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Impaired Kidney Function and Atrial Fibrillation in Elderly Subjects

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Abstract

Background—Impaired kidney function is associated with increased risk for cardiovascular events. We evaluated whether kidney function is associated with atrial fibrillation (AF) risk in elderly persons.

Methods and Results—Subjects were participants in the Cardiovascular Health Study (CHS), a population-based cohort of ambulatory elderly. Measures of kidney function were cystatin C and creatinine-based estimated glomerular filtration rate (GFR). Among the 4663 participants, 342 (7%) had AF at baseline, and 579 (13%) developed incident AF during follow-up (mean 7.4 years). In unadjusted analyses cystatin C quartiles were strongly associated with prevalent AF with a nearly 3-fold odds in the highest quartile compared with the lowest [HR = 1.19, 95% CI (0.80-1.76) in quartile 2; HR = 2.00, 95% CI (1.38-2.88) in quartile 3; and HR = 2.87, 95% CI (2.03-4.07) in quartile 4]. This increased risk for prevalent AF remained significant after multivariate adjustment. The risk for incident AF increased across cystatin C quartiles in the unadjusted analysis [HR = 1.37, 95% CI (1.07-1.75) in quartile 2; HR = 1.43, 95% CI (1.11-1.84) in quartile 3; and HR = 1.88, 95% CI (1.47-2.41) in quartile 4]; however, after multivariate adjustment, these findings were no longer

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significant. Estimated GFR < 60 ml/min/1.73m^2 was associated with prevalent and incident AF in unadjusted, but not multivariate analyses.

Conclusions—Impaired kidney function, as measured by cystatin C, is an independent marker of prevalent AF; however, neither cystatin C nor estimated GFR are predictors of incident AF.

Keywords

kidney function; cystatin C; arrhythmias; elderly; epidemiology

Introduction

Atrial fibrillation (AF) affects approximately 2.2 million persons in the United States. Due to the aging population and increased survival of persons with cardiovascular disease, the prevalence and incidence of AF have been steadily rising.(1) Despite the morbidity and mortality associated with atrial fibrillation, it has not been included as an outcome in traditional epidemiological studies that evaluate the cardiovascular effects of chronic kidney disease. Impaired kidney function is associated with increased risk for several cardiovascular complications including death, myocardial infarction (MI), stroke and congestive heart failure (CHF).(2-6) The association between kidney disease and atrial fibrillation, however, has been unexplored.

Activation of the renin angiotensin aldosterone axis (RAAS) could potentially link kidney dysfunction with increased risk for AF. Small decrements in kidney function can impair regulation of extracellular fluid volume, resulting in impaired renal sodium excretion and increased RAAS activity.(7,8) Several studies have suggested a mechanistic link between activation of the RAAS and the initiation and maintenance of AF.(9-15) In addition, increased levels of renin, angiotensin and aldosterone are responsible for multiple structural changes within the cardiovascular system including atrial and ventricular fibrosis, left atrial dilation and LVH.(16-19) These intra-cardiac structural changes, which may occur more commonly in patients with kidney disease (20,21), increase the risk of atrial fibrillation.(22)

We evaluated this hypothesis by determining the association between impaired kidney function and atrial fibrillation in the Cardiovascular Health Study (CHS), a population based cohort of outpatient elderly persons. We used two measures of kidney function: cystatin C and creatinine-based estimated glomerular filtration rate (eGFR) and determined their association with prevalent and incident AF.

Methods

Design

The CHS (23) is a population-based study of cardiovascular disease in the elderly, sponsored by the National Institute of Health. This analysis included both a cross-sectional analysis of the association between measures of kidney function and prevalent AF, and a longitudinal analysis to evaluate the association between baseline kidney function and the incidence of AF.

Study Population

The CHS recruited participants from Medicare eligibility lists in Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. To be eligible, persons had to be at least 65 years of age, not institutionalized (i.e., living in the community), expected to remain in the current community for three years or longer, not under active treatment for cancer, and be able to provide written informed consent. The initial 5201 participants were enrolled from January 1989 to June 1990; an additional 687

black participants (with race self-reported) were recruited and enrolled by June 1993. All participants provided written informed consent, and the institutional review boards at all participating sites approved the study protocol.

