Journal of Geriatric Cardiology | JGC
RESEARCH ARTICLE
J Geriatr Cardiol 2021; 18(11): 867–876

Chronic kidney disease and risks of adverse clinical events in patients with atrial fibrillation

Si-Tong LI[1,*], Chao JIANG[1,*], Liu HE[1], Qi-Fan LI[1], Zuohan DING[2], Jia-Hui WU[1], Rong HU[1], Qiang LV[1], Xu LI[1], Chang-Qi JIA[1], Yan-Fei RUAN[1], Man NING[1], Li FENG[1], Rong BAI[1], Ri-Bo TANG[1], Xin DU[1,3,✉], Jian-Zeng DONG[1], Chang-Sheng MA[1,✉]

1. Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University and National Clinical Research Center for Cardiovascular Diseases, Beijing, China; 2. University of Edinburgh, Edinburgh, UK; 3. Heart Health Research Centre, Beijing, China

[*]The authors contributed equally to this manuscript

✉ Correspondence to: duxinheart@sina.com; chshma@vip.sina.com

https://doi.org/10.11909/j.issn.1671-5411.2021.11.002

ABSTRACT

BACKGROUND Chronic kidney disease (CKD) is highly prevalent in patients with atrial fibrillation (AF). However, the association between CKD and clinical consequences in AF patients is still under debate.

METHODS We included 19,079 nonvalvular AF patients with available estimated glomerular filtration rate (eGFR) values in the Chinese Atrial Fibrillation Registry from 2011 to 2018. Patients were classified into no CKD (eGFR ≥ 90 mL/min per 1.73 m^2), mild CKD (60 ≤ eGFR < 90 mL/min per 1.73 m^2), moderate CKD (30 ≤ eGFR < 60 mL/min per 1.73 m^2), and severe CKD (eGFR < 30 mL/min per 1.73 m^2) groups. The risks of thromboembolism, major bleeding, and cardiovascular mortality were estimated with Fine-Gray regression analysis according to CKD status. Cox regression was performed to assess the risk of all-cause mortality associated with CKD.

RESULTS Over a mean follow-up of 4.1 ± 1.9 years, there were 985 thromboembolic events, 414 major bleeding events, 956 cardiovascular deaths, and 1,786 all-cause deaths. After multivariate adjustment, CKD was not an independent risk factor of thromboembolic events. As compared to patients with no CKD, those with mild CKD, moderate CKD, and severe CKD had a 45%, 47%, and 133% higher risk of major bleeding, respectively. There was a graded increased risk of cardiovascular mortality associated with CKD status compared with no CKD group: adjusted hazard ratio [HR] was 1.34 (95% CI: 1.07–1.68, $P = 0.011$) for mild CKD group, 2.17 (95% CI: 1.67–2.81, $P < 0.0001$) for moderate CKD group, and 2.95 (95% CI: 1.97–4.41, $P < 0.0001$) for severe CKD group, respectively. Risk of all-cause mortality also increased among patients with moderate or severe CKD.

CONCLUSIONS CKD status was independently associated with progressively higher risks of major bleeding and mortality, but didn't seem to be an independent predictor of thromboembolism in AF patients.

Atrial fibrillation (AF) is the most common arrhythmia worldwide, being associated with increased risks of cardiovascular diseases and death. Chronic kidney disease (CKD) often coexists with AF,[1,2] present in 10% to 40% of AF patients.[3,4] Besides, CKD is an independent risk factor of incident AF[5] and shares common risk factors with AF, such as older age, hypertension and diabetes mellitus.[6,7] Both CKD and AF were associated with poor prognosis, bringing growing burden to healthcare systems.[8,9]

Nevertheless, whether CKD independently confers increased risks of cardiovascular outcomes and mortality in AF patients remains controversial.[10–14] Although studies have indicated that CKD was an independent predictor of stroke,[10,11,15] the widely-used CHA_2DS_2-VASc stroke score recommended by the current guidelines did not include CKD.[6,16] Abnormal renal function was also precluded from a biomarker-based death score,[17] but was incorporated into the HAS-BLED score for bleeding risk prediction. Thus, a better understanding of the rela-

tionship between CKD and adverse outcomes is essential to the comprehensive management of AF patients.

Using data from the large, prospective Chinese Atrial Fibrillation Registry (China-AF) cohort, we intend to determine the risks of thromboembolism, major bleeding, cardiovascular mortality and all-cause mortality associated with CKD in individuals with AF.

METHODS

Study Population

The design of the China-AF study has been reported in detail previously.[18] Briefly, China-AF study is an ongoing, prospective, multicenter registry study recruiting adult patients with a documented AF from 31 tertiary and non-tertiary hospitals in Beijing, China. Informed consent was obtained from all participants. Each enrolled patient was followed up every six months by trained clinical staff. Between August 2011 and December 2018, consecutive patients ≥ 18 years old were enrolled in China-AF. From a total of 25,512 participants, we excluded those with a follow-up less than six months (n = 655), and those with mitral stenosis or valvular repair or replacement (n = 1 012). In our study, 4 766 patients having no available serum creatinine were also excluded. Finally, 19,079 eligible patients were included in the present study (Figure 1).

