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Maintenance dose of warfarin beyond time in therapeutic range for preventing vascular events

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ABSTRACT

Background: The quality of anticoagulation is closely associated with efficacy and safety in warfarin users. Although genetic polymorphisms have been related to warfarin dosages and vascular events(VE), genetic evaluations have not been recommended for all warfarin users. The aim is to evaluate the significance of the maintenance dose of warfarin (MDW) on VE, considering the time in therapeutic range (TTR).

Methods: This retrospective study analyzed the data of patients who received warfarin for any reasons. A total of 11,835 patients with warfarin were divided into quartiles by MDW. We assessed TTR using the Rosendaal method and VE.

Results: VE occurred in 9.1% of the warfarin users. The mean TTR level was 34.0 ± 25.7%, and the MDW was 3.38 ± 1.06 mg per day. Patients with VE were more likely to have a lower MDW and lower TTR levels. In moderate- or well-controlled TTR status, a lower MDW was significantly related to under-controlled anticoagulation and associated with higher risks of VE. Lower MDW had a higher risk of stroke or arterial/venous thromboembolism (Q1: OR, 1.57; 95% CI 1.25 to 1.96; Q2: OR, 1.40; 95% CI 1.12 to 1.75; Q3: OR, 1.35; 95% CI 1.08 to 1.68).

Conclusions: We suggest that patients with very low MDW might be at risk when using warfarin. Therefore, we propose that patients with a very low MDW might be alternatively considered for novel oral anticoagulants rather than warfarin.

1. Introduction

Recent studies have demonstrated that novel oral anticoagulants (NOACs) display efficacy, safety and convenience in preventing vascular events (VE) compared to warfarin [1–4]. The availability of NOACs indicates that physicians should now have adequate drug choices for preventing VE. The effectiveness of warfarin is dependent on the quality of anticoagulation control within the recommended International Normalised Ratio (INR) range of 2.0–3.0. The time in therapeutic range (TTR), which reflects the proportion of time spent within the therapeutic range of 2.0 to 3.0, is closely associated with morbidity and mortality [5,6]. A real-world study found that warfarin users with poor INR control (TTR < 50%) had a higher risk of stroke compared with patients who did not receive warfarin [7]. In patients with atrial fibrillation (AF), the American Medical Association recommended that physicians should consider NOACs instead of warfarin in cases of inadequate anticoagulation control [8] [9].

To adjust the INR, as with age and sex, the existence of genetic polymorphisms in the vitamin K epoxide reductase enzyme (VKORC1) and cytochrome P450 complex subunit 2C9 (CYP2C9) genes may influence functional enzyme activity. Patients with those polymorphisms typically receive lower maintenance doses of warfarin (MDW) [10] and have greater risks of VE [11]. However, physicians do not perform genetic evaluations of all warfarin users, and the current guidelines do not consider these evaluations to be necessary inspections. As a result, each person's MDW linked to their genetic factors might be a stronger variable than TTR itself for determining the appropriate anticoagulation strategy in practice.

In this regard, we hypothesized that MDW might play a significant role in the risk of VE such as stroke or arterial/venous thromboembolism and major bleeding. Therefore, the aim of this study was to evaluate the effect of MDW on VE, considering TTR, in warfarin users.

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2. Patients and methods

2.1. Study subjects

A total of 15,719 patients who were prescribed warfarin in Seoul National University Hospital Between 2003 and 2014 were identified. Inclusion criteria for warfarin treatment were 1) receiving warfarin for any reason in any department, 2) receiving warfarin for at least 90 days, 3) the number of INR count ≥ 3 for TTR calculation.

Among them, 74 patients who did not have the INR-checked and 14 patients with errors in their hospital charts were excluded. Subsequently, subjects with a history of cardiac valve implantation ($n = 328$) were excluded because of multiple influences on determining the target range of warfarin. Of these 15,303 patients, patients for whom the TTR could not be calculated using the Rosendaal method (INR count < 3, $n = 950$) were excluded. Patients for whom the prescription duration of warfarin under 90 days ($n = 2518$) were also excluded. Finally, a total of 11,835 patients who were prescribed warfarin (target range: INR 2–3) were enrolled. (Supplementary Fig. 1) Since the issue between MDW and VE was not only limited to patients with AF, we initially planned to study all warfarin users.

