

# BMJ Open Survival benefits of oral anticoagulation therapy in acute kidney injury patients with atrial fibrillation: a retrospective study from the MIMIC-IV database

Dan Bo ,<sup>1</sup> Xinchun Wang,<sup>2</sup> Yu Wang<sup>3</sup>

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DB and XW contributed equally.

DB and XW are joint first authors.

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<sup>1</sup>Department of Cardiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

<sup>2</sup>Department of Cardiology, The Fourth Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

<sup>3</sup>Department of Geriatrics, The Fourth Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China

## Correspondence to

Dr Yu Wang;  
[wangyu@stu.njmu.edu.cn](mailto:wangyu@stu.njmu.edu.cn)

## ABSTRACT

**Objective** To find out the effect of different oral anticoagulation therapies (OAC) on mortality rate in patients with acute kidney injury (AKI) and atrial fibrillation (AF).

### Design

A retrospective study.

**Setting** This study was conducted in the Medical Information Mart for Intensive Care IV database.

**Participants** A total of 19672 patients diagnosed with AKI.

**Main outcome measures** Patients were categorised into three groups: (1) AF; (2) AKI and AF, OAC–; (3) AKI and AF, OAC+. The primary endpoint was 30-day mortality. Secondary endpoints were the length of stay (LOS) in the intensive care unit (ICU) and hospital. Propensity score matching (PSM) and Cox proportional hazards model adjusted confounding factors. Linear regression was applied to assess the associations between OAC treatment and LOS.

**Results** After PSM, 2042 pairs of AKI and AF patients were matched between the patients who received OAC and those without anticoagulant treatment. Cox regression analysis showed that, OAC significantly reduce 30-day mortality compared with non-OAC (HR 0.30; 95% CI 0.25 to 0.35;  $p < 0.001$ ). Linear regression analysis revealed that OAC prolong LOS in hospital (11.3 days vs 10.0 days;  $p = 0.013$ ) and ICU (4.9 days vs 4.4 days;  $p < 0.001$ ). OAC did not improve survival in patients with haemorrhage (HR 0.67; 95% CI 0.34 to 1.29;  $p = 0.23$ ). Novel OAC did not reduce mortality in acute-on-chronic renal injury (HR 2.03; 95% CI 1.09 to 3.78;  $p = 0.025$ ) patients compared with warfarin.

**Conclusion** OAC administration was associated with improved short-term survival in AKI patients concomitant with AF.

## INTRODUCTION

Acute kidney injury (AKI) is common in critically ill patients and has a high mortality rate.<sup>1</sup> Atrial fibrillation (AF) is the most commonly occurring sustained arrhythmia worldwide and is associated with an increased risk of all-cause mortality.<sup>2</sup> The prevalence of AF is approximately 30% among AKI patients,<sup>3</sup> and new-onset AF before renal replacement

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Given the respectable number of cases covered, this study provides important information about the appropriateness of anticoagulant therapy in acute kidney injury patients with atrial fibrillation.
- ⇒ Propensity score matching and Cox proportional hazards model were applied to decrease the bias by adjusting as many possible confounders as possible.
- ⇒ Because of the evolving nature of the adoption of oral anticoagulants into clinical practice and not fixed dose, the drug doses in each group were not included in the study, which may affect mortality.

therapy is associated with increased mortality.<sup>4</sup> Furthermore, AF patients with renal failure have a higher risk of ischaemic stroke than patients without renal failure.<sup>5</sup> Finding the optimal treatment for AF and renal impairment patients may be complicated.

Warfarin and novel oral anticoagulants (NOACs) are most commonly prescribed in clinical anticoagulation treatment. Warfarin could reduce the risk of mortality (HR 0.65; 95% CI 0.59 to 0.72;  $p < 0.00001$ ) in patients with AF and non-end-stage chronic kidney disease (CKD).<sup>6</sup> Several studies have reported that NOACs are beneficial in patients with CKD, including dialysis patients.<sup>7–9</sup> Uncertainty remains regarding the administration of anticoagulation in patients who had a sudden decline in renal function. Thus, we designed this study to determine whether OAC can reduce mortality in AKI patients concomitant with AF and evaluate the difference between NOACs and warfarin.

## MATERIALS AND METHODS

### Study population

This was a retrospective cohort study using the Medical Information Mart for Intensive Care IV database. A total of 19672 AKI patients were included in the study.<sup>10</sup> The inclusion

criteria for the patient's enrolment was AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 criteria.<sup>11</sup> The exclusion criteria were: (1) patients who had intensive care unit (ICU) stay <48 hours; (2) patients who had AF receiving OAC before AKI; (3) patients who had AF receiving OAC only after discharging from ICU and (4) AKI patients who had concomitant AF but using multiple anticoagulants. Finally, 19672 patients were divided into three groups based on the presence or absence of AF and the anticoagulation strategy for AF. A total of 13706 patients who had AKI without AF were assigned to the AKI, no AF group, which was regarded as the control group. A total of 2212 patients who had AKI concomitant with AF using OAC were assigned to (AKI and AF, OAC+group), while 3754 patients who had AKI concomitant with AF but did not take OAC were assigned to (AKI and AF, OAC- group). The flow chart of the study is presented in online supplemental figure 1. The baseline value of serum creatinine (SCr) was defined as (1) the minimum SCr measured during the 7 days before ICU admission and (2) the first SCr measured at ICU admission if no SCr data were available before ICU admission. Moreover, we used the KDIGO criteria to identify the severity of AKI patients, and the AKI stage was defined as the maximum AKI stage during hospitalisation. OAC included warfarin and NOACs (apixaban, dabigatran and rivaroxaban) in patients with AKI.