Estimation of Renal Function

Renal function was evaluated by the level of estimated glomerular filtration rate (eGFR),[19] using the Chronic Kidney Disease Epidemiology Collaboration equation based on baseline serum creatinine: eGFR (mL/min per 1.73 m^2) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if black), where κ is 0.7 for females and 0.9 for males; α is −0.329 for females and −0.411 for males; 'min' indicates the minimum of Scr/κ or 1; 'max' indicates the maximum of Scr/κ or 1; and Scr is serum creatinine expressed in mg/dL[20]. Patients were divided into four groups according to eGFR values: no CKD (eGFR ≥ 90 mL/min per 1.73 m^2), mild CKD (60 ≤ eGFR < 90 mL/min per 1.73 m^2), moderate CKD (30 ≤ eGFR < 60 mL/min per 1.73 m^2), and severe CKD (eGFR < 30 mL/min per 1.73 m^2) group.

Data Collection

Baseline demographic and clinical data including medical history and treatment were collected by trained staff. CHA_2DS_2-VASc score[21] (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, and sex category (female)) and HAS-BLED score[22] (hypertension (uncontrolled systolic blood pressure > 160 mmHg), abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age > 65 years), drugs and/or alcohol concomitantly) were used to assess stroke and bleeding risk, respectively.

Study Outcomes

We analyzed the time to the first occurrence of adverse clinical outcomes based on renal function. Thromboembolic events were defined as ischemic stroke or systemic embolism. Major bleeding events were defined as bleeding that was fatal, intracranial, affecting another critical anatomical site, or causing a fall in hemoglobin level ≥ 20 g/L, or leading to transfusion of ≥ 2 units of whole blood or red cells.[23] Cardiovascular mortality events were defined as death from myocardial infarction, congestive heart failure, sudden death, stroke, intracranial bleeding, other bleeding, or other cardiovascular diseases. All suspected adverse clinical outcomes were adjudicated by a central committee.

Statistical Analysis

Means ± SD or medians (interquartile range (IQR)) were calculated for continuous variables as appropriate. Categorical variables were described as percentages. Differences among groups of continuous variables were analyzed using the One-Way ANOVA test or Kruskal-Wallis test. Categorical variables were analyzed using the Chi-Square test. Cumulative incidence function (CIF) curves were employed to estimate the cumulative incidence of thromboembolism, major bleeding and cardiovascular mortality, while taking competing risks of death from other causes into account. Differences among the four groups were assessed using non-

parametric Gray's test.[24] Kaplan-Meier curves were used to illustrate cumulative incidence rates of all-cause mortality and compared by log-rank test according to renal function. Hazard ratios (HRs) and their 95% confidence intervals (CIs) of renal dysfunction groups for the risks of thromboembolism, major bleeding and cardiovascular mortality were estimated using Fine and Gray's models, separately, which took competing risks into consideration. The association between renal function and all-cause mortality was calculated by Cox proportional hazards regression models. During the process of multivariate analysis, baseline demographics, concomitant diseases and medical treatment were adjusted as confounders in each model. We defined statistical significance as a two-tailed $P < 0.05$. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Study Population

We included 19,079 eligible patients in our analysis, of whom the mean age at baseline was 63.9 ± 12.0 years, and 7229 (37.9%) were women. The median eGFR was 86.10 (IQR = 72.17–96.07) mL/min per 1.73 m^2. Among overall patients, 7626 (40.0%), 9342 (49.0%), 1925 (10.1%), and 186 (1.0%) were in no CKD group, mild CKD group, moderate CKD group, and severe CKD group, respectively. Table 1 shows the baseline characteristics in relation to eGFR values. Compared with patients with no CKD, individuals with moderate or severe CKD were older, more likely to be female and to have a history of concomitant diseases, including congestive heart failure, hypertension, diabetes mellitus, hyperlipidemia, vascular disease, and previous bleeding. Therefore, it is unsurprising that higher CHA_2DS_2-VASc and HAS-BLED scores were seen in moderate and severe CKD group. Considering antithrombotic treatment, patients with no CKD had the highest proportion of oral anticoagulation (OAC) use among the four groups, while patients with severe CKD were least likely to receive OAC therapy, even less used direct oral anticoagulants. Proportion of patients on OAC during follow-up was shown in Supplementary Figure 1.

Risk of Thromboembolism

During a mean follow-up of 4.0 ± 1.9 years, thromboembolic events occurred in 985 patients (5.2%), consisting of 230 patients (3.0%) in no CKD group, 554 patients (5.9%) in mild CKD group, 188 patients (9.8%) in moderate CKD group, and 13 patients (7.0%) in severe CKD group. The incidence rate was 1.30 per 100 person-years overall, with the highest rate of 2.47 per 100 person-years in moderate CKD group (Table 2). In patients without antithrombotic therapy at baseline, the trend of thromboembolism incidence across different CKD status was consistent with the whole population (Supplementary Table 1). The most recent antithrombotic therapy in patients with incident thromboembolism was shown in Supplementary Table 2. Cumulative incidence for thromboembolism in patients with CKD was higher than that of patients with normal renal function (Figure 2A). However, after adjustment for known risk factors, mild CKD (adjusted HR = 1.12, 95% CI: 0.94–1.33, $P = 0.201$), moderate CKD (adjusted HR = 1.21, 95% CI: 0.96–1.54, $P = 0.104$), and severe CKD (adjusted HR = 0.80, 95% CI: 0.44–1.44, $P = 0.451$) were not an independent predictor of thromboembolism (Figure 3).