Participants underwent a comprehensive examination at baseline, which included a thorough medical history, physical examination, laboratory testing, a 12-lead ECG, and assessment of cardiovascular disease status. The study design, quality-control procedures, laboratory methods, and procedures for blood-pressure measurement have been published previously.(23,24)

This analysis includes a total of 4663 participants who attended the second study visit in 1992 or 1993 and for whom serum was available for measurement of creatinine and cystatin C. Creatinine measurements were performed in proximity to the 1992-1993 visit, whereas cystatin C was measured in 2003 using frozen sera from the 1992-93 exam. Follow-up for events continued until June 30, 2001 (median follow-up 7.4 years, maximum 8.1).

AF Case Definitions

Prevalent AF was defined by participant's self-report and ECG. Previous work in CHS found self-report of AF to be reliable based on the subsequent ECG and the participant's medication list.(25) Incident AF was identified by self-report, annual ECG, or by hospital discharge diagnosis. Annual ECGs were reviewed at the CHS Electrocardiographic Reading Center.(26) The reported accuracy of the hospital discharge diagnosis of AF in CHS (International Classification of Diseases, 9th Revision [ICD 9] codes 427.3, 427.31, or 427.32) was 98.3%.(27)

Kidney Function Assays

Measurements were performed on fasting sera specimens that had been stored at −70°C. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring).(28) The assay range is 0.195 to 7.330 mg/L, with the reference range for young, healthy individuals reported as 0.53 – 0.95 mg/L. The assay was demonstrated to remain stable over 5 cycles of freeze/thaw without change in the measurement.(6)

Serum creatinine was assayed by a colorimetric method (Ektachem 700, Eastman Kodak). The mean coefficient of variation for monthly controls was 1.94 percent (range, 1.16 to 3.90). We estimated the GFR with the use of the four-variable version of the Modification of Diet in Renal Disease (MDRD) equation.(29) Prior to estimating the GFR, creatinine levels were indirectly calibrated to the Cleveland Clinic lab as previously described.(30)

Cystatin C was categorized into *quartiles*. We also modeled cystatin C as a continuous variable per standard deviation (0.3mg/L). Estimated glomerular filtration rate (eGFR) was dichotomized at 60 ml/min/1.73m^2 based on the current National Kidney foundation guidelines (31) for the definition of chronic kidney disease.

Prior work from CHS has compared cardiovascular risk across quintiles of cystatin C and eGFR.(6) In this study mortality and cardiovascular risk increased linearly across cystatin C quintiles; however, increased cardiovascular risk was only observed in the fifth eGFR quintile, which corresponded to an eGFR <60 ml/min/1.73m^2. Based on this prior work from CHS, we dichotomized eGFR at 60ml/min/1.73m^2.

Covariates or Secondary Predictors

Covariates were selected as candidates for multivariate analysis based on their potential to confound the association of kidney function with AF. These included age, sex and race (self-reported); hypertension, diabetes, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol levels, congestive heart failure, coronary heart disease (CHD), left ventricular hypertrophy (LVH) and C-reactive protein.(32) Additionally, anti-hypertensive medications including diuretics, angiotensin converting enzyme inhibitors, beta blockers, angiotensin receptor blockers, and calcium channel blockers were included in the multivariate analysis.

Statistical Methods

Baseline characteristics of participants with prevalent, incident or no AF were compared by chi-squared or Kruskal-Wallis tests. The association between cystatin C measurements and prevalent AF was determined with multivariate logistic regression models that compared each ascending quartile of cystatin C with the lowest quartile. A similar evaluation was performed to determine the association of eGFR<60 ml/min/1.73m^2 with prevalent AF. In these multivariate models, candidate variables for adjustment (listed above) were retained in the final models if they changed the beta coefficient of the primary predictor of interest (kidney function) by at least 5 percent.

The association between kidney function and incident AF was determined with multivariate Cox proportional hazards regression models. Event time was defined as the date of first follow-up examination ECG or first hospitalization in which AF occurred. Model selection was conducted as in the logistic regression models described above. The proportional hazards assumption was not violated.

