General Cardiology

Low-Intensity Warfarin Therapy for the Prevention of Stroke in Patients with High-Risk Nonvalvular Atrial Fibrillation

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Background: The aim of this study was to determine whether warfarin therapy with the target of INR < 2.0 (low-intensity) could be as effective as that with INR ≥ 2.0 (conventional-intensity) in stroke prevention for Taiwanese patients with high-risk nonvalvular atrial fibrillation (AF) while simultaneously reducing the risk of bleeding.

Methods: We conducted a retrospective study on patients with high-risk nonvalvular AF. The clinical outcomes of patients receiving different antithrombitic therapies and the efficacy and safety of two different intensities of warfarin therapy with a target INR of < 2.0 or a target INR of ≥ 2.0 were compared.

Results: A total of 815 patients were enrolled consecutively, and were followed for an average of 2.5 years. Among them, 226 patients (28%) received warfarin therapy and 512 (63%), antiplatelet therapy whereas, 77 (9%) of the patients received none of the antithrombotic therapy. The overall event rates were 3.6 per 100 person-years with warfarin, 6.0 per 100 person-years with antiplatelet therapy, and 10.1 per 100 person-years with no treatment (p = 0.013). Although there was no significant difference in the frequencies of ischemic stroke between the two different intensities of warfarin therapy, noticeably more bleeding episodes occurred to the conventional-intensity group than the low-intensity one.

Conclusion: The results of our study clearly demonstrated how Taiwanese patients with high-risk nonvalvular AF benefited from warfarin therapy in reducing adverse clinical outcomes; however, the low-intensity treatment was proved to be as effective as that of conventional-intensity but less likely to cause any bleeding during the treatment.

Key Words: Bleeding • Nonvalvular atrial fibrillation • Stroke prevention • Warfarin

INTRODUCTION

Current guidelines for the management of patients with atrial fibrillation recommend that all patients with AF should receive long-term anticoagulant therapy with warfarin with a target International Normalized Ratio (INR) of 2.0 to 3.0 unless they are younger than 65 years old and have none of the risk factors for stroke, or unless there is a major contraindication to the use of warfarin.[1-3]

In Asian people, warfarin therapy with a target INR of 2.0 to 3.0 in preventing stroke for high-risk patients with nonvalvular AF is associated with a substantial risk of bleeding.[10-12] Several clinical trials demonstrated that lower-intensity anticoagulant therapy (INR < 2.5) is as effective as but may be safer than conventional intensity anticoagulant therapy in Asian patients.[13-15]

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To assess the real-world practice pattern and appropriateness of antithrombotic use in Taiwanese patients with nonvalvular AF at high risk of stroke and to determine whether low-intensity warfarin treatment is as effective as conventional-intensity warfarin recommended by well-established Western guidelines, we undertook a retrospective study (1) to compare the clinical outcomes among patients receiving different antithrombotic therapies for high-risk nonvalvular AF and (2) to compare long-term warfarin therapy targeted to an INR of < 2.0 with therapy targeted to an INR of ≥ 2.0. Our hypothesis was that low-intensity warfarin would be as effective as conventional-intensity therapy in preventing stroke while reducing the risk of any bleeding.

METHODS

Study patients

Between 2001 and 2006, 1052 consecutive patients with nonvalvular AF identified in the Cardiology Section of the Cheng-Hsin General Hospital were enrolled in an AF registry. Nonvalvular AF was identified on the basis of both physician-assigned diagnoses of AF during a routine visit (international Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM], code 427.31) and electrocardiographic databases. Patient who took only one antithrombotic therapy (anticoagulant, antiplatelet or no treatment) during follow-up period were included.

Patients with diagnosed mitral stenosis, or heart-valve repair or replacement, transient perioperative AF, or recent hyperthyroidism were excluded. For the present study, we excluded low-risk patients who had no risk factors (lone AF) and those younger than 75 years. Patients were also excluded if they had a clinically significant bleeding diathesis; a history of intracranial hemorrhage, or gastrointestinal bleeding within the previous three months; a contraindication to warfarin; malignancy; or severe renal impairment defined as a serum creatinine level of > 3 mg/dl. Only patients with complete INR records were included. Therefore, the final study cohort consisted of 815 patients. The study was approved by the local institutional review board. Because of the retrospective nature of the study, the requirement for informed consent was waived.

