Factors influencing adherence to non-vitamin K antagonist oral anticoagulants in the early period after atrial fibrillation catheter ablation in China

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Anticoagulants are routinely prescribed in the first several weeks after atrial fibrillation (AF) catheter ablation. Non-vitamin K antagonist oral anticoagulants (NOACs) have been recommended over warfarin for their superiority. Unlike warfarin need regular clinical visit to perform blood test, NOACs are more patient friendly. But the lack of routine medical contact may lead to poor adherence. Strict adherence to anticoagulant treatment is essential for both efficacy and safety. Considering NOACs are increasingly commonly used in China, it is therefore necessary to evaluate the adherence of NOACs after AF catheter ablation. The purpose of this research was to investigate the treatment adherence and identify factors that could improve the quality of anticoagulation.

This single-center, retrospective observational survey was performed between September 2018 and January 2019. The survey was approved by the Local Ethics Committee (No. 2015-ZX51). Patients who met the following criteria were eligible: (1) aged ≥18 years; (2) definitive diagnosis of AF by electrocardiogram before catheter ablation; (3) underwent AF catheter ablation during current admission; and (4) prescribed NOACs on discharge and were required to continue NOAC treatment for at least 3 months. Patients were excluded if (1) they were prescribed NOACs for other indications; (2) they were currently participating in another clinical study; (3) NOAC was suspended under instruction of doctors within 3 months after ablation; or (4) they were incapable of understanding the research purpose and process, or could not complete surveys. Patients received routine care. The choice of NOAC and the therapeutic initiation date were decided by electro-

physiologists. AF recurrence was defined as a documented AF episode of ≥30 s.

Demographic characteristics, medical history, biochemical parameters, self-rating depression scale (SDS) and self-rating anxiety scale (SAS) scores were collected within 24 h after admission. An interview investigating patient management of NOAC medication, the anticoagulation knowledge tool (AKT) questionnaire, and the eight-item Morisky Medication Adherence Scale (MMAS) questionnaire were conducted via an online questionnaire interview website during anticoagulation. All scales were translated into the Chinese language. The standard cutoff score of 50 in the SDS or SAS was used to diagnose depression or anxiety, respectively. The AKT scores are presented as percentages of correct answers. In the eight-item MMAS, a score of 6 to 8 was defined as adequate adherence, and <6 was defined as inadequate adherence. Patients were then divided into groups according to treatment adherence, as defined by the MMAS score. The CHA_2DS_2-VASc score, HAS-BLED score, and Charlson index of comorbidity were calculated at discharge.

Numerical data are presented as means ± standard deviations, while categorical data are presented as frequencies and ratios. The independent Student's *t* test was used to assess differences between two groups. The χ^2 was used to compare categorical data. The variables associated with adherence in the univariate analysis ($P < 0.20$) were included in the multivariate logistic regression analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using standard methods. A *P*-value of <0.05 was considered statistically

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significant. All statistical analyses were performed using SPSS 19.0 (SPSS Inc, Chicago, IL, USA).

A total of 373 patients were evaluated, 41 of whom met the exclusion criteria, for a final sample size of 332. All patients had received NOACs for ≥6 weeks. In general, 233 (70.2%) patients exhibited adequate adherence to NOAC therapy. The demographic and clinical characteristics are provided in Supplemental Table 1, http://links.lww.com/CM9/A266. The mean age of the cohort was 59.2 ± 10.2 years, and 41.4% was female. Patients in the inadequate adherence group were significantly younger than those in the adequate adherence group $(57.4 \pm 10.7$ vs. 60.1 ± 9.8 years, $Z = 0.07, P = 0.03)$. A significantly higher SDS score and lower SAS score were found in the inadequate adherence group than the adequate adherence group $(52.0 \pm 10.2$ vs. $49.7 \pm 8.3, Z = 0.13, P = 0.03; 46.3 \pm 8.1$ vs. $48.7 \pm 8.9, Z = 0.02, P = 0.02$; respectively). A significantly higher percentage of AF recurrence was observed in the adequate adherence group than the inadequate adherence group $(31.3\%$ vs. $16.2\%, \chi^2 = 8.15, P = 0.004)$.

The overall mean MMAS score was 6.25 ± 1.18. Details related to NOAC therapy are provided in Supplemental Table 1, http://links.lww.com/CM9/A266. More patients in the adequate adherence group used methods to assist NOAC adherence than in the inadequate group $(45.9\%$ vs. $21.2\%, \chi^2 = 17.91, P < 0.001)$. Among all methods, the most common was being reminded by others (24.8%), followed by using a pill sorting box and written reminders (8.4%). Only 3.3% of patients used two methods to remind themselves, and these patients exhibited adequate adherence.

