Long-Term Persistence with Newly-Initiated Warfarin or Non-VKA Oral Anticoagulant (NOAC) in Patients with Non-Valvular Atrial Fibrillation: Insights from the Prospective China-AF Registry

Chang Liu
Xin Du*
Chao Jiang
San-Shuai Chang
Xue-Yuan Guo
Rong-Hui Yu
De-Yong Long
Rong Bai
Nian Liu
Cai-Hua Sang
Chen-Xi Jiang
Jian-Zeng Dong
Gregory Y.H. Lip*
Chang-Sheng Ma*

* Xin Du, Gregory Y.H. Lip and Chang-Sheng Ma are co-senior authors

Corresponding Author:
Chang-Sheng Ma, e-mail: chshma@vip.sina.com

Background:
Oral anticoagulants (OACs) such as warfarin and non-VKA oral anticoagulants (NOACs) have been recommended for patients with atrial fibrillation (AF) who are at risk for stroke. Whether NOACs have a higher persistence than warfarin is still unclear. This is especially true in China.

Material/Methods:
Data from a large hospital-based cohort in China (China-AF Registry) from 2011 to 2017 were used for this study. Non-valvular AF patients with newly initiated OACs were included. A time-to-event approach was used to analyze patient persistence. The survival distributions of persistence were compared using the log-rank test. A multivariable Cox regression model was used to explore predictors of warfarin and NOACs non-persistence.

Results:
Patients with newly initiated warfarin (n=4845) or NOACs (n=854) were included in this study. Persistence rates at 1, 2, and 3 years were 93.2%, 89.4%, and 87.2% in the warfarin group and 88.8%, 84.3%, and 81.3% in the NOAC group respectively. Non-persistence was significantly higher with NOACs than with warfarin. On multivariate analysis, age <75 years old, outpatient clinic visits, asymptomatic AF, paroxysmal AF, duration of AF <3 years, history of peptic ulcer, and no previous TIA, stroke or thromboembolism were strong predictors of warfarin non-persistence, while in the NOACs group, age <75 years old, outpatient clinic visits, lower education status and no history of congestive heart failure were predictors.

Conclusions:
Treatment persistence of NOACs was lower than that of warfarin among Chinese patients with AF. Patients with characteristics of non-persistence predictors need special attention to maintain their therapy.

MeSH Keywords:
Anticoagulants • Atrial Fibrillation • Medication Adherence

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/915875
Background

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide and is an important risk factor for ischemic stroke, and it is associated with high mortality and morbidity, and considerable medical costs [1]. Therefore, stroke prevention is central to the management of AF. Oral anticoagulants (OACs) decrease the risk of thromboembolic events and mortality in AF patients and are recommended for all AF patients at risk of stroke [2].

Optimal stroke prevention with OACs in AF patients depends on medication adherence, defined as the accurate intake of medications based on the dose, frequency, and schedule prescribed [3]. Medication persistence to OACs, defined as the duration of time from the initiation to discontinuation of therapy, is also widely adopted metrics to evaluate medical therapy [4]. Non-persistence to OACs is a major obstacle to stroke prevention in AF [5–7].

The OACs include vitamin K antagonists (VKAs) such as warfarin, and non-VKA oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban. The most commonly used NOACs in China are dabigatran and rivaroxaban. Before NOACs were introduced, VKA warfarin was the standard anticoagulant therapy for patients with AF [8–10]. NOACs have been shown to be non-inferior to warfarin in terms of efficacy in stroke prevention, with a lower risk of major bleeding, with even better efficacy and safety in Asians compared to non-Asians [11]. NOACs also have the advantage of not needing routine monitoring and dose-adjustment, due to limited food-drug and drug-drug interactions. While some studies have shown that patients taking NOACs generally have higher persistence than patients taking VKAs [12], other studies have shown the opposite [13,14]. No treatment persistence data exist in Chinese AF populations.

The purpose of this study was to investigate and compare therapeutic persistence of warfarin and NOACs and explore factors associated with non-persistence to warfarin and NOACs therapy in Chinese AF patients, using data of a large, prospective hospital-based registry cohort, the China AF Registry.