Risk of Major Bleeding

Over a mean follow-up of 4.1 ± 1.9 years, there were 414 (2.2%) major bleeding events, with a corresponding rate of 0.54 per 100 person-years. Incidence rates of major bleeding events increased with worse renal function, with 0.31, 0.64, 0.81, and 1.16 per 100 person-years for patients with no CKD, mild CKD, moderate CKD, and severe CKD, respectively (Table 2). In patients without antithrombotic therapy at baseline, the trend of major bleeding incidence across different CKD status was consistent with the whole population (Supplementary Table 1). The most recent antithrombotic therapy in patients with incident major bleeding was shown in Supplementary Table 3. CIF curves by CKD status reveals a higher incidence of major bleeding in patients with CKD (Figure 2B). In multivariate analysis, there was a 45%, 47%, and 133% higher risk of major bleeding associated with mild CKD (adjusted HR = 1.45, 95% CI: 1.12–1.89, $P = 0.005$), moderate CKD (adjusted HR = 1.47, 95% CI: 1.02–2.12, $P =$

Table 1 Baseline characteristics.

	No CKD (*n* = 7626)	Mild CKD (*n* = 9342)	Moderate CKD (*n* = 1925)	Severe CKD (*n* =186)	*P* value
Age, yrs	56.3 ± 10.4	67.6 ± 10.0	74.6 ± 8.4	74.7 ± 10.2	< 0.0001
Female	2454 (32.2%)	3648 (39.1%)	1124 (53.2%)	103 (55.4%)	< 0.0001
BMI, kg/m^2	25.7 ± 3.4	25.5 ± 3.4	25.3 ± 3.7	24.8 ± 3.9	< 0.0001
eGFR, mL/min per m^2	98.2 (94.1, 104.0)	78.9 (71.0, 85.1)	50.2 (45.1, 56.6)	19.7 (13.2, 26.9)	< 0.0001
AF type					< 0.0001
Newly diagnosed	387 (5.1%)	591 (6.3%)	169 (8.8%)	23 (12.4%)	
Paroxysmal	4832 (63.4%)	5295 (56.7%)	940 (48.8%))	99 (53.2%)	
Persistent	2407 (31.6%)	3456 (37.0%)	816 (42.4%)	64 (34.4%)	
Concomitant diseases					
Congestive heart failure	645 (8.5%)	1418 (15.2%)	644 (33.5%)	102 (54.8%)	< 0.0001
Hypertension	3830 (50.2%)	6225 (66.6%)	1572 (81.7%)	162 (87.1%)	< 0.0001
Diabetes mellitus	1707 (22.4%)	2321 (24.8%)	659 (34.2%)	86 (46.2%)	< 0.0001
Thromboembolism	744 (9.8%)	1551 (16.6%)	456 (23.7%)	47 (25.3%)	< 0.0001
Vascular disease	726 (9.5%)	1724 (18.5%)	543 (28.2%)	75 (40.3%)	< 0.0001
Hyperlipidemia	1746 (22.9%)	2796 (29.9%)	688 (35.7%)	64 (34.4%)	< 0.0001
Previous bleeding	206 (2.7%)	384 (4.1%)	126 (6.6%)	9 (4.8%)	< 0.0001
CHA_2DS_2-VASc score	1 (1, 2)	3 (1, 4)	4 (3, 5)	5 (3, 6)	< 0.0001
HAS-BLED score	1 (0, 2)	2 (1, 3)	3 (2, 4)	4 (3, 5)	< 0.0001
Current smoking	1073 (14.1%)	955 (10.2%)	111 (5.8%)	10 (5.4%)	< 0.0001
Alcohol consumption	1079 (14.2%)	903 (9.7%)	108 (5.6%)	7 (3.8%)	< 0.0001
Completed high school	5271 (69.1%)	6273 (67.2%)	1242 (59.3%)	102 (54.8%)	< 0.0001
Health insurance coverage					< 0.0001
100%	304 (4.0%)	876 (9.4%)	255 (13.3%)	17 (9.1%)	
Partially	5331 (70.0%)	6968 (74.6%)	1509 (78.4%)	157 (84.4%)	
None	1991 (26.1%)	1498 (16.0%)	161 (8.4%)	12(6.5%)	
Antithrombotic treatment					
OAC	5382 (70.6%)	6169 (66.0%)	947 (49.2%)	61 (32.8%)	< 0.0001
Warfarin	3018 (39.6%)	4066 (43.5%)	744 (38.7%)	54 (30.7%)	< 0.0001
DOAC	2364 (31.0%)	2103 (22.5%)	203 (10.6%)	4 (2.2%)	< 0.0001
Antiplatelet	1050 (13.8%)	2015 (21.6%)	682 (35.4%)	81 (43.6%)	< 0.0001
None	1194 (15.7%)	1158 (12.4%)	296 (15.4%)	44 (23.7%)	< 0.0001
Concomitant medication					
AADs	3675 (48.2%)	3828 (41.0%)	527 (27.4%)	40 (21.5%)	< 0.0001
Rate-controlling drugs	2542 (33.3%)	4213 (45.1%)	1178 (61.2%)	117 (62.9%)	< 0.0001
ACEI/ARBs	1993 (26.1%)	3418 (36.6%)	948 (49.3%)	52 (28.0%)	< 0.0001
Statins	2348 (30.8%)	3943 (42.2%)	998 (51.8%)	91 (49.0%)	< 0.0001

