

## Antithrombotic treatment before stroke onset and stroke severity in patients with atrial fibrillation and first-ever ischemic stroke: An observational study

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### Abstract

**Background and Objectives:** Atrial fibrillation (AF) is an important, independent risk factor for stroke. The value of antithrombotic therapy to prevent stroke is well established in numerous randomized controlled trials. The objectives of this study were to determine the rate and the factors associated with the prescription of antithrombotic treatment before first-ever ischemic stroke in patients with known AF; and to assess the association between preadmission antithrombotic therapy and stroke severity, death or disability. **Methods:** Consecutive patients with acute first-ever ischemic stroke and AF admitted to Mackay Memorial Hospital from July 2005 to June 2007 were included in the study. We reviewed the use of antithrombotic agents before stroke onset, the international normalized ratio at admission and coexisting illness. The severity of stroke was graded using the National Institute of Health Stroke Scale. Disability was measured at discharge and during 90 days follow-up according to modified-Rankin Scale. **Results:** A total of 1,952 patients were admitted with ischemic stroke during the study period. Of these, 152 patients with AF experienced first-ever ischemic stroke. Of 152 patients, 124 (82%) were known to have AF and 28 (18%) were diagnosed with AF during admission. Before stroke, 69 out of 124 patients with known AF (56%) were not on antithrombotic therapy, 30 (24%) were receiving antithrombotic treatment but inadequately treated, and 25 (20%) were adequately treated according to the current guidelines. Younger age (<75 years), history of ischemic heart disease, diabetes mellitus and congestive heart failure were associated with the use of antithrombotic therapy before stroke onset. At discharge and during 90 days follow-up, 28% of the adequately treated patients died or were severely disabled compared with 57% of those inadequately treated. **Conclusion:** Antithrombotic treatment was underutilized before stroke onset, and this underuse is associated with increased mortality or disability in ischemic stroke patients with AF.

### INTRODUCTION

Atrial fibrillation (AF) is a common cardiac dysrhythmia. Strokes associated with AF often cause substantial neurologic disability and mortality<sup>1</sup>, and consequently, primary prevention rather than belated prophylaxis after an initial stroke is the most sensible approach. Rhythm control has not been shown to be superior to rate control in reducing the risk of stroke in several randomized clinical trials.<sup>2-4</sup> Antithrombotic therapies are the mainstay for stroke prevention. Despite compelling evidence indicates the beneficial effects of antithrombotic therapy in primary prevention of stroke in patients with AF, it has been found to be underused.<sup>5-10</sup>

Our study had 2 objectives. First, we determined the rate and the factors associated with the prescription of antithrombotic treatment before first-ever ischemic stroke in patients with

known AF. Second, we assessed the association between preadmission antithrombotic therapy and stroke severity, death or disability at discharge and 90 days follow-up.

### METHODS

Consecutive patients with acute first-ever ischemic stroke and AF (known previously or diagnosed during admission) admitted to the neurology service of Mackay Memorial Hospital between July 1, 2005 to June 30, 2007 were included in the study. Mackay Memorial Hospital is a 2060-bed medical center in the northern part of Taipei, Taiwan serving a population of heterogeneous social class. We defined stroke using the World Health Organization definition.<sup>11</sup> Patients presenting with transient ischemic attacks (TIAs), recurrent ischemic stroke and cerebral venous sinus thrombosis were excluded from

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the current study. All patients underwent brain CT scan without contrast upon admission to exclude intracerebral hemorrhage. Follow-up MRI examination or brain CT scan was repeated 3 to 5 days after the qualifying event. Twelve-lead electrocardiogram (ECG) was performed in all patients during admission and the diagnosis of AF was confirmed by the cardiologist. Information on clinical variables known to affect stroke outcome were obtained from all available sources. History of AF, use of antithrombotic treatment before stroke, and admission international normalized ratio (INR) values were also recorded. The use of antithrombotic agents prior to stroke onset was determined from a review of medical charts or inquires to patient's cardiologists or family physicians. We used the CHADS<sub>2</sub> score to quantify stroke risk in these patients.<sup>12</sup> The score is formed by assigning 1 point each for congestive heart failure, hypertension, age 75 years or older, diabetes and 2 points for a past history of stroke or TIA. Baseline stroke severity was graded using the National Institute of Health Stroke Scale (NIHSS).<sup>13</sup> Ischemic stroke subtype was categorized according to the popularly used classifications, the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria and the OCSF (Oxfordshire Community Stroke Project) classification.<sup>14,15</sup>