Material and Methods

Study population and data collection

The China-AF Registry enrolled AF patients in routine clinical practice from 31 tertiary and non-tertiary hospitals in Beijing [15]. Eligible patients were recruited from outpatient clinics and in-hospital wards and all patients signed informed consent to participate. From August 2011 to December 2017, a total of 19 515 AF patients were recruited. Information on baseline characteristics included age, gender, body mass index (BMI), smoking status, alcohol consumption, education status, health insurance coverage, AF type, history of congestive heart failure, hypertension, diabetes, previous stroke/transient ischemic attack (TIA)/thromboembolism, prior bleeding events, peptic ulcer, use of antiplatelet drugs, CHA2DS2-VASc score, and duration of AF were recorded upon patient enrollment.

The CHA2DS2-VASc score [16] was calculated by assigning 1 point for age between 65 and 74 years, a history of hypertension, diabetes, previous stroke/transient ischemic attack (TIA)/thromboembolism, and female sex and 2 points for a history of stroke/TIA/thromboembolism and age ≥75 years. All definitions were consistent with the American College of Cardiology/American Heart Association recommendations for establishing an AF database [17].

A flowchart of patient-selection for the current analysis is shown in Figure 1. New initiation was defined as no OACs usage at the last time of follow-up while reported to be on the OAC therapy at the index follow-up. Exclusion criteria were as follows: age <18 years; follow-up time <6 months; with valvular AF (presence of mitral stenosis or mechanical valve implantation); and those undergoing AF radiofrequency ablation.

Patients were categorized into a warfarin group and a NOACs group depending on the initial OACs. Patients who initiated warfarin and then switched to NOACs during follow-up were
allocated into the NOACs group and the initiation time was calculated from the time of switching. Patients who initiated NOAC and switched to warfarin during follow-up were excluded from the analysis as the number of these patients was small and therefore the impact would be minimal. Finally, 5699 patients (4845 in the warfarin group and 854 in the NOACs group) were included.

Each patient was followed through outpatient interview or telephone interview by trained nurse practitioners every 6 months after enrollment during a follow-up period of 3 years as NOACs were available in China 3 years ago. At follow-up intervals, medical conditions, serious adverse events (including bleeding complications), adverse drug reactions, and the date of discontinuation of warfarin or NOACs were recorded. All data were entered into an electronic data collection platform.

Ethics

The project has been reviewed by the Beijing Anzhen Hospital Ethics Committee (No: D11110700300000) on June 10, 2011.

Definitions

Therapy persistence was defined as the duration of time from initiation to discontinuation of therapy. Initiation of therapy was defined as the index date for the first dose of the drug. Discontinuation was determined by self-reported cessation of warfarin or NOAC therapy during follow-up. Non-persistence was the cumulative incidence, which was evaluated by a Kaplan-Meier time-to-event analysis for each medication separately [9,18].

Meta-analysis

A meta-analysis was performed to compare the persistence rate between NOACs and warfarin. Systematic searches were conducted in Medline, Embase, and Cochrane using terms such as warfarin, dabigatran, rivaroxaban, apixaban, non-VKA oral anticoagulants, non-valvular atrial fibrillation, and persistence. Research studies containing persistence rate data of both NOACs and warfarin were included. Target study designs included randomized clinical trials, prospective cohorts, and retrospective analysis. Studies in which time of follow-up was <6 months and group participants <200 were excluded.

Quality of the data was analyzed. Data of persistence rates and the total number of participants were extracted for meta-analysis. To minimize heterogeneity of different studies, the time point of follow-up at about 1 year in each study was selected for data extracted. Heterogeneity between studies was assessed using I-squared and the P-value of the Cochrane Q test. Random effects model was used according to the heterogeneity between studies. Analyses were conducted using Revman 5.3. Meta-analysis results are presented as Relative Risk (RR) with its 95% confidence interval (CI).

