



Quality of Anticoagulation with Warfarin in Korean Patients with Atrial Fibrillation and Prior Stroke: A Multicenter Retrospective Observational Study

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Background and Purpose The quality of anticoagulation is critical for ensuring the benefit of warfarin, but this has been less well studied in Korean ischemic stroke patients with atrial fibrillation (AF).

Methods This study retrospectively analyzed the data of patients who had an AF-related ischemic stroke and were treated with long-term warfarin therapy in 16 Korean centers. The quality of warfarin therapy was primarily assessed by the time in therapeutic range [TTR; international normalized ratio (INR), 2.0–3.0] and additionally by the proportion of INR values within the therapeutic range.

Results The long-term warfarin-treated cohort comprised 1,230 patients. They were aged 70.1±9.7 years (mean±SD), 42.5% were female, and their CHA₂DS₂-VASc score was 4.75±1.41. The TTR analysis included 33,941 INR measurements for 27,487 months: per patients, 27.6 (SD, 22.4) INR measurements for 22.4 (SD, 12.9) months. The mean TTR of individual patients was 49.1% (95% confidence interval, 47.9–50.3%), and the TTR quartiles were <34.5, 34.5–49.1, 49.1–64.5%, and >64.5%. None of the 16 centers achieved a mean TTR of >60%. Of all INR measurements, 44.6% were within the therapeutic range, 41.7% were <2.0, and 13.7% were >3.0.

Conclusions In Korean ischemic stroke patients who had AF, the quality of warfarin therapy was low and might be inadequate to effectively prevent recurrent stroke or systemic embolism.

Key Words warfarin, quality, time in therapeutic range, atrial fibrillation, secondary stroke prevention.

INTRODUCTION

Cardioembolic stroke has increased and now accounts for one in five ischemic strokes in Korea.^{1,2} Among Korean patients with acute ischemic stroke, 19% had atrial fibrillation (AF), who require long-term anticoagulation for secondary stroke prevention.²

Before the introduction of non-vitamin K antagonist oral antagonists (NOACs), warfarin was the only available oral anticoagulant and is still widely used in clinical practice. The efficacy and safety of warfarin are critically dependent on maintaining the international normalized ratio (INR) within the therapeutic range.^{3,4} However, it is widely perceived that adequate anticoagulation with warfarin is not well achieved in Koreans, which is partially attributable to their high intake of vitamin-K-rich foods and high frequency of genetic polymorphisms that are unfavorable for stable anticoagulation with warfarin.⁵⁻⁷ In pivotal NOAC trials, Korean patients randomized to warfarin achieved a mean time in therapeutic range (TTR) of less than 60%, which was lower than the average TTR of overall patients.⁸⁻¹¹ TTR in real-world practice is expected to be lower than in a clinical trial setting. A single-center

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study in which warfarin therapy was managed by a formal anticoagulation clinic showed that the TTR in AF-related stroke patients was 57.5%.¹² However, a formal anticoagulation clinic is not widely available in Korean centers, and the quality of anticoagulation with warfarin in more-representative Korean AF-related stroke patients has not been systematically investigated.

The current multicenter study aimed to assess the quality of anticoagulation with warfarin in patients with AF-related stroke who received long-term warfarin therapy. Additionally, we explored demographic and clinical factors associated with poor INR control.

METHOD

Study subjects

This was a retrospective observational study designed to analyze data of patients who had AF-related ischemic stroke and were treated with long-term warfarin therapy (long-term warfarin-treated cohort) in the neurology departments of 16 participating centers between January 1, 2011 and December 31, 2012. We collected INR data for this study until December 31, 2014.

