Optimal International Normalized Ratio for Warfarin Therapy in Elderly Korean Patients with Non-Valvular Atrial Fibrillation

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ABSTRACT

Background and Objectives: Optimal international normalized ratio (INR) in elderly atrial fibrillation (AF) patients at higher risk of hemorrhagic events remains unclear. We investigated the efficacy and safety of low-intensity warfarin therapy (target international normalized ratio [INR], 1.6–2.6) in elderly Korean patients with non-valvular AF (NVAF).

Subjects and Methods: We enrolled 528 NVAF patients (mean age, 67 ± 9 years; 361 men) who were actively taking warfarin. Major events were defined based on the annual rates of ischemic stroke, systemic embolism, and major bleeding events requiring blood transfusion or hospitalization. Time in therapeutic range (TTR) was $45 \pm 19\%$ for all patients.

Results: Ischemic stroke and systemic embolism occurred in 20 patients with INR between 1.00 and 2.44 (16 ischemic strokes and 4 systemic embolisms) and major bleeding in 37 patients with INR between 1.74 and no coagulation (exceed laboratory detection capability, more than 10 [7 intracranial hemorrhages, 21 gastrointestinal bleedings, and 9 others]). Incidence rates of ischemic or hemorrhagic events at $\text{INR} < 2.00$, 2–3, and > 3 were 3.0%, 1.4%, and 20.1% per year, respectively. In patients who were ≥ 70 years old, CHADS₂, CHA₂DS₂VASc, and HAS-BLED scores were significantly higher compared with those in patients who were < 70 years old. When we applied the INR between 1.6 and 2.6, as recommended by the Japanese AF Guideline for patients ≥ 70 years old, the TTR increased from 43.8% to 58.6%. In addition, ischemic or hemorrhagic event rates decreased from 1.9% to 1.2% within the optimal INR range.

Conclusion: Low-intensity warfarin therapy (INR, 1.6–2.6) should be considered in elderly Korean patients with NVAF.

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Key Words: ■ Warfarin ■ Atrial Fibrillation ■ INR

Introduction

Atrial fibrillation (AF) is a common and serious arrhythmia that is frequently associated with the development of stroke and systemic embolism. The efficacy of warfarin therapy for the prevention of stroke or systemic embolization has been previously established. Current guidelines recommend maintaining the optimal international normalized ratio (INR) intensity range at between 2.0 to 3.0 in patients with non-valvular AF (NVAF) who are at a moderate to high risk of stroke.^{1,2} However, an INR in the therapeutic range (2.0–3.0) occurs in only 50% to 80% of cases even in well-monitored clinical trials.³ Moreover, optimal intensity of the INR was often lower in the observational or registry data, including the Korean AF registry, where the INR was in the therapeutic range of 42.4% of the time.⁴ Among the numerous causes for lower INR intensity, bleeding complications, including intracranial hemorrhage, are the main obstacles in warfarin therapy. Japanese guidelines recommend INR control between 1.6 and 2.6 in patients who are ≥ 70 years old because old age is associated with the occurrence of severe bleeding events.⁵ In addition, hemorrhagic stroke occurs more frequently in Asian patients than in Caucasians.⁵ However, the efficacy and safety of low-intensity warfarin therapy in elderly Korean patients with NVAF is unknown. Therefore, we investigated the optimal INR target range and the risks of stroke, systemic embolism, and major bleeding based on age in Korean patients with NVAF.

