Preceding Antithrombotic Treatment is Associated With Acute Ischemic Stroke Severity and Functional Outcome at 90 Days Among Patients With Atrial Fibrillation

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Background: Antithrombotic therapies are known to prevent ischemic stroke (IS) for patients with atrial fibrillation (AF), but are often underused in clinical practice. The aim of present study was to investigate the prevalence of patients with acute IS with known history of AF who were not receiving antithrombotic treatment before stroke and to evaluate the association of preceding antithrombotic treatment with stroke severity and outcomes at 90 days after admission. *Materials and Methods:* This was a retrospective, multi-center, observational study of 748 patients with acute IS and known history of AF admitted to 6 participating hospitals between March 2016 and October 2017. The primary outcome was stroke severity at admission as assessed using National Institutes of Health Stroke Scale (NIHSS) score. The secondary outcome was functional outcome at 90 days after admission as measured by modified Rankin Scale (mRS) score. *Results:* A total of 748 patients, 54 (7.2%) were receiving therapeutic warfarin (international normalized ratio [INR] $\geq$ 2) and 100 (13.4%) had subtherapeutic warfarin anticoagulation (INR $<$ 2), 340 (45.5%) were receiving antiplatelet treatment, and 254 (34.0%) were not receiving any antithrombotic treatment prior to stroke. Compared with no antithrombotic treatment, therapeutic warfarin (OR: 0.64; 95% CI: 0.52-0.82; P = .022), and antiplatelet therapy only (OR: 0.89; 95% CI: 0.76-0.96; P = .041) were associated with lower odds ratio of moderate or severe stroke (NIHSS $\geq$ 16). Patients receiving preceding therapeutic warfarin (OR: 1.32; 95% CI: 1.22-3.57; P = .025), antiplatelet therapy only (OR: 1.13; 95% CI: 1.07-2.59; P = .043), and subtherapeutic warfarin with INR 1.5 to 1.99 (OR: 1.15; 95% CI: 1.10-2.66; P = .042) had higher odds ratio of better functional outcome (mRS $\leq$ 2) at 90 days. *Conclusions:* Among patients with AF who had experienced an acute IS, inadequate therapeutic warfarin preceding the stroke was very prevalent in China. Therapeutic warfarin was associated with less severe stroke and better functional outcome at 90 days.

Key Words: Anticoagulation—atrial fibrillation—ischemic stroke—warfarin—stroke severity—outcome

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Introduction

Stroke is a leading cause of mortality and disability, and there are approximately 3 million new stroke cases every year in China, with roughly 80% being ischemic strokes (IS).[1-3] Atrial fibrillation (AF) is an independent risk factor for IS, increases stroke risk by 5 times, and accounts for 10% to 25% of all ischemic strokes.[4-6] AF, either sustained or paroxysmal AF, is a common and serious cardiac rhythm disturbance, and is responsible for substantial morbidity and mortality in the population.[4] Paroxysmal AF increases stroke risk similar to sustained AF.[7] Although the burden of AF-related stroke is high, AF is a potentially treatable risk factor. Numerous studies have revealed that vitamin K antagonists, such as warfarin, or non-vitamin K antagonist oral anticoagulants (NOACs), such as rivaroxaban, dabigatran, and edoxaban, reduce the risk of IS.[8-10] Based on these data, current guidelines recommend warfarin or NOACs over aspirin for stroke prevention in the high-risk patients with AF.[4,11]

Despite guidelines recommendations, oral anticoagulants such as warfarin are often underused in community practice.[12,13] Several studies have demonstrated that oral anticoagulants are associated with reduced initial severity of IS at presentation and reduced disability or death at discharge in patients with AF.[14-17] However, these findings are based on the patients from a single health plan or a local health system. More importantly, stroke severity either was assessed at discharge, which might have been affected by in-hospital treatment, or was not assessed using the National Institutes of Health Stroke Scale (NIHSS), which is a generally accepted standard for stroke severity. Furthermore, although preceding antithrombotic treatment improves early (at discharge) outcomes after IS in patients with AF,[14-17] these studies did not assess late outcomes, including recurrent ischemic stroke (RIS), hemorrhagic episodes, and functional outcome after IS with modified Rankin Scale (mRS) at 90 days.

