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RESEARCH ARTICLE

INR optimization based on stroke risk factors in patients with non-valvular atrial fibrillation

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Abstract *Background* Bleeding complications have been frequently reported in East Asian patients on warfarin with a target international normalized ratio (INR) of 2.0–3.0. *Objective* This study aimed to identify the optimal therapeutic range of the INR in Korean patients with non-valvular atrial fibrillation (NVAF). *Setting* Cardiovascular department of a 1320 inpatient bed Korean hospital. *Method* Retrospective chart review was conducted on 1014 patients for a total follow-up period of 2249.2 patient years. Major thromboembolic and bleeding complications were evaluated. The INR incidence of complication curve was plotted, and the optimal therapeutic range of INR was determined from the intersection of curves to ensure the lowest incidences of both thromboembolic and bleeding complications. For subgroup analysis, all patients were stratified by the following factors: age (above 75), disease (presence of hypertension, diabetes, congestive heart failure, and a history of stroke or thromboembolism), rhythm control procedure, and concurrent aspirin therapy. *Main outcome measure* Optimal therapeutic ranges of INR according to the risk factors. *Results* A total of 41 thromboembolic and 91 bleeding events occurred during the follow-up period. The complication rates were the lowest at an INR of 1.9 and the optimal therapeutic range was estimated to be 1.7–2.2 for the overall patients. The optimal therapeutic ranges of INR in the stratified patients were determined as follows: 1.3–1.8 in the patients ≥75 years of age; 1.5–2.0 in patients with hypertension, diabetes and concurrent aspirin therapy; 1.8–2.3 in patients with congestive heart failure; 1.9–2.4 in patients with previous stroke or thromboembolism; 1.7–2.2 in patients who had undergone rhythm control procedures. It has been shown that, by keeping the INR within these ranges, complication risks could be significantly reduced by up to 81 %. *Conclusion* The intensity of anticoagulation therapy for Korean patients with NVAF is optimal when INR is between 1.7 and 2.2.

Keywords International normalized ratio · Korea · Non-valvular atrial fibrillation · Warfarin

Impacts on practice

- Bleeding complications occur more frequently than expected in Korean patients on warfarin with a target value of 2.0–3.0.
- An INR of 1.7–2.2 appears to be associated with the lowest incidence rate of major thromboembolic and bleeding complications in Korean patients with NVAF.

Introduction

Atrial fibrillation (AF) is the most common form of arrhythmia, not only in Western countries but also in Korea. With the aging of Koreans, the prevalence of atrial fibrillation

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is projected to increase dramatically [1, 2]. The development of AF is associated with morbidity and mortality, the most detrimental contributor being strokes. Therefore, the goal of the therapy includes preventing thromboembolic events as well as controlling ventricular rate.

To determine the most appropriate chronic antithrombotic therapy, stroke risk stratification is an essential process for the patients with AF. According to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines published in 2006, the $CHADS_2$ index ($CHADS_2$; congestive heart failure, hypertension, ages above 75, diabetes mellitus, and prior stroke or transient ischemic attack) has been recommended for the stratification in these patients. With this index, the guidelines recommend that the patients with AF and $CHADS_2$ scores of $\geq$2 points be treated with warfarin therapy [3]. Also, the American College of Chest Physicians (ACCP) updated the guidelines to provide the recommendations regarding antithrombotic therapy for the patients undergoing rhythm control therapy as well as for those with AF [4].

Although warfarin is the most widely used anticoagulant, its therapy requires precise monitoring and dose adjustments to ensure that the patients remain within a narrow therapeutic window as defined by the international normalized ratio (INR) [5]. The optimal therapeutic range of anticoagulation therapy varies according to different indications and various characteristics of the patients. Based on clinical evidence, the ACCP recommended that the target INR of 2.0–3.0 is effective in patients with non-valvular atrial fibrillation (NVAF) [6]. INR levels above and below this target range are associated with substantial increases in bleeding and thromboembolic risks, respectively.