Inclusion criteria for the long-term warfarin-treated cohort were 1) admission due to AF-related ischemic stroke (known AF or newly detected AF), 2) receiving long-term warfarin therapy for at least 90 days after the 7-day warfarin adjustment period, 3) for TTR calculation, the number of consecutive INR measurements of ≥ 3 after the 7-day warfarin adjustment period, and 4) TTR evaluable for ≥ 90 days. Exclusion criteria were 1) AF in the presence of a mechanical valve, 2) enrollment in a randomized clinical trial testing anticoagulation, and 3) enrollment in another study affecting the INR target range. Patients who met inclusion criteria of 1) and 3) were included in the warfarin-initiated cohort (Fig. 1).

For TTR analysis, the INR values measured during the following periods were excluded: 1) first 7 days after warfarin initiation, 2) interval between two consecutive INR measurements of >9 weeks, and 3) 7 days before and 21 days after intentional temporary warfarin interruption due to bleeding, surgery, or other invasive procedures. In addition, for patients who received NOAC, the period of NOAC treatment was also excluded.

For each patient, we collected data on demographics, individual components of CHADS₂ and CHA₂DS₂-VASc, dates of first and last warfarin treatments, INR values with dates, and warfarin interruptions and their reasons. This study was approved by the Institutional Review Board (IRB) of each participating center. The informed consent from individual patients or their legally authorized representatives was waived by the

relevant IRBs because this was a retrospective study and data were collected while ensuring the anonymity of individual patients.

Outcomes

The primary outcome was the TTR as measured by the proportion of time that INR was within the therapeutic range of 2.0–3.0, using the Rosendaal linear interpolation method.¹³ We assessed the TTR of each patient and calculated the mean TTR. The secondary outcome was the proportion of INR values within the therapeutic range of 2.0–3.0 as indicated by the numbers of INR values within the therapeutic range divided by the total number of INR measurements.

Statistical analysis

Categorical variables are summarized as frequencies and percentages, while continuous variables are presented as mean \pm SD or median (interquartile range) values. To assess the quality of warfarin treatment, we calculated the individual TTR for each patient using the Rosendaal linear interpolation method, which assumes a linear relationship between two consecutive INR values and determines the proportion of time that the INR is within the therapeutic range of 2.0–3.0.¹³ To delineate the overall quality of warfarin treatment, we analyzed the mean TTR with 95% confidence interval (CI) and the overall distribution of TTRs of individual patients. We also analyzed the proportion of INR values within the therapeutic range of 2.0–3.0 and the overall distribution of INR values. In addition, the mean TTR and the proportion of INR values within the therapeutic range were analyzed for each participating center with anonymity.

To explore the factors associated with poor anticoagulation quality, patients were dichotomized into groups with TTR $\geq 60\%$ and $<60\%$. For univariable analysis, categorical variables were compared using the chi-square test or Fisher's exact test as appropriate, while continuous variables were compared using Student's *t*-test or the Wilcoxon rank-sum test. For multiple logistic regression analyses to explore the independent factors for TTR $<60\%$, we used the generalized-estimating-equation model to adjust for the within-hospital clustering of the collected data. Covariates with $p < 0.1$ in the comparisons of baseline characteristics between the two groups were adjusted. We analyzed the tolerance limit, variance inflation factor, eigenvalue, and condition index in order to evaluate the presence of multicollinearity in the multivariable models, if indicated.

Sample size calculation

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study, the mean TTR of the enrolled

Korean patients was 55%.⁸ In clinical practice, TTR would be lower than that found in the RE-LY trial, and so we assumed that the mean TTR would be 45%. Including 1,057 subjects would ensure that TTR would be within 3% of the two-sided 95% CI for the expected TTR (namely, 42 to 48%) using the large-sample approximation.¹⁴ Noting that no dropout is expected due to a retrospective nature of this study, we aimed to enroll at least 1,057 subjects who met the criteria for the long-term warfarin-treated cohort.