In China, warfarin was especially underused in patients with known nonvalvular AF (NVAF).[18] Although our previous study has shown that prestroke concomitant statin and aspirin use is associated with lower neurological deterioration and platelet activity in IS patients with atherothrombosis or small artery disease.[19] There is a lack of data regarding the prevalence of preceding antithrombotic treatment among patients with known history of AF who develop acute IS, and how stroke severity and outcomes differ by such treatment in Chinese populations. Therefore, the aims of present study were to investigate the prevalence of preceding antithrombotic treatment among patients with AF who had experienced an acute IS and to evaluate the association of preceding antithrombotic treatment with initial stroke severity and functional outcome at 90 days after admission.

Materials and Methods

Study Populations

This was a retrospective, multicenter, observational study, which was conducted in the Third Affiliated Hospital of Wenzhou Medical University, the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, the People's Hospital of Deyang City, the Affiliated Wenling Hospital of Wenzhou Medical University, the Affiliated Longyan first Hospital of Fujian Medical University, and the Affiliated Hospital of Southwest Medical University between March 2016 and October 2017. The study protocol was reviewed and approved by the Ethics Committee of the participating hospitals.

We consecutively enrolled the patients with known history of AF or atrial flutter who had experienced a first-ever acute IS and were admitted to the participating hospitals within 48 hours of stroke onset, had relevant cerebral lesions on diffusion weighted magnetic resonance imaging (DWI) consistent with acute IS between March 2016 and October 2017. History of AF or atrial flutter was defined as AF or atrial flutter known to exist prior to the acute IS admission and documented in the medical record, and was confirmed by common electrocardiogram or 24-hour Holter electrocardiogram during in-hospital. All patients were performed a baseline brain computed tomography (CT) scan and magnetic resonance imaging on admission, and a follow-up CT during 10-14 days after admission. Magnetic resonance angiography or CT angiography of the brain as well as color duplex ultrasound investigation of the carotid arteries were assessed in all patients. The inclusion criteria were: (1) acute IS patients with known nonvalvular AF or atrial flutter (NVAF); (2) the baseline mRS score was zero point. Exclusion criteria were: (1) valvular AF, previous stroke or TIA; (2) AF with prosthetic heart valve; (3) patients who were receiving unfractionated heparin, low-molecular-weight heparin within 7 days of stroke onset; (4) In addition to aspirin, clopidogrel, or dual antiplatelet therapy with aspirin and clopidogrel, the patients who were receiving aspirin-dipyridamole, prasugrel, ticagrelor, or ticlopidine; (5) intravenous thrombolytic therapy or intra-arterial catheter-based treatment; (6) hypoxia, fever, or any relevant hemodynamic compromise at admission; (7) severe cardiovascular, liver, or renal disease; and (8) no information on study variables for the analysis. All enrolled patients received standard therapies based on standard guidelines.[11,20]

Preceding antithrombotic treatment was defined as documentation of patients receiving an antithrombotic agent within 7 days before their index stroke onset. For the purpose of this study, antithrombotic treatments were categorized into 4 groups: (1) no antithrombotic therapy; (2) antiplatelet therapy only (aspirin, clopidogrel, or dual antiplatelet therapy with aspirin and clopidogrel); (3) subtherapeutic warfarin with an admission international normalized ratio (INR) < 2; (4) therapeutic warfarin with an INR ≥ 2. Because of the low proportion of NOACs treatment in patients with AF before IS in China (only 11 patients took NOACs in the participating hospitals between March 2016 and October 2017); therefore, these patients were excluded in this study.

The following data were obtained at baseline: (1) age, and sex; (2) history of hypertension, diabetes mellitus, hyperlipidemia, smoking, and coronary artery disease (CAD) or myocardial infarction (MI); (3) fasting total plasma cholesterol, triglycerides (TG), low-density lipoprotein cholesterol, fasting glucose, and hemoglobin A1c. Hyperlipidemia was defined as total plasma cholesterol > 200 mg/dL, TG > 180 mg/dL or use of lipid-lowering medication[21]; (4) prestroke CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes, stroke/ transient ischemic attack (TIA)/ thromboembolism [doubled], vascular disease [prior MI, peripheral artery disease, or aortic plaque], age 65-75 years, sex category [female]). A CHA_2DS_2-VASc score < 2 is defined as low to moderate thromboembolic risk and ≥2 indicates high risk prior to the index stroke event[22]; (5) prestroke medication and in-hospital treatment. The documented reasons for no anticoagulation prior to stroke were also analyzed.

