Original Article
Impact of stroke risk factors on warfarin prescription among patients with non-valvular atrial fibrillation

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Abstract: Despite potential advantages of warfarin in reducing stroke risk, the percentage of patients with non-valvular atrial fibrillation (NVAF) using warfarin is relatively low. Our aim was to investigate the effects of stroke risk factors on warfarin, which was prescribed for inpatients with NVAF. A retrospective analysis was conducted using the data from 232, 237 and 251 NVAF inpatients obtained in 2003, 2008 and 2013 respectively from Beijing Anzhen Hospital, China. The Cochran-Armitage test was used to assess the trend of warfarin prescription in the NVAF inpatients. Logistic regression was used to analyze the association between stroke risk factors and prescribed warfarin. The results showed that inpatients with NVAF who were prescribed for warfarin lifted from in 2003 to in 2013. Although $CHADS_2$ score was not associated with the warfarin usage, coronary heart disease (CHD) and radiofrequency ablation (RFA) were negatively and positively respectively correlated with the warfarin use among NVAF inpatients. The study addressed anti-coagulation by using $CHADS_2$ scoring to identify patient groups that are not receiving optimal medical therapy. Thought a substantial number of patients were under treated for thromboembolic prophylaxis in the management of NVAF, the work identified sub-groups such as those with CHD as being most at risk of under treatment.

Keywords: Atrial fibrillation, warfarin, stroke, risk factor

Introduction

Non-valvular atrial fibrillation (NVAF) is a serious atrial rhythm disturbance. NVAF become more prevalent in population as the age advanced with increased incidence of hypertension, coronary heart disease (CHD) and obesity caused by unhealthy lifestyle [1, 2].

Cardioembolic stroke is a serious complication in NVAF cohorts and is associated with higher disability and mortality. Patients with NVAF reported with approximately fivefold increase in stroke compared with patients without NVAF, and NVAF may be conferred as a strong independent risk factor for ischemic stroke [3]. As a result, NVAF patients are most widely risk-stratified using the $CHADS_2$ or CHA_2DS_2-VASc scoring systems in order to optimize anticoagulant therapy. Although the 2014 American Heart Association/American College of Cardiology atrial fibrillation (AF) guidelines

recommend the use of CHA_2DS_2-VASc scoring system in place of $CHADS_2$ for stroke-risk assessment, $CHADS_2$ score is a well-validated method to determine the risk of cardioembolic stroke. Compared with CHA_2DS_2-VASc score, $CHADS_2$ score is simpler and still recommended to assess the stroke risk in China [4]. In both score systems, those at high risk ($CHADS_2$ or CHA_2DS_2-VASc score $\geq$ 2) have traditionally been treated with warfarin for stroke prevention [5]. Warfarin is a vitamin K antagonist, which is a well-known recognized oral anticoagulant that may significantly reduce ischemia stroke and the combined endpoint (peripheral artery embolism, ischemia stroke, and death) [6, 7].

In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, it was indicated that warfarin utilization ratio of AF in China was 11.2%, which was distinctly lower than in North America (65.7%) [8]. The factors

related to physician prescribing warfarin for AF patients may be bleeding risk, stroke risk, duration of AF, and personal preference as well [9]. High bleeding risk and brief duration of NVAF are the main factors contraindicated for warfarin prescription in NVAF patients. However, the studies on the association of ischemic stroke risk factor and the use of warfarin have been still discussed. This work was aimed to describe the effects of stroke risk factors on the use of warfarin among patients with NVAF. We expect that this study will provide some useful information for prevention and control of ischemic stroke in the patients with NVAF.

Material and methods

Data source and patients selection

This retrospective study was conducted using the data from Beijing Anzhen Hospital, China. The study period for this analysis was from January 1 to December 31, 2003, 2008 and 2013. Patients enrolled in this study were not less than 18 years old and required persistent AF as primary or secondary discharge diagnosis.

