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Original Article

Use of Oral Anticoagulant for Secondary Prevention of Stroke in Very Elderly Patients With Atrial Fibrillation: An Observational Study†

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SUMMARY

Background: Oral anticoagulant (OAC) is proven to be more effective than antiplatelet therapy in the secondary prevention of ischemic stroke in patients with atrial fibrillation (AF). The objective of this study was to determine the effect of age on the prescription of OAC and its actual use by neurologists for secondary prevention among the very elderly patients with AF hospitalized for ischemic stroke.
Methods: In this prospective observational study, data from patients with first-ever ischemic stroke and AF were included. We reviewed the use of antithrombotic agents before stroke onset and at discharge in patients with AF who were aged 80 years or older. We analyzed the trends of oral anticoagulation as secondary prevention in very elderly patients and identify the reasons why anticoagulant was not prescribed at discharge.
Results: A total of 152 patients with AF experienced first-ever ischemic stroke. Of these, 51 patients (33.6%) were ≥80 years of age, and 101 were <80 years of age. Thirteen patients died during the acute stroke and thus were excluded from the analysis. Of 139 ischemic stroke survivors at discharge, 45 were ≥80 years of age and 94 were <80 years of age. For those aged ≥80 years, 62.2% received neither antiplatelet nor anticoagulant agents before stroke onset. Surprisingly, only one patient (2.2%) was treated with OAC. At discharge, only 12 patients (26.7%) aged ≥80 years were treated with OAC compared with those aged <80 years (48/94 [51.1%]).
Conclusion: This study suggests that OAC is underused in most of the very elderly patients despite its proven efficacy. A history of stroke did alter the trend of use of antithrombotic agents in this age group.

1. Introduction

The prevalence of atrial fibrillation (AF) increases dramatically with age, from 5% in people aged 65 years and older to approximately 10% in those aged 80 years or older[1]. AF is a major risk factor for stroke. The risk of stroke is increased fivefold[2] and is even higher in those with additional cardiovascular risk factors[3]. Because risk of stroke increases with age[4], and strokes associated with AF cause substantial neurologic disability or death, therefore stroke prevention in the very elderly people with AF is of particular importance.

Elderly patients with an ischemic stroke associated with AF are at especially high risk for recurrent stroke with an annual rate of more than 10%. The European Atrial Fibrillation Trial (EAFT)[5] showed that the annual risk was 12% in controls as compared with 4% in those treated with oral anticoagulant (OAC). The Stroke Prevention in Atrial Fibrillation (SPAF) III trial[6] confirmed the results of the EAFT. A combined analysis of the EAFT and Stroke Prevention in Atrial Fibrillation III showed a similar benefit of OAC[7]. Despite the proven efficacy of OAC in prevention of recurrent stroke and the clear recommendations from the guidelines[8,9] it is still underused worldwide[10–16]. The aim of the present study was to determine the effect of age and the prescribing patterns of neurologist at discharge in very elderly patients with a recent ischemic stroke and a known AF.

2. Methods

A prospective observational study is conducted from July 1, 2005 to June 30, 2007, in a medical center located in the northern part of Taipei, Taiwan. Patients with an acute first-ever ischemic stroke and previously known or newly diagnosed AF admitted to the neurology service were included in the study. We defined stroke using the World Health Organization definition[17]. Patients with

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transient ischemic attacks, recurrent ischemic stroke, and cerebral venous sinus thrombosis were excluded. All patients had a non-contrast computed tomography (CT) scan at admission to exclude intracerebral hemorrhage. Follow-up magnetic resonance imaging or CT scan was repeated 3–5 days after the index stroke. Twelve-lead electrocardiogram was performed in all patients during admission and the diagnosis of AF was confirmed by the cardiologist. Patient clinical features that have been associated with increased stroke risk in patients with AF were obtained from all available sources. These included history of hypertension, type I or type II diabetes, ischemic heart disease, hyperlipidemia, and congestive heart failure. Use of antithrombotic treatment before stroke and the prescription of OAC at the time of discharge were recorded. The use of antithrombotic agents before stroke onset was determined from a review of medical records or inquires to patient's cardiologists or family physicians. We also try to identify if there was any documentation in the medical notes explaining why OAC was not prescribed at the time of discharge.

