Mild Renal Dysfunction and Risk of Thromboembolism and Bleeding in Patients with Atrial Fibrillation: The Chinese Atrial Fibrillation Registry Study

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Abstract

Objective: Previous studies indicated that patients with atrial fibrillation (AF) and moderate-to-severe chronic kidney disease (CKD) are at a higher risk of thromboembolism and bleeding during anticoagulation. Whether mild CKD is associated with an increased risk of thromboembolism and bleeding in AF patients remains unknown. This study aimed to evaluate the impact of mild CKD on thromboembolism and major bleeding among patients with AF.

Methods: Baseline serum creatinine was available in 17,559 of 25,512 patients enrolled in the China-AF study between August 2011 and December 2018. After excluding those who underwent AF ablation or with moderate-to-severe CKD, 7191 non-valvular AF patients (2059 with mild CKD and 5132 with normal renal function) with regular follow-up for at least 6 months were included. Primary outcomes were the time to the first occurrence of thromboembolic and major bleeding events.

Results: Over a mean follow-up of (44.4 ± 23.4) months, 639 thromboembolism and 231 major bleeding events occurred. The crude incidence rates of thromboembolism were higher in the mild CKD group than that of the normal renal function group (3.0/100 person-years vs. 2.2/100 person-years, P < 0.0001), while the crude incidence rates of major bleeding were comparable between the two groups (1.0/100 person-years vs. 0.8/100 person-years, P = 0.076). After multivariate analyses, mild CKD was not associated with an increased risk of thromboembolism (HR = 1.05, 95% CI: 0.89–1.25, P = 0.547) or major bleeding (HR = 1.11, 95% CI: 0.84–1.47, P = 0.476).

Conclusions: Mild CKD was not an independent risk factor of thromboembolism or major bleeding in patients with AF.

Keywords: Atrial fibrillation; Chronic kidney disease; Major bleeding; Thromboembolism

Introduction

Atrial fibrillation (AF) and chronic kidney disease (CKD) often coexist1-3 and share common predisposing factors, such as age, hypertension, diabetes mellitus (DM) and obesity.4-6 The presence of CKD predisposes to incident AF,1,2,7,8 whereas AF

CLINICAL PERSPECTIVE

WHAT IS NEW?

- In the China Atrial Fibrillation Registry cohort, incidence rates of thromboembolism and major bleeding were higher in atrial fibrillation (AF) patients with mild chronic kidney disease (CKD) than patients with normal renal function.
- Mild CKD was not an independent predictor of thromboembolism or major bleeding in patients with AF. The association remained nonsignificant in both oral anticoagulant (OAC) patients and off-OAC patients.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Considering the higher risk of thromboembolism and major bleeding in patients with mild CKD, more attention should be paid to the regular monitoring of renal function in AF patients.
- The use of OACs was independently associated with a lower risk of thromboembolism and a higher risk of major bleeding among AF patients with mild or no CKD. With the increasing proportion of patients prescribed with OACs, balancing the benefits and risks of OAC treatment is essential in decision-making.
plays a role in the development and progression of CKD. Moderate-to-severe CKD has previously been associated with a higher risk of stroke and bleeding in patients with AF and is, therefore, included in the R2CHADS2 score and HAS-BLED score. There are several pathophysiological mechanisms for increased thromboembolism and bleeding risk in CKD patients. For thromboembolism, CKD can cause impairment of endothelial function, platelet activation and is responsible for increased procoagulant and inflammatory biomarkers. For bleeding, CKD may lead to reduced production of thromboxane A2, decreased stimulation for platelets, and biochemical abnormalities in platelet adenosine diphosphate and serotonin content.

However, information about the influence of mild CKD on outcomes of AF patients is scarce and yields conflicting results. Subgroup analysis of the direct oral anticoagulants (DOACs) trials indicated that mild CKD was associated with an increased risk of thromboembolism and bleeding. But these findings were mainly driven by Western European and North American populations. Conversely, a recent report from the GARFIELD-AF registry found no significant association between mild CKD and stroke or bleeding in a large cohort of Asian patients.

Hence, the present study used data from the China Atrial Fibrillation Registry (China-AF) cohort to address whether mild CKD was an independent risk factor for stroke and major bleeding after controlling for known risk factors in Chinese AF patients.