First, 30 cases were collected every month in a year by simple random sampling and 360 patients were obtained in each year. Second, patients with the following criteria were excluded from the study: valvular heart disease, active cancer, severe cognitive impairment, autoimmune systemic diseases, hemorrhagic diseases or documented contraindications for anticoagulation treatment. In the data, usage of novel oral anticoagulants such as dabigatran and rivaroxaban were not recorded until October 2013. Therefore, we also excluded the patients who were administered novel oral anticoagulants. 232, 237 and 251 patients in 2003, 2008 and 2013 respectively were finally included in the study.

All the information was collected from the patient's medical history. Hypertension was defined as elevated blood pressure ($\geq 140/\geq 90$ mmHg) or taking antihypertensive therapy regimen [10]. Diabetes was defined as a casual plasma glucose ≥ 200 mg/dL (11.1 mmol/L), fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L), or patient already on antidiabetic treatment [11]. Heart failure was defined as the presence of signs and symptoms typical of heart failure or reduced ejection fraction

(EF $\leq 40\%$) [12]. Diagnoses of "stroke" and "transient ischemic attack (TIA)" conformed to the classical World Health Organization definitions.

Patient confidentiality was preserved and the anonymity of all patient data was safeguarded throughout the study. Institutional Review Board approval was not required for this study as researchers only had access to a limited data set.

Study measure of interest

Variables of interest included inpatient demographic and clinical characteristics, including patient age, gender, complication (CHD, ischemic stroke, TIA, heart failure, hypertension, peripheral artery disease, diabetes). $CHADS_2$ stroke risk factors and total score (congestive heart failure, hypertension, diabetes mellitus, age ≥ 75 years [each was assigned 1 point], stroke or TIA previous event [each was assigned 2 points] [13]) were calculated for study cohorts. Additionally, pharmacy prescriptions dispensed in hospital were described for the following medication: warfarin, anti-platelet therapy (clopidogrel, aspirin).

Statistical analysis

Continuous variables as mean ± standard deviation (SD) and group comparisons were performed using analysis of variance. Categorical data was reported as percentages, and independence of categorical data was tested by x^2-test. Fisher exact test was applied when theoretical value of the cell was less than 5. All variables being significant in univariate analysis were then included in a logistic regression model. The statistical analyses of all the above data were conducted using SPSS (version 17.0; SPSS Inc.). The significance of trend was assessed by the Cochran-Armitage test using SAS (version 9.3; SAS Institute Inc.). $P < 0.05$ was considered statistically significant.

Results

Demographic characteristics and comorbidities

The incidence of ischemic stroke/TIA, peripheral artery disease, heart failure and diabetes mellitus was statistically different among the

Table 1. Patient baseline characteristics in 2003, 2008 and 2013

Variables	2003 (n = 232)	2008 (n = 237)	2013 (n = 251)	*P*-value
Anthropometric data				
Age (years, mean ± SD[†])	65.84 ± 12.09	63.85 ± 11.45	64.00 ± 12.29	0.134
Gender (female/male)	105/127	102/135	123/128	0.408
Comorbidities (n, %)				
Ischemic stroke/TIA[†]	48 (20.7%)	23 (9.7%)	36 (14.3%)	0.004
Heart failure	51 (22.0%)	83 (35.0%)	57 (22.7%)	0.001
Coronary heart disease	77 (33.2%)	67 (28.3%)	90 (35.9%)	0.195
Hypertension	130 (56.0%)	121 (51.1%)	143 (57.0%)	0.341
Diabetes mellitus	29 (12.5%)	47 (19.8%)	51 (20.3%)	0.044
Peripheral artery disease	36 (15.5%)	9 (3.8%)	20 (8.0%)	0.001
Antithrombotic therapies (n, %)	160 (69.0%)	180 (75.9%)	214 (85.3%)	< 0.001
Warfarin	71 (30.6%)	115 (48.5%)	129 (51.4%)	< 0.001
Platelet inhibitor[‡]	89 (38.4%)	65 (27.4%)	85 (33.9%)	0.041
None[§]	72 (31.0%)	57 (24.1%)	37 (14.7%)	< 0.001
Radiofrequency ablation (n, %)	7/232 (3.0%)	75/237 (31.6%)	95/251 (37.8%)	< 0.001

