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Original Article

Factors Predicting Stroke Recurrence in Stroke Patients with Atrial Fibrillation

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SUMMARY

Background: Following acute ischemic stroke in patients with atrial fibrillation, the risk of stroke recurrence is relatively high. The purpose of this study is to determine the factors that influence the risk of recurrent stroke.
Methods: In this registry-based prospective cohort study, we included patients with acute ischemic stroke and atrial fibrillation who were admitted consecutively from December 1, 2012, to December 31, 2016. Patients were divided into 2 groups based on stroke recurrence. We tried to identify factors predicting stroke recurrence and evaluate the impact of treatment on recurrent ischemic events.
Results: A total of 511 patients (mean age, 76 years; 262 women) was analyzed. During the follow-up period, 58 patients (11.4%) had at least one ischemic event. The diameter of the left atrium in the recurrence group is larger (in millimeters) (39.6 ± 8.2 vs. 35.9 ± 6.9, $p < 0.001$), and is more likely to have left atrial enlargement (n = 32, 55.2% vs. n = 143, 31.6%, $p = 0.001$). Patients who received inappropriately low doses (n = 16, 27.6%) and who did not receive oral anticoagulation treatment (n = 25, 43.1%) were significantly higher in the recurrence group ($p < 0.001$). Surprisingly, the stroke severity at baseline in the recurrence group was less severe and the hospital stay was shorter.
Conclusion: Our study suggests that patients who have left atrial enlargement and receiving inappropriate low dose or not receiving oral anticoagulant treatment were associated with increased risk of recurrent stroke in patients with atrial fibrillation.

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1. Introduction

Prior stroke or transient ischemic attack (TIA) is the most powerful predictor of stroke recurrence in patients with atrial fibrillation (AF), with an annual recurrence rate of > 5%.[1] After an ischemic stroke, the risk may be as high as 8% in the 90 days following an acute event.[2] In contrast, relatively low rates of stroke recurrence were observed for other ischemic stroke subtypes. Cardioembolic stroke tends to be severe and lead to more disability than other stroke subtypes.[3,4] Studies have shown that up to 75% of ischemic strokes can be prevented with appropriate anticoagulant therapy.[5,6] Although there is clear evidence that oral anticoagulant (OAC) treatment is beneficial in preventing recurrent ischemic stroke, many studies have found that it is underutilized.[7,8] The aim of the present study is to determine the factors that influence the risk of stroke recurrence in patients with AF. We also assessed the effect of treatment on recurrent ischemic events.

2. Methods

This registry-based prospective cohort study includes consecutive patients with acute ischemic stroke in the setting of AF admitted to our hospital between December 1, 2012, and December 31, 2016. Our hospital is a 2011-bed Medical Center in the northern part of Taipei, Taiwan serving a population of heterogenous social class. We excluded: (1) patients who were lost to follow-up; (2) patients with missing information on OAC medication after the index event; (3) patients who were dead at discharge, as stroke severity or early death may have precluded cardiac evaluation (Figure 1). A systematic follow-up of at least 3 months or longer after the occurrence of the index event to determine whether there is a recurrent acute ischemic stroke. The occurrence of recurrent acute ischemic stroke is defined as new neurological symptoms and evidence of ischemic stroke on computed tomography (CT) or magnetic resonance imaging (MRI). According to the recurrence of stroke, patients are divided into two main groups: (1) recurrence group and (2) recurrence-free group.

We collected the following clinical data: age, sex, smoking, timing of AF detection (known prior to or detected after the index event), the type of AF (paroxysmal or sustained), vascular risk factors (hypertension, diabetes mellitus, dyslipidemia), and past medical history (stroke, congestive heart failure, and coronary heart disease). The CHA_2DS_2-VASc score was calculated for each patient. Baseline stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) score. All patients had a non-contrast CT upon admission. Follow-up MRI was repeated 3-5 days after the index stroke. Aside from 12-lead electrocardiogram, all patients underwent further 24 hours Holter monitoring. The cardiologist confirmed the diagnosis of AF. Transthoracic echocardiography was performed for each patient. Left atrial (LA) diameter in millimeters (mm) was measured at the level of the aortic valve leaflets in the para-

