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Do NOACs Improve Antithrombotic Therapy in Secondary Stroke Prevention in Nonvalvular Atrial Fibrillation?

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Abstract: Guidelines recommended oral anticoagulant (OAC) for ischemic stroke patients related to atrial fibrillation (AF). But, underprescription or underdose of warfarin was observed worldwide. We aimed to explore if the use of antithrombotic therapy in nonvalvular AF (NVAF) ischemic stroke patients improved after novel oral anticoagulants (NOACs) became available.

Between January 2011 to December 2013, 360 acute ischemic stroke patients related to NVAF were recruited. Patients were categorized into 2 groups based on the date (July 2012) of NOACs' availability. There were 184 patients recruited before July 2012, and whereas 176 patients after July 2012. Demographic data, interested factors, and the percentage of patient on OAC were compared.

One month after discharge, percentage of OAC utilization was significantly higher (29% versus 41%; $P = 0.022$) as well as effective anticoagulation (22.2% versus 80.6%; $P < 0.001$); warfarin utilization was significantly less (28.3% versus 11%; $P < 0.001$) after NOACs became available. Antiplatelet agent utilization was high in 2 groups (57% versus 52%; $P = 0.36$). Age (odd ratios [OR] 0.947; 95% confidence intervals [CI] 0.912–0.984; $P = 0.005$), Barthel index (OR 1.012; 95% CI 1.000–1.025; $P = 0.05$), and NOACs' availability (OR 1.857; 95% CI 1.086–3.175; $P = 0.024$) were the significant factors affecting the use of OAC.

A higher percentage of NVAF ischemic stroke patients returning for their 1-month follow-up were treated with NOACs than with warfarin. The use of antithrombotic therapy improved after NOACs became available. But, the majority of the patients were still received antiplatelet agent for emboli stroke prevention.

(*Medicine* 94(38):e1627)

Abbreviations: AF = atrial fibrillation, BI = Barthel index, INR = international normalized ratio, MRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Scale, NVAF = nonvalvular atrial fibrillation, OAC = oral anticoagulant, TTR = time in therapeutic range.

Editor: Gregory Bix.
Received: June 12, 2015; revised: August 24, 2015; accepted: August 26, 2015.
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The authors have no funding and conflicts of interest to disclose.
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ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001627

INTRODUCTION

Taiwan's Health Department reported that cerebrovascular disease remained the top 3 leading causes of death in recent 10 years. Among the stroke population, approximately 15% are related to atrial fibrillation (AF).[1] AF-related ischemic strokes are generally more disabling and more often fatal than other ischemic stroke subtypes, thus represents a major healthcare burden.[2] Stroke prevention is central to the management of AF patients. Fortunately, clinical trials had showed that emboli events can be significantly reduced by oral anticoagulant (OAC) for those patients at moderate or high risk of emboli events.[3–5] But, due to the disadvantages of warfarin, OAC utilization was suboptimal worldwide.[6,7] Recently, meta-analysis comparing novel OACs (NOACs) with warfarin had demonstrated that NOACs to be at least noninferior to warfarin in the prevention of emboli events in patients with nonvalvular AF (NVAF) and more importantly associated with significantly lower rate of intracranial hemorrhage.[8] Thus, it is assumed that the advent of NOACs would improve the use of OAC in NVAF patients. In this retrospective study, we tried to answer if the use of antithrombotic therapy in NVAF ischemic stroke patients improved after NOACs became available, as well as describe the factors associated the use of OACs in a real-world clinical practice.

PATIENTS AND METHODS

Study Population

This was a 1 center, retrospective medical chart review study. The study protocol was approved by the institutional ethics committee of Chang Gung Memorial Hospital, Taiwan.

