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Review

Current strategies of anticoagulation therapy for patients with non-valvular atrial fibrillation

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ABSTRACT

Cardioembolic stroke accounts for 20–30% of acute brain infarctions in Japan. This condition is often severe and has poor outcomes. Non-valvular atrial fibrillation (NVAF) is the most common cardiac source of emboli in cardioembolic stroke. Anticoagulants are recommended for preventing stroke in patients with NVAF, and these patients were usually treated with warfarin. However, the use of warfarin has many limitations. Approximately half of the patients with NVAF, who show indications for warfarin treatment, are treated with warfarin. Bleeding complications, including intracranial hemorrhages, are common during warfarin treatment; this is a huge concern of warfarin treatment. Warfarin-associated intracranial hemorrhage is often severe and devastating. Several novel anticoagulants that can overcome the limitations of warfarin have been introduced in the market or are under development. In this review, we discuss the pharmacological properties of novel anticoagulants and current strategies of anticoagulation therapy for preventing stroke in patients with NVAF.

Contents

1. Characteristics of the new anticoagulants

Several new anticoagulants have been developed recently to overcome the limitations of warfarin. The new anticoagulants are either thrombin inhibitors, such as dabigatran, or factor Xa inhibitors, such as rivaroxaban, apixaban, and edoxaban, and these anticoagulants suppress either thrombin or factor Xa directly [1]. The characteristics of new anticoagulants differ from those of warfarin and are summarized in Table 1. In particular, their absorption time is short, the time-to-peak-concentration (*T*max) is 1–4 h, and the serum concentration corresponds to the anticoagulatory effect. Although the half-life of the new anticoagulants is about 12 h, the rivaroxaban and the edoxaban are taken once a day and the dabigatran and the apoxaban twice a day. The efficacy of the new anticoagulants is not influenced by food intake or vitamin K levels; therefore, food restriction is not required during treatment. Compared to warfarin, the new anticoagulants interact much less with other medicines. The therapeutic range of the new anticoagulants is wide, and the effect of anticoagulation can be predicted from the amount of drug administered; thus, it is not necessary to monitor their anticoagulation effect. Overall, the characteristics of these novel anticoagulants are such that treatment with these anticoagulants does not have many of the difficulties that are frequently encountered with warfarin treatment.

2. Results of phase III trials of the novel anticoagulants

The efficacy and safety of dabigatran, a direct thrombin inhibitor, and rivaroxaban and apixaban, direct factor Xa inhibitors, have been

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Table 1
Characteristics of warfarin and novel anticoagulants.

	Warfarin	New anticoagulants
Monitoring	Required	Not required
	Established	Not established
Influence of food	Vitamin K-rich food	None
Interactions with other medicines	Frequent	Small
Absorption	Fast, but its anticoagulatory effect appears several days later	Fast (*T*max of 1–4 h)
Half-life	40 h	12 h
Risk of stroke with missed doses	Low	High
Perioperative management	Complicated	Uncomplicated
Resistance	Reported	Not reported
Volume of research	Large	Small
Price	Inexpensive	Expensive
	1 mg 9.6 yen	Dabigatran
		150 mg bid, 530.4 yen
		110 mg bid, 465.4 yen
		Rivaroxaban
		15 mg qd, 530.4 yen
		10 mg qd, 372.4 yen
Methods of reversal		
Vitamin K	Effective	Not effective
Gastric lavage or oral administration of activated charcoal	Not effective	Effective, soon after taking dabigatran
Hemodialysis	Not effective	Possible[a]
FFP	Effective	Possible[a]
PCC	Effective	Possible[a]
rFVII	Effective	Possible[a]

FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; rFVII, recombinant activated factor VII.

[a] No available clinical data.

Table 2
Results of phase III trials to compare the efficacy of novel anticoagulants and warfarin.