Baseline characteristics of the patients with non-valvular atrial fibrillation using warfarin (an oral anticoagulant) from Anzhen hospital, Beijing, China in 2003, 2008 and 2013 were analyzed. [†]SD: Standard deviation. TIA: Transient ischemic attack. [‡]Platelet inhibitor includes in aspirin and clopidogrel. [§]None indicated that warfarin, aspirin and clopidogrel were not used.

Table 2. Trend of patient baseline characteristics in 2003, 2008 and 2013

Characteristics %	2003	2008	2013	Z	P
Comorbidities					
Ischemic stroke/TIA[†]	20.7%	23.0%	36.0%	-1.8972	0.0289
Heart failure	22.0%	35.02%	22.71%	0.0990	0.4606
Diabetes mellitus	12.5%	19.8%	20.3%	2.2274	0.0130
Peripheral artery disease	15.5%	3.8%	9.0%	-2.8142	0.0024
Antithrombotic therapies					
Warfarin	30.6%	48.5%	51.4%	4.5598	< 0.0001
Platelet inhibitor[‡]	38.4%	27.4%	33.9%	-0.9964	0.1595
Radiofrequency ablation	3.0%	31.6%	37.8%	8.8104	< 0.0001

The trends of baseline characteristics of the patients with non-valvular atrial fibrillation using warfarin (an oral anticoagulant) from Anzhen hospital, Beijing, China in 2003, 2008 and 2013 were analyzed. [†]TIA: Transient ischemic attack. [‡]Platelet inhibitor includes in aspirin and clopidogrel.

NVAF inpatients in 2003, 2008, and 2013 ($P < 0.05$) (**Table 1**). Furthermore, the incidence of ischemic stroke/TIA and peripheral artery disease decreased and the incidence of diabetes mellitus increased in these patients from 2003 to 2013 (**Table 2**). There was no statistical difference in the patients' gender, age, and CHD, hypertension and other comorbidities in 2003, 2008, and 2013 (**Table 1**).

The use of overall antithrombotic drugs including in aspirin, clopidogrel and warfarin in 2013 and 2008 were increased obviously than them in 2003 among inpatients with NVAF ($P < 0.01$), yet there was no statistically significant difference between the drug usage in 2008 and in 2013 ($P > 0.05$), and a similar situation could be seen in the use of warfarin in NAVF. The use of prescribed clopidogrel or aspirin was not statistically different in three years ($P > 0.05$). Radiofrequency ablation (RFA) was substantially higher performed than before in these populations (**Tables 1** and **2**).

In addition, in this study, it could be seen that, after using stratified CHADS$_2$ score, a large proportion of the inpatients (> 60%) with NVAF belong to high-risk stroke (≥ 2) clinical scenarios, which could highlight important considerations regarding anticoagulants. The use of warfarin increased among the patients with CHADS$_2$ = 1 or ≥ 2 from 2003 to 2013 ($P < 0.05$), while the use of warfarin was not changed among the patients with CHADS$_2$ = 0 from 2003 to 2013 ($P > 0.05$) (**Table 3**). We also could not see a statistically significant difference in the warfarin usage among the

Table 3. Trend in the use of warfarin among the same risk-stroke inpatients stratified by $CHADS_2$ score in 2003, 2008, and 2013

$CHADS_2$ score	2003			2008			2013			Z	P
	N	Prescribed warfarin		N	Prescribed warfarin		N	Prescribed warfarin			
		n	%		n	%		n	%		
0	24	10	41.70%	19	12	63.20%	28	15	53.60%	0.8111	0.2087
1	38	11	28.90%	63	36	57.10%	44	26	59.10%	2.6499	0.0040
≥ 2	170	50	29.45%	155	67	43.25%	179	88	49.10%	3.7428	< 0.001

The trends of the use of warfarin (an oral anticoagulant) in the patients with non-valvular atrial fibrillation from Anzhen hospital, Beijing, China in 2003, 2008 and 2013 were analyzed. $CHADS_2$ score: Congestive heart failure, hypertension, diabetes mellitus, age ≥ 75 years (each was assigned 1 point), stroke or TIA (transient ischemic attack) previous event (each was assigned 2 points).