Antithrombotic treatment

The administration of antithrombotic therapy in this study was at the discretion of the treating physician. Patients were classified into three groups: patients receiving continuous warfarin therapy (n = 226, 28%), patients receiving antiplatelet therapy (n = 512, 63%), and patients receiving no antithrombotic therapy therapy (n = 77, 9%). The compliance of antithrombotic therapy was assessed through chart review and telephone contacts. Commercially available antiplatelet agents in this study included aspirin (100 mg-325 mg), clopidogrel (75 mg), and ticlopidine (200 mg).

For patients receiving warfarin therapy, the mean INR was calculated by multiplying the INR value by the duration from the date of INR to the next INR test date, and then dividing the sum by the total duration of therapy, according to the method described by previous reports.[15,17] The INR values at the time of events were also recorded. If the INR had not been measured on the day of the episode, the reported INR value was the value at the last scheduled visit before diagnosis of the episode.

Data collection

Information on clinical variables, obtained from medical charts, included age, gender, type and duration of AF, a history of ischemic stroke; a history of cerebrovascular disease, defined by known carotid or vertebrobasilar atherosclerosis or prior carotid endarterectomy; congestive heart failure; coronary artery disease; peripheral artery disease; diabetes mellitus; and hypertension. Clinical event data during a median follow-up period of 2.5 years were collected by cardiology nurses and research coordinators through patient interviews, chart reviews and serial telephone contacts.

The primary outcome measure with respect to efficacy was cardiovascular death, an episode of nonfatal ischemic stroke or systemic thromboembolism (myocardial infarction, peripheral arterial thrombosis). A validated ischemic stroke was defined as a neurologic deficit of sudden onset that persisted for more than 24 hours, corresponded to a vascular territory in the absence of primary hemorrhage, and was not explained by other causes (e.g., trauma, infection, or vasculitis). The primary outcome measure with respect to safety was any bleeding (combined major and minor bleeding). Major bleeding was defined as a fatal hemorrhage, an intra-

cranial bleeding, a clinically overt hemorrhage associated with a decrease in the hemoglobin level of at least 20 g per liter, a need for the transfusion, or a bleed requiring hospitalization. Minor bleeding referred to other bleeding, not requiring transfusion or causing hemodynamic compromise.

Finally, we combined primary outcome of efficacy and safety as our clinical outcomes.

Statistical analysis

Continuous variables were expressed as mean ± SD. Categorical data were displayed as frequencies and percentages. Patient demographics, risk factors for stroke, and the primary outcomes measure with respect to efficacy and safety were compared among the three antithrombotic therapy groups with one-way ANOVA test.

Kaplan-Meier estimation and Cox proportional hazards modeling were used respectively for unadjusted and adjusted survival analysis. Kaplan-Meier analyses of cumulative event-free rates were constructed for different antithrombotic medication groups. The differences between event-free curves were tested by a log-rank test. In multivariable Cox proportional hazards analyses, the association between the use of warfarin therapy and clinical outcomes was examined. The models were adjusted for variables that were considered to be associated with adverse clinical events, including age, gender, type and duration of AF, and the presence of coronary artery disease, peripheral artery disease, hypertension, diabetes mellitus, previous stroke or transient ischemic attack, and heart failure. Data are reported as the estimated hazard ratios and 95% confidence intervals (CI).

All statistical analyses were performed using SAS statistical software (SAS Institute location). All values are 2 tailed, and a p value < 0.05 was considered statistically significant.

RESULTS

Baseline clinical characteristics

The baseline characteristics of the study patients for the three antithrombotic medication groups are shown in Table 1.

Of the 815 patients, 226 (28%) were taking warfarin, 512 (63%) were taking antiplatelet agent, and 77 (9%) were not taking any antithrombotic drug.