Baseline stroke severity was graded using the National Institute of Health Stroke Scale[18]. Ischemic strokes were classified according to the popularly used subtype classification, the Trial of ORG 10172 in Acute Stroke Treatment criteria[19]. We also determined on CT or magnetic resonance imaging scan ischemic stroke subtype and localization as defined by the Oxfordshire Community Stroke Project[20].

We used the modified Rankin Scale (mRS)[21] to measure the functional outcome at hospital discharge. Patients with a score of 0–3 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 our hospital. Because of the nature of the study, the requirement for informed consent was waived.

For statistical analysis, the baseline characteristics of patients aged ≥80 years or <80 years were reported as percentages or mean (median). Statistical comparisons were carried out by means of Pearson's χ^2 or unpaired t test for categorical and continuous variables, respectively. We considered a $p \leq 0.05$ to be statistically significant. Multivariate logistic regression analysis was performed to identify independent predictors for medication with OAC at the time of discharge in AF patients with ischemic stroke. Clinical variables that were considered to be potential predictors for treatment with OAC as prevention of recurrent stroke were included in the analyses. All the statistical analyses were computed using the commercially available software package (SPSS version 12; SPSS Inc., Chicago, IL, USA).

3. Results

There were 1,952 patients admitted with ischemic stroke during the study period. Among these patients, 235 (12%) had AF; 83 patients diagnosed as recurrent stroke were excluded from analysis. Of the remaining 152 first-ever ischemic stroke patients, 51 (33.6%) were ≥80 years of age and 101 (66.4%) were <80 years of age. The baseline characteristics of the patients are listed in Table 1. More than 66% of the very elderly patients were female (66.7% vs. 47.5%; $p = 0.025$). The presence of hypertension, diabetes, congestive heart failure, and ischemic heart disease was relatively consistent among all patients. Very elderly patients were less likely (17.6% vs. 39.6%; $p = 0.006$) to have hyperlipidemia than patients aged <80 years. Most ischemic strokes were deemed to be cardioembolic (81%). Thirteen patients died during the acute stroke and thus were excluded from further analysis. Of 139 ischemic stroke survivors at discharge, 45 were ≥80 years of age and 94 were <80 years of age. Before stroke, 28 (62.2%) of 45 were not receiving antithrombotic treatment, 16 (35.6%) on antiplatelet agents, and only 1 (2.2%) on OAC. There was a trend toward a higher rate of OAC and antiplatelets use at the time of discharge to prevent recurrent stroke. Table 2 illustrates the type of antithrombotic treatment prescribed both for primary and secondary prevention of stroke in very elderly patients. There were significant differences in the type of antithrombotic treatment given at discharge between patients aged ≥80 years and <80 years as shown in Table 3. The rate of the prescription of OAC at discharge for very elderly patients was 26.7% compared with the 51.1% found in the population younger than 80 years ($p = 0.003$). Only eight patients were not treated with any antithrombotic medication at discharge. Of these, five were aged ≥80 years (four severely disabled [mRS 5] and one died of aortic aneurysm) and three were aged <80 years (two severely disabled

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

Characteristics	<80 yr of age	≥80 yr of age
No. of patients	101	51
Age—yr (mean ± SD)	68.33 ± 9.34	85.12 ± 3.82
Gender—*n* (%)		
Male	53 (52.5)	17 (33.3)
Female	48 (47.5)	34 (66.7)
NIHSS (median ± SD)	12	9
Risk factors—*n* (%)		
Hypertension	85 (84.2)	44 (86.3)
Congestive heart failure	38 (37.6)	25 (49.0)
Ischemic heart disease	41 (40.6)	17 (33.3)
Diabetes	35 (34.7)	15 (29.4)
Hyperlipidemia	40 (39.6)	9 (17.6)
Tobacco use	16 (15.8)	4 (7.8)
Functional outcome (mRS)—*n* (%)		
mRS (0–3)	55 (54.5)	20 (39.2)
mRS (4–5)	35 (34.6)	24 (47.1)
Death	11 (10.9)	7 (13.7)
TOAST stroke subtype—*n* (%)		
Large artery	4 (4.0)	3 (5.9)
Cardioembolic	88 (87.1)	35 (68.6)
Lacunar	9 (8.90)	13 (25.5)
OCSP stroke subtype—*n* (%)		
TACI	30 (29.7)	16 (31.4)
PACI	41 (40.6)	14 (27.4)
POCI	21 (20.8)	8 (15.7)
LACI	9 (8.9)	13 (25.5)