Baseline demographic variables, including age, gender, ethnicity, weight and medical history like mean blood pressure (MBP), AKI stage, CKD, congenital heart failure (CHF), hypertension, diabetes mellitus (DM), thromboembolism (ischaemic stroke and systemic embolism), haemorrhage (gastrointestinal haemorrhage and intracranial haemorrhage), hyperlipidaemia, coronary atherosclerotic heart disease (CAD), neoplasm, liver disease, sepsis, the use of heparin, vasopressin, amiodarone, antibiotic, furosemide, non-steroidal anti-inflammatory drug (NSAID), insulin, dialysis and mechanical ventilation, the first 24 hours were collected from the database. Baseline laboratory profile including urine output, SCr, urea nitrogen (BUN), alanine aminotransferase, aspartate aminotransferase, total bilirubin, haemoglobin, CHA2DS2-VASc score, Sequential Organ Failure Assessment score and Simplified Acute Physiology Score (SAPS) II were extracted from the database and analysed. Only the data for the first measurement of each patient after ICU admission were used.

### The primary and secondary outcome

The primary outcome of the study was 30-day mortality. Secondary outcomes of the study consisted of the length of stay (LOS) in ICU (LOS ICU) and the LOS in hospital.

### Propensity score matching

Propensity score matching (PSM) was performed by a greedy nearest neighbour matching with a calliper of 0.2 SD of the logit of the estimated propensity score<sup>12</sup> to balance the baseline characteristics. Patients were

matched in a 1:1 ratio, such that each AKI patient with AF who was treated with OAC was matched to 1 AKI patient without OAC. An SMD greater than 0.1 was used as an indicator of unbalance.

### Kaplan-Meier survival curve analysis

The Kaplan-Meier (K-M) survival analysis and log-rank test<sup>13</sup> showed the cumulative rates among AKI patients. We plotted survival curves between the three groups (non-OAC, warfarin and NOAC groups) in AKI patients complicated with AF and compared them in pairs.

### Cox proportional hazard regression

A Cox proportional hazard regression model was used to estimate the association between 30-day mortality and OAC medication adjusted for confounding variables<sup>14</sup> selected based on a  $p < 0.05$  in univariate analysis and potential confounders judged by clinical experts who were blind to the study.

### Linear regression

A linear regression model was used to evaluate the association between OAC administration and LOS with adjustments for confounding variables, and the HRs were calculated using the formula  $HR = e^{\beta}$ .<sup>15</sup>

### Stratification analysis and interaction effect

Stratification analysis with multivariate-adjusted regression was done to explore whether the association between OAC administration and 30-day mortality differed across various subgroups classified by AKI severity, CKD, haemorrhage, CHA2DS2-VASc score and dialysis. The influence of warfarin and NOACs on mortality was also evaluated for subgroups according to CKD and severity of AKI. In regression analysis, interaction effects occur when the influence of one variable is dependent on the value of another variable.<sup>16</sup> To test for effect modification, the interaction terms for study covariates and OAC were evaluated with the Cox regression model.

Continuous variables were presented as medians and IQR, and the differences were identified with the Mann-Whitney test because of their non-normal distribution. Categorical variables were summarised as numbers (percentage) and were compared using the  $\chi^2$  test. All statistical analyses were performed using R package (V.4.2.1), and a  $p < 0.05$  was considered statistically significant.

### Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

## RESULTS

### Baseline characteristics for all people

The baseline demographic, clinical characteristics and comparisons are presented in online supplemental table 1. The patients in AKI, no AF group were younger, had a higher incidence of AKI stage 1, more urine output,

less creatinine and nitrogen, lower rates of CKD, CHF, hypertension, DM, thromboembolism, hyperlipidaemia, CAD and less use of heparin, vasopressin, amiodarone, antibiotic, furosemide, NSAID, insulin and ventilation, compared with AKI patients without AF. The 30-day cumulative mortality curve showed that the AF increased mortality in AKI people (online supplemental figure 2). Furthermore, the mortality rate was significantly higher in the AKI and AF, OAC- group but lower in the AKI and AF, OAC+ group, compared with AKI and non-AF group ( $p<0.001$ ) (online supplemental figure 3).

