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Relation of Renal Function to Risk for Incident Atrial Fibrillation in Women

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Abstract

Few prospective studies have explored the association between renal function and risk of incident atrial fibrillation (AF) in apparently healthy populations. A total of 24,746 women participating in the Women's Health Study who were free of cardiovascular disease (CVD), AF and provided a blood sample at baseline were prospectively followed for incident AF from 1993 to 2010. AF events were confirmed by medical chart review. Estimated glomerular filtration rate (eGFR) was calculated from baseline creatinine using the Chronic Kidney Disease – Epidemiology equation. Cox models were used to estimate hazard ratios (HR) and 95% CI for incident AF across eGFR categories controlling for AF risk factors. During 15.4 years (median) of follow-up, 786 incident AF events occurred. The multivariable-adjusted HR for incident AF across eGFR categories (<60, 60–74.9, 75–89, and ≥ 90 ml/min/1.73 m^2) were:1.36 (1.00–1.84), 0.90 (0.71–1.14), 0.99 (0.84–1.18) and 1.00, respectively, without evidence of a linear association (P for trend, 0.48). Similarly, there was no significant curvilinear association (P quadratic, 0.10) in multivariable analysis across categories. As compared to women with an eGFR ≥ 60 ml/min/1.73 m^2, the 1008 women with an eGFR < 60 ml/min/1.73 m^2 had a multivariable adjusted HR for AF of 1.39 (1.04–1.86, p value 0.03). In conclusion, no significant linear or curvilinear relationship was observed between incident AF and less severe impairment of renal function in this large prospective cohort of women. However, a significant elevation in AF risk was observed at a threshold eGFR of < 60 ml/min/1.73 m^2.

Keywords

atrial fibrillation; renal function

INTRODUCTION

Several cross-sectional studies have found the prevalence of atrial fibrillation (AF) to be associated with decreasing glomerular filtration rate (GFR), increasing cystatin C and

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urinary albumin levels.[1–3] Among those with end-stage renal disease, the prevalence of AF is 3 to 15 times greater than in a general population.[4–8] However, results from prospective studies involving more modest degrees of renal dysfunction have been conflicting, with positive associations observed in some[1, 10] but not all studies. [2] In particular, there are few prospective data on the association between moderate renal dysfunction and incident AF in apparently healthy populations, where confounding of the relation by established vascular disease would be expected to be lower. Therefore, we evaluated the association between kidney function as assessed by GFR and the subsequent development of incident AF among 24,746 women without prior cardiovascular disease.

METHODS

All subjects were participants of the Women's Health Study, a randomized placebo controlled trial evaluating the benefits and risks of low dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. The study has previously been published[11–13]. Briefly, a total of 39 876 US female health professionals in 1993 who were ≥ 45 years of age and free of cardiovascular disease (CVD), cancer, and other major illnesses were randomly assigned to 100 mg aspirin every other day, 600 IU vitamin E every other day, both agents, or placebo. Randomized treatment ended on March 31, 2004, and women were invited to participate in continued observational follow-up with self reported questionnaires regarding cardiovascular risk factors and life-style variables.

Blood samples were available for 28 345 women at the time of randomization. Of these women, 626 women with AF, 3 with CVD, and 568 women with missing values for important clinical characteristics at baseline were excluded. An additional 2402 women who opted out of further observational follow-up were also excluded because self reported AF cases within this group could not be reliably confirmed. Excluding these participants left 24 746 for the present analysis. The median follow-up was 15.4 years (interquartile range, 14.7–15.8 years). All participants provided written informed consent and the Institutional Review Board of Brigham and Women's Hospital (Boston MA, USA) approved the study.

In a core laboratory certified by the National Heart, Lung, and Blood Institute-Centers for Disease Control and Prevention Lipid Standardization Program, all blood samples are collected in tubes containing EDTA and stored in vapour phase liquid nitrogen (−170 °C), and analyzed for lipids and a panel of inflammatory markers. Creatinine was measured by a rate blanked method based on the Jaffe reaction. Total cholesterol was assayed with reagents from Roche Diagnostics (Basel, Switzerland) and high sensitivity C reactive protein concentrations were measured with immunoturbidimetric assays on a Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, USA) using reagents and calibrators from Denka Seiken (Tokyo, Japan).