Materials and methods

Study population

The design of China-AF study has been described previously. In brief, China-AF study is a prospective, multicenter, ongoing registry study of patients diagnosed with AF from 31 tertiary and non-tertiary hospitals in Beijing, China. The study was approved by the ethics committee at each center, and the written informed consent was obtained from each participant. A total of 25,512 patients older than 18 years were enrolled in China-AF between August 2011 and December 2018. Of these, 4953 with unknown/missing data for baseline serum creatinine within 12 months were excluded. In this analysis, we also excluded patients with moderate-to-severe CKD (eGFR < 60 mL/(min·1.73 m²)) (n = 742), patients with mitral stenosis or valvular repair or replacement (n = 630), patients with a follow-up less than 6 months (n = 1994), patients who underwent catheter ablation (n = 8909), and patients who had no available AF duration (n = 1093). Finally, 7191 patients were included in the current study. Information of patients with unknown/missing data for baseline serum creatinine and patients who underwent catheter ablation was shown in supplemental digital content [Supplemental Digital Content 1, http://links.lww.com/CD9/A0] [Figure 1].

Estimation of renal function

Renal function was estimated based on baseline serum creatinine using the Modification of Diet in Renal Disease (MDRD) equation modified for the Chinese population: eGFR = 186 × (serum creatinine × 0.011)−1.154 × (age)−0.203 × (0.742 if female) × 1.233. The patients were divided into two groups: patients with normal renal function (eGFR ≥ 90 mL/(min·1.73 m²)) and patients with mild CKD (60 ≤ eGFR < 90 mL/(min·1.73 m²)).

Study outcomes

The effectiveness outcome was the time to the first occurrence of a thromboembolic event, including ischemic stroke, transient

![Figure 1: Flow chart of patients included as part of the China-AF cohort. AF: Atrial fibrillation; CKD: Chronic kidney disease.](http://links.lww.com/CD9/A0)
ischemic attack, or systemic embolism. The safety outcome was the time to the first occurrence of a major bleeding event, 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] All suspected outcomes were adjudicated by a central clinical event committee.

**Statistics**

Means and standard deviations (SD) were calculated for continuous variables, and percentages were calculated for categorical variables. Continuous variables were analyzed using the t test or Wilcoxon rank-sum test. Categorical variables were analyzed using the chi-square test. Cumulative incidence rates were presented with Kaplan-Meier curves and compared with the log-rank test according to renal function.

The risks of thromboembolism and major bleeding associated with mild CKD were examined using Cox proportional hazards regression models. The covariates adjusted were age, sex, AF type, AF duration, body mass index (BMI), mild CKD, smoking, alcohol consumption, congestive heart failure, hypertension, DM, hyperlipidemia, previous thromboembolism, vascular disease, previous bleeding, use of oral anticoagulants (OACs), antiplatelet drugs, education and health insurance. All covariates with P<0.2 in the univariate Cox regression model were included in the multivariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported.

Significance was indicated by a two-sided P value <0.05. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC).

**Results**

**Patient characteristics**

2059 AF patients with mild CKD and 5132 AF patients with normal renal function were included in this analysis. Compared with patients without CKD, patients with mild CKD were older ((72.75 ± 9.24) years vs. (65.22 ± 11.86) years, P < 0.0001), more likely to be female (49.98% vs. 38.82%, P < 0.0001), with a higher prevalence of persistent AF (44.00% vs. 38.17%, P < 0.0001) and longer AF duration ((4.86 ± 7.15) years vs. (3.80 ± 5.91) years, P < 0.0001) [Table 1]. In addition, patients with mild CKD had a higher burden of congestive heart failure, hypertension, DM, previous thromboembolism, previous bleeding and vascular disease. Thus, the proportion of patients with CHA2DS2-VASc score ≥2 (93.30% vs. 76.89%, P < 0.0001) or HAS-BLED score ≥3 (49.78% vs. 34.43%, P < 0.0001) was higher in the mild CKD group. As for OAC treatment, patients with mild CKD were more likely to receive warfarin (35.02% vs. 31.37%, P = 0.003), while DOACs were more frequently prescribed in patients with normal renal function (6.76% vs. 3.30%, P < 0.0001).

**Thromboembolic events**

Over a mean follow-up of (44.4 ± 23.4) months, thromboembolic events occurred in 233 patients (11.3%) in the mild CKD group and in 406 patients (7.9%) in the no CKD group. The crude incidence rate was 3.0/100 person-years for mild CKD and 2.2/100 person-years for no CKD. Cumulative incidence rates of thromboembolic events subdivided by renal function showed that mild CKD patients were at a higher risk of thromboembolism [Figure 2A]. On univariate Cox regression model, mild CKD (HR = 1.39, 95% CI: 1.18–1.63, P < 0.0001) was significantly associated with thromboembolic risk [Supplemental Table 1, http://links.lww.com/CVD9/A1]. However, after adjusting for all covariates with P < 0.2 in univariate analysis (including age, sex, AF type, BMI, renal function, smoking, alcohol consumption, heart failure, hypertension, DM, hyperlipidemia, previous thromboembolism, vascular disease, OAC treatment and antiplatelet treatment), mild CKD was no longer an independent risk factor (HR = 1.05, 95% CI: 0.89–1.25, P = 0.547) for thromboembolism [Figure 3].

