Original Article
Frequency and predictors of bleeding complications associated with anti-coagulant therapy using dabigatran in Japanese patients with atrial fibrillation

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Abstract: Background: Few data exist regarding frequency and predictors of bleeding complications associated with anticoagulant therapy using dabigatran in Japanese patients with atrial fibrillation (AF). Methods and Results: We retrospectively studied 184 patients with AF who were administered dabigatran from April 2011 to August 2012 in our institution. Twenty-eight patients (15%) developed some type of bleeding complication. In the Bleeding group, age, $CHADS_2$ and HAS-BLED score were higher (75 vs. 71 years, p=0.067, 2.7 vs. 1.9, p=0.006 and 2.3 vs. 1.8, p=0.01, respectively), hemoglobin concentration was lower (13.1 vs. 13.7 g/dL, p=0.04), casual activated partial thromboplastin time (APTT) was longer (60.2 vs. 47.4 sec., p<0.0001) and frequency of aspirin use was higher (29 vs. 15%, p=0.09) than those in the Non-bleeding group. Multivariate regression analysis showed that casual APTT was an independent significant predictor of any type of bleeding complications (β=0.431, p<0.0001). Moreover, casual APTT (β=0.359, p=0.049), pre-existing anemia (β=0.457, p=0.02) and aspirin use (β=0.597, p=0.02) were significant predictors of major bleeding. ROC analysis showed that casual APTT exhibited 83.3% sensitivity and 72.5% specificity as predictors of major bleeding and its cut-off value was 54.7 sec. Conclusion: Casual APTT level can serve as a predictor of bleeding complications, while pre-existing anemia and aspirin use may be associated with major bleeding in patients with AF treated with dabigatran.

Keywords: Activated partial thromboplastin time, anticoagulant therapy, bleeding complication, dabigatran

Introduction

Dabigatran, an oral direct thrombin inhibitor, was approved in 2011 in Japan for the prevention of embolic events in patients with non-valvular atrial fibrillation (NVAF). The randomized evaluation of long-term anticoagulation therapy (RE-LY) compared the use of dabigatran, at doses of 110 mg twice daily and 150 mg twice daily, with warfarin in patients with atrial fibrillation (AF); and included patients from non-Asian and Asian countries [1, 2]. In RE-LY, overall, dabigatran 110 mg twice daily was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as with lower rate of major bleeding. Dabigatran 150 mg twice daily, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but with similar rates of major hemorrhage. Moreover,

the efficacy and safety of dabigatran for Asian patients with AF at high risk of stroke were essentially equal to those for the overall RE-LY study population [3].

Dabigatran has a predictable pharmacodynamic effect enabling thereby fixed-dose regimens to be used without the need for routine laboratory testing [4]. However, patients receiving dabigatran are at risk of bleeding, particularly in association with trauma [5] and surgery and in those with impaired renal function [6]. Moreover, there are currently no antidotes available for reversing the anticoagulant effect of dabigatran, although preclinical work is underway to develop a neutralizer [7]. Thus, we should clearly identify the patients at a high risk for bleeding complications. The aim of this study was to determine the frequency and predictors of bleeding complications associated with antico-

Table 1. Bleeding complications associated with dabigatran etexilate

	All patients	DE 75 mg BID	DE 110 mg BID	DE 150 mg BID
	(n=184)	(n=2)	(n=101)	(n=81)
Major bleeding	6 (3)	0	6 (6)	0
Intracranial	1		1	
Extracranial	5		5	
Gastrointestinal	5		5	
Non-gastrointestinal	0		0	
Life-threatening bleeding	1		1	
Fatal bleeding	0		0	
Minor bleeding	22 (12)	1 (50)	11 (11)	10 (12)
Gastrointestinal	4	1	1	2
Non-gastrointestinal	18	0	10	8

Data are expressed as the number (%). DE, dabigatran etexilate; BID, bis in die.