Besides, age, MBP, BUN, haemoglobin, the incidence of AKI stage 3, hypertension, haemorrhage, neoplasm, liver disease, sepsis, vasopressin and antibiotic use, and SAPS II scores were lower in the AKI and AF, OAC+ group than the AKI and AF, OAC- group. AKI patients merging AF with a higher incidence of CKD, CHF, DM, hyperlipidaemia, CAD and thromboembolic events were more likely to be given OAC.

After PSM, 2042 AKI patients with AF who received OAC were matched to patients who did not to eliminate this bias. The baseline variables in the as well as have similar distributions (table 1).

Multivariable Cox regression model before PSM show that OAC can significantly decrease the risk of 30-day mortality up to 70% (HR 0.30, 95% CI: 0.25 to 0.36,  $p<0.001$ ) (online supplemental table 2). Multiple linear regression analyses show that OAC was associated with prolonged LOS in ICU (HR 1.16; 95% CI 1.11 to 1.20;  $p<0.001$ ) and in the hospital (HR 1.07; 95% CI 1.02 to 1.12;  $p=0.002$ ).

After PSM, the K-M curve shows that the risk of death was lower in AKI and AF, OAC+ group, than in AKI and AF, OAC- group (figure 1). In the AKI patients with AF, OAC significantly reduce 30-day mortality (HR 0.30; 95% CI 0.25 to 0.35;  $p<0.001$ ). OAC increased the LOS in ICU (HR 1.15; 95% CI 1.08 to 1.23;  $p<0.001$ ) and in the hospital (HR 1.08; 95% CI 1.02 to 1.14;  $p=0.013$ ).

### Subgroup analysis

To identify subgroups of patients with differential OAC-related survival benefit, we tested cross-interactions between OAC use and AKI stage, CKD, haemorrhage, CHA2DS2-VASc score and dialysis. A number of patients in each subgroup are shown in figure 2. The OAC significantly reduce 30-day mortality in patients with AKI stage 1–2 (HR 0.24; 95% CI 0.18 to 0.31;  $p<0.01$ ) or 3 (HR 0.35; 95% CI 0.28 to 0.44;  $p<0.01$ ). OAC also decreased mortality rate in patients who had CKD (HR 0.39; 95% CI 0.30 to 0.49;  $p<0.01$ ) or with CHA2DS2-VASc score less than 2 (HR 0.12; 95% CI 0.05 to 0.29;  $p<0.01$ ). The use of OAC significantly reduced the risk of death in patients with or without dialysis (HR 0.35; 95% CI 0.27 to 0.44;  $p<0.01$  and HR 0.27; 95% CI 0.22 to 0.35;  $p<0.01$ ). OAC could not improve mortality in patients with haemorrhage (HR 0.67; 95% CI 0.34 to 1.29;  $p=0.23$ ). AKI stage (P for interaction=0.03), CKD (P for interaction<0.01), haemorrhage (P for interaction=0.01) and CHA2DS2-VASc

score (P for interaction=0.02) modified the association between OAC treatment and mortality. The interaction test for OAC and dialysis was not significant (P for interaction=0.11).

Among 2212 AKI and AF patients using OACs, warfarin was administered in 87.4% (1,934), apixaban, rivaroxaban and dabigatran were administered in 7.7% (171), 3.7% (81) and 1.2% (26) of patients, respectively. The univariate and multivariate Cox proportional hazard regression model was used to evaluate factors, including OACs, with 30-day mortality rates. Univariate regression analysis showed that warfarin (HR 0.23; 95% CI 0.19 to 0.27;  $p<0.001$ ) and NOAC (HR 0.36; 95% CI 0.25 to 0.51;  $p<0.001$ ) groups were associated with a lower risk of death (online supplemental table 3). Multivariate regression analysis indicated that warfarin (HR 0.28; 95% CI 0.24 to 0.34;  $p<0.001$ ) and NOACs (HR 0.43; 95% CI 0.30 to 0.62;  $p<0.001$ ) both significantly reduced mortality compared with the non-OAC group (online supplemental figure 4). Online supplemental figure 5 shows that the non-OAC group had a higher mortality rate ( $p<0.05$ ). The LOS in ICU and hospitals were significantly longer in the (warfarin and NOAC) OAC groups than in the non-OAC group ( $p<0.05$ ) (online supplemental figure 6).

### Effects of warfarin and NOAC on 30-day mortality in the subgroups of CKD and AKI stage

Multivariate Cox regression analysis found that apixaban (HR 1.26; 95% CI 0.74 to 2.14;  $p=0.395$ ) and rivaroxaban (HR 1.98; 95% CI 0.91 to 4.31;  $p=0.085$ ) had similar mortality rates as warfarin, but dabigatran was associated with a high risk of death than warfarin treatment (online supplemental table 4) (HR 6.79; 95% CI 2.66 to 17.30;  $p<0.001$ ).