From the data of stroke center registry between January 2011 and December 2013, we recruited acute cardiogenic emboli ischemic stroke patients according to Trial of Org 10172 in Acute Stroke Treatment criteria.[9] All patients had NVAF which was defined when there was absence of prosthetic mechanical heart valves or significant valve disease that warrant intervention. All patients were cared by neurologists during their hospitalization. Only patients who returned to neurologists' outpatient clinic in the study hospital 1 month after discharge were enrolled.

To compare the status of OAC utilization before and after NOACs became available in this study population, patients were categorized into 2 groups, patients in or not in NOACs era based on the date (July 2012) of NOACs' availability in the study hospital. Patients were also categorized into 2 groups, with and without OACs to explore factors significantly associated the use of OACs.

Demographic data including age, gender, length of stay in hospital, stroke risk factors, National Institutes of Health Stroke Scale (NIHSS) score at admission, Barthel index (BI) at discharge, modified Rankin scale (MRS) at discharge, type of antithrombotic agents, and past medical history were registered. CHA_2DS_2VASc score for stroke risk stratification according to

the European Society of Cardiology (ESC) guidelines for the management of AF was used.[5]

For patients not receiving OAC or any antithrombotic therapy, we reviewed the medical charts for the reasons of not prescribing antithrombotic therapy. Postulated reasons included gastrointestinal bleeding (active peptic ulcers or gastrointestinal tract bleeding), old cerebral hemorrhage, thrombocytopenia (platelet count < 100,000), anemia (hemoglobin < 10 g/dL or hemoglobin decreased > 2 g/dL during admission), gross hematuria, ischemic stroke with hemorrhagic transformation, and any ecchymosis.

Statistical Analysis

The data were analyzed by using SPSS 20.0 statistics software (SPSS Inc, Chicago, IL). We expressed the categorical data by number (n) and percentage (%). Continuous data were reported as mean and standard deviation. Nonparametric data were presented as median value and interquartile range (IQR). Chi-squared test was used for comparing categorical variables in 2 groups, and the independent-sample Student's *t*-test for the continuous variables. Mann–Whitney *U* tests were performed to compare associations between variables measured on a nonparametric scale, including length of stay in hospital, NIHSS score, BI, MRS, and CHA_2DS_2VASc score. Logistic regression analyses were performed to estimate the odds ratios along with 2-sided 95% confidence intervals for interested factors affecting the use of OAC. Multivariable logistic regression analysis was performed including all factors. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

During the study period, there were 405 NVAF ischemic stroke patients admitted to neurological ward, 24 patients died during their hospitalization, and 21 patients lost follow-up after discharge. In total, 360 patients fulfilled our inclusion criteria. A total of 184 patients comprised the group when only warfarin can be used and 176 patients were in NOACs era. 72% (259/360) of the patients had previously diagnosed NVAF and for those with CHA_2DS_2VASc score ≥ 2, only 8.8% (29/328) were given OAC and no patients had international normalized ratio (INR) within 2 to 3.

The demographic data of all subjects were summarized in Table 1. There were no statistically significant differences in age, gender, length of stay in hospital, NIHSS score, BI, MRS, and CHA_2DS_2VASc score in 2 groups.

Comparing the status of antithrombotic therapy 1 month after discharge, there was significantly less patients (14.1% versus 7.4%, $P = 0.04$) received no antithrombotic therapy in patients who were in NOACs era. The majority of all subjects (57% versus 52%, $P = 0.36$) still received antiplatelet agent in 2 groups. For those who were giving OAC, there was significantly (29% versus 41%, $P = 0.022$) more patients in NOACs era and also more patients (22.2% versus 80.6%, $P < 0.001$) received effective therapy (INR 2–3 for those receiving warfarin and those with NOACs). The percentage of patients with warfarin was significantly less (28% versus 11%, $P < 0.001$) in patients who were in NOACs era. The majority of patients in NOACs era were prescribed NOAC (Table 2).

Univariate analysis showed that patients who received OACs were significantly associated with age, gender, length of stay in hospital, NIHSS, MRS, BI, CHA_2DS_2VASc score, NOACs availability, and diabetic mellitus (Table 3). Table 4 shows the results of multivariable logistic regression analyses.

