The use status of anticoagulation drugs for inpatients with nonvalvular atrial fibrillation in Southwest China

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Background: Oral anticoagulants (OACs) are effective for the prophylaxis of stroke in patients with atrial fibrillation (AF). This cross-sectional study aimed to investigate the status of anticoagulation treatment for hospitalized AF patients in Southwest China.

Methods: A total of 4760 hospitalized patients with AF were enrolled from 21 hospitals in Chongqing city from January 1 to December 31, 2013.

Results: Among the enrolled patients, 3785 were diagnosed with nonvalvular AF. These patients had a mean age of 74.4±10.1 years. The mean CHADS, score of all subjects was 2.60±1.34, and 80.7% of the patients had CHADS, ≥2. The use rate of OACs was only 11.5% for patients with a high risk for stroke (CHADS, \geq 2) and was much lower in patients from the second-level hospitals than in patients from the third-level hospitals (5.8% vs. 16.9%, P<0.001). The leading reason for the underuse of OACs in high-risk patients was physician's nonfeasance.

Conclusion: This study demonstrated that the underuse of anticoagulation therapy in hospitalized patients with nonvalvular AF was particularly serious in Southwest China, especially in the second-level hospitals. Urgent and effective measures are desperately needed to improve this alarming situation in China.

Keywords: atrial fibrillation, anticoagulation therapy, oral anticoagulant, antiplatelet therapy, international normalized ratio

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in China and worldwide. Approximately 1% of the total population is estimated to suffer from AF worldwide, and its prevalence rate has a tendency to rise with increasing age. 1 In China, morbidity due to AF is as high as 0.77%, and 7.5% of these subjects are >80 years of age.² AF is one of the important causes of stroke. The Framingham study indicated that AF could raise the risk of stroke by >5-fold, compared with subjects without AF.3 An overwhelming number of studies have demonstrated that anticoagulation therapy can remarkably reduce the incidence of stroke in AF patients. ⁴⁻⁶ A meta-analysis ⁴ of 21 studies confirmed that the use of adjusted-dose warfarin reduced the risk of stroke by ~60% and all-cause death by ~25%, compared with subjects without antithrombotic treatment. However, the narrow therapeutic window and broad interactions with other drugs and foods have hampered the widespread use of warfarin. Consequently, the proportion of AF patients treated for anticoagulation was only 2.7% in China according to a nationwide survey carried out in 2003. Even worse, more than one-third of these patients were treated with only aspirin, which is not as effective in preventing stroke in AF patients. During the latest 10 years, the anticoagulant use rate has grown by 28.7%; however, the rate is

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Tel +86 23 8901 1565 Fax +86 23 8901 1565 Email xiaoheart1974@163.com still far lower than the rates in North America, Europe, and even other Asian countries.^{2,7–10} Reasonable anticoagulant therapy is of great importance to improve the quality of life and the long-term prognosis of AF patients. Therefore, in this study, we investigated the status of anticoagulation therapy for inpatients with nonvalvular AF in Chongqing, which is the largest city in Southwest China, in order to guide and optimize the anticoagulation management of AF.

Methods

Study population

Participating institutions

The hospital classification management system in China is different from the health care systems in other countries. In China, hospitals are divided into three different levels (ie, first-level health care institutes [primary hospitals], second-level health care institutes [secondary hospitals], and third-level health care institutes [tertiary hospitals]) according to their different functions and tasks. Secondary and tertiary hospitals are usually the medical centers of a county or a city and are responsible for the diagnosis and treatment of an overwhelming majority of AF patients. Based on the above rationale, we included secondary and tertiary hospitals in this study.

Chongqing city is the biggest municipality directly under the central government and is one of the central cities in Southwest China. Chongqing city covers an area of 82,402.95 km²; in 2013, it contained 38 administrative regions, including 19 districts, 15 counties, and 4 autonomous counties. Its population was 29.7 million and it had 18 tertiary hospitals and 37 secondary hospitals in 2013. Twenty-one hospitals (9 tertiary hospitals and 12 secondary hospitals) were randomly chosen by multistage random sampling in the current study.