The Chronic Kidney Disease Epidemiology (CKD-EPI)[14] equation, which has been validated to perform better than the Modification of Diet in Renal Disease Study[14] (MDRD) equation at higher GFRs, was used to calculate estimated glomerular filtration rate (eGFR). The CKD-EPI equation is eGFR = 141 × min (serum creatinine/0.7,1) $^{-0.32}$ × max (serum creatinine/0.7,1) $^{-1.209}$ × 0.993(Age) × 1.018 (female) × 1.159 (if black). As a secondary analysis, we used an abbreviated version of the MDRD equation[1415] to examine whether our results were substantially influenced by the equation used to calculate eGFR. MDRD eGFR (in ml/min/1.73 m^2) = 186 × [serum creatinine (in mg/dL) $^{-1.154}$ × Age $^{-0.203}$ × 0.742 (female) × 1.210 (if black)]. Using both equations, participants were categorized based on classification of the National Kidney Foundation eGFR <60, 60–74, 75–89, ≥ 90 ml/min/ 1.73 m^2.[15]

Women were asked to report diagnoses of incident AF at baseline, at 48 months, and then annually thereafter.[16, 17] Women enrolled in the continued observational follow-up and who reported an incident AF event on at least 1 yearly questionnaire were sent an additional questionnaire beginning on September 19, 2006 to confirm the episode and collect additional information. Permission was obtained to review medical records, available ECGs, rhythm strips, 24-hour ECG monitoring, and information on cardiac structure and function. For deceased participants reporting AF during the trial and observational period, family members were contacted to obtain consent for medical records. An end-point committee of physicians reviewed medical records according to pre-defined criteria. An incident AF event was confirmed if there was ECG evidence of AF or if a medical report clearly indicated a personal history of AF. The earliest date in the medical records was set as the date of onset of AF. Only confirmed AF events are included in this analysis.

Baseline characteristics across eGFR categories were compared with Jonckheere-Terpstra test for continuous variables and Mantel Haenszel trend χ^2 test for categorical variables. For each women, person-years of follow-up were calculated from the date of return of the baseline questionnaire to date of first endpoint, death, loss to follow-up, or March 16, 2010, whichever came first.

Cox-proportional hazards models were used to compute hazard ratio (HR) and 95% CI for incident AF across eGFR categories, with the highest eGFR category (≥ 90 ml/min/1.73 m^2) serving as the reference category in all analyses. In a secondary analysis, eGFR was dichotomized at 60 ml/min/1.73 m^2 based on GFR definition of chronic kidney disease. [15] Model 1 adjusted for age and assigned treatment. The multivariable model 2 controlled for age (continuous), systolic blood pressure (10mm Hg increments), antihypertensive treatment (yes/no), smoking (yes/no), diabetes (yes/no), body mass index (BMI, continuous kg/m^2), alcohol consumption (rarely/never, <1 drink/week, 1–6 drinks/week, ≥ drinks/day), exercise (rarely/never, <1 time/week, 1–3 times/week, ≥ 4 times/week), total cholesterol (continuous mg/dL), high sensitive C reactive protein concentration (continuous mg/dL), and postmenopausal hormone use (never, past, current). The proportionality assumption was tested by including an interaction term for eGFR categories with follow- up time in the Cox models and found no statistically significant violation. In addition, we checked for significant effect modification by adding indicator variables to the models and compared nested models using a likelihood ratio (LH) test.

Tests for linear trend across eGFR categories were performed by assigning the median value to each category and modeling this as a continuous variable in separate proportional hazards models. To test for a curvilinear association, a quadratic term (median value squared) was added to the above linear term in a separate model.

Furthermore, a quadratic term (continuous squared) was added to the continuous variable of eGFR in a separate model. Statistical analysis was performed with SAS statistical software (SAS Institute Inc, Cary NC) version 9.1. A 2-tailed value of $p<0.05$ was considered to indicate statistical significance.

RESULTS

The association between baseline characteristics and eGFR categories are shown in Table I. There were significant differences for all baseline characteristics across the eGFR categories except for BMI, high sensitive C reactive protein (hsCRP), systolic blood pressure, diabetes, smoking and alcohol consumption.

During a median follow-up of 15.4 years, 786 women had at least 1 confirmed episode of incident AF. The age adjusted incidence rate per 1000 person-years across eGFR categories

are shown in Table II. We did not find a significant linear association with incident AF across the full range of GFR categories in the age or multivariable adjusted models (Table II). Similarly, there was no association across eGFR categories and incident AF using the MDRD equation in both models (data not shown). These results were not significantly altered when possible biologic intermediaries (systolic blood pressure, antihypertensive treatment and hsCRP) were excluded from the model (P for linear trend =0.50). We also did not find any definitive evidence for a curvilinear relationship between eGFR and AF in multivariable models using the medians across CKD-EPI categories (P quadratic=0.10) or the continuous CKD-EPI variable for eGFR (P quadratic=0.08).