Information about age, gender, vascular risk factors such as hypertension, diabetes, dyslipidemia, AF and liver cirrhosis was extracted from the medical records, based on previous reports [12]. The MDW was defined as a mean daily dose of the warfarin prescription at each outpatient department (OPD) visit. Patients were divided into quartiles by warfarin maintenance dose (1Q: warfarin 0.29–2.538 mg, 2Q: warfarin 2.539–3.364 mg, 3Q: warfarin 3.365–4.142 mg, 4Q: warfarin 4.143–10.0 mg). The total number of INR evaluations and total days of warfarin prescriptions were also observed at each OPD visit. The TTR was calculated using both the Rosendaal and traditional methods. The percentage of time during which a subject had an INR between 2.0 and 3.0 was considered the TTR. The Rosendaal method assumes that the INR levels vary linearly between two measurements [13]. Using this assumption, the date at which a patient achieved or deviated from an INR within the therapeutic range was computed. The INR values on the days without measurement were interpolated [13]. We classified the TTR levels into three groups (TTR 0–40%, 40–60% and 60–100%) according to previous reports [7]. Additionally, we calculated the percentage of time with low INR (under 2.0) and high INR (over 3.0) among all INR evaluations. The LINR50 and HINR50 were defined as the percentages of low INR under 2.0 and high INR over 3.0 exceeding 50%, respectively.

2.2. Outcomes

We assessed stroke or arterial/venous thromboembolism and major bleeding as VE. The thromboembolic endpoints consisted of symptomatic cerebral infarction, splenic infarction, spinal cord infarction, renal infarction, pulmonary embolism, deep vein thrombosis, cerebral venous thrombosis and aortic, abdominal, or limb artery thrombosis. Major bleeding endpoints included intracerebral hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, epidural hemorrhage, epidural hemorrhage, and gastrointestinal hemorrhage that were not explained by other etiologies (e.g., trauma, infection) (see Supplementary Table 1). The definition of major bleeding consists of bleeding of critical site (intracranial bleeding), fatal bleeding requiring hospitalization. [2]

2.3. Statistical analyses

Continuous variables are presented as the mean ± standard deviation (SD). Statistical comparisons of clinical characteristics were conducted using Student's *t*-test or χ^2 test. The trends were also calculated using the χ^2 test for trends in proportion. Odds ratios (ORs) and 95% confidence intervals (CIs) were expressed for results and probability. All tests were 2-sided, and a probability value of < 0.05 was considered statistically significant. Analyses were performed using SPSS Version 21.0 (SPSS Inc., Chicago, IL, USA).

The institutional review board of Seoul National University Hospital (H-1409-044-608) approved this study protocol, and written informed consent was obtained from all participants or next of kin when obtaining consent from the patient was not possible.

Table 1
Baseline characteristics of total population.

