

# Long-Term Persistence of Newly Initiated Warfarin Therapy in Chinese Patients With Nonvalvular Atrial Fibrillation

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**Background**—Despite its therapeutic efficacy, warfarin is extremely underused in Chinese patients with nonvalvular atrial fibrillation (AF). Whether the nonpersistence of warfarin treatment contributes to its underuse is not known. The aims of this study were to determine nonpersistence rates of newly started warfarin treatment in Chinese patients with nonvalvular AF and to identify the factors associated with discontinuation of the treatment.

**Methods and Results**—We identified 1461 patients with nonvalvular AF enrolled in the Chinese Atrial Fibrillation Registry (CAFR) who newly started on warfarin therapy in the period between August 1, 2011, and June 30, 2014. During a follow-up of 426±232 days, 22.1% of patients discontinued warfarin within 3 months, 44.4% within 1 year, and 57.6% within 2 years of initiation of therapy. Patients with no or partial insurance coverage had a higher likelihood to discontinue warfarin than those with full insurance coverage (adjusted hazard ratio 1.65, 95% confidence interval [1.03–2.64];  $P=0.038$  and 1.66 [1.13–2.42];  $P=0.009$ , respectively). Paroxysmal AF (1.56 [1.28–1.92];  $P<0.0001$ ), no prior stroke/transient ischemic attack/thromboembolism (1.60 [1.24–2.05];  $P=0.0003$ ), and no dyslipidemia (1.34 [1.06–1.70];  $P=0.016$ ) were also found to be independent predictors for nonpersistence of warfarin therapy.

**Conclusions**—Nonpersistence of warfarin treatment becomes a serious problem for stroke prevention in Chinese patients with nonvalvular AF. Our findings can be used to identify patients who require closer attention or to develop better management strategy for oral anticoagulation therapy. (*Circ Cardiovasc Qual Outcomes*. 2016;9:380-387. DOI: 10.1161/CIRCOUTCOMES.115.002337.)

**Key Words:** adherence ■ anticoagulation ■ nonvalvular atrial fibrillation ■ persistence ■ warfarin

Atrial fibrillation (AF) is the most common form of arrhythmia encountered in clinical settings.<sup>1-4</sup> The condition is associated with high morbidity and mortality, which is largely attributable to the increased risk of stroke and systemic thromboembolism.<sup>5</sup> Compared with stroke from other causes, stroke associated with AF tends to be more severe and has higher mortality and disability.<sup>6,7</sup> Stroke prevention is central to the management of AF, irrespective of the rate or rhythm control strategy.<sup>5</sup>

The vitamin K antagonist warfarin remains the mainstay of anticoagulation therapy since several decades. In the United States, increasing use of warfarin among patients with AF (26.7% in 1992 to 63.1% in 2007) was associated with declining trend in incidence of ischemic stroke but without any significant increase in hemorrhagic stroke rates.<sup>8</sup> However, warfarin is extremely underused<sup>9,10</sup> in Chinese patients with AF, particularly in those with a higher stroke risk.<sup>11,12</sup> Besides physicians' compliance with guideline recommendations for

stroke prevention,<sup>13</sup> patients' nonadherence and nonpersistence to warfarin are major barriers to improved anticoagulation treatment in patients with AF.

The purpose of this study was to investigate the nonpersistence of newly started warfarin treatment in Chinese patients with nonvalvular AF (NVAF) and to determine the potential correlates and determinants of the nonpersistence with warfarin therapy.

## Methods

### Patient Cohort

We identified 1461 patients with NVAF (mean age, 67.8±10.4 years; males, 54.6%) who were enrolled in the Chinese Atrial Fibrillation Registry (CAFR) and were newly started on warfarin anticoagulation therapy in the period between August 1, 2011, and June 30, 2014. The CAFR is a prospective, multicenter, hospital-based, ongoing registry study of patients diagnosed with AF in Beijing, China. The participating hospitals in this study included most tertiary and nontertiary hospitals in Beijing that were able to provide a clinical

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## WHAT IS KNOWN

- For patients with atrial fibrillation, anticoagulation therapy is necessary to lower the risk for ischemic stroke, but nonpersistence and nonadherence of oral anticoagulation therapy remains a significant problem, which can reduce efficacy of the treatment.
- Various studies, mostly from Western societies, showed that >25% of patients discontinued warfarin 1 year after initiation; nonpersistence rates of warfarin treatment in Chinese atrial fibrillation patients remain undetermined.

