Impact of Renal Dysfunction on Clinical Outcome in Patients With Low Risk of Atrial Fibrillation

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Background: The impact of renal dysfunction has been investigated in patients with non-valvular atrial fibrillation (AF). The aim of this study was to assess its additive prognostic value in low thromboembolic risk AF patients with CHA2DS2-VASc score 0–1.

Methods and Results: A total of 617 non-valvular AF patients were enrolled and baseline serum creatinine was measured. Estimated glomerular filtration rate and estimated clearance of creatinine were calculated using the Modification of Diet in Renal Disease equation and Cockcroft-Gault formula, respectively. The primary endpoint was cardiovascular death and systemic thromboembolic events, including acute ischemic stroke, transient ischemic attack, and peripheral artery embolism. Of these, 338 individuals had clinical CHA2DS2-VASc score 0–1. Among these individuals, 23 patients had impaired renal function. During the follow-up period of 53.6±32.1 months, the annual composite outcome rate in AF patients with CHA2DS2-VASc score 0–1 was 0.40%/year. As compared with patients with preserved renal function, the annual composite outcome rate was significantly higher in patients with impaired renal function (2.92%/year vs. 0.21%/year, P<0.001). Moreover, on multivariate Cox regression analysis, renal dysfunction was the only risk predictor in these low-risk patients.

Conclusions: Impaired renal function has an additive prognostic value for thromboembolic events and cardiovascular mortality in low-risk AF patients with CHA2DS2-VASc score 0–1. (Circ J 2014; 78: 853–858)

Key Words: Anticoagulation; Atrial fibrillation; Mortality; Renal dysfunction; Thromboembolism

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and is associated with increased risks of thromboembolic event and cardiovascular mortality. Risk stratification with CHADS2 or CHA2DS2-VASc score is widely used for decision making in thromboprophylaxis with oral anticoagulation and predicts clinical outcome in non-valvular AF patients.1 AF patients with CHA2DS2-VASc score 0–1, however, currently considered as low thromboembolic risk, still carry 1.3% of residual cardiovascular risks every year.3 Chronic kidney disease (CKD), defined as progressively decreased glomerular filtration rate (eGFR), contributes to increased thromboembolism and cardiovascular mortality. Some studies found that impaired renal function was strongly associated with the incidence of AF independently,2,4 and the risk of stroke was higher in AF patients with CKD than in those without CKD.5,6 Moreover, the impact of impaired renal function in non-valvular AF patients has been investigated recently.5–7 The present study was designed to assess the additive prognostic value of renal dysfunction in low-risk AF patients with CHA2DS2-VASc score 0–1.

Methods

Patients

From January 2001 to December 2010, 617 consecutive patients with non-valvular AF were enrolled from 1 tertiary medical center. Patients aged ≥18 years who presented with documented AF or a history of AF (within 1 year from diagnosis) were included. Out of these, 338 individuals had clinical CHA2DS2-VASc score 0–1. Among these individuals, 23 patients had impaired renal function. During the follow-up period of 53.6±32.1 months, the annual composite outcome rate in AF patients with CHA2DS2-VASc score 0–1 was 0.40%/year. As compared with patients with preserved renal function, the annual composite outcome rate was significantly higher in patients with impaired renal function (2.92%/year vs. 0.21%/year, P<0.001). Moreover, on multivariate Cox regression analysis, renal dysfunction was the only risk predictor in these low-risk patients.

Conclusions: Impaired renal function has an additive prognostic value for thromboembolic events and cardiovascular mortality in low-risk AF patients with CHA2DS2-VASc score 0–1. (Circ J 2014; 78: 853–858)
nosed on 12-lead electrocardiogram or 24-h Holter monitoring were considered for enrollment in the study. Patients meeting any of the following criteria were ineligible for inclusion: AF resulting from a transient cause; recent cardiac surgery for AF (<3 months); life expectancy <1 year owing to severe disease; participation in an AF clinical trial in the previous 3 months; unable to comply with follow-up visits; history of or scheduled pregnancy or lactating. After enrollment, baseline characteristics, including underlying comorbidities, and serum creatinine, were obtained at the first visit. Transthoracic echocardiography was scheduled for each patient and left atrium diameter (LAD) and left ventricular ejection fraction (LVEF) were measured. In this study, CHA2DS2-VASc and left atrium diameter (LAD) and left ventricular ejection fraction rate were obtained at the first visit. Serum creatinine, fibrinogen, and uric acid were obtained at the first visit.