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RESULTS

Characteristics of the patients

Between January 1, 2011 and December 31, 2012 there were 3,025 patients who had an acute ischemic stroke or transient ischemic attack and AF and were admitted to 16 participating centers. In three centers the warfarin therapy was managed by a formal anticoagulation clinic. We excluded 1,211 patients due to no warfarin therapy being administered, presence of a mechanical valve, duration of warfarin therapy of <7 days, or less than 3 consecutive INR measurements after the warfarin adjustment period. Therefore, the warfarin-initiated cohort comprised 1,814 patients. From the warfarin-initiated cohort, 1,230 patients were finally included in the long-term warfarin-treated cohort after excluding 584 patients for whom TTR was evaluable for <90 days (Fig. 1). During the study period, only three patients were enrolled in clinical trials that potentially affected the target INR range. For these patients, INR data after the trials were included in this study. The long-term warfarin-treated cohort was the main population of the current analysis. Data for the warfarin-initiated cohort were additionally analyzed and are provided in the Supplementary Tables 1, 2, and 3 (in the online-only Data Supplement).

The demographic and clinical characteristics of the long-term warfarin-treated cohort are provided in Table 1. In brief, the subjects were aged 70.1 ± 9.7 years, 42.5% were female, their National Institutes of Health Stroke Scale (NIHSS) score at admission was 6.0 ± 5.9 , their CHADS₂ score was $3.39 \pm$

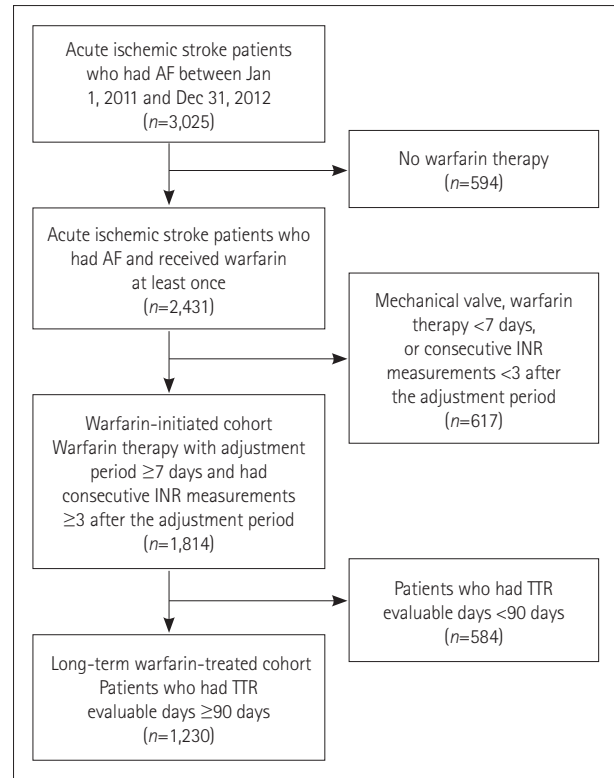


Fig. 1. Selection of patients. AF: atrial fibrillation, INR: international normalized ratio, TTR: time in therapeutic range.

0.96, and their CHA₂DS₂-VASc score was 4.75 ± 1.41 .

During the study period there was a total of 46,483 INR measurements, corresponding to 37.8 ± 22.9 per patient. The total duration of INR measurements was 34,735 months, corresponding to 28.2 ± 13.6 months per patient, and the interval between consecutive INR measurements was 28.3 ± 16.1 days. After excluding INR data obtained ≤ 7 days after initiation warfarin, during an intentional temporary warfarin interruption, and with a consecutive INR measurement interval of >9 weeks, the current TTR analysis included 33,941 INR measurements over 27,487 months, constituting 27.6 ± 22.4 INR measurements over 22.4 ± 12.9 months per patient. The interval between two consecutive INR measurements was 21.7 ± 11.9 days; the average interval was 0–15 days in 34.6%, 16–30 days in 44.2%, 31–45 days in 18.3%, 46–60 days in 2.7%, and >60 days in 0.2% of the patients.