Values are mean ± SD, median (IQR), or *n* (%). AAD: antiarrhythmic drug; ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; BMI: body mass index; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, age 65–74 years, female sex; DOAC: direct oral anticoagulant; eGFR: estimated glomerular filtration rate; HAS-BLED: hypertension, abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age > 65 years), drugs and/or alcohol concomitantly; OAC: oral anticoagulant.

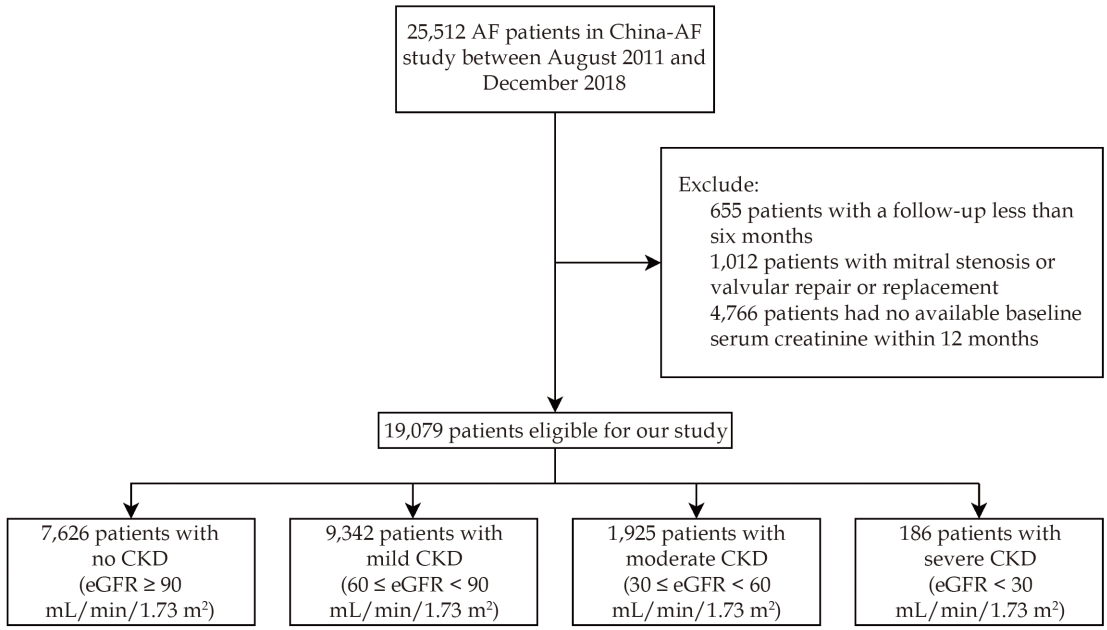

Figure 1 Flowchart of the study population selection. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

0.040), and severe CKD (adjusted HR = 2.33, 95% CI: 1.04–5.22, $P = 0.039$), respectively (Figure 3).

Risk of Cardiovascular Mortality and All-cause Mortality

During a mean follow-up of 4.1 ± 1.9 years, 1786 patients (9.4%) died and 956 patients (5.0%) died from cardiovascular diseases, with the corresponding rates of 2.31 and 1.24 per 100 person-years, respectively. Incidence rates of cardiovascular mortality ranged from 0.40 in patients with normal renal function to 8.87 per 100 person-years in severe CKD patients (Table 2). The corresponding mortality rates ranged from 0.83 to 15.83 per 100 person-years. CIF curves for cardiovascular-mortality and Kaplan-Meier curves for mortality are shown in Figure 2C and Figure 2D. After multivariate adjustment, the hazard ratios for cardiovascular mortality and all-cause mortality of patients with severe CKD were 2.95 (95% CI: 1.97–4.41, $P < 0.0001$) and 2.80 (95% CI: 2.15–3.64, $P < 0.0001$), compared with non-CKD patients. The corresponding hazard ratios for moderate CKD were 2.17 (95% CI: 1.67–2.81, $P < 0.0001$) and 1.75 (95% CI: 1.46–2.08, $P < 0.0001$) (Figure 3). Mild CKD was associated with a higher risk of cardiovascular mortality (adjusted HR = 1.34, 95% CI: 1.07–1.68, $P = 0.011$), but no significant association was found with all-cause mortality among these patients (Figure 3).

