Factors Associated with a Large Decline in Renal Function or Progression to Renal Insufficiency in Hospitalized Atrial Fibrillation Patients with Early-Stage CKD

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Summary

Clinicians must consider renal function when administering anticoagulants for atrial fibrillation (AF). Determination of risk factors for renal function decline may enable identification of patients who require closer monitoring. We investigated the characteristics associated with renal function decline in patients with AF. The study cohort consisted of 631 AF patients who had at least one readmission during the follow-up period and stages 1-3 chronic kidney disease (CKD). The primary outcome measure was large renal function decline ($\geq 30\%$ decrease from baseline estimated glomerular filtration rate [eGFR]). The secondary outcome measure was a final eGFR < 60 mL/minute/1.73 m² for those with a baseline eGFR above this level. The mean eGFR was 74.4 ± 18.5 mL/minute/1.73 m², and the mean follow-up time was 30.2 ± 13.2 months. The primary outcome occurred in 155 patients (24.6%) and was associated with congestive heart failure (CHF), proteinuria, type of AF, and left atrial diameter (LAD) ≥ 45 mm. Among 478 patients with a baseline eGFR ≥ 60 mL/minute/1.73 m², 137 (28.7%) progressed to renal failure (eGFR < 60 mL/minute/1.73 m²). A decreasing eGFR was associated with age ≥ 75 years, CHF, lower baseline eGFR, and LAD ≥ 45 mm. CHF, proteinuria, type of AF, and LAD ≥ 45 mm were associated with eGFR decline $\geq 30\%$ in AF patients with CKD stages 1-3. Advanced age, CHF, lower baseline eGFR, and LAD ≥ 45 mm were associated with progression to renal insufficiency. These results should be considered when identifying patients who require more frequent monitoring of eGFR.

(Int Heart J 2020; 61: 239-248)

Key words: Left atrial diameter, eGFR decline

Atrial fibrillation (AF), the most common type of cardiac arrhythmia, affects 8%-10% of individuals older than 75 years and increases the risk of stroke and all-cause mortality.¹⁾ Renal insufficiency is a common co-morbidity in patients with AF that has a major adverse impact on clinical outcomes.^{2,3)} Reduced renal function may also be associated with AF complications. In particular, a study that followed 617 patients with AF for more than 2 years reported that a decline in the estimated glomerular filtration rate (eGFR) of 25% or more over 6 months was associated with a more than two-fold increase in the rate of stroke and death.⁴⁾ Diagnosis and evaluation of renal function is a key component of AF management, especially for patients taking novel oral anticoagulants (NOACs).

Previous studies of patients with AF reported the following risk factors were associated with renal outcome,

based on different definitions of worsening renal function: anticoagulation therapy,⁵⁾ chronic kidney disease (CKD),⁶⁾ coronary artery disease (CAD),⁶⁾ old age,⁷⁾ ratio of early mitral inflow velocity to global diastolic strain rate,⁸⁾ ankle-brachial pressure index,⁹⁾ and CHA₂DS₂-VASc score.¹⁰⁾ Other studies reported that echocardiographic measures of impaired left ventricular function¹¹⁾ and increased left atrial diameter (LAD)¹²⁾ predict progression to dialysis or faster renal function decline in patients with and without AF who have CKD stages 3-5.

However, few studies have evaluated the association between echocardiographic parameters and renal outcome in AF patients with early-stage CKD. We performed a retrospective, case-control study to investigate changes in the eGFR over time and the relationship between the echocardiographic parameters and renal function decline in hospitalized AF patients with CKD stages 1-3.

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This work was supported by National Natural Science Foundation of China (Grant No. 81530013 and 81600243), National Key R&D Program of China (2017YFC1307804), Jiangxi Provincial Science Foundation (210171ACB20033).

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Received for publication April 22, 2019. Revised and accepted November 14, 2019.

Released in advance online on J-STAGE March 14, 2020.

doi: 10.1536/ihj.19-205

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Methods

Study patients: This retrospective cohort study recruited inpatients with AF from the cardiovascular department of the Second Affiliated Hospital of Nanchang University (Ji-angxi, China) who had more than two measurements of serum creatinine (SCr) from June 2011 to August 2017. All patients had non-valvular AF, were at least 18 years old and had available SCr for more than 1 year interval. The exclusion criteria were the presence of rheumatic valvular disease or a prosthetic heart valve, an eGFR < 30 mL/minute/1.73 m², and having received chemotherapy for cancer. The data extracted at baseline were the laboratory data and comorbidities (hypertension, diabetes mellitus, congestive heart failure [CHF], stroke/transient ischemic attack [TIA], CAD, peripheral artery disease [PAD], and chronic obstructive pulmonary disease [COPD]). The presence of proteinuria was defined by a urine dipstick test result of 1+ or higher. Information on the use of medications during the study period, including antiplatelet drugs, NOACs, warfarin, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β -blockers, calcium channel blockers, diuretics, and HMG-CoA reductase inhibitors (statins), was obtained from the medical records.