Table 2. Characteristics of the patients who developed major bleeding

Case	age	gender	Dose of dabigatran	Hb	CCr	Casual APTT		CHADS$_2$ score	HAS-BLED score	Aspirin use	Causes of bleeding	Duration
			(mg/day)	(g/dL)	(mL/min)	(sec.)	sampling time					(days)
1	76	male	220	14.3	49.8	80	afternoon	5	3	no	Colon diverticulum	174
2	79	male	220	11.9	61.0	55	afternoon	5	4	yes	Chronic subdural hematoma	160
3	83	female	220	12.7	30.3	44	afternoon	2	2	no	Gastric ulcer	55
4	87	female	220	11.4	30.5	100	afternoon	2	1	no	Colon diverticulum	772
5	72	male	220	9.6	67.6	61	afternoon	1	3	yes	Colon diverticulum	102
6	74	male	220	14.4	64.1	65	afternoon	1	3	yes	Colon diverticulum	119
Mean	78±6		220	12.4±1.8	50.6±16.7	68±20		2.7±1.9	2.7±1.0			230±269

Duration means the time to the development of bleeding complications from the beginning of administration of Dabigatran. Number in the bottom layer reveals the mean value of 6 cases. Hb, hemoglobin; CCr, creatinine clearance; APTT, activated partial thromboplastin time; DAPT, dual antiplatelet therapy.

agulant therapy using dabigatran in Japanese patients with AF.

Materials and methods

Subjects

We retrospectively studied NVAF patients who were administered dabigatran from April 2011 to August 2012 at Yokohama Sakae Kyosai Hospital. Adjustment of dosage of dabigatran was left to the discretion of individual physicians. Clinical data of all patients were collected from clinical records. CHADS$_2$ [8] score was calculated as previously reported. HAS-BLED score was calculated except for labile international normalized ration (INR), because we could not collect data of INR from all patients.

Definition of bleeding complications

The definition of bleeding complications was based on the RE-LY study [2]. Major bleeding was defined as a reduction of the hemoglobin concentration by more than 2.0 g/dL, blood transfusion of more than 2 units, or symptomatic bleeding into a critical area or organ. Major bleeding was separated into intracranial (intracerebral, subdural) and extracranial (gastrointestinal, non-gastrointestinal) bleeding. Life-threatening bleeding was a subset of major bleeding that included fatal or symptomatic intracranial bleeding, with a reduction of the hemoglobin concentration by more than 5 g/dL, requiring blood transfusion of more than 4 units, or bleeding necessitating surgery. All other bleeding episodes were considered minor in nature.

Laboratory determinations

Creatinine clearance (CCr) (mL/min) was calculated using Cockcroft-Gault equations [calculated by (140-age [years])×body weight (kg)/72/

Table 3. Baseline clinical characteristics of patients with and without bleeding complication

Variables	Bleeding group (n=28)	Non-bleeding group (n=156)	p value
Age (years)	75±10	71±10	0.067
Gender (male/female)	17/11	104/52	0.54
BMI (kg/m^2)	22.8±3.2	23.2±3.4	0.53
Type of atrial fibrillation			
Paroxysmal	15 (54)	71 (46)	0.43
Persistent	0 (0)	7 (4)	0.54
Permanent	13 (46)	78 (50)	0.73
Previous stroke or TIA	11 (39)	40 (26)	0.14
Heart failure	11 (39)	35 (22)	0.058
Diabetes mellitus	6 (21)	41 (26)	0.59
Hypertension	20 (71)	91 (58)	0.19
Chronic kidney disease	13 (46)	60 (38)	0.43
LVEF (%)	57±9	59±11	0.34
Left atrial diameter (mm)	44±8	44±7	0.77
NT-proBNP (pg/mL)	1682±1135	981±1503	0.18
Hb (g/dL)	13.1±1.4	13.7±1.5	0.04
Cr (mg/dL)	0.85±0.17	0.87±0.21	0.62
eGFR (mL/min/1.73 m^2)	62.4±14.7	63.3±14.7	0.76
CCr (mL/min)	61.4±23.5	67.9±23.7	0.18
Casual APTT (sec.)	56.8 (41.0-101.8)	47.0 (28.0-62.1)	0.0004
CHADS$_2$ score	2.7±1.4	1.9±1.3	0.006
HAS-BLED score	2.3±0.9	1.8±1.0	0.01
Dosage of dabigatran (mg/day)	246±43	256±41	0.24
75 mg BID	1 (4)	1 (1)	
110 mg BID	17 (61)	84 (54)	
150 mg BID	10 (35)	71 (45)	
Concomitant Medication			
Aspirin	8 (29)	24 (15)	0.09
Thienopyridine	1 (4)	4 (3)	0.99
Cilostazol	1 (4)	2 (1)	0.94
Dual antiplatelet therapy	2 (7)	4 (3)	0.5
Antiarrhythmic drug	8 (29)	48 (31)	0.82
Proton pump inhibitor	6 (21)	38 (24)	0.74
H$_2$ receptor antagonist	5 (18)	19 (12)	0.61
Previous warfarin use	7 (25)	48 (31)	0.54