TABLE 1. Demographic Data of 360 NVAF Ischemic Stroke Patients

	Patients Not in NOACs Era n = 184	Patients in NOACs Era n = 176	*P* Value
Age, y	74+/−10	75+/−10	0.651
Age = 65–74	154 (84%)	142 (81%)	0.455
Age > = 75	97 (53%)	97 (55%)	0.648
Gender (male:female)	107:77 (58%:42%)	113:63 (64%:36%)	0.239
Length of stay, d	12.5 (6, 28)	11.0 (6, 31)	0.613
NIHSS	9 (5, 17)	7 (3, 15)	0.054
Barthel index	55 (10, 90)	50 (10, 95)	0.332
MRS	4 (1.75, 5)	4 (1, 5)	0.622
CHA_2DS_2VASc	4 (4, 6)	5 (4, 6)	0.789
CHF (LVEF <= 40%)	9 (5%)	3 (2%)	0.092
Hypertension	151 (82%)	149 (85%)	0.509
Diabetes mellitus	50 (27%)	62 (35%)	0.099
Ischemic stroke/TIA	81 (44%)	74 (42%)	0.705
History of vascular events	22 (12%)	17(10%)	0.483

CHF = congestive heart failure, CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥75, diabetes mellitus, old ischemic stroke/TIA, peripheral occlusive vascular disease, age 65–74, and sex category (female), LVEF = left ventricular ejection fraction, MRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, NOAC = novel oral anticoagulant, TIA = transient ischemic attack.

Factors that were identified to be significantly associated with the use of OAC included NOACs' availability, BI, and age.

For those patients not receiving OAC, 35% of the patient who were not in NOACs era and 41% in NOACs era, found no

TABLE 2. Types of Antithrombotic Therapy 1 month After Discharge

	Patients Not in NOACs Era n = 184	Patients in NOACs Era n = 176	*P* Value
Nil	26 (14.1%)	13 (7.4%)	0.04
Aspirin	70 (38.0%)	55 (31.3%)	0.18
Aggrenox	1 (0.5%)	1 (0.6%)	1
Clopidogrel	31 (16.8%)	31 (17.6%)	0.85
Cilostazol	0	1 (0.6%)	
Warfarin	52 (28.3%)	20 (11%)	<0.001
Dabigatran	0	36 (20.5%)	
Rivaroxaban	0	15 (8.5%)	
Aspirin + clopidogrel	1 (0.5%)	1 (0.6%)	1
Aspirin + warfarin	2 (1.1%)	0	
Clopidogrel + cilostazol	1 (0.5%)	1 (0.6%)	1
Aspirin + dipyridamole	0	1 (0.6%)	
Aspirin + dabigatran	0	1 (0.6%)	
Any antiplatelet agent	104 (57%)	91 (52%)	0.36
Any OACs	54 (29%)	72 (41%)	0.022
Effective OACs	12 (22.2%)	58 (80.6%)	<0.001
Warfarin (INR 2-3)	11 (21.6%)	6 (30%)	0.45

OACs = oral anticoagulants.

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TABLE 3. Univariate Analysis of Interested Factors in Patients With/Without OACs

	Without OAC n = 234	With OAC n = 126	*P* Value
Age	77+/−10	70+/−10	<0.001
Age = 65–74	206 (88%)	90 (71.4%)	<0.001
Age >= 75	152 (65%)	42 (33.3%)	<0.001
Gender (male:female)	103:102 (56%:44%)	88:38 (70%:30%)	0.01
Length of stay, days	14 (7, 29)	9.5 (6.25, 25)	0.03
NIHSS	10 (4.25, 19)	5 (3, 11)	<0.001
MRS	4 (3, 5)	3 (1, 4)	<0.001
Barthel index	25 (0, 80)	70 (45, 100)	<0.001
CHA_2DS_2VASc	5 (4, 6)	5 (3.5,5.5)	<0.001
NOACs era	104 (44.4%)	72 (57.1%)	0.02
CHF (LVEF <= 40%)	6 (2.6%)	6 (4.8%)	0.2
Hypertension	201 (85.9%)	99 (78.6%)	0.08
Diabetes mellitus	82 (35%)	30 (23.8%)	0.03
Ischemic stroke/TIA	107 (45.7%)	48 (38.1%)	0.16
History of vascular events	29 (12.4%)	10(7.9%)	0.19