Echocardiography was used to measure LAD, left ventricular end-diastolic dimension (LVEDd), left ventricular end-systolic dimension (LVESd), left ventricular posterior wall thickness (LVPWT), interventricular septal thickness (IVST), and left ventricular ejection fraction (LVEF). Left ventricular mass (LVM) was calculated using the standard formula:¹³⁾ $LVM (g) = 0.8 \times 1.04 [(LVEDd + IVST + LVPWT)^3 - LVEDd^3] + 0.6$. The baseline stroke risk was assessed using the CHADS₂ score (in which 1 point was given for CHF, hypertension, age 75 years or older, and diabetes mellitus and 2 points for a history of stroke/TIA/thromboembolism) and the CHA₂DS₂-VASc score (in which 1 point was given for CHF, hypertension, diabetes mellitus, age of 65-74 years, vascular disease, and female sex and 2 points for age of 75 years or older and previous stroke/TIA/thromboembolism).¹⁴⁾

The reasons for readmission include stroke/TIA; CHF; myocardial infarction; new angina; AF or other supraventricular arrhythmia; ventricular arrhythmia; implantation of a pacemaker; syncope; surgery (catheter ablation for AF, percutaneous transluminal coronary angioplasty, lower extremity arterial thrombectomy, or other); other non-cardiovascular cause (gastrointestinal, diabetic, injury/fall, fracture, psychiatric, hematologic, genitourinary, or other); and non-severe infection. Major bleeding was defined as a reduction in the hemoglobin level of at least 2 g/L, transfusion of at least two units of blood, or intracranial bleeding.

Renal outcomes: At baseline and the last follow-up, SCr was measured by the same laboratory, and measurements were also recorded at hospital admission. The mean follow-up was 30.2 ± 13.2 months, with a mean of 2.5 ± 1.9 measurements per patient. The eGFR was calculated using the CKD Epidemiology (CKD-EPI) collaboration equation.¹⁵⁾ All patients were classified into four eGFR categories according to the Kidney Disease: Improving

Global Outcomes guidelines:¹⁶⁾ normal renal function (eGFR ≥ 90 mL/minute/1.73 m², CKD stage 1), mild reduction of eGFR (60-89 mL/minute/1.73 m², CKD stage 2), moderate reduction in eGFR (30-59 mL/minute/1.73 m², CKD stage 3), and severe reduction in eGFR (< 30 mL/minute/1.73 m², CKD stages 4-5). Longitudinal changes in eGFR were determined during the follow-up period, based on two measures of renal function. The sequential change in eGFR at the last follow-up was calculated as the relative difference. The relative difference was defined as (eGFR at the last measure - eGFR at baseline)/eGFR at baseline. The annual rate of renal function decline (Δ eGFR/year) was defined as (eGFR at the last measure - eGFR at baseline)/eGFR at baseline/follow-up period. The primary endpoint was a $\geq 30\%$ decrease in eGFR, based on the previous finding that this decrease predicts subsequent end-stage renal disease.¹⁷⁾ A secondary analysis, which excluded 153 patients, examined the development of an incident eGFR < 60 mL/minute/1.73 m², and only included patients whose eGFR was 60 mL/minute/1.73 m² or more at baseline.

Statistical analysis: Each continuous variable is expressed as mean $\pm$ SD or as median and interquartile range, and each categorical variable is expressed as a percentage. Differences between groups were evaluated using the χ^2 test for categorical variables and an independent *t*-test for continuous variables.

The change in the percentage of patients in each of the four eGFR categories from baseline to follow-up were determined for patients with an LAD < 45 mm and for patients with an LAD ≥ 45 mm, as described previously.¹⁸⁾ The variables associated with large renal function decline during the follow-up period ($\geq 30\%$ decline in eGFR) and with the development of an eGFR < 60 mL/minute/1.73 m² were identified. The independent effects of different variables on renal function were identified using multivariate logistic regression analysis. All variables with *P*-values < 0.10 in the univariate logistic regression analysis were included as independent variables in the multivariable logistic regression analysis. A two-sided *P*-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS ver. 23 (IBM Corp).

Results

The detailed rehospitalization reasons were shown in Table I. The most common reasons for rehospitalization were cardiovascular event (49.1%), non-cardiovascular disease (30.3%), and non-severe infection (11.7%). We examined the records of 631 patients who were hospitalized with AF. The mean age was 72.3 ± 8.9 years, 289 patients (45.8%) were female, the mean CHADS₂ score was 2.4 ± 1.4 , and the mean CHA₂DS₂-VASc score was 3.9 ± 1.7 . A total of 72.6% of patients had a CHADS₂ score ≥ 2 , and 91.6% had a CHA₂DS₂-VASc score ≥ 2 . The overall mean baseline eGFR was 74.4 ± 18.5 mL/minute/1.73 m². In addition, 54.2% of patients (*n* = 342) had mild renal impairment (eGFR 60-89 mL/minute/1.73 m²) and 24.2% of patients (*n* = 153) had moderate renal impairment (eGFR 30-59 mL/minute/1.73 m²).