Time in therapeutic range

The mean TTR in the long-term warfarin-treated cohort was 49.1% (95% CI, 47.9–50.3%). The quartiles of TTR were <34.5, 34.5–49.1, 49.1–64.5, and >64.5% (Table 2). Of the patients, 30.8% had TTR $\geq 60\%$ and 17.4% had TTR $\geq 70\%$ (Fig. 2). Across the 16 centers, the mean TTR ranged from 37.3 to 58.4%, and no center achieved a mean TTR of $\geq 60\%$. The mean (95% CI) TTR values of the three centers with formal anticoag-

Table 1. Demographics and baseline characteristics

Variable	Long-term warfarin-treated patients (n=1,230)
Age, years	70.1±9.7
<65	300 (24.4)
65–74	515 (41.9)
≥75	415 (33.7)
Female	523 (42.5)
Height, cm	162.7±8.7
Weight, kg	63.1±11.4
NIHSS score*	
Mean±SD	6.0±5.9
Median (IQR)	4.0 (2.0–9.0)
<8	865 (70.7)
8–16	261 (21.2)
>16	97 (7.9)
Creatinine level, mg/dL	1.01±0.54
CHADS ₂ score	3.39±0.96
CHA ₂ DS ₂ -VASc score	4.75±1.41
Congestive heart failure	142 (11.5)
Hypertension	842 (68.5)
Diabetes mellitus	315 (25.6)
Stroke/transient ischemic attack	1,230 (100.0)
Vascular disease	210 (17.1)
Total INR measurements included in TTR analysis	33,941
Number of INR measurements per patient included in TTR analysis	27.6±22.4
Total duration in TTR analysis, months	27,487
Duration per patient in TTR analysis, months	22.4±12.9
Interval between consecutive INR measurements included in TTR analysis, days	21.7±11.9

Data are n (%), mean±SD, or mean (IQR) values.

*NIHSS score was not available in seven patients.

INR: international normalized ratio, IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale, TTR: time in therapeutic range.

Table 2. TTR and INR included in TTR analysis

	Long-term warfarin-treated patients (n=1,230)
Mean TTR (95% CI)	49.1 (47.9–50.3)
TTR quartiles, %	
1st quartile	<34.5
2nd quartile	34.5–49.1
3rd quartile	49.1–64.5
4th quartile	>64.5
INR, mean	2.25±0.89
INR 2.0–3.0, %	44.6
INR range, %	
<1.50	16.5
1.50–1.99	25.2
2.00–2.49	27.8
2.50–3.00	16.7
3.01–3.50	7.3
3.51–4.00	3.1
>4.00	3.3

Data are mean (95% CI), mean±SD, or % values.

INR: international normalized ratio, TTR: time in therapeutic range.

ulation clinics were 58.4% (54.9–61.9%), 57.5% (53.7–61.3%), and 50.4% (46.0–54.8%), which were generally higher than those of the 13 centers without formal anticoagulation clinics (Table 3).

Proportion of INR values within the therapeutic range

Of 33,941 INR measurements included in the TTR analysis, 44.6% were within the therapeutic range of 2.0–3.0, 41.7% were <2.0, and 13.7% were >3.0 (Table 2). Across the 16 centers, the proportion of INR values of 2.0–3.0 ranged from 36.1 to 53.4% (Table 3).

Predictors of poor quality of anticoagulation with warfarin

Table 4 presents the results of unadjusted and adjusted analyses for predictors of poor INR control as determined by TTR <60%. On unadjusted analysis, baseline variables of old age, female sex, small height, low weight, high NIHSS score, high creatinine level, high CHADS₂ score, high CHA₂DS₂-VASc score, and diabetes were associated with TTR <60%. However,

when three multivariable models were applied [model 1 was adjusted for age, sex, height, weight, NIHSS score category, creatinine level, and diabetes (variables with $p < 0.1$ based on the protocol); model 2 was the same as model 1 plus adjustment for CHADS₂ score; and model 3 was the same as model 1 plus adjustment for CHA₂DS₂-VASc score], only the highest baseline NIHSS score category (NIHSS score >16) was consistently associated with poor INR control. For models 2 and 3, no significant multicollinearity among variables was found.

