Accumulation of Risk Factors Increases Risk of Thromboembolic Events in Patients With Nonvalvular Atrial Fibrillation

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Background Accumulation of risk factors could increase thromboembolic event rates in patients with nonvalvular atrial fibrillation (NVAF). To validate this hypothesis, a post hoc analysis was performed to determine the relationship of risk levels and thromboembolic events in patients with NVAF from our previous prospective study.

Methods and Results Risk levels were quantified using the CHADS2 index in 509 patients with NVAF (66.3±10.3 years old). One point each was given for patients with advanced age (≥75 years), hypertension, congestive heart failure, and diabetes mellitus, and 2 points, to those with prior ischemic stroke or transient ischemic attack. Patients with a CHADS2 score of 0 were classified as low risk, 1 to 2 a moderate risk and 3 or more were high risk. Because hypertrophic cardiomyopathy had emerged as an independent risk factor for thromboembolism, the original CHADS2 score was modified by adding 1 point to patients with hypertrophic cardiomyopathy. Warfarin was given to 263 patients (mean international normalized ratio (INR) at enrollment, 1.86), antiplatelets (aspirin or ticlopidine) to 163 patients and no antithrombotic therapy to 83. During a mean follow-up period of 2 years, 31 thromboembolic events occurred. As the risk level (modified CHADS2 score) increased, the event rate increased for both the patient groups receiving warfarin ($p=0.035$) and those not receiving warfarin ($p=0.048$). When a thromboembolic event occurred in patients who had been treated with warfarin, the mean INR level was 1.41. Twelve (75%) of 16 patients complicated with thromboembolism during warfarin treatment had INR levels below the optimal levels (1.6–2.6) for Japanese patients.

Conclusion Accumulation of risk factors could increase risk of thromboembolic events in patients with NVAF. Adherence to the guidelines for anticoagulation therapy is recommended. (Circ J 2006; 70: 651–656)

Key Words: Anticoagulation; Atrial fibrillation; INR level; Thromboembolic events

It has been well established that adjusted doses of warfarin are effective in reducing the incidence of thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF).¹ Therefore, an objective scheme to stratify the risk of thromboembolism in patients with NVAF and to select optimal antithrombotic therapy needs to be established.² Based on the previous prospective studies, some clinical factors have emerged as risk factors for thromboembolism,¹ and a new stroke risk index, CHADS2, is reported to quantify the risk of stroke accurately for patients with NVAF.³

In the current guidelines for some Western countries,² the optimal warfarin anticoagulation intensity to prevent thromboembolic events ranges from 2 to 3 as expressed by the international normalized ratio (INR) of prothrombin time. However, prospective, secondary prevention trials in

Japan indicated that INR levels of 1.6 to 2.6 were optimal for Japanese patients with NVAF.⁴ These figures were a little lower than those reported in the Western countries.² Although warfarin is effective in preventing thromboembolic events in patients with NVAF, some patients are likely to suffer from ischemic stroke even when treated with warfarin. Recent clinical trials clearly demonstrated that insufficient anticoagulation levels could contribute to thromboembolic events in patients with NVAF receiving warfarin for anticoagulation.^{5,6} Therefore, we performed post hoc analyses to determine whether the accumulation of risk factors as estimated with CHADS2 index were related to a higher risk of thromboembolism in patients with NVAF. Additionally, INR levels at the time of thromboembolic episodes in those receiving warfarin were determined.

Methods

Study Population

The study population of our prospective study has been reported elsewhere.^{7,8} Briefly, a total of 509 patients (mean age, 66.6±10.3 years), including 309 patients with chronic atrial fibrillation (AF) and 200 patients with paroxysmal AF, were enrolled at 5 university hospitals from September 1999. Patients with mitral stenosis or mechanical heart valves were excluded. The inclusion criteria were reported previously.⁷ Chronic AF was confirmed electrocardiograph-

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Table 1 Clinical Profile of Study Groups