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as raw numbers and percentages. A time-to-event approach was used to analyze patient persistence to warfarin or NOACs respectively. The survival distributions of persistence between the warfarin group and the NOACs group were compared using the log-rank test. Cox proportional hazards regression models were carried out to determine the association between OAC categories (warfarin or NOAC) and non-persistence, with adjustment for age, gender, education status, type of AF, co-morbid diseases, and medications (all covariates with P<0.2 in the univariate models). For the analysis of predictors of warfarin and NOACs non-persistence, Cox proportional hazards regression was conducted. Variables that showed significant association on univariate analysis and of clinical importance were adjusted using multivariate Cox regression. These factors included age, gender, BMI, education status, health insurance coverage, outpatient clinic visit within 6 months before the last follow-up, paroxysmal or persistent AF, duration of AF< or ≥ 3 years, as well as those with or without previous TIA, stroke or thromboembolism, congestive heart failure, hypertension, diabetes, prior bleeding, peptic ulcer, or use of antiplatelet drugs. Multiple imputation methods were used to calculate the missing covariate data in Cox proportional hazard regression analysis.

All P-values tests were 2-tailed and P-values <0.05 was considered statistically significant. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

Patients characteristics

The mean age of the 4845 patients in the warfarin group was 67.9±10.2, similar to that of the 854 patients in the NOACs group (68.3±11.4). Compared to patients in the NOACs group, patients in the warfarin group were less likely to be male (56.7% versus 60.9%), older than 75 years of age (29.1% versus 34.8%), have paroxysmal AF (44.7% versus 51.8%), have a high level of education (29.4% versus 49.3%), while a higher proportion of patients had congestive heart failure (19.1% versus 11.9%) and CHA2DS2-VASc score ≥2 (85.8% versus 83.0%) (Table 1).
Treatment persistence and persistence rates

Persistence rates at 1, 2, and 3 years were 93.2%, 89.4%, and 87.2% in the warfarin group and 88.8%, 84.3%, and 81.3% in the NOACs group respectively (Figure 2). The treatment persistence was significantly higher for warfarin than for NOACs (\(P<0.001\)). Patients in the NOACs group were more likely to be non-persistent than those in the warfarin group [hazard ratio (HR) for NOACs, 1.63; 95%CI: 1.31–2.02; \(P<0.001\)].

Table 1. Baseline characteristics.

|                          | All N = 5699 | Warfarin N = 4845 | NOAC N = 854 |
|--------------------------|--------------|------------------|--------------|
| Male, n/N (%)            | 3265/5699 (57.3) | 2745/4845 (56.7) | 520/854 (60.9) |
| Age, years               | 67.9±10.4    | 67.9±10.2        | 68.3±11.4    |
| age ≥75 years, n/N (%)    | 1706/5699 (29.9) | 1409/4845 (29.1) | 297/854 (34.8) |
| BMI, kg/m²               | 25.6±3.7     | 25.6±3.7         | 25.6±3.8     |
| Drinking, n/N (%)        | 974/5641 (17.3) | 829/4804 (17.3)  | 145/837 (17.3) |
| Smoking, n/N (%)         | 752/5615 (13.3) | 654/4807 (13.6)  | 98/838 (11.7) |
| Completed high school, n/N (%) | 1680/5170 (32.5) | 1286/4371 (29.4) | 394/799 (49.3) |
| All health insurance covered, n/N (%) | 657/5634 (11.7) | 541/4829 (11.2)  | 116/805 (14.4) |
| Paroxysmal AF, n/N (%)   | 2604/5691 (45.8) | 2164/4841 (44.7) | 440/850 (51.8) |
| Congestive heart failure, n/N (%) | 1028/5699 (18.0) | 926/4845 (19.1)  | 102/854 (11.9) |
| Hypertension, n/N (%)    | 4228/5697 (74.2) | 3599/4845 (74.3) | 629/852 (73.8) |
| Diabetes, n/N (%)        | 1498/5698 (26.3) | 1287/4845 (26.6) | 211/853 (24.7) |
| Stroke/TIA/Thromboembolism, n/N (%) | 1266/5694 (22.2) | 1096/4842 (22.6) | 170/852 (20.0) |
| Major bleeding, n/N (%)  | 310/5693 (5.5)  | 249/4842 (4.1)   | 61/851 (7.2)  |
| CHA2DS2-VASc risk score ≥2, n/N (%) | 4637/5431 (85.4) | 3972/4630 (85.8) | 665/801 (83.0) |
| Symptomatic AF, n/N (%)  | 2105/5699 (36.9) | 1794/4845 (37.0) | 311/854 (36.4) |
| Peptic ulcer, n/N (%)    | 179/5699 (3.1)  | 130/4845 (2.7)   | 49/854 (5.7)  |
| Duration of AF, years    | 4.5±6.5       | 4.6±6.6          | 3.9±5.9      |
| Use of antiplatelet drugs, n/N (%) | 3498/5699 (61.4) | 2947/4845 (60.8) | 551/854 (64.5) |
| Number of drugs used     | 1.9±1.4       | 1.9±1.5          | 1.8±1.4      |

AF – indicates atrial fibrillation; SD – standard deviation; BMI – body mass index; TIA – transient ischemic attack.