Table 4. Analyses of the warfarin usage among different risk-stroke inpatients stratified by $CHADS_2$ score in 2003, 2008, or 2013

$CHADS_2$ score	2003			2008			2013		
	N	Prescribed warfarin		N	Prescribed warfarin		N	Prescribed warfarin	
		n	%		n	%		n	%
0	24	10	41.70%	19	12	63.20%	28	15	53.60%
1	38	11	28.90%	63	36	57.10%	44	26	59.10%
≥ 2	170	50	29.45%	155	67	43.25%	179	88	49.10%
x^2		4.452			5.244			1.454	
P		0.108			0.073			0.483	

The uses of warfarin (an oral anticoagulant) were analyzed in the patients with non-valvular atrial fibrillation from Anzhen hospital, Beijing, China in 2003, 2008 and 2013. $CHADS_2$ score: Congestive heart failure, hypertension, diabetes mellitus, age ≥ 75 years (each was assigned 1 point), stroke or TIA (transient ischemic attack) previous event (each was assigned 2 points).

patients with different $CHADS_2$ score ($CHADS_2$ = 0, 1 and ≥ 2) in the year of 2003 (x^2 = 4.452; P = 0.108), 2008 (x^2 = 5.244; P = 0.073) and 2013 (x^2 = 1.454; P = 0.483), which indicated that the use of warfarin was not influenced by $CHADS_2$ score in these years.

Furthermore, RFA can converse AF. The study showed that the patients with NVAF who were performed RFA in 2008 and 2013 were significantly increased than those in 2003 (< 0.0001) (**Table 1**). In 2013, 37.8% of the NVAF inpatients were performed for RFA, and 90.5% of them were administered with warfarin after RFA; 62.2% of the patients with NVAF were not subjected to RFA, 27.6% of them were administered with warfarin.

Univariable and multivariable analysis on stroke risk factors

On univariable analyses, age (≥ 75 years), presence of heart failure and CHD diagnosis and RFA were all strongly associated with the prescribed warfarin in NVAF. RFA was positively related to the prescribed warfarin in NVAF.

However, there was an inverse correlation between heart failure and CHD and the prescribed warfarin in NVAF. There was no association between the prescribed warfarin and $CHADS_2$ score among the patients with NVAF (P = 0.682). Collectively, we speculate that, the clinician often focus on a few of risk factors for stroke in patients (e.g., age, heart failure and CHD), less of a mix of risk factors for stroke ($CHADS_2$ score) in prescribing warfarin for the patients with NVAF (**Table 4**).

Furthermore, logistic regression analysis showed that CHD and RFA were independently associated with the prescribed warfarin in NVAF (**Table 5**). The patients with RFA and prescribed warfarin were twenty-two times more likely than the patients without RFA who were prescribed warfarin. The patients with CHD are three times less likely to be prescribed warfarin than the patients without CHD (**Table 6**).

Discussion

Although the previous studies showed that $CHADS_2$ score was helpful and provided conve-

Table 5. Univariate risk factor analysis for the prescribed warfarin among the patients in 2013