Prognosis

The primary outcome measures with respect to effi-

Table 1. Baseline characteristics of the study patients for the three antithrombotic medication groups

	Warfarin n = 226 (28%)	Antiplatelet n = 512 (63%)	No treatment n = 77 (9%)	p value
Age (yr)	71.5 ± 11.7	75.2 ± 10.6	76.6 ± 11.5	< 0.001
Age > 75 y/o, n (%)	110 (48.7%)	318 (62.1%)	51 (66.2%)	0.001
Male gender, n (%)	150 (66.4%)	339 (66.2%)	43 (55.88%)	0.188
Type of atrial fibrillation				< 0.001
Permanent, n (%)	127 (60.2%)	197 (40.8%)	26 (40.0%)	
Persistent, n (%)	5 (2.4%)	14 (2.9%)	2 (3.1%)	
Paroxysmal, n (%)	79 (37.4%)	272 (56.3%)	37 (56.9%)	
Duration of atrial fibrillation				< 0.001
< 6 months, n (%)	82 (40.0%)	281 (59.0%)	39 (60.0%)	
6-2 years, n (%)	21 (10.2%)	27 (5.7%)	3 (4.7%)	
> 2 years, n (%)	102 (49.8%)	168 (35.3%)	22 (34.4%)	
Prior stroke/TIA, n (%)	26 (11.5%)	50 (9.8%)	7 (9.1%)	0.730
Heart failure, n (%)	54 (23.9%)	103 (20.1%)	29 (37.7%)	0.003
CAD, n (%)	56 (24.8%)	181 (35.4%)	10 (13.0%)	< 0.001
PAD, n (%)	8 (3.5%)	13 (2.5%)	1 (1.3%)	0.540
Diabetes mellitus, n (%)	64 (28.3%)	161 (31.4%)	19 (24.7%)	0.396
Hypertension, n (%)	159 (70.4%)	348 (68%)	46 (59.7%)	0.226

CAD, coronary artery disease; PAD, Peripheral artery disease; TIA, transient ischemic attack.

cacy and safety of the study patients for the three antithrombotic medication groups are presented in Table 2. The median follow-up period was 2.5 years (0.9 to 4.3 years, 25th to 75th percentiles).

There was a 15% (124 of 815) overall event rate in the study population. The overall event rates were 3.6 per 100 person-years with warfarin, 6.0 per 100 person-years with antiplatelet therapy, and 10.1 per 100 person-years with no treatment (p = 0.013), while the rates of any bleeding were similar among the three groups (p = 0.196). The incidence of cardiovascular death was also significantly lower in the warfarin group compared to the other two groups (p = 0.029). During follow-up, no significant differences among the three groups were observed with respect to the incidence of the incidences of non-fatal ischemic stroke and systemic thromboembolism.

Kaplan-Meier analyses of cumulative event-free rates were further performed with the AF patients being stratified into three groups on the basis of which antithrombotic therapy was administered. (see Figure 1) The difference in event-free survival curves among the three groups was statistically significant (p = 0.001, log-rank test).

In multivariable Cox proportional hazards analyses, the association between warfarin use and clinical outcomes was examined. After adjustment for variables that were considered to be associated with adverse clinical events, patients not receiving warfarin therapy had a significant increase in the risk of adverse clinical events [hazard ratio (HR) 2.14, 95% CI 1.35 to 3.40, p = 0.001] (Table 3). In this model, age ≥ 75 y/o (HR 1.87, 95% CI 1.20 to 2.93, p = 0.006), hypertension (HR 1.88, 95% CI 1.18 to 2.99, p = 0.008) and presence of previous stroke (HR 4.86, 95% CI 3.07 to 7.69, p < 0.001), heart failure (HR 2.23, 95% CI 1.43 to 3.46, p < 0.001), and peripheral artery disease (HR 2.93, 95% CI 1.24 to 6.94, p = 0.014) were also significantly related to clinical outcomes.