## WHAT THE STUDY ADDS

- In the Chinese Atrial Fibrillation Registry cohort, we found a much higher and earlier discontinuation rate of warfarin therapy (22.1% of patients discontinued warfarin therapy within 3 months, 44.4% within 1 year) in Chinese patients with nonvalvular atrial fibrillation.
- Partial or no health insurance coverage, no prior stroke/transient ischemic attack/thromboembolism, paroxysmal atrial fibrillation, and no dyslipidemia were identified as independent predictors for warfarin discontinuation; younger age, male sex, and CHA<sub>2</sub>DS<sub>2</sub>-VASc score, which were found in previous studies, were not associated with warfarin discontinuation in the present study.

service of AF management. Telephone or face-to-face interviews were conducted by trained staff at 3 and 6 months after enrollment and every 6 months thereafter. Cases of valvular AF associated with mitral stenosis or postoperative AF after mechanical valve implantation, those who had previously received warfarin treatment, or those who did not receive warfarin at registry entry were excluded from this analysis.

## Definitions

Persistence was defined as the self-reported compliance with warfarin therapy. Nonpersistence was defined as warfarin discontinuation at any time during follow-up, except for instances of temporary interruption. Persistence and nonpersistence rates of warfarin therapy were calculated from warfarin initiation to patient self-reported discontinuation. Nonpersistence was the main outcome of interest in this study. If the patient could not clearly report the date of discontinuation of warfarin, the median date between the date of interview and that of last documented follow-up was regarded as the date of discontinuation. The average follow-up period was 426±232 days.

The covariates incorporated in this study included the patients' demographic and clinical characteristics at baseline, status of health insurance coverage, and the different levels of hospital that the patients visited. Patients' education levels were stratified into 2 categories, low level and high level, based on whether the patient had completed high school education, respectively. Health insurance coverage was divided into 3 levels, full, partial, and no insurance coverage, based on the proportion of patient copayment. The hospitals that patients visited were stratified into 2 levels, tertiary and nontertiary hospital. Hospitals in China are classified into 3 grades: community hospitals are defined as grade I, hospitals that serve several communities are defined as grade II, and central hospitals for a certain district or city are defined as grade III or namely

tertiary hospitals, which generally have more resources and expertise than the nontertiary hospitals (grade I and II), especially the community hospitals.

## CHA<sub>2</sub>DS<sub>2</sub>-VASc Score

Stroke risk was calculated by using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>14</sup> (1 point each for hypertension, heart failure, diabetes mellitus, vascular disease, age 65–74 years, female sex; 2 points each for age ≥75 years, prior stroke/transient ischemic attack [TIA]/thromboembolism [TE]). Vascular disease was defined as prior myocardial infarction or established coronary artery disease or peripheral arterial disease.<sup>15</sup>

## Dropouts and Missing Values

At each follow-up period, a patient was considered a dropout if the patient clearly refused to further participate in the study or could not be reached after 3 phone contact attempts each day (morning, afternoon, and early evening) for a working week. Any covariates with missing rates >10% were excluded in later analyses or indicated otherwise. Medians and most common categories were considered as replacement of missing values for continuous and categorical variables, respectively. Degrees of freedom needed to be adjusted if any imputation for missing values occurred.

## Statistical Analysis

Data are presented as mean±SD, percentages, or absolute or relative frequencies, as appropriate. A time-to-event approach was used for Kaplan–Meier survival analysis to delineate the dynamics of warfarin use. Univariate and multivariate Cox proportional hazard regression analyses were conducted to identify covariates of nonpersistence to warfarin therapy. Variables that showed significant association on univariate analysis were entered in the multivariate stepwise Cox proportional analysis.