Warfarin-initiated cohort

The warfarin-initiated cohort comprised 1,814 patients, and

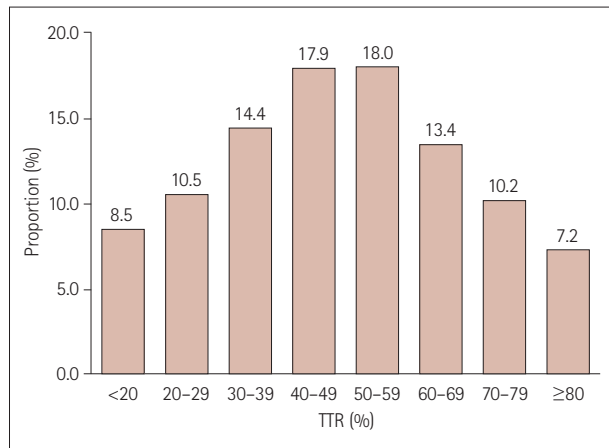


Fig. 2. Proportion of patients according to TTRs in the long-term warfarin-treated cohort. TTR: time in therapeutic range.

Table 3. TTR and proportion of INR 2.0–3.0 included in TTR analysis in each center

Center	No.	Mean TTR (95% CI)	INR 2.0–3.0 (%)
1	88	55.9 (52.3–59.5)	46.3
2	95	47.4 (43.1–51.7)	42.9
3	63	51.7 (47.5–56.0)	40.9
4	56	42.7 (38.0–47.4)	36.1
5*	121	58.4 (54.9–61.9)	51.7
6	64	45.6 (40.8–50.4)	46.1
7	31	45.6 (39.3–51.8)	40.4
8	60	37.1 (32.2–42.0)	37.0
9	48	50.0 (45.0–55.0)	44.2
10	38	49.2 (41.7–56.7)	44.9
11*	107	57.5 (53.7–61.3)	53.4
12	39	50.6 (44.0–57.2)	47.9
13	129	38.6 (35.1–42.0)	36.4
14	131	53.6 (49.9–57.2)	50.1
15	59	37.3 (32.0–42.6)	37.7
16*	101	50.4 (46.0–54.8)	43.6

Data are mean (95% CI) or % values.

*Centers in which warfarin therapy was managed by a formal anticoagulation clinic during the study period.

INR: international normalized ratio, TTR: time in therapeutic range.

their demographic and clinical characteristics are provided in Supplementary Table 1 (in the online-only Data Supplement). In this cohort, the mean TTR was 47.3% (95% CI, 46.2–48.3%). Of 42,634 INR measurements included in the TTR analysis, 44.6% were within the therapeutic range of 2.0–3.0 (Supplementary Table 2 in the online-only Data Supplement). Across the 16 centers, the mean TTR ranged from 35.2 to 57.3%, and the proportion of INR values of 2.0–3.0 ranged from 35.4 to 53.8% (Supplementary Table 3 in the online-only Data Supplement).

DISCUSSION

This study shows that the quality of long-term oral anticoagulation with warfarin therapy is inadequate for secondary stroke prevention in Korean AF patients who have experienced stroke. The mean TTR was 49.1%, and only 31% of patients achieved TTR >60%, and 17% had TTR >70%. Given that no single center achieved the mean TTR of >60%, inadequate INR control is likely to be widespread. The proportion of INR values within the therapeutic range of 44.6% also indicates that anticoagulation with warfarin is inadequate in Korean stroke patients with AF.