	Non-VE	VE	*p*-Value
	(n = 10,753)	(*n* = 1082)	
Age, years	65 ± 18	67 ± 18	< 0.01
Gender, female, n (%)	4653(43.3)	491 (45.4)	0.18
Vascular risk factor			
Hypertension, n (%)	1672 (15.5)	228 (21.1)	< 0.001
Diabetes, n (%)	1574 (14.6)	238 (22.0)	< 0.001
Dyslipidemia, n (%)	624 (5.8)	145 (13.4)	< 0.001
Atrial fibrillation	6485 (60.3)	520 (48.1)	< 0.001
Liver cirrhosis	368 (3.4)	40 (3.7)	0.94
Total days of warfarin prescription, days	2264 ± 2607	1422 ± 1695	< 0.001
Warfarin mean dose, mg/day	3.39 ± 1.06	3.37 ± 1.03	0.537
Warfarin mean dose, quariles, n (%)			< 0.01*
1Q (warfarin 0.29–2.538 mg)	2649 (24.6)	310 (28.7)	
2Q (warfarin 2.539–3.364 mg)	2680 (24.9)	278 (25.7)	
3Q (warfarin 3.365–4.142 mg)	2699 (25.1)	265 (24.5)	
4Q (warfarin 4.143–10.0 mg)	2725 (25.3)	229(22.2)	
Total number of INR count	41.6 ± 44.5	46.1 ± 43.7	0.001
Time within therapeutic range by Rosendaal method, %	34.43 ± 25.88	30.08 ± 23.15	< 0.001
Time within therapeutic range by Rosendaal method _3 group, n(%)			< 0.001*
TTR 0–40%	6190 (57.6)	699 (64.6)	
TTR 40–60%	2253 (21.0)	236 (21.8)	
TTR 60–100%	2310 (21.5)	147 (13.6)	
Low INR percentile by Rosendaal method	58.89 ± 30.18	63.27 ± 27.73	< 0.001
Low INR (INR < 2) > 50%, n (%)	6280 (58.4)	712 (65.8)	< 0.001
High INR percentile by Rosendaal method	6.68 ± 9.76	6.63 ± 9.51	0.87
High INR (INR > 3) > 50%, n (%)	77 (0.7)	8 (0.7)	0.93
Time within therapeutic range by Traditional method, %	32.95 ± 19.37	32.08 ± 16.15	0.10
Low INR percentile by Traditional method	58.23 ± 23.00	58.56 ± 19.59	0.60
High INR percentile by Traditional method	8.85 ± 9.09	9.40 ± 8.67	0.06
Laboratory findings			
White blood cell	7134 ± 4875	7721 ± 7368	0.01
Hematocrit	39.22 ± 6.16	37.38 ± 6.68	< 0.001
Platelet	216 K ± 83 K	220 K ± 92 K	0.20
ESR	26.2 ± 26.2	31.2 ± 27.7	< 0.001
BUN	18.73 ± 12.47	20.56 ± 15.53	< 0.001
Creatine	1.15 ± 1.10	1.23 ± 1.29	0.04
GFR	74.77 ± 34.91	74.89 ± 34.64	0.92
Total cholesterol	164.7 ± 40.1	160.5 ± 45.4	< 0.01
Albumin	4.04 ± 0.56	3.79 ± 0.67	< 0.001
HbA1c	6.26 ± 1.09	6.16 ± 0.93	< 0.01
D-dimer	4.62 ± 13.12	5.91 ± 15.03	0.26
HsCRP	1.97 ± 3.89	2.38 ± 4.40	< 0.01

* *P*-for trend.

3. Results

Among the 11,835 patients who were prescribed warfarin (mean age; 65.3 ± 17.6, women; 42.8%), VE occurred in 9.1% ($n = 1082$). The mean TTR level was 34.0 ± 25.7%, and the mean INR at the time of the VE was 1.60 ± 1.42. The MDW was 3.38 ± 1.06 mg per day.