In the univariate regression analysis, the significant predictors of adequate NOAC adherence included aged >50 years, employed, retired, living alone, using an alarm and timer, using a pill sorting box, being reminded by others, anxiety, and AF recurrence. These factors were evaluated in the multivariate regression analysis and the results are presented in Table 1. The multivariate regression analyses indicated that using a pill sorting box (OR = 3.22, 95% CI: 1.04–9.93, P = 0.04), being reminded by others (OR = 3.02,

95% CI: 1.43–6.35, P = 0.003), anxiety (OR = 2.16, 95% CI: 1.12–3.41, P = 0.02), and AF recurrence (OR = 2.16, 95% CI: 1.12–4.16, P = 0.03) were predictors of adequate adherence.

Anticoagulants are administrated to those at high risk of thromboembolic events in the early period after AF catheter ablation, and NOACs have become increasingly popular in recent years. NOACs have a shorter half-life and require stricter adherence than warfarin.[1] One prior study found that adherence to warfarin in China was poor,[2] but no data regarding adherence to NOACs was provided. The results of this study revealed that 70.2% patients exhibited adequate adherence to NOAC therapy in the early period after AF catheter ablation. This study also demonstrated that using a pill sorting box, being reminded by others, anxiety, and AF recurrence were predictors of adequate adherence.

Using a pill sorting box, alarms, calendars, and caregiver help have already been confirmed as effective methods for improving treatment adherence in chronic diseases.[3] However, the relationship between adherence and anxiety is inconsistent. Some studies have reported that anxiety was associated with a high activation level and better medication adherence, while others drew the opposite conclusion.[4,5] The result of our study indicated that anxiety was beneficial to NOAC adherence. In patients with AF, anxiety mainly arises from fear of both symptoms of AF and thromboembolic events. Since anticoagulation is the primary method to prevent thromboembolic events, it is reasonable that anxiety makes patients with AF adhere to NOAC treatment. The relationship between AF recurrence after ablation and NOAC adherence has not been reported before. Our study demonstrated that patients with AF recurrence exhibited better compliance to NOACs than non-recurrence patients. Patients with AF were assumed to be serious regarding NOAC adherence as they may regard anticoagulants as preventers of thrombosis caused by AF. However, once patients restore their sinus rhythm, some may form the assumption that there is no risk of thrombosis and no need for anticoagulant therapy. Indeed, 15.7% (52/332) of the patients in our study admitted that they had ever stopped

Table 1: Multivariate analysis of 332 patients associated with adequate adherence.

Characteristic	β	SE	Wals	P	OR (95% CI)
Aged >50 years	0.44	0.40	1.25	0.26	1.91 (0.89–4.12)
Occupation (reference = unemployed)					
Employed	1.50	0.80	3.57	0.06	4.49 (0.88–10.82)
Retired	1.52	0.80	3.58	0.06	4.57 (0.84–9.73)
Living alone	−0.38	0.45	0.73	0.39	0.68 (0.2–1.64)
Alarm or timer	1.82	1.10	2.72	0.10	6.12 (0.71–52.57)
Pill box use	1.17	0.58	4.15	0.04	3.22 (1.04–9.93)
Reminded by others	1.10	0.38	8.48	0.003	3.02 (1.43–6.35)
Anxiety	0.61	0.28	5.62	0.02	2.16 (1.12–3.41)
AF recurrence	0.77	0.24	5.24	0.03	2.16 (1.12–4.16)

A multivariate logistic regression analysis model was used to identify significant predictors. See Supplemental Table 1, http://links.lww.com/CM9/A266 for the total list of examined variables. β: Coefficient of predictor variables; SE: Standard error; OR: Odds ratio; CI: Confidence interval; AF: Atrial fibrillation; NCD: necessity-concerns differential.

taking NOACs when they believed the AF was under control. In contrast, patients with AF recurrence were eager to avoid thromboembolic events. The reason for early anticoagulant therapy after AF ablation is to prevent thromboembolic events caused by endocardial injury from ablation and AF rhythm. Thus, physicians need to clarify this and emphasize the importance of anticoagulant therapy to patients.

Although methods were used to ensure the quality of this study, the limitations were as follows. First, self-reported methods may overestimate the adherence rate. Meanwhile, the factors related to adherence are complicated, and we may have failed to consider other influencing factors. Finally, selection bias may be present as patients were recruited from a single medical center. Prospective studies are warranted to establish the relationship between such factors and adherence to NOACs.

In summary, improvement in adherence to NOACs is critical and has been a long-term challenge in the treatment of AF. Greater attention is needed to improve adherence to NOACs in patients with AF at high risk of thromboembolic events.

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Conflicts of interest

None

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