Canadian Journal of Cardiology 35 (2019) 736–743

Clinical Research

Excessive Prolongation of Coagulation Time During Treatment With Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation

Mihoko Kawabata, MD, PhD,[a] Masahiko Goya, MD, PhD,[a] Yoshihide Takahashi, MD, PhD,[b] Shingo Maeda, MD, PhD,[b] Atsuhiko Yagishita, MD, PhD,[a] Masahiro Sekigawa, MD,[a] Kiko Akiyoshi, MD,[a] Tasuku Yamamoto, MD,[a] Takatoshi Koyama, MD, PhD,[c] and Kenzo Hirao, MD, PhD[a]

[a] *Department of Cardiovascular Medicine, Tokyo Medical and Dental University, Tokyo, Japan*

[b] *Advanced Arrhythmia Research, Tokyo Medical and Dental University, Tokyo, Japan*

[c] *Department of Hematology, Tokyo Medical and Dental University, Tokyo, Japan*

See editorial by Pollak et al., pages 694–698 of this issue.

ABSTRACT

Background: Conventional coagulation assays have poor sensitivity and specificity for assessing the anticoagulant effect of direct oral anticoagulants (DOACs). This study aimed to evaluate the causes and consequences of the excessive prolongation of coagulation time in patients with nonvalvular atrial fibrillation who receive DOACs.

Methods: We retrospectively analysed 1521 patients (age, 66 ± 12 years). The prothrombin time (PT) and activated partial thromboplastin time (APTT) were averaged if they were measured more than twice depending on the respective DOAC and dosage across individuals. Excessive coagulation time prolongation was defined as PT or APTT of >2 standard deviations over the median for each DOAC.

Results: In all, 1913 DOAC cases were found. Excessive prolongation (EP), which was noted in 88 patients (5.8%), was found to be significantly associated with inappropriately high DOAC dosage and body weight (≤ 60 kg). During follow-up (median, 8.9 months), thromboembolisms

RÉSUMÉ

Contexte : La sensibilité et la spécificité des épreuves de coagulation classiques sont insuffisantes pour évaluer l'effet anticoagulant des anticoagulants oraux directs (AOD). Cette étude visait à évaluer les causes et les conséquences d'une prolongation excessive du temps de coagulation chez des patients présentant une fibrillation auriculaire non valvulaire traités par AOD.

Méthodologie : Nous avons effectué une analyse rétrospective de 1521 patients (âge, 66 ± 12 ans). Les moyennes du temps de prothrombine (TP) et du temps partiel de thromboplastine activée (TPTA) ont été calculées si ces valeurs étaient mesurées plus de deux fois selon l'AOD et la posologie de chaque patient. La prolongation excessive du temps de coagulation était définie par un TP ou un TPTA > 2 écarts types par rapport à la médiane pour chaque AOD.

Résultats : En tout, 1913 patients traités par un AOD ont été recensés. La prolongation excessive (PE), observée chez 88 patients (5,8 %),

Direct oral anticoagulants (DOACs), including the direct thrombin inhibitor (dabigatran) and FXa inhibitors (apixaban, edoxaban, and rivaroxaban), are being increasingly used for the prevention of thromboembolic events in patients with nonvalvular atrial fibrillation (NVAF).[1] Unlike for warfarin, monitoring the coagulation status is not required during treatment with DOACs because of their wide effective and safe blood concentration range, allowing for different patients to be treated at the same dose.[2] Although conventional coagulation assays involving the measurement of the activated partial thromboplastin time (APTT) and prothrombin time (PT) are widely used, they have poor sensitivity and specificity for assessing the anticoagulant effect of DOACs.[3,4] We encountered a case of a 67-year-old woman taking rivaroxaban for persistent atrial fibrillation (AF) who exhibited the APTT of over 100 seconds in a routine evaluation before catheter ablation. She was then diagnosed with positive antiphospholipid antibody, and the anticoagulation therapy was continued. Thus, we began to assess the standard coagulation tests performed in patients taking DOACs that were inexpensive and easily available. Excessive prolongation (EP) of coagulation time was occasionally observed in patients taking

Received for publication November 9, 2018. Accepted February 10, 2019.

Corresponding author: Dr Mihoko Kawabata, Department of Cardiovascular Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan. Tel.: +81-358035231; fax: +81-358030131.

E-mail: mihoko_kawabata.cvm@tmd.ac.jp

See page 742 for disclosure information.

https://doi.org/10.1016/j.cjca.2019.02.012

developed in 10 patients (0.66%) and bleeding events in 85 (5.6%). Bleeding events were significantly higher in patients with excessive prolongation (EP group) than in those without ($P = 0.013$). Of the 53 patients in the EP group, 15 (28%) were positive for antiphospholipid antibodies, 6 (11%) had inappropriately high prescription dosages, 4 (8%) had coagulation factor deficiencies, and 3 (6%) had severe liver dysfunction.