	Antithrombotic therapy		
	None (n=83)	Antiplatelet (n=163)	Warfarin (n=263)
Male	56 (68)	96 (59)	178 (68)
Age (years)	63.4±12.0	67.5±11.0**	67.0±9.0*
Chronic AF	27 (33)	91 (56)**	191 (73)**##
Hypertension	32 (39)	67 (41)	119 (45)
Diabetes mellitus	12 (14)	22 (14)	44 (17)
Hyperlipidemia	19 (23)	37 (23)	59 (22)
Ischemic heart disease	4 (5)	27 (17)*	30 (11)
HCM	3 (4)	6 (4)	16 (6)
Prior stroke or TIA	7 (8)	22 (14)	71 (27)**##
NYHA ≥II	9 (11)	29 (18)	75 (29)**##

Values are mean ± SD or number (%).

None, patients without antiplatelet and warfarin therapy; AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; TIA, transient ischemic attack; NYHA, New York Heart Association functional class.

* $p < 0.05$, ** $p < 0.01$ vs none, # $p < 0.05$, ## $p < 0.01$ vs antiplatelet group.

ically on at least 2 separate occasions (≥ 4 weeks apart). Paroxysmal AF was defined as AF documented electrocardiographically at least once in the preceding 12 months and lasting at least 1 h. The choice of antithrombotic therapy was left for each physician to decide, since the present study was conducted primarily to determine the significance of levels of hemostatic markers in the prediction of subsequent thromboembolic events.⁸ Two hundred sixty-three patients received oral anticoagulants with the mean INR being 1.86 at the time of enrollment, and 163 patients received antiplatelet therapy as aspirin or ticlopidine, but 83 patients did not receive any antithrombotic therapy.

Physicians were encouraged to continue antiplatelet therapy or anticoagulation, and also to maintain the intensity of anticoagulation throughout the study period. Levels of INR were determined twice a year for research purposes and as required for treatment. The primary end points included clinically evident cerebral infarction, transient ischemic attack (TIA), or embolism of the peripheral arteries. The diagnostic criteria for these thromboembolic events have been reported previously.^{7,8} The INR levels at

the time of enrollment, within 6 months of the primary end point and at the time of thromboembolic events were analyzed.

The accumulation of risk factors was scored according to the CHADS2 index.³ That is, 1 point each was assigned for the presence of congestive heart failure, hypertension, an age of 75 years or older and diabetes mellitus, and 2 points for a history of cerebral infarction or TIA. For instance, when a patient had all of the risk factors, the CHADS2 score would be 6. To stratify the thromboembolic risk, patients with a CHADS2 score of 0 is classified as low risk, those with a score of 1 or 2, as moderate risk, and those with a score of ≥ 3 , as high risk.

Data are presented as mean ± SD. Comparison of continuous variables was performed with a paired t-test but not with one-way analysis of variance, because some INR levels were missing. Categorical variables were compared with chi-square test. A p value of less than 0.05 was defined as statistically significant.

Results

In Table 1, the clinical profiles of the study subjects are shown. Patients receiving warfarin had a higher prevalence of chronic AF, prior stroke or TIA, and New York Heart Association functional class $\geq$ II than those not receiving warfarin. The patients not receiving any antithrombotic drugs were younger and had a higher prevalence of paroxysmal AF as compared with the remaining groups.

Distribution of Antithrombotic Treatment

Fig 1 shows the distribution of antithrombotic treatment according to CHADS2 score. As the CHADS2 score increased, the proportion of patients receiving warfarin increased ($p = 0.005$). There were no patients with a CHADS2 score of 6 in the present study.

Risk of Thromboembolic Events

During a follow-up period of 2.0 ± 0.4 years, no patients were lost to follow up. There were 31 primary end points: ischemic stroke occurred in 21 patients, TIA in 7 patients and peripheral artery embolism in 3 patients. Patients not

Fig 1. Distribution of antithrombotic therapies according to CHADS2 score. There were no patients with a CHADS2 score of 6. Prevalence of warfarin usage increased as the CHADS2 score increased ($p = 0.005$). None, patients not receiving antiplatelet or warfarin therapy.