When stratified by AKI stage (online supplemental figure 7), 30-day mortality was similar among patients who had received NOACs at stage 1–2 (HR 1.44; 95% CI 0.75 to 2.77;  $p=0.278$ ) or stage 3 (HR 1.70; 95% CI 0.92 to 3.11;  $p=0.089$ ) compared with those who received warfarin. In patients complicated with CKD, warfarin ( $p<0.001$ ) and NOACs ( $p=0.049$ ) were both associated with improved mortality (figure 3A), but NOACs were associated with higher mortality than warfarin (HR 2.03; 95% CI 1.09 to 3.78;  $p=0.025$ ) (online supplemental figure 7). When the analysis was restricted to patients without CKD, there was no significant difference in mortality between warfarin and NOACs (HR 1.42; 95% CI 0.77 to 2.61;  $p=0.258$ ) (online supplemental figure 7). Warfarin and NOACs both treatments significantly reduced mortality ( $p<0.001$ ) compared with the non-OAC group (figure 3B).

### DISCUSSION

In patients diagnosed with AKI and AF, OAC administration could reduce 30-day mortality. But there was no significant survival benefit from OAC use in patients with bleeding complications. OAC treatment has increased LOS in ICU and hospitals compared with non-OAC

**Table 1** Baseline characteristics for the two groups after PSM

	All (n=4084)	AKI and AF, OAC- (n=2042)	AKI and AF, OAC+ (n=2042)	SMD	P value
Age (year)	76.0 (67.0–83.0)	76.0 (67.0–84.0)	76.0 (67.3–83.0)	0.021	0.191
Gender				0.004	0.924
M (%)	2452 (60.0)	1228 (60.1)	1224 (59.9)		
Ethnicity				0.013	0.697
White (%)	2992 (73.3)	1490 (73.0)	1502 (73.6)		
Weight (kg), (IQR)	83.6 (69.6–99.0)	83.0 (69.0–98.5)	84.0 (70.0–99.3)	0.037	0.148
MBP (mm Hg), (IQR)	78.0 (68.0–90.0)	79.0 (68.0–91.0)	78.0 (69.0–90.0)	0.001	0.611
AKI stage (%)				0.009	0.964
1	691 (16.9)	348 (17.0)	343 (16.8)		
2	2044 (50.1)	1018 (49.9)	1026 (50.2)		
3	1349 (33.0)	676 (33.1)	673 (33.0)		
Urine output (mL, (IQR))	1380.0 (880.0–2100.0)	1370.0 (861.3–2115.0)	1389.0 (898.5–2075.0)	0.031	0.315
Creatinine (mg/dL), (IQR)	1.1 (0.8–1.7)	1.1 (0.8–1.7)	1.1 (0.8–1.7)	0.008	0.422
BUN (mg/dL), (IQR)	23.0 (16.0–37.0)	23.5 (17.0–38.0)	23.0 (16.0–36.0)	0.047	0.344
ALT (IU/L), (IQR)	29.0 (18.0–59.3)	29.0 (17.0–59.0)	29.0 (18.0–60.0)	0.009	0.405
AST (IU/L), (IQR)	44.0 (26.0–88.0)	43.0 (25.0–88.0)	45.0 (26.0–87.0)	0.005	0.381
Total bilirubin (mg/dL), (IQR)	0.6 (0.4–1.0)	0.7 (0.4–1.0)	0.6 (0.4–1.0)	0.083	0.360
Haemoglobin (g/L), (IQR)	104.0 (89.0–123.0)	105.0 (90.0–123.0)	104.0 (89.0–122.0)	0.029	0.243
CKD (%)	1311 (32.1)	646 (31.6)	665 (32.6)	0.020	0.546
CHF (%)	2214 (54.2)	1092 (53.5)	1122 (55.0)	0.029	0.362
Hypertension (%)	1143 (28.0)	568 (27.8)	575 (28.2)	0.008	0.834
DM (%)	1232 (30.2)	611 (29.9)	621 (30.4)	0.011	0.759
Thromboembolism (%)	419 (10.3)	196 (9.6)	223 (10.9)	0.044	0.180
Haemorrhage (%)	103 (2.5)	47 (2.30)	56 (2.7)	0.028	0.425
Hyperlipidaemia (%)	2019 (49.4)	987 (48.3)	1032 (50.5)	0.044	0.169
CAD (%)	1954 (47.9)	972 (47.6)	982 (48.1)	0.010	0.778
Neoplasm (%)	982 (24.1)	507 (24.8)	475 (23.3)	0.037	0.256
Liver disease (%)	140 (3.4)	69 (3.4)	71 (3.5)	0.005	0.932
Sepsis (%)	756 (18.5)	402 (19.7)	354 (17.3)	0.061	0.058
Heparin (%)	2046 (50.1)	1012 (49.6)	1034 (50.6)	0.022	0.511
Vasopressin (%)	519 (12.7)	264 (12.9)	255 (12.5)	0.013	0.707
Amiodarone (%)	1300 (31.8)	628 (30.8)	672 (32.9)	0.046	0.149
Antibiotic (%)	2255 (55.2)	1138 (55.7)	1117 (54.7)	0.021	0.529
Furosemide (%)	2941 (72.0)	1463 (71.7)	1478 (72.4)	0.016	0.626
NSAID (%)	1966 (48.1)	969 (47.5)	997 (48.8)	0.027	0.398
Insulin (%)	1509 (37.0)	746 (36.5)	763 (37.4)	0.017	0.604
Dialysis (%)	1835 (44.9)	926 (45.4)	909 (44.5)	0.017	0.615
Ventilation (%)	2966 (72.6)	1463 (71.7)	1503 (73.6)	0.044	0.171
CHA2DS2-VASc score, (IQR)	4.0 (2.0–5.0)	4.0 (2.0–5.0)	4.0 (3.0–5.0)	0.040	0.276
SOFA, (IQR)	6.0 (4.0–9.0)	6.0 (4.0–9.0)	6.0 (4.0–9.0)	0.013	0.220
SAPSII, (IQR)	41.0 (33.0–50.0)	41.0 (33.3–50.0)	41.0 (33.0–50.0)	0.021	0.528