In the secondary pre-specified analysis, women with an eGFR < 60 ml/min/1.73 m^2) had a multivariable adjusted hazard ratio for AF of 1.39 (95% CI, 1.04–1.86, p value 0.03) as compared to those women with an eGFR ≥ 60 ml/min/1.73 m^2 (Table III). Similarly, there was a significant association between eGFR < 60 ml/min/1.73 m^2 and incident AF using the MDRD equation in a multivariable analysis (HR 1.37 95% CI 1.04–1.82, p=0.03). More severe degrees of renal dysfunction (eGFR<30 ml/min/1.73 m^2) were uncommon in this healthy population (n=6) and there were no AF events among these women. We found no evidence that the lack of association across eGFR categories and incident AF was modified by age, hypertension, BMI, and smoking status (all p interactions>0.1). When we explored if the association between eGFR < 60 ml/min/1.73 m^2 and incident AF was modified by the same covariates, we found a marginally significant effect modification by age (P for interaction=0.04) suggesting increased risk associated with a eGFR< 60 ml/min/1.73 m^2 of AF for older women.

DISCUSSION

In this large prospective cohort of women without known cardiovascular disease at baseline, there was no evidence of a significant linear or curvilinear relationship between eGFR measured at baseline and incident AF. However, we observed a marginally significant elevation in AF risk at a threshold of eGFR determined to be indicative of chronic kidney disease (GFR<60 ml/min/1.73 m^2). As compared to women with an eGFR greater than 60 ml/min/1.73 m^2, women with an eGFR below 60 ml/min/1.73 m^2 had a 39% elevation in the hazard ratio for incident AF even after controlling for AF risk factors.

Several prospective studies in patients with varying degrees of cardiovascular disease reported similar relationships between an eGFR threshold of < 60 ml/min/1.73 m^2 and incident AF.[12, 9] In a community-based cohort in Niigata Japan, as compared to individuals with an eGFR > 60, those with an eGFR of 30–59 ml/min/1.73 m^2 and <30 ml/min/1.73 m^2 had a multivariable HR of 1.29 (95% CI, 1.05–1.58) and1.42 (95% CI, 0.81–2.51) respectively for AF documented on annual electrocardiograms.[1] Among hypertensive patients, CKD defined as an eGFR < 60 ml/min/1.73 m^2 and presence of proteinuria (≥ 1+) was even more strongly associated with incident AF in multivariate analyses (HR 2.18; 95% CI, 1.21–3.90).[9] Recently, the Atherosclerosis Risk in Communities Studies found a strong linear association between eGFR based upon Cystatin C levels and hospitalized AF (p<0.0001)[10]. For creatinine based eGFR, multivariable relative risks were significantly elevated only in a subgroup of individuals with eGFR<30 ml/min/1.73 m^2.[10]

These results stand in contrast to those found among ambulatory elderly individuals enrolled in the Cardiovascular Health Study[2]. GFR dichotomized at 60 ml/min/1.73 m^2 was associated with prevalent AF but not incident AF in multivariable models, suggesting that residual confounding by comorbidities associated with renal dysfunction and AF might explain part of the association. Our finding that eGFR < 60 ml/min/1.73 m^2 was associated with incident AF diagnosed in both the outpatient and inpatient settings among women with

minimal comorbidities argues that confounding and bias are unlikely to account for the entire relationship between moderate renal dysfunction and AF.

The observed association between impaired renal function and incident AF may be explained by shared risk factors including hypertension, diabetes, obesity, and cardiovascular disease. Moderately impaired renal function may represent a marker of underlying end organ damage caused by these risk factors.[18] The association between renal impairment and AF may also be mediated through shared mechanistic pathways. Declining kidney function is associated with increased activation of RAAS, which can lead to elevated left atrial pressure, atrial dilatation, and myocardial fibrosis resulting in atrial structural and electrical remodeling implicated in the development of AF.[19–23] Elevation in inflammatory markers such as C reactive protein (CRP), interleukin-6 and fibrinogen have also been demonstrated in mild to moderately impaired renal disease[24, 25] and have been directly associated with risk of incident AF.[26–28]

This study has several strengths, including the prospective design, large number of participants with long follow-up, and outcome events confirmed by medical record review. There are also potential limitations of the study. First, under detection of asymptomatic AF episodes likely led to some degree of underestimation of AF incidence. Although the number of asymptomatic cases in our cohort was similar to others where screening electrocardiograms are performed[29], only continuous electrocardiographic monitoring would detect all asymptomatic AF episodes. Second, our results in healthy, middle-aged, female health professionals who were mostly white may not be generalizable to men or other ethnicities or demographics. Third, eGFR was based on a baseline measurement, consequently changes in plasma creatinine concentration and risk of incident AF could not be evaluated. Fourth, the use of eGFR equations may result in misclassification of renal function. Misclassification in eGFR would be expected to be non-differential, and could have biased our results toward the null. Finally, because of the observational nature of our study, residual or unmeasurable confounding may be present.