Inclusion and exclusion criteria

Patients (aged \geq 18 years) admitted to the 21 selected hospitals between January and December 2013 with a diagnosis of AF were enrolled in this study. The diagnosis of AF was based on a 12-lead electrocardiogram, Holter electrocardiogram, clinical diagnosis, or relevant medical records. Information from rehospitalized individuals was recorded again if any one of the four factors (CHADS₂ score [congestive heart failure, hypertension, age \geq 75, diabetes, stroke {double}] CHA₂DS₂-VASc score [congestive heart failure, hypertension, age \geq 75 {double}, diabetes, stroke {double}, vascular disease, age 65–74, and sex {female}] HAS-BLED score [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly { \geq 65 years}, drugs/alcohol concomitantly], or antithrombotic scheme) differed from the previous entry.

Patients who had participated in clinical research related to interventional treatment were excluded.

Ethical statements

This study was in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was not obtained. In view of this, this study was approved by the Medical Ethics of Chongqing Municipal Health and the Family Planning Commission without the informed consent.

Data collection

Clinical information for the included patients was collected from the electronic medical record system, including the date of birth, gender, type of AF, concomitant diseases, history of thromboembolism, administration of antithrombotic agents during hospitalization, and reasons for not prescribing anticoagulant drugs. Both the CHADS, and CHA2DS,-VASc scores were calculated to develop stroke risk stratification schemes that divided the risk of thromboembolism into low (CHADS₂/CHA₂DS₂-VASc score =0), moderate (CHADS₂/ CHA₂DS₂-VASc score =1), and high (CHADS₂/CHA₂DS₂-VASc score ≥2) risk strata. The HAS-BLED score was calculated to develop bleeding risk stratification schemes that divided the risk of bleeding into low (HAS-BLED score <3) and high (HAS-BLED score ≥3) risk strata. For warfarin-treated AF patients, the last international normalized ratio (INR) before their discharge was recorded and used to categorize the INR values into four strata: <1.50, 1.50–1.99, 2.00-3.00, and >3.00.

Definitions

Nonvalvular AF (NVAF) is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair¹¹ The diagnosis of heart failure was made by two attending physicians together according to the symptoms, signs, blood brain natriuretic peptide or N-terminal pro-brain natriuretic peptide, and Doppler echocardiography. Disagreements were resolved by a third senior physician. Ischemic stroke was defined as a focal neurologic deficit diagnosed by a neurologist or manifested by computed tomography or magnetic resonance imaging. The diagnosis of coronary heart disease was primarily based on clinical symptoms or was manifested by coronary artery computed tomography or coronary angiography. Chronic kidney disease was diagnosed if there was persistent proteinuria or if the estimated glomerular filtration rate was $<60 \text{ mL/min}/1.73 \text{ m}^2 \text{ for } >3 \text{ months}.$

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 20.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were presented as the mean with standard deviation (SD) and categorical variables as percentages. To assess baseline characteristic differences between the NVAF patients in the secondary and tertiary hospital groups, Pearson's χ^2 test or Fisher's exact test was used to compare categorical variables and Student's *t*-test to compare continuous variables. Mann–Whitney U test was used to compare the average values of the CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores. For all analyses, a two-sided probability value <0.05 was considered statistically significant.

Results

A total of 4760 AF inpatients were enrolled in the present study, of which 3785 (79.5%) were NVAF patients. In the present study, we primarily present the data from the NVAF inpatients.

Baseline characteristics of all patients

The baseline characteristics of all NVAF inpatients are summarized in Table 1. The mean age was 74.4±10.1 years, and more than half of all patients (56.1%) were aged ≥75 years. In contrast to other studies, more females (55.2%) were enrolled in this investigation. With regard to the type of AF, 27.3% of the cases were paroxysmal AF and 72.7% were persistent or permanent AF. The major concomitant diseases were coronary artery disease (68.4%), myocardial infarction (7.5%), heart failure (57.3%), hypertension (57.1%), stroke (19.4%), diabetes (16.8%), and chronic kidney disease (11.2%). Of all patients, 21.9% had suffered from thromboembolic events. Only 11.5% of the total patients had been prescribed oral anticoagulants (OACs), 32.4% had taken aspirin, and 27.1% received no antithrombotic drugs. In this study, the mean INR of the patients using warfarin was 1.48±0.66. More than 60% of the warfarin-treated patients had an INR <1.50, whereas 16.9% had an INR between 1.50 and 1.99, and only 13.5% had an INR between 2.00 and 3.00.

CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores

Among all patients, the mean CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores were 2.60 ± 1.34 , 3.30 ± 1.54 , and 1.75 ± 1.04 , respectively. Figure 1 shows a histogram of the CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores. The percentages of patients with CHADS₂ scores of 0, 1, 2, 3, 4, 5, and 6 were 4.0%, 15.3%, 33.5%, 23.8%, 13.1%, 8.5%, and 1.9%, respectively. A total of 80.7% of the NVAF patients had a CHADS₂ score ≥ 2 and < 30% had a HAS-BLED score ≥ 3 .