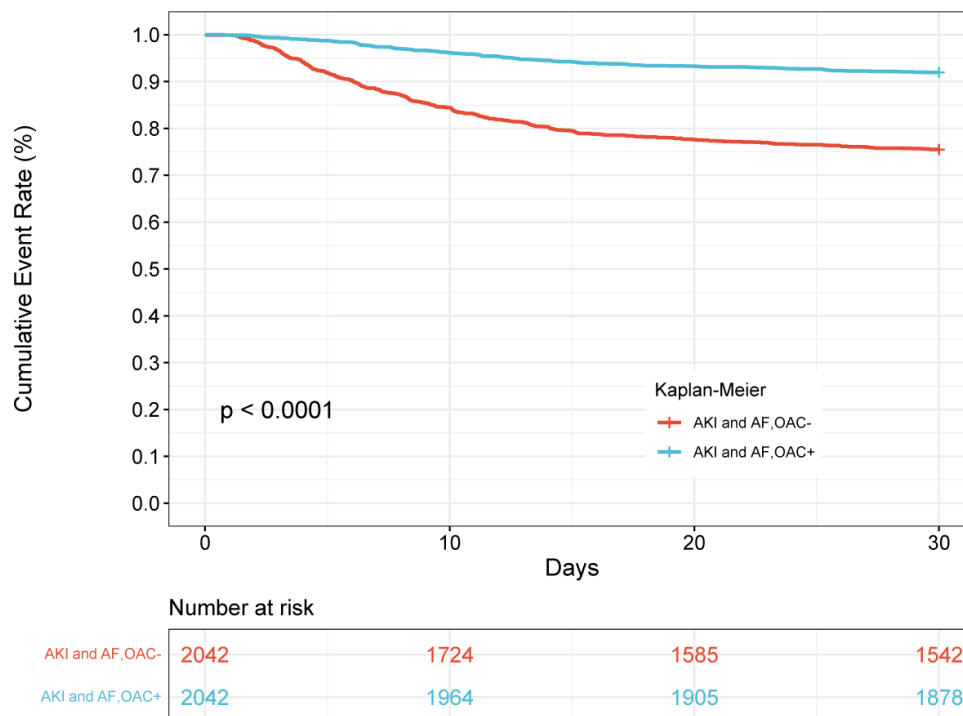
AF, atrial fibrillation; AKI, acute kidney disease; ALT, alanine Aminotransferase; AST, aspartate Aminotransferase; BUN, urea nitrogen; CAD, coronary atherosclerotic heart disease; CHF, congenital heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; MBP, mean blood pressure; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulation; PSM, propensity score matching; SAPSII, Simplified Acute Physiology Score; SOFA, sequential organ failure assessment.

treatment. Moreover, warfarin shows a significantly lower risk of 30-day mortality than NOACs in the CKD subgroup.

OAC could reduce 30-day mortality in AKI patients with AF in our study. Similarly, a retrospective observational

study reported that moderate to severe renal impairment increased ischaemic stroke risk in AF patients not receiving antithrombotic treatments.<sup>17</sup> Since the benefit of OAC is strongly related to the CHA2DS2-VASc score,