Subjects and Methods

We enrolled 528 patients with NVAF who have been taking warfarin at our institution between January 2010 and July 2013. Major events were defined as ischemic stroke, systemic embolism, and major bleeding events. Major bleeding was defined based on the International Society for Thrombosis and Hemostasis criteria as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dL or transfusion of at least 2 units of packed red cells, occurring at a critical site or resulting in death.⁶ Patients underwent warfarin therapy for ≥ 2 years, except for those who developed major events during the follow-up period. The enrolled patients were evaluated monthly by physicians for the occurrence of ischemic stroke, systemic

embolism, and major bleeding events, as well as for INR monitoring. The target INR intensity was decided by the physician-in-charge. Knowing the length of the target INR range during the oral anticoagulation period was difficult. We calculated time in therapeutic range (TTR) by the Rosendaal method. Rosendaal *et al.*⁷ proposed a method to determine the time interval between two INR measurements based on the assumption that the actual difference in INR between any two consecutive measurements was linear, and the data were interpolated accordingly. The patients were divided into two groups based on their age. We compared TTR between target INR of 2.0–3.0 and 1.6–2.6 in patients ≥ 70 years old. Values of INR on the events were counted as INR associated with the events. The INRs that corresponded with the development of ischemic or bleeding events were assessed.

Data were expressed as the mean $\pm$ SD for continuous variables and percentages for categorical variables. Left ventricular ejection fraction (LVEF), E/E' and left atrium diameter were assessed by using two-dimensional echocardiography. All comparisons between baseline variables were assessed using the Student t-test for continuous variables and the Pearson chi-square test for categorical variables. For all analyses, a two-sided p value of <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software (version 18.0 for Windows, SPSS Inc., Chicago, IL, USA)

Results

The baseline characteristics of the study subjects are shown in Table 1. The mean age of the surveyed population was 67 ± 9 years, and 68.4% were male. The mean follow-up period was 1035 ± 255 days. During the study period, 57 patients developed ischemic stroke, systemic embolism, or major bleeding events. Ischemic stroke and systemic embolism occurred in 20 patients with INR between 1.00 and 2.44 (16 ischemic strokes and 4 systemic embolisms). Major bleeding was noted in 37 patients with an INR between 1.74 and no coagulation (exceed laboratory detection capability, more than 10 [7 intracranial hemorrhages, 21 gastrointestinal bleedings, and 9 others]). The TTR during the follow-up period was $45.2 \pm 19.2\%$. No difference was found in the TTR value between patients with and without the events.

Table 1. Baseline clinical characteristics of the patients with and without any events

	All patients (n=528)	Ischemic or hemorrhagic events		P value
		No (n=471)	Yes (n=57)	
Demographics				
Age (year)	66.5±9.5	66.2±9.6	69.0±8.1	0.022
Male (%)	361 (68.4)	322 (68.4)	39 (68.4)	0.993
Body mass index (kg/m ²)	24.0±3.3	24.1±3.3	23.2±2.8	0.082
History				
CHF (%)	196 (37.1)	172 (36.5)	24 (42.1)	0.410
Hypertension (%)	277 (52.5)	242 (51.4)	35 (61.4)	0.152
Diabetes mellitus (%)	129 (24.4)	112 (23.8)	17 (29.8)	0.316
CVA (%)	318 (60.2)	281 (59.8)	37 (64.9)	0.444
Previous MI (%)	32 (6.1)	29 (6.2)	3 (5.3)	1.000
PAD (%)	16 (3.0)	13 (2.8)	3 (5.3)	0.400
CHADS ₂ score	2.6±1.3	2.5±1.3	2.8±1.2	0.062
CHA ₂ DS ₂ VASc score	4.6±1.6	4.5±1.6	5.0±1.5	0.036
HAS-BLED score	2.3±1.1	2.3±1.1	2.6±1.2	0.041
Mean daily dose of warfarin				
<3 mg	151 (28.6)	133 (28.2)	18 (31.6)	0.598
≥3 mg and <5 mg	277 (52.5)	246 (52.2)	31 (54.4)	0.758
≥5 mg	100 (18.9)	92 (19.5)	8 (14.0)	0.317
Time in therapeutic range (%)	45.2±19.2	45.4±19.1	43.3±19.8	0.424
Co-administration of anti-platelet drug	133 (25.2)	121 (25.7)	12 (21.1)	0.446
Echocardiographic findings				
LVEF (%)	50.8±12.5	51.1±12.3	48.7±14.1	0.230
E/E' (%)	13.8±6.1	13.7±6.2	14.9±5.5	0.271
LA diameter (mm)	47.9±7.6	47.7±7.6	49.1±7.5	0.200