Figure 2. Therapy persistence with warfarin and NOAC: Kaplan-Meier curve of time to treatment discontinuation over 3 years. The persistence rates at 1, 2, and 3 years were 93.2%, 89.4%, and 87.2% in the warfarin group and 88.8%, 84.3%, and 81.3% in the NOAC group, respectively. Warfarin persistence was significantly higher than that of NOAC using the log-lank test (\(P<0.001\)).

Treatment persistence and persistence rates

Persistence rates at 1, 2, and 3 years were 93.2%, 89.4%, and 87.2% in the warfarin group and 88.8%, 84.3%, and 81.3% in the NOACs group respectively (Figure 2). The treatment persistence was significantly higher for warfarin than for NOACs (\(P<0.001\)). Patients in the NOACs group were more likely to be non-persistent than those in the warfarin group [hazard ratio (HR) for NOACs, 1.63; 95%CI: 1.31–2.02; \(P<0.001\)].
Of the 105 patients who discontinued NOACs, 14 patients (13.3%) stopped because of bleeding complications. Of the 538 patients who discontinued warfarin, 50 patients (9.29%) stopped because of bleeding complications. The proportions of patients who stopped OACs due to bleeding events were not different between the 2 groups ($P=0.206$).

### Meta-analysis of non-persistence risk of NOACs compared with warfarin

To summarize and review the literature about persistence comparison between NOACs and warfarin, we sought to conduct a meta-analysis. A total of 11 studies were included finally [9,13,19–26]. The outcomes showed that there was no significant difference of non-persistence risk between NOACs and warfarin (RR: 0.97, 95%CI: 0.82–1.15) (Figure 3).

### Predictors of treatment non-persistence

Factors associated with higher risk of warfarin non-persistence include outpatient clinic visit within 6 months before OACs termination [HR 3.78 (3.16–4.52)], paroxysmal AF [HR 2.37 (1.67–3.37)], duration of AF less than 3 years [HR 1.27 (1.07–1.52)], and history of peptic ulcer [HR 1.65 (1.09–2.51)]. Patients older than 75 years of age [HR 0.53 (0.35–0.79)], symptomatic AF [HR 0.81 (0.67–0.97)], previous TIA, stroke or thromboembolism [HR 0.67 (0.53–0.84)] were associated with lower risk of non-persistence (Table 2).

In the NOACs group, patients with higher risk of non-persistence were associated with factors including outpatient clinic visit within 6 months before OACs termination [HR 3.93 (2.49–6.19)] and lower education status [HR 1.56 (1.03–2.38)] while patients older than 75 years of age [HR 0.55 (0.34–0.88)] and history of congestive heart failure [HR 0.46 (0.22–0.96)] were associated with lower risk of non-persistence (Table 2).

### Discussion

To the best of our knowledge, this study is the first to investigate long-term persistence and factors associated with discontinuation in newly-initiated OAC patients with non-valvular AF in China. The most notable finding of our study was that the OAC treatment persistence was significantly higher for warfarin than for NOACs in China, which is generally counter-intuitive to our perceptions, based on data in non-Asian cohorts. Previous studies had proposed the need for structured educational programs to improve the persistence of OAC [27]. Our study suggests that warfarin and NOACs may have different risk factors for treatment non-persistence, and therefore, different strategies need to be developed to address different issues affecting their treatment persistence.