Age and sex were made mandatory in multivariate analyses. All *P* values were 2-tailed; *P*<0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 9.2 (SAS Institute Inc, Cary, NC). This study was approved by the institutional ethics committee at Beijing Anzhen Hospital. Written informed consent was obtained from all patients before inclusion in this analysis.

## Results

### Patient Characteristics

A total of 1461 patients with NVAF who were newly started on warfarin after registry enrollment were identified (mean age, 67.8±10.4 years; male, 54.6%). 44.4% cases were those of paroxysmal AF, 46.8% of persistent AF, and 8.8% were unclear of AF type. About 75.8% patients had hypertension, 28.0% had diabetes mellitus, 20.9% had congestive heart failure, 23.0% had prior stroke/TIA/TE; 18.0% had prior myocardial infarction/established coronary artery disease/peripheral arterial disease, and 25.9% had dyslipidemia. The stroke risk of patients was estimated by CHA<sub>2</sub>DS<sub>2</sub>-VASc score: 4.5%, 11.8%, and 83.6% of patients scored 0, 1, and ≥2, respectively. The baseline characteristics of the patients are listed in Table 1.

### Nonpersistence of Warfarin Therapy

Of the 1461 patients included in the analysis, 22.1% discontinued warfarin within 3 months of initiation, 33.6% within 6 months, 44.4% within the first year, and 57.6% within 2 years of initiation. Kaplan–Meier curve for cessation of warfarin treatment is shown in Figure 1.

Patients with no or partial insurance coverage had a higher risk of nonpersistence to warfarin than patients with full insurance coverage (adjusted hazard ratio [aHR] 1.65

**Table 1. Baseline Characteristics of Patients**

Characteristics	N=1461
Age (mean±SD) N (%)	
Total	67.8±10.4
<65 y	521 (35.7%)
≥65 y	940 (64.3%)
Sex, N (%)	
Male	798 (54.6%)
Female	663 (45.4%)
Education, N (%)	
High	363 (28.8%)
Low	898 (71.2%)
Unavailable	200
Health insurance, N (%)	
No	141 (9.7%)
Partial	1147 (78.5%)
Full	173 (11.8%)
Hospital level, N (%)	
Tertiary	1383 (94.7%)
Nontertiary	78 (5.3%)
Type of AF, N (%)	
Unclear	128 (8.8%)
Paroxysmal	649 (44.4%)
Persistent or permanent	684 (46.8%)
BMI (mean±SD)	
<25	616 (46.4%)
≥25	712 (53.6%)
Unavailable	133
Smoking status, N (%)	
Yes	219 (15.1%)
No	1234 (84.9%)
Unavailable	8
Alcohol abuse, N (%)	
Yes	266 (18.3%)
No	1184 (81.7%)
Unavailable	11
Hypertension, N (%)	
Yes	1106 (75.8%)
No	353 (24.2%)
Unavailable	2
Diabetes mellitus, N (%)	
Yes	409 (28.0%)
No	1052 (72.0%)

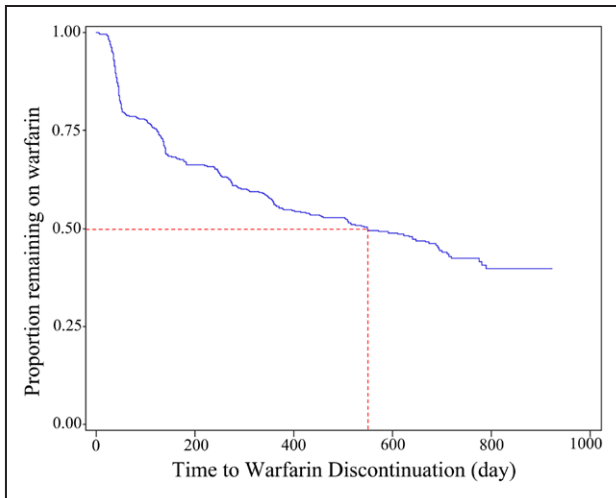
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**Table 1. Continued**