In East Asian populations including Koreans, low intensity of anticoagulation was recommended due to differences by ethnicity regarding coagulation characteristics, lifestyle (including vitamin K intake), and their vulnerability to hemorrhagic diseases [7]. Practically, major bleeding complications including intracranial hemorrhage have been frequently reported in East Asian patients when target INR of 2.0–3.0 was applied [7–9]. Thus, optimizing the target INR in East Asian patients is important, but only a few relevant studies have been conducted [10–12].

Aim of the study

This study was designed primarily to evaluate the relationship between the intensity of INR and the incidence of thromboembolic and bleeding complications in Korean patients with NVAF. The secondary and main objective was to identify the optimal therapeutic ranges of INR, based on the risk factors of both complications.

Ethical approval

This protocol was approved by the Ethics Committee of the Seoul St. Mary's Hospital (No. KC13RASI0325).

Method

Patients and data collection

This retrospective study was conducted at a tertiary hospital in Korea. A total of 1014 patients who had NVAF were included between January 2011 and December 2012. All patients had received warfarin for their anticoagulation therapy with a target INR of 2.0–3.0. Patients who had valvular disease, active endocarditis, or were under 16 years of age were excluded. The patients' medical records were reviewed until May 2013 to collect clinical information such as duration of AF, duration and dose of warfarin intake, results of all INR assessments, co-morbidity, and occurrence of warfarin-related complications. For subgroup analysis, all patients were stratified by the following factors: age (above 75), disease (presence of hypertension, diabetes, or congestive heart failure and a history of stroke or other thromboembolic events), rhythm control procedure [direct current cardioversion or radiofrequency catheter ablation (RFCA)] and concurrent aspirin therapy.

Anticoagulation complications

The anticoagulation-related complications were classified into thromboembolic and bleeding events. Thrombotic events included transient ischemic attack, cerebral infarction, valve thrombosis, and other thrombosis. Cerebral infarction was defined as the neurologic deficit of sudden onset documented by brain scans indicating the presence of infarction or the absence of hemorrhage. Embolism was defined as an acute vascular occlusion of the extremities or any organs. A bleeding event was any episode of major bleeding that caused hospitalization, permanent injury, death or necessitated transfusion [13]. Bleedings occurred after surgery or after any other invasive procedure were excluded in our analysis. All other bleedings that did not require supportive therapy were considered as minor and were excluded.

INR assessments

The patients were followed up to the endpoints of clinical events. INR levels were measured at the time of clinical events. If the values were not available, the last INR record before the event was obtained, but only if the test had been performed $<$7 days before the events. The precipitating

factors of the complications were also obtained from the electronic medical records.

The total number of patient-years for all patients was calculated. INR values measured in clinical events were categorized into five sections: <1.75, 1.75–2.24, 2.25–2.74, 2.75–3.24, and ≥3.25. INR values in each section were then given the values 1.5, 2.0, 2.5, 3.0, and 3.5, respectively, for plotting purposes. The INR-incidence of complication curves was plotted using these values, and 95 % confidence intervals (CIs) for the incidence rates were calculated. The optimal INR was determined from the intersection of the curves of both complication rates with intervals of 0.5 and validated by comparing the incidence rates of INR within the ranges to those of INR below or over the ranges [14].

Statistical analysis

All data were analyzed using SAS version 9.3 (SAS institute, Inc, Cary, NC). Complication rates are expressed as linearized incidences per 100 patient-years. All data are expressed as the mean ± SD, while 95 % CI for incidences were computed based on the assumption of a poisson distribution. A Chi square test was used to detect a statistical difference in complication rates between the groups. A p value <0.05 was considered to be statistically significant.

Results

A total of 1014 patients were included in this study. The mean (SD) age of the patients was 65.5 (12.0) years old, and 62.9 % of the patients were male. Of these, 209 (20.6 %) were aged above 75, and 167 (16.5 %) had a history of previous stroke or thromboembolic disease. The characteristics of study population are described in Table 1. The patients were followed for 25.2 (23.5) months on average (SD), and the total period of follow-ups was 2249.2 patient-years. The mean number of times (SD) of measuring INR per patient was 21.0 (19.1).

A total of 132 complications occurred during the follow-up period. Of these events, 41 (1.82 per 100 patient-years) were thromboembolic events and 91 (4.05 per 100 patient-years) were bleeding events. Gastrointestinal bleeding was the most frequently observed bleeding complication; every gastrointestinal bleeding required transfusion. Major complications are shown in Table 2.