Stroke Severity and Clinical Outcomes

The primary outcome was initial stroke severity on admission. The NIHSS score was used as an assessment of stroke severity (range of 0-42, with a higher score indicating greater stroke severity). Patients with an NIHSS score ≥ 16 were classified as having a moderate or severe stroke.[23] The secondary outcome was functional outcome at 90 days after admission as measured by mRS score (range from 0 [no symptoms] to 6 [death]).[24] Patients with an mRS score ≤ 2 were classified as having good functional outcome and those with an mRS score > 2 were classified as having poor functional outcome. The safety outcome was a composite of RIS, MI, death, and intracerebral hemorrhagic episodes during the 90 days after admission. RIS was defined as a new focal neurologic deficit of vascular origin lasting at least 24 hour, DWI-positive lesion which corresponded to their clinical symptom and proven to be nonhemorrhagic. Death was defined as vascular mortality due to MI, IS, or other vascular causes. MI was defined as the presence of at least two of below criteria: prolonged angina >30 minutes; total creatinine kinase isoenzyme elevation more than twice the upper limit of normal; electrocardiographic evidence of infarction. Intracerebral hemorrhagic episodes included intracerebral hemorrhage (ICH) and hemorrhagic transformation (HT).

Statistical Analysis

Categorical variables are presented as percentages and continuous variables are expressed as mean ± Standard Deviation. Baseline characteristics for study subjects, primary outcome, secondary outcome, and safety outcomes were compared across 4 preceding antithrombotic treatment groups using the Pearson Chi-square test for categorical variables and variance (ANOVA) followed by Student-Newman-Keuls test for continuous variables. Multivariable logistic regression models were employed to investigate the relationships between preceding antithrombotic therapies with mRS score at 90 days and initial stroke severity at admission. These analyses adjusted for baseline demographic and clinical variables prior to the index stroke event, including age, CAD or prior MI, hypertension, diabetes mellitus, hyperlipidemia. The preceding antithrombotic treatment was included as an independent variable, with no antithrombotic therapy as the reference group.

All statistical analyses were performed using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL). All tests were two-sided, with P value < .05 considered statistically significant.

Results

Baseline Characteristics and Preceding Antithrombotic Treatment

A total of 748 patients with known history of AF or atrial flutter who had experienced an acute IS and were admitted to the participating hospitals within 48 hours of stroke onset were enrolled between March 2016 and October 2017. Among the 748 patients, 340 (45.5%) were receiving antithrombotic treatment prior to stroke, 154 (20.6%) were receiving warfarin (100 [13.4%] had a subtherapeutic warfarin, 54 [7.2%] had a therapeutic warfarin), and 254 (34.0%) were not receiving any antithrombotic treatment before stroke. A total of 718 patients (96.0%) had a prestroke CHA_2DS_2-VASc score ≥ 2 (i.e., high risk); of these patients, 569 (79.2%) were not receiving warfarin prior to stroke, only 52 (7.2%) had a therapeutic warfarin (Table 1).

Patients receiving warfarin were slightly younger, and had a higher prevalence of CAD or MI than those receiving antiplatelet therapy only or receiving no antithrombotic treatment (P < .05; Table 1). The overall mean INR at admission was 1.4 ± 0.5 in warfarin-treated patients, with a mean INR of 1.5 ± 0.4 in patients receiving subtherapeutic warfarin and 2.4 ± 0.6 in those receiving therapeutic warfarin (P < .001; Table 1). Ischemic lesion areas

Table 1. *Baseline characteristics of study patients who had known AF or atrial flutter and experienced first ever acute ischemic stroke*