Data are expressed as the mean±SD, median (range) or number (%). BMI, body mass index; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; Hb, hemoglobin; Cr, creatinine; eGFR, estimated glomerular filtration rate; CCr, creatinine clearance; APTT, activated partial thromboplastin time. Data are expressed as the mean±SD or number (%). BID, bis in die.

serum creatinine (Cr) (mg/dL), and×0.85 if female] [10]. Estimated glomerular filtration rate (eGFR) was calculated using the modified Modification of Diet in Renal Disease (MDRD) equation [11]: eGFR (mL/min/1.73 m^2)= 194×serum Cr (mg/dL)$^{-1.094}$×Age (years)$^{-0.287}$ (×0.739 for female subjects). Activated partial thromboplastin time (APTT) was measured at least 2 weeks after the beginning of the administration of dabigatran. APTT was calculated using Coagpia^{TM} APTT-N testing kits (SEKISUI MEDICAL CO., Tokyo, Japan). The reference interval of APTT was from 24 to 35 sec in our institution. The intervals from administration of dabigatran to blood sampling differed among individuals because these blood samples were
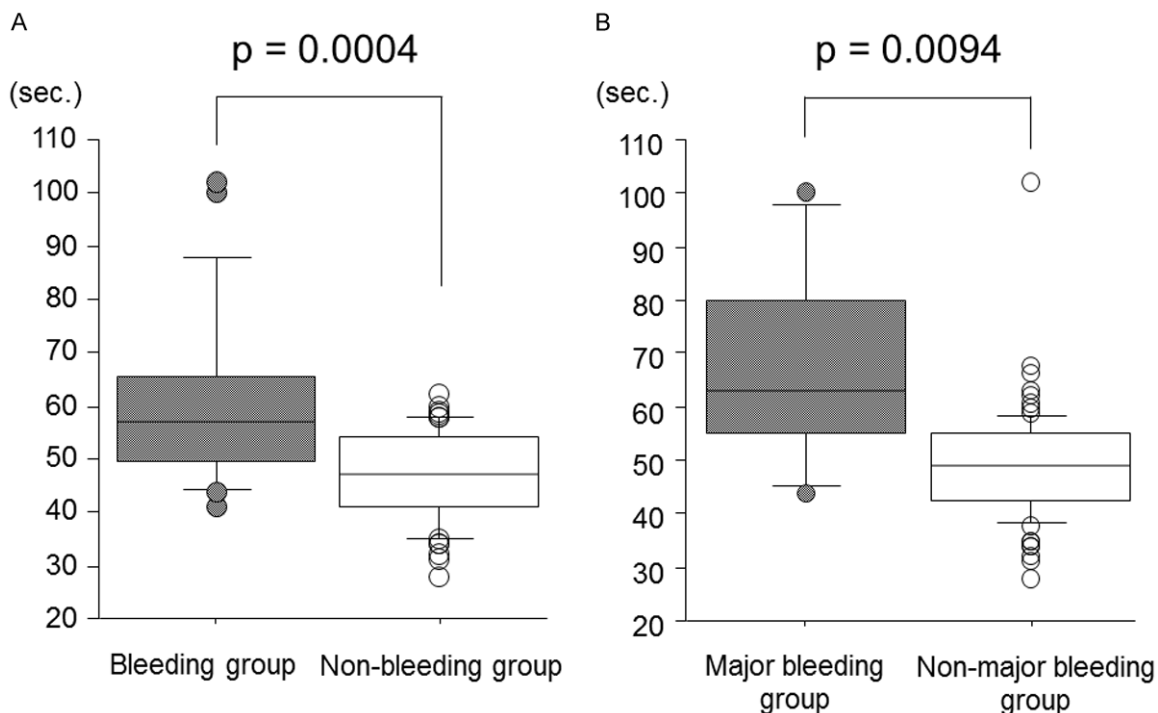
Figure 1. Distribution of casual activated partial thromboplastin time (APTT). A: Comparison Comparison between the Bleeding group (n=28) and the Non-bleeding group (n=156). B: Comparison Comparison between the Major-bleeding group (n=6) and the Non-major bleeding group (n=178). The box plots show the 25th, 50th (median) and 75th percentiles. The whiskers show the 10 to 90th percentiles.