Characteristics	N=1461
Congestive heart failure, N (%)	
Yes	306 (20.9%)
No	1155 (79.1%)
Prior stroke/TIA/TE, N (%)	
Yes	336 (23.0%)
No	1125 (77.0%)
Prior MI/known CAD/PAD, N (%)	
Yes	263 (18.0%)
No	1198 (82.0%)
CHA <sub>2</sub> DS <sub>2</sub> -VASC score, N (%)	
=0	66 (4.5%)
=1	173 (11.8%)
≥2	1222 (83.6%)
Dyslipidemia, N (%)	
Yes	377 (25.9%)
No	1081 (74.1%)
Unavailable	3
Prior bleeding, N (%)	
Yes	52 (3.6%)
No	1409 (96.4%)
Antiplatelet drugs, N (%)	
Yes	137 (9.4%)
No	1324 (90.6%)
Statin use, N (%)	
Yes	541 (37.0%)
No	920 (63.0%)

AF indicates atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral arterial disease; SD, standard deviation; TE, thromboembolism; and TIA, transient ischemic attack.

[95% confidence interval, 1.03–2.64];  $P=0.038$  and 1.66 [1.13–2.42];  $P=0.009$ , respectively; Figure 2A). Patients with paroxysmal AF had poorer persistence than those with persistent AF (aHR 1.56 [95% confidence interval 1.28–1.92];  $P<0.0001$ ). There was no difference between unclear AF and persistent AF (aHR 0.96 [0.64–1.42];  $P=0.822$ ; Figure 2B). Patients with no prior stroke/TIA/TE were more likely to discontinue warfarin (aHR 1.60 [1.24–2.05];  $P=0.0003$ ) than those with prior stroke/TIA/TE (Figure 2C). Patients with no dyslipidemia were more likely to discontinue warfarin (aHR 1.34 [1.06–1.70];  $P=0.016$ ). In univariable analysis, patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC=0 were more likely to discontinue warfarin than those with CHA<sub>2</sub>DS<sub>2</sub>-VASC≥2 (HR 1.56 [1.03–2.36];  $P=0.037$ ). After multivariable adjustment, there was no difference between CHA<sub>2</sub>DS<sub>2</sub>-VASC=0 and CHA<sub>2</sub>DS<sub>2</sub>-VASC≥2. Statistical significance was found in neither univariable analysis nor multivariable analysis between patients with CHA<sub>2</sub>DS<sub>2</sub>-VASC=1 and CHA<sub>2</sub>DS<sub>2</sub>-VASC≥2 (Figure 2D).



**Figure 1.** Kaplan–Meier curve for long-term persistence with warfarin therapy in patients with nonvalvular atrial fibrillation. 22.1% of the patients discontinued warfarin within 3 months, 33.6% within 6 months, 44.4% within 1 year, and 57.6% within 2 years of initiation of warfarin therapy.

### Univariate Analysis for Predictors of Warfarin Discontinuation

Patients with no health insurance coverage or those with partial insurance were more likely to discontinue warfarin as compared with those with full health insurance coverage (hazard ratio [HR] 1.67 [95% confidence interval 1.04–2.68];  $P=0.032$  and 1.63 [1.11–2.38];  $P=0.012$ , respectively). Compared with patients with persistent AF, those with paroxysmal AF were more likely to discontinue warfarin (HR 1.51 [1.23–1.85];  $P<0.0001$ ); no difference was observed between unclear AF and persistent AF in this respect (HR 0.94 [0.64–1.40];  $P=0.768$ ).