Medical non-persistence is associated with adverse outcomes, and this will result in more healthcare costs [3]. Non-persistence...
Table 2. Main predictors of warfarin and NOAC non-persistence.

|                           | Warfarin |          |          | NOAC |          |
|---------------------------|----------|----------|----------|------|----------|
|                           | N = 538  | HR (95% CI) | P      | N = 105 | HR (95% CI) | P  |
| Age class                 |          |          |          |      |          |    |
| <75 years                 | 390/3436 (11.35) | Ref. | 0.002 | 78/557 (14.00) | Ref. | 0.014 |
| ≥75 years                 | 148/1409 (10.50) | 0.53 (0.35–0.79) | 0.55 (0.34–0.88) | 27/297 (9.09) | Ref. | 0.34 |
| Sex                       |          |          |          |      |          |    |
| Male                      | 286/2745 (10.42) | Ref. | 0.343 | 65/520 (12.50) | Ref. | 0.295 |
| Female                    | 252/2100 (12.00) | 1.09 (0.91–1.30) | 0.80 (0.53–1.22) | 40/334 (11.98) | Ref. | 0.12 |
| BMI, kg/m²                 |          |          |          |      |          |    |
| <28                       | 389/3548 (10.96) | Ref. | 0.361 | 84/653 (12.86) | Ref. | 0.413 |
| ≥28                       | 124/1005 (12.34) | 1.10 (0.89–1.36) | 0.81 (0.49–1.34) | 20/177 (11.30) | Ref. | 0.34 |
| Education status          |          |          |          |      |          |    |
| High                      | 146/1286 (11.35) | Ref. | 0.806 | 42/394 (10.66) | Ref. | 0.034 |
| Low                       | 344/3085 (11.15) | 0.97 (0.79–1.19) | 1.56 (1.03–2.38) | 59/405 (14.57) | Ref. | 0.02 |
| Health insurance coverage |          |          |          |      |          |    |
| Partially or none         | 479/4288 (11.17) | 0.93 (0.70–1.23) | 0.594 | 84/689 (12.19) | Ref. | 0.393 |
| All covered               | 58/541 (10.72) | Ref. | 15/116 (12.93) | 1.29 (0.72–2.33) | Ref. | 0.36 |
| Outpatient clinic visit*   |          |          |          |      |          |    |
| Yes                       | 241/1009 (23.88) | 3.78 (3.16–4.52) | <0.001 | 34/130 (26.15) | 3.93 (2.49–6.19) | <0.001 |
| No                        | 297/3836 (7.74) | Ref. | 71/724 (9.81) | Ref. | 0.44 |
| Type of AF                |          |          |          |      |          |    |
| Paroxysmal AF             | 273/2164 (12.62) | 2.37 (1.67–3.37) | <0.001 | 60/440 (13.64) | 1.21 (0.81–1.80) | 0.36 |
| Persistent or Permanent AF| 264/2677 (9.86) | Ref. | 44/410 (10.73) | Ref. | 0.36 |
| Categorization of AF      |          |          |          |      |          |    |
| Symptomatic               | 209/1794 (11.65) | 0.81 (0.67–0.97) | 0.022 | 43/310 (13.87) | 1.04 (0.68–1.58) | 0.858 |
| Asymptomatic              | 329/3051 (10.78) | Ref. | 62/544 (11.40) | Ref. | 0.36 |
| Duration of AF <3 years   |          |          |          |      |          |    |
| Yes                       | 335/2790 (12.01) | 1.27 (1.07–1.52) | 0.008 | 73/555 (13.15) | 1.38 (0.90–2.11) | 0.144 |
| No                        | 203/2055 (9.88) | Ref. | 32/299 (10.70) | Ref. | 0.44 |
| Previous TIA/stroke/thromboembolism |          |          |          |      |          |    |
| Yes                       | 91/1096 (8.30) | 0.67 (0.53–0.84) | 0.001 | 18/170 (10.59) | 0.85 (0.50–1.44) | 0.536 |
| No                        | 446/3746 (11.91) | Ref. | 87/682 (12.76) | Ref. | 0.36 |
| Congestive heart failure  |          |          |          |      |          |    |
| Yes                       | 91/926 (9.83) | 0.83 (0.66–1.04) | 0.112 | 38/102 (7.84) | 0.46 (0.22–0.96) | 0.038 |
| No                        | 447/3919 (11.41) | Ref. | 97/752 (12.90) | Ref. | 0.36 |
| Either hypertension or diabetes |          |          |          |      |          |    |
| Yes                       | 432/3827 (11.29) | 0.70 (0.46–1.08) | 0.107 | 78/664 (11.75) | 0.87 (0.54–1.40) | 0.564 |
| No                        | 106/1018 (10.41) | Ref. | 27/189 (14.28) | Ref. | 0.44 |
of OAC increases the risk of ischemic stroke in AF patients [28]. Indeed, warfarin persistence has been well-documented in previous studies, and the non-persistence rates at 1 year ranged from 22% to 33% [13,29,30]. A previous study described warfarin discontinuation rates at 1 year and 2 years as 44.4% and 57.6% in China [31], which were much higher than rates in the present study; this might be because the population selected included patients who underwent AF radiofrequency ablation and these patients might stop OACs after restoring sinus rhythm.