Factors associated with large decline in renal function:

Table I. Reasons for Hospitalization

Characteristic	Overall (<i>n</i> = 631)	eGFR decline < 30% (<i>n</i> = 476)	eGFR decline ≥ 30% (<i>n</i> = 155)
Patients with a cardiovascular hospitalization			
Congestive heart failure	102 (16.2%)	70 (14.7%)	32 (20.6%)
Ischemic stroke or TIA	97 (15.4%)	73 (15.3%)	24 (15.5%)
AF and other supraventricular rhythm disorders	71 (11.3%)	56 (11.8%)	15 (9.7%)
Ventricular arrhythmia	6 (1.0%)	5 (1.1%)	1 (0.6%)
New angina	9 (1.4%)	5 (1.1%)	4 (2.6%)
Myocardial infarction	10 (1.6%)	5 (1.1%)	5 (3.2%)
Implantation of a pacemaker	10 (1.6%)	5 (1.1%)	5 (3.2%)
Syncope	5 (0.8%)	3 (0.6%)	2 (1.3%)
Patients with hospitalization due to any bleeding	16 (2.5%)	11 (2.3%)	5 (3.2%)
Patients hospitalized for non-cardiovascular reason	191 (30.3%)	164 (34.5%)	27 (17.4%)
Non-severe infection	74 (11.7%)	50 (10.5%)	24 (15.5%)
Surgery	40 (6.3%)	29 (6.1%)	11 (7.1%)

Table II compares the baseline characteristics of all patients (*n* = 631), those with a small eGFR decline (< 30%, *n* = 476), and those with a large eGFR decline (≥ 30%, *n* = 155). The mean decline in eGFR was 2.4% ± 7.0% per year in patients with a small eGFR decline and 20.5% ± 9.9% per year in patients with a large eGFR decline (*P* = 0.000). Relative to patients with a small eGFR decline, those with a large decline were older, more likely to have persistence or permanent AF, CHF, proteinuria, and a high level of brain natriuretic peptide and to use an ACEI and/or ARB, a diuretic, and a β-blocker. In addition, patients with a large eGFR decline had significantly increased LAD, LVEDd, LVESd, and LVM, and lower LVEF. The use of anticoagulants was not different between the two groups. Interestingly, although eGFR at baseline was lower in the group with the large eGFR decline, the two groups had no significant difference in SCr at baseline.

Table III shows the results of univariate and multivariate analyses of the factors associated with a large eGFR decline. The univariate analysis showed that a large eGFR decline had significant positive correlations with baseline eGFR and LVEF and significant negative correlations with persistence or permanent AF, CHF, proteinuria, LAD, LVEDd, LVESd, LVM, and use of a β-blocker, a diuretic, and an ACEI and/or ARB. The multivariate analysis indicated that a large eGFR decline was independently associated with type of AF, CHF, proteinuria, and LAD ≥ 45 mm after adjustment for potential confounders.

Effect of LAD on changes in renal function: We compared the decline of renal function in patients who had a large LAD (≥ 45 mm, *n* = 190) with those who had a small LAD (< 45 mm, *n* = 434) (Figure 1). Most patients experienced a decreased eGFR, and there was a parallel increase in the prevalence of moderate and severe renal dysfunction in both groups. A total of 13.7% of the patients with a large LAD progressed to severe renal impairment, but only 6.2% of those with a small LAD progressed to severe renal impairment (*P* = 0.002).

We also analyzed the effect of LAD in a subgroup of patients (*n* = 492) who had an LVEF ≥ 50% (Figure 2). Patients with a large LAD had a 19.4% decline in eGFR, but those with a small LAD had an 11.5% decline in

eGFR (*P* = 0.003). Thus, patients who had left atrial dilation experienced greater reductions in eGFR.

Risk of progression to low eGFR (< 60 mL/minute/1.73 m²): At baseline, 478 (75.8%) patients had an eGFR ≥ 60 mL/minute/1.73 m². During follow-up (mean duration: 30.5 ± 13.1 months), 137 (28.7%) patients with an eGFR ≥ 60 mL/minute/1.73 m² developed an eGFR < 60 mL/minute/1.73 m² (Table IV); these patients were older, more likely to have CHF and CAD, had higher levels of brain natriuretic peptide and SCr, had higher CHADS₂ and CHA₂DS₂-VASc scores, and were more likely to use a β-blocker and a diuretic. Echocardiography indicated that patients with an eGFR < 60 mL/minute/1.73 m² had a lower mean LVEF and a greater mean LAD, LV dimension, and LVM than those with an eGFR ≥ 60 mL/minute/1.73 m². There was no significant difference in the use of anticoagulants between two groups.

Table V displays the results of univariate and multivariate analyses of factors associated with progression to an eGFR < 60 mL/minute/1.73 m². CHADS₂ and CHA₂DS₂-VASc scores were excluded from the multivariate analysis because the other factors in the model already considered age, sex, CAD, and CHF. The multivariate analysis indicated that an eGFR < 60 mL/minute/1.73 m² at follow-up correlated independently with age of 75 years or more, CHF, an initial eGFR < 90 mL/minute/1.73 m², and an LAD ≥ 45 mm.