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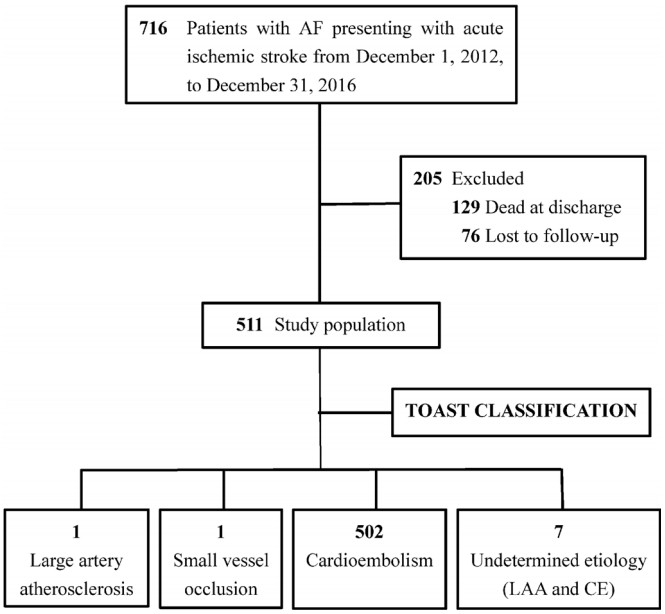

Figure 1. Flow chart showing inclusion and exclusion criteria, and TOAST classification of the patients. LAA = large artery atherosclerosis, CE = cardioembolism.

sternal long axis view. Measurements were taken according to the guidelines of the American Society of Echocardiography.[9] Taking into account the difference between sexes, we defined LA enlargement (LAE) as LA diameter of > 40 mm in men or > 38 mm in women; and LA diameter below these values was defined as normal LA size.

The length of stay for the index stroke was also recorded. We used modified Rankin Scale (mRS) to measure the functional outcome at 1 month and 3 months after the index stroke. We checked the use of OAC at the time of discharge and during follow-up period. Direct-acting oral anticoagulant (DOAC) treatments were categorized into 4 groups based on the doses as follows: (1) appropriate full dose, (2) appropriate low dose, (3) inappropriate dose, and (4) no anticoagulant. Patients who were prescribed a reduced dose but did not meet the criteria for dose reduction were grouped in the inappropriate dose group. Patients who were prescribed a reduced dose but met the criteria for dose reduction were grouped in the appropriate dose group. The DOAC dose was evaluated based on the manufacturer's labeling recommendations in Taiwan. We also try to identify if there are any documentation in the medical records explaining why OAC is not prescribed for secondary stroke prevention. The study was approved by the Institutional Review Board of MacKay Memorial Hospital, and the need for patient consent was waived.

For statistical analysis, we used independent-sample t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables to compare the clinical characteristics between the two groups. Using the Kaplan-Meier method, we determined the association between recurrent ischemic events and the prescribed dose and LA size. For the cut-off value of LA diameter, Youden's index was used to determine the optimal cut-off point in the receiver operating characteristics curve to maximize the sensitivity and specificity. We used the Cox proportional hazards model to assess the association between LA size, anticoagulation status, and recurrent ischemic events. A hazard ratio (HR) with a 95% confidence interval (CI) was calculated. All reported *p* values are based on a two-tailed test, and if they are < 0.05, they are considered statistically significant. All analyses were performed using a commercially available software package (IBM SPSS version 26).

3. Results

A total of 511 patients was analyzed. Overall, the mean age is 76 years and 51.3% (262/511) were women. The mean follow-up period was 794.8 ± 557 days. The end point of follow-up was the occurrence of recurrent ischemic stroke. During the follow-up period, 58 patients (11.4%) developed at least one ischemic event. The baseline demographic and clinical characteristics of the patients are summarized in Table 1 based on the presence or absence of stroke recurrence. No significant differences were found in the demographic information between the two groups. The presence of hypertension, diabetes, dyslipidemia, smoking, congestive heart failure, coronary heart disease and previous stroke or TIA was relatively consistent among all patients. No other significant differences were found between the two groups in the type of AF, known AF before stroke (KAF), and AF diagnosed after stroke (AFDAS). The cut-off value for

Table 1
Baseline demographics and clinical characteristics of the patients based on the presence or absence of stroke recurrence.