There were 6 thromboembolic events and 35 bleeding events in patients above 75 years of age, with incidence rates of 1.34 and 7.79 per 100 patient-years, respectively. The total incidence of both complications was the highest in patients older than 75 years of age, followed by the patients receiving concurrent aspirin therapy. The distribution of every event and the incidence in each subgroup are shown in Fig. 1.

Table 1 Characteristics of the study patients (n = 1014)

Characteristics	Number (%)
Age at diagnosis[a]	65.5 ± 12.0 (16.5–94.9)
Gender	
Male	638 (62.9)
Female	376 (37.1)
Risk factors for stroke	
Age ≥75 years	209 (20.6)
Hypertension	608 (60.0)
Diabetes mellitus	247 (24.4)
Heart failure	219 (21.6)
Previous stroke/thromboembolism	167 (16.5)
Rhythm control procedure	
Direct current cardioversion	227 (22.4)
Radiofrequency catheter ablation	325 (32.1)
Concurrent aspirin therapy	360 (35.5)

[a] Mean ± SD (range)

With the increase in INR levels, the rate of thromboembolic events decreased whereas the rate of bleeding events increased. The incidence rates for thromboembolic and bleeding events at the specific INR levels formed a right-shifted U-shaped distribution, because there was a higher incidence of bleeding compared to thromboembolic events. It was approximated that an INR value of 1.9 was the lowest point of both complications (Fig. 2a) in the study population.

In the patients above 75 years of age, bleeding complications increased more steeply with the increase in INR. Therefore, it was estimated that the incidence of both complications was the lowest at an INR level of 1.5 (Fig. 2b). The INR levels at the point of intersection were 1.75 in the patients with hypertension, diabetes, and concurrent aspirin therapy (Fig. 2c, d, i), 2.0 in the patients with congestive heart failure (Fig. 2e), 2.1 in the patients with prior stroke (Fig. 2f), 1.9 in the patients who underwent rhythm control procedure (Fig. 2g, h).

The optimal therapeutic ranges of INR were established on the basis of target INR values, which were derived from the intersections of complication rates in Fig. 2. The optimal ranges were determined as the center of the target value at a confined distance of 0.5, and they were shown as follows: 1.7–2.2 for the overall patients; 1.3–1.8 for elderly patients (≥75 years); 1.5–2.0 for patients with hypertension, diabetes and concurrent aspirin therapy; 1.8–2.3 for patients with heart failure; 1.9–2.4 for patients with prior stroke; and 1.7–2.2 for patients with direct current cardioversion and RFCA.

Table 2 Major complication events

Complications	No. of events	Incidence (per 100 patient-years)
Thromboembolism		
Cerebral infarction	28	1.24
TIA	11	0.49
Mesenteric infarction	1	0.04
Renal infarction	1	0.04
Total	41	1.82
Bleeding events		
Gastrointestinal bleeding	24	1.07
Hematuria	17	0.76
Hematoma	14	0.62
Intracranial bleeding	12	0.53
Other major/fatal bleedings	24	1.07
Total	91	4.05