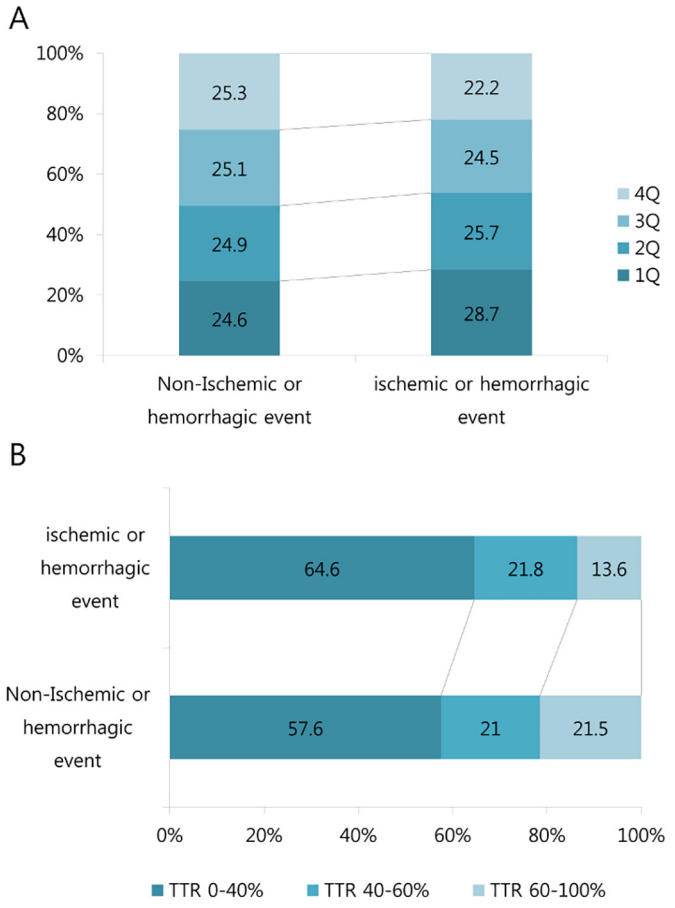

Fig. 1. (A) Association of maintenance dose of warfarin quartiles and vascular events (B) Association of vascular events and time in therapeutic range.

Compared to those without VE, patients with VE were older (67 ± 18 versus 65 ± 18 years) and had some conventional vascular risk factors, such as hypertension, diabetes or dyslipidemia. However, AF was less prevalent in those subjects (Table 1). After categorizing the MDW into quartiles, patients with VE were more likely to have lower levels of MDW than were patients without VE (p for trend < 0.01). There is a significant linear trend in proportions across MDW groups between patients with VE and non-VE. We performed the linear by linear association using chi-square test for trend. (Fig. 1A) Patients with VE had INR evaluated more frequently than did those without VE (46.1 ± 43.7 versus 41.6 ± 44.4) and frequently had lower TTR levels (TTR 0–40%, 64.6% versus 57.6%). (Fig. 1B) Among all patients, the total proportion of LINR50 was 59.1%, and the total proportion of HINR50 was 0.7%. (Table 1) Compared to patients without VE, patients with VE had lower INR more frequently (65.8% versus 58.4%).

Compared to patients with major bleeding events, fewer patients with stroke or arterial/venous thromboembolism had AF. Although there were no significant differences in TTR and MDW between the groups, the mean INR at the time of VE was higher in the major bleeding-group than in the stroke or arterial/venous thromboembolism group (3.27 ± 4.36 versus 1.52 ± 1.03). (see Supplementary Table 2).

After dividing TTR into three groups, all quartiles of MDW in the lowest TTR group had high risks of VE. In contrast, in the moderate or highest TTR groups, the incidence of VE decreased with increasing MDW levels in this study (Fig. 2).

After adjusting for age, gender, hypertension, diabetes, dyslipidemia, AF, glomerular filtration rate, liver cirrhosis, TTR, and MDW, we conducted a binary logistic regression analysis for LINR50 and HINR50 (Table 2). Compared with the highest group of MDW (Q4), the lowest

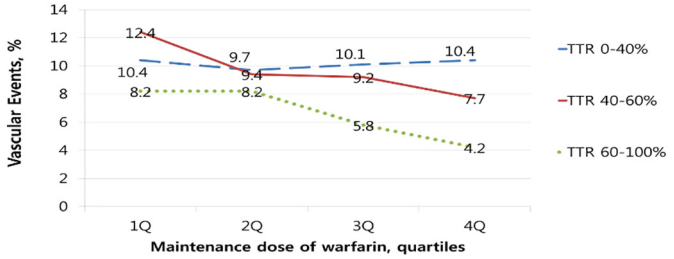

Fig. 2. The incidence of vascular events with increasing maintenance dose of warfarin levels according to the three levels of time in therapeutic range.

group (Q1) had an increased risk of having LINR50 (odds ratio, OR 2.90; 95% confidence interval, 95% CI 2.52–3.33). As the MDW increased, the odds of having LINR50 decreased (Q2: OR, 2.08; 95% CI 1.83 to 2.37; Q3: OR, 1.60; 95% CI 1.41 to 1.82) (Table 2).