### Pharmacological Therapy

All non-valvular AF patients received medical control for AF during the study period, and none received radiofrequency catheter ablation for AF. The use of anti-arrhythmic drug was decided on by the clinical physicians. The following drugs were acceptable for use: amiodarone, propafenone, and flecainide. The clinical decision of anticoagulation use was made according to European Society of Cardiology (ESC) guidelines for the management of AF.1 In patients with CHA2DS2-VASc score 1, either oral anticoagulation or aspirin was chosen by the physician unless contraindications were present. There was no need for anticoagulation in patients with CHA2DS2-VASc score 0. Once anticoagulation was given, the goal for anticoagulation was international normalized ratio (INR) 2.0–3.0. Detailed information of AF medication was reviewed.

### eGFR Calculation and Classification

To assess eGFR, all outpatient serum creatinine tests were done at baseline. eGFR was calculated using the Modification of Diet in Renal Disease equation: eGFR (ml·min⁻¹·1.73 m⁻²)= 186×serum creatinine (mg/dl)⁻¹·154×(age)⁻⁰·²⁰³×(0.742 if female)⁻¹·212 if black). Patients were categorized using an eGFR cut-off of 60 ml·min⁻¹·1.73 m⁻²: impaired renal function was defined as eGFR <60 ml·min⁻¹·1.73 m⁻². Moreover, estimated clearance of creatinine (eCr) was evaluated using the Cockcroft-Gault formula: eCr (ml/min)=(140-age)×body weight (kg)/72×serum creatinine (mg/dl), and impaired renal function was defined as eCr<60 ml/min.

### Follow-up

The composite endpoint in this study was thromboembolic events and cardiovascular death. All patients were followed up every 1–3 months at the cardiology clinic. Thromboembolic events consisted of acute ischemic stroke, TIA, and peripheral artery embolism. Acute ischemic stroke was defined as the presence of focal neurological deficit requiring hospitalization, persistent for >24 h and clinical documented imaging of ischemic cerebral lesions on computed tomography or nuclear magnetic resonance imaging. TIA was defined as clinical neurological deficit of vascular etiology that resolved within 24 h. The causes and dates of cardiovascular death were obtained from the database, which was linked to the National Death Registry through a unique personal identification number given to every Taiwanese citizen. The National Death Registry database registers valid information based on certified death certificate, which were coded according to the International Classification of Disease, Ninth Revision (ICD-9). The ICD-9 codes for cardiovascular death are 390–459. The accuracy of cause-of-death coding in Taiwan’s National Death Registry database has been validated.9

### Statistical Analysis

Data are presented as mean±SD for normally distributed continuous variables and as proportions for categorical variables. The differences between the continuous values were assessed using unpaired 2-tailed t-test or 1-way analysis of variance post-hoc Bonferroni test for normally distributed continuous variables, Mann-Whitney rank-sum test for skewed variables, and chi-squared test for nominal variables. Univariate Cox regression analysis of the various clinical variables was done to identify predictors of major adverse cardiovascular events in all AF patients. The variables selected for multivariate analysis were those with P<0.1 in the univariate models. Log-rank test was used to determine statistical significance (set at P<0.05) for major cardiovascular effect-free Kaplan-Meier survival curves. Statistical analysis was carried out with SPSS 18.0 (SPSS, Chicago, IL, USA).

### Results

#### Baseline Characteristics

The present study enrolled a total of 617 non-valvular AF patients with a mean age of 53.7±12.0 years (range, 22–87 years). Of 617 patients, 472 (76.4%) had clinical CHADS2 score 0–1 and 338 (54.8%) had clinical CHADS2-VASc score 0–1. The mean eGFR in patients with CHADS2 score 0–1 and CHADS2-VASc score 0–1 was 91.8±27.3 and 91.7±26.5 ml·min⁻¹·1.73 m⁻², respectively. Staging of renal function according to eGFR level in patients with CHADS2-VASc score 0–1 is shown in Table 1. A total of 315 patients (93.2%) were categorized as having preserved renal function and 23 patients (6.8%) were categorized as having impaired renal function. Table 2 lists the baseline characteristics of patients with CHADS2-VASc score 0–1. Subjects with impaired renal function were older (57.09±6.49 vs. 48.38±11.26 years, P<0.001). There was no statistically significant difference in sex, hypertension, diabetes mellitus, dyslipidemia, prior coronary artery disease, congestive heart failure, or thyroid disease between males and females.
Renal Dysfunction and Outcome in AF