Table I Baseline characteristics

Variable All patients (N=3785) Age, mean (SD), years 74.4±10.1 Age, years <65	Table 1 baseline characteristics	
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75.00	>3.00	15 (4.3)

Notes: Data are presented as number (%) or mean \pm SD. $^a\!C$ ilostazol and cilostazol plus clopidogrel.

Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; LMWH, low-molecular-weight heparin; OAC, oral anticoagulant; SD, standard deviation; SEE, systemic embolic event; TIA, transient ischemic attack.

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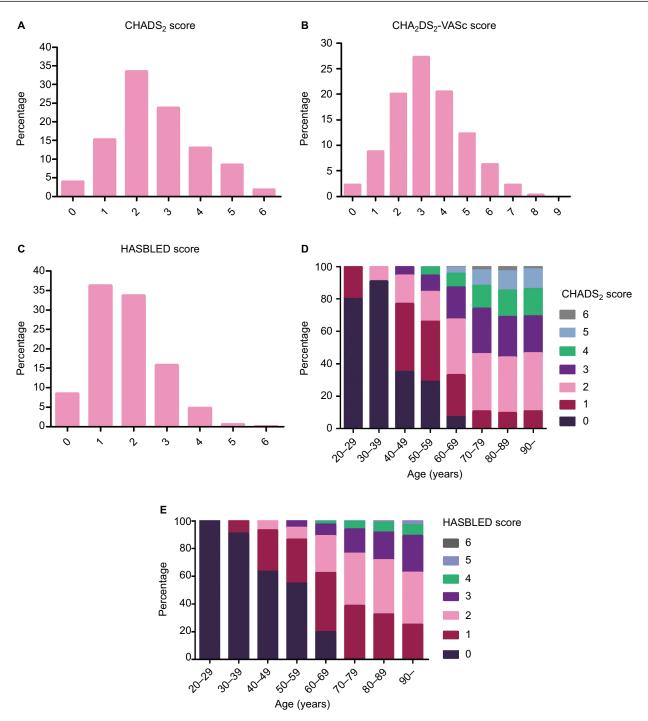


Figure I The CHADS₂ (**A**), CHA₂DS₂-VASc (**B**), and HAS-BLED (**C**) score histograms. More than 80% patients had a CHADS₂/CHA₂DS₂-VASc \ge 2. The CHADS₂ (**D**) and HAS-BLED scores (**E**) increased with age.

Also, we observed a growing tendency for the CHADS₂ score and HAS-BLED score with increasing age, with patients having a CHADS₂ score \geq 2 accounting for >80% of the elderly patients (\geq 70 years old).

Antithrombotic treatment patterns for stroke prevention

Figure 2A and B shows the relationship between stroke risk classification and anticoagulant treatment. According

to the CHADS₂ score, 4.0% of the patients were stratified into the low risk, 15.3% into the moderate risk, and 80.7% into the high-risk groups. OACs (including warfarin and non-vitamin K antagonist oral anticoagulants [NOACs]) were only prescribed to 11.5% of the 3055 patients with a high risk of stroke (CHADS₂ \geq 2), whereas antiplatelet drugs (including aspirin, clopidogrel, cilostazol, or dual antiplatelet) were prescribed to more than half of the patients. Aspirin was the most frequently prescribed drug