Age, diabetes, and dyslipidemia were associated with an increased risk of stroke or arterial/venous thromboembolism after adjusting for multiple variables including TTR. Compared with poorly controlled TTR (0–40%), well-controlled TTR (60–100%) reduced the risk of stroke or arterial/venous thromboembolism (OR 0.62; 95% CI 0.50–0.77). Compared to the highest MDW group (Q4), the lowest MDW group had an increased risk of having VE (OR, 1.57; 95% CI 1.26 to 1.95). These findings were similarly observed at other MDW levels (Q2: OR, 1.35; 95% CI 1.09 to 1.68; Q3: OR, 1.35; 95% CI 1.10 to 1.68). The MDW as a continuous variable, although not shown in this paper, was also significantly associated with VE. In binary logistic regression for stroke or arterial/venous thromboembolism, this pattern of significance remained (Table 3). After dividing 3 groups according to the TTR status, the lowest MDW group (Q1) had significantly associated with increased VE in all three groups. (The data was not shown in detail.)

In addition, we conducted binary logistic regression analysis by using LINR50 or HINR50 instead of TTR. In model I, LINR50 had a 1.17-fold risk of VE, and the lower MDW groups (Q1, Q2 and Q3) were significant predictors for VE. In model II, although HINR was not a significant predictor of VE, the lower MDW groups (Q1, Q2 and Q3) were also significantly related to VE (see Supplementary Table 3).

4. Discussion

This study found that the quality of warfarin treatment is insufficient in multi-department of the tertiary care hospital based population. The mean TTR was 34.0 ± 25.7% and only 20.7% of patients with warfarin prescribed achieved TTR over 60%. Although the incidence of high INR over 3.0 was not high, the incidence of low INR (under 2.0) was approximately 60% in our study. Even considering in this study involving not only neurology but also all departments in our hospital, inadequate INR control seems to be widespread.

As we expected, low TTR was a strong predictor of VE, consistent with previous reports. In moderate- or well-controlled TTR status, lower MDW was significantly related to under-controlled anticoagulation (lower INR < 2.0) and was associated with a higher risk of VE, especially of stroke or arterial/venous thromboembolism. Therefore, we suggest that patients with very low MDW might be at risk when using warfarin for stroke or arterial/venous thromboembolism prevention.

Although our hospital was a tertiary care center, the quality of anticoagulation control was not good (mean TTR, 34.0 ± 25.7%). According to a previous study that included 37,907 AF patients, warfarin users with < 50% of TTR had a higher risk of stroke compared with those with no adjustment for anticoagulation [7]. However, even in randomized clinical trials, the quality of anticoagulation has been poor. In the data from the ROCKET AF Clinical trial, the mean TTR was 55.2 ± 21.3%. Furthermore, there was a differential representation based on racial and regional groups. The TTRs in East Asia

Table 2
Binary logistic regression for low INR50 and high INR50.

	Low INR 50		High INR 50	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Age	1.01 (1.00–1.01)	0.55	1.04 (1.01–1.07)	0.01
Gender, female	0.82 (0.75–0.90)	< 0.001	1.85 (1.01–3.36)	0.05
Vascular risk factor				
Hypertension	1.45 (1.28–1.64)	< 0.001	0.67 (0.30–1.48)	0.32
Diabetes	1.51 (1.33–1.70)	< 0.001	1.40 (0.71–2.75)	0.33
Dyslipidemia	0.99 (0.83–1.17)	0.87	0.75 (0.22–2.51)	0.64
Atrial fibrillation	0.57 (0.52–0.64)	< 0.001	2.04 (0.93–4.48)	0.08
Liver cirrhosis	1.82 (1.42–2.33)	< 0.001	NA	NA
Glomerular Filtration Rate,	1.00 (0.998–1.00)	0.19	1.00 (1.00–1.01)	0.05
Warfarin mean dose_quartiles				
1Q (warfarin 0.29–2.538 mg)	2.90 (2.52–3.33)	< 0.001	1.53 (0.60–3.91)	0.37
2Q (warfarin 2.539–3.364 mg)	2.08 (1.83–2.37)	< 0.001	1.19 (0.46–3.11)	0.72
3Q (warfarin 3.365–4.142 mg)	1.60 (1.41–1.82)	< 0.001	1.13 (0.42–3.00)	0.81
4Q (warfarin 4.143–10.0 mg)	Referance		Referance	