Other recent studies have described the persistence rates for NOAC at 1 year ranging from 63% to 79% [22,28,32]. In our study, treatment persistence rates were relatively higher than those studies. This could possibly be explained by the differences in terms of patient populations, study designs, and definitions of persistence. Comparing persistence rates across studies is difficult, even those focused on the same OAC.

Persistence comparisons between NOAC and warfarin remain controversial. The majority of previous data published showed that patients taking NOACs had better persistence compared with VKAs [12]. However, other studies showed the opposite results. In the RE-LYs trial, warfarin had higher 2-year persistence rates compared with dabigatran 110 mg (83.4% versus 79.3%) [22]. Observational studies have generally been consistent. For example, a recent study enrolled 7150 American AF patients treated with warfarin [N=6691 (93.6%)] and dabigatran [N=459 (6.4%)] between June 29, 2010 and August 09, 2011, and defined non-persistence as discontinuing dabigatran or warfarin at 6 months or 1 year for any reason, and showed lower persistence of dabigatran versus warfarin at 1 year, with persistence rates 66% versus 82% [13]. In Japan, Shiga et al. retrospectively studied 401 Japanese patients with NVAF who had newly started NOACs and 200 patients with NVAF who had newly started warfarin during the same period; persistence rates of patients prescribed NOACs were consistently lower than those of patients prescribed warfarin at 3, 6, and 12 months (85% versus 93%, 79% versus 88%, and 70% versus 82% respectively) [14].

Our results are therefore in line with these studies, showing a lower persistence for NOACs than for warfarin. The lower persistence rate of NOACs in our study might be explained by the higher incidence of adverse events including dyspepsia and hepatobiliary disorders of NOACs compared with warfarin [22], as well as high price and non-coverage by health insurance of NOACs in China. Indeed, high costs of medications often contribute to non-persistence [33]. Some studies showed a significant difference of non-persistence risk between NOACs and warfarin. However, the meta-analysis did not show a significant difference between them. This might be due to the heterogeneity between studies. Further research studies should be undertaken to delineate the comparison of persistence rate by subgroups.

### Table 2 continued. Main predictors of warfarin and NOAC non-persistence.

|                                      | Warfarin | NOAC |
|--------------------------------------|----------|------|
|                                      | N = 538  | N = 105 |
| Prior bleeding                        |          |      |
| Yes                                  | 28/249 (11.24) | 11/61 (18.03) |
| No                                   | 509/4593 (11.08) | 94/790 (11.90) |
| Peptic ulcer                         |          |      |
| Yes                                  | 23/130 (17.69) | 4/49 (8.16) |
| No                                   | 515/4715 (10.92) | 101/805 (12.54) |
| Use of antiplatelet drugs            |          |      |
| Yes                                  | 349/2947 (11.84) | 70/555 (12.61) |
| No                                   | 189/1898 (9.96) | 35/299 (11.70) |
| Number of drugs used*                |          |      |
| ≥3                                   | 214/1642 (13.03) | 36/274 (13.14) |
| <3                                   | 324/3203 (10.11) | 69/580 (11.89) |

CI – indicates confidence interval; HR – hazard ratio; BMI – body mass index; TIA – transient ischemic attack. * Within 6 months before following up termination.
We subsequently identified several clinical factors significantly associated with warfarin discontinuation. Patients older than 75 years of age were less likely to discontinue warfarin. Prior studies also found older patients were more likely to be persistence [34–36]. Older patients are at high risk of stroke, and they might contact healthcare professionals more frequently and are supervised more strictly. It was interesting that patients who had been to outpatient clinic within 6 months before OACs termination were more likely to be non-persistence. Outpatient clinic visits were commonly associated with adverse drug reactions. These patients might stop warfarin due to serious side effects such as intracranial hemorrhage and gastrointestinal bleeding [37]. Patients with a history of peptic ulcer also had a lower likelihood of persistence in the warfarin group. Bleeding risk will be higher for those with a history of peptic ulcer when treated by warfarin [38]. This risk worries the patients and doctors which might be reflected by a lower treatment persistence for warfarin.