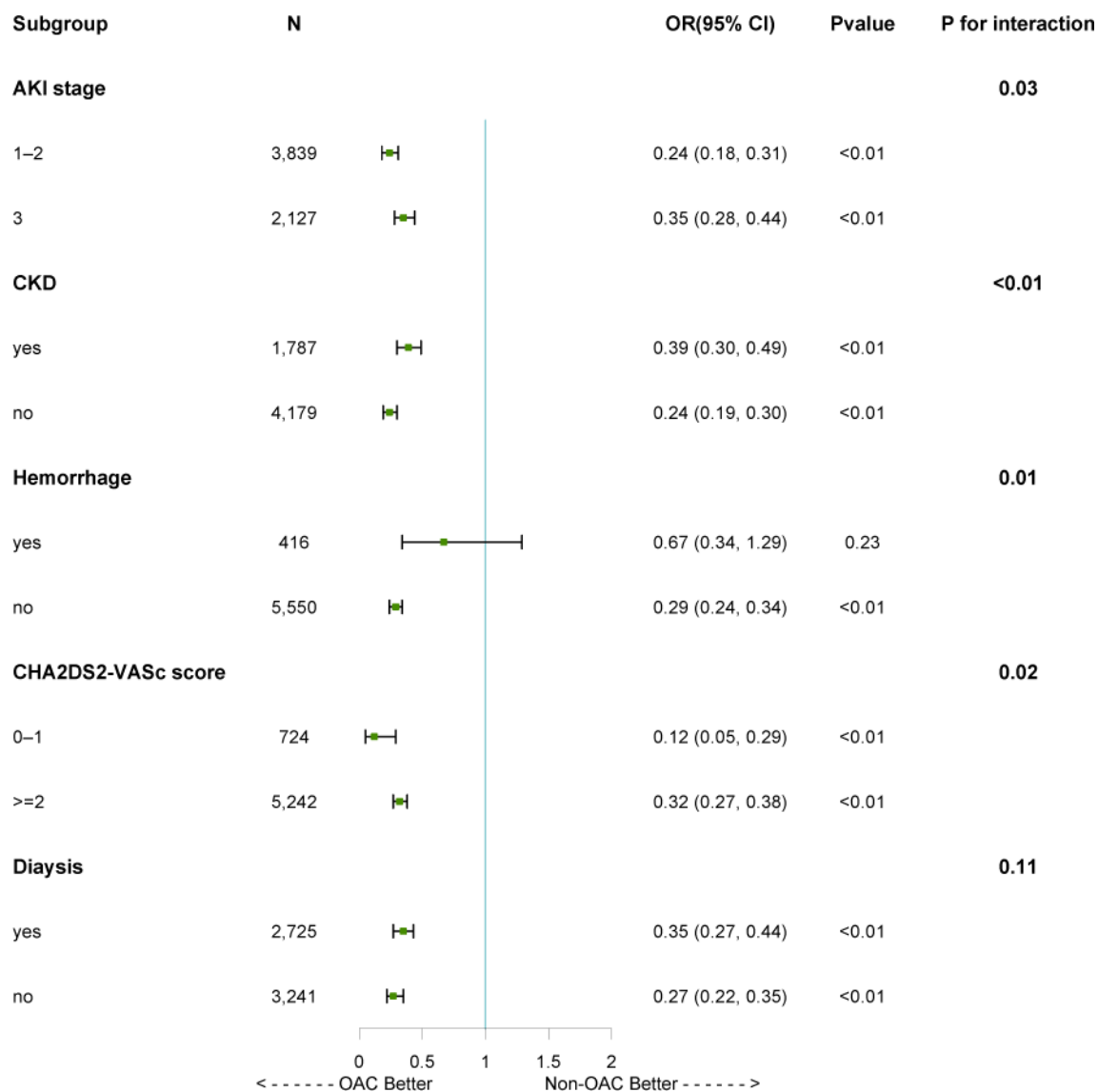


**Figure 1** Kaplan-Meier survival curve between OAC treatment and 30-day mortality after PSM. AKI, acute kidney injury; AF, atrial fibrillation; OAC, oral anticoagulation.

subjects with lower CHA2DS2-VASc scores also had a decreased risk of mortality by using OAC in our study. This may be due to the higher rates of thromboembolism and bleeding in patients with the deterioration of renal function,<sup>5 18</sup> but the absolute benefits of OAC in this population outweigh the risks, and OAC should be considered for AKI patients with AF. Additionally, there was an interaction between OAC and CHA2DS2-VASc on mortality. It could be that CHA2DS2-VASc score was strongly associated with all-cause mortality in hemodialysis patients,<sup>19</sup> and survival benefit is partially offset. Several studies show that altered clot properties resulting in denser clots with thinner fibres<sup>20</sup> and routine heparin during dialysis could lead to an increased bleeding risk in dialysis patients. However, a previous study found that haemodialysis patients with AF taking OAC at recruitment had significantly lower mortality than those not taking it (HR 0.53; 95% CI 0.28 to 0.90;  $p=0.04$ ).<sup>21</sup> Consistent with the result, our study showed the benefits of OAC outweighed an increased risk of fatal side effects in dialysis patients. It is possible that, OAC might have a survival benefit not only through a reduction of thromboembolic risk, but also protecting against myocardial infarction in a considerable number of patients with AF complicated with CAD.<sup>22 23</sup> However, OAC treatment did not significantly reduce the risk of 30-day mortality among AKI patients complicated by haemorrhage. Lin *et al* also reported that OACs did not reduce the risk of all-cause mortality (OR 0.85, 95% CI 0.72 to 1.01) in patients with AF and intracranial haemorrhage.<sup>24</sup> One guideline indicates that OAC agents should be discontinued immediately after an intracranial haemorrhage episode.<sup>25</sup> Therefore,

OAC therapy after a bleeding event in AKI people is a difficult choice, which requires balancing the risk of rebleeding and the occurrence of thromboembolism. There might be concerns that the statistically significant moderation effects observed in our study were false positive signal, given the interaction terms tested. Subgroup analyses should always be considered as explorative, and other confounding factors were adjusted. Nevertheless, the moderation observed in our study was biologically plausible. Hence, this study provides sufficient evidence to further investigate this important aspect of patient profiling.