Dietary and genetic factors in Koreans might contribute to the current low TTR values. According to the Korean National Health and Nutrition Examination Survey, the estimated daily intake of vitamin K was $322.40 \pm 6.33 \mu\text{g}$ for men and $271.20 \pm 4.92 \mu\text{g}$ for women, and it increased significantly with age.⁵ This daily intake of Koreans was much greater than those estimated in the United Kingdom and the United States,^{15,16} and higher than those observed in Japanese subjects.¹⁷ *CYP2C9* and *VKORC1* polymorphisms are well known to influence the anticoagulation quality with warfarin. More than 90% of Koreans carry *VKORC1* variants that lead to enhanced sensitivity to warfarin.⁷ In a previous study, the *VKORC1* TT variant was an independent predictor for low TTR in Korean stroke patients.¹² In addition, the frequency of the *CYP2C9**3 allele, which is related to decreased warfarin metabolism, was higher in the Korean population than in other populations.⁶

The physician factor might also account for the current low TTR rate. Across all INR measurements, 41.7% were INR <2.0 but only 13.7% were >3.0. Therefore, Korean physicians might tend to avoid a high INR level because of bleeding concerns due to Asian populations being at a greater risk of major bleeding with anticoagulation and having a higher incidence rate of primary intracerebral hemorrhage compared to non-Asian populations. This finding is in accordance with data from NOAC trials showing that Asians had higher proportions of INR <2.0 and lower proportions of INR >3.0 compared to non-Asians.¹⁸ Since the target INR of 2.0–3.0 has

Table 4. Predictors of poor anticoagulation quality (TTR <60%)

Variable	TTR ≥60% (n=379)	TTR <60% (n=851)	Unadjusted analysis		Adjusted analysis		
			p*	OR (95% CI) [†]	Model 1 OR (95% CI) [†]	Model 2 OR (95% CI) [†]	Model 3 OR (95% CI) [†]
Age, years	69.2±10.0	70.5±9.6	0.0275	1.01 (1.00–1.03)	1.01 (0.99–1.02)	1.01 (0.99–1.02)	1.01 (0.99–1.03)
Age category for CHADS ₂			0.1209				
<75 years	263 (69.4)	552 (64.9)		Reference			
≥75 years	116 (30.6)	299 (35.1)		1.24 (0.95–1.61)			
Age category for CHA ₂ DS ₂ -VASc			0.2831				
<65 years	99 (26.1)	201 (23.6)		Reference			
65–74 years	164 (43.3)	351 (41.3)		1.06 (0.78–1.43)			
≥75 years	116 (30.6)	299 (35.1)		1.28 (0.93–1.77)			
Female	45 (38.3)	378 (44.4)	0.0436	1.31 (1.02–1.67)	0.82 (0.56–1.22)	0.82 (0.56–1.23)	0.85 (0.55–1.30)
Height, cm	164.0±8.4	162.1±8.8	0.0003	0.97 (0.96–0.99)	0.97 (0.94–0.99)	0.97 (0.94–0.99)	0.97 (0.94–0.99)
Weight, kg	64.3±11.1	62.5±11.6	0.0117	0.99 (0.98–1.00)	1.00 (0.99–1.02)	1.00 (0.99–1.02)	1.00 (0.99–1.02)
NIHSS score	5.29±5.3	6.24±6.2	0.0063	1.03 (1.01–1.05)			
NIHSS score category			0.0056				
<8	287 (76.1)	578 (68.3)		Reference			
8–16	72 (19.1)	189 (22.3)		1.30 (0.96–1.77)	1.22 (0.88–1.69)	1.22 (0.88–1.69)	1.22 (0.88–1.69)
>16	18 (4.8)	79 (9.3)		2.18 (1.28–3.71)	2.51 (1.44–4.37)	2.50 (1.43–4.36)	2.50 (1.44–4.35)
Creatinine level, mg/dL	0.97±0.34	1.03±0.61	0.0367	1.26 (0.96–1.65)	1.27 (0.96–1.69)	1.27 (0.96–1.69)	1.28 (0.96–1.71)
CHADS ₂ score	3.28±0.93	3.44±0.96	0.0065	1.20 (1.06–1.37)		1.04 (0.85–1.27)	
CHA ₂ DS ₂ -VASc score	4.58±1.38	4.82±1.42	0.0061	1.13 (1.04–1.24)			0.98 (0.82–1.16)
Congestive heart failure	38 (10.0)	104 (12.2)	0.2661	1.29 (0.87–1.91)			
Hypertension	251 (66.2)	591 (69.5)	0.2617	1.16 (0.90–1.51)			
Diabetes mellitus	81 (21.4)	234 (27.5)	0.0231	1.39 (1.04–1.85)	1.42 (1.05–1.93)	1.36 (0.93–2.01)	1.46 (1.01–2.10)
Vascular disease	67 (17.7)	143 (16.8)	0.7067	0.93 (0.67–1.27)			