collected at the time of routine medical check-ups. Thus, we compared the APTT value between patients who visited our hospital in the morning and in the afternoon.

Statistical analysis

Statistical analyses were performed using StatView 5.0 for Windows (SAS Institute, Cary, NC) and Statistical Package for the Social Sciences version 19.0 (SPSS Inc., Chicago, IL). Results are expressed as the mean±standard deviation (SD) or the median (range). Differences in continuous variables between the 2 groups were compared using Student's unpaired *t*-test when the variable showed a normal distribution or Mann-Whitney U-test when it did not. Categorical variables in the 2 groups were compared using chi-square test or Fisher's exact test. Univariate analysis was performed to determine the factors that correlated with the occurrence of bleeding complications. Univariate predictors with a *p* value<0.2 were entered into the multivariate regression model. The receiver-operating characteristic (ROC) was analyzed to determine the cut-off value of APTT

as a predictor of major bleeding. A probability value of p<0.05 was considered statistically significant.

Results

One-hundred and eighty-four patients were included in this analysis. The mean follow-up period was 383±190 days. Eighty-one patients were administered 150 mg of dabigatran twice daily, and 101 patients were administered 110 mg twice daily. Two patients were treated with an off-label dose of 75 mg twice daily.

Frequency of bleeding complications associated with dabigatran

Bleeding complications occurred in 28 (15.2%) patients and of them 6 presented major bleeding (**Table 1**). The mean duration from the beginning of the administration of dabigatran to the occurrence of bleeding complication was 219±181 days (range 21 to 772 days). Major bleeding included intracranial bleeding in 1 patient and extracranial bleeding in 5. Characteristics of the patients who developed major bleeding are shown in the **Table 2**. They

Table 4. Predictors of bleeding complication

Variables	Univariate		Multivariate	
	r	p value	β	p value
Age	0.135	0.067	0.1	0.66
BMI	-0.046	0.53		
Previous stroke or TIA	0.109	0.14		
Heart failure	0.14	0.058		
Hypertension	0.096	0.19		
Dosage of dabigatran	-0.087	0.24		
Aspirin (concomitant use)	0.125	0.09	0.51	0.064
Hb	-0.155	0.04	-0.025	0.89
NT-proBNP	0.162	0.18	0.042	0.83
Casual APTT	0.461	<0.0001	0.445	0.03
CHADS$_2$ score	0.203	0.006	-0.061	0.83
HAS-BLED score	0.184	0.01	0.044	0.89

Presence of previous stroke or TIA, heart failure, and hypertension and aspirin use were assigned a value of 1. Absence of previous stroke or TIA, heart failure, and hypertension and no aspirin use were assigned a value of 0. BMI, body mass index; TIA, transient ischemic attack; Hb, hemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide; APTT, activated partial thromboplastin time.