To further evaluate the nature of heart disease as a potential confounding factor on the association between impaired kidney function and atrial fibrillation, we conducted sensitivity analyses that excluded participants with CHD or CHF.

Results were considered statistically significant at a level of $P<0.05$. All analyses were performed with S-Plus (release 6.1, Insightful Inc, Seattle, WA) and SPSS statistical software (release 14.0.2, SPSS Inc, Chicago, IL).

Results

Among the 4663 subjects enrolled at the 1992-1993 visit of CHS, 342 (7%) had AF at baseline, and 579 developed incident AF during the 7.4 year follow-up. Those participants with prevalent and incident AF were on average older and more likely to be male, white, former smokers, and to have a history of hypertension, diabetes, LVH, CHD, and CHF (table 1). In addition, prevalent and incident AF were associated with lower LDL and HDL, higher glucose and CRP levels, and worse kidney function.

In unadjusted analyses cystatin C quartiles were strongly associated with prevalent AF with a nearly 3-fold odds in the highest quartile compared with the lowest (table 2). These estimates remained significantly associated with prevalent AF after adjustment for multiple variables including baseline demographics, cardiovascular risk factors, prevalent cardiovascular disease and use of anti-hypertensive medications (table 2). When modeled as a continuous variable, cystatin C was a strong predictor in unadjusted analyses [HR = 1.25, 95% CI (1.15-1.36)] but was no longer significant after multivariate adjustment [HR = 1.07, 95% CI (0.97-1.18)]. After excluding participants with prevalent CHD and CHF, there were 194 prevalent cases of atrial fibrillation. In the analysis that excluded prevalent heart disease, there was an association of higher quartiles of cystatin C with prevalent AF after multivariate adjustment [HR = 1.16, 95%

CI (0.71-1.90) in quartile 2; HR = 1.52, 95% CI (0.94-2.47) in quartile 3; and HR = 1.68, 95% CI (1.01-2.80) in quartile 4].

Low eGFR was associated with a near 2-fold odds of prevalent AF in unadjusted analysis; however, this association was not independent after multivariate adjustment (table 3). After excluding participants with prevalent heart disease, low eGFR was an independent predictor of prevalent atrial fibrillation after multivariate adjustment [HR = 1.53, 95% CI (1.01-2.31)].

Incident Atrial Fibrillation

In subjects without prevalent AF, cystatin C quartiles predicted annual risk of incident AF, which ranged from 1.2% per year in quartile 1 to 2.7%/year in quartile 4. However, after multivariate adjustment, these associations were no longer significant (table 2). After excluding prevalent heart disease, cystatin C quartiles had no association with incident AF in adjusted analysis [HR = 1.15, 95% CI (0.85-1.55) in quartile 2; HR = 1.02, 95% CI (0.74-1.41) in quartile 3; HR = 1.23, 95% CI (0.87-1.74) in quartile 4]. When modeled as a continuous variable, cystatin C had a significant association in unadjusted analysis [HR = 1.18, 95% CI (1.12-1.25)] that did not remain significant after multivariate adjustment [HR = 1.07, 95% CI (0.98-1.16)].

Estimated GFR was associated with risk of incident AF in unadjusted analysis; however, it was no longer associated after multivariate adjustment (table 3). After excluding participants with prevalent heart disease, low eGFR was similarly not associated with incident atrial fibrillation [HR = 1.03, 95% CI (0.73, 1.45)].

Discussions

In this population-based study of ambulatory elderly, impaired kidney function assessed via cystatin C measures was an independent marker of prevalent AF. Chronic kidney disease defined by an estimated GFR < 60ml/min/m^2 was also associated with prevalent AF among participants without baseline cardiovascular disease. These measures of kidney function were associated with incident AF in unadjusted analysis and resulted in a 2 fold risk of developing AF in the highest cystatin C quartile compared to the lowest one. Kidney dysfunction, however, was not an independent predictor of AF risk after adjustment for confounding factors.