DISCUSSION

In the large multicenter China-AF cohort with a long-term follow-up, we found that reduced eGFR was associated with graded, higher risks of major bleeding, cardiovascular mortality, and all-cause mortality. However, CKD was not an independent predictor of thromboembolism.

AF confers to an increased risk of stroke, and accurate risk stratification is crucial. Of note, whether renal function is an independent predictor of thromboembolic events in AF patients remains conflicting. Some studies supported renal disease for thromboembolism prediction.[10,11] A study of anticoagulated AF patients even added renal function to a stroke risk model called R_2CHADS_2 score, showing improvement of predictive value for thromboembolism, compared with CHA_2DS_2-VASc score.[25] However, it was derived from patients who were at moderate-to-high risk for stroke and patients with severe renal dysfunction were excluded. Other studies reported that CKD was not independently associated with an increased risk of stroke.[3,13,26] Our study also demonstrated that CKD had no significant association with thromboembolism. Moreover, the Loire Valley Atrial Fibrillation Project (LVAFP) study and a large Swedish cohort study indicated that renal impairment did not improve the predictive ability of the CHA_2DS_2-VASc score.[13,26] Owing

Table 2 Incidence rates of adverse clinical events per 100 person-years according to CKD status.

Outcomes	No. of person-years	No. of events	Event rate per 100 person-years (95% CI)
Thromboembolism			
No CKD	29741	230	0.77 (0.68–0.88)
Mild CKD	38676	554	1.43 (1.34–1.58)
Moderate CKD	7623	188	2.47 (2.14–2.85)
Severe CKD	588	13	2.21 (1.28–3.81)
Major bleeding			
No CKD	30047	94	0.31 (0.26–0.38)
Mild CKD	38769	249	0.64 (0.57–0.73)
Moderate CKD	7854	64	0.81 (0.64–1.04)
Severe CKD	603	7	1.16 (0.55–2.44)
Cardiovascular mortality			
No CKD	30123	120	0.40 (0.34–1.48)
Mild CKD	38769	471	1.21 (1.11–1.33)
Moderate CKD	7739	314	4.06 (3.63–4.53)
Severe CKD	575	51	8.87 (6.74–11.68)
All-cause mortality			
No CKD	30123	251	0.83 (0.74–0.94)
Mild CKD	38769	906	2.34 (2.19–2.49)
Moderate CKD	7739	538	6.95 (6.39–7.57)
Severe CKD	575	91	15.83 (12.89–19.44)

CKD: chronic kidney disease.

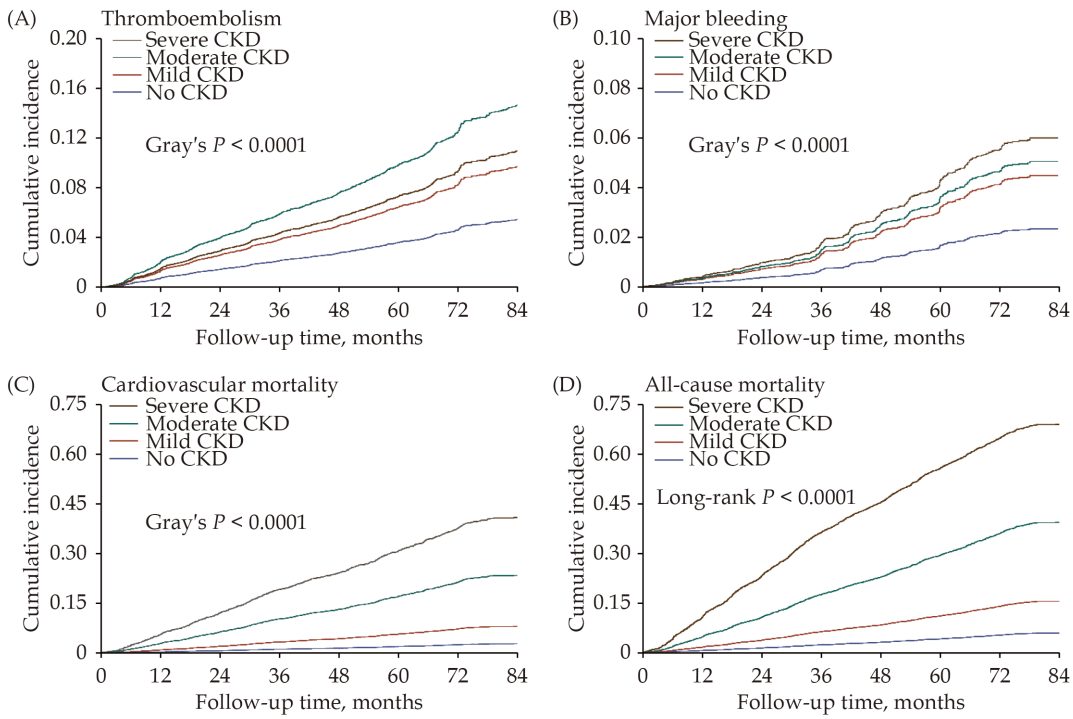

Figure 2 Cumulative incidence rates of adverse clinical events according to CKD status. (A): CIF curves of thromboembolism events; (B): CIF curves of major bleeding events; (C): CIF curves of cardiovascular mortality events; and (D): Kaplan-Meier curves of all-cause mortality events. CKD: chronic kidney disease; CIF: cumulative incidence function.