	Preceding antithrombotic therapy			
	None (n = 254)	Antiplatelet therapy (n = 340)	Warfarin, INR < 2 (n = 100)	Warfarin, INR ≥2 (n = 54)
Age (years)	72.8 ± 13.7	72.9 ± 15.8	69.2 ± 12.5†	68.8 ± 12.7†
Males (n, %)	140 (55.1)	188 (55.3)	55 (55.0)	30 (55.6)
Current smoker (n, %)	104(40.9)	141 (41.5)	42 (42.0)	23 (42.6)
Hypertension (n, %)	208 (81.9)	284 (83.5)	83 (83.0)	45 (83.3)
Diabetes mellitus (n, %)	79 (31.1)	104 (30.6)	32 (32.0)	18 (33.3)
History of CAD or MI (n, %)	11 (4.3)	23 (6.8)	16 (16.0)†	9 (16.7)†
Hyperlipidemia (n, %)	154 (60.6)	210 (61.8)	63 (63.0)	34 (63.0)
Fasting glucose (mmol/L)	6.3 ± 1.8	6.3 ± 2.5	6.2 ± 2.3	6.4 ± 2.7
Hemoglobin A1c (%)	6.4 ± 2.0	6.4 ± 2.2	6.3 ± 1.8	6.3 ± 2.3
Onset to admission time (h)	30.2 ± 16.2	29.9 ± 17.3	30.1 ± 15.1	29.7 ± 14.8
INR on admission	1.1 ± 0.3	1.1 ± 0.4	1.5 ± 0.4‡	2.4 ± 0.6‡
Baseline mRS on admission	0	0	0	0
Prestroke CHA_2DS_2-VASc score (n, %)				
0-1	14 (5.5)	11 (3.2)	3 (3.0)	2 (3.7)
≥ 2	240 (94.5)	329 (96.8)	97 (97.0)	52 (96.3)
Prestroke treatment (n, %)				
Antihypertensive	204 (80.3)	271 (79.7)	80 (80.0)	43 (79.6)
Hypoglycemic	75 (29.5)	103 (30.3)	30 (30.0)	16 (29.6)
Statins	46 (18.1)	65 (19.1)	20 (20.0)	12 (22.2)
In-hospital treatment (n, %)				
Antihypertensive	212 (83.5)	291 (85.6)	86 (86.0)	47 (87.0)
Hypoglycemic	85 (33.5)	119 (35.0)	36 (36.0)	19 (35.2)
Statins	235 (92.5)	316 (92.9)	94 (94.0)	50 (92.6)
Large cerebral artery stenosis ≥ 50% (n, %)				
Carotid artery	12 (4.7)	15 (4.4)	5 (5.0)	3 (5.5)
Middle cerebral artery	18 (7.1)	23 (6.8)	7 (7.0)	4 (7.4)
Anterior cerebral artery	13 (5.1)	18 (5.3)	5 (5.0)	2 (3.7)
Vertebrobasilar artery	7 (2.8)	9 (2.6)	3 (3.0)	2 (3.7)
Ischemic lesion areas (cm^2)	8.2 ± 2.6	8.1± 2.4	7.6 ± 2.3†	7.4 ± 2.1†
Distribution of ischemic lesion (n, %)				
Anterior circulation	192 (75.6)	260 (76.5)	75 (75.0)	192 (77.8)
Posterior circulation	62 (24.4)	80 (23.5)	25 (25.0)	12 (22.2)
Multiple lesions (n, %)	25 (9.8)	30 (8.8)	8 (8.0)	4 (7.4)

AF, atrial fibrillation; CAD, coronary artery disease; INR, international normalized ratio; MI, myocardial infarction; mRS, modified Rankin Scale; TIA, transient ischemic attack; CHA_2DS_2-VASc score, congestive heart failure, hypertension, age≥75 years (doubled), diabetes, stroke/transient ischemic attack/thromboembolism (doubled), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65-75 years, sex category (female).

†$P < .05$, compared with patients with no antithrombotic therapy or antiplatelet therapy only. ‡, $P < .001$, compared with patients with no antithrombotic therapy or antiplatelet therapy only.

on DWI were smaller in patients receiving therapeutic warfarin and subtherapeutic warfarin than those receiving no antithrombotic treatment ($P < .05$; Table 1). There were no significant differences in large cerebral artery atherosclerosis (stenosis ≥ 50%), distribution of ischemic lesion, and multiple lesions among the 4 groups (Table 1).

Initial Stroke Severity

The proportion of patients presenting with moderate or severe stroke (NIHSS score ≥ 16) at admission for no antithrombotic treatment, antiplatelet therapy only, subtherapeutic warfarin, and therapeutic warfarin was 31.1%, 23.8%, 24.0%, and 11.1%, respectively. Patients receiving no antithrombotic treatment, antiplatelet therapy only, or subtherapeutic warfarin were more likely to present with moderate or severe stroke than those receiving therapeutic warfarin ($P < .05$ for univariate analysis, Table 2).