Compared with patients with  $\text{CHA}_2\text{DS}_2\text{-VASc}\geq 2$ , those with  $\text{CHA}_2\text{DS}_2\text{-VASc}$  of 0 were more likely to discontinue warfarin (HR 1.56 [1.03–2.36];  $P=0.038$ ); no difference was observed between those with  $\text{CHA}_2\text{DS}_2\text{-VASc}$  of 1 and  $\geq 2$  (HR 1.25 [0.92–1.69];  $P=0.150$ ). Patients with no prior stroke/TIA/TE, those who were not dyslipidemic, and those receiving no combined statin therapy were more likely to discontinue warfarin (HR 1.63 [1.27–2.09];  $P=0.0001$ ; HR 1.40 [1.11–1.78];  $P=0.005$ ; and HR 1.36 [1.10–1.67];  $P=0.004$ , respectively).

Compared with patients who received treatment at a tertiary-level hospital, those being treated at a nontertiary hospital seemed more persistent with warfarin therapy (HR 0.59 [0.35–0.99];  $P=0.045$ ). Age (as a dichotomized variable), sex, patients' education, hypertension, diabetes mellitus, prior heart failure, and other patient-related factors were found not to be associated with nonpersistence to warfarin use (Table I in the [Data Supplement](#)).

### Predictors of Warfarin Discontinuation on Multivariate Analysis

After adjustment for potential confounding influences in the multivariate analysis, only health insurance coverage, type of AF, prior stroke/TIA/TE event, and dyslipidemia appeared to have had an effect on patient persistence with warfarin

treatment. Compared with full health insurance, no insurance or partial insurance greatly increased the risk of nonpersistence to warfarin (aHR 1.65 [1.03–2.64];  $P=0.038$  and aHR 1.66 [1.13–2.42];  $P=0.009$ , respectively).

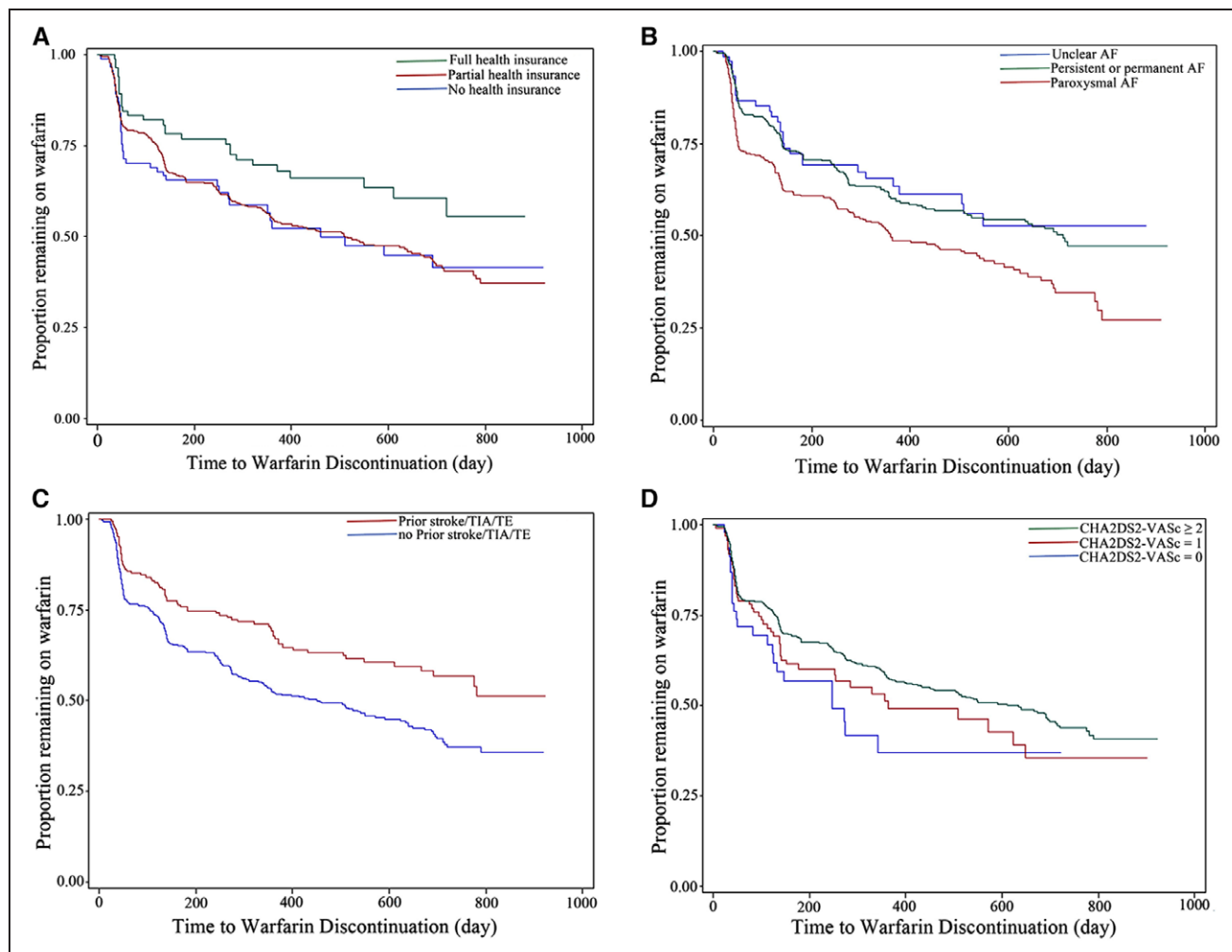
Patients with paroxysmal AF were considerably more likely to discontinue warfarin treatment than those with persistent AF (aHR 1.56 [1.28–1.92];  $P<0.0001$ ); there was no difference between unclear AF and persistent AF (aHR 0.96 [0.64–1.42];  $P=0.822$ ) in this respect. No prior stroke/TIA/TE (aHR 1.60 [1.24–2.05];  $P=0.0003$ ) and no dyslipidemia (aHR 1.34 [1.06–1.70];  $P=0.016$ ) were found to be independent predictors for nonpersistence with warfarin therapy. The influences of hospital level,  $\text{CHA}_2\text{DS}_2\text{-VASc}$  score, and statin use on nonpersistence to warfarin use were attenuated after adjusting for confounding factors (Table 2).