Conclusions: Bleeding event rates were remarkably higher in patients receiving DOACs that caused EP of PT or APTT. Thus, following the current guidelines and administering the recommended dose of DOACs are fundamentally important. Patients with the body weight of <60 kg should be considered for dosage reduction or DOAC withdrawal.

s'est avérée être associée de façon significative avec une posologie d'AOD trop élevée et avec le poids corporel ($\leq$ 60 kg). Au cours de la période de suivi (durée médiane, 8,9 mois), on a noté l'apparition de thromboembolies chez 10 patients (0,66 %) et d'événements hémorragiques chez 85 patients (5,6 %). Le nombre d'événements hémorragiques était significativement plus élevé chez les patients présentant une prolongation excessive (groupe PE) que chez ceux ayant un temps de coagulation normal ($p = 0,013$). Parmi les 53 patients du groupe PE, 15 (28 %) avaient obtenu un résultat positif au dépistage des anticorps antiphospholipides, 6 (11 %) s'étaient vus prescrire une posologie trop élevée, 4 (8 %) avaient des déficits en facteurs de coagulation et 3 (6 %) présentaient une dysfonction hépatique grave.

Conclusions : Les taux d'événements hémorragiques étaient nettement plus élevés chez les patients recevant des AOD causant une PE du TP ou du TPTA. Par conséquent, il est d'une importance fondamentale de suivre les lignes directrices en vigueur et d'administrer la dose d'AOD recommandée. Chez les patients dont le poids corporel est < 60 kg, il est conseillé d'envisager une diminution de la dose ou la cessation de l'AOD.

DOACs, and whether this can be ignored or warrants closer scrutiny is not yet known.

The results for standard coagulation assays vary among the DOACs.[3,4] Further, the APTT or PT has been shown to be influenced by the DOAC concentration, that is, DOAC dosages.[5-8] These results suggest that a change in the DOAC therapy, such as a switch to a different DOAC or change in the DOAC dosage, could yield different results for routine coagulation assays even in the same patient.

This study aimed to retrospectively evaluate the prevalence and cause of EP of coagulation time in the routine coagulation assays (APTT and PT) in patients with NVAF receiving DOACs and its relationship with bleeding events.

Methods

We included all patients with NVAF with a DOAC prescription, who had undergone 1 or more standard anticoagulation tests, treated between April 2011 and December 2016 at our institution. The subjects were identified using International Statistical Classification of Diseases and Related Health Problems, tenth revision codes for the diagnosis of AF. The medical records were reviewed to determine eligibility. Patients who had not received PT and APTT tests or renal/hepatic function tests and whose body weight had not been checked were excluded. The patients were followed up until October 2018, but some were lost to follow-up earlier because they were transferred to other hospitals, or developed clinical events. If the DOACs were discontinued for any reason, follow-up was terminated at that point to evaluate the bleeding and thrombotic events only in patients actively taking DOACs.

Data extraction

Data were extracted from the records of eligible subjects. The clinical and demographic data, including the age, gender, weight, DOAC prescription, laboratory data, concomitant drugs, **C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) score, HAS-BLED score, and clinical events, were collected. The renal function was evaluated using the creatinine clearance rate (Ccr; mL/min) averaged over the study period. The Ccr was calculated using the formula developed for the Japanese population: (140 − age [years]) × body weight [kg]/72/serum creatinine [mg/dL], and × 0.85 for women.

Thromboembolic events included ischemic strokes, transient ischemic attacks, and systemic emboli. Major bleeding was defined as fatal bleeding, symptomatic bleeding in a critical area or organ, bleeding causing a fall in the haemoglobin level of 2 g/dL or more, or bleeding leading to a transfusion of 2 or more units of whole blood or red blood cells.[9] Other bleeding events were defined as minor. Liver dysfunction was defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin/aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase > 3 × upper limit of normal).

Sample collection and coagulation testing

Serial blood samples were collected from each subject via a venipuncture. In all samples, laboratory-based PT and APTT were measured using a single reagent (HemosIL RecombiPlasTin 2G [Instrumentation Laboratory, Bedford, MA; normal range: 9.0-11.0 s] and Thrombocheck APTT-SLA [Sysmex, Japan; normal range: 24.5-39.7 s], respectively) on a CS-5100 (Sysmex).

We previously found that the PT and APTT varied widely in DOAC patients even within individuals;[10] therefore, we averaged these values across patients in whom they had been measured more than twice. As a change in the DOAC therapy, a switch to a different DOAC or a change in the dosage of the DOACs could result in different values of coagulation assays even among individuals; the aforementioned averaging was evaluated in the respective DOAC cases and not in each patient. We did not consider the sample measurement time relative to the start of DOAC (eg, how many days later) or the number of hours after DOAC ingestion. The prescribed

DOAC dose was compared with the recommended dose, to identify patients who were receiving inappropriately large or small dosages.