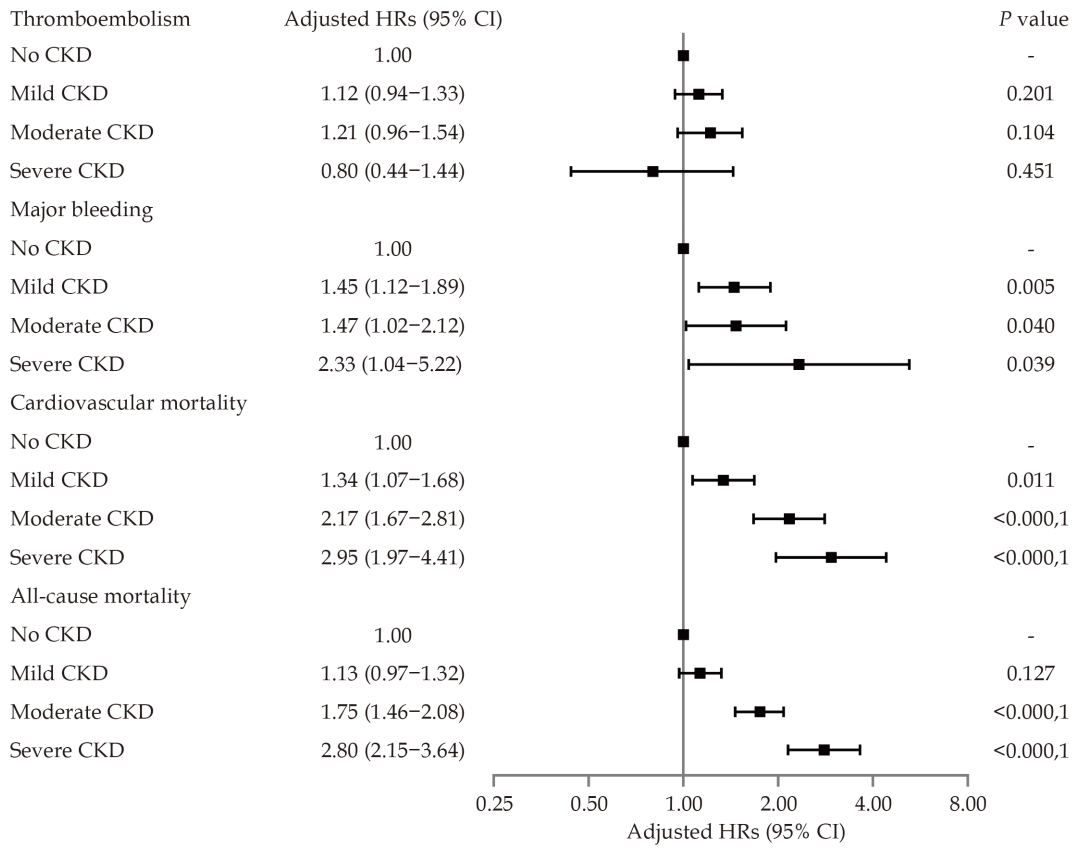

Figure 3 Adjusted hazard ratios of adverse clinical events according to CKD status. Analyses were adjusted for age, sex, body mass index, AF type, smoking, alcohol consumption, congestive heart failure, hypertension, diabetes mellitus, thromboembolism, vascular disease, previous bleeding, oral anticoagulants (time-dependent), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, statins, education level and health insurance. AF: atrial fibrillation; CKD: chronic kidney disease; CI: confidence interval; HR: hazard ratio.

to the relationship of CKD with components of CHA_2DS_2-VASc score such as age, heart failure, hypertension and diabetes mellitus, it may be plausible that CKD didn't provide incremental information to the stroke risk stratification.

OAC has become the cornerstone of AF management, but the risk of major bleeding is an inevitable clinical concern. Our findings confirmed that worse renal function was associated with a higher risk of major bleeding in AF patients, which was consistent with previous cohort studies.[3,10,26] To some extent, we supported the inclusion of abnormal renal function as a component of bleeding risk stratification schemes such as HAS-BLED, ORBIT and ATRIA bleeding scores.[22,27,28] Several possible mechanisms may explain the findings. CKD is associated with reduced platelet activity, decreased binding of platelets to the vessel wall, as well as low platelet adhesion and aggregation, which may facilitate the formation of prohemorrhagic conditions.[29,30]