Adjusted for age, gender, hypertension, diabetes, dyslipidemia, atrial fibrillation, Glomerular Fitration Rate, liver cirhosistherapeutic target of range, and mean dose of warfarin.

(50.4 ± 21.4%), India (35.9 ± 23.3%), and Eastern Europe (49.7 ± 21.2%) were relatively lower than those in Western countries. Even within the same regions, there was variability across the countries, such as 47% in China and 38% in Taiwan but 66% in Hong Kong and 64% in Singapore [14]. It thus remains to be determined why non-white patients had relatively lower TTR than white patients did. A considerable point is whether all races require the same anticoagulation intensity. Because Asians are prone to bleeding when they are treated with warfarin and the optimal range of INR might be narrower than for non-Asians [15], one study suggested that a target INR of 1.8 to 2.4 was related to better clinical outcomes than INR of 2.0–3.0 [16]. In a similar study, among 8754 Chinese patients with AF, the median TTR was only 38.8% [17].

Because we collected all patients who were prescribed warfarin in our hospital, multiple confounders might influence this result. According to the Korean National Health and Nutrition Examination Survey, the daily intake of vitamin K in Koreans was much higher than those in the United Kingdom and the United States [18–20]. The 2012 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines give a class IIb recommendation for targeting warfarin to a lower INR (2.0–2.5) for patients requiring triple therapy for the management of patients with coronary artery disease [21]. Therefore, patients with combined antiplatelet and anticoagulation therapy might be set to a lower target INR range. In our study, although we could not assess the exact reasons for taking warfarin at the initial prescription, we examined the department initially prescribing warfarin for each person. The Department of Internal Medicine earned the top ranking; this might have affected this result (see Supplementary Table 4).

Furthermore, we found that low INR levels (INR < 2.0) were less sensitively adjusted than high INR (INR > 3.0). In our study, while LINR50 was approximately 58.4% (n = 6280), HINR50 was only 0.7% (n = 77). This phenomenon might be reflected in other countries. In Eastern Europe and East Asia, the mean time at low INR was 35–40%, the time at high INR was much lower (below 20%) [14]. We assume that the fear of severe hemorrhage has been cited as a reason for more strictly adjusting INR for patients with high INR than those with low INR. Among 251 physicians, one hundred twenty-nine (51.4%) believed that the risk of hemorrhage related to warfarin outweighs the benefit [22]. However, high INR was not associated with major bleeding in our study. Therefore, physicians would rather pay more attention to control a low INR than a high INR.

Table 3
Binary logistic regression for ischemic or hemorrhagic events.