Characteristics	Recurrence	Recurrence-free	*p*-value
No. of patients	58	453	
Age, yr (mean ± SD)	76.45 ± 10.2	75.6 ± 11.3	0.558
Female sex, n (%)	31 (53.4%)	231 (50.9%)	0.676
Risk factors, n (%)			
Hypertension	50 (86.2%)	360 (79.5%)	0.293
Diabetes	16 (27.6%)	138 (30%)	0.762
Dyslipidemia	41 (70.7%)	293 (64.7%)	0.384
Congestive heart failure	1 (1.7%)	14 (3.1%)	0.562
Coronary heart disease	16 (27.6%)	128 (28.3%)	1.0
Prior stroke or TIA	16 (27.6%)	138 (30.5%)	0.762
Tobacco use	10 (17.2%)	87 (19.2%)	0.859
AF type (sustained versus paroxysmal)	47:11	361:92	1.0
Known AF	24 (41.4%)	219 (48.3%)	0.332
AF detected after stroke	34 (58.6%)	234 (51.7%)	
CHA_2DS_2-VASc score (mean ± SD)	5 ± 1.3	5 ± 1	0.421
NIHSS score at baseline (mean ± SD)	7 ± 5.5	11 ± 8	< 0.001
Length of hospital stay (days)	13.8 ± 12.8	19.8 ± 14.8	0.003
Functional outcome (mRS) (mean ± SD)			
mRS score at 30 days	2 ± 1.2	3 ± 1.2	0.420
mRS score at 90 days	3 ± 1.3	3 ± 1	0.432

AF = atrial fibrillation; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale.

LA diameter was 38 mm (69% sensitivity, 60.8% specificity). Compared with the recurrence-free group, the LA diameter (mm) of the recurrence group was larger (39.6 ± 8.2 vs. 35.9 ± 6.9, $p < 0.001$). Moreover, LA diameter was correlated with AF duration. Patients with sustained AF had a larger LA diameter than those with paroxysmal AF (37.4 ± 7 vs. 31.7 ± 5.8, $p < 0.001$). The incidence of LAE is also significantly higher in patients with recurrent ischemic stroke (55.2% vs. 31.6%, $p = 0.001$) (Table 2). Figure 2 shows the Kaplan-Meier curves for recurrent ischemic events according to the size of the LA.

There was no significant difference in mRS between the two groups at 1 month and 3 months after the index stroke. Surprisingly, the NIHSS scores at baseline in patients with a recurrent stroke were significantly lower than in patients without a recurrent stroke (7 ± 5.5 vs. 11 ± 8, $p < 0.001$). Furthermore, the length of hospital stay (in days) was also significantly shorter in patients with recurrent ischemic stroke (13.8 ± 2.8 vs. 19.8 ± 14.8, $p = 0.003$).

The proportion of patients receiving appropriate doses, inappropriate doses and no anticoagulant in relation to recurrent ischemic stroke is shown in Table 3. However, we were not able to identify the reasons for off-label underdosing or not prescribing OAC as prevention of recurrent stroke. Figure 3 shows the Kaplan-Meier curves for recurrent ischemic events based on anticoagulant therapy.

4. Discussion

It has been found that patients with stroke and AF have a particularly high risk of stroke recurrence. Clinical trials have demonstrated the benefits of OAC therapy for recurrent ischemic stroke prevention in the weeks following an acute ischemic stroke in patients with AF.[10–13] Our study shows that the proportion of patients receiving OAC as secondary prevention after ischemic stroke is 76.1%. Nearly 24% of the patients were not receiving OAC for the prevention of recurrent stroke. Compared with our previous study,[14] OAC use in our hospital increased from 43.2% to 76.1% after the introduction of DOAC.