Table 5. Predictors of major bleeding

Variables	Univariate		Multivariate	
	r	p value	β	p value
Age	0.125	0.09	0.13	0.52
BMI	-0.059	0.42		
Previous stroke or TIA	0.023	0.76		
Heart failure	0.106	0.15		
Hypertension	0.086	0.24		
Diabetes mellitus	0.108	0.15		
Chronic kidney disease	0.164	0.03	0.154	0.34
Dosage of dabigatran	-0.154	0.04	-0.027	0.86
Aspirin (concomitant use)	0.158	0.03	0.597	0.02
Hb	-0.16	0.03	-0.457	0.02
NT-proBNP	0.26	0.03	0.264	0.13
Casual APTT	0.389	0.0002	0.359	0.049
CHADS$_2$ score	0.082	0.27	0.005	0.99
HAS-BLED score	0.151	0.04	0.198	0.45

Presence of previous stroke or TIA, heart failure, hypertension, diabetes mellitus, and chronic kidney disease and aspirin use were assigned a value of 1. Absence of previous stroke or TIA, heart failure, hypertension, diabetes mellitus, and chronic kidney disease and no aspirin use were assigned a value of 0. BMI, body mass index; TIA, transient ischemic attack; Hb, hemoglobin; NT-proBNP, N-terminal pro-brain natriuretic peptide; APTT, activated partial thromboplastin time.

were older patients with a mean age of 78±6 years. All patients were administered dabigatran with 110 mg twice daily. Three out of 6 patients were treated with concomitant use of aspirin. Melena due to colon diverticulum occurred in 4 patients and 1 patient developed hematemesis due to gastric ulcer. Life-threatening bleeding occurred in 1 patient. He developed gastrointestinal bleeding and received 4 units of blood transfusion. The majority of minor bleeding episodes (18 out of 22 patients) were non-gastrointestinal bleeding such as mucosal hemorrhage.