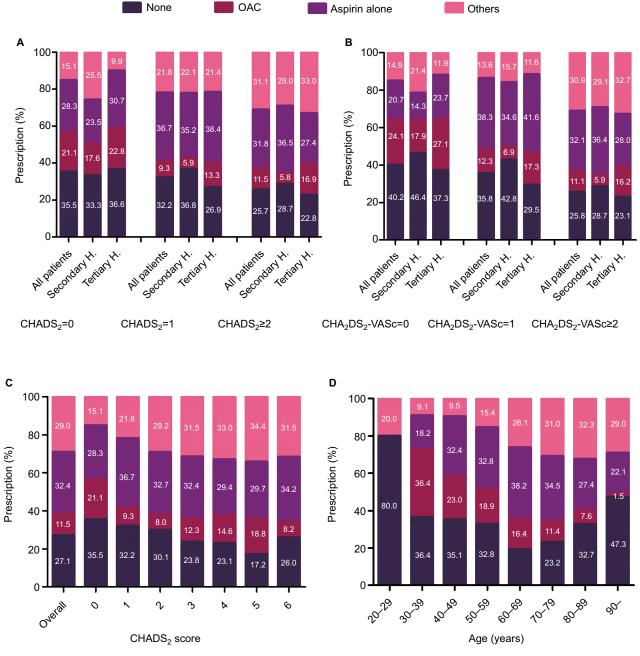


Figure 2 Differences in the antithrombotic strategy for stroke prevention according to the CHADS₂ score (**A**) and CHA₂DS₂-VASc score (**B**) between the secondary and tertiary hospitals. For patients with CHADS₂ ≥2, the OAC use rate in the secondary hospitals was significantly lower than the rate in the tertiary hospitals (P<0.001). The distribution of antithrombotic drugs according to the CHADS₂ scores (**C**) showed that the proportion of anticoagulant therapy did not increase with the CHADS₂ score. Antithrombotic drug use in the different age groups (**D**) showed that OAC was rarely prescribed to the elderly patients. Others indicate clopidogrel, cilostazol, low-molecular weight heparin, and fondaparinux sodium; secondary H. indicates the secondary hospitals; and tertiary H. indicates the tertiary hospitals. **Abbreviation:** OAC, oral anticoagulation.

for stroke prevention for AF patients in our study. However, 25.7% of the high-risk patients did not receive any antithrombotic treatment. In the low-risk group (CHADS₂=0), the treatment rate with an anticoagulant was as high as 21.1%. Overall, the proportion of anticoagulant therapy did not correspondingly increase with the increase in the CHADS₂ score (Figure 2C). Furthermore, the percentage of anticoagulation therapy decreased with advancing age

(Figure 2D). Among the elderly patients (≥80 years), the OAC use rate was only 7.0%.

NVAF patients in the secondary hospitals vs. NVAF patients in the tertiary hospitals

Among all NVAF inpatients, 48.7% (1842/3785) came from secondary hospitals and 51.3% (1943/3785) came from tertiary hospitals. Table 2 shows the comparison of

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Table 2 NVAF patients in secondary hospitals vs. NVAF patients in tertiary hospitals

Variable	Secondary	Tertiary	P-value
	hospitals	hospitals	
	(n=1842)	(n=1943)	
CHADS ₂ score			
$Mean \pm SD$	2.53±1.26	2.66±1.41	0.003
0	51 (2.8)	101 (5.2)	
I	307 (16.7)	271 (13.9)	
≥2	1484 (80.6)	1571 (80.9)	0.821
CHA ₂ DS ₂ -VASc sc	ore		
$Mean \pm SD$	3.25±1.46	3.35±1.61	0.03
0	28 (1.5)	59 (3.0)	
1	159 (8.6)	173 (8.9)	
≥2	1655 (89.8)	1711 (88.1)	
HAS-BLED score			
$Mean \pm SD$	1.70±0.98	1.80±1.09	0.007
<3	1497 (81.3)	1475 (75.9)	
≥3	345 (18.7)	468 (24.1)	
Anticoagulant stra	itegy		
None	556 (30.2)	468 (24.1)	<0.001
OAC	113 (6.1)	324 (16.7)	< 0.001
Warfarin	113 (6.1)	320 (16.5)	< 0.001
Factor Xa/direct	0 (0)	4 (0.2)	
thrombin inhibitor			
Aspirin	661 (35.9)	565 (29.1)	<0.001
Others ^a	512 (27.8)	586 (30.2)	
INR			
$Mean \pm SD$	1.79±0.93	1.44±0.60	0.001
<1.50	19 (46.3)	209 (67.9)	
1.50-1.99	11 (26.3)	48 (15.6)	
2.00-3.00	8 (19.5)	39 (12.7)	0.227
>3.00	3 (7.3)	12 (3.9)	

Notes: Data are presented as number (%) or mean \pm SD. *Clopidogrel, cilostazol, low-molecular-weight heparin, fondaparinux sodium.

Abbreviations: INR, international normalized ratio; NVAF, nonvalvular atrial fibrillation; OAC, oral anticoagulant; SD, standard deviation.

antithrombotic treatment for NVAF patients in the secondary and tertiary hospitals. The mean CHADS $_2$ score was significantly different between the secondary and tertiary hospitals $(2.53\pm1.26~{\rm vs.}~2.66\pm1.41,~P=0.003)$. The antithrombotic strategy was also different between the two types of hospitals. OAC was less prescribed in the secondary hospitals than in the tertiary hospitals $(6.1\%~{\rm vs.}~16.7\%,~P<0.001)$, and the percentage of patients who received no antithrombotic drugs in the secondary hospitals was higher than the percentage in the tertiary hospitals $(30.2\%~{\rm vs.}~24.1\%,~P<0.001)$.