## Discussion

Warfarin is widely recommended for the prevention of ischemic stroke in patients with NVAF. Nonpersistence of warfarin treatment has been recognized as one of the major barriers for its efficacy improvement. In our CAFR cohort, 44.4% of the Chinese patients with NVAF who newly started warfarin therapy discontinued warfarin use within 1 year and 57.6% within 2 years. Furthermore, we found that no or partial health insurance coverage, paroxysmal AF, no prior stroke/TIA/TE, and no dyslipidemia were predictive for nonpersistence of warfarin use. To our knowledge, this is the first study to investigate persistence of warfarin therapy in Chinese patients with NVAF.

Medical adherence is drawing large attention in recent years because nonadherence to medication is associated with adverse outcomes and higher costs.<sup>16</sup> Medication adherence behavior has been divided into 2 main concepts, namely adherence and persistence. Adherence refers to the intensity of drug use, whereas persistence refers to the overall duration of drug therapy.<sup>17–19</sup> Nonpersistence to anticoagulation treatment for NVAF is prevalent and may impair efficacy for the treatment and pose patients on increased risk for ischemic stroke. Previously, Fang et al showed that 26.3% of patients from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study cohort discontinued therapy within 1 year after warfarin initiation.<sup>20</sup> However, in another cohort study by Gomes et al, of 125 195 Canadian patients who were newly started on warfarin for AF, 31.8% discontinued therapy within 1 year, 43.2% discontinued within 2 years, and 61.3% discontinued within 5 years.<sup>21</sup> Generally, 22% to 33% of patients discontinued warfarin within the first year after initiating therapy for AF.<sup>20,22–25</sup> Compared with known data mostly from Western society, the present study showed that Chinese patients discontinued warfarin earlier, and the nonpersistence rate within the same time period was significantly higher. A sharp decline on persistence was seen during the first 3 months.