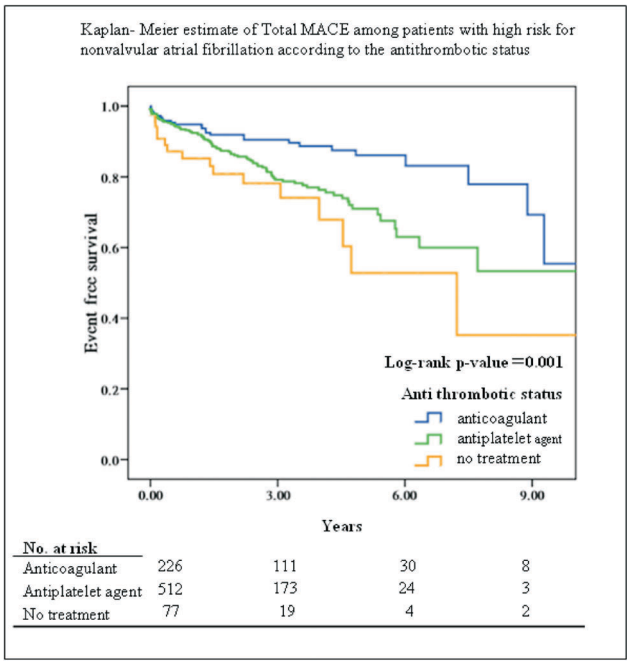

Figure 1. *Kaplan-Meier analyses of cumulative event-free rates were performed with the AF patients being stratified into three groups on the basis of which antithrombotic therapy was administered. The difference in event-free survival curves among the three groups receiving different antithrombotic therapy was statistically significant (p = 0.001, log-rank test).*

Table 2. The primary outcome measure with respect to efficacy and safety of the study patients for the three antithrombotic medication groups

	Warfarin n = 226 (28%)	Antiplatelet n = 512 (63%)	No treatment n = 77 (9%)	p value
Follow-up (person-years)	896	1177	139	
Overall event rate n (n/100 person-years)	36 (4.0)	73 (6.2)	15 (10.8)	0.013
Cardiovascular death	2 (0.3)	16 (1.4)	5 (3.6)	0.029
Non-fatal ischemic				
Stroke	26 (2.9)	43 (3.7)	8 (5.8)	0.395
Other systemic thromboembolism	4 (0.4)	11 (0.9)	1 (0.7)	0.856
Any bleeding				0.196
Major bleeding	4 (0.4)	3 (0.2)	1(0.7)	
Minor bleeding	6 (0.6)	6 (0.5)	0 (0)	

Intensity of anticoagulation and clinical outcomes

The AF patients who were taking warfarin were further stratified into two groups according to whether a target INR was < 2.0 (median 1.4, 25th to 75th percentiles 1.12-1.7) or ≥ 2.0 (median 2.5, 25th to 75th percentiles 2.2-2.9). Kaplan-Meier analyses of cumulative event-free rates were constructed for the four antithrombotic medication groups, and these groups were compared with use of the log-rank test. Although there was no significant difference in the frequency of ischemic stroke between the two different intensities of warfarin therapy, the difference in event-free survival curves of the two warfarin groups were significantly better than those of the other two antithbombotic medication groups (Figure 2A, log-rank p = 0.013). On the other hand, patients receiving conventional-intensity warfarin experienced significantly more bleeding episodes than those who receiving low-intensity warfarin (Figure 2B, log-rank p < 0.001). In multivariable Cox proportional hazards analyses, the association between different INR level and clinical outcomes was examined. After adjustment for variables that were considered to be associated with adverse clinical events, patients who received warfarin didn't have significant increase in the risk of adverse clinical events between INR ≥ 2.0 and INR < 2 (hazard ratio [HR] 1.93, 95% CI 0.80-4.70, p = 0.146) (Table 4). In history of peripheral arterial disease (HR 7.14, 95% CI 1.60-31.85, p = 0.010) and presence of previous stroke (HR 4.72, 95% CI 1.49-14.99, p = 0.008) were also significantly related to clinical outcomes.