The independent association observed between kidney dysfunction and prevalent AF was not replicated in the incident AF analysis. These findings suggest that kidney disease and AF may share a common pathologic link. Residual confounding most likely explains the significant discrepancy seen between the unadjusted and adjusted analysis of incident AF. Both kidney disease and AF have several common risk factors including hypertension, CHD and CHF. The presence of impaired kidney function appears to reflect the cumulative effects and severity of hypertension, other cardiovascular risk factors, and atherosclerosis. Unlike the associations of kidney dysfunction with cardiovascular events and heart failure, which are independent of these other risk factors, we found almost no residual association with incident AF. It is possible that we may have over-fitted our multivariate models, as hypertension and elevated CRP levels may, in part, be a consequence of kidney impairment. In addition, severe kidney dysfunction could have an independent association with AF; *however*, few participants in CHS had advanced kidney disease. Finally, given the independent association observed with prevalent AF, it is possible that the follow-up time was not adequate to appreciate the risk of incident AF among patients with kidney dysfunction.

We had hypothesized that kidney dysfunction would have an independent association with *the risk for developing* AF. Atrial remodeling and AF are closely related to angiotensin overproduction (15,33-36) and are inhibited by agents that block RAAS activation.(13) In addition, the pathophysiology behind CHF, LVH and poorly controlled hypertension are

influenced by impaired kidney function, which has been implicated in neurohormonal activation including angiotensin and aldosterone overproduction.(16-19) These mechanisms may explain the association observed with prevalent AF as has been observed with CHF, LVH and hypertension.

This study has certain limitations. In our multivariate analyses, we adjusted for predictors of incident atrial fibrillation that may, in part, be exacerbated by impaired kidney function, such as CRP levels and the presence of CHF, LVH and hypertension. These covariates could, therefore, actually be mediators of an underlying causal effect between kidney dysfunction and AF, rather than simply confounders. As a result, our multivariate models may have overfit. In addition there may have been misclassification of the outcome as AF may have occurred and disappeared outside of the annual clinic visits or hospitalizations. As a result, subjects with paroxysmal AF may have been in sinus rhythm during the annual follow-up visits, which would underestimate the true incidence of AF. In addition, the type of AF, whether symptomatic or asymptomatic (paroxysmal, persistent, or chronic), cannot be fully discriminated in this study. Glomerular filtration rate was not directly measured in this study. Although cystatin C concentrations are largely determined by kidney function, non-renal influences on cystatin C may exist.(37)

In summary, we found that impaired kidney function has an independent association with prevalent AF. These associations, however, do not remain independent for the risk of incident AF.

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Table 1

Comparison of baseline characteristics

Characteristics	No Atrial Fibrillation N=3742	Incident Atrial Fibrillation N=579	Prevalent Atrial Fibrillation N=342	P-value
Demographic				
Age (years)	75 (5.2)	76 (5.4)	77 (5.9)	< 0.001
Male (% male)	1494 (40%)	277 (48%)	174 (51%)	< 0.001
African-American	686 (18%)	72 (12%)	44 (13%)	< 0.001
Smoking Status				
Never	1685 (46%)	256 (45%)	140 (41%)	0.099
Former	1598 (44%)	261 (46%)	183 (54%)	<0.001
Current	383 (10%)	53 (9%)	16 (5%)	0.001
Medical history				
Hypertension	1488 (40%)	291 (50%)	160 (47%)	< 0.001
Anti HTN meds	1774 (47%)	352 (61%)	236 (69%)	<0.001
Diabetes	543 (15%)	110 (19%)	71 (21%)	< 0.001
Prevalent CHD	715 (19%)	170 (29%)	122 (36%)	< .0001
Prevalent CHF	170 (5%)	48 (8%)	61 (18%)	< 0.001
ECG LVH	169 (5%)	40 (7%)	29 (9%)	0.001
Measurements				
BMI	27 ± 4.7	27 ± 5.0	26 ± 4.6	0.007
LDL (mg/dL)	129 ± 34	124 ± 32	119 ± 32	< 0.001
HDL (mg/dL)	54 ±15	52 ± 14	51 ± 14	< 0.001
Triglycerides (mg/dL)	144 ± 59	144 ± 80	144 ± 92	0.999
Albumin (g/dL)	3.9 ± 0.3	3.9 ± 0.3	3.9 ± 0.3	0.008
Glucose (mg/dL)	108 ± 35	110 ± 35	113 ± 40	0.061
Fibrinogen (mg/dL)	330 ± 68	329 ± 74	334 ± 68	0.501
CRP (mg/dL)	2.6 [1.2, 5.7]	3.0 [1.3-6.7]	3.4 [1.6-7.8]	< 0.001
Renal Function				
Cystatin-C (mg/L)	1.10 ± 0.34	1.16 ± 0.31	1.23 ± 0.41	< 0.001
Creatinine (mg/dL)	0.91 ± 0.41	0.94 ± 0.31	1.00 ± 0.35	< 0.001
eGFR (ml/min/1.73m^2)	82.6 ± 23.3	80.6 ± 23.7	76.1 ± 23.1	< 0.001
Medications				
ACE-I	394 (11%)	78 (14%)	54 (16%)	0.003
B-Blockers	403 (11%)	98 (17%)	57 (17%)	0.001
Calcium channel blockers	565 (18%)	138 (24%)	102 (30%)	<0.001
Diuretics	936 (25%)	189 (33%)	137 (40%)	<0.001