CHF = congestive heart failure, CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥75, diabetes mellitus, old ischemic stroke/TIA, peripheral occlusive vascular disease, age 65–74, and sex category (female), LVEF = left ventricular ejection fraction, MRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, NOAC = novel oral anticoagulant, TIA = transient ischemic attack.

contraindications of OACs' utilization. Two groups did not differ in terms of the postulated reasons (Table 5). Gastrointestinal bleeding, thrombocytopenia, and unknown reason were the significant factors associated with no antithrombotic therapy comparing with those receiving only 1 antiplatelet agent (Table 6).

DISCUSSION

This hospital-based study demonstrated that underprescription or underdose of OAC significantly improved after NOACs became available and as well as effective treatment.

TABLE 4. Multivariate Logistic Regression Analysis of Factors Potentially Associated With the Use of Oral Anticoagulation Therapy

	OR	95% CI	*P* Value
Age	0.947	0.912–0.984	0.005
age = 65–74	1.038	0.429–2.512	0.934
age >= 75	0.462	0.218–0.977	0.043
Gender	0.704	0.340–1.457	0.344
length of stay	1.019	1.000–1.039	0.055
NIHSS	1.01	0.947–1.078	0.757
MRS	0.949	0.838–1.075	0.414
Barthel index	1.012	1.000–1.025	0.05
CHA_2DS_2VASc	0.912	0.632–1.315	0.621
NOACs era	1.857	1.086–3.175	0.024
diabetes mellitus	0.589	0.287–1.209	0.149

CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥75, diabetes mellitus, old ischemic stroke/TIA, peripheral occlusive vascular disease, age 65–74, and sex category (female), LVEF = left ventricular ejection fraction, MRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, NOAC = novel oral anticoagulant, TIA = transient ischemic attack.

TABLE 5. Postulated Reasons for no Anticoagulant Therapy

	Patients Not in NOACs Era n = 130	Patients in NOACs Era n = 104	*P* Value
Gastrointestinal bleeding	27 (20.8)	33 (31.7%)	0.06
Old cerebral hemorrhage	8 (6.2%)	5 (4.8%)	0.66
Thrombocytopenia	9 (6.9%)	0	
Anemia	8 (6.2%)	7 (6.7%)	0.86
Gross hematuria	6 (4.6%)	3 (2.9%)	0.74
Hemorrhagic transformation	25 (19.2%)	13 (12.5%)	0.17
Ecchymosis	1 (0.8%)	0	
Unknown	46 (35%)	43 (41%)	0.35

Patients with ischemic stroke related to NVAF were almost 2-fold more likely to be given OAC and mainly NOACs. On the other hand, patients with older age and more severe stroke were less likely to receive OAC.

ESC guidelines recommend OAC using well-controlled adjusted dose vitamin K antagonists (eg, warfarin) or NOACs for patients with AF and ≥1 stroke risk factor(s).[5] The ESC guidelines also recommend the use of the CHA_2DS_2VASc score for stroke risk assessment. Effective stroke prevention with OAC or NOACs can be offered to AF patients with ≥1 stroke risk factor(s). All subjects in our study were high risk for recurrent embolic ischemic stroke, therefore recommended using OAC. In NOACs era, 29% of the patients received warfarin but INR within 2 to 3 was only 21.6%. This mirrored the result of Taiwan Stroke Registry study, 28% of cardiogenic embolic stroke patients received warfarin after discharge.[10] Three other Taiwan's studies showed that the prescription rate of warfarin was even less, ranging from 11% to 25%, and 1 reported only 22.9% of patients received warfarin had INR 2 to 3.[11–13] This situation was better in western countries but still suboptimal, one-third to one-half of candidates eligible for warfarin use left untreated.[14,15] Similar with our study population (ischemic stroke/TIA), several studies reported that percentage of OAC treatment was below 60%.[6] Data from the United States demonstrated that there were up to 80% patients spending most of their time in the sub- or supratherapeutic range