The percentages of patients with CHADS₂ \geq 2 were similar between the two different hospital levels (80.6% vs. 80.9%, P=0.821). However, the use of anticoagulant therapy remained markedly different between these patients, who should receive anticoagulation therapy according to the guidelines (Figure 2A and B). Compared with the tertiary hospitals, the secondary hospitals gave priority to aspirin

Table 3 Main reasons why warfarin was not prescribed to NVAF patients with CHADS, \geq 2

Reasons	All patients (N=2704)	Secondary hospitals (n=1398)	Tertiary hospitals (n=1306)
Patient refusal	258 (9.5)	87 (6.2)	171 (13.1)
Physician's choice	2094 (77.4)	1181 (84.5)	913 (69.9)
Already taking other anticoagulants drugs for other medical conditions	110 (4.1)	52 (3.7)	58 (4.4)
Taking medication is contraindicated	242 (8.9)	78 (5.6)	164 (12.6)

Note: Data are expressed as number (%). **Abbreviation:** NVAF, nonvalvular atrial fibrillation.

Abbreviation: NVAF, nonvalvular atrial fibrillation.

(36.5% vs. 27.4%, *P*<0.001) to prevent stroke and rarely prescribed OACs (5.8% vs. 16.9%, *P*<0.001).

Reasons for the underuse of warfarin

Table 3 shows the reasons for the underuse of warfarin, including patient refusal (9.5%), physician's choice (77.4%), already taking other anticoagulant drugs for other medical conditions (4.1%), and contraindication for taking medicines (8.9%).

Discussion

This cross-sectional study investigated the use of anticoagulant therapy in Southwest China. The results demonstrated that the prescription of anticoagulation drugs were highly insufficient for hospitalized NVAF patients. Only 9.3% (351/3785) of the NVAF patients who received anticoagulant therapy were prescribed the correct anticoagulation agents according to the CHADS₂ score system recommended by the 2011 American College of Cardiology Foundation/American Heart Association and Heart Rhythm Society guidelines. This study showed a large space for the improvement of stroke prevention for the Chinese population and demonstrated that an effective prevention system is urgently needed to improve anticoagulation therapy in NVAF patients.

One of the most important findings of this study is that the underuse of anticoagulant therapy in NVAF patients is more serious than we thought in Southwest China, especially in the secondary hospitals. According to a nationwide survey of hospitalized AF patients in mainland China carried out in 2004, only 6.6% of these patients received warfarin, 57.9% had antiplatelet therapy, and 35.5% did not receive any antithrombotic therapy. Although the overall proportion of antithrombotic therapy (72.9%) and anticoagulation therapy (11.5%) obviously increased in Southwestern China over the past 10 years, it is still far behind Eastern China and other countries. Liu et al's study enrolled 2220 NVAF patients

at six tertiary hospitals located in three of the most developed cities of China and found the percentages of patients receiving warfarin, aspirin, or no antithrombotic regimen to be 31%, 21%, and 17%, respectively.¹³ The Fushimi AF Registry was a community-based survey of AF patients in Japan that enrolled 3183 patients from March 2011 to June 2012.8 In this study, warfarin was prescribed for 48.5% of the patients. A retrospective cohort study of inpatients with NVAF showed 54% used warfarin; this study was performed at 21 teaching hospitals, 13 community hospitals, and 4 veteran administration hospitals in the USA.¹⁴ Moreover, the PREFER in AF registry (Prevention of thromboembolic events – European Registry in Atrial Fibrillation), 15 which enrolled 7243 patients in seven representative European countries, showed that >80% of AF patients received OAC and that 85.6% of patients with a CHA₂DS₂-VASc score ≥2 were prescribed OAC. In light of these data, the deficiency of anticoagulant administration to NVAF patients in Southwestern China is obvious.