In this study, recurrent ischemic stroke occurred in 58 (11.4%) of the 511 patients. We found that LA size, LAE and dosing methods of DOAC (including not prescribing OAC) are predictors of stroke recurrence in our patients. Previous studies have found that even in patients with no evidence of AF, the size of LA is associated with an increased risk of ischemic stroke.[15–17] In addition, several published studies have found that there seems to be an association between LAE and stroke recurrence in patients with atrial fibrillation.[18–20] Correspondingly, our present study clearly showed that LAE was associated with an increased risk of stroke recurrence in patients with AF. However, in other studies, no such association was found.[21,22] The differences in the characteristics of the included patients may partially explain the discrepancies. Compared with previous studies,[23,24] our study also did not show the influence of a specific gender on the size of LA as a predictor of recurrent stroke.

Several mechanisms could explain how LAE is associated with higher risk of stroke in AF patients. First, LAE may promote blood stasis,[23] leading to thrombus formation and the potential for embolization. Second, LAE reflects the increased burden of AF and is associated with an increased risk of thromboembolism.[25] Third, LAE is considered to be a marker of the severity of other risk factors for cardiovascular events such as hypertension[26] or carotid atherosclerosis, which increases the risk of stroke recurrence. Finally, LAE is regarded as a marker of atrial cardiopathy that may lead to an increased risk of thromboembolism.[27] It may be suggested that a simple measurement of LA size can be used as an additional risk stratification for AF patients to predict recurrence of ischemic stroke.

Oral anticoagulant therapy is the standard of care for secondary stroke prevention. In real-world clinical practice, the appropriate dose of DOAC is usually not prescribed. The incidence of inappropriate dosing ranges from 14% to 45% in previous reports.[28–32] Although a recent meta-analysis of Asian patients demonstrated that standard-dose DOAC is a more appropriate therapeutic option than low-dose DOAC,[33] the use of low-dose is still more common in Asia than in Europe and North America.[28,29]

In this prospective registration study reflecting daily clinical practice in the real world, we found that the proportion of patients who did not receive anticoagulation therapy or received inappropriate doses of DOAC was significantly higher. Physicians tend to choose doses that are inconsistent with labeling when choosing an anticoagulation regimen for a patient with AF. This may reflect concerns about drug-related bleeding and may lead to a higher rate of stroke recurrence. Consistent with previous studies,[32,34–37] our study confirmed that patients who received inappropriate doses or did not receive OAC played an important role as a potential risk factor for stroke recurrence.

Another interesting finding in our study is that the recurrence

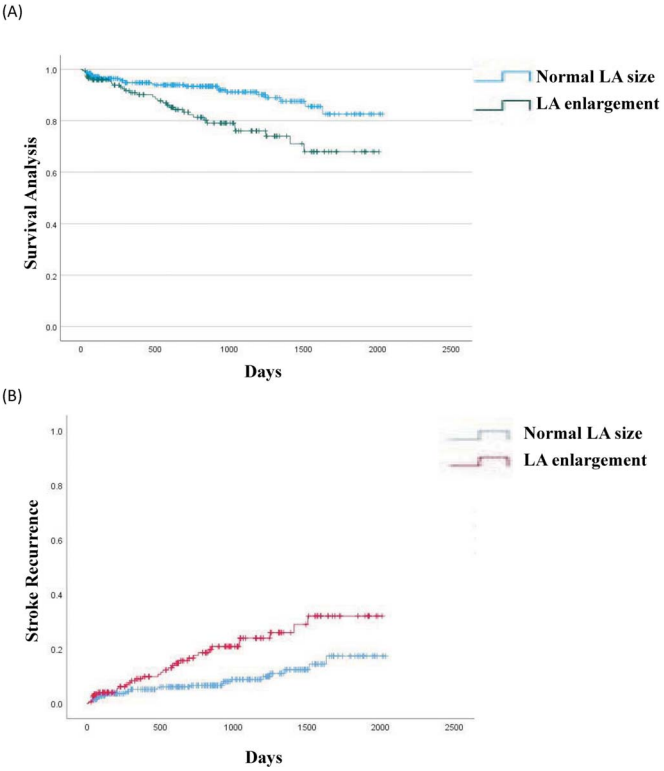

Figure 2. Kaplan-Meier curves for survival analysis (A), and stroke recurrence (B) according to LA size. LA = left atrial.

Table 2
Association of left atrial size, left atrial enlargement and stroke recurrence.