EP of coagulation time was defined as the prolongation of PT or APTT of more than 2 standard deviations over the median value for each DOAC. Patients receiving 2 or more DOACs or requiring changes in the dosage of DOAC over time were categorized into the excessive coagulation time prolongation group (EP group) if EP was observed with at least 1 drug or dosage. At the stage of defining excessively prolonged PT or APTT values, the data were handled separately for each DOAC. Additional assays were performed for patients in the EP group to identify the cause for the prolongation. These assays were performed in the DOAC-free state, or if the anticoagulant could not be discontinued, the blood sample was obtained when the serum concentration was made as low as possible by delaying the next dose. In particular, this was >12 hours after the last drug intake for dabigatran and apixaban and > 24 hours for rivaroxaban and edoxaban. For patients with EP of APTT, the activities of fibrinogen; prothrombin; blood coagulation factors V, VIII, IX, X, XI, and XII; antiphospholipid antibodies (IgM, IgG, anticardiolipin β_2-glycoprotein I complex antibody, and antibodies to the phosphatidylserine/prothrombin complex, and lupus anticoagulant); and the von Willebrand factor were evaluated. For patients with EP of PT, the blood coagulation factor VII activity and protein induced by the vitamin K absence or antagonist-II were evaluated. Because the criteria for EP were defined after the coagulation assay data had been collected from all patients, additional assays to determine the possible causes were not performed immediately after very long PT or APTT was observed, but after the study period. The study was approved by the Tokyo Medical and Dental University institutional review board. The requirement for informed consent was waived.

Statistical methods

Normally distributed continuous variables are expressed as the mean ± standard deviation, non-normally distributed continuous variables as the median and interquartile range, and categorical variables as the number and percentage. The differences between continuous variables were assessed using Student's *t*-test or Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test, or Fisher's exact test when the data were very unequally distributed among the cells of the table resulting in expected values in any of the cells of a contingency table to drop below 5. A receiver operating characteristic curve was used to determine the cutoff point with the highest sensitivity/specificity. Multivariable logistic regression analysis was performed to identify the independent clinical predictors of excessive coagulation time prolongation. Kaplan-Meier curves were traced to compare the incidence of thromboembolic and bleeding events between patients with and without EP. The existing differences were assessed using a log-rank test. *P* values of < 0.05 were considered statistically significant. SPSS statistics 22 software (SPSS Inc, Chicago, IL) was used for all statistical analyses.

Results

During the approximately 7.5-year study period, 1720 patients with NVAF received DOACs. Of those, 1530 patients (89%) received PT and APTT tests, of whom 1521 were eligible patients (1105 men; mean age, 66 ± 12 years; Fig. 1). The CHA_2DS_2-VASc score ranged from 0 to 8, and 1001 patients (66%) had a score of ≥ 2. The patient characteristics and baseline laboratory values are shown in Table 1.

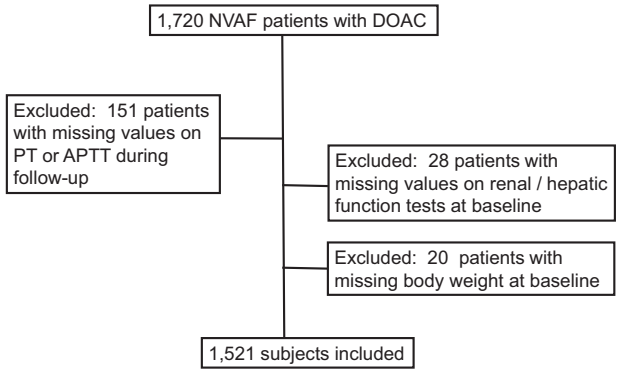

Figure 1. Flow chart for subject selection. APTT, activated partial thromboplastin time; DOAC, direct oral anticoagulants; NVAF, nonvalvular atrial fibrillation; PT, prothrombin time.

In all, 124 patients received 2 different doses of the same DOAC; 258, two DOACs; and 5, three DOACs over time. Further, in 54 patients, the DOAC was switched to a different one or the dosage of DOACs was changed. In total, in 392 instances, the anticoagulant regimen was changed during the study period, resulting in a total of 1913 cases: dabigatran (n = 497), rivaroxaban (n = 651), apixaban (n = 576), and edoxaban (n = 189). The prescribed dose of dabigatran was 300, 220, 150, 110, and 75 mg/d in 189, 282, 18, 5, and 3 cases, respectively. For rivaroxaban, the doses were 15 mg/d in 426 and 10 mg/d in 225 cases. For apixaban, the dose was 10 mg/d in 312, 5 mg/d in 251, and 2.5 mg/d in 13 cases; for edoxaban, the dose was 60 mg/d in 36, 30 mg/d in 140, and 15 mg/d in 13 cases. Among the DOAC prescriptions, 64% were found to be appropriate dosages. A reduced dose was prescribed in 31% of subjects with no clear indication, and 5% received a higher than recommended dose that was not reduced, although clinical factors indicated the decrease.

