and some cross-sectional studies have found higher prevalence of atrial fibrillation among those with decreased kidney function. However, evidence from prospective studies in the general population is limited. In an analysis of 10,328 men and women participating in the Atherosclerosis Risk in Communities Study, we observed that impaired kidney function, measured by lower cystatin-based or creatinine-based estimated glomerular filtration rate, was strongly associated with a higher risk of atrial fibrillation. Similarly, individuals with increased levels of urinary albumin-to-creatinine ratio, a marker of kidney damage, had a higher risk of developing atrial fibrillation. Our study highlights the potential role of chronic kidney disease as a risk factor for atrial fibrillation. Interventions aimed at preventing and treating chronic kidney disease could also contribute to reduce the burden of atrial fibrillation in the population.
Chronic Kidney Disease Is Associated With the Incidence of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study
Alvaro Alonso, Faye L. Lopez, Kunihiro Matsushita, Laura R. Loehr, Sunil K. Agarwal, Lin Y. Chen, Elsayed Z. Soliman, Brad C. Astor and Josef Coresh

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**Supplemental table 1.** Hazard ratio (95% confidence interval) of atrial fibrillation identified in study ECGs by categories of estimated glomerular filtration rate (eGFR) calculated from blood creatinine levels at visit 1, ARIC, 1987-1998

<table>
<thead>
<tr>
<th>eGFR_{cys} (mL/min/1.73 m^2)</th>
<th>≥90</th>
<th>60-89</th>
<th>15-59</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF cases</td>
<td>59</td>
<td>55</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>175998</td>
<td>70915</td>
<td>3209</td>
<td></td>
</tr>
<tr>
<td>AF incidence*</td>
<td>0.54</td>
<td>0.85</td>
<td>1.49</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (ref.)</td>
<td>1.60 (1.09-2.33)</td>
<td>1.54 (1.05-2.26)</td>
<td>1.53 (1.05-2.24)</td>
</tr>
<tr>
<td>2.90 (1.15-7.32)</td>
<td>2.34 (0.91-6.00)</td>
<td>2.32 (0.91-5.96)</td>
<td></td>
</tr>
</tbody>
</table>

* Per 1,000 person-year. Adjusted for age, gender, and race.

Model 1: Cox proportional hazard model adjusted for age, gender and race.

Model 2: Model 1, additionally adjusted for study site, education, income, height, smoking, drinking status, diabetes, systolic blood pressure, use of antihypertensive medication, body mass index, high sensitivity C-reactive protein

Model 3: Model 2, additionally adjusted for prevalent coronary heart disease and prevalent heart failure.
**Supplemental table 2.** Hazard ratio (95% confidence interval) of atrial fibrillation by categories of estimated glomerular filtration rate (eGFR) calculated from blood creatinine levels at visit 1, ARIC, 1987-2007

<table>
<thead>
<tr>
<th>eGFR&lt;sub&gt;cys&lt;/sub&gt; (mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>≥90</th>
<th>60-89</th>
<th>15-59</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF cases</td>
<td>937</td>
<td>557</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>175995</td>
<td>70915</td>
<td>3209</td>
<td></td>
</tr>
<tr>
<td>AF incidence*</td>
<td>4.53</td>
<td>5.07</td>
<td>8.44</td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1 (ref.)</td>
<td>1.13 (1.01-1.25)</td>
<td>2.05 (1.54-2.74)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Model 2</td>
<td>1 (ref.)</td>
<td>1.12 (1.00-1.25)</td>
<td>1.73 (1.29-2.31)</td>
<td>0.001</td>
</tr>
<tr>
<td>Model 3</td>
<td>1 (ref.)</td>
<td>1.10 (0.99-1.23)</td>
<td>1.71 (1.28-2.29)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

* Per 1,000 person-year. Adjusted for age, gender, and race.

**Model 1:** Cox proportional hazard model adjusted for age, gender and race.

**Model 2:** Model 1, additionally adjusted for study site, education, income, height, smoking, drinking status, diabetes, systolic blood pressure, use of antihypertensive medication, body mass index, high sensitivity C-reactive protein.

**Model 3:** Model 2, additionally adjusted for prevalent coronary heart disease and prevalent heart failure.
**Supplemental figure 1.** Association of eGFR$_{cys}$ with incidence of atrial fibrillation by gender, race, history of cardiovascular disease, use of antihypertensive medications, and hypertension, ARIC, 1996-2007