![Table 1 Baseline characteristics of AF patients with or without CKD](image_url)
Major bleeding

Two hundred and thirty-one patients (3.2%) experienced a major bleeding event during the follow-up. The overall incidence rate of major bleeding was 1.0/100 person-years in the mild CKD group and 0.8/100 person-years in the no CKD group. Mild CKD patients had nonsignificantly different incidences of major bleeding, compared with no CKD patients \( (P = 0.076) \) [Figure 2B]. The association remained nonsignificant both in univariate Cox regression model [Supplemental Table 2, http://links.lww.com/CD9/A2] and after adjustment (HR = 1.11, 95% CI: 0.84–1.47, \( P = 0.476 \)) for all covariates with \( P < 0.2 \) in univariate cox regression model, including age, AF type, AF duration, BMI, renal function, smoking, alcohol consumption, heart failure, hypertension, DM, previous thromboembolism, previous bleeding, OAC treatment and antiplatelet treatment [Figure 4].

Subgroup analysis

Patients were further divided into on-OAC (2750 patients) and off-OAC (4441 patients) subgroups. After multivariate analysis, mild CKD was not an independent predictor of thromboembolism (adjusted HR = 1.04, 95% CI: 0.77–1.39, \( P = 0.807 \)) and major bleeding (adjusted HR = 1.00, 95% CI: 0.67–1.51, \( P = 0.985 \)) in anticoagulated patients. Similarly, in off-OAC subgroup, mild CKD was also not an independent predictor of thromboembolism (adjusted HR = 1.06, 95% CI: 0.86–1.30, \( P = 0.598 \)) and major bleeding (adjusted HR = 1.20, 95% CI: 0.80–1.78, \( P = 0.384 \)) [Figure 5].

Discussion

Main findings

In this large cohort of Chinese AF patients, we found that although crude incidence rates of thromboembolism were higher in patients with mild CKD, mild CKD was not an independent risk factor of thromboembolism or major bleeding.

Risk of thromboembolism and bleeding associated with mild CKD

Previous studies indicated that impaired renal function was associated with increased risks of thromboembolism and major bleeding in patients with AF.\[^{3,15,24,25}\] Of note, most of these studies mainly focused on the influence of moderate-to-severe CKD, without taking a more in-depth insight into the significance of mild CKD. Mild CKD presents in nearly 16.9% to 50% of AF patients.\[^{14,26–28}\] As the most common renal dysfunction in AF patients, its impact on stroke and major bleeding remains controversial.

Results from randomized controlled trials on DOACs showed that the annual rate of thromboembolism and major bleeding increased as renal function deteriorated. Even patients with mild CKD experienced more thromboembolic and bleeding events compared with patients with normal renal function.\[^{18–20}\] However, the AMEDESU trial performed a receiver operating characteristic analysis and found that the cut-off value of calculated creatinine clearance with the highest predictive performance for the outcome of thromboembolism was nearly 60 mL/min.\[^{29}\] Several cohort studies also revealed a stepwise higher risk of thromboembolism and major bleeding associated with decreasing levels of eGFR.\[^{26,28}\] But their findings could be influenced by the small sample size or lack of information about lifestyle factors, such as BMI, smoking and alcohol consumption, which were related risk factors for thromboembolism among AF patients.\[^{30–32}\]

A population-based cohort study in Canada reported a higher rate of major bleeding in patients with an eGFR < 90 mL/(min·1.73 m\(^2\)) compared with those with an eGFR ≥ 90 mL/(min·1.73 m\(^2\)), but it was driven mainly by patients with an eGFR < 15 mL/(min·1.73 m\(^2\)).\[^{27}\] Furthermore, a recent report from the international, prospective GARFIELD-AF registry found no significant association between mild CKD and thromboembolism, major bleeding or all-cause mortality in 9491 AF patients recruited from Asia.\[^{14}\] The study threw light on the different influence of CKD on patients from Asia compared with the rest of the world.
Nevertheless, an important limitation to consider was that the CKD stage was based on the investigators’ judgment instead of the laboratory data, which might cause a significant bias.