TABLE 6. Postulated Reasons for no Antithrombotic Therapy

	Patients Without Antithrombotic Therapy n = 39	Patients With Only Antiplatelet Agent n = 195	*P* Value
Gastrointestinal bleeding	16 (41.0%)	44 (22.6%)	0.016
Old cerebral hemorrhage	1 (2.6%)	12 (6.2%)	0.372
Thrombocytopenia	4 (10.3%)	5 (2.6%)	0.023
Anemia	3 (7.7%)	12 (6.2%)	0.72
Gross hematuria	2 (5.1%)	7 (3.6%)	0.648
Hemorrhagic transformation	10 (25.6%)	28 (14.4%)	0.081
Ecchymosis	1	0	
Unknown	2 (5.1%)	87 (44.6%)	<0.001

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when using warfarin.[15] In our study, only about 30% of patients receiving warfarin had INR 2 to 3.

The low prescription rate of warfarin in clinical practice results from its many disadvantages, including unpredictable response, narrow therapeutic window requiring routine coagulation monitoring and therefore frequent dose adjustment, slow onset/offset of action, numerous drug–drug or drug–food interactions, warfarin resistance, and finally the concerns of bleeding complications. Demographic and genetic differences exist between Asian populations and other ethnic groups, which may affect the use and dosing of OAC. Data from 2 studies have shown East Asian populations to be more sensitive to warfarin than Indian and white populations.[16,17] Dosage of warfarin had been shown to be lower in Chinese versus White population to obtain same coagulation effect.[18] Warfarin may also interact with herbal remedies which are common in Chinese.[19] The incidence of intracranial hemorrhage was increased in patients of Asian ethnicity who receive warfarin compared with other ethnic groups.[20,21] As a result, OACs are suboptimal used within this region.[10–13,22] Recently, a simple score (SAMe-TT2R2) which has been validated can predict poor INR control and aid decision-making by identifying those patients with AF who require additional interventions to achieve acceptable anticoagulation control (SAMe-TT2R2 score $>=2$), among the predicting factors, race which is nonwhite score 2 and then would predict poor INR control.[23] To be effective in embolic event prevention using warfarin, time in therapeutic range should be better greater than 60%, but Asian data from NOACs' clinical trials, the time in therapeutic range was less than 60% in most of the patients.[24–26]

In recent years, the availability of NOACs (dabigatran, rivaroxaban, apixaban, and endoxaban) for the prevention of thromboembolism has been anticipated. NOACs have more pharmacologic advantages, such as rapid onset/offset of action, predictable pharmacokinetics, less drug interactions, and a wide therapeutic window thereby facilitating fixed dosing in adult.[27] The results of RE-LY, ROCKET-AF, ARISTOLE, and ENGAGE AF-TIMI 48 trials had proved that NOACs offered at least noninferior stroke protection as compared with warfarin and a significant reduction in intracranial hemorrhage.[8]

The Global Anticoagulant Registry in the FIELD, an observational worldwide study on NVAF collected at the end of the warfarin-only era during 2009 to 2011, warfarin was prescribed in 45% of AF patients, whereas the NOACs in 4.5% of patients overall.[28] In our study, the percentage of OAC prescription was significantly higher in NOACs era. Most of our patients received NOACs instead of warfarin. This favorable change in OAC treatment was mainly the impact of the advent of NOACs.