Discussion

The present retrospective longitudinal cohort “real-world” study of patients hospitalized with AF indicated that 24.6% of patients with early-stage CKD experienced a decrease of eGFR ≥ 30% from baseline. This is similar to the value of 24.4% reported by Yao and colleagues.⁵ Moreover, 28.7% of patients with normal or mild loss of renal function (eGFR ≥ 60 mL/minute/1.73 m²) at baseline experienced a decline in renal function to moderate/severe renal insufficiency (eGFR < 60 mL/minute/1.73 m²). CHF, proteinuria, and type of AF were associated with a large decline in renal function; older age, CHF, and lower baseline eGFR were associated with progression to renal insufficiency. In addition, an LAD ≥ 45 mm was independ-

Table II. Baseline Characteristics of Patients Who Did and Did Not Have a Large Decline of eGFR ($\geq 30\%$) at Follow-Up

Characteristic	Overall (<i>n</i> = 631)	eGFR decline < 30% (<i>n</i> = 476)	eGFR decline $\geq 30\%$ (<i>n</i> = 155)	<i>P</i> value
Δ eGFR/year	6.8% $\pm$ 11.0%	2.4% $\pm$ 7.0%	20.5% $\pm$ 9.9%	0.000
Age (years)	72.3 $\pm$ 8.9	71.9 $\pm$ 9.0	73.5 $\pm$ 8.6	0.062
Age ≥ 75 years	290 (46.0%)	213 (44.7%)	77 (49.7%)	0.285
Atrial fibrillation				0.005
Paroxysmal	415 (65.8%)	329 (69.1%)	86 (55.5%)	
Persistence	173 (27.4%)	120 (25.2%)	53 (34.2%)	
Permanent	43 (6.8%)	27 (5.7%)	16 (10.3%)	
Duration of AF (years)	2.3 $\pm$ 5.2	2.3 $\pm$ 5.2	2.4 $\pm$ 5.1	0.865
Female sex	289 (45.8%)	210 (44.1%)	79 (51.0%)	0.137
Hypertension	437 (69.3%)	325 (68.3%)	112 (72.3%)	0.351
Diabetes mellitus	136 (21.6%)	100 (21.0%)	36 (23.2%)	0.560
CHF	288 (45.6%)	196 (41.2%)	92 (59.4%)	< 0.001
Previous stroke	181 (28.7%)	142 (29.8%)	39 (25.2%)	0.264
CAD	103 (16.3%)	73 (15.3%)	30 (19.4%)	0.240
PAD	15 (2.4%)	13 (2.7%)	2 (1.3%)	0.472
COPD	68 (10.8%)	51 (10.7%)	17 (11.0%)	0.930
CHADS ₂ score, mean	2.4 $\pm$ 1.4	2.4 $\pm$ 1.4	2.6 $\pm$ 1.4	0.112
Score ≥ 2	458 (72.6%)	337 (70.8%)	121 (78.1%)	0.078
CHA ₂ DS ₂ -VASc score, mean	3.9 $\pm$ 1.7	3.8 $\pm$ 1.7	4.1 $\pm$ 1.7	0.041
Score ≥ 2	578 (91.6%)	431 (90.5%)	147 (94.8%)	0.094
Laboratory parameters				
Total cholesterol (mg/dL)	150.2 $\pm$ 32.2	151.4 $\pm$ 31.5	146.5 $\pm$ 34.1	0.111
LDL cholesterol (mg/dL)	89.7 $\pm$ 29.8	91.1 $\pm$ 30.3	85.6 $\pm$ 28.1	0.051
HDL cholesterol (mg/dL)	39.6 $\pm$ 11.0	39.9 $\pm$ 10.8	38.8 $\pm$ 11.6	0.301
Proteinuria	51 (8.3%)	29 (6.2%)	22 (14.7%)	0.001
Brain natriuretic peptide (pg/mL)	337.1 (146.6, 648.5)	287.8 (140.2, 589.9)	474.7 (198.4, 714.5)	0.013
Serum creatinine (μ mol/L)	82.4 $\pm$ 25.8	81.3 $\pm$ 24.5	85.9 $\pm$ 29.3	0.083
eGFR (mL/minute/1.73 m ²), mean	74.4 $\pm$ 18.5	75.5 $\pm$ 18.2	70.8 $\pm$ 19.0	0.006
≥ 90 (%)	136 (21.6%)	111 (23.3%)	25 (16.1%)	0.051
60–89 (%)	342 (54.2%)	259 (54.4%)	83 (53.5%)	—
30–59 (%)	153 (24.2%)	106 (22.3%)	47 (30.3%)	—
Medication use				
Antiplatelet	252 (40.6%)	193 (41.1%)	59 (39.1%)	0.665
NOAC	49 (7.9%)	36 (7.7%)	13 (8.6%)	0.706
Warfarin	254 (40.9%)	192 (40.9%)	62 (41.1%)	0.964
β -blocker	427 (68.8%)	308 (65.5%)	112 (74.2%)	0.048
Calcium channel blocker	201 (32.4%)	149 (31.7%)	52 (34.4%)	0.532
Diuretic	207 (33.3%)	141 (30.0%)	66 (43.7%)	0.002
ACEI and/or ARB	337 (54.4%)	236 (50.3%)	91 (60.3%)	0.033
Statin	342 (55.1%)	267 (56.8%)	75 (49.7%)	0.125
Echocardiographic data				
LVEF (%)	57.5 $\pm$ 11.9	58.2 $\pm$ 11.8	55.4 $\pm$ 11.9	0.013
LVEF < 50%	132 (21.2%)	90 (19.1%)	42 (27.3%)	0.032
LAD (mm)	41.6 $\pm$ 7.3	40.9 $\pm$ 7.0	43.5 $\pm$ 7.7	< 0.001
LAD ≥ 45 mm (%)	190 (30.4%)	126 (26.8%)	64 (41.6%)	0.001
LVEDd (mm)	49.7 $\pm$ 7.5	49.1 $\pm$ 7.1	51.6 $\pm$ 8.2	< 0.001
LVESd (mm)	34.6 $\pm$ 8.4	34.0 $\pm$ 8.2	36.5 $\pm$ 8.8	0.001
LVPWT (mm)	9.6 $\pm$ 1.2	9.6 $\pm$ 1.2	9.7 $\pm$ 1.2	0.307
IVST (mm)	10.2 $\pm$ 1.3	10.2 $\pm$ 1.2	10.3 $\pm$ 1.4	0.688
LVM (g)	181.5 $\pm$ 55.6	177.3 $\pm$ 53.1	194.0 $\pm$ 61.1	0.001
Follow-up period (months)	30.2 $\pm$ 13.2	29.7 $\pm$ 12.8	31.9 $\pm$ 14.3	0.090