TIA transient ischemic attack

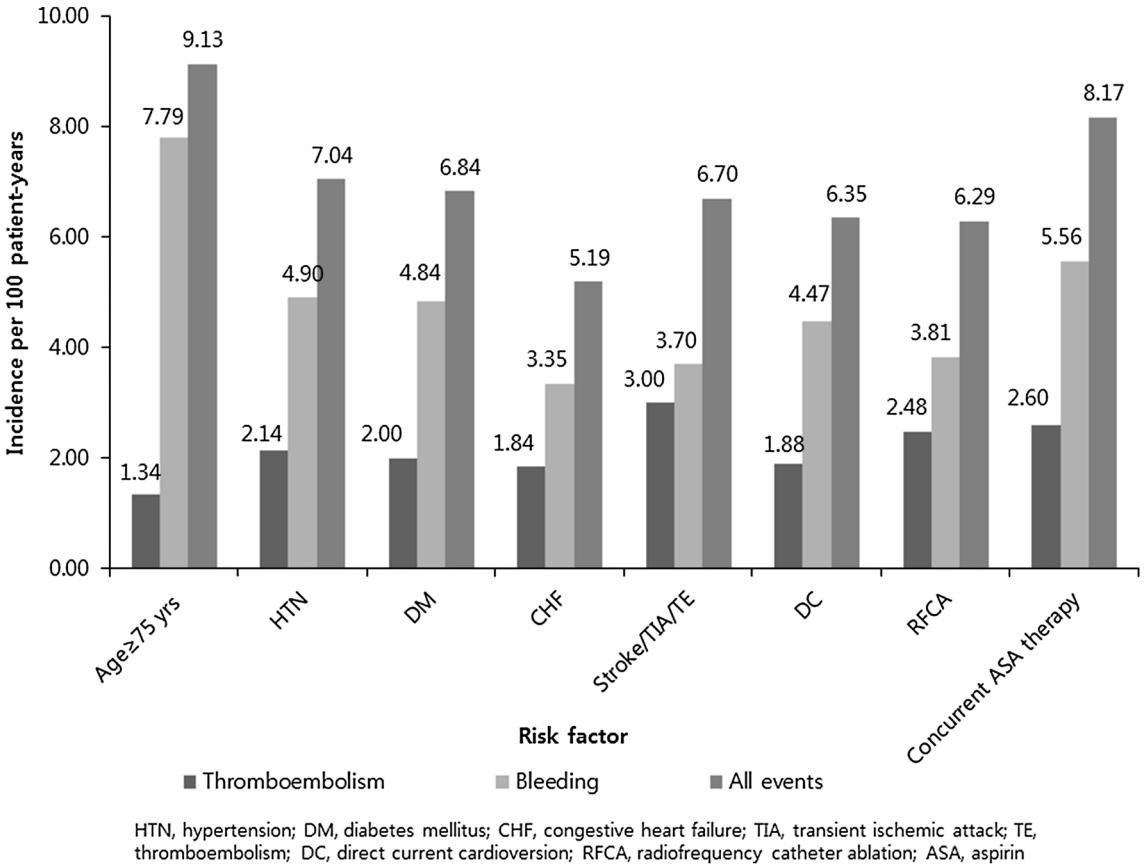


Fig. 1 The incidence rates of thromboembolic and bleeding events by each risk factor

The optimal ranges were validated by comparing the complication rates of INR within the ranges to those of INR below or over the ranges. Patients within this therapeutic range had significantly lower complication rates compared to patients outside this therapeutic range. The hazard ratio (HR) of all events within this target range was 0.41 (CI 0.24–0.66). The HRs of the complications by risk factors are summarized in Table 3.

We evaluated $CHADS_2$ score for each subgroup. As shown in Table 4, $CHADS_2$ scores ranged between 1.8 and

3.3 in patients with risk factors whereas those were between 0.6 and 1.2 in patients without risk factors. Differences in $CHADS_2$ scores between the groups divided by the presence and absence of a risk factor of age, hypertension, diabetes, congestive heart failure, and stroke/transient ischemic attack/thromboembolism were 0.6, 1.3, 1.4, 1.1, and 2.3, respectively.

Discussion

Bleeding is the major complication of warfarin therapy, and it is strongly related to the intensity of anticoagulation. Therefore, studies have placed emphasis on establishing the lowest effective therapeutic range to find the optimal intensity of warfarin [11]. Several guidelines recommended that the target INR of 2.0–3.0 is effective for the prevention of stroke in the patients with AF [6]. Some studies have recommended that the optimal INR in elderly patients should be between 2.0 and 2.5, because old age was the most important risk factor for bleeding complications [15]. However, some researchers reported that the elderly patients with AF not only had higher rates of bleedings during anticoagulation but also had higher rates of ischemic strokes when anticoagulation therapy lessened in intensity [16].

A number of studies have suggested lower target INR in Asian populations. In a retrospective study in Japan, a target INR range of 1.6–2.6 was recommended in patients over the age of 70 [10]. In case of Chinese patients with NVAF, an optimal INR value of 1.8–2.4 was considered safe from both thromboembolic and bleeding complications, and all complication rate was the lowest in INR of 1.5–1.9 [11]. The effectiveness of low intensity anticoagulation therapy has also been reported in several Korean studies [12]. However, the target INR of 2.0–3.0 is still recommended in patients with AF, according to the guidelines for prevention of stroke in Korea [17]. The optimal ranges of INR are being disputed in clinical practice.