with CHA2DS2-VASc score 0–1, however, 6 patients reached the endpoints (thromboembolic events, n=4; cardiovascular death, n=2). One patient died due to congestive heart failure and the other died because of chronic ischemic heart disease. The annual composite outcome rate in AF patients with CHADS2 score 0–1 and CHA2DS2-VASc score 0–1 was 0.58%/year and 0.40%/year, respectively. As compared with patients with preserved renal function (eGFR ≥60 ml·min⁻¹·1.73 m⁻²), the annual composite outcome rate was significantly higher in patients with impaired renal function (2.92%/year vs. 0.21%/year, P<0.001) among patients with CHA2DS2-VASc score 0–1, and the same was true for patients with CHADS2 score 0–1: that is, the annual composite outcome rate was higher in patients with impaired renal function than preserved renal function (4.15%/year vs. 0.31%/year, P<0.001). The Kaplan-Meier curve for event-free rate in low-risk AF patients with CHA2DS2-VASc score 0–1 is shown in Figure.

Pharmacological Therapy

The prevalence of antiplatelet therapy was the same between patients with preserved renal function and impaired renal function, but there was a high prevalence of anticoagulant use in patients with impaired renal function (21.7% vs. 6.7%, P=0.027). In AF patients with CHA2DS2-VASc score 0–1, 107 (31.7%) received anti-arrhythmic drugs therapy: 44 (41.1%) with amiodarone; 55 (51.4%) with propafenone; and 8 (7.5%) with flecainide. There was no difference in anti-arrhythmic drug use (30.8% vs. 43.5%, P=0.303) and the sinus rhythm maintenance rate was also similar in the 2 groups (31.4% vs. 21.7%, P=0.461; Table 2).

Follow-up of Thromboembolic Events and Cardiovascular Death

The overall annual composite outcome rate was 1.52%/year, and the annual composite outcome rate according to CHA2DS2-VASc score and eGFR level is given in Table 3. The mean follow-up period in patients with CHADS2 score 0–1 and CHA2DS2-VASc score 0–1 was 52.6±31.6 months and 53.6±32.1 months, respectively. With regard to endpoints, there were 10 patients with thromboembolic events and 2 cardiovascular deaths in patients with CHADS2 score 0–1. In patients with CHA2DS2-VASc score 0–1, however, 6 patients reached the endpoints (thromboembolic events, n=4; cardiovascular death, n=2). One patient died due to congestive heart failure and the other died because of chronic ischemic heart disease. The annual composite outcome rate in AF patients with CHADS2 score 0–1 and CHA2DS2-VASc score 0–1 was 0.58%/year and 0.40%/year, respectively. As compared with patients with preserved renal function (eGFR ≥60 ml·min⁻¹·1.73 m⁻²), the annual composite outcome rate was significantly higher in patients with impaired renal function (2.92%/year vs. 0.21%/year, P<0.001) among patients with CHA2DS2-VASc score 0–1, and the same was true for patients with CHADS2 score 0–1: that is, the annual composite outcome rate was higher in patients with impaired renal function than preserved renal function (4.15%/year vs. 0.31%/year, P<0.001). The Kaplan-Meier curve for event-free rate in low-risk AF patients with CHA2DS2-VASc score 0–1 is shown in Figure.

Clinical Predictors of Thromboembolic Events and Cardiovascular Death

On univariate Cox regression analysis, age, eCcr <60 ml/min, and eGFR <60 ml·min⁻¹·1.73 m⁻² predicted the incidence of thromboembolic events and cardiovascular death in low-risk AF patients with CHA2DS2-VASc score 0–1 (hazard ratio [HR], 1.157; 95% confidence interval [CI]: 1.006–1.331, P=0.040; HR, 10.213; 95% CI: 2.017–51.709, P=0.005; and HR, 12.465;
CHA 2DS 2-VASc score 0–1, impaired renal function, defined as eGFR <60 ml·min⁻¹·1.73 m⁻², may be associated with increased risk of systemic thromboembolism and cardiovascular mortality.