Hu and Sun previously reported that the percentage of AF patients on oral anticoagulation therapy was extremely low in China based on their epidemiological study. Only 6.75% of patients with NVAF received warfarin.<sup>26</sup> It is not clear whether the current findings of warfarin discontinuation may correlate with its underutilization in Chinese patients with NVAF. Further investigation is needed.



**Figure 2.** Kaplan–Meier curve for long-term persistence with warfarin therapy disaggregated by (A) status of health insurance coverage; (B) by type of AF; (C) by history of stroke/TIA/TE; (D) by CHA<sub>2</sub>DS<sub>2</sub>-VASc score. In univariable analysis, patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc=0 were more likely to discontinue warfarin than those with CHA<sub>2</sub>DS<sub>2</sub>-VASc≥2 (HR 1.56 [1.03–2.36];  $P=0.037$ ). After multivariable adjustment, there was no difference between CHA<sub>2</sub>DS<sub>2</sub>-VASc=0 and CHA<sub>2</sub>DS<sub>2</sub>-VASc≥2. Statistical significance was found in neither univariable analysis nor multivariable analysis between patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc=1 and CHA<sub>2</sub>DS<sub>2</sub>-VASc≥2. AF indicates atrial fibrillation; aHR, adjusted hazard ratio; CI, confidence interval; TE, thromboembolism; and TIA, transient ischemic attack.

Previous studies usually adopted consecutive prescription refill date and international normalized ratio data to determine warfarin discontinuation; a long interval gap of 30 days, 60 days, and even 180 consecutive days off warfarin was allowed.<sup>21–25,27</sup> However, in this study, discontinuation of warfarin was acquired by patient self-report at any time point during follow-up. We did not set a time interval allowed for warfarin off, nor did we consider restarting warfarin after a specific period, which may contribute to the relatively low rate of the persistent use of warfarin in this study.

By using Cox regression analysis, we identified several factors significantly associated with warfarin discontinuation. Partial or no health insurance coverage, which means higher cost sharing, were among the most potent predictors for warfarin discontinuation. Numerous studies showed that health insurance coverage could affect adherence and persistence to medications to chronic diseases, such as lipid-lowering and antihypertensive medications. Increased cost sharing was associated with worse adherence and more frequent discontinuation of therapy.<sup>28–32</sup> Our current findings of insurance

coverage on warfarin discontinuation are consistent with previous studies.

In the present study, no prior stroke/TIA/TE was found to be the second strongest predictor for nonpersistence of warfarin therapy, although paroxysmal AF was found predictive for warfarin discontinuation as well. To some extent, both the predictors might have correlations with low stroke risk. Various previous studies have shown that patients with prior stroke/TIA/TE were at high risk for recurrence of stroke and less likely to discontinue warfarin treatment. Under this condition, it is not surprising that both clinicians and patients would be more readily persistent on anticoagulation therapy with warfarin for stroke prevention. Meanwhile, an increasing body of evidence showed that AF type may affect risk of ischemic stroke. Most recently, Vanassche et al showed that pattern of AF was a strong independent predictor for stroke risk based on their analysis of stroke and systemic embolism in 6563 aspirin-treated patients with AF. Patients with paroxysmal AF may have lower risk for ischemic stroke than those with persistent or permanent AF.<sup>33,34</sup> Therefore, physicians and patients may consider a lower stroke

**Table 2. Multivariable Analysis of Clinical Factors Associated With Warfarin Discontinuation in Patients With NVAF Newly Starting Warfarin**

Variable	n/N (%)	aHR (95% CI)	P Value
Health insurance			
Full	59/150 (39.3%)	1.00	
No	52/120 (43.3)	1.65 (1.03–2.64)	0.038
Partial	415/998 (41.6)	1.66 (1.13–2.42)	0.009
Type of AF			
Persistent or permanent	282/594 (47.5)	1.00	
Paroxysmal	198/564 (35.1)	1.56 (1.28–1.92)	<0.0001
Unclear	46/110 (41.8)	0.96 (0.64–1.42)	0.822
Prior stroke/TIA/TE			
Yes	144/299 (48.2)	1.00	
No	382/969 (39.4)	1.60 (1.24–2.05)	0.0003
Dyslipidemia			
Yes	150/319 (47)	1.00	
No	375/946 (39.6)	1.34 (1.06–1.70)	0.016