Other predictors for the persistence of warfarin therapy included symptomatic AF, persistent or permanent AF, duration of AF ≥3 years, history of peptic ulcer, and previous TIA, stroke or thromboembolism. These factors primarily either reflected the severity of the AF or were associated with a higher risk of stroke [39,40]. Clinicians and the patients might thus pay more attention to the anticoagulation therapy and be less likely to discontinue the medication. Furthermore, patients who experienced a previous TIA, stroke or thromboembolism, or who have been suffering AF for a long period might be more likely to take care of their condition and to continue their anticoagulation therapy. However, we did not find these factors associated with NOACs persistence in our study.

Patients older than 75 years of age or who had been to an outpatient clinic within 6 months before OACs termination had similar effects on NOAC persistence and warfarin. Possible explanations might also be similar. Patients with a history of congestive heart failure were associated with higher persistence only for NOACs, possibly because heart failure patients are generally followed by cardiologists, who appreciate the importance of anticoagulation better than other specialists. Low educated status was associated with non-persistence for NOACs but not for warfarin, perhaps reflecting that social economic status and affordability of the medicine is important for therapeutic persistence.

Limitations

This study had several limitations that should be considered. First, the patients in our study primarily came from the Beijing area, an area at a higher economic level than that of other areas. Therefore, the patients might not be representative of the entire Chinese population, especially the rural areas where low-income people resident. Second, discontinuation of OAC was calculated by self-reported time, and we did not consider restarting of OAC usage, which might result in lower persistence. Third, clinical factors such as the liver and renal function and international normalized ratio testing were not incorporated in the study because of incomplete data. Fourth, the reasons for discontinuation remained unclear in a majority of cases.

Conclusions

Treatment persistence of NOACs was lower than that of warfarin amongst Chinese patients with AF. Strategies are needed for better management of OACs therapy.

Conflict of interest

Dr. Ma received honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer-Ingelheim (Bj), and Bayer for giving lectures. Dr. Lip was a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Other authors report no conflicts.
10. Song X, Sander SD, Varker H, Amin A: Patterns and predictors of use of warfarin and dabigatran in patients with atrial fibrillation. Am J Cardiovasc Drugs, 2012; 12(4): 245–53

11. Wang KL, Lip GY, Lin SJ, Chiang CE: Non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation: meta-analysis. Stroke, 2015; 46(9): 2555–61

12. Obamiro KO, Chalmers L, Bereznicki LR: A summary of the literature evaluating adherence and persistence with oral anticoagulants in atrial fibrillation. Am J Cardiovasc Drugs, 2016; 16(5): 349–63

13. Jackson LR 2nd, Kim S, Shader P et al: Early therapeutic persistence on dabigatran versus warfarin therapy in patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. J Thromb Thrombolysis, 2018; 46(4): 435–39

14. Shiga T, Nagamama M, Nagao T et al: Persistence of non-vitamin K antagonist oral anticoagulant use in Japanese patients with atrial fibrillation: A single-center observational study. J Arrhythm, 2015; 31(6): 339–44

15. Du X, Ma C, Wu J et al: Rationale and design of the Chinese Atrial Fibrillation Registry Study. BMC Cardiovasc Disord, 2016; 16: 130

16. 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(2): 263–72

17. McNamara RL, Brass LM, Drozda JP, Jr., et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Data Standards on Atrial Fibrillation). Circulation 2004;109(25): 3223-3243.