Data are n (%) or mean±SD values except where indicated otherwise. Model 1: adjusted for age, sex, height, weight, NIHSS score category, creatinine level, and diabetes (variables with p<0.1 based on protocol), Model 2: adjusted for age, sex, height, weight, NIHSS score category, creatinine level, diabetes, and CHADS₂ score, Model 3: adjusted for age, sex, height, weight, NIHSS score category, creatinine level, diabetes, and CHA₂DS₂-VASc score.

*p value for unadjusted analysis: for categorical variables, chi-square test or Fisher's exact test; for continuous variables, t-test or Wilcoxon rank-sum test, [†]By logistic regression model; modeling the probability of TTR <60%.

NIHSS: National Institutes of Health Stroke Scale, OR: odds ratio, TTR: time in therapeutic range.

been established in Caucasian populations, some physicians might consider applying the Japanese guidelines that recommend a target INR of 1.6–2.6 for elderly patients aged >70 years.¹⁹ However, this recommendation was based on a small randomized trial (Japanese Nonvalvular Atrial Fibrillation–Embolism Secondary Prevention Cooperative Study) involving only 115 patients and another small retrospective study of 203 patients,^{20,21} and 115 of the 203 patients in the latter study were those included in the former study. Recent data from a large registry in Japan support the lower target INR of 1.6–2.6 for efficacy and safety, but that study only used the baseline INR level and did not analyze follow-up INR or TTR values.²² Because there is no strong evidence for recommending the lower target INR of 1.6–2.6 in Asian populations, our study used the target INR of 2.0–3.0 for the current TTR analysis.

The low quality of warfarin therapy observed in this study suggests that warfarin treatment does not effectively prevent

recurrent stroke or systemic embolism in Korean stroke patients. In a post-hoc analysis of Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE-W), patients who were treated at centers with TTR <65% did not benefit from warfarin over clopidogrel plus aspirin, and the minimum TTR threshold driven from a population-average model was about 58%.²³ In the present study, only one center exceeded the minimum TTR threshold of 58%. Furthermore, in a large UK population-based study, compared to patients with no antithrombotic therapy, those with TTR >60% had a significant reduction of stroke risk, but those with TTR <50% had a higher risk of stroke.⁴ Applied to our results, only 31% of our patients were likely to benefit from warfarin therapy, whereas 51.2% of our patients who achieved TTR <50% might be exposed to a higher risk with warfarin therapy compared to no antithrombotic treatment. Therefore, the current findings indicate that the proportion of patients endangered by warfarin might be greater than the pro-

portion of patients who benefit from warfarin.