AF indicates atrial fibrillation; aHR, adjusted hazard ratio; CI, confidence interval; TE, thromboembolism; and TIA, transient ischemic attack.

risk with paroxysmal AF and have a higher likelihood to discontinue the oral anticoagulation therapy under these conditions.<sup>35</sup> Similar results were found in other studies.<sup>36</sup>

Furthermore, no dyslipidemia has been found to be a modest but significant predictor for nonpersistence of warfarin treatment in our study, which have not been reported before. The exact mechanism is still unclear. We would propose that documentation of an asymptomatic cardiovascular risk factor like hyperlipidemia may also be a sign of a generally more careful or involved clinician or a stronger clinician–patient relationship. The presence of such a diagnosis may be partly dependent on that as much as on any physiological difference in the patient. This in turn may contribute to a higher likelihood of persistence with therapy.

On the other hand, CHA<sub>2</sub>DS<sub>2</sub>-VASc score, age, and sex were not found to be associated with nonpersistence of warfarin treatment in the current study. The 2012 European Society of Cardiology guideline<sup>37</sup> and the 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society<sup>38</sup> guideline recommended adjusted dose of warfarin on the treatment of NVAF patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 1$ . For patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0, no antithrombotic therapy is recommended. However, 4.5% of patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc=0 from our CAFR cohort were prescribed warfarin, which suggests a trend toward overanticoagulation. Patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc=0 contributed to the high rate of warfarin discontinuation on univariate analysis; however, the impact was abolished after adjustment in the multivariate analysis.

Prior studies indicated that younger (age <65 years) and male patients were more likely to discontinue warfarin.<sup>20,39</sup> However, we did not find age or sex having an impact on the long-term persistence to warfarin therapy in this study.

## Limitations

There are several limitations in the present study. First, the representativeness of patient samples could be one limitation. The majority of patients in our CAFR cohort were from tertiary hospitals in Beijing area, who had higher educational and economic level compared with patients from other area in the nation. The patients in CAFR might not represent the general population in China and better represent the population with higher socioeconomic level and better health insurance coverage. In addition, participating hospitals in this study, especially those tertiary hospitals, may represent the institutes with more resources and expertise than county-level or even more grassroots-level hospitals. It is not known what proportion of AF patients in China currently have access to similar levels of hospital care as those who participated in our study. Second, we mainly studied the impact of patient-specific characteristics on the nonpersistence to warfarin treatment in patients with NVAF; clinical factors such as the patients' liver and renal function, risk of bleeding, frequency of international normalized ratio testing, and stability of international normalized ratio were not incorporated in the study because of unclear or incomplete data. Third, we did not clarify the reasons for nonpersistence to warfarin treatment. We could not distinguish whether the reasons for warfarin discontinuation depended more on the physicians' decision, the patients' compliance, or the drug's adverse effects. Fourth, the exact date of warfarin discontinuation was not available in some cases and may also have been affected by recall bias because the data were self-reported. Finally, the relatively small sample size is also a limitation. Further in-depth investigation is needed.

## Conclusions

Along with its underuse in Chinese patients with NVAF, the high incidence of nonpersistence of warfarin therapy becomes another outstanding problem in the management of AF in China. Our findings can be used to identify patients who require closer attention or to develop better management strategy to maximize benefit and minimize harm from oral anticoagulation therapy.

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## Disclosures

C.-S. Ma has received honoraria from Bristol-Myers Squibb (BMS), Pfizer, Johnson & Johnson, Boehringer-Ingelheim (BI), and Bayer for giving lectures. J.-Z. Dong has also received honoraria from Johnson & Johnson for giving lectures. The other authors report no conflicts.

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