CHF, congestive heart failure; CVA, cerebrovascular accident; LA, left atrium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease

Incidence rates of ischemic or hemorrhagic events at an INR of <2, 2–3, and >3 were 3.0%, 1.4%, and 20.1% per year, respectively. In patients with ischemic or hemorrhagic events, the age, and CHA₂DS₂VASc and HAS-BLED scores, were

significantly higher compared with those in patients without events.

As mentioned earlier, patients were divided into two groups based on age. Overall, 233 patients (44%) were ≥70 years old.

Table 2. Clinical characteristics of the patients according to age

	Age $\geq$ 70 years (n=233)	Age <70 years (n=295)	P value
Age (year)	74.8 $\pm$ 3.7	60.1 $\pm$ 7.5	<0.001
Male (%)	140 (60.1)	221 (74.9)	<0.001
Body mass index (kg/m ²)	23.2 $\pm$ 3.0	24.6 $\pm$ 3.3	<0.001
CHF (%)	78 (33.5)	118 (40.0)	0.123
Hypertension (%)	133 (57.1)	144 (48.8)	0.059
Diabetes mellitus (%)	67 (28.8)	62 (21.0)	0.040
CVA (%)	165 (70.8)	153 (51.9)	<0.001
Previous MI (%)	14 (6.0)	18 (6.1)	0.964
PAD (%)	12 (5.2)	4 (1.4)	0.012
CHADS ₂ score	3.1 $\pm$ 1.2	2.1 $\pm$ 1.1	<0.001
CHA ₂ DS ₂ VASc score	3.8 $\pm$ 1.3	5.6 $\pm$ 1.4	<0.001
HAS-BLED score	2.8 $\pm$ 0.8	1.9 $\pm$ 1.0	<0.001
Mean daily dose of warfarin			
<3 mg	76 (32.6)	75 (25.4)	0.069
$\geq$ 3 mg and <5 mg	120 (51.5)	157 (53.2)	0.695
$\geq$ 5 mg	37 (15.9)	63 (21.4)	0.111
Time in therapeutic range (%)	43.8 $\pm$ 19.0	46.4 $\pm$ 19.3	0.141
Co-administration of anti-platelet drug	59 (25.3)	74 (25.1)	0.950
Echocardiographic findings			
LVEF (%)	52.6 $\pm$ 11.0	49.5 $\pm$ 13.5	0.005
E/E' (%)	15.0 $\pm$ 6.4	12.9 $\pm$ 5.8	0.001
LA diameter (mm)	47.4 $\pm$ 7.9	48.3 $\pm$ 7.2	0.190
Any events (%)	29 (12.4)	28 (9.5)	0.277
Stroke or systemic embolism (%)	13 (5.6)	7 (2.4)	0.055
Major bleeding (%)	16 (6.9)	21 (7.1)	0.910
ICH (%)	2 (0.9)	5 (1.7)	0.473

CHF, congestive heart failure; CVA, cerebrovascular accident; ICH, intracerebral hemorrhage; LA, left atrium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease

More percentage of females were found in this age range, and the body mass index was significantly lower. A history of diabetes mellitus, cerebrovascular accident, and peripheral artery disease in patients who were ≥ 70 years old was more commonly reported than that in those who were < 70 years old. Echocardiographic findings showed that patients who were ≥ 70 years old had slightly higher ejection fractions and higher E/E' values compared with those in patients who were < 70 years old. No difference was found in the left atrium size between the two groups. In patients who were ≥ 70 years old, CHADS₂, CHA₂DS₂VASc, and HAS-BLED scores were significantly higher compared with those in patients who were < 70 years old. The TTR in patients ≥ 70 years old was $43.8 \pm 19.0\%$ (Table 2). However, no difference was found in the TTR value between patients with and without the events in patients who were ≥ 70 years old ($41.5 \pm 19.6\%$ versus $44.1 \pm 18.9\%$, $p=0.492$). When we applied the INR between 1.6 and 2.6, as recommended by the Japanese AF guidelines for patients who were ≥ 70 years old, TTR increased from 43.8% to 58.6% (Figure 1). Stroke and systemic embolism event rates within this range slightly increased from 0.6% to 0.9% (Figure 2), whereas hemorrhagic event rates decreased from 1.3% to 0.2% (Figure 3). Overall, any event rates within this TTR range decreased from 1.9% to 1.2% (Figure 4).

Discussion

The main finding of this study is that lower intensity warfarin therapy (INR, 1.6–2.6) is favorable in elderly Korean patients with NVAF. In Korea, the prevalence of AF increased as the population ages. AF will become a serious clinical problem in the future because elderly patients survive longer.⁸ The increasing incidence and prevalence of AF increases the likelihood of anticoagulation use in the AF population, which usually includes the elderly.⁹ Warfarin is effective for the primary and secondary prevention of both arterial and venous thromboembolic disorders.^{10,11} However, anticoagulation intensity correlates with bleeding risk in warfarin-anticoagulated patients.^{12–14} In addition, the benefits of warfarin are lost because of the higher rates of intracranial hemorrhage. In addition, racial differences may affect the risk of bleeding.¹⁵ The maintenance doses of warfarin for the Japanese and Chinese are approximately 30% and 40% lower than those for Caucasians, respectively.¹⁶ Genetic determinants of warfarin dosing may alter the effect of warfarin.^{17,18} In fact, the incidence of intracerebral hemorrhage was reported to be higher in Japan than in Western countries.¹⁹ Older age particularly increases the risk of bleeding in patients who have been treated with warfarin.²⁰ In addition, warfarin cessation after major bleeding events increases the risk of stroke, confirming that bleeding prevention can help reduce the risk of stroke in patients taking anticoagulants. Therefore, the Japanese Circulation Society has recommended a lower INR (1.6–2.6) for elderly patients due to the risk of stroke and hemorrhage.⁵ However, no Korean data

Figure 1. Changes of time in the therapeutic range among patients ≥ 70 years old.
INR, international normalized ratio

Figure 2. Stroke and systemic embolism event rates within the time in the therapeutic range in patients ≥ 70 years old.
INR, international normalized ratio

Figure 3. Hemorrhagic event rates within the time in therapeutic range in patients ≥ 70 years old.

INR, international normalized ratio

Figure 4. Any event rates within the time in therapeutic range in patients ≥ 70 years old.

INR, international normalized ratio

exist on the optimal intensity of INR in warfarin therapy for stroke prevention in elderly patients with NVAf. Our study shows that low intensity INR (1.6–2.6) in Korean patients with NVAf who are ≥ 70 years old results in slightly increased ischemic event rates, but with markedly decreased hemorrhagic event rates within TTR. Any event rates eventually decreased within TTR.

Our study has some limitations that should be considered. The retrospective analysis of the small single-center data is a major limitation of this study. Therefore, our results should only be considered for hypothesis generation. Secondly, the co-administration of antiplatelet agents might influence bleeding events. However, our data showed that no difference was found in the administration of antiplatelet agents between the two groups based on age.

Conclusion

Our Study adds insight to previous literature showing how low-intensity warfarin therapy (INR 1.6–2.6) might be considered in elderly Korean patients with NVAf. Fear of hemorrhage may prompt some physicians to avoid prescribing anticoagulation, particularly in elderly patients.^{20,21} However, anticoagulation may prevent stroke or systemic embolism in elderly patients with a lower target INR.

Conflict of interest

All authors reported no conflicts of interest.

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None

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