Patients were categorized as treated and non-treated with antithrombotic agents, and patients on antithrombotic therapy were further classified as adequately and inadequately treated. Patients were considered as adequately treated when they were receiving the following treatments:

- Warfarin therapy with INR 2.0 to 3.0 at the time of stroke;
- Aspirin (100 mg per day) for patients with non-valvular atrial fibrillation (NVAf) and CHADS<sub>2</sub> score of 0 to 2;
- Clopidogrel (75 mg per day) or ticlopidine (200 mg per day)<sup>16-18</sup> when aspirin was contraindicated;
- Aspirin (100 mg per day) for patients unable to receive warfarin.

Patients treated with warfarin but with INR < 2.0 at the time of stroke or with aspirin for patients with a CHADS<sub>2</sub> score of > 2 were considered inadequately treated. Contraindications for aspirin were defined as history of gastric ulcer, aspirin intolerance or allergy to aspirin.

We used the modified-Rankin Scale (mRS) to measure the functional deficit at hospital discharge

and during 90 days follow-up.<sup>19</sup> Patients with a score of 0 to 3 were classified as no or mild-moderate dependency. Patients with a score of 4 or 5 were classified as severe dependency. A score of 6 denoted a severe stroke that resulted in death.

The study was approved by the Institutional Review Board of Mackay Memorial Hospital. Because of the nature of the study, the requirement for informed consent was waived.

For statistical analysis, continuous variables were compared using analysis of variance with post-hoc analysis using the Scheffe correction for multiple comparisons. Categorical variables were compared using chi-square test. We considered a  $p \leq 0.05$  to be statistically significant. Multivariable logistic regression analysis was used to ascertain the effect of clinical variables on the use of antithrombotic therapy before stroke onset in patients with known AF. The independent effect of adequate antithrombotic treatment on functional deficit and mortality was assessed using multivariable logistic regression model. All analyses were undertaken with a commercially available software package (SPSS version 12).

## RESULTS

During the study period, 1,952 patients were admitted with ischemic stroke. Of these, 235 (12%) had AF; 83 patients diagnosed as recurrent stroke were excluded from analysis. Of the remaining 152 first-ever ischemic stroke patients, 124 (82%) had known AF and 28 patients (18%) had new diagnosis of AF on ECG performed on admission. The baseline characteristics of the patients are listed in Table 1. Most ischemic strokes were deemed to be cardioembolic (81%). Before stroke, 69 out of 124 with known AF (56%) were not receiving antithrombotic treatment, 47 (38%) on antiplatelet agents and 8 (6%) on warfarin. Table 2 illustrates descriptive variables of patients with known AF prior to stroke onset. The type of antithrombotic treatment in patients with known AF is listed in Table 3. Only 25 patients out of 55 treated patients were adequately treated according to current guidelines. Twelve patients had contraindication to aspirin (9 gastric ulcer, 2 aspirin intolerance, and one allergy to aspirin). Instead, other antiplatelet agents were used. Multivariate analysis corroborated the results of the univariate analyses: We found younger age (<75 years), history of ischemic heart-disease, diabetes mellitus and congestive heart failure were factors associated with the

**Table 1: Baseline characteristics of the 152 patients with atrial fibrillation and first-ever ischemic stroke**

Characteristic	
Age – years	
Mean ± SD	73.96 ± 11.2
Range	42 – 94
Sex– number (%)	
Male	70 (46.1%)
Female	82 (53.9%)
Known atrial fibrillation	124 (81.6%)
New diagnosis of atrial fibrillation	28 (18.4%)
NIHSS (median)	11
INR (mean ± SD)	1.2 ± 0.34
Risk factors – number (%)	
Hypertension	129 (84.9%)
Congestive heart failure	63 (41.4%)
Ischemic heart disease	58 (38.1%)
Diabetes	50 (32.9%)
Hyperlipidemia	49 (32.2%)
Tobacco use	20 (13.1%)
TOAST stroke subtype	
Large artery atherosclerosis	7 (4.6%)
Cardioembolic	123 (80.9%)
Lacunar	22 (14.5%)
OCSF stroke subtype	
TACI	46 (30.2%)
PACI	55 (36.2%)
POCI	29 (19.1%)
LACI	22 (14.5%)

NIHSS, National Institute of Health Stroke Scale; INR, international normalized ratio; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; OCSF, Oxfordshire Community Stroke Project; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct.

use of antithrombotic therapy either adequate or inadequate before stroke onset in patients with known AF ( $p < 0.05$ ). Total anterior circulation and posterior circulation infarcts were noted to be more common in the non-treated group. Given the results of the above analysis of patients with known AF, we estimated that only 20% of our patients with history of AF were adequately treated with antithrombotic agent before stroke onset.