Predictors associated with any types of bleeding complications

Baseline clinical characteristics are shown in **Table 3**. There was no difference between the 2 groups regarding the type of AF. In the Bleeding group, age and the frequency of heart failure tended to be higher than those in the Non-bleeding group (75±10 years vs. 71±10 years, p=0.067 and 39% vs. 22%, p=0.058, respectively). The mean concentration of hemoglobin was significantly lower in the Bleeding group (13.1±1.4 g/dL vs. 13.7±1.5 g/dL, p=0.04). There were no significant differences in the frequency of previous stroke or transient ischemic attack, diabetes mellitus, and hypertension. Baseline renal function was similar in the 2 groups. There was no difference in the mean dosage of dabigatran (246±43 mg/day vs. 256±41 mg/day, p=0.24) between the 2 groups, whereas the frequency of combined usage of aspirin tended to be higher in the Bleeding group than that in the Non-bleeding group (29% vs. 15%, p=0.09). In the Bleeding group, the CHADS$_2$ and the HAS-BLED score were significantly higher than those in the Non-bleeding group (2.7±1.4 vs. 1.9±1.3, p=0.006 and 2.3±0.9 vs. 1.8±1.0, p=0.01, respectively). The median value of casual APTT was significantly longer (56.8 sec. vs. 47.0 sec., p=0.0004) in the Bleeding group than in the Non-bleeding group (**Figure 1A**). Univariate analysis showed that casual APTT value (r=0.461, p<0.0001), CHADS$_2$ score (r=0.203, p=0.006), and HAS-BLED score (r=0.184, p=0.01) were positively and the baseline hemoglobin concentration (r=-0.155, p=0.04) was negatively correlated with the occurrence of bleeding complication. Multivariate regression
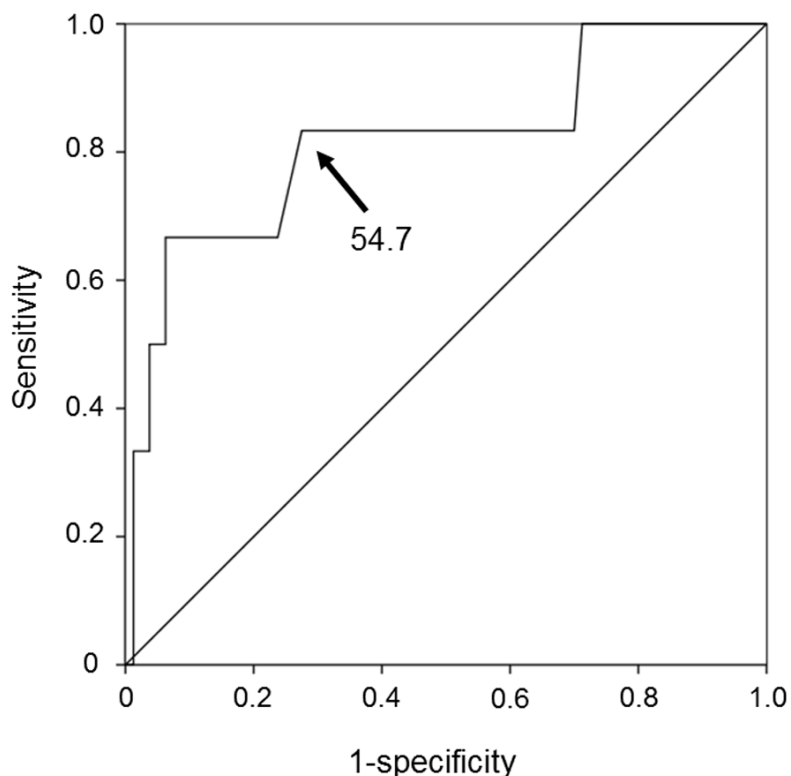
Figure 2. Receiver operating characteristic analysis of casual APTT as a predictor of major bleeding. At a cut-off value of >54.7 sec., casual APTT exhibited 83.3% sensitivity and 72.5% specificity for predicting major bleeding in NVAF patients treated with dabigatran. APTT, activated partial thromboplastin time; NVAF, non-valvular atrial fibrillation.

complications of major bleeding (**Table 5**). The median value of casual APTT was significantly longer in the Major-bleeding group than in the Non-major bleeding group (63.1 sec. vs. 49.1 sec., p= 0.0094) (**Figure 1B**).

Cut-off point of causal APTT as a predictor of major bleeding

ROC analysis showed that at a cut-off value of 54.7 sec., casual APTT measured at afternoon exhibited 83.3% sensitivity and 72.5% specificity for the occurrence of major bleeding, and the area under the curve (AUC) was 0.82 (**Figure 2**).

Distribution of APTT value according to sampling time

We compared the value of APTT between patients who were collected the blood sample in the morning and afternoon. One hundred and eleven APTT values were obtained in the morning and 73 were obtained in the afternoon. APTT values in the morning ranged from 28.0 to 101.8 sec. (median 49.7) and from 31.3 to 100.0 sec. (median 49.5) in the afternoon. There was no significant difference in casual APTT value between the 2 groups (p=0.76) (**Figure 3**).

Discussion

The present study demonstrated that casual APTT value was an independent predictor associated with any type of bleeding complications in NVAF patients treated with dabigatran. Moreover, pre-existing anemia and combined usage of aspirin as well as casual APTT value were independent predictors of major bleeding. We suggest that a casual APTT value of 54.7 sec. during dabigatran therapy may serve as a predictor of the development of major bleeding.

analysis demonstrated that casual APTT was an independent significant predictor of bleeding complication (β=0.445, p=0.03) (**Table 4**).