Table 2 Comparison of Event Rates (%/Year) Among 3 Risk Levels for Thromboembolism in Patients Receiving Warfarin and Those Not Receiving Warfarin (Non-Warfarin)

	CHADS2 score			p value
	0	1+2	≥3	
<i>All patients</i>				
Warfarin	5/64 (3.9%)	5/134 (1.9%)	10/65 (7.7%)	0.015
Non-warfarin	1/87 (0.6%)	7/126 (2.8%)	3/33 (4.5%)	0.110
<i>HCM excluded</i>				
Warfarin	2/59 (1.7%)	5/126 (2.0%)	8/62 (6.5%)	0.033
Non-warfarin	1/84 (0.6%)	6/121 (2.5%)	2/32 (3.1%)	0.450
<i>1 point given to HCM*</i>				
Warfarin	2/59 (1.7%)	8/135 (3.0%)	10/69 (7.2%)	0.035
Non-warfarin	1/84 (0.6%)	6/126 (2.4%)	4/36 (5.6%)	0.048

HCM, hypertrophic cardiomyopathy.

*One point was added to the original CHADS2 score in patients having HCM.

Table 3 Comparison of Event Rates Among 3 Risk Levels for Thromboembolism in Patients Receiving Warfarin and Those Receiving Antiplatelets (Aspirin or Ticlopidine)

	CHADS2 score			p value
	0	1+2	≥3	
<i>All patients</i>				
Warfarin	5/64 (3.9%)	5/134 (1.9%)	10/65 (7.7%)	0.015
Antiplatelets	1/51 (1.0%)	6/86 (3.5%)	3/26 (5.8%)	0.210
<i>HCM excluded</i>				
Warfarin	2/59 (1.7%)	5/126 (2.0%)	8/62 (6.5%)	0.033
Antiplatelets	1/49 (1.0%)	5/83 (3.0%)	2/25 (4.0%)	0.449
<i>1 point given to HCM*</i>				
Warfarin	2/59 (1.7%)	8/135 (3.0%)	10/69 (7.2%)	0.035
Antiplatelets	1/49 (1.0%)	5/85 (3.0%)	4/29 (6.9%)	0.098

Abbreviations as in Table 2.

receiving any antithrombotic treatment were few in each risk group, and therefore this patient group and the patient group receiving antiplatelets were pooled as a single, non-warfarin group in the following analyses.

Table 2 shows the risk of thromboembolic events between the 2 groups of patients (warfarin group vs non-warfarin group) of different risk levels. The event rate increased as the risk level estimated with CHADS2 score increased in patients in the non-warfarin group, although the difference did not reach the significance level ($p=0.11$). In contrast, the event rate differed significantly between the 3 different risk level groups of patients receiving warfarin ($p=0.015$), but paradoxically the event rate of the low risk group was higher than that of the moderate risk group (3.9% vs 1.9%). Surprisingly, the event rate was 7.7%/year for high-risk patients receiving warfarin (Table 2 Top). INR levels at the time of enrollment did not differ between the 3 groups of warfarin-treated patients (low risk, 1.82 ± 0.81 ; moderate risk, 1.92 ± 0.87 ; high risk, 1.78 ± 0.70).

The unpredictable results shown above could be attributed to the fact that patients with hypertrophic cardiomyopathy but without any clinical risk factors for thromboembolism were defined as low risk, but they actually experienced thromboembolic events frequently as reported in the previous study.⁸ When patients with hypertrophic cardiomyopathy were excluded from the analyses, the event rates increased in patients receiving warfarin as the risk level increased ($p=0.033$, Table 2 Middle). For those in the non-warfarin group, the result was similar to that shown above.

Since hypertrophic cardiomyopathy is an independent risk factor for thromboembolism, as reported in our previ-

ous study, the original CHADS2 index was modified by adding 1 point to patients with hypertrophic cardiomyopathy.⁸ Consequently, the event rates increased significantly as the risk level increased for both patients receiving warfarin ($p=0.035$) and those not receiving warfarin ($p=0.048$, Table 2 Bottom). The event rate was still, unpredictably, higher for the high-risk patients having modified CHADS2 score of 3 or more.