Even worse, anticoagulation is not only underused, but also misused. First, there was no significant difference in anticoagulant therapy in patients with different risk scores and warfarin was overused in patients at low risk (CHADS₂=0). We speculate that most patients' anticoagulant strategies were not prescribed in accordance with the guidelines. Second, to circumvent the risk of bleeding, antiplatelet drugs (especially aspirin) were overused to replace clinical anticoagulant agents. Studies have shown that aspirin is far less powerful than warfarin in preventing stroke in AF patients.⁴ Dual antiplatelet therapy, such as clopidogrel plus aspirin, had an increased bleeding risk, but was still less effective than warfarin.^{16,17}

Elderly AF patients (≥80 years) were less likely to receive OACs in this study. In the USA, only 30% of older AF patients received anticoagulation therapy, which was much less than the rate in younger patients. Thus, underused anticoagulant therapy in older AF patients is a global problem. However, the Birmingham Atrial Fibrillation Treatment of the Aged Study trial (BAFTA) confirmed the superiority of warfarin over aspirin in reducing the risk of ischemic stroke in AF patients aged ≥75 years without an increase in major bleeding events. ¹⁸ Aspirin therapy is limited in older patients because the efficacy of aspirin seems to decline beyond the age of 70 years, whereas the risk of bleeding increases. ¹⁹ Therefore, age is not a contraindication to anticoagulation and warfarin should be more prescribed in older AF patients to prevent stroke.

The underutilization of anticoagulant therapy for NVAF patients is a common phenomenon. However, the factors that

lead to the poor warfarin prescription rates are unknown. This study demonstrated that physician's choice was the most important reason, followed by patient refusal. A large number of doctors lacked knowledge concerning the management of AF and knew less about anticoagulation therapy.²⁰ Also, the majority of physicians feared the bleeding risk related to warfarin, which was likely to lead to conflicts between doctors and patients.^{21,22} However, previous studies reported that the lack of knowledge concerning AF in patients who do not understand the risks and/or benefits of anticoagulant therapy led to their poor compliance and bad disease selfmanagement. 23-27 Other reasons, such as frequently monitoring INR, no specialized anticoagulation clinic, and economic considerations, also contributed to the underuse of warfarin. Taken together, the underutilization of warfarin was strongly related to the lack of an effective management system and concerns about security. Recently, NOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, have changed the landscape of thromboprophylaxis for ischemic stroke due to their effective stroke prevention and removal of the need to monitor INR.²⁸ However, in this study, only four patients who had a high risk of stroke and bleeding were prescribed NOACs. The expensive prices of NOACs make them unaffordable for most Chinese patients because they are not covered by health care insurance. Thus, although NOACs are attractive alternatives, warfarin will most likely continue to be used in China for many AF patients.

Anticoagulation is a lifelong treatment for patients with AF, but the sharp contrast between the guidelines and reality is thought provoking. We need to do a great deal more to improve this bad situation. First, we should strengthen doctor training programs on coagulation management of AF, improve patient—physician communication, and add a post-discharge phone call follow-up. Second, educational intervention for AF patients is necessary to raise their awareness of anticoagulation treatment. Also, establishing specialized anticoagulation clinics for easy follow-up or developing mobile medical apps for ease of management may be helpful. Finally, AF should be brought into the scope of coverage, which will lighten the financial burden caused by monitoring INR or NOACs.

Limitations

There are several limitations to be addressed in the present study. This study was conducted only in secondary and tertiary hospitals and not in primary hospitals; thus, the representativeness of the sample is limited. However, because first-level hospitals are rarely responsible for the diagnosis and treatment Zheng et al Dovepress

of AF in China, we speculate that not including these hospitals in this study did not lead to a serious bias in the sample. Next, this study is a hospital-based study instead of a population-based study and, therefore, may miss many undiagnosed or out-of-hospital AF patients; thus, the data in the real world may be even worse. Finally, we did not record the reasons why patients refused to take warfarin or why doctors refused to prescribe warfarin in detail, which hampered the analysis of the causes of the deficiency in anticoagulant use.

Conclusion

After our comprehensive study of hospitalized AF patients in Southwest China, we demonstrated that NVAF inpatients received a lower level of anticoagulation drugs for stroke prevention than the national level. Anticoagulation therapy was not only underused, but also incorrectly used. Risk stratification and the guidepost for treatment in international guidelines had little effect on warfarin use. According to the China National Stroke Registry,²⁹ inadequate anticoagulant therapy in patients with AF is one reason for the high incidence of stroke in China. Consequently, immediate steps, such as strengthening doctor training, improving the quality of doctor–patient communication, and launching patient's health education initiatives, are urgently needed to promote the prophylaxis of thromboembolism in China.

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Author contributions

All authors contributed toward research design, data collection, data analysis, drafting, and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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