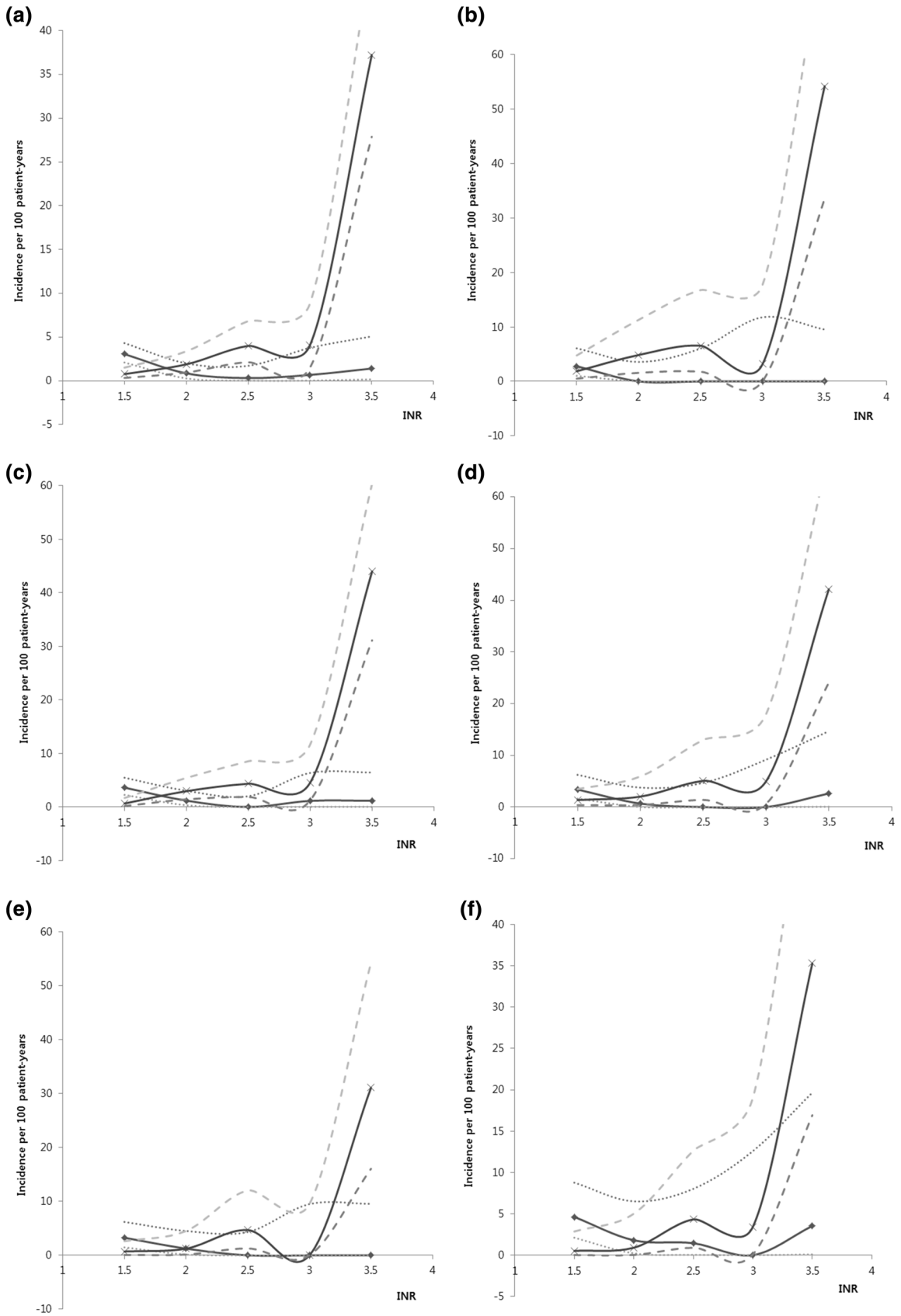
In the present study, the incidence of thromboembolism was 1.82 per 100 patient-years, and the incidence of bleeding was 4.05 per 100 patient-years. The risk of thromboembolic events was higher when INR was below 1.75, and the risk of bleeding was higher when INR was above 3.25. Although the study population had received warfarin therapy with a target value of 2.0–3.0, bleeding complications occurred more frequently. The INR value at the point of intersection of both complications was lower than 2.5, which was the middle point of 2 and 3. This result implies that the optimal therapeutic range in Korean should be lower than what is generally recommended.