These results were also true when patients not receiving any antithrombotic treatment were excluded from the analyses (Table 3). The event rate reached 6–7%/year for high-risk patients with CHADS2 score of either the original or modified type of 3 or more when these patients were treated with antiplatelets. The event rate was approximately 1%/year for those with an original CHADS2 score of 0 and without hypertrophic cardiomyopathy even when these patients received antiplatelets.

INR Levels and Thromboembolic Events in Patients Receiving Warfarin

In 263 patients who had been treated with warfarin, there were 20 primary end points: cerebral infarction in 13 patients, TIA in 6 patients and peripheral artery embolism in a patient during the follow-up period of 2 years (Table 4). The mean INR level of these 20 patients at the enrollment was within the recommended target range for Japan.⁴

INR levels within 6 months before the onset of the primary end point were obtained in 14 of 20 patients. These levels did not differ significantly from those obtained at the enrollment (mean INR = 2.06) in these 14 patients. INR levels were obtained at the time of the primary end point in 17 patients. When compared with data within 6 months of

Table 4 Changes in International Normalized Ratio of Prothrombin Time in Patients Receiving Warfarin but Complicated With Thromboembolism

Patient no.	Age/sex	Risk factors	International normalized ratio of prothrombin time			Events
			Enrollment	Within 6 months before events	At the time of events	
1. YD	55M	CI, CHF, HCM	2.58	(–)	1.90	TIA
2. NN	64F	CI	1.17	2.93	1.23	CI
3. AS	65M	CI	7.11	2.47	1.68	CI
4. MK	70M	HCM	1.22	(–)	1.00	CI
5. MO	78M	CI, HCM	1.73	2.28	(–)	TIA
6. KT	73F	CI	1.96	1.97	1.60	CI
7. TK	73M	(–)	1.09	1.21	1.00	TIA ^(a)
8. MY	84M	CI, CHF, DM	2.19	3.06	1.16	CI
9. SS	72M	CHF	1.27	1.66	1.49	CI
10. MI	60F	CI, HT	1.67	1.96	1.65	TIA
11. KK	57F	(–)	3.08	1.89	0.92	TIA ^(b)
12. HA	83F	CHF, HT	1.11	(–)	1.43	CI
13. YY	74M	HCM	1.47	(–)	(–)	TIA
14. KT	72F	HT	1.06	(–)	1.25	CI
15. NS	60F	CHF	1.19	2.87	2.71*	CI ^(c)
16. SM	79M	CI, HT	1.58	1.36	(–)	CI
17. TN	75M	CI	1.96	1.94	1.10	CI
18. TS	62M	HCM	1.63	(–)	1.24	CI
19. NN	76M	CI, CHF, HT	1.65	2.67	1.39	Peri. E
20. ZT	64M	CI, HT	1.12	1.33	1.19	CI
Mean			1.89	2.11	1.41	
SD			1.34	0.62	0.43	
N			20	14	17	

CI, cerebral infarction; CHF, congestive heart failure; HCM, hypertrophic cardiomyopathy; TIA, transient ischemic attack; DM, diabetes mellitus; HT, hypertension; Peri. E, peripheral embolism.

(a) Warfarin had been withdrawn for 3 months. (b) Dosage of warfarin had been decreased from 3.5 mg to 1.0 mg per day. (c) Vitamin K was injected before temporary cardiac pacing.

*Determined before vitamin K injection.

the events in 12 of these 17 patients, INR levels decreased significantly at the time of the primary end point (2.16 ± 0.63 to 1.43 ± 0.48 , $n=12$, $p<0.001$). When compared with data at the enrollment, INR levels tended to decrease at the time of the event (1.94 ± 1.45 to 1.41 ± 0.43 , $n=17$, $p=0.08$).

Three patients had apparent reasons for occurrence of thromboembolic complication. Warfarin treatment had been stopped in Patient 7 for 3 months prior to the event, and the daily dosage decreased from 3.5 mg to 1 mg in Patient 11. Patient 15 received vitamin K administration for temporary cardiac pacing. Her INR level before vitamin K administration was 2.71, but that after vitamin K administration was not obtained. Thus the INR level was $\geq 1.6^4$ only in 4 (25%) of 16 patients with a primary end point. The INR level of Patient 15 was excluded from this analysis.