A total of 1879 PT and 1705 APTT values were obtained. The distribution of APTT values for the direct thrombin inhibitor and that of PT values for the FXa inhibitors are shown in Figure 2, exhibiting a remarkable range in values for each panel. For dabigatran, the cutoff value for excessive APTT was 63.6 seconds, and that for PT was 16.8 seconds. The cutoff for PT and APTT was 22.8 and 59.4 seconds for rivaroxaban, 17.7 and 48.2 seconds for apixaban, and 16.7 and 50.0 seconds for edoxaban, respectively. In 88 patients (5.8%), PT or APTT was excessively prolonged. The EP group was significantly older (69 vs 66 years, $P = 0.012$), weighed significantly less (60 vs 66 kg, $P = 0.0001$), and had lower Ccr (66 vs 76 mL/min, $P = 0.002$), higher CHA_2DS_2-VASc score (2.8 vs 2.3, $P = 0.011$), and higher HAS-BLED score (1.6 vs 1.3, $P = 0.017$) than the group without excessive coagulation time prolongation (non-EP group). Significantly more female patients (36% vs 27%, $P = 0.036$) and greater than recommended dose prescription (13% vs 6%, $P = 0.021$) were noted in the EP group (Table 1).

Table 1. Baseline characteristics of the patients

	Total (n = 1521)	EP group (n = 88)	Non-EP group (n = 1433)	*P* value
Age (y)	66 ± 12	69 ± 11	66 ± 12	0.012
Male, n (%)	1105 (72.6)	56 (63.6)	1049 (73.2)	0.036
Body weight (kg)	66 ± 14	60 ± 14	66 ± 14	0.0001
Ccr (mL/min)	76 ± 31	66 ± 29	76 ± 31	0.002
CHA_2DS_2-VASc score	2.4 ± 1.7	2.8 ± 1.7	2.3 ± 1.7	0.011
0	208 (13.7%)	10 (11.3%)	198 (13.8%)	
1	312 (20.5%)	13 (14.8%)	299 (20.9%)	
≥2	1001 (65.8%)	65 (73.9%)	936 (65.3%)	
HAS-BLED score	1.3 ± 1.1	1.6 ± 1.3	1.3 ± 1.1	0.017
0	397 (26.1%)	20 (22.7%)	377 (26.3%)	
1	561 (36.9%)	25 (28.4%)	536 (37.4%)	
≥2	563 (37.0%)	43 (48.9%)	520 (36.3%)	
DOACs				0.77
Dabigatran	414 (27.2%)	21 (23.9%)	393 (27.4%)	
Rivaroxaban	447 (29.4%)	30 (34.1%)	417 (29.1%)	
Apixaban	529 (34.8%)	30 (34.1%)	499 (34.8%)	
Edoxaban	131 (8.6%)	7 (8.0%)	124 (8.7%)	
Inappropriately high dose	97 (6.4%)	11 (12.5%)	86 (6.0%)	0.021
Liver dysfunction	111 (7.3%)	7 (8.0%)	104 (7.3%)	0.81
Antiplatelet drugs	165 (10.8%)	14 (15.9%)	151 (10.5%)	0.11

Values are shown as the mean ± SD or n (%).

Ccr, creatinine clearance; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); DOAC, direct oral anticoagulants; EP, excessive prolongation; SD, standard deviation.

The receiver operating characteristics showed that age greater than 66 years, a CHA_2DS_2-VASc score of 3, a HAS-BLED score of 1, or body weight less than 60 kg or Ccr of 74 mL/min abruptly increased the possibility of excessive coagulation time prolongation. A multivariate analysis, which included female gender, inappropriately high dosing, age of ≥ 66 years, body weight of ≤ 60 kg, Ccr of ≤ 74 mL/min, CHA_2DS_2-VASc score of ≥ 3, and HAS-BLED score of ≥ 1 as variables, revealed that high dosing and body weight of ≤ 60 kg remained independent predictors of excessive coagulation time prolongation (odds ratio = 2.29 with 95% confidence interval 1.17-4.50, $P = 0.016$ for an inappropriately high dose prescription and odds ratio = 2.12 with 95% confidence interval 1.20-3.72, and $P = 0.009$ for a body weight of ≤ 60 kg; Table 2).

The causes of excessive coagulation time prolongation were assessed in 53 of the 88 EP group patients (60%). Among them, positive antiphospholipid antibodies were observed in 15 patients (28%), an inappropriately high-dose prescription in 6 (11%), a coagulation factor deficiency in 4 (8%), and severe liver dysfunction in 3 (6%). The breakdown of coagulation factor deficiencies was as follows: FVII deficiency heterozygote in 2, and FX deficiency heterozygote and FXII deficiency heterozygote in 1 each. In the remaining 25 patients (47%), no discernible abnormalities were found (Table 3). Among the 15 patients with positive antiphospholipid antibodies (10 men, mean age of 66 years), 6 exhibited EP of APTT under dabigatran and the remaining 9 under FXa inhibitors. The baseline APTT (before starting the DOAC) was normal in 5 patients and became excessively prolonged only after the DOACs were started. Two patients had cerebral thromboembolisms before the DOACs were started and were diagnosed as having antiphospholipid antibody syndrome. None of the patients with positive antiphospholipid antibody had bleeding events or thromboembolic events under the DOACs.