Predictors associated with major bleeding

We also evaluated the predictors associated with major bleeding (**Table 5**). Univariate analyses showed that age (r=0.125, p=0.09), presence of chronic kidney disease (CKD) (r=0.164, p=0.03), combined usage of aspirin (r=0.158, p=0.03), N-terminal pro-brain natriuretic peptide (r=0.260, p=0.03), HAS-BLED score (r=0.151, p=0.04), and casual APTT value (r=0.389, p=0.0002) correlated positively with the occurrence of major bleeding, whereas the mean dosage of dabigatran (r=-0.154, p=0.04) and baseline hemoglobin concentration (r=-0.160, p=0.03) correlated negatively with the development of major bleeding. Multivariate regression analysis demonstrated that combined usage of aspirin (β=0.597, p=0.02), baseline hemoglobin concentration (β=-0.457, p=-0.02), and casual APTT (β=0.359, p=0.049) were significant predictors associated with
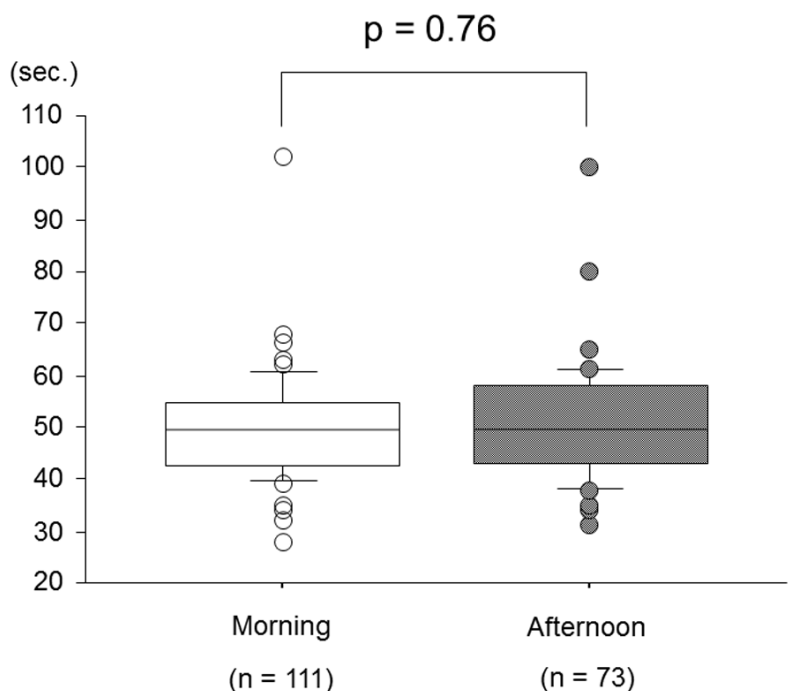
Figure 3. Distribution of APTT value according to sampling time. Comparison of APTT value between those collected in the morning and afternoon. The box plots show the 25th, 50th (median) and 75th percentiles. The whiskers show the 10 to 90th percentiles.

Atrial fibrillation is responsible for ischemic stroke in 20% to 30% of the cases [12] and anticoagulation reduces this risk, but this benefit is off-set by increased hemorrhage, including hemorrhagic stroke. Moreover, patients of Asian ethnicity are at greater risk of hemorrhage while under vitamin K antagonist therapy [13]. Although the efficacy and safety of dabigatran compared to vitamin K antagonist in Asian AF patients were evaluated by the sub-analysis of the RE-LY study [3], the risk of bleeding still remained in patients administered dabigatran. Furthermore, we have no antidotes available for reversing the anticoagulant effect of dabigatran. Therefore, it is necessary to pay close attention to the occurrence of bleeding complications associated with anticoagulant therapy using dabigatran. However, there are few reports about predictors of bleeding complication associated with dabigatran in Japanese patients with AF.