The high incidence of bleeding complications in this population was consistent with results from other studies; it has been reported that Asians showed twofold to fourfold increase in the risk of hemorrhage compared to non-Asians, despite similar anticoagulation intensity [7]. A possible explanation is that d-dimer level suppression occurs in lower INR in Asians compared to Western populations. d-Dimer is known to reflect intravascular fibrin turnover. The level is increased in patients with AF. A study showed that significant suppression of d-dimer level was found in Asian patients with INR of 1.5–1.99 and in Western patients with INR of 2.0–3.0 [18, 19].

In the era of new oral anticoagulants, the benefits of warfarin therapy have been highlighted because it has been proved to be effective. A number of studies have revealed that good anticoagulation control was related to the quality of the anticoagulation services [20]. Although it is difficult to keep a narrow INR range in clinical settings, it was expected that a narrower therapeutic range could increase the quality of warfarin therapy and anticoagulation services, especially in populations with high incidence of fatal bleeding. Several previous studies reported that, in terms of stroke prevention, using a narrow range of INR 1.6–2.0 showed effectiveness up to 90 % of that provided by higher intensive therapy [21].

This study aimed to reduce complications by more than 50 % with new INR ranges. In case of an interval of 1.0, the INR range of 1.4–2.4 was determined, and complication rates were reduced by 29 % to those beyond the range. On the other hand, the complication rates were reduced up to 59 % with the INR range of 1.7–2.2. Thus, the optimal INR range with an interval of 0.5 was determined based on the complication rates. Our results showed that the optimal target INR appeared to be lower than what is generally recommended.

To analyze the subgroups, all participants were stratified by several factors including the stroke risk factors such as $CHADS_2$ and other well-known factors that affect the quality of oral anticoagulation [22]. Then, the rates of both complications were evaluated, and the optimal target ranges were estimated in each group. For the results, elderly patients above 75 had higher rates of bleeding complications compared to the whole group. This study revealed that patients with previous strokes displayed higher incidence rates of thromboembolic complications than those in all patients. Therefore, for patients $\geq$75 years of age, the target INR was optimized to be 1.3–1.8. Conversely, for the patients with previous strokes, the intersection point of both complications slightly increased compared to that of the whole group, and the optimal target level was determined to be 1.9–2.4. It was noticed that the addition of antiplatelet agents to warfarin therapy potentially increased the risk of bleeding. In the present study, for patients taking


(a)
Incidence per 100 patient-years
INR
(b)
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(c)
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INR
(e)
Incidence per 100 patient-years
INR
(f)
Incidence per 100 patient-years
INR

◀**Fig. 2** Incidence of thromboembolic and bleeding complications in Korean patients with NVAF. *Filled diamond*: thromboembolic complications; *asterisk*: bleeding complications; *dotted lines*: 95 % CI of thromboembolic complications; *dashed lines*: 95 % CI of bleeding complications. **a** All patients, **b** patients ≥75 years of age, **c** patients with hypertension, **d** patients with diabetes, **e** patients with congestive heart failure, **f** patients with prior stroke, **g** patients with direct cardioversion, **h** patients with radiofrequency catheter ablation, **i** patients with concurrent aspirin therapy

aspirin concurrently, an INR of 1.5–2.0 was recommended, which was lower compared to the whole group.

According to $CHADS_2$ index, one point was assigned for each risk factor except for prior stroke or transient ischemic attack. In our subgroup analysis, differences in $CHADS_2$ scores between groups in the presence and absence of risk factors with one point were ranged between 0.6 and 1.4. In the case of stroke or transient ischemic attack, score difference was 2.3. Since the difference was not much less or greater than the point of risk factors (one or two), it was suggested that anticoagulation intensity was considerably attributed to each risk factor while minimizing effects of other covariates.