eGFR indicates estimated glomerular filtration rate; CHF, congestive heart failure; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NOACs, non-vitamin K antagonist oral anticoagulants; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LVPWT, left ventricular posterior wall thickness; IVST, interventricular septal thickness; and LVM, left ventricular mass.

ently associated with a large decline in renal function and a low eGFR (< 60 mL/minute/1.73 m²). These results suggest that renal function should be more closely monitored

in this group of patients.

Previous epidemiological studies have used the decline of eGFR as a clinical endpoint.^{19,20} However, the cri-

Table III. Logistic Regression Analysis of Factors Associated with a Large eGFR Decline ($\geq 30\%$) at Follow-Up

Characteristic	Univariate		Multivariate	
	OR (95% CI)	P value	aOR (95% CI)	P value
Age ≥ 75 years	1.22 (0.85 to 1.75)	0.285	—	—
Atrial fibrillation				
Paroxysmal	1.00 (reference)	—	1.00 (reference)	—
Persistence	1.69 (1.13 to 2.52)	0.010	1.58 (1.04 to 2.41)	0.032
Permanent	2.27 (1.17 to 4.40)	0.015	2.07 (1.01 to 4.26)	0.047
Duration of AF (years)	1.00 (0.97 to 1.04)	0.865	—	—
Female sex	1.32 (0.92 to 1.89)	0.138	—	—
Hypertension	1.21 (0.81 to 1.81)	0.351	—	—
Diabetes mellitus	1.14 (0.74 to 1.75)	0.560	—	—
CHF	2.09 (1.44 to 3.02)	< 0.001	2.04 (1.37 to 3.02)	0.000
Previous stroke	0.79 (0.52 to 1.20)	0.265	—	—
CAD	1.33 (0.83 to 2.12)	0.241	—	—
PAD	0.47 (0.10 to 2.09)	0.318	—	—
COPD	1.03 (0.57 to 1.84)	0.930	—	—
CHADS ₂ score, mean	1.11 (0.98 to 1.27)	0.113	—	—
Score ≥ 2	1.47 (0.96 to 2.25)	0.079	—	—
CHA ₂ DS ₂ -VASc score, mean	1.12 (1.00 to 1.24)	0.041	—	—
Score ≥ 2	1.92 (0.88 to 4.16)	0.099	—	—
Laboratory parameters				
Total cholesterol (mg/dL)	1.00 (0.99 to 1.00)	0.111	—	—
LDL cholesterol (mg/dL)	0.99 (0.99 to 1.00)	0.051	—	—
HDL cholesterol (mg/dL)	0.99 (0.97 to 1.01)	0.301	—	—
Proteinuria	2.60 (1.44 to 4.67)	0.001	2.43 (1.29 to 4.55)	0.006
Brain natriuretic peptide (pg/mL)	1.00 (1.00 to 1.01)	0.152	—	—
Serum creatinine ($\mu\text{mol/L}$)	1.01 (1.00 to 1.01)	0.058	—	—
eGFR (mL/minute/1.73 m ²)				
≥ 90	1.00 (reference)	—	—	—
60–89	1.42 (0.86 to 2.34)	0.166	—	—
30–59	1.97 (1.13 to 3.42)	0.016	—	—
Medication use				
Antiplatelet	0.92 (0.63 to 1.34)	0.665	—	—
NOAC	1.14 (0.59 to 2.20)	0.707	—	—
Warfarin	1.01 (0.70 to 1.46)	0.964	—	—
β -blocker	1.51 (1.00 to 2.28)	0.049	—	—
Calcium channel blocker	1.13 (0.77 to 1.67)	0.532	—	—
Diuretic	1.81 (1.24 to 2.64)	0.002	—	—
ACEI and/or ARB	1.50 (1.03 to 2.17)	0.034	—	—
Statin	0.75 (0.52 to 1.08)	0.126	—	—
Echocardiographic data				
LVEF (%)	0.98 (0.97 to 1.00)	0.014	—	—
LAD ≥ 45 mm (%)	1.94 (1.33 to 2.84)	0.001	1.55 (1.03 to 2.32)	0.035
LVEDd (mm)	1.04 (1.02 to 1.07)	< 0.001	—	—
LVESd (mm)	1.04 (1.01 to 1.06)	0.001	—	—
LVPWT (mm)	1.08 (0.93 to 1.26)	0.306	—	—
IVST (mm)	1.03 (0.89 to 1.19)	0.688	—	—
LVM (g)	1.01 (1.00 to 1.01)	0.002	—	—
Follow-up period (months)	1.01 (1.00 to 1.03)	0.073	—	—