In the present study, prolongation of casual APTT was associated with bleeding complications in NVAF patients treated with dabigatran. Although coagulation can be monitored after warfarin treatment by measuring the prothrombin time, no protocols have been established to measure coagulation in patients treated with novel anticoagulants including dabigatran that have peak and trough phases in their concentration curves. The APTT assay targets the intrinsic pathway of the coagulation cascade. Prolongation of APTT occurs with increasing plasma concentrations of dabigatran although the APTT concentration-response curve is curvilinear and flattens at a concentration of ≥200 ng/mL [4]. We demonstrated that casual APTT at a cut-off value of 54.7 sec. and an AUC of 0.82 exhibited 83.3% sensitivity and 72.5% specificity for the development of major bl-eeding. Suzuki et al. suggested that patients whose APTT exceeded 60 sec. should have the dose of dabigatran carefully adjusted not to develop the bleeding complications [14]. Moreover, Hapgood et al. demonstrated that an APTT of 46 to 54 sec. corresponded to the therapeutic range of dabigatran (90 to 180 ng/mL) and an APTT of ≥64 sec. correlated with a plasma concentration of dabigatran ≥300 ng/mL [15]. Consistent with these reports, the cut-off value of casual APTT in our present study was considered to be a reasonable predictor of major bleeding. However, different APTT reagents demonstrated different responsiveness to dabigatran that resulted in different calculated therapeutic ranges [15]. Therefore, it is necessary to establish the APTT range using calibrated plasma samples in each laboratory.

The time to reach a peak concentration of dabigatran was considered to be affected by factors such as age, gender, and renal function [16, 17]. However, some studies reported that there was little difference in APTT values according to the sampling time, whether obtained at the peak and trough concentration or in the morning and afternoon at the outpatient clinic [14, 18]. Consistent with these

reports, we also demonstrated that there was no significant difference in the APTT value according to the sampling time. Moreover, although dabigatran usually reaches a peak plasma concentration in 1.5 to 3 h [17, 19], it has been reported to be delayed to closer to 6 h with an extent of absorption [20]. Therefore, we considered that casual APTT collected at any time might be a useful predictor of bleeding risk in outpatients administered dabigatran daily in clinical practice.

The sub-analysis of RE-LY trial reported that extracranial bleeding risk was similar or higher with both dose levels of dabigatran (110 mg twice daily and 150 mg twice daily) as compared with warfarin in patients aged ≥75 years whereas the risks of both extracranial and intracranial bleeding were lower in patients aged <75 years treated with either dose of dabigatran as compared with warfarin [21]. Advanced age itself is a risk factor for bleeding in patients treated with dabigatran. Furthermore, elderly patients often have comorbidities such as diabetes mellitus, which is an important risk factor for renal dysfunction [22]. Indeed, in the present study, age and presence of CKD correlated with the occurrence of major bleeding as shown by univariate analysis.

Another important result of this study was that pre-existing anemia and concomitant use of aspirin were also useful predictors of major bleeding. Five out of 6 patients who developed major bleeding were complicated with gastrointestinal bleeding. We consider that pre-existing anemia indicates that patients might have hemorrhagic lesions such as gastrointestinal ulcers, colon diverticulum, or malignancy. Moreover, concomitant use of aspirin with an anticoagulant drug may aggravate this bleeding tendency. Thus, it is necessary to screen these diseases before providing anticoagulant therapy. Eikelboom et al. reported that the risk of bleeding associated with dabigatran increased with patient age, decreased CCr, and concomitant use of anti-platelet agents [21]. Consistent with this report, our results demonstrated that we should pay attention to patients having these characteristics.

The present study has several limitations. First, this study involved a small number of patients at a single center and was done retrospectively. Thus, we could not evaluate the efficacy and safety of dabigatran compared with Warfarin. Second, dabigatran was prescribed based on each physician's decision. This means that our results cannot be directly extrapolated to all the population. Third, we did not measure the plasma concentration of dabigatran. It is necessary to compare the plasma concentration of dabigatran with casual APTT value. Thus, a large scale prospective study is necessary to confirm the results of this study.

Conclusions

The present study demonstrates that a casual APTT value can be a useful predictor of bleeding complication in NVAF patients treated with dabigatran. Moreover, we should pay more attention to patients with pre-existing anemia and to those under concomitant therapy with aspirin.

Disclosure of conflict of interest

The authors have no conflict of interest to disclose.

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