In most studies on NOACs, their safety profile seems to be at least non-inferior or even superior to VKAs in patients with mild/moderate CKD.<sup>26 27</sup> Siontis *et al* reported that apixaban's standard dose (5 mg two times per day) was associated with a decrease in mortality as compared with warfarin (HR 0.63, 95% CI 0.46 to 0.85,  $p=0.003$ ) among end-stage kidney disease (ESKD) patients with AF on dialysis.<sup>28</sup> Yet a study found no significant difference between Vitamin K antagonists and NOACs and all-cause mortality (HR 0.99, 95% CI 0.77 to 1.26) in patients with AF and CKD.<sup>9</sup> Trevisan *et al* reported NOAC use was associated with a lower risk of CKD progression, AKI, and major bleeding, but a similar risk of the composite of stroke/systemic embolism and death.<sup>29</sup> Our study confirmed the similar effect between warfarin and NOACs (apixaban and rivaroxaban). Some possibilities could explain this discrepancy. First, the use of warfarin is associated with additional risks related to inhibition of vitamin K-dependent pathways, including a greater decline in kidney function and pathways affecting dystrophic calcification



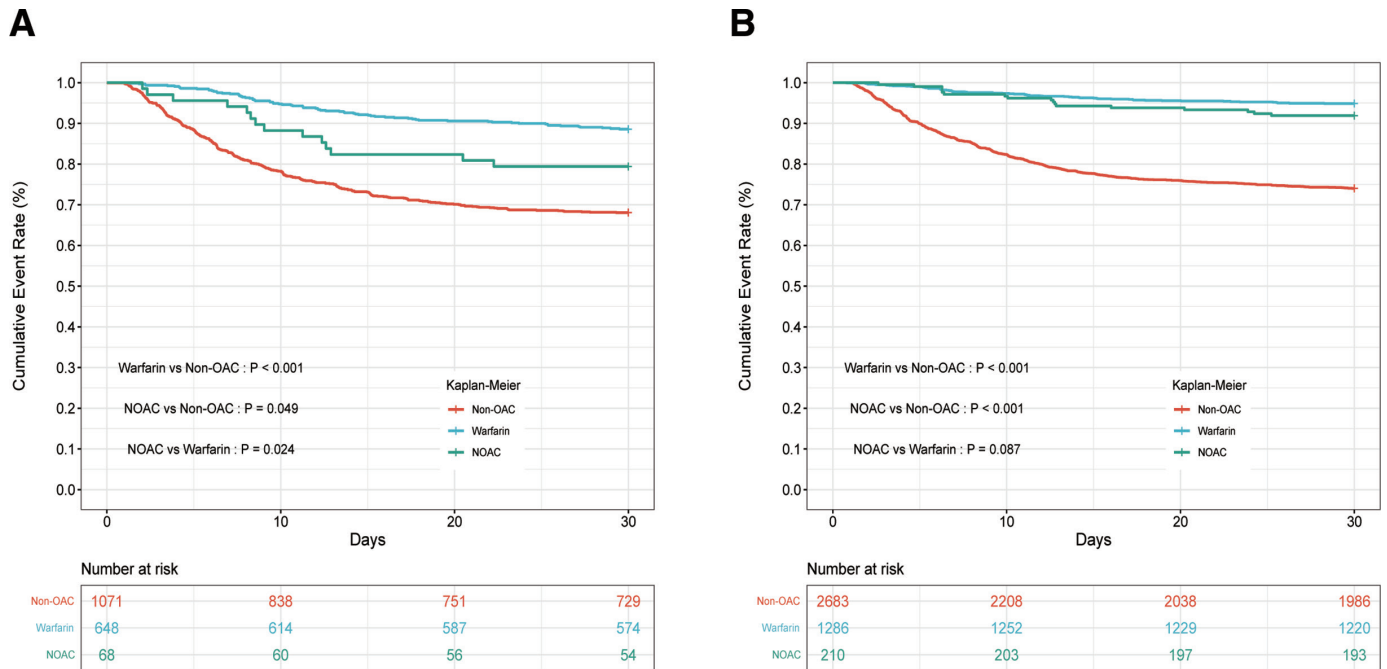
**Figure 2** Stratified Cox regression analysis between OAC use and 30-day mortality. After excluding subgroup variable, other variables including age, weight, ethnicity, AKI stage, creatinine, BUN, total bilirubin, CKD, hypertension, thromboembolism, haemorrhage, hyperlipidaemia, CAD, neoplasm, liver disease, sepsis, heparin, vasopressin, antibiotic, NSAID, insulin, dialysis, ventilation, CHA2DS2-VASc, SAPSII and SOFA were adjusted in the Cox regression. AKI, acute kidney injury; CAD, coronary atherosclerotic disease; CKD, chronic kidney disease; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulation.

for prolonged time.<sup>30</sup> But previous studies might have overlooked that warfarin relationship with survival is time-dependent,<sup>31</sup> and the association manifested early after therapy initiation was not related to the severity of kidney function.<sup>32</sup> Second, the majority of NOACs used were apixaban and rivaroxaban in our study. They are predominantly metabolised by the liver and levels are only modestly affected by kidney disease.<sup>33</sup> But we did not consider the influence of doses on death, which might lead to NOACs with similar results to warfarin.