The current study evaluated the risks of thromboembolism and major bleeding associated with mild CKD in a large cohort of Chinese AF patients with long-time follow-up and comprehensive administrative data. Consistent with prior studies, AF patients with renal impairment in our analysis had a higher prevalence of comorbidities, higher CHA2DS2-VASc scores and HAS-BLED scores compared with normal renal function counterparts. However, after controlling for baseline characteristics, antithrombotic treatment, socioeconomic and lifestyle-related factors, mild CKD was no longer an independent risk factor for thromboembolism or major bleeding in AF patients. One possible explanation could be that mild CKD was merely a marker of organ damage from ageing, hypertension, DM, and AF. Thus, there was no significant increase in risk attributable to mild CKD after adjustment for potential confounders.

Clinical implications
Balancing the risks of stroke and bleeding is a dilemma often encountered by clinical physicians when deciding on OAC treatment in AF patients with CKD. Our data also indicated that the use of OACs was associated with a higher risk of major bleeding irrespective of the CKD stage. Concerns about bleeding may prevent providers from prescribing anticoagulants and patients from adhering to OAC treatment.

Limitations
First, the CKD stage was evaluated only at the time of enrollment, time-dependent changes in the CKD stage throughout the
follow-up and its association with stroke and bleeding were not assessed. But the potential bias was likely to be minimal, given the very slow decline of renal function over time in AF patients. Second, patients with moderate-to-severe CKD were not included in our study. Because large amounts of studies have revealed the association between moderate-to-severe CKD and risks of thromboembolism or major bleeding, so our study focused on patients with mild CKD. Third, the low use of OAC in China may have an influence on thromboembolism and major bleeding. However, after subgroup analysis, mild CKD was not associated with thromboembolism and major bleeding in both on-OAC subgroup and off-OAC subgroup. In addition, we lacked information about time in therapeutic range (TTR) for warfarin, which was reported to be lower in a Chinese cohort compared with the White or the Japanese. Since a high proportion of patients on OAC treatment were taking warfarin in this study, poorly managed TTR could result in higher risks of both thromboembolism and major bleeding.

**Conclusion**

AF patients with mild CKD had a higher risk profile compared with patients with normal renal function, but mild CKD was not an independent predictor of thromboembolism and major bleeding in patients with AF.

**Funding**

This work was supported by the National Key Research and Development Program of China (2016YFC0900901, 2016YFC1301002, and 2020YFC2004803) and grant from Beijing Municipal Commission of Science and Technology (D171100006817001). The construction of the Chinese

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**Adjusted HR (95% CI)**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild CKD</td>
<td>1.11 (0.84-1.47)</td>
</tr>
<tr>
<td>Age, per 10 years</td>
<td>1.13 (0.97-1.30)</td>
</tr>
<tr>
<td>AF type, persistent AF</td>
<td>1.33 (1.01-1.75)</td>
</tr>
<tr>
<td>AF duration, per year</td>
<td>1.00 (0.99-1.02)</td>
</tr>
<tr>
<td>BMI &gt; 28kg/m²</td>
<td>1.04 (0.74-1.45)</td>
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<tr>
<td>Smoking</td>
<td>0.95 (0.67-1.35)</td>
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<tr>
<td>Alcohol consumption</td>
<td>1.02 (0.71-1.48)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.89 (0.68-1.16)</td>
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<tr>
<td>Hypertension</td>
<td>1.27 (0.92-1.75)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>0.98 (0.72-1.31)</td>
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<tr>
<td>Previous thromboembolism</td>
<td>1.07 (0.79-1.45)</td>
</tr>
<tr>
<td>Previous bleeding</td>
<td>2.39 (1.57-3.63)</td>
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<tr>
<td>OAC</td>
<td>2.13 (1.46-3.11)</td>
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<tr>
<td>Antiplatelet</td>
<td>1.30 (0.89-1.89)</td>
</tr>
</tbody>
</table>

**Figure 4:** Forest plot showing adjusted HRs (95% CI) for multivariate predictors of major bleeding in AF patients with or without CKD. AF: Atrial fibrillation; BMI: Body mass index; CI: Confidence interval; CKD: Chronic kidney disease; HR: Hazard ratio; OAC: Oral anticoagulant.
Atrial Fibrillation Registry was also supported by grants from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim, and Bayer.

Conflicts of interest

Changsheng Ma has received honoraria from Bristol-Myers Squibb, Pfizer, Johnson & Johnson, Boehringer-Ingelheim and Bayer for giving lectures. Jianzeng Dong has received honoraria from Johnson & Johnson for giving lectures. The other authors have declared no conflict of interest.

References