CKD and Clinical Outcome
The importance of cardiovascular disease and clinical prognosis in CKD patients has been well established. A recent large cohort study showed that CKD was associated with an increased risk of stroke or systemic thromboembolism in patients with AF. Go et al noted an independent, graded association between reduced eGFR and risk of death, cardiovascular events, and hospitalization once eGFR decreased below 60 ml·min⁻¹·1.73 m⁻².

Discussion
Major Findings
In the present study, we found that among AF patients with CHA 2DS 2-VASc score 0–1, impaired renal function, defined as eGFR <60 ml·min⁻¹·1.73 m⁻², was the only risk predictor in these low-risk patients.

Table 4. Predictors of TEE and CV Mortality: Univariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHA 2DS- VASc score 0–1 non-valvular AF patients</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value†</th>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td>1.157</td>
<td>1.006–1.331</td>
<td>0.040</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>3.560</td>
<td>0.650–19.505</td>
<td>0.143</td>
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<tr>
<td>LVEF (%)</td>
<td></td>
<td>0.931</td>
<td>0.840–1.031</td>
<td>0.169</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td></td>
<td>1.051</td>
<td>0.966–1.143</td>
<td>0.249</td>
</tr>
<tr>
<td>Use of anticoagulant</td>
<td></td>
<td>1.700</td>
<td>0.195–14.809</td>
<td>0.631</td>
</tr>
<tr>
<td>eCcr &lt;60 (ml/min)</td>
<td></td>
<td>10.213</td>
<td>2.017–51.709</td>
<td>0.005</td>
</tr>
<tr>
<td>eGFR &lt;60 (ml·min⁻¹·1.73 m⁻²)</td>
<td></td>
<td>12.465</td>
<td>2.430–63.827</td>
<td>0.002</td>
</tr>
</tbody>
</table>

† Cox proportional hazard model.
CI, confidence interval; CV, cardiovascular; eCcr, estimated clearance of creatinine; HR, hazard ratio; TEE, thromboembolic events. Other abbreviations as in Tables 1, 2.

Table 5. Predictors of TEE and CV Mortality: Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P-value‡</td>
<td>HR</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>eCcr &lt;60 (ml/min)</td>
<td>5.655</td>
<td>1.068–29.932</td>
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<tr>
<td>eGFR &lt;60 (ml·min⁻¹·1.73 m⁻²)</td>
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<td></td>
<td></td>
<td>6.420</td>
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</tbody>
</table>

‡ Model 1, age + eCcr; model 2, age + eGFR.
Abbreviations as in Tables 1, 4.
eGFR <15 ml·min⁻¹·1.73 m⁻² in the absence of dialysis were associated with a strikingly high mortality rate (11.4 and 14.1 per 100 person-years, respectively). Moreover, some studies found that AF patients (with either paroxysmal or persistent AF), with renal dysfunction had a higher recurrence rate after radiofrequency catheter ablation.¹¹⁻¹²

**Concomitant AF and CKD**

A high prevalence of AF has been reported among patients with end-stage renal disease on dialysis, and the incidence of AF ranged from 7% to 27% in dialysis patients according to previous reports.¹³⁻¹⁵ Besides dialysis patients, some recent studies also found that impaired renal function without dialysis was strongly associated with the incidence of AF independently of other risk factors.²⁻⁴⁻¹⁸⁻¹⁹ The mechanisms by which CKD leads to AF are not completely understood, but CKD is associated with increased levels of inflammatory factors, elevated plasma homocysteine, enhanced coagulability, endothelial dysfunction, increased arterial stiffness, and pathological activation of the renin-angiotensin-aldosterone system and sympathetic system with subsequent enhanced myocardial fibrosis, which are likely to play an important role.