Compared with no antithrombotic treatment, therapeutic warfarin (OR: 0.64; 95% CI: 0.52-0.82; $P = .022$), and antiplatelet therapy only (OR: 0.89; 95% CI: 0.76-0.96; $P = .041$)

Table 2. *Association of preceding antithrombotic treatment with outcomes*

	Preceding antithrombotic therapy			
	None (n = 254)	Antiplatelet therapy (n = 340)	Warfarin, INR <2 (n = 100)	Warfarin, INR ≥2 (n = 54)
mRS score 0-2 at 90 days (n, %)	75 (29.5) †	144 (42.4)	41 (41.0)	26 (48.1)
NIHSS score ≥ 16 on admission (n, %)	79 (31.1)	81 (23.8)	24 (24.0)	6 (11.1) †
Safety outcomes (n, %)				
RIS	9 (3.5)	11 (3.2)	3 (3.0)	2 (3.7)
MI	3 (1.2)	4 (1.2)	1 (1.0)	0 (0.0)
Death	17 (6.7)	16 (4.7)	5 (5.0)	2 (3.7)
HT	23 (9.1)	38(11.2)	15 (15.0)	9 (16.7)
ICH	2 (0.8)	3 (0.9)	2 (2.0)	1 (1.9)

ICT, intracerebral hemorrhage; HT, hemorrhagic transformation; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; RIS, recurrent ischemic stroke.
† $P < .05$, compared with other three groups.

were associated with lower odds ratio of moderate or severe stroke after adjusting for the covariates (Table 3).

Functional Outcome

All enrolled patients completed 90 days follow-up. Good functional outcome was defined as mRS scores ≤ 2 points at 90 days after admission. The percentage of good functional outcome was significantly higher in patients receiving antiplatelet therapy only, subtherapeutic warfarin, or therapeutic warfarin than those patients receiving no antithrombotic treatment ($P < .05$ for univariate analysis, Table 2). With regard to the patients receiving subtherapeutic warfarin, the percentage of good functional outcome was 47.4% (18/38), 45.5% (10/22), and 32.5% (13/40) in patients with INR 1.5 to 1.99, INR 1.0 to 1.49, and INR < 1.0, respectively. The percentage of good functional outcome was lower in patients with INR < 1.0 than those patients with INR 1.0 to 1.49 and INR 1.5 to 1.99 ($P < .05$ for univariate analysis).

Compared to the patients receiving no antithrombotic treatment, therapeutic warfarin (OR: 1.32; 95% CI: 1.22-3.57; $P = .025$), antiplatelet therapy only (OR: 1.13; 95% CI: 1.07-2.59; $P = .043$), and subtherapeutic warfarin with INR 1.5 to 1.99 (OR: 1.15; 95% CI: 1.10-2.66; $P = .042$) had higher odds ratio of having better functional outcome at 90 days after adjustment for the covariates (Table 4).

Safety Outcomes

There were no significant differences of the safety outcomes, including RIS, MI, HT, ICH, and death during the 90 days after admission among the no antithrombotic treatment group, antiplatelet therapy only group, subtherapeutic warfarin group, or therapeutic warfarin group (all $P > .05$, Table 2).

Possible Reasons for No Anticoagulation

Among 718 patients with prestroke CHA_2DS_2-VASc score ≥ 2, 569 patients were not receiving warfarin prior to stroke. The reasons for no oral warfarin before stroke were shown in Table 5. The most common reasons were risk of bleeding (15.8%), risk of falls (9.8%), patient or family refusal (13.0%), terminal illness (5.3%), mental status (1.4%), serious adverse effects (2.6%), or allergy (0.9%).

Table 3. *Multivariable logistic regression analysis of independent predictors for initial stroke severity (NIHSS score ≥ 16)*

Factor	OR	95% CI	*P* value
Preceding antithrombotic treatment			
None (reference)			
Antiplatelet therapy only	0.89	0.76-0.96	.041
Subtherapeutic warfarin	0.95	0.87-1.06	.082
Therapeutic warfarin	0.64	0.52-0.82	.022
Age	0.96	0.88-1.46	.423
Diabetes mellitus	1.01	0.94-1.83	.425
Hypertension	0.98	0.91-2.05	.372
CAD or prior MI	0.96	0.86-1.28	.352
Hyperlipidemia	0.83	0.77-1.62	.538

CAD, coronary artery disease; CI, confidence interval; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; TIA, transient ischemic attack.