18. Paquette M, Riou Franca L, Teutsch C et al: Persistence with dabigatran therapy at 2 years in patients with atrial fibrillation. J Am Coll Cardiol, 2017; 70(13): 1573–83

19. Johnson ME, Lefevre C, Collings SL et al: Early real-world evidence of persistence on oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a cohort study in UK primary care. BMJ Open, 2016; 6(9): e011471

20. Coleman CI, Tangirala M, Evers T: Medication adherence to rivaroxaban and dabigatran for stroke prevention in patients with non-valvular atrial fibrillation in the United States. Int J Cardiol, 2016; 212: 171–73

21. Beyer-Westendorf J, Ehlken B, Evers T: Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. Europace, 2016; 18(8): 1150–57

22. Connolly SJ, Ezekowitz MD, Yusuf S et al: Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med, 2009; 361(12): 1139–51

23. Patel MR, Mahaffey KW, Garg J et al: Rivaroxaban versus warfarin in non-valvular atrial fibrillation. N Engl J Med, 2011; 365(10): 883–91

24. Granger CB, Alexander HJ, McMurray JJV et al: Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med, 2011; 365(11): 981–92

25. Nelson WW, Song X, Coleman CI et al: Medication persistence and discontinuation of rivaroxaban versus warfarin among patients with non-valvular atrial fibrillation. Curr Med Res Opin, 2014; 30(12): 2461–69

26. Laliberté F, Cloutier M, Nelson WW et al: Real-world comparative effectiveness and safety of dabigatran versus warfarin in patients with atrial fibrillation. Curr Med Res Opin, 2014; 30(7): 1317–25

27. Amara W, Larsen TB, Sciaraffia E et al: Patients’ attitude and knowledge about oral anticoagulation therapy: Results of a self-assessment survey in patients with atrial fibrillation conducted by the European Heart Rhythm Association. Europace, 2016; 18(1): 151–55

28. Martinez C, Katholing A, Warenhoven G, Freedman SB: Therapy persistence in newly diagnosed non-valvular atrial fibrillation treated with warfarin or NOAC. A cohort study. Thromb Haemost, 2016; 115(1): 31–39

29. Hylek EM, Evans-Molina C, Shea C et al: Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation, 2007; 115(21): 2689–96

30. Mant J, Hobbs FD, Fletcher K et al: Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): A randomised controlled trial. Lancet, 2007; 370(9586): 493–503

31. Wang ZZ, Du X, Wang W et al: Long-term persistence of newly initiated warfarin therapy in Chinese patients with nonvalvular atrial fibrillation. Circ Cardiovasc Qual Outcomes, 2016; 9(4): 380–87

32. Beyer-Westendorf J, Forster K, Ebertz F et al: Drug persistence with rivaroxaban therapy in atrial fibrillation patients-results from the Dresden non-interventional oral anticoagulation registry. Europace, 2015; 17(4): 530–38

33. Herkert D, Vijayakumar P, Luo J et al: Cost-related insulin underuse among patients with diabetes. JAMA Intern Med, 2019; 179(1): 112–14

34. Fang MC, Go AS, Chang Y et al: Warfarin discontinuation after starting warfarin for atrial fibrillation. Circ Cardiovasc Qual Outcomes, 2010; 3(6): 624–31

35. Kneeland PP, Fang MC: Current issues in patient adherence and persistence: Focus on anticoagulants for the treatment and prevention of thromboembolism. Patient Prefer Adherence, 2010; 4: 51–60

36. Harper P, Pollock D, Stephens M: Dabigatran persistence and adherence in New Zealand: A nationwide retrospective observational study. BMJ Open, 2018; 8(4): e020212

37. Ruff CT, Giugliano RP, Braunwald E et al: Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. Lancet, 2014; 383(9921): 955–62

38. Sherwood MW, Nessel CC, Hellkamp AS et al: Gastrointestinal bleeding in patients with atrial fibrillation treated with rivaroxaban or warfarin: ROCKET AF Trial. J Am Coll Cardiol, 2015; 66(21): 2271–81

39. Mohan KM, Wolfe CD, Rudd AG et al: Risk and cumulative risk of stroke recurrence: A systematic review and meta-analysis. Stroke, 2011; 42(5): 1489–94

40. Coull AJ, Lovett JK, Rothwell PM, Oxford Vascular Study: Population based study of early risk of stroke after transient ischaemic attack or minor stroke: Implications for public education and organisation of services. BMJ, 2004; 328(7455): 326