	VE		Stroke or arterial/venous thromboembolism		Major bleedings	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-Value
Age	1.01(1.00–1.02)	< 0.01	1.01 (1.00–1.01)	0.01	1.02 (0.99–1.05)	0.18
Gender, female	1.09(0.94–1.26)	0.25	1.09(0.94–1.27)	0.24	0.95 (0.51–1.74)	0.86
Vascular risk factor						
Hypertension	1.00(0.84–1.20)	0.96	1.01 (0.84–1.21)	0.95	0.99 (0.46–2.13)	0.97
Diabetes	1.26(1.06–1.50)	< 0.01	1.30 (1.09–1.55)	< 0.01	0.65 (0.28–1.50)	0.31
Dyslipidemia	2.03(1.64–2.52)	< 0.001	2.11 (1.70–2.62)	< 0.001	0.62 (0.15–2.60)	0.51
Atrial fibrillation	0.46(0.39–0.53)	< 0.001	0.44 (0.38–0.51)	< 0.001	0.90 (0.46–1.79)	0.77
Liver cirrhosis	1.05(0.74–1.48)	0.79	0.98 (0.68–1.41)	0.90	2.46 (0.86–7.03)	0.09
Glomerular Filtration Rate,	1.00(0.999–1.00)	0.64	1.00 (1.00–1.003)	0.40	0.98 (0.97–1.00)	0.01
Time within therapeutic range						
TTR 0–40%	Referance	Referance	Referance	Referance	Referance	Referance
TTR 40–60%	1.11(0.92–1.32)	0.27	1.09 (0.91–1.31)	0.34	1.46 (0.70–3.04)	0.31
TTR 60–100%	0.64(0.52–0.79)	< 0.001	0.62 (0.50–0.77)	< 0.001	1.24 (0.55–2.78)	0.60
Warfarin mean dose_quartiles						
Q1 (warfarin 0.29–2.538 mg)	1.57(1.26–1.95)	< 0.01	1.57 (1.25–1.96)	< 0.001	1.40 (0.57–3.44)	0.46
Q2 (warfarin 2.539–3.364 mg)	1.35(1.09–1.68)	< 0.01	1.40 (1.12–1.75)	< 0.01	0.57 (0.20–1.65)	0.30
Q3 (warfarin 3.365–4.142 mg)	1.35(1.10–1.68)	< 0.01	1.35 (1.08–1.68)	< 0.01	1.33 (0.56–3.16)	0.52
Q4(warfarin 4.143–10.0 mg)	Referance	Referance	Referance	Referance	Referance	Referance

Adjusted for age, gender, hypertension, diabetes, dyslipidemia, atrial fibrillation, Glomerular Fitration Rate, liver cirrhosis, therapeutic target of range, and mean dose of warfarin.

Several reports have demonstrated that to achieve the same INR range, Asians require lower warfarin doses, whites require moderate doses, and blacks require higher warfarin doses [23]. Adequate anticoagulation control for warfarin users has been associated with a reduced risk of VE and mortality [7,17]. In our study, TTR was a significant predictor of VE, in concurrence with previous reports. However, in sub-analysis after categorizing TTR into 3 levels, all quartiles of MDW in the lowest TTR group had a higher risk of VE. On the contrary, in the moderate or highest TTR groups, VE incidence decreased with increasing MDW levels in our study. Additionally, after adjusting multiple variables including TTR, the lowest MDW (Q1, Q2, and Q3) groups had a 1.57-, 1.35- and 1.35-fold greater risk for VE, particularly stroke or arterial/venous thromboembolism E. Therefore, we suggest that MDW might play a more profound role beyond TTR than anticipated in the prevention of VE among warfarin users.

It then remains to be determined why the low MDW was related to VE. There might be multiple possible factors determining the dose of warfarin in patients. The decreasing MDW was related to increased age, female, decreased body weight, and patients with heart disease or AF [24]. According to previous reports, genetic polymorphisms of the VKORC1 and CYP2C9 genes were associated with reduced doses of warfarin [10,11,25]. The VKORC1 gene is responsible for the conversion of vitamin K epoxide to vitamin K. Among a group of 124 patients in the anticoagulant clinic, patients with low doses of warfarin were more likely to have one or more CYP2C9 variant alleles than was the normal population. Those in the low-dose warfarin group had frequent difficulties at the time of induction and had a higher risk of major bleeding compared to the standard-dose group [11]. The functional promoter polymorphism -1639G > A in the VKORC1 gene required lower warfarin doses to maintain INR in the target range (4.72 mg/day versus 3.6 mg/day) [25].