It was reported that the risk of stroke increased up to 2 % and the incidence rate of thromboembolic complications increased to 0.5–0.9 % when catheter ablation was performed on the left atrium [23]. In this study, the target INR of the group that underwent RFCA was determined to be 1.7–2.2, and the HR of complication rates in the patients within this range was 0.32 compared to those outside of this range (CI 0.11–0.90). In a retrospective study of 1133

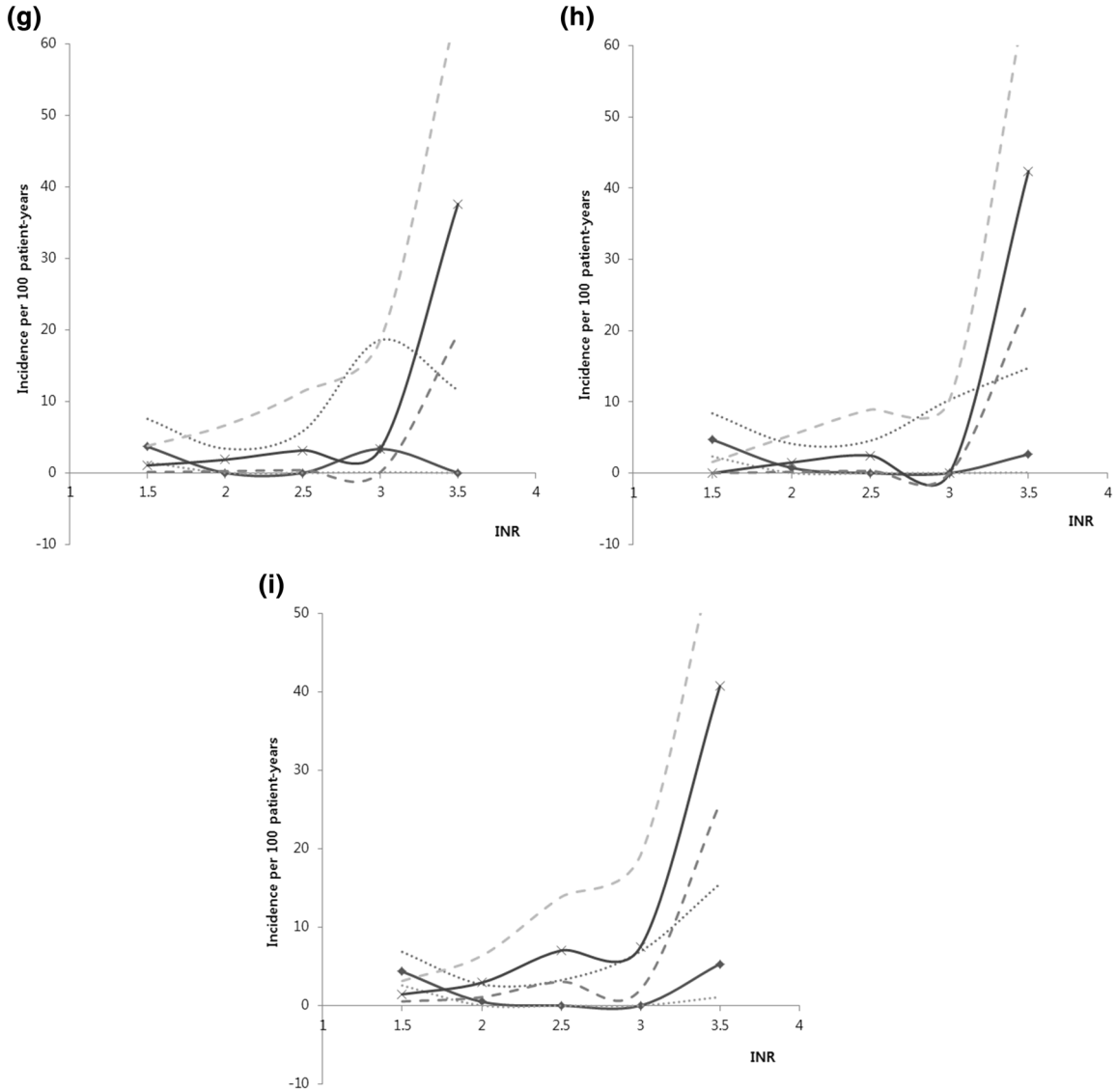

Fig. 2 continued

Table 3 Hazard ratio of complications in patients with non-valvular atrial fibrillation