Variables	Prescribed warfarin		OR (95% CI)	*P*-value
	No	Yes		
Age				
< 75	88 (45.1%)	107 (54.9%)	1	
≥ 75	34 (60.7%)	22 (39.3%)	0.61 (0.38, 0.99)	0.04
Sex				
Male	65 (50.8%)	63 (49.2%)	1	
Female	57 (46.3%)	66 (53.7%)	1.10 (0.85, 1.41)	0.482
Stroke/TIAs[†]				
Negative	101 (47.0%)	114 (53.0%)	1	
Positive	21 (58.3%)	15 (41.7%)	0.68 (0.37, 1.25)	0.207
Heart failure				
Negative	86 (44.3%)	108 (55.7%)	1	
Positive	36 (63.2%)	21 (36.8%)	0.55 (0.34, 0.89)	0.012
Hypertension				
Negative	51 (47.2%)	57 (52.8%)	1	
Positive	71 (49.7%)	72 (50.3%)	0.96 (0.77, 1.19)	0.703
Coronary heart disease				
Negative	58 (36.0%)	103 (64.0%)	1	
Positive	64 (71.1%)	26 (28.9%)	0.38 (0.26, 0.56)	< 0.001
Diabetes mellitus				
Negative	92 (46.0%)	108 (54.0%)	1	
Positive	30 (58.8%)	21 (36.2%)	0.662 (0.40, 1.09)	0.102
Peripheral artery disease				
Negative	115 (49.8%)	116 (50.2%)	1	
Positive	7 (35.0%)	13 (65.0%)	1.76 (0.73, 4.23)	0.204
CHADS$_2$ score				
< 2	14 (45.2%)	17 (54.8%)	1	
≥ 2	108 (49.1%)	112 (50.9%)	1.15 (0.59, 2.23)	0.682
Radiofrequency ablation				
Negative	113 (72.4%)	43 (27.6%)	1	
Positive	9 (9.5%)	86 (90.5%)	3.28 (2.53, 4.27)	< 0.001

Univariate risk factor analysis was used for the prescribed warfarin (an oral anticoagulant) among the patients with non-valvular atrial fibrillation from Anzhen hospital, Beijing, China in 2013. [†]TIA: Transient ischemic attack. CHADS$_2$ score: Congestive heart failure, hypertension, diabetes mellitus, age ≥ 75 years (each was assigned 1 point), stroke or TIA (transient ischemic attack) previous event (each was assigned 2 points).

nient indices for predicting subsequent stroke among a cohort of patients with NVAF, the NVAF patients with high-risk stroke should be prescribed for warfarin. In this study, clinicians would prefer to take into account a few of stroke risk factors, rather than the aggregate CHADS$_2$ score when they prescribed warfarin for the patients with NVAF. On the contrary, compared with low-risk stroke NVAF patients with overused warfarin, high-risk stroke NVAF patients were accompanied with relatively underused warfarin. Moreover, the most important thing we noticed was, when the NVAF patients were accompanied with CHD, warfarin could not be used in time. Obviously, the usage of warfarin increased in recent years, and RFA might be one of the key factors for its wide popularity.

In clinical practice, anticoagulation is a key strategy for reducing the risk of stroke in patients with AF. Despite the recent introduction of novel oral anticoagulants, warfarin is proved to be the only commercially available oral anticoagulant for stroke prevention in AF. Even though, dabigatran was introduced in

Table 6. Parameter estimates from multivariable logistic regression model predicting the prescribed warfarin among the patients, 2013

Correlation factors of prescribed warfarin	B	P-value	Adjusted OR	95% CI	
				Lower	Upper
Radiofrequency ablation (No)			1		
Radiofrequency ablation	3.081	< 0.001	21.783	9.645	49.198
Age (< 75 years)			1		
Age	0.035	0.927	1.036	0.489	2.194
Coronary heart disease (No)			1		
Coronary heart disease	-1.249	< 0.001	0.287	0.143	0.574
Heart failure (No)			1		
Heart failure	-0.585	0.131	0.557	0.261	1.189

Parameter estimates from multivariable logistic regression model predicted the use of prescribed warfarin (an oral anticoagulant) among the patients with non-valvular atrial fibrillation from Anzhen hospital, Beijing, China in 2013.

China in 2013, in the present study, only one patient was administered with dabigatran in 2013. These findings points towards the fact that, warfarin is the sole representative in anti-coagulant therapy in NVAF in China.