Discussion

The present study was conducted primarily to determine whether measurements of hemostatic markers would be effective in predicting subsequent embolic events in patients with NVAF, as reported elsewhere.^{7,8} The major findings of the present post hoc analyses are as follows. First, the prevalence of patients receiving warfarin increased along with the accumulation of risk factors estimated by CHADS2 score. Second, antiplatelets were not effective in preventing embolic events in patients at high risk (CHADS2 score ≥ 3) of thromboembolism. The primary event rate among patients at high risk was 6–7%/year when treated with antiplatelets in the present study, while adjusted-dosage warfarin could decrease the risk of embolic events to 3–4%/year in secondary Japanese prevention

trials.⁴ Third, warfarin seemed ineffective in the prevention of embolic events for high-risk patients with a CHADS2 score of 3 or more. This could be attributed to an insufficient anticoagulation level, for various reasons, at the time of the embolic event. Fourth, when the original CHADS2 scoring system was modified by adding 1 point to patients with hypertrophic cardiomyopathy, embolic events could be predicted more accurately in our selected subjects with NVAF.

Risk Stratification of Embolic Events in Patients With NVAF

On the basis of randomized, prospective trials, several clinical variables emerged as risk factors for thromboembolism in patients with NVAF.^{1,2} Although some differences existed between the reports,^{1,2,9} advanced age, recent congestive heart failure, history of hypertension, diabetes mellitus, and prior embolic events, including TIA, commonly emerged as the risk factors.^{1,3} Patients complicated by at least one of these risk factors could be in a hypercoagulable state.¹⁰ Therefore, many guidelines recommend patients be anticoagulated with warfarin when complicated by at least one of these risk factors.^{1,2}

Our previous study showed warfarin usage was not sufficient enough in this cohort of patients.¹¹ When analyzed differently in the present study, it became apparent that warfarin usage increased along with accumulation of risk factors (Fig 1) and was given to >90% of patients with a CHADS2 score of 5. However, warfarin usage ranged from 50 to 70% for patients with a CHADS2 score of 1–4; a finding of insufficient adherence to the guidelines.²

It seems conceivable that an accumulation of risk factors would increase the risk of thromboembolism in patients

with NVAF. The CHADS2 score was thus introduced to stratify the risk of thromboembolism in patients with NVAF.³ This score was useful for predicting thromboembolism both in patients receiving aspirin or no antithrombotic therapy.³ With an increase in this score, the thromboembolic events rate would also increase. In the original study, low-risk group was defined as patients having a CHADS2 score of 0 or 1; moderate risk, 2 or 3; and high risk, 4 or more.³ However, anticoagulation is recommended when patients with NVAF have at least one risk factor.² Therefore, a score of 0 was classified as low risk; 1 or 2, as moderate risk; and 3 or more, as high risk in the present study. The crude stroke rate in the study of Gage et al was 1.2, 2.8–3.6 and 6.4–7.7%/year for those with CHADS2 scores of 0, 1–2 and 3–5, respectively.³ These figures were a little greater than those of our patients not receiving warfarin (Table 2).

In our cohort of patients with NVAF, hypertrophic cardiomyopathy emerged as an independent risk for thromboembolism.⁸ Previous studies indicated that patients with hypertrophic cardiomyopathy could be at high risk of thromboembolism.^{12,13} This could explain the higher incidence of primary end points in patients with an original CHADS2 score of 0 and treated with warfarin (Table 2 Top). When patients with hypertrophic cardiomyopathy were excluded from the analyses or the original CHADS2 score was modified by adding 1 point to these patients, the risk of thromboembolism actually increased along with the accumulation of risk factors in our patients with NVAF (Table 2 Middle or Bottom). Patients with a modified CHADS2 score of 3 or more should be anticoagulated with warfarin, because thromboembolic event rate could reach approximately 6–7%/year unless they are anticoagulated (Tables 2 and 3).