	Recurrence	Recurrence-free	*p*-value	HR (95% CI)
Left atrial size (millimeters, mean ± SD)	39.6 ± 8.2	35.9 ± 6.9	< 0.001	
Left atrial enlargement, n (%)	32 (55.2%)	143 (31.6%)	0.001	2.39 (1.43–4.02)

HR (95% CI) = hazard ratio (95% confidence interval).

Table 3
Association of prescribed dose and stroke recurrence.

	Recurrence	Recurrence-free	*p*-value	HR (95% CI)
OAC prescribed after index stroke			< 0.001	5.7 (3.23–10.07)
Appropriate full dose, n (%)	16 (27.6%)	258 (57%)		
Appropriate low dose, n (%)	1 (1.7%)	54 (11.9%)		
Inappropriate dose, n (%)	16 (27.6%)	44 (9.7%)		
No OAC, n (%)	25 (43.1%)	97 (21.4%)		

HR (95% CI) = hazard ratio (95% confidence interval); OAC = oral anticoagulant.

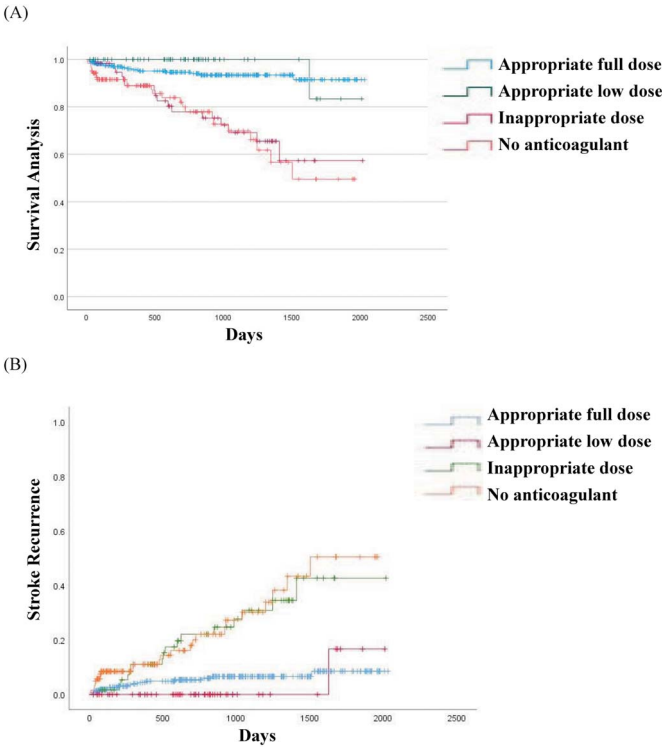

Figure 3. Kaplan-Meier curves for survival analysis (A), and stroke recurrence (B) based on anticoagulation treatment.

group had a higher incidence of mild strokes and shorter hospital stays at the time of their index stroke. A possible explanation is that OAC was not used in these patients due to the milder stroke severity and earlier discharge.

Several limitations of this study should be considered. First, the study was conducted in a single center hospitalized stroke patients, and the generality of the results may be limited. Second, we only measured LA diameter. Our study lacked data on LA volume, which is a more reliable estimator of LA size[38] and also a more accurate predictor of cardiovascular events.[39] However, the LA diameter is easier to obtain and is more widely used in daily clinical practice. Third, because transesophageal echocardiograms were not routinely performed in our patients, we lacked data on the other cardiac biomarkers such as morphology of LA appendage and spontaneous echo contrast, which have been associated with recurrent stroke in patients with AF.[40] Fourth, the selection of OAC and its dosing regimen were at the discretion of the attending physicians, and we stratified the entire cohort by OAC prescription only at the baseline. Finally, we were unable to identify the reason why the physician did not prescribe OAC or prescribed off-label underdose.

In conclusion, LAE and receiving inappropriate doses of DOAC are predictors of recurrent stroke in patients with AF-associated ischemic stroke. Careful monitoring of changes in LA size can be advocated so that physicians can optimize stroke prevention strategies for patients with AF, thereby improving the patient's prognosis. Patients with ischemic stroke and AF will benefit from prescribing appropriate doses of DOAC to prevent stroke recurrence. Therefore, the use of appropriate doses should be reinforced.

Conflicts of interest

None.

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