The $CHADS_2$ risk-scoring system utilizes five variables to determine the risk of stroke (congestive heart failure, hypertension, diabetes mellitus, age ≥ 75 years, and history of previous stroke/TIA). The newer CHA_2DS_2-VASc score added more new risk factors (history of vascular disease, age 65-74 years, and female sex) to the risk assessment [14]. CHA_2DS_2-VASc needs more complex examination and $CHADS_2$ risk-scoring system is suitable for retrospective study. Based on the $CHADS_2$ score, no antithrombotic therapy is recommended for patients with a score of 0. Despite the existing evidence, the translation of clinical trial into routine clinical practice is often challenging. In this study, 31.25% of the NVAF patients with $CHADS_2$ = 0 who were not performed with RFA were administered warfarin, suggesting that the use of warfarin was excessive, which could lead to complications associated with hemorrhage. Based on the aggregate $CHADS_2$ score, warfarin is advised for those with a $CHADS_2$ score of ≥ 2. The study reported that greater than 60% had been as at high risk of stroke ($CHADS_2$ score ≥ 2) and only 29.5%, 43.2%, and 49.1% of those received warfarin in 2003, 2008 and 2013 respectively. In this study, the usage rate of warfarin for NVAF patients with $CHADS_2$ score of ≥ 2 in 2013 was similar to that in western country in RE-LY's study (50~70%).

CHD has been shown to be highly prevalent in individuals with AF, affecting 30.5% to 46.5% of individuals [15, 16]. In present study, 20% of patients with CHD were accompanied with NVAF. To reduce the risk of major vascular events, patients with CHD were administered antiplatelet drugs, including aspirin, clopidogrela and combination of aspirin and clopidogrel. In order to reduce the risk of bleeding, immediately after coronary revascularization in patients with $CHADS_2$ score ≥ 2, clopidogrel may concurrently be reasonable to use with oral anticoagulants but without aspirin [17]. The combination of antiplatelet drugs and oral anticoagulants could increase the risk of hemorrhage among NVAF patients with CHD thereby reducing its usage in these populations.

It is well known that cardioversion increases the risk of thromboembolism, and anticoagulation is recommended after electrical cardioversion of AF [18], so the patients with NVAF after RFA would be administered warfarin actively, and in this study most of them were prescribed for warfarin.

As noted, the present study showed that aggregate $CHADS_2$ score was not considered when clinicians prescribed warfarin, which would lead to unoptimized anticoagulation therapy among the patients with NVAF. The choice of antithrombotic therapy in patients with chronic NVAF is not straightforward and should be assessed of the patients' risk of embolism and risk of bleeding complications, as well as individual preferences [19]. HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly) is recommend to estimate the risk of bleeding in the patients with AF [17]. At higher levels of stroke risk, relatively higher levels of bleeding risk could be obtained, so warfarin was underuse for the patients at high risk of stroke ($CHADS_2$ score ≥ 2). In addition, the patients with congestive heart failure will be accompanied with abnormal renal/liver function and greater bleeding

risk, which might result that there was an inverse correlation between heart failure and the prescribed warfarin in NVAF in this study. Some results suggest a trade-off (rather than a fixed cut-off) using CHA_2DS_2-VASc and HAS-BLED scores in combination for choice of antithrombotic therapy in patients with chronic NVAF [20].

As a conclusion, the study addressed anticoagulation in China by using retrospective $CHADS_2$ scoring to identify patient groups that are not receiving optimal medical therapy. Thought a substantial number of patients were under treated for thromboembolic prophylaxis in the management of NVAF, the work identified sub-groups such as those with CHD as being most at risk of under treatment.

The current work had several limitations. The single-center study had small patient numbers, which would lead to biased results. In addition, therapeutic International Normalized Ratio in the use of warfarin would be considered, and CHA_2DS_2-vasc score system could identify the low-risk stroke patients better compared to $CHADS_2$ score system. In order to delineate more significant factors associated with the stroke risk factors in patients with NVAF, future studies should be aimed with careful analysis in a large group of patients with more clinical details.

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Disclosure of conflict of interest

None.

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