eGFR indicates estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; CHF, congestive heart failure; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NOACs, non-vitamin K antagonist oral anticoagulants; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LVPWT, left ventricular posterior wall thickness; IVST, interventricular septal thickness; and LVM, left ventricular mass.

teria used to define a decline of eGFR vary widely among previous studies, making comparisons difficult. We selected a $\geq 30\%$ decline in the eGFR as the endpoint, based on the December 2012 scientific workshop co-

sponsored by the National Kidney Foundation and the US Food and Drug Administration. This workshop concluded that a 30% to 40% decline in the eGFR over 2 to 3 years is an acceptable clinical endpoint for CKD progression.¹⁷⁾

Figure 1. Distribution of eGFR in patients with LAD < 45 mm (A) and ≥ 45 mm (B) at baseline and follow-up.

Figure 2. Relative reduction of eGFR in patients with LAD < 45 mm and ≥ 45 mm groups.

We also determined whether echocardiographic parameters can predict large loss of renal function in AF patients with CKD stages 1-3. Our results showed that an increased LAD at baseline was associated with an eGFR decline ≥ 30% and with an incident eGFR < 60 mL/minute/1.73 m². Relative to patients with an LAD < 45 mm, those with an LAD ≥ 45 mm were more likely to progress to severe renal impairment. In addition, our analysis of the subgroup of patients with an LVEF ≥ 50% indicated those with an LAD ≥ 45 mm experienced greater reductions in eGFR. AF is frequently associated with LA enlargement in patients with organic heart disease and in those with AF but no underlying disease.²¹⁾ However, it is difficult to establish a causal relationship between AF and LA remodeling,²²⁾ because AF frequently accompanies hypertension, CHF, and diabetes mellitus, all of which can lead to changes in the left atrial structure and function. Our cohort had high baseline prevalence of other comorbid illnesses (hypertension: 69.3%, CHF: 45.6%, diabetes mellitus: 21.6%), similar to previous reports.²³⁾ In addition, 30.4% of our patients had an LAD ≥ 45 mm, similar to the 31% reported in the AFFIRM trial.¹⁸⁾

Recent studies have reported that an enlarged left atrium is an independent predictor of adverse cardiovascular outcomes (stroke, AF, CHD, and cardiovascular death) in patients with various pathologic conditions.^{24,25)} The Fushimi AF Registry, a large community-based prospective cohort study, found that an LAD > 45 mm was an independent predictor of stroke/systemic embolism.²⁶⁾ Interestingly, a multivariate analysis by Chen, *et al.* demonstrated that an enlarged LAD was independently associated with progression to end-stage renal disease, implying that LA enlargement is a better predictor of CKD.¹²⁾ Furukawa, *et al.* determined that the LA volume index was an independent risk factor for progression to hemodialysis in 140 patients with CKD stages 4-5.²⁷⁾ Another cohort study of 121 patients undergoing peritoneal dialysis reported that an LA volume index > 32 mL/m² was significantly associated with more rapid decline in residual renal function.²⁸⁾

We found that an older age, CHF, albuminuria, type of AF, and a lower baseline eGFR were associated with a large decline in eGFR. Previous studies also reported correlations of CHF and baseline eGFR with decline in renal

Table IV. Baseline Characteristics of Patients Who Did and Did Not Develop a Low eGFR (< 60 mL/minute/1.73 m²) at Follow-Up