Indeed, renal function-impaired patients with concomitant AF had a higher risk of stroke compared with those without AF. Vazquez et al found that AF could increase mortality risk by 1.72-fold and ischemic stroke risk by 9.8-fold in dialysis patients.⁹ In addition, in a recent large prospective AF study, Go et al reported that lower eGFR was associated with a graded, increased risk of ischemic stroke and other systemic embolisms, which was independent of known risk factors in AF.⁵ Nakagawa et al found that the combination of eGFR and CHADS² score could powerfully predict cardiovascular events and cardiovascular mortality in AF patients. Long-term mortality, cardiac events, and stroke risk were more than 8-fold higher when eGFR <60 ml·min⁻¹·1.73 m⁻² and CHADS² score ≥2 were combined.⁶ In the present study, we also found that decreased eGFR could independently predict thromboembolic events and cardiovascular death in patients with non-valvular AF. Moreover, in low-risk AF patients with CHA²DS²-VASc score 0–1, impaired renal function (eGFR <60 ml·min⁻¹·1.73 m⁻²) was associated with significantly higher annual cardiovascular mortality and thromboembolic event rates compared with eGFR ≥60 ml·min⁻¹·1.73 m⁻². This indicates that knowing the grade of kidney dysfunction may improve clinical risk stratification and help decision making on the use of anticoagulation therapy in AF patients with CHA²DS²-VASc score 0–1.

**Anticoagulation Risk-Benefit Profile**

In the recent guidelines for the management of AF, oral anticoagulation therapy was absolutely indicated in AF patients with CHA²DS²-VASc score ≥2.¹ Oral anticoagulation therapy was optional or unnecessary in AF patients with 1 or no clinically relevant non-major risk factors.¹ There was, however, residual stroke risk in AF patients with CHA²DS²-VASc score <2, and the current stroke risk stratification in AF patients deliberately excludes patients with severe renal impairment. Vazquez et al found that approximately 1 in 3 hemodialysis patients with AF had thromboembolic complications within 1 year of follow-up.²⁴ Given the high incidence of thromboembolic complications, renal impairment may play a role in predicting residual thromboembolic risk in AF patients with CHA²DS²-VASc score <2.

The risk–benefit profile of anticoagulation therapy in AF patients with renal function impairment, however, is still controversial.⁷⁻¹³ Many stroke risk factors are also risk factors for bleeding, and the commonly used bleeding risk score, HAS-BLED, includes renal impairment as a risk factor.²² Based on this, oral anticoagulation in renally impaired patients with AF presents a treatment dilemma.²³⁻²⁴ Previously some studies noted a distorted risk–benefit profile of anticoagulation in AF patients with coexisting uremia.²⁵⁻²⁶ In CKD stage 3 individuals without hemodialysis, however, Hart et al reported that adjusted-dose warfarin therapy reduced the risk of ischemic stroke/systemic embolism in such patients by 76%.²⁷ Recently, Olesen et al showed that use of warfarin decreased the risk of stroke or thromboembolism significantly in CKD patients, even in those requiring hemodialysis. Meanwhile, the risk of bleeding was also increased among these patients with warfarin use.²⁸ With regard to the novel anticoagulant agents, the majority of clinical trials studied only patients with eGFR ≥30 ml·min⁻¹·1.73 m⁻². In some of the trials the dose of study drug was adjusted for those patients with moderate CKD because of the high renal excretion of the novel anticoagulant agents.²⁹ Other novel oral anticoagulants, such as Betrixaban, a novel factor Xa inhibitor with lower renal excretion (17%), may improve the balance between stroke risk reduction and bleeding risk in patients with impaired renal function.³⁰⁻³¹ Certainly, clinicians must adequately assess the individual patient’s risk of thromboembolism and bleeding before anticoagulation. Once anticoagulation is given, efforts should be made to ensure appropriate monitoring and that INR is maintained in the therapeutic range to ensure best outcome.

**Study Limitations**

There were several limitations in this study. The major limitation was the small sample size and the small number of patients with renal dysfunction. Consequently, there were only 4 thromboembolic events and 2 cardiovascular deaths in the present study.

First, the sample number from a single institution might have affected the significance of the results. Second, the strategy of anticoagulation was determined by physicians according to the ESC guidelines and the individual characteristics of each patient. There was a higher prevalence of warfarin use in low-risk AF patients with impaired renal function (21.7% vs. 6.7%, P=0.027), but the use of warfarin did not predict outcome of thromboembolic events and cardiovascular mortality. Third, detailed description of bleeding events in the different patient groups was lacking, therefore it was not possible to evaluate the risk–benefit of anticoagulation in patients with impaired renal function.

**Conclusions**

Impaired renal function, defined as eGFR <60 ml·min⁻¹·1.73 m⁻², has clinical additive prognostic value for thromboembolic events and cardiovascular mortality even in low-risk AF patients with CHA²DS²-VASc score 0–1. Further consideration of anticoagulation should be made in such patients.

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None of the authors has any conflicts of interest to declare.

**References**