Table 4. *Multivariable logistic regression analysis of independent predictors for good functional outcome (mRS score ≤ 2)*

Factor	OR	95% CI	*P* value
Preceding antithrombotic treatment			
None (reference)			
Antiplatelet therapy only	1.13	1.07-2.59	.043
Subtherapeutic warfarin			
INR < 1	0.88	0.81-1.41	.512
INR 1-1.49	1.01	0.87-1.98	.357
INR 1.5-1.99	1.15	1.10-2.66	.042
Therapeutic warfarin	1.32	1.22-3.57	.025
No warfarin after IS	0. 96	0.91-1.31	.326
Age	0.90	0.73-1.69	.311
Diabetes mellitus	0.95	0.91-199	.468
Hypertension	1.02	0.93-2.28	.346
CAD or prior MI	0.92	0.83-1.26	.378
Hyperlipidemia	0.83	0.69-1.48	.601
NIHSS score ≥ 16	0.78	0.58-0.99	.022

CAD, coronary artery disease; CI, confidence interval; INR, international normalized ratio; IS, ischemic stroke; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

However, among the 569 patients, 248 (43.6) did not have a documented reason for not receiving oral warfarin.

Discussion and Conclusion

In this study, the main findings were: (1) warfarin was significantly underused (20.6% [154/748]) before stroke in IS patients with known NVAF in China; (2) 65% [100/154] of warfarin treated patients were receiving subtherapeutic warfarin (INR < 2) at the time of stroke; (3) compared with no antithrombotic treatment, preceding use of therapeutic warfarin (INR ≥ 2) was independently associated with lower odds of moderate or severe stroke at the time of stroke and higher odds ratio of having better functional outcome at 90 days after adjustment for the covariates.

AF is a highly prevalent and important, but treatable risk factor for stroke.[4] Despite numerous international guideline recommendations, many patients fail to receive proper treatment for stroke prevention. A systematic review of 54 studies from 11 countries in Europe, North America, and South America found consistent patterns of oral anticoagulation underuse in patients with AF who had an elevated risk of stroke.[25] The studies from the China QUEST (Quality evaluation of stroke care and treatment) registry also showed that only 16.2% of patients with known NVAF in China were on warfarin, and warfarin use is lower in China than that in Western countries.[18,26] In the United States, 60% of AF patients with a CHA_2DS_2-VASc score ≥ 2 were treated with warfarin or NOACs.[27] Unlike previous studies that evaluated the prevalence of warfarin therapy in patients at risk for stroke, this analysis investigated how many AF patients presenting with acute IS were treated with warfarin prior to their stroke event. This approach has implications for clinical practice because it identifies potentially preventable strokes in high-risk patients with AF who either were not treated with warfarin or did not receive adequate warfarin. In China, there are nearly 3 million new stroke cases every year, and 15% to 25% of these strokes are estimated to be of cardioembolic origin.[1,18,28] Based on results from anticoagulation trials and the prevalence of inadequate therapeutic anticoagulation observed in this study, a substantial number of strokes may be due to underuse or inadequate anticoagulation in AF. Thus, the incidence of IS in patients with AF may reduce by improving appropriate AF treatment.

Table 5. *Documented reasons for no warfarin use prior to stroke (n = 569) among patients with a prestroke CHA_2DS_2-VASc score ≥ 2*

	No. (%)
Risk of bleeding	90 (15.8)
Risk of falls	56 (9.8)
Patient or family refusal	74 (13.0)
Serious adverse	15 (2.6)
Allergy to or complication with warfarin	5 (0.9)
Mental status	8 (1.4)
Terminal illness	30 (5.3)
≥ 1 Documented reason	321 (56.4)
No documented reason	248 (43.6)

Prior studies have demonstrated that warfarin therapy reduces the risk of severe stroke when stroke occurs.[15,16] However, these previous research relied on nonstandard stroke severity measures at discharge. In current study, stroke severity was assessed using NIHSS score at admission, which is considered the reference standard for stroke severity.[23] Our results showed that the proportion of patients presenting with moderate or severe stroke on admission was lower in patients receiving therapeutic warfarin than those patients receiving no antithrombotic treatment, antiplatelet therapy only, or subtherapeutic warfarin. Xian et al.[14] showed that inadequate therapeutic anticoagulation preceding the stroke was prevalent among patients with AF who had experienced an acute IS, and therapeutic anticoagulation was associated with lower odds of moderate or severe stroke at admission. The results were consistent with our current study. Although preceding antithrombotic treatment improves early functional outcome at discharge after IS in patients with AF,[14-17] these studies did not assess the functional outcome at 90 days after stroke. Our results demonstrated that patients receiving preceding therapeutic warfarin or subtherapeutic warfarin with INR 1.5 to 1.99 were independently associated with better functional outcome at 90 days after stroke admission compared with patients receiving no antithrombotic treatment. However, patients receiving preceding subtherapeutic warfarin with INR < 1.5 were not