Characteristic	No (n = 341)	Yes (n = 137)	P value
Age (years)	70.3 ± 9.3	73.9 ± 8.1	< 0.001
≥ 75 years	120 (35.2%)	74 (54.0%)	< 0.001
Atrial fibrillation			0.118
Paroxysmal	233 (68.3%)	80 (58.4%)	
Persistence	89 (26.1%)	47 (34.3%)	
Permanent	19 (5.6%)	10 (7.3%)	
Duration of AF (years)	2.4 ± 5.1	2.8 ± 6.3	0.441
Female sex	151 (44.3%)	72 (52.6%)	0.101
Hypertension	222 (65.1%)	98 (71.5%)	0.177
Diabetes mellitus	68 (19.9%)	34 (24.8%)	0.239
CHF	122 (35.8%)	77 (56.2%)	< 0.001
Previous stroke	96 (28.2%)	37 (27.0%)	0.801
CAD	44 (12.9%)	29 (21.2%)	0.023
PAD	8 (2.3%)	2 (1.5%)	0.796
COPD	35 (10.3%)	10 (7.3%)	0.316
CHADS ₂ score, mean	2.1 ± 1.3	2.6 ± 1.4	0.001
Score ≥ 2	214 (62.8%)	106 (77.4%)	0.002
CHA ₂ DS ₂ -VASc score, mean	3.5 ± 1.8	4.2 ± 1.7	< 0.001
Score ≥ 2	296 (86.8%)	131 (95.6%)	0.005
Laboratory parameters			
Total cholesterol (mg/dL)	152.4 ± 32.7	145.7 ± 31.4	0.043
LDL cholesterol (mg/dL)	91.1 ± 30.5	88.1 ± 28.3	0.325
HDL cholesterol (mg/dL)	40.0 ± 10.6	38.9 ± 11.4	0.365
Proteinuria	15 (4.5%)	11 (8.3%)	0.106
Brain natriuretic peptide (pg/mL)	228.3 (120.2, 451.2)	354.0 (189.3, 665.2)	0.007
Serum creatinine (μmol/L)	70.1 ± 15.1	76.5 ± 16.4	< 0.001
eGFR (mL/minute/1.73 m ²)	85.2 ± 11.7	76.2 ± 11.4	< 0.001
Medication use			
Antiplatelet	133 (39.6%)	61 (45.5%)	0.238
NOACs	25 (7.4%)	11 (8.2%)	0.777
Warfarin	137 (40.8%)	54 (40.3%)	0.925
β-blocker	210 (62.5%)	99 (73.9%)	0.019
Calcium channel blocker	108 (32.1%)	41 (30.6%)	0.745
Diuretic	90 (26.8%)	57 (42.5%)	0.001
ACEI and/or ARB	163 (48.7%)	78 (58.2%)	0.062
Statin	184 (54.8%)	77 (57.5%)	0.595
Echocardiographic data			
LVEF (%)	58.6 ± 11.8	56.0 ± 11.9	0.033
LVEF < 50%	64 (18.9%)	31 (22.6%)	0.362
LAD (mm)	40.5 ± 6.8	42.6 ± 7.5	0.002
LAD ≥ 45 mm (%)	80 (23.7%)	56 (40.9%)	< 0.001
LVEDd (mm)	48.9 ± 6.9	50.6 ± 7.6	0.019
LVESd (mm)	33.7 ± 8.0	35.7 ± 8.4	0.013
LVPWT (mm)	9.5 ± 1.1	9.6 ± 1.2	0.108
IVST (mm)	10.1 ± 1.2	10.2 ± 1.3	0.587
LVM (g)	173.6 ± 51.3	186.8 ± 57.7	0.014
Follow-up period (months)	30.1 ± 12.7	31.5 ± 14.1	0.311

eGFR indicates estimated glomerular filtration rate; CHF, congestive heart failure; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NOACs, non-vitamin K antagonist oral anticoagulants; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LVPWT, left ventricular posterior wall thickness; IVST, interventricular septal thickness; and LVM, left ventricular mass.

function.²³⁾ The aging process adversely affects the kidneys and leads to an irreversible decline of renal function.²⁹⁾ Thus, our finding that a lower baseline eGFR correlated with and predicted renal function decline was an

expected result.³⁰⁾ In fact, some studies have reported that the presence of proteinuria was associated with a more rapid decline of renal function.^{31,32)} Notably, factors such as age and CHF are components of the widely used

Table V. Logistic Regression Analysis of Factors Associated with a Low eGFR (< 60 mL/minute/1.73 m²) at Follow-Up