HTN, hypertensive; CHD, coronary heart disease; CHF, congestive heart failure; LVH, left ventricular hypertrophy; BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein; CRP, C reactive protein; and eGFR, estimated glomerular filtration rate.

Table 2

Association of CystatinC with Atrial Fibrillation

Measure and Outcome	Quartile I	Quartile 2	Quartile 3	Quartile 4
Cystatin C and Prevalent AF				
Range of Values — mg/liter	≤0.92	0.93-1.05	1.06-1.22	≥1.23
No.	1172	1227	1108	1156
No. with prevalent atrial fibrillation	48	66	97	131
Odds Ratio (95% CI)				
Unadjusted	1.00	1.19 (0.80-1.76)	2.00 (1.38-2.88)	2.87 (2.03-4.07)
Adjusted*	1.00	1.05 (0.71-1.57)	1.52 (1.03-2.23)	1.53 (1.03-2.28)
Cystatin C and Incident AF				
Range of Values — mg/liter	≤0.92	0.93-1.05	1.06-1.22	≥1.23
No. at risk	1124	1161	1011	1025
No. with incident atrial Fibrillation	111	162	141	165
Hazard Ratio (95% CI)				
Unadjusted	1.00	1.37 (1.07-1.75)	1.43 (1.11-1.84)	1.88 (1.47-2.41)
Adjusted*	1.00	1.21 (0.95-1.55)	1.11 (0.85-1.44)	1.14 (0.87-1.50)

*Adjusted for age, gender, race, diabetes , CRP, LDL, HDL, prevalent CHD, prevalent CHF, left ventricular hypertrophy, SBP, DBP, use of angiotensin converting enzyme inhibitor, beta blocker, calcium channel blocker and diuretic.

Table 3

Association of eGFR with Atrial Fibrillation

Measure and Outcome		
eGFR and Prevalent atrial fibrillation		
Range of Values — ml/min/1.73m^2	≥60	<60
No.	4027	636
No. with atrial Fibrillation	268	74
Odds Ratio (95% CI)		
Unadjusted	1.00	1.92 (1.45-2.56)
Adjusted*	1.00	1.22 (0.89-1.66)
eGFR and Incident atrial fibrillation		
Range of Values — ml/min/1.73m^2	≥60	<60
No. at risk	3759	562
No. with atrial Fibrillation	494	85
Hazard Ratio (95% CI)		
Unadjusted	1.00	1.29(1.02-1.64)
Adjusted*	1.00	0.92 (0.72-1.19)

*Adjusted for age, gender, race, diabetes, CRP, LDL, HDL, prevalent CHD, prevalent CHF, left ventricular hypertrophy, SBP, DBP, use of angiotensin converting enzyme inhibitor, beta blocker, calcium channel blocker and diuretic.