LACI = lacunar infarct; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; OCSP = Oxfordshire Community Stroke Project; PACI = partial anterior circulation infarct; POCI = posterior circulation infarct; SD = standard deviation; TACI = total anterior circulation infarct; TOAST = Trial of ORG 10172 in Acute Stroke Treatment.

Table 2
Type of antithrombotic treatment given both for primary and secondary prevention in very elderly patients

Treatment	Primary prevention (before stroke)	Secondary prevention (after stroke)
	n = 45	*n* = 45
OAC alone	1 (2.2%)	12 (26.7%)
Aspirin alone	7 (15.6%)	8 (17.8%)
Aspirin and other antiplatelet	0	1 (2.2%)
Ticlopidine	5 (11.1%)	4 (8.9%)
Clopidogrel	2 (4.4%)	15 (33.3%)
Other antiplatelet alone	2 (4.4%)	0
No antithrombotic treatment	28 (62.2%)	5 (11.1%)

Values are number of patients, with percentages in parentheses. The total may differ from 100% because of rounding.
OAC = oral anticoagulant.

Table 3
Comparison between the type of antithrombotic treatment prescribed at discharge among all patients

Treatment at discharge	<80 yr of age ($n = 94$)	≥80 yr of age ($n = 45$)
OAC alone	45 (47.9%)	12 (26.7%)
OAC and any antiplatelet	3 (3.2%)	0
Aspirin alone	19 (20.2%)	8 (17.8%)
Aspirin and other antiplatelet	0	1 (2.2%)
Ticlopidine	4 (4.3%)	4 (8.9%)
Clopidogrel	19 (20.2%)	15 (33.3%)
Other antiplatelet alone	1 (1.1%)	0
No antithrombotic treatment	3 (3.2%)	5 (11.1%)

Values are number of patients, with percentages in parentheses. The total may differ from 100% because of rounding.
OAC = oral anticoagulant.

[mRS 5] and one liver cirrhosis). In multivariate logistic regression analysis, higher age, greater baseline stroke severity on the NIHSS, and severe disability or functional dependency on the mRS were significantly associated with the nonprescription of OAC at discharge (Table 4).

We were not able to identify reasons documented in the medical records, which may explain why OAC was not prescribed to the very elderly patients at the time of hospital discharge as prevention of recurrent stroke. Given the results of the above analysis of patients, it appears that only less than half of our patients are receiving anticoagulation therapy for prevention of recurrent stroke at the time of discharge.

4. Discussion

Although age was not regarded as a contraindication to OAC *per se*, it is one of the strongest determinants for the chance of receiving treatment with OAC, both for primary and secondary prevention of stroke. Our study showed that at stroke onset, only 2.2% of very elderly patients with AF and first-ever stroke received OAC as primary prevention. After ischemic stroke, the proportion of very elderly patients receiving OAC as secondary prevention at discharge was only 26.7%. Before the Birmingham Atrial Fibrillation Treatment of the Aged Study trial[22], elderly patients were significantly underrepresented in randomized trials. Participants in earlier trials were younger than patients commonly encountered in clinical practice, and the efficacy and safety of OAC in the very elderly is less clear. Clinicians are frequently reluctant to prescribe anticoagulants to elderly patients with AF to prevent first and recurrent stroke. However, the recent publication of The Atrial Fibrillation Investigators[23] have found that above age 80, the relative and absolute benefits of anticoagulants increase as patients get older, whereas the benefit of antiplatelet therapy for preventing ischemic stroke decreased significantly as patients aged.