Table 3. Independent predictors of adverse clinical outcomes during follow-up: multivariate Cox proportional hazard analysis

Risk factor	Hazard ratio (95% CI)	p value
Age ≥ 75 y/o	1.87 (1.20-2.93)	0.006
Male gender	0.88 (0.59-1.31)	0.524
Type of AF	0.93 (0.43-2.00)	0.847
Duration of AF	1.06 (0.49-2.29)	0.884
Prior stroke or TIA	4.86 (3.07-7.69)	< 0.001
Heart failure	2.23 (1.43-3.46)	< 0.001
Coronary artery disease	1.23 (0.82-1.84)	0.311
Peripheral artery disease	2.93 (1.24-6.94)	0.014
Diabetes mellitus	1.29 (0.86-1.93)	0.216
Hypertension	1.88 (1.18-2.99)	0.008
No warfarin use	2.14 (1.35-3.40)	0.001

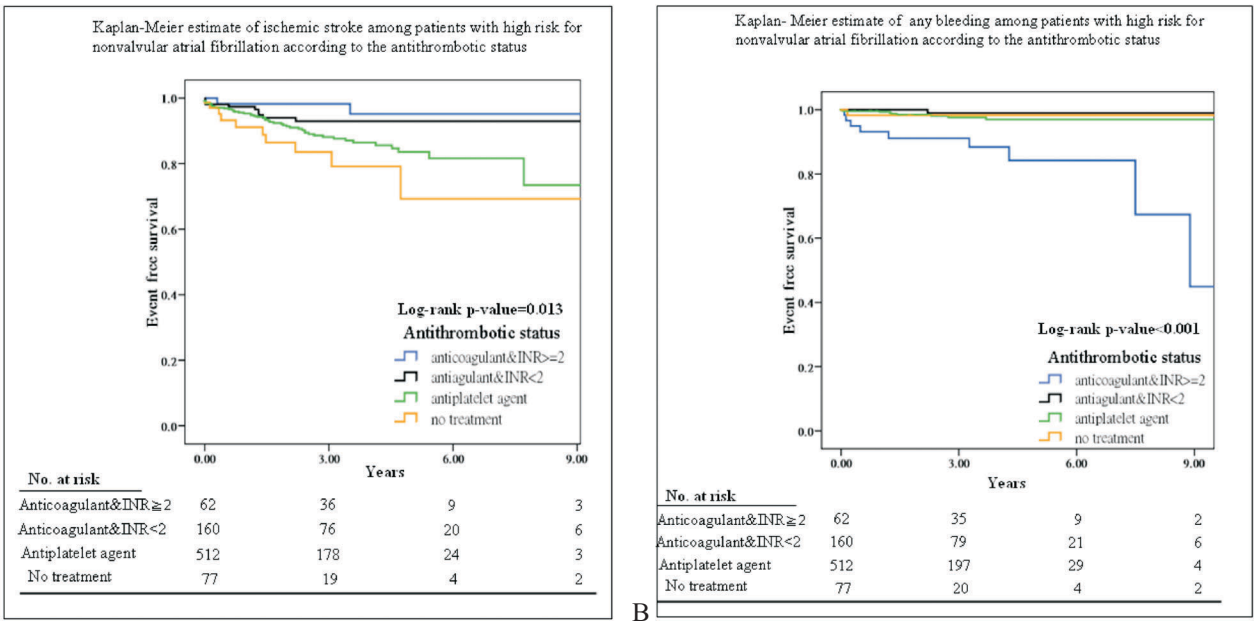

Figure 2. *The AF patients who were taking warfarin were further stratified into two groups according to whether a target INR was < 2.0 or ≥ 2.0. Kaplan-Meier analyses of cumulative event-free rates were constructed for the four antithrombotic medication groups. Although there was no significant difference in the frequency of ischemic stroke between the two different intensities of warfarin therapy (A), patients receiving conventional-intensity warfarin experienced significantly more bleeding episodes than those who receiving low-intensity warfarin (B).*

Table 4. Independent predictors of adverse clinical outcomes during follow-up between INR ≧ 2 and INR < 2: multivariate Cox proportional hazard analysis (Event = Total Mace)

Variable	Hazard ratio (95% CI)	p-value
Sex	0.52 (0.21-1.26)	0.147
Age	1.02 (0.95-1.09)	0.621
AF type	3.77 (0.22-64.03)	0.359
Duration of AF	6.81 (0.39-118.97)	0.189
PAD	7.14 (1.60-31.85)	0.010
DM	1.03 (0.38-2.76)	0.958
Angiographic CAD	2.24 (0.89-5.61)	0.086
HTN	2.70 (0.75-9.63)	0.127
Age ≧ 75 y/o	0.89 (0.22-3.62)	0.867
Stroke or TIA	4.72 (1.49-14.99)	0.008
CHF	1.42 (0.50-4.01)	0.506
INR Group	1.93 (0.80-4.70)	0.146