The OAC group seemed to have longer LOSs in the ICU and hospital than the non-OAC group in this study. The warfarin and NOAC groups were also longer than those not taking OAC. A previous study also showed warfarin therapy during hospitalisation is associated with a significant increase in mean LOS among AF patients.<sup>34</sup> The

possible reason may be the differences in the survival rate between these groups; non-OAC patients who died early in the ICU would have a short ICU stay and hospital stay. It is also challenging to establish a consistent therapeutic. International normalised ratio requires that patients using warfarin stay at hospitals longer. Therefore, it needs to be confirmed by further randomised controlled trials.

There was insufficient evidence to establish the benefits or harms of NOACs for AKI patients with prior CKD, named acute-on-chronic (A-on-C) renal injury,<sup>35</sup> which was reported that 44.9% of patients with CKD had at least one AKI episode.<sup>36</sup> We found that warfarin appeared to be safer than NOACs in the risk of mortality in patients with A-on-C renal injury. Similarly, a study reported that dabigatran and rivaroxaban were associated with a higher death risk than warfarin in the ESKD population.<sup>37</sup> One



**Figure 3** Kaplan-Meier survival curve of non-OAC, warfarin and NOAC groups in the AF patients. (A) Shows the Kaplan-Meier survival curve in the CKD group. (B) Shows the Kaplan-Meier survival curve in the non-CKD group. AF, atrial fibrillation; CKD, chronic kidney disease; OAC, oral anticoagulation; NOAC, novel oral anticoagulant.

mechanism that may explain the result is that warfarin is minimally dependent on the kidney for elimination,<sup>33</sup> such that acute changes in creatinine can minimally influence anticoagulation levels from the drug. Participants with both AKI and CKD had a 41-fold increase in the risk of ESKD compared with those without a history of either disease.<sup>38</sup> For patients with a creatinine <25 mL/min, there is a residual risk of accumulation with NOACs,<sup>39</sup> all dependent on renal clearance to a varying degree. Additionally, 80% of dabigatran needs to undergo renal elimination through proximal tubule secretion despite the drug being also dialyzable.<sup>40</sup> Meanwhile, rivaroxaban is not dialyzable as the drug is highly bound to plasma proteins (92%–95%),<sup>33</sup> hence there is no way to deal with excessive exposure to rivaroxaban when patients were aggressively dialyzed. These allow NOACs to accumulate in patients with severe kidney injury, while warfarin does not.

The previous studies mainly focused on the utilisation of OAC in patients with CKD with AF. But our study provides novel insights into analysing the influence of OAC on outcomes in AKI patients and further researched patients with A-on-C renal injury. This study also has some limitations. First of all, although it is retrospective, given the respectable number of cases covered, provides important information about the appropriateness of anticoagulant therapy in patients with AF who had renal insufficiency. Nonetheless, the sample size for some of the subgroups was small and the confidence intervals of the point estimates were large which indicates uncertainty of evidence. This was especially the case for dabigatran. Second, the diagnosis of CKD relies on ICD code in the study, which results in a significant number of patients lacking renal

stage. So we did not limit past renal function, but added CKD to the subgroup analysis. Third, the warfarin and NOAC doses in each group were not completely fixed because of the evolving nature of the adoption of OACs into clinical practice. There was no certainty evidence that the doses of these drug are sufficient. Therefore, further work is needed to understand what the stable state drug levels are in patients with renal insufficiency, particularly given the potential for drug accumulation. Finally, the effect of OAC on outcomes should be viewed with caution, since it may reflect selection bias favouring patients with better prognosis and clinical characteristics for OAC. We adjusted as many possible confounders as possible and achieved a good balance in the PSM cohorts. But no firm conclusions can be drawn without assessing their effect in these patients in a randomised clinical trial.

## CONCLUSION

This study suggested that OAC could reduce 30-day mortality among AKI patients with AF. In haemorrhagic patients, OAC did not significantly improve survival. Warfarin and NOAC both improve the survival rate. In addition, patients with A-on-C kidney injury seemed to benefit more from warfarin than NOAC. However, the data we analysed were obtained from an observational database. Additional randomised trials should further verify the results reported in our study.

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#### ORCID iD

Dan Bo <http://orcid.org/0000-0002-3031-3345>

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