Prevention of recurrent stroke in the very elderly patients is a challenge. Elderly patients had higher levels of comorbidity, they are at particularly high risk for recurrent stroke and are the most likely to benefit from anticoagulation. Our work demonstrated, even for this very high-risk population, OAC is underused. The rate of the prescription of OAC at discharge for very elderly patients was 26.7% compared with the 51.1% found in the population younger than 80 years. Being older than 80 years appeared as one of the major independent factors for not receiving OAC at discharge in our present study. Similar results were found in a Swedish study[16] where patients with an age 75 years or older had a chance to be treated with OAC as secondary prevention was only a third (11.4%) as compared with patients younger than 75 years (33.5%). In another European study[11], several factors were associated with the nonprescription of OAC at discharge. They also found that patients older than 75 years were less likely to be discharged under OAC.

Another independent predictor for not prescribing OAC as secondary stroke prevention in our study was the poor functional outcome at the time of discharge as assessed with the mRS. This is in line with many observational studies, which reported that severe disability or high functional dependency was identified as predictor for underuse of OAC at discharge[24,25]. Furthermore, the precise benefits of OAC in patients with ischemic stroke because of AF who are left with severe disability (mRS of 3–5) are unclear because few such patients were included in the studies[5,6].

Guo et al.[26] reported in their study that a previous stroke did not alter the trend of use of OAC in patients with AF. However, data from our study suggest that a history of stroke did alter the trend of use of antithrombotic agents among our patients. Among these 45 very elderly patients, 28 (62.2%) were not under any antithrombotic treatment before stroke, whereas only 5 (11.1%) were not receiving any antithrombotic treatment as prevention of recurrent stroke.

Although not the focus of our study, we found a surprisingly high rate of antiplatelet therapies (including aspirin and other antiplatelet drugs) in our very elderly patients. Despite their weak efficacy in the secondary prevention of stroke in AF patients, more than 62% of our very elderly patients were receiving antiplatelet therapy as prevention of recurrent stroke. One possible explanation is a lack of evidence related to the risks of OAC use in Asians[10]; instead, antiplatelet agents were prescribed in these patients.

Compared with Western countries, the rate of OAC prescribing was lower in Taiwan[10]. One of the reasons is the uncertainty over the optimal treatment of elderly patients with AF still exist. Few guidelines on the use of OAC specific for the geriatric patient population are available. Confusion in the current guidelines[8,27] is reflected in clinical practice. A lower INR goal than normally used is in fact well tolerated and effective in Chinese patients as reported in several studies[28–30]. This may be attributed to differences in thromboembolic and bleeding risks between races.

Several limitations of our study must be acknowledged. First, the study focuses on hospitalized stroke patients in one hospital with small number of patients eligible for analysis. The results may be of limited generalizability. Second, as shown in this study, almost three-quarters of the very elderly stroke patients with AF were not on OAC at the time of hospital discharge. The reasons for not prescribing OAC were not clearly documented in most of the medical notes. Some physicians may have deliberately avoided OAC, whereas others may have overlooked prophylaxis. Third, we did not differentiate between paroxysmal (or intermittent) and chronic (or sustained) AF. However, this should not influence our results as the rates of stroke are surprisingly similar in both circumstances and many elderly patients with recurrent paroxysmal AF benefit substantially from anticoagulation[31,32].

In conclusion, our study identifies an important underuse of OAC in very elderly stroke patients with AF. Assessing the benefit-risk ratio of anticoagulation is indeed a challenging issue in the very elderly patients. Increased physician education regarding the benefits and optimal monitoring of OAC therapy will lead to lower

Table 4
Independent predictors of oral anticoagulation at discharge in stroke patients with atrial fibrillation

	OR	95%CI	*p*
Age ≥80 yr	0.334	0.154–0.725	0.006
Baseline NIHSS	2.466	1.215–5.008	0.012
mRS at discharge	1.058	1.011–1.108	0.016

CI = confidence interval; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; OR = odds ratio.

stroke rates in the future. A specialized anticoagulation clinic may make it easier for physicians to initiate and maintain safe OAC therapy in geriatric patients.

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