Risk factor (no. of patients)	Optimal TR	Within TR[a]	Outside TR	HR[b]	95 % CI
All patients (1014)	1.7–2.2	20 (3.00)*	112 (7.07)	0.41	0.24–0.66
Age ≥75 years (209)	1.3–1.8	5 (3.80)*	36 (11.3)	0.33	0.13–0.85
Hypertension (608)	1.5–2.0	15 (3.62)*	77 (8.63)	0.41	0.23–0.71
Diabetes (247)	1.5–2.0	6 (3.22)*	35 (8.47)	0.36	0.15–0.87
Congestive heart failure (219)	1.8–2.3	5 (3.08)	26 (5.98)	0.50	0.19–1.30
Stroke/TIA/thromboembolism (167)	1.9–2.4	6 (5.50)	23 (7.10)	0.74	0.30–1.81
Direct current cardioversion (227)	1.7–2.2	2 (1.60)*	25 (8.34)	0.19	0.04–0.78
RFCA (325)	1.7–2.2	4 (2.55)*	29 (7.89)	0.32	0.11–0.90
Concurrent aspirin therapy (360)	1.5–2.0	9 (3.46)*	60 (10.26)	0.33	0.16–0.66

TR therapeutic range, *HR* hazard ratio, *CI* confidence interval, *TIA* transient ischemic attack, *RFCA* radiofrequency catheter ablation

* $p < 0.05$

[a] Number of complications (incidence per 100 patient-years)

[b] Hazard ratio within TR group compared to outside TR group

Table 4 $CHADS_2$ score in each group

	$CHADS_2$ score[a]	Difference between two groups
Age ≥75 years		
Yes	1.8 ± 1.2	0.6
No	1.2 ± 1.1	
Hypertension		
Yes	1.9 ± 1.1	1.3
No	0.6 ± 0.9	
Diabetes		
Yes	2.5 ± 1.1	1.4
No	1.1 ± 1.0	
Congestive heart failure		
Yes	2.3 ± 1.2	1.1
No	1.2 ± 1.1	
Stroke/TIA/thromboembolism		
Yes	3.3 ± 0.9	2.3
No	1.0 ± 0.8	

TIA transient ischemic attack

[a] Mean ± SD

patients with RFCA, which was conducted in the United States, a narrow range of 2.1–2.5 was recommended [24].

The target INR range in patients with direct current cardioversion was the same as that in patients with catheter ablation. It has been shown that, by keeping the INR within these ranges in patients with cardioversion, complication risks could be significantly reduced by 81 % (HR 0.19, CI 0.04–0.78). Therefore, to minimize the risk of complications for patients with rhythm control procedures, it may be helpful to monitor INR more frequently to achieve stable INR values within the target range.

The present study has the advantages of targeting only NVAF patients and optimizing the target INR by subgroups, but it also has several limitations. The inherent limitation of this retrospective study was that the data on some of the risk factors for complications, such as vitamin K intake and blood pressures, could not be collected. This study was performed in a single center, which might be considered as an additional limitation. Also, recently, $CHADS_2$ was modified to CHA_2DS_2–VASc score. However, our study population was stratified according to the $CHADS_2$ risk factors because this study was started before establishing the new guideline.

Nevertheless, this is the first long-term follow-up study of a large population to evaluate the optimal therapeutic ranges of warfarin therapy in Korean patients with NVAF. In addition, the method of determining adequate INR levels by using INR-incidence of complications curves might be employed in many clinical settings. An INR of 1.7–2.2 appeared to be associated with the lowest incidence rate of major thromboembolic and bleeding complications. These results support the implementation of less intensive anticoagulation therapy for East Asian populations, including Koreans.

Conclusion

An INR of 1.7–2.2 appeared to be associated with the lowest incidence rate of major thromboembolic and bleeding complications in Korean patients with NVAF.

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Conflicts of interest The authors have declared no potential conflict of interests.

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