During the follow-up of a median of 8.9 months (1 day to 89 months), thromboembolisms developed in 10 patients (0.66%), and bleeding events in 85 (5.6%; Table 4). The Kaplan-Meier curves for thromboembolic and bleeding events in the EP and non-EP groups are shown in Figure 3. Although the difference in the incidence of thromboembolic events was not significant ($P = 0.556$), bleeding events appeared to occur at a constant rate in proportion to the time from the initiation of DOACs in both the groups and were significantly higher in the EP group ($P = 0.013$).

In the EP group, patients who had bleeding events had a significantly higher HAS-BLED score than those without any bleeding events (2.3 vs 1.5, $P = 0.03$). The other characteristics were similar between the groups.

Discussion

In this retrospective single centre study, we found instances of EP in PT or APTT in 88 (5.8%) of 1521 patients with NVAF. Multivariable analysis revealed significant associations of inappropriately high prescription dosages and a body weight of ≤ 60 kg with excessive coagulation time prolongation. Bleeding events were statistically significantly higher in the EP group patients.

The performance of standard anticoagulation tests varies across DOACs and depends on the reagents, and most assays have been shown to be inadequate for the assessment of DOAC effects.[2,4,11,12] Therefore, what is the relevance of real-world use of DOACs to clinicians? Should clinicians be more cautious of some patient populations and monitor their anticoagulation status? Studies on the factors leading to excessive coagulation time prolongation in the standard coagulation assays are lacking. Patients with renal and/or hepatic impairment; advanced age; concomitant interacting drug use; low body weight; and higher $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores are known to be at a high risk for bleeding complications with DOACs;[5,13-19] these factors are similar to those for warfarin. In our study, the same risk factors were found to lead to EP of PT and APTT. Although we did not measure the DOAC plasma

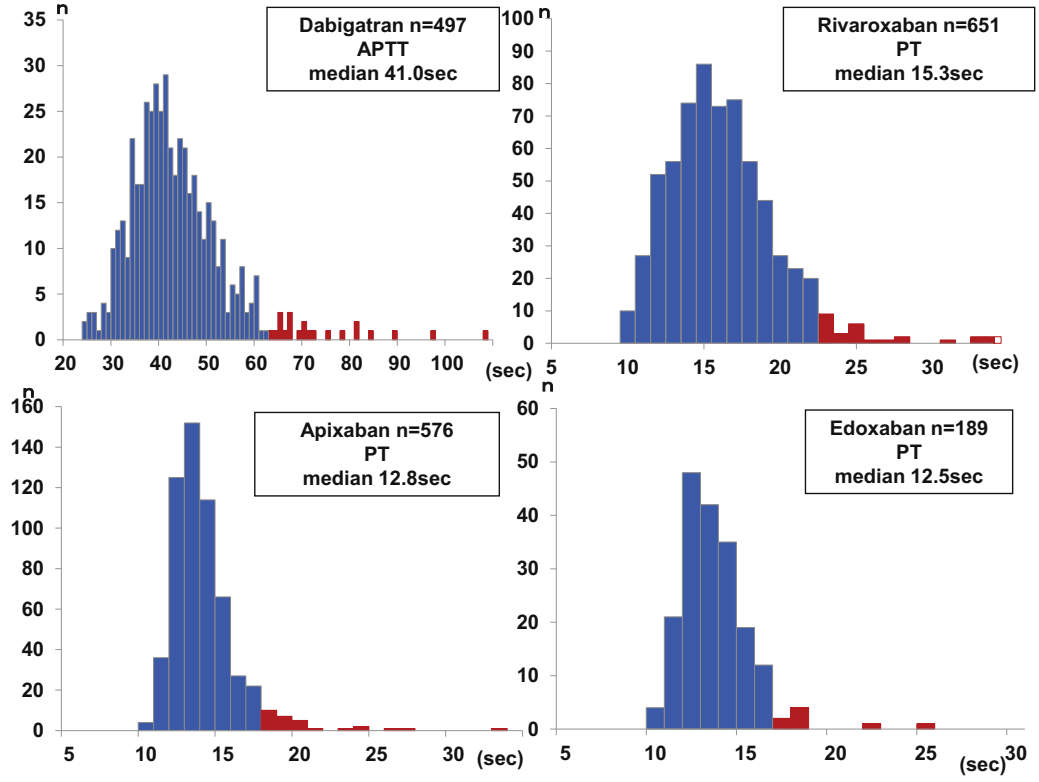

Figure 2. The distribution of activated partial thromboplastin time (APTT) values for direct thrombin inhibitors and prothrombin time (PT) values for FXa inhibitors. In patients with 2 or more measurements, the measurements were averaged. The **red bars** indicate the distribution of the excessive prolongation group defined as those in whom PT or APTT was prolonged by more than 2 standard deviations over the median value for each direct oral anticoagulant. The **blue bars** indicate the distribution of the group without excessive prolongation. In 88 patients (5.7%), coagulation time was excessively prolonged.