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Table I

Baseline Characteristics Across Glomerular Filtration Rate Categories

Variable	Glomerular Filtration Rate (ml/min/1.73m^2) CKD-EPI				P value*
	≥ 90 (n=15 374)	75–89 (n= 5901)	60–74 (n= 2463)	<60 (n= 1008)	
Mean (SD) Age (years)	53.2 (6.0)	56.4 (7.7)	57.8 (8.0)	58.1 (8.2)	<0.0001
Mean (SD) total cholesterol concentration (mg/dL)	203.7(37.7)	215.8(38.2)	229.6(44.5)	259.7(58.9)	<0.0001
Mean (SD) BMI (kg/m^2)	26.0 (5.1)	25.6 (4.7)	25.9 (4.8)	25.8(4.6)	0.05
Median (IQR) C reactive protein (mg/dL)	2.0(0.8–4.4))	1.9(0.8–4.2)	2.1(0.9–4.3)	2.4(1.0–5.0)	0.05
Mean (SD) systolic blood pressure (mmHg)	123.0 (13.3)	124.0(13.8)	124.8(13.7)	125.5(14.5)	0.06
Hypertension	22.9%	25.8%	29.2%	32.6%	<0.0001
Antihypertensive Treatment	11.6%	13.9%	17.2%	20.1%	<0.0001
Diabetes Mellitus	2.4%	2.1%	2.4%	2.4%	0.73
Physical Activity					
Rarely/Never	37.1%	35.8%	37.8%	36.1%	0.003
< 2 time/week	20.3%	17.8%	18.4%	18.7%	
2–3 times/week	31.6%	33.8%	31.6%	31.3%	
≥ 4 times/week	10.9%	12.6%	12.1%	14.0%	
Smoker					
Never	11.8%	9.9%	10.6%	9.9%	0.05
Past	36.2%	37.7%	36.5%	38.4%	
Current	52.0%	52.4%	52.9%	51.7%	
Alcohol consumption					
Rarely/Never	43.9%	42.2%	44.2%	43.3%	0.16
< 1 time/week	13.6%	13.0%	12.6%	13.4%	
1–6 times/week	32.4%	33.4%	32.9%	33.3%	
≥ 1 time/day	10.1%	11.3%	10.4%	10.0%	
Post menopausal hormone use					
Never	50.2%	46.8%	45.5%	44.6%	0.0002
Past	7.2%	9.9%	11.5%	11.6%	

Variable	Glomerular Filtration Rate (ml/min/1.73m^2) CKD-EPI				P value*
	≥ 90 (n=15 374)	75–89 (n= 5901)	60–74 (n= 2463)	<60 (n= 1008)	
Current	42.6%	43.3%	43.1%	43.8%	

Values may not equal 100% due to missing data. CKD-EPI =Chronic Kidney Disease-Epidemiology equation, BMI=body mass index

*based on Jonckheere-Terpstra test for continuous variables and Mantel Haenszel trend χ^2 test for categorical variables.

Table II

Hazard Ratios for Risk of Incident Atrial Fibrillation According to Glomerular Filtration Rate Categories

Variable	Glomerular filtration rate (ml/min/1.73m^2) CKD-EPI				P for linear trend
	≥ 90 (n=15374)	75–89 (n=5901)	60–74 (n=2463)	< 60 (n=1008)	
No of Events	426	214	93	53	
Age-adjusted Incidence Rate	2.15	2.21	2.01	2.61	
Model 1	Referent	0.94(0.80–1.12)	0.86(0.68–1.08)	1.22(0.91–1.63)	0.97
Model 2	Referent	0.99(0.84–1.18)	0.90(0.71–1.14)	1.36(1.00–1.84)	0.48

Model 1 – age and assigned treatment

Model 2 – age, assigned treatment, systolic blood pressure, high sensitive C reactive protein, hypertension medication, smoking, body mass index, alcohol, exercise, cholesterol, post menopausal hormone use, diabetes mellitus

CKD-EPI= Chronic Kidney Disease – Epidemiology equation

Incidence rate per 1000 person-years

P value for trend using median value across GFR categories

Table III

Hazard Ratios for Risk of Incident Atrial Fibrillation According to Glomerular Filtration Rate Dichotomized at 60 ml/min/1.73 m^2

	≥ 60 ml/min/1.73 m^2	< 60 ml/min/1.73 m^2	P value
No of Events	733	53	
Age-adjusted Incidence Rate	2.16	2.61	
Model 1	Referent	1.27 (0.96–1.69)	0.09
Model 2	Referent	1.39 (1.04–1.86)	0.03

Model 1 – age and assigned treatment

Model 2 – age, assigned treatment, systolic blood pressure, high sensitive C reactive protein, hypertension medication, smoking, body mass index, alcohol, exercise, cholesterol, diabetes mellitus, post menopausal hormone use

Incidence rate per 1000 person-years