To improve the target INR achievement, 1) anticoagulation clinics, 2) patient self-testing and self-management using a point-of-care monitor, or 3) computer-software-assisted dose adjustment are recommended.²⁴ However, the accessibility to such approaches is very limited in real-world practice in Korea. Even in the present study in which academic and teaching hospitals participated, only 3 out of 16 centers were able to provide an anticoagulation clinic service. Although the centers with an anticoagulation clinic service had numerically higher TTRs compared to the centers without such a service, their mean TTRs were still less than 60%. Therefore, in Korea, the provision of an anticoagulation clinic service alone would not ensure an improvement in the quality of anticoagulation with warfarin. Moreover, the poor INR control in Korea is not limited to stroke patients. In Korean AF patients who took warfarin for more than 1 year and were largely managed by cardiologists, the proportion of INR values within the target range of 2.0–3.0 was 42.4%, which was slightly lower than observed in the present study; however, that study did not analyze TTR.²⁵

Given the poor INR control observed in the present study, warfarin would not be an ideal oral anticoagulant in Korean AF patients. In the pivotal NOAC trials, for most of the efficacy and safety endpoints, the absolute risk reductions with NOACs compared to warfarin were numerically greater in Asians than in non-Asians. In analyses restricted to Asian populations, compared to warfarin, all NOACs had significantly lower risks of intracranial hemorrhage, and most NOACs had lower risks of both major bleeding and any bleeding.²⁶ Although NOACs are more expensive than warfarin, cost-effective analyses showed that NOACs were more cost-effective than warfarin in various health-care settings.²⁷ Because the risks of thromboembolism and major bleeding are higher in Asians than non-Asians, NOACs might be particularly cost-effective in Asians; for example, a Taiwan study found that dabigatran was highly cost-effective in a clinical practice setting.²⁸

When we explored the predictors of poor anticoagulation control in several multivariable models, severe stroke indicated by an NIHSS score of >16 at admission was consistently associated with TTR <60%. Patients with severe stroke at presentation were likely to have more severe residual disability, which might contribute to poor INR control. In a large observation study involving 23,425 AF patients, TTR was significantly lower in patients with prior stroke than in those without prior stroke.²⁹ A previous study that derived the SAME-TT₂R₂ score showed that clinical factors of female sex, age <60 years, multiple comorbidities, treatment with interacting medications, tobacco use, and nonwhite race were associated with poor INR control. However, the SAME-TT₂R₂ score was derived

from and validated in AF populations in which more than 85% of patients had no history of stroke.³⁰ In a Korean study that enrolled AF patients with ischemic stroke, the SAME-TT₂R₂ score as well as other clinical factors were not associated with the quality of anticoagulation control as measured by TTR, whereas only *VKORC1* genotype was an independent predictor. Because of the retrospective nature of the present study, we were not able to fully evaluate the genetic factors and clinical factors included in the SAME-TT₂R₂ score. Furthermore, we could not adjust unmeasured confounders such as physician attitude, patient compliance, and diet change that potentially influence INR control. Therefore, our findings should be interpreted as exploratory.

This study has several limitations. The included patients were exclusively treated in academic or teaching hospitals, which limits the generalizability of our findings. The mean TTR of 49.1% was obtained from the long-term warfarin-treated cohort, and was lower in the warfarin-initiated cohort than in the warfarin-treated cohort alone. Of 2,431 patients who received warfarin at least once, 617 patients were not eligible for the TTR analysis, largely due to warfarin therapy being administered for less than 7 days or consecutive INR values being less than 3 after the adjustment period. Therefore, the overall quality of oral anticoagulation with warfarin would be worse for patients who are indicated for anticoagulation. This study had a retrospective design, and hence we were not able to analyze whether a low TTR was associated with clinical events. Finally, the findings from the exploration of independent factors for poor INR control should be interpreted with caution.

In conclusion, this study showed that, in Korean AF patients who had experienced stroke, the quality of oral anticoagulation with warfarin was low and might be inadequate to effectively prevent recurrent stroke or systemic embolism. Unless the quality of warfarin therapy substantially improves, a NOAC might be a preferred oral anticoagulant for secondary stroke prevention in Korean AF patients.

Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.3988/jcn.2017.13.3.273>.

Conflicts of Interest

The authors have no financial conflicts of interest.

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