concentrations, both inappropriately high prescription dosages and lower body weight have been shown to be associated with higher DOAC plasma concentrations.[5-8] Therefore, we speculate that excessively long PT and APTT result from high DOAC plasma concentrations in patients with inappropriately high dosages or low body weight. A few clinical studies on DOACs have evaluated the clinical outcomes based on coagulation assays.[20,21] We previously reported that bleeding events were not correlated with APTT in patients taking dabigatran, provided that the APTT was not excessively prolonged.[10] In this study, we found a higher risk for haemorrhagic events in patients with excessively prolonged PT or APTT.

Table 2. Multivariate analysis for the predictors of excessive prolongation

Risk factors	Odds ratio	95% CI	*P* value
Female	1.04	0.63-1.73	0.87
Inappropriately high dose	2.29	1.17-4.50	0.016
Age ≥66 y	1.46	0.69-3.09	0.32
Body weight ≤60 kg	2.12	1.20-3.72	0.009
Ccr ≤ 74 mL/min	0.95	0.52-1.71	0.85
CHA_2DS_2-VASc score ≥ 2	1.34	0.80-2.45	0.24
HAS-BLED score ≥ 1	0.60	0.27-1.36	0.22

Ccr, creatinine clearance; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); CI, confidence interval.

What measures need to be taken if the test results show excessively long PT and APTT in DOAC patients? Our study emphasized the need to follow the recommendations for DOAC dosage, based on patients' age, renal function, and body weight. Among them, body weight is an important factor to consider during the prescription of DOACs. Our results also suggested that patients with hepatic dysfunction need to be monitored more closely. In addition to these basic considerations of dosing amounts, our assessment of underlying patient-specific causes of excessive PT or APTT prolongation found many patients with latent abnormalities of the anticoagulation system (8% with a coagulation factor deficiency) and positive antiphospholipid antibodies (28%). The actual prevalence of antiphospholipid antibody positivity in the general population is not yet known. Although patients with antiphospholipid antibodies might present with no related symptoms, antiphospholipid antibody syndrome in these patients is

Table 3. The causes of excessive prolongation in 53 patients

Causes	Number of patients
No discernible abnormality	25 (47%)
Positive antiphospholipid antibodies	15 (28%)
Inappropriately high dose DOACs	6 (11%)
Coagulation factor deficiency	4 (8%)
Severe liver dysfunction	3 (6%)

DOAC, direct oral anticoagulant.

Table 4. The outcome data

	Total (n = 1521)	EP group (n = 88)	Non-EP group (n = 1433)	*P* value
Thromboembolism	10 (0.66%)	2 (2.3%)	8 (0.42%)	0.11
Bleeding events	85 (5.6%)	14 (16.0%)	71 (5.0%)	0.0002
Major	24 (1.6%)	5 (5.7%)	19 (1.3%)	0.010
Minor	61 (4.0%)	9 (10.2%)	52 (3.6%)	0.007

Values are shown as n (%).
EP, excessive prolongation.

characterized by thrombosis, pregnancy complications, or both. Thrombotic risk calculators are being developed for antiphospholipid antibody-positive patients.[22] However, at present, evidence to determine the relative efficacy and safety of DOACs in this patient population is insufficient.[23]

None of the 15 antiphospholipid antibody-positive patients in this study had thromboembolic events after the start of DOACs. This included the 2 patients with prior cerebral thromboembolisms who were diagnosed with antiphospholipid antibody syndrome. The presence of antiphospholipid antibodies was revealed because of the excessive prolongation of APTT under DOACs. Some of the patients had undergone pulmonary vein isolation and have been free from AF. Further studies are required to determine whether anticoagulants need to be continued in such patients.

Clinical implication

All patients receiving a DOAC should be checked to determine whether they are being dosed according to the guidelines. If there is unease concerning the choice of a dose, a patient could be screened once by measuring the coagulation parameters for reassurance that their response to DOAC therapy matches that of the majority of the population. As no clear relationship exists to guide the adjustment of DOAC dosing with regard to anticoagulation parameters, routinely monitoring them in a patient or attempting to use them for a dose adjustment would be inappropriate. If a patient receiving the recommended dose has a body weight of < 60 kg in combination with excessively prolonged coagulation parameters, the dosage should be reduced or the DOAC should be discontinued. If a patient with excessive coagulation time prolongation is receiving the recommended dose and has an adequate body weight, he/she should be tested for antiphospholipid antibodies. If positive, then proper anticoagulation therapy becomes necessary to prevent thromboembolisms.