Current guidelines emphasized the identification and management of risk factors and concomitant diseases in AF patients. Even with effective anticoagulation, the mortality rate was as high as 4.72% per year.[31] Beyond stroke prevention, more interventions are needed to reduce the risk of mortality in this population. Previous studies about the impact of CKD on mortality in AF patients yielded contradictory results. A study of 4554 anticoagulated AF patients reported that CKD was not an independent predictor of cardiovascular mortality and non-cardiovascular mortality in AF patients.[14] The results may be partly explained by the younger age in the CKD group and short median follow-up time of less than 1 year. Besides, the ABC (Age, Biomarkers, Clinical history) death score for mortality risk prediction in anticoagulated AF patients merely included heart failure as the component of

clinical history.[17] However, the ABC-death score was derived from patients on anticoagulation. Thus, the score may not apply to the entire AF population. A Japanese multicenter registry study demonstrated that moderate-to-severe CKD was associated with a higher risk of mortality.[32] Moreover, four other studies found that a lower level of renal function was associated with a stepwise elevated risk of mortality.[4,33–35] Our study also indicated that CKD was independently associated with cardiovascular mortality and all-cause mortality. Indeed, CKD could contribute to mortality by several possible mechanisms, such as hypertension,[36,37] persistent and low-grade inflammation, abnormal bone morphology, vascular calcification, and destruction of mineral homeostasis.[38,39]

CKD was undoubtedly an important comorbidity of AF, associated with higher risks of bleeding and mortality. Given that over 60% of AF patients in our study had different degrees of renal dysfunction, more attention should be paid to these patients to reduce the occurrence of adverse events. Particular efforts on well-controlled risk factors, such as blood pressure and plasma glucose, have the potential to slow the progression of CKD and reduce subsequent complications. Although some patients had a normal eGFR level at baseline, renal function could deteriorate over time. Thus, monitoring eGFR regularly is necessary, regardless of current CKD status.[40,41] In addition, studies about the efficacy and safety of OAC among AF patients with end-stage renal dysfunction illustrated contentious results.[30,42] There is no recommendation in current guidelines with regard to OAC use among these patients. Moreover, all OACs are partly excreted via the kidney. Appropriate OAC prescription should be given after cautious assessment of the benefits and risks, especially to patients with advanced CKD.[43] The efficacy and safety of OAC in patients with severe renal dysfunction still needs to be investigated in further randomized controlled trials.

Study Limitations

First, the predictive value of renal dysfunction may be partly influenced by the contribution of age, as renal function could deteriorate with increasing age. Despite adjustment for potential risk factors, there were still residual confounders we could not identify and control. Second, we lacked of data of sequential changes in eGFR. Risks of stroke, bleeding and death in AF patients could increase with a deterioration of renal function.[40,44] Third, a majority of patients in our study were on warfarin, but the time in therapeutic range was not available. Also, we did not collect the information about the dose of DOAC. However, we used time-dependent regression models with adjustment for changes in OAC therapy during follow-up.

CONCLUSIONS

In the large cohort of AF populations, CKD was independently associated with stepwise higher risks of major bleeding, cardiovascular mortality, and all-cause mortality. However, it seemed not to be an independent predictor of thromboembolism in AF patients.

ACKNOWLEDGEMENTS

This work was supported by the National Key Research and Development Program of China (grant number: 2017YFC0908803, 2018YFC1312501, 2020YFC2004803), the National Natural Science Foundation of China (82100326) and Beijing Municipal Commission of Science and Technology (Z1811000001618011).

TRIAL REGISTRATION

Chinese Clinical Trial Registry, ChiCTR-OCH-13003729, http://www.chictr.org.cn/showproj.aspx?proj=5831.

REFERENCES

[1] Soliman EZ, Prineas RJ, Go AS, *et al*. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J* 2010; 159: 1102–1107.

[2] Reinecke H, Nabauer M, Gerth A, *et al*. Morbidity and treatment in patients with atrial fibrillation and chronic kidney disease. *Kidney Int* 2015; 87: 200–209.

[3] Bonde AN, Lip GY, Kamper AL, *et al*. Renal Function and the Risk of Stroke and Bleeding in Patients With atrial fibrillation: an observational cohort study. *Stroke* 2016; 47: 2707–2713.

[4] Goto S, Angchaisuksiri P, Bassand JP, *et al*. Management and 1-year outcomes of patients with newly dia-