INR Levels and Embolic Events

Guidelines in some Western countries recommend optimal INR levels ranging from 2 and 3.² When INR level is below 2, thromboembolic events would not be prevented sufficiently, and above 3, rates of hemorrhagic complications would increase. However, INR levels of 1.6 to 2.6 could be optimal for Japanese patients with NVAF, based on the secondary prevention trials in Japan.⁴ In the present study, the INR level at the enrollment was 1.89 on the average, and fell into the optimal ranges as a whole group.⁴

Recent clinical trials demonstrated that patients treated with warfarin were complicated with thromboembolic stroke when warfarin was withdrawn or INR levels were below 2.^{5,6} In the AFFIRM trial, 157 patients were complicated with ischemic stroke occurring after the withdrawal of warfarin in 69 patients (43.9%) or while INR was subtherapeutic (<2) in 44 patients (28%).⁶ This was also true for the RACE trial; thromboembolism occurred after the withdrawal of warfarin in 6 of 35 patients and during warfarin treatment with subtherapeutic INR in 23 patients.⁵ This means that more than 70% of patients complicated with thromboembolic stroke did not receive warfarin or received insufficient anticoagulation levels.

In the present study, 20 patients were complicated with thromboembolism during warfarin treatment. The anticoagulation state could be determined in 17 of these 20 patients at the time of the thromboembolic events. Warfarin had been withdrawn in one patient, decreased in dosage in another patient, and neutralized with vitamin K in the third patient. The INR level at the time of thromboembolic events

was below the optimal level for Japanese patients (ie, <1.6) in another 10 patients on warfarin (Table 4). Therefore, anticoagulation was not adequate at the time of thromboembolic events in 13 of 17 patients (77%) in the present study. A previous, prospective study demonstrated that greater variation of anticoagulation levels would be related to thromboembolic events in patients with AF.¹⁴ Therefore, adequate and stable anticoagulation levels seem mandatory for the prevention of thromboembolism in patients with NVAF.

Study Limitations

The present study was limited for several reasons as reported previously.⁸ First, patients were followed up prospectively, but the treatment was not randomized. The present study had been planned primarily to determine the significance of coagulation marker levels for the prediction of subsequent thromboembolic events in patients with NVAF.⁸ Therefore, the clinical characteristics differed among the 3 patient groups. Patients on warfarin had a higher prevalence of chronic AF, prior history of stroke or TIA and congestive heart failure. This could lead to slightly but insignificantly higher rates of primary end points in patients receiving warfarin in the present study. The higher prevalence of paroxysmal AF in the group not receiving any antithrombotic therapy would contribute to the lower event rate in this patient group (Tables 2 and 3).¹⁵ Second, the present analyses were post hoc in nature. This could affect the conclusion, and the data need to be interpreted cautiously. Third, intensities of anticoagulation in the present study were slightly below those recommended in the guidelines of Western countries.² However, the optimal anticoagulation level seems a little lower for Japanese patients with NVAF.⁴ As a whole group, INR levels were within the optimal range for Japanese patients at enrollment and within 6 months of the events in the present study. Fourth, the reasons for insufficient levels of anticoagulation were not determined in most of patients when complicated with thromboembolism during warfarin treatment. Finally, hypertrophic cardiomyopathy, accounting for 5% of our cohort of patients, emerged as an independent risk factor for thromboembolism.⁸ This could explain why the original CHADS2 score was not accurate enough to stratify the thromboembolic risk in patients receiving warfarin.³ However, when patients with hypertrophic cardiomyopathy were excluded from the analyses or the CHADS2 score was modified by adding 1 point to these patients, thromboembolic events increased in line with the accumulation of the risk factors. Dilated cardiomyopathy was not classified specifically in the present study, because the patients having dilated cardiomyopathy are prone to congestive heart failure, thereby being given 1 point.¹³

Clinical Implications

Although limited for the reasons mentioned above, the present post hoc analyses clearly showed that anticoagulation with warfarin was not necessarily required in patients with NVAF when not complicated with risk factors for thromboembolism, including hypertrophic cardiomyopathy. However, when the risk of thromboembolism is high, as determined with either original or modified CHADS2 score, treatment options other than warfarin can not be justified. When warfarin is used for prophylaxis of thromboembolism, INR levels need be maintained within the optimal ranges.⁴

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