DISCUSSION

In the present study, we clearly demonstrated the benefits of warfarin therapy in patients with high-risk nonvalvular AF for reducing cardiovascular mortality and overall event rate, indicating that warfarin therapy is highly effective at stroke prevention in those AF and can provided survival benefit. These findings are consistent with those of previous reports.[4-6]

Although warfarin is effective at preventing strokes in patients with AF, it has several limitations. The complex pharmacokinetics and narrow therapeutic window of warfarin make its long-term use in clinical practice challenging and probably contribute to its underutilization.[7,8] The major concern with the use of warfarin is the risk of bleeding.[9] Patients taking conventional-intensity warfarin were more likely to experience bleeding, particularly Asian patients.[10-12] Even through long-term treatment with warfarin at a modest level of anticoagulation (a mean INR of 1.9) in a Chinese population did not seem to be counterbalanced by more frequent thromboemolic complications, bleeding events remains a concern.[17] In Chinese patients, there is a general perception that warfarin is less commonly used since many local physicians question whether the benefits and risks shown in major antithrombotic therapy trials in Western populations can equally apply to Chinese populations. Therefore, it is not surprising that only 28% of patients in the present study received warfarin and the mean age of the warfarin group in our study was significantly younger than those of the other two antithrombotic treatment groups.

To overcome the problem with warfarin and minimize the risk of bleeding, new strategies have been developed, however, warfarin anticoagulation remains the mainstay of therapy for stroke prevention in AF. Since a racial difference in the response to warfarin[25,26] and a racial difference in stroke subtypes between Taiwanese and Caucasian patients with stroke[27-29] does exist, long-term anticoagulation therapy may be less effective in preventing stroke but increase the risk of bleeding risk in non-Caucasian population.[4,5,27-29] Therefore a lower-intensity warfarin therapy may be a reasonable and safer approach for Asian patients with AF.

Given that an INR of 1.5 to 2.7 reduced the level of activity of the hemostatic system by 70%,[30] that low-intensity of warfarin is still highly effective in treating left atrial thrombus[31] and in preventing stoke in patients with non-rheumatic AF and may be safer than conventional-intensity warfarin in Asian patients,[13,14,17,32-34] and that low-intensity warfarin (INR < 2) was not associated with increased thromboembolic events in Taiwanese patients,[16] we hypothesize that a target INR of < 2.0 may be an appropriate goal INR. In the present study, we did find that low-intensity warfarin was as effective as conventional-intensity therapy in preventing stroke while reducing the risk of any bleeding.

Study limitations

First, the current study was limited by its use of a historical cohort. Many new guidelines have since been published, influencing the prescribing trends. Furthermore, the study population may not be representative of other Chinese populations. Second, the present study was based on diagnostic coding; therefore, that coding may be incomplete and imprecise. In addition, most of the clinical information obtained in the present study is based on medical records. Although we have tried our best to minimize the impact of inhomogeneous information in the medical records, it is likely that we have somewhat underestimated the presence of some risk factors and comorbid diseases affecting the indications for warfarin and clinical outcomes. Third, it remains possible that some patients who had a minor stroke either did

not seek medical care or were treated as out-patients. Finally, the present study was an observational assessment of the effect of antithrombotic treatment. Administration of antithrombotic therapy in our study was neither prospective nor randomized, but was at the discretion of the treating physician. Despite careful use of models to adjust for potential factors that may affect clinical outcomes, immeasurable factors may still exist. Physician bias may have influenced patient selection, type and dose of antithrombotic medication. Therefore, additional studies are needed to determine the generalizability of our findings.

CONCLUSION

In summary, our study demonstrated the benefits of warfarin therapy in patients with high-risk nonvalvular AF for reducing cardiovascular mortality and overall adverse event rate. Although the results support the use of warfarin in those patients, warfarin therapy was underutilized in the study patients (28%). Furthermore, low-intensity warfarin being as effective as conventional-intensity warfarin while reducing the risk of any bleeding need to be confirmed in further and larger randomized controlled trial.

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