gnosed atrial fibrillation and chronic kidney disease: results from the prospective GARFIELD-AF Registry. *J Am Heart Assoc* 2019; 8: e010510.
[5] Alonso A, Lopez FL, Matsushita K, *et al*. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation* 2011; 123: 2946–2953.
[6] Hindricks G, Potpara T, Dagres N, *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2021; 42: 373–498.
[7] Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. *JAMA* 2019; 322: 1294–1304.
[8] Benjamin EJ, Muntner P, Alonso A, *et al*. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* 2019; 139: e56–e528.
[9] Massera D, Wang D, Vorchheimer DA, *et al*. Increased risk of stroke and mortality following new-onset atrial fibrillation during hospitalization. *Europace* 2017; 19: 929–936.
[10] Olesen JB, Lip GY, Kamper AL, *et al*. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012; 367: 625–635.
[11] Go AS, Fang MC, Udaltsova N, *et al*. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation* 2009; 119: 1363–1369.
[12] Lip GY, Laroche C, Ioachim PM, *et al*. Prognosis and treatment of atrial fibrillation patients by European cardiologists: one year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry). *Eur Heart J* 2014; 35: 3365–3376.
[13] Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J* 2015; 36: 297–306.
[14] Ding WY, Lip GYH, Pastori D, *et al*. Effects of Atrial Fibrillation and Chronic Kidney Disease on Major Adverse Cardiovascular Events. *Am J Cardiol* 2020; 132: 72–78.
[15] Boriani G, Laroche C, Diemberger I, *et al*. Glomerular filtration rate in patients with atrial fibrillation and 1-year outcomes. *Sci Rep* 2016; 6: 30271.
[16] January CT, Wann LS, Calkins H, *et al*. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019; 140: e125–e151.
[17] Hijazi Z, Oldgren J, Lindbäck J, *et al*. A biomarker-based risk score to predict death in patients with atrial fibrillation: the ABC (age, biomarkers, clinical history) death risk score. *Eur Heart J* 2018; 39: 477–485.
[18] Du X, Ma C, Wu J, *et al*. Rationale and design of the Chinese Atrial Fibrillation Registry Study. *BMC Cardiovasc Disord* 2016; 16: 130.
[19] Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med* 2013; 158: 825–830.
[20] Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.
[21] Lip GY, Nieuwlaat R, Pisters R, *et al*. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010; 137: 263–272.
[22] Pisters R, Lane DA, Nieuwlaat R, *et al*. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; 138: 1093–1100.
[23] Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; 3: 692–694.
[24] Abdel-Qadir H, Fang J, Lee DS, *et al*. Importance of considering competing risks in time-to-event analyses: application to stroke risk in a retrospective cohort study of elderly patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2018; 11: e004580.
[25] Piccini JP, Stevens SR, Chang Y, *et al*. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation* 2013; 127: 224–232.
[26] Banerjee A, Fauchier L, Vourc'h P, *et al*. Renal impairment and ischemic stroke risk assessment in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *J Am Coll Cardiol* 2013; 61: 2079–2087.
[27] O'Brien EC, Simon DN, Thomas LE, *et al*. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J* 2015; 36: 3258–3264.
[28] Fang MC, Go AS, Chang Y, *et al*. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011; 58: 395–401.
[29] Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. *Nat Rev Nephrol* 2018; 14: 337–351.
[30] Kumar S, Lim E, Covic A, *et al*. Anticoagulation in concomitant chronic kidney disease and atrial fibrillation: JACC review topic of the week. *J Am Coll Cardiol* 2019; 74: 2204–2215.
[31] Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, *et al*. Causes of death in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol* 2016; 68: 2508–2521.
[32] Yuzawa Y, Kuronuma K, Okumura Y, *et al*. Relationship between the renal function and adverse clinical

events in patients with atrial fibrillation: a Japanese multicenter registry substudy. *J Clin Med* 2020: 9.

[33] Arnson Y, Hoshen M, Berliner-Sendrey A, *et al*. Risk of stroke, bleeding, and death in patients with nonvalvular atrial fibrillation and chronic kidney disease. *Cardiology* 2020; 145: 178–186.

[34] Banerjee A, Fauchier L, Vourc'h P, *et al*. A prospective study of estimated glomerular filtration rate and outcomes in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *Chest* 2014; 145: 1370–1382.

[35] Wan H, Wang J, Yang Y, *et al*. Impact of estimated glomerular filtration rate on long-term clinical outcomes among Chinese patients with atrial fibrillation. *BMC Cardiovasc Disord* 2020; 20: 490.

[36] Romagnani P, Remuzzi G, Glassock R, *et al*. Chronic kidney disease. *Nat Rev Dis Primers* 2017; 3: 17088.

[37] Freedman BI, Cohen AH. Hypertension-attributed nephropathy: what's in a name? *Nat Rev Nephrol* 2016; 12: 27–36.

[38] Mihai S, Codrici E, Popescu ID, *et al*. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J Immunol Res* 2018; 2018: 2180373.

[39] Felsenfeld AJ, Levine BS, Rodriguez M. Pathophysiology of calcium, phosphorus, and magnesium dysregulation in chronic kidney disease. *Semin Dial* 2015; 28: 564–577.

[40] Fauchier L, Bisson A, Clementy N, *et al*. Changes in glomerular filtration rate and outcomes in patients with atrial fibrillation. *Am Heart J* 2018; 198: 39–45.

[41] Turakhia MP, Blankestijn PJ, Carrero JJ, *et al*. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J* 2018; 39: 2314–2325.

[42] Goel N, Jain D, Haddad DB, *et al*. Anticoagulation in patients with end-stage renal disease and atrial fibrillation: confusion, concerns and consequences. *J Stroke* 2020; 22: 306–316.

[43] Boriani G, Savelieva I, Dan GA, *et al*. Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2015; 17: 1169–1196.

[44] Guo Y, Wang H, Zhao X, *et al*. Sequential changes in renal function and the risk of stroke and death in patients with atrial fibrillation. *Int J Cardiol* 2013; 168: 4678–4684.

Please cite this article as: LI ST, JIANG C, HE L, LI QF, DING ZH, WU JH, HU R, LV Q, LI X, JIA CQ, RUAN YF, NING M, FENG L, BAI R, TANG RB, DU X, DONG JZ, MA CS. Chronic kidney disease and risks of adverse clinical events in patients with atrial fibrillation. *J Geriatr Cardiol* 2021; 18(11): 867–876. DOI: 10.11909/j.issn.1671-5411.2021.11.002