It is noteworthy that a low MDW was associated with a higher risk of stroke or arterial/venous thromboembolism but that a high MDW did not increase the risk of major bleeding. Because low MDW was significantly associated with under-controlled INR (INR < 2.0), we can assume that it might affect the hypercoagulable state. However, a previous study reported that low MDW linked to low INR also provoked hemorrhagic VE. In a systematic review from a Human Genome Epidemiology Network, compared with the wild-type CYP2C9*1 allele, CYP2CP*2 and CYP2C9*3 alleles reduced daily doses of warfarin and had a relatively higher bleeding risk [10]. Furthermore, patients in the low warfarin dose of 1.5 mg/day or less were more likely to have increased risk (3.68-fold) of bleeding complications [11]. In this regard, we may suspect that a very small dose may be more difficult to adjust than a very high dose of warfarin. For example, to increase the dose by 10%, patients with a daily 10 mg MDW might be prescribed 11 mg daily. However, subjects with a daily 1 mg MDW cannot be prescribed a new dose of 1.1 mg. They might be prescribed 1.5 mg or 1 mg alternatively, or they might be prescribed 1 mg on weekdays and 1.5 mg on weekends. In this case, physicians may mistakenly believe that they are adjusting the dose of warfarin well. However, a low MDW may be associated with a greater fluctuation of INRs. This fluctuation, coupled with narrower therapeutic ranges, may lead to ischemic or bleeding complications.

A remaining point to consider is the relationship between AF and VE in our study. In contrast to other conventional risk factors such as hypertension, diabetes, and dyslipidemia, AF was frequently detected in patients with non-VE. However, we should be careful in interpreting the results. Because we assessed all patients prescribed warfarin in our hospital as well as ischemic stroke patients, multiple confounders may affect this interpretation. Based on a previous observational study, the mean TTRs in patients with AF were higher than those in patients with venous thromboembolism [26]. We may assume that patients with AF may more often use a preventive drug and be under well-controlled medical management because of their concerns for health. According to the guidelines, those with AF might more frequently use the renin-angiotensin inhibitors and lipid-lowering agents [8]. In our study, we found that patients with AF had more well-controlled TTR than did those without AF (proportion of TTR 60–100%, 19.0% versus 15.4%; see Supplementary Table 5).

There are some caveats to this study. First, this is a retrospective observational study of a single center, and unknown factors might have confounded our results. However, this is still, to the best of our knowledge, the first study to assess the MDW and VE. Second, the total number of INR evaluations and the durations of warfarin prescriptions were different among included patients. However, we calculated individual TTRs by using a longitudinal linear extrapolation of INR levels with the Rosendaal method, which is known to be more sensitive than other methods. Third, we did not obtain information on pre-stroke medication history, which might affect the incidence of VE. Finally, the target range of INR could have been variable, although the implicit range of INR was 2.0–3.0. Because we analyzed all patients with warfarin medications, physicians might consider the medical characteristics of their patients, such as recurrent episodes of hemorrhage, triple antiplatelet therapy or severe cardiac disease. These unknown confounders could have influenced the result. To reduce this bias, we excluded some patients who underwent cardiac valve operations.

Collectively, maintaining high-quality anticoagulation is important. The European Society of Cardiology (ESC) Working Group had proposed an algorithm for risk stratification and selection of anticoagulation therapy for stroke prevention in atrial fibrillation (SAMe-TT2R2 score) to achieve well-controlled anticoagulation. A SAMe-TT2R2 score > 2 suggests that patients are unlikely to achieve a good TTR by taking warfarin. Therefore, an NOAC should be considered initially in these patients without a trial of warfarin. The definition of inadequate anticoagulation control was TTR < 65% or INR > 5 twice/INR > 8 once/INR < 2 twice within the past 6 months [9]. It is difficult to evaluate genetic polymorphisms in all warfarin users because of economic or medical resource issues. However, MDW might reflect valuable information about the quality of anticoagulation without requiring genetic evaluations.

Therefore, we suggest that patients with a very low MDW, which reflects low TTR and INR fluctuations, might be considered for NOACs alternatively instead of warfarin.

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Conflict of interest

Authors declares that he/she has no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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