associated with better functional outcome at 90 days. Our current results were consistent with one other study.[29] Several possible reasons exist for the benefits observed in our study. Our results showed that therapeutic warfarin or subtherapeutic warfarin with INR 1.5 to 1.99 was associated with smaller acute DWI lesion areas and lower NIHSS scores on admission. In a detailed magnetic resonance imaging study, warfarin was also associated with lower infarct volumes, greater frequency of small distal infarcts, and lower acute NIHSS scores.[30] Possible mechanisms include enhanced early spontaneous fibrinolysis, smaller embolus size, and reduced thrombus propagation. In the Canadian Stroke Network Registry, an INR of 2 to 3 was associated with milder stroke at stroke onset.[16] These findings reinforce the importance of INR monitoring and dose adjustment to improve compliance and keep the INR in the therapeutic range for patients receiving warfarin.

For patients with IS and AF who are unable to take oral anticoagulants, antiplatelet treatment (aspirin, clopidogrel, or aspirin plus clopidogrel) is recommended.[4,11] In this study, prior antiplatelet treatment was associated with lower initial stroke severity and good functional outcome at 90 days compared with no antithrombotic treatment. This result was consistent with our previous studies and some other studies.[14,19,31] Antiplatelet treatment may improve microcirculation in the ischemic penumbra, inhibit platelet activation and platelet-derived vasoconstrictors,[32] limit clot size, and protect against thrombus extension and subsequent embolism.[33] In addition, neuroprotective and anti-inflammatory properties of antiplatelet treatment may be expected as other beneficial mechanisms for acute IS.[34,35] These potential mechanisms of antiplatelet treatment might contribute to lower stroke severity and good functional outcome.

There have been concerns that some patients with AF may not be ideal candidates for oral anticoagulants, and the selection of an antithrombotic agent should be individualized on the basis of patient risk factors, preference, and other clinical characteristics. Because of absence of documentation, reasons for no antithrombotic therapy were unclear. The risk of bleeding and falls, and patient or family refusal are very common reasons for no anticoagulation therapy in patients with AF.[11,18,23] Although risks of bleeding and falls may be considered to make a patient ineligible for anticoagulation therapy, some studies suggested that the perceived risk of bleeding and falls may have been overestimated, especially in elderly individuals.[36-38] Even if patients were unable to use oral anticoagulants due to contraindications, antiplatelet therapy could have been considered.[4,11] Our current results also revealed that preceding antiplatelet treatment, in addition to therapeutic warfarin, was associated with less severe stroke and better functional outcome at 90 days after admission in IS patients with AF. Nevertheless, 34% of high-risk AF patients were not receiving any form of antithrombotic therapy before stroke, highlighting the opportunities for stroke prevention by improving appropriate AF treatment.

This study had several limitations. First, this was a retrospective, observational study. It is impossible to randomize patients with stroke to different antithrombotic agents because treatment was given before the stroke. Treatment selection of an antithrombotic agent and unmeasured confounding could affect the validity of study findings. Baseline characteristics were quite different among the different antithrombotic groups. Although we attempted to control confounding using multivariable logistic regression analysis, we could not eliminate bias because of imbalance baseline characteristics. Second, this study included only AF patients who had an IS. Patients with AF treated with different antithrombotic regimens who did not have an IS were not included in this study. Because of absence of a cohort or case-control design with patients who had AF and defining by anticoagulant exposure and subsequent stroke incidence, thus, we could not assess the potential protective effect of adequate anticoagulation, and conversely the harm of inadequate anticoagulation in this study. Third, some patients did not have information on study variables in the medical record, such as NIHSS or mRS scores. These patients were excluded because it is inappropriate to impute outcome measures in this study. Excluding missing values might bias this analysis. Finally, due to the limited sample size and six-center study, the results of this study may not represent the full spectrum of Chinese population. Thus, the findings must be validated in larger, multicenter studies.

In conclusion, among patients with AF who had experienced an acute IS, inadequate therapeutic anticoagulation therapy prior to the stroke was very prevalent. Preceding therapeutic anticoagulation was associated with lower odds of moderate or severe stroke at admission, and could improve functional outcome at 90 days after admission.

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