For all antithrombotic therapy, more than half of the subjects were prescribed with antiplatelet agents. Those not receiving OAC, 35% of the patient not in NOACs era and 41% in NOACs era found no reason for no OAC treatment. But, older age was the significant factor associated with not using OAC. Knowing that the efficacy of aspirin declines at aged >70 years while the risk of bleeding increases, this observation was interesting. Studies have found that aged patients were less likely to receive anticoagulation therapy than younger patients.[29,30] A retrospective review of hospital admissions for ischemic stroke in patients with AF found that the percentage of patients receiving OAC treatment declined as age advanced, 75% of patients treated with OAC at aged <75 years and dropped to 33% when aged >85 years.[30]

The efficacy of anticoagulant treatment crossed all aged patients with AF. Especially those with advanced age showed in a study after analyzing almost 9000 patients with AF, the benefit of stroke prevention by OAC was even more pronounced.[31] Beyond considering advanced age as a contraindication to warfarin, fear of elderly patients to have more bleeding complications is a frequently cited reason why clinicians do not prescribe anticoagulant therapy to older patients.[32] However, The Birmingham Atrial Fibrillation Treatment of the Aged trial demonstrated that there was no difference in major bleeding events comparing patients treated with warfarin and patients treated with aspirin while showing the superiority of warfarin over aspirin in reducing the risk of ischemic stroke in patients with AF aged >75 years.[33]

In a recent review article done by Yates focused on NOACs for stroke prevention in older patients with AF had also concluded that NOACs are suitable alternatives to warfarin in preventing embolic events based on the benefits of these agents in this particular population.[34] But, properties such as individual drug metabolism and route of elimination should be considered when older patients especially those with chronic kidney disease were given these agents. The reduction in stroke risk must be balanced against the increased risk of bleeding and currently there is no antidote existed to reverse the anticoagulant effect of NOACs.[34]

Another significant factor associated with no OAC was stroke severity as measured by BI. This may be attributed to the consideration of the total dependency of daily activities, high risk of falling accidents, and tendency to bleed. Besides, previous clinical trials of stroke prevention in AF excluded patients with severe stroke, therefore effect and safety of OAC in this subgroup was not well understood. Considering our limited medical resources and the insurance reimbursement policy, these might partly explained why these patients were not giving OAC treatment.

Among the postulated reasons of not giving OAC, peptic ulcers or gastrointestinal tract bleeding comprised the majority followed by ischemic stroke with hemorrhagic transformation, anemia, history of old intracranial hemorrhage, gross hematuria, thrombocytopenia, and any ecchymosis. No significant difference was found but when comparing patients receiving only 1 antiplatelet agent and those with no antithrombotic therapy, patient with gastrointestinal bleeding and thrombocytopenia were likely to receive no treatment, in contrary, the percentage of unknown reason was only 5% in patients with no treatment compared to 44.6% in patients with antiplatelet agent. The results implied that doctors still considered antiplatelet agent was safer than OAC (either warfarin or NOACs) in this real-world clinical practice. Our observational data were similar to the recent report from England, 41% of the patients without reasons for not using warfarin when eligible.[35]

There were limitations in our study. First, the results were from small numbers of subjects in a single hospital and medical center, and it may not apply to whole AF population in Taiwan. Second, we only discussed about anticoagulation therapy of secondary prevention for stroke, but not disclose the clinical practice of primary prevention in AF patients with a moderate to high risk of stroke. Third, some important issues such as the impact on clinical outcome or dropout rate between the users of warfarin and NOACs were not explored in the study, which warrants further follow-up.

CONCLUSIONS

NOACs improved the use of antithrombotic therapy in NVAF ischemic stroke patients for further embolic events prevention but age and stroke severity hindered the use of OAC. Although the percentage of patients with effective

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anticoagulation treatment increased, it is apparently more room for improvement. Most of the patients still received antiplatelet agent for further stroke prevention.

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