At the time of discharge and during 90 days follow-up, none of the 25 patients with adequate antithrombotic treatment had died while 10 of the 30 patients treated inadequately (33%) died. Compared with those receiving antithrombotic treatment before stroke onset, more than half of the non-treated patients (54%) had a modified-Rankin score of 4 to 5 at discharge and on 90 days follow-up ( $p=0.005$ ). After adjustment for

baseline variables in the multivariable logistic regression model, adequate antithrombotic treatment (odds ratio, 3.638; 95% confidence interval, 1.392–9.503;  $p=0.006$ ) remained an independent factor for the severity of functional outcome and death.

## DISCUSSION

In our study, AF was present in 12% of patients admitted with ischemic stroke. Approximately two-thirds of these patients had first-ever stroke and only about 20% of patients with history of AF were receiving an adequate antithrombotic treatment prior to stroke onset. Paciaroni *et al.* reported that only 10% of their patients with known AF were adequately treated with antithrombotic agents before their first-ever

**Table 2: Descriptive variables of patients with known atrial fibrillation in multivariate analysis**

	Total (n=124)	Non- Treated (n=69)	Treated (n=55)		P Value
			Inadequate (n=30)	Adequate (n=25)	
Age – years					
Mean ± SD	74.9 ± 10.7	75.4 ± 10.6	78.0 ± 10	69.5 ± 10	NS
< 75 years	54	30 (43.5%)	6 (20%)	18 (72%)	0.001
Gender					
Female	67	39 (56.5%)	19 (63.3%)	9 (36%)	NS
Hypertension	105	58 (84.1%)	28 (93.3%)	19 (76%)	NS
Hyperlipidemia	39	17 (24.6%)	11 (36.7%)	11 (44%)	NS
Tobacco use	15	8 (11.6%)	3 (10%)	4 (16%)	NS
Ischemic heart disease	48	19 (27.5%)	16 (53.3%)	13 (52%)	0.017
Diabetes mellitus	43	20 (29%)	18 (60%)	5 (20%)	0.003
Congestive heart failure	51	18 (26.1%)	9 (30%)	24 (96%)	<0.001
NIHSS (median)	11	12	9.5	6	NS
Disability					
Rankin (0-3)	59	28 (40.6%)	13 (43.3%)	18 (73%)	
Rankin (4-5)	51	37 (53.6%)	7 (23.3%)	7 (28%)	
Death	14	4 (5.8%)	10 (33.3%)	0 (0%)	0.005
TOAST stroke subtype					
Large artery atherosclerosis	4	3 (4.3%)	1 (3.3%)	0 (0%)	
Cardioembolic	101	57 (82.6%)	25 (83.3%)	19 (76%)	
Lacunar	19	9 (13%)	4 (13.3%)	6 (24%)	
OCSF stroke subtype					
TACI	36	24 (34.8%)	6 (20%)	6 (24%)	
PACI	46	21 (30.4%)	16 (53.3%)	9 (36%)	
POCI	23	15 (21.7%)	4 (13.3%)	4 (16%)	
LACI	19	9 (13%)	4 (13.3%)	6 (24%)	

NIHSS, National Institute of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; OCSF, Oxfordshire Community Stroke Project; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; LACI, lacunar infarct; NS, not significant.

**Table 3: The type of antithrombotic treatment in 55 patients with known atrial fibrillation**

	Adequate treatment (n=25)	Inadequate treatment (n=30)
Anticoagulant		
Warfarin	3 (INR ≥ 2)	5 (INR < 2)
Antiplatelet		
Aspirin	16	14
Ticlopidine	2	5
Clopidogrel	4	1
Dipyridamole	0	4
Cilostazol	0	1

INR, international normalized ratio.

stroke.<sup>8</sup> The SAFE II study found that only 22% of patients with new ischemic stroke and NVAf were taking oral anticoagulant therapy at the time of admission.<sup>20</sup> In another study, only 27% of patients with known AF, who had  $\geq 1$  stroke risk factor and no contraindications to warfarin, were adequately treated with warfarin at the time of stroke.<sup>21</sup> Despite impressive results from previous studies demonstrating the efficacy of antithrombotic therapy in the prevention of ischemic stroke among patients with AF<sup>22-24</sup>, underutilization still occurred primarily before stroke onset. This means that once a stroke had occurred, it was too late to use antithrombotic therapy in approximately half of the patients.