Limitations

First, our results were obtained retrospectively from a limited population from a single institution. During a review of the medical records, we did not find any written records explaining why standard coagulation assays were performed in particular patients. Therefore, we cannot deny the possibility that the patients who received coagulation assays were those who already showed signs of the risk for bleeding during the anticoagulation therapy, thereby leading to a selection bias of the study population. However, of the entire population of 1720 patients with NVAF who received DOACs, 1530 (89%) had their coagulation parameters measured, of whom 1521 (88.4%) satisfied our study criteria. Because such a large proportion of DOAC patients received coagulation assays, we believe that the likelihood of selection bias affecting our results was diminished. Our definition of excessive coagulation time prolongation—2 standard deviations > median—was arbitrary, and selection of a different criterion might have led to different results. Future studies are warranted to determine the best cutoff value to evaluate the bleeding risk and trigger a search for underlying genetic causes.

Second, commercial reagents differ widely in their sensitivity to DOACs. We used only a single reagent for the PT

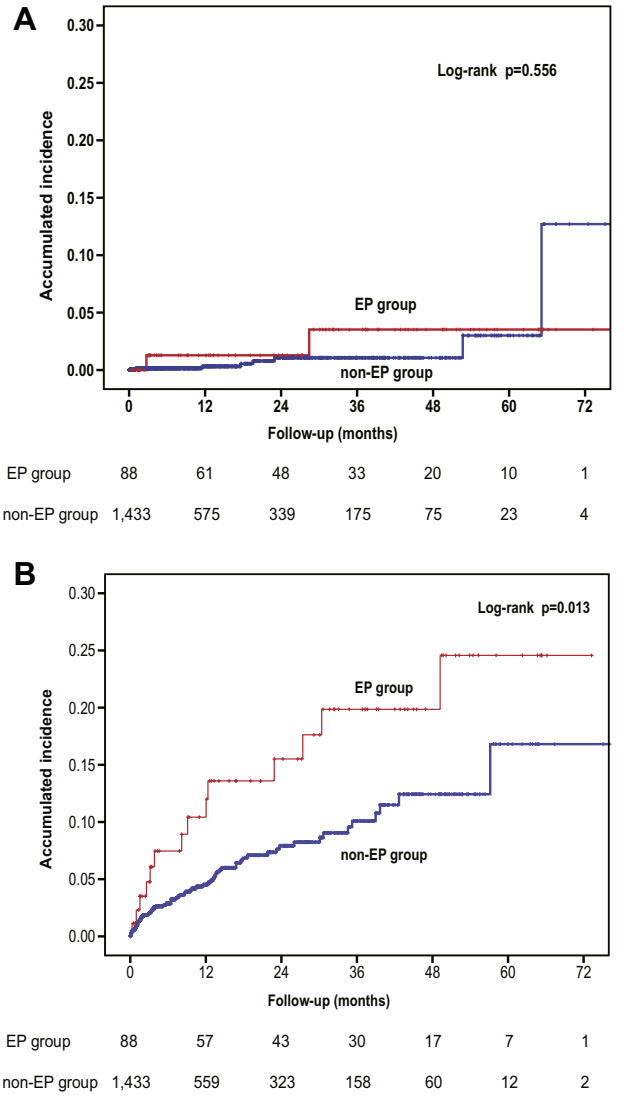

Figure 3. Kaplan-Meier curves for the thromboembolic (**A**) and bleeding events (**B**) in the group with excessive prolongation (EP group) and in the group without excessive prolongation (non-EP group).

and APTT testing. Previous studies have shown a high reactivity to DOACs for the reagent we used for PT testing—HemosIL RecombiPlasTin 2G, but not for our reagent used for the APTT testing—Thrombocheck APTT-SLA.[24,25] The rate of detecting patients with excessive coagulation time prolongation would depend on the sensitivity of the reagents used.

Third, the time between the last drug intake and blood draw needs to be considered because the DOAC plasma concentrations increase rapidly after intake until reaching the maximum plasma concentration.[20] In clinical practice, laboratory data are speculated to vary according to the time of sampling relative to drug ingestion. However, in our previous study, no obvious relationship was noted between the APTT and the timing of blood collection for dabigatran.[10] We extrapolated this finding to the other DOACs and did not consider the sampling time in this study.

Fourth, DOACs have shorter half-lives and require stricter adherence, but this study did not assess patient compliance.

Fifth, we acknowledge that studies on DOAC-specific coagulation tests are available, such as the calibrated anti-Xa activity for FXa inhibitors and diluted thrombin time, ecarin-based assays for dabigatran, and the measurement of DOAC plasma concentrations.[26-28] In this study, we assessed only the results of the commonly administered global coagulation tests. The DOAC-specific tests might become the best way to monitor the anticoagulation levels in patients receiving DOACs; however, we intended to determine the extent and factors that are responsible for EP of widely used and inexpensive anticoagulation assay measurements.