	Univariate		Multivariate	
	OR (95% CI)	P value	aOR (95% CI)	P value
Age ≥ 75 years	2.16 (1.45 to 3.24)	< 0.001	1.84 (1.17 to 2.90)	0.008
Atrial fibrillation				
Paroxysmal	1.00 (reference)	—	—	—
Persistence	1.54 (0.99 to 2.38)	0.053	—	—
Permanent	1.53 (0.68 to 3.44)	0.299	—	—
Duration of AF (years)	1.01 (0.98 to 1.05)	0.442	—	—
Female sex	1.39 (0.94 to 2.07)	0.102	—	—
Hypertension	1.35 (0.87 to 2.08)	0.177	—	—
Diabetes mellitus	1.33 (0.83 to 2.12)	0.240	—	—
CHF	2.30 (1.54 to 3.45)	< 0.001	1.89 (1.20 to 2.98)	0.006
Previous stroke	0.94 (0.61 to 1.47)	0.801	—	—
CAD	1.81 (1.08 to 3.04)	0.024	—	—
PAD	0.62 (0.13 to 2.94)	0.544	—	—
COPD	0.69 (0.33 to 1.43)	0.318	—	—
CHADS ₂ score, mean	1.29 (1.11 to 1.49)	0.001	—	—
Score ≥ 2	2.03 (1.29 to 3.20)	0.002	—	—
CHA ₂ DS ₂ -VAsC score, mean	1.28 (1.14 to 1.43)	< 0.001	—	—
Score ≥ 2	3.32 (1.38 to 7.97)	0.007	—	—
Laboratory parameters				
Total cholesterol (mg/dL)	0.99 (0.99 to 1.00)	0.044	—	—
LDL cholesterol (mg/dL)	1.00 (0.99 to 1.00)	0.324	—	—
HDL cholesterol (mg/dL)	0.99 (0.97 to 1.01)	0.365	—	—
Proteinuria	1.92 (0.86 to 4.30)	0.111	—	—
Brain natriuretic peptide (pg/mL)	1.00 (1.00 to 1.00)	0.122	—	—
Serum creatinine (μmol/L)	1.03 (1.01 to 1.04)	< 0.001	—	—
eGFR ≥ 90 mL/minute/1.73 m ²	1.00 (reference)	—	—	—
eGFR 60–89 mL/minute/1.73 m ²	3.50 (2.03 to 6.03)	< 0.001	3.28 (1.75 to 6.16)	< 0.001
Medication use				
Antiplatelet	1.28 (0.85 to 1.91)	0.238	—	—
NOAC	1.11 (0.53 to 2.33)	0.777	—	—
Warfarin	0.98 (0.65 to 1.48)	0.925	—	—
β-blocker	1.70 (1.09 to 2.65)	0.020	—	—
Calcium channel blocker	0.93 (0.60 to 1.44)	0.745	—	—
Diuretic	2.02 (1.33 to 3.08)	0.001	—	—
ACEI and/or ARB	1.47 (0.98 to 2.20)	0.062	—	—
Statin use	1.12 (0.75 to 1.67)	0.595	—	—
Echocardiographic data				
LVEF (%)	0.98 (0.97 to 1.00)	0.033	—	—
LAD ≥ 45 mm (%)	2.23 (1.46 to 3.40)	< 0.001	2.20 (1.36 to 3.56)	0.001
LVEDd (mm)	1.03 (1.01 to 1.06)	0.020	—	—
LVESd (mm)	1.03 (1.01 to 1.06)	0.014	—	—
LVPWT (mm)	1.15 (0.97 to 1.36)	0.109	—	—
IVST (mm)	1.05 (0.89 to 1.22)	0.586	—	—
LVM (g)	1.00 (1.00 to 1.01)	0.016	—	—
Follow-up period (months)	1.01 (0.99 to 1.02)	0.311	—	—

eGFR indicates estimated glomerular filtration rate; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; CHF, congestive heart failure; CAD, coronary artery disease; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NOACs, non-vitamin K antagonist oral anticoagulants; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVEDd, left ventricular end-diastolic dimension; LVESd, left ventricular end-systolic dimension; LVPWT, left ventricular posterior wall thickness; IVST, interventricular septal thickness; and LVM, left ventricular mass.

CHADS₂ and CHA₂DS₂-VAsC scores. Previous studies have also assessed the relationship between single baseline eGFR values and the risk of future stroke in patients with AF.³³⁾ Recent studies proposed that renal dysfunction had an additive effect with the CHADS₂ or CHA₂DS₂-VAsC

scores, thus improving their predictive ability;^{34,35)} in contrast, two recent “real-world” cohort studies found no additive effect of renal impairment in the ability of these scores to predict thromboembolism.^{36,37)} In contrast to previous studies, some studies reported progressive renal

function decline and subsequent risk of stroke or death in patients with AF.^{4,23)}

Potential mechanisms for the association between AF and CKD progression include systemic inflammation, repeated microemboli, and hemodynamic factors.³⁸⁾ AF promotes systemic inflammation, which has been strongly related with progression of CKD. In addition, AF can induce fibrosis of the myocardium as well as kidney fibrosis, perhaps through a systemic pro-fibrotic tendency.³⁸⁾ Moreover, AF contributes to deterioration of left ventricular systolic and diastolic function over time, which may promote CKD progression through altered hemodynamics, venous congestion, and activation of the renin-angiotensin-aldosterone system.³⁹⁾ Indeed, eGFR improved in patients whose AF was ablated successfully, compared with patients whose arrhythmia persisted after ablation intervention.⁴⁰⁾

There were some limitations to this study. First, the LA volume may provide a more accurate estimate of the LA chamber than LAD. However, we used LAD because it is easier to measure and is more frequently used in routine echocardiographic evaluations.^{24,26,41)} Second, this was an observational retrospective study; thus, we cannot infer causality from the observed associations. Third, we only included hospitalized patients in the registry; thus, selection bias cannot be ruled out. However, our study mainly focused on patients with a high risk of stroke. Fourth, only 7.9% of the included patients were taking NOACs, but 40.6% were taking antiplatelet drugs and 40.9% were taking warfarin. Thus, our patient population reflects a “real life” cohort of Chinese patients with AF who have a high risk of stroke and do not adhere to treatment guidelines.⁴²⁾

Conclusions

In conclusion, our study showed that older age, low baseline eGFR, CHF, and albuminuria were significant risk factors for a large decline of renal function in hospitalized AF patients with CKD stages 1-3. Moreover, LAD ≥ 45 mm was independently associated with a greater deterioration of renal function.

Disclosure

Ethics approval and consent to participate: This study was approved by the ethics committee of Department of Cardiovascular Medicine, the Second Affiliated Hospital of Nanchang University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon request.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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