Preadmission antithrombotic treatment was significantly associated with reduction in baseline stroke severity, severe disability and death when ischemic stroke does occur.<sup>9,25,26</sup> The effect of the intensity of prior oral anticoagulant therapy on the severity of stroke was also studied by Hylek *et al.*<sup>25</sup> Their results provide further support that an INR of 2.0 or greater reduces not only the frequency of ischemic stroke but also its severity and the risk of death from stroke. Consistent with the previous findings, our results clearly demonstrated the effect of antithrombotic treatment on the reduction in stroke disability at hospital discharge and during 90 days follow up. Significant reduction in baseline stroke severity and death were particularly seen in patients receiving adequate antithrombotic treatment.

In this present study, patients treated with aspirin with dose of 100 mg per day were regarded as adequately treated. The rationale for use of low-dose aspirin in Taiwanese patients is based on the risk of gastrointestinal intolerance and dose-dependent risk of bleeding. Similarly, low-dose aspirin (81 mg per day) are also administered to the majority of Japanese patients with NVAf for the primary prevention of stroke.<sup>27,28</sup> Because of lack of well-designed randomized trials among Japanese and other Asians, use of low-dose aspirin must be considered speculative.<sup>29</sup>

The plethora of currently available stroke risk stratification schemes with different patient management recommendations can lead to variance in clinical practice. In the CHADS<sub>2</sub><sup>11</sup> scoring system, a score of 2 was designated as having moderate risk for stroke. Because most guidelines recommend either warfarin or aspirin for patients at moderate risk, patients place in this category might confuse clinicians when choosing optimal antithrombotic prophylaxis.<sup>30-32</sup> Patient's values and physician's attitude toward

stroke risk and the risks of anticoagulation greatly influence the choice of treatment.<sup>31</sup> In our study, we considered moderate risk patients receiving antiplatelet agent prior to stroke onset as adequately treated because of the uncertainty about antithrombotic prophylaxis in this group of patients.

History of ischemic heart disease, congestive heart failure and diabetes mellitus were factors that significantly influenced the decision of the doctors at our institution to prescribed antithrombotic agent to patients with known AF. Our data reflect the reluctance of physicians to prescribe antithrombotic therapy as primary prevention or in patients without additional risk factors. Other studies found a similar association between previous clinical circumstances and antithrombotic treatment in patients with known AF.<sup>33-35</sup>

In addition, the results of our study suggested that younger patients (<75 years) with known AF were more likely to receive adequate treatment than older patients. The mean age of adequately and inadequately treated patients was 69 years and 78 years respectively. Despite the proven substantial benefits in elderly patients, antithrombotic is underused because of the alleged increased bleeding risk in this age group.<sup>36-38</sup> The tendency of our physicians to use subtherapeutic INRs or antiplatelet agents in older patients further support that the choice of therapy is based on avoiding complications rather than on maximizing expected benefit.

Similar to the results of other studies<sup>1,17,39-41</sup>, the potential explanations for underuse of antithrombotic therapy in patients with known AF at our institution were old age, limited life expectancy, high risk of falls, physician's inappropriate and excessive fear of bleeding, the inconvenience of anticoagulation which requires frequent monitoring and the inadequate appreciation of data from clinical trials.

Inherent to any observational study, our study has several potential limitations. First, the study focuses on hospitalized stroke patients; it would most likely result in underestimation of the proportion of patient not properly treated. It remains possible that some patients with minor stroke either did not seek medical care or were treated as outpatients. Second, the study was done on a single institution; the results may be of limited generalizability. Third, the number of patient with an adequate treatment was too low for definitive conclusions.

In conclusion, efficacious antithrombotic

prophylaxis to prevent stroke in patients with AF remain underused in clinical practice. Our results suggest that there is considerable room for improvement. Antithrombotic therapy has to be tailored for each patient individually according to the risk of stroke and of bleeding during anticoagulation. All clinicians should be aware of this common cause of preventable stroke.

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