Lastly, because of the retrospective nature of this study, in some patients with excessive coagulation time prolongation, further evaluation of the anticoagulant system could not be performed. We could not assess the concentration of prekallikrein or high-molecular-weight kininogen, as well as the value of coagulation factor inhibitors. Therefore, we could not diagnose whether excessive coagulation time prolongation was caused by these factors.

Conclusions

Excessive coagulation time prolongation is occasionally noted in the standard coagulation assessments during treatment with DOACs and is associated with an increase in bleeding events. Observing and prescribing doses of DOAC agents that adhere to the current guidelines are critically important. If a patient has a body weight of <60 kg, a dosage reduction or withdrawal of the DOAC should be considered. Because factors leading to excessive coagulation time prolongation exhibited a remarkable diversity, a subset of patients with positive antiphospholipid antibodies need to be included to determine the clinical response to address the underlying mechanism, if any, is found. Further studies are needed to identify the best monitoring practices for patients on DOACs.

Acknowledgement

We would like to thank Hiroko Ozaki for her technical assistance with data collection.

Funding Sources

This work was supported by a program for women researchers from the Tokyo Medical and Dental University, Japan, through 2015 and 2016. This study was partially supported by the Japan Agency for Medical Research and Development, Japan (Grant Number: 18ek0210082h0002).

Disclosures

The authors have no conflicts of interest to disclose.

References

1. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. Am J Med 2015;128:1300-5.
2. Miyares MA, Davis K. Newer oral anticoagulants: a review of laboratory monitoring options and reversal agents in the hemorrhagic patient. Am J Health Syst Pharm 2012;69:1473-84.
3. Blann AD, Lip GYH. Laboratory monitoring of the non-vitamin K oral anticoagulants. J Am Coll Cardiol 2014;64:1140-2.
4. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory assessment of the anticoagulant activity of direct oral anticoagulants (DOACs): a systematic review. Chest 2016;151:127-38.
5. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol 2007;47:218-26.
6. Stangier J, Rathgen K, Stähle H, Gansser D, Roth W. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. Br J Clin Pharmacol 2007;64:292-303.
7. Frost C, Wang J, Nepal S, et al. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. Br J Clin Pharmacol 2013;75:476-87.
8. Krekels EH, Niebecker R, Karlsson MO, et al. Population pharmacokinetics of edoxaban in patients with non-valvular atrial fibrillation in the ENGAGE AF-TIMI 48 Study, a phase III clinical trial. Clin Pharmacokinet 2016;55:1079-90.
9. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
10. Kawabata M, Yokoyama Y, Sasano T, et al. Bleeding events and activated partial thromboplastin time with dabigatran in clinical practice. J Cardiol 2013;62:121-6.
11. Favaloro EJ, Lipppi G, Koutts J. Laboratory testing of anticoagulants: the present and the future. Pathology 2011;43:682-92.
12. Ebner M, Birschmann I, Peter A, et al. Emergency coagulation assessment during treatment with direct oral anticoagulants. Limitations and solutions. Stroke 2017;48:2457-63.
13. Gladstone DJ, Geerts WH, Douketis J, et al. How to monitor patients receiving direct oral anticoagulants for stroke prevention in atrial fibrillation: a practice tool endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. Ann Intern Med 2015;163:382-5.
14. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess one year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. Chest 2010;138:1093-100.

15. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363-72.

16. Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Ann Intern Med 2011;155:660-7.

17. Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. Lancet 2012;380:1749-58.

18. Kundu A, Sardar P, Chatterjee S, et al. Minimizing the risk of bleeding with NOACs in the elderly. Drugs Aging 2016;33:491-500.

19. Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. Best Pract Res Clin Haematol 2013;26:191-202.

20. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with nonvalvular atrial fibrillation. Europace 2015;17:1467-507.

21. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulation therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e44S-88S.

22. Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. N Engl J Med 2018;378:2010-21.

23. Andrade D, Cervera R, Cohen H, et al. 15th International Congress on Antiphospholipid Antibodies Task Force on Antiphospholipid Syndrome treatment trends report. In: Erkan D, Lockshin MD, eds. Antiphospholipid syndrome: current research highlights and clinical insights. New York: Springer, 2017:317-38.

24. Helin TA, Pakkanen A, Lassila R, Joutsi-Korhonen L. Laboratory assessment of novel oral anticoagulants: method suitability and variability between coagulation laboratories. Clin Chem 2013;59:807-14.

25. Samama MM, Martinoli JL, LeFlem L, et al. Assessment of laboratory assays to measure rivaroxaban—an oral, direct factor Xa inhibitor. Thromb Haemost 2010;103:815-25.

26. Favaloro EJ, Bonar R, Butler J, Marsden K. Laboratory testing for the new oral anticoagulants: a review of current practice. Pathology 2013;45:435-7.

27. Tripodi A. The laboratory and the direct oral anticoagulants. Blood 2013;121:4032-5.

28. Crowther M, Crowther MA. Antidotes for novel oral anticoagulants: current status and future potential. Arterioscler Thromb Vasc Biol 2015;35:1736-45.