	Dabigatran (1) 150 mg	110 mg	Rivaroxaban (2) 20 mg qd	Apixaban (3) 5 mg qd
Stroke and systemic embolism	Superior	Non-inferior	Non-inferior	Superior
Major bleeding	Non-inferior	Superior	Non-inferior	Superior
Ischemic stroke	Superior			
Any death				Superior
Major and clinically relevant bleeding	Superior	Superior		Superior
Gastrointestinal bleeding	Inferior		Inferior	
Hemorrhagic stroke	Superior	Superior	Superior	Superior
Intracranial hemorrhage	Superior	Superior	Superior	Superior
Withdrawal	Inferior	Inferior		Superior

Analysis was on-treatment for rivaroxaban (2), and intention-to-treat for dabigatran (1) and apixaban (3). Superior, non-inferior, and inferior indicate that superiority, non-inferiority and inferiority to warfarin were proven, respectively in each phase III trial.

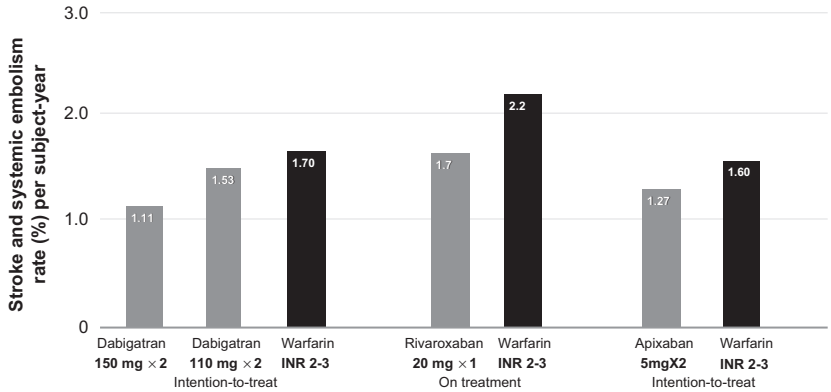

Fig. 1. Rate of stroke and systemic embolism expressed per subject years in patients treated with a new anticoagulant (dabigatran (2), rivaroxaban, (3) or apixaban (4); gray bars) and in patients treated with warfarin (black bars) as determined in each study. Drug dosage and method of analysis (intention-to-treat or on treatment) are indicated on the *x*-axis.

compared to those of warfarin in phase III trials [2–4]. The patients and warfarin management, particularly the time in therapeutic range, differed between these studies, precluding direct comparison of the primary or secondary endpoints and adverse events. However, a descriptive summary of the findings of each trial is presented in Table 2. All 3 drugs were not inferior to warfarin in terms of incidence of stroke, systemic embolism as the primary endpoint, and major bleeding (Fig. 1) [2–4]. Superiority to warfarin was observed

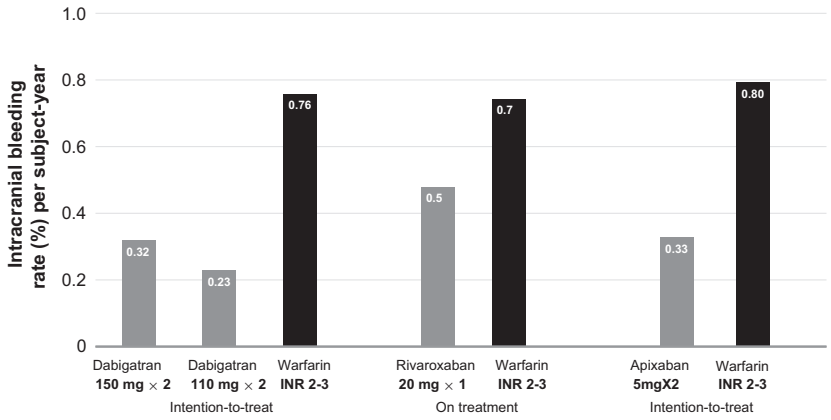

Fig. 2. Rate of intracranial bleeding expressed per subject–years in patients treated with a new anticoagulant (dabigatran (2), rivaroxaban, (3) or apixaban (4); gray bars) and in patients treated with warfarin (black bars) as determined in each study. Drug dosage and method of analysis (intention-to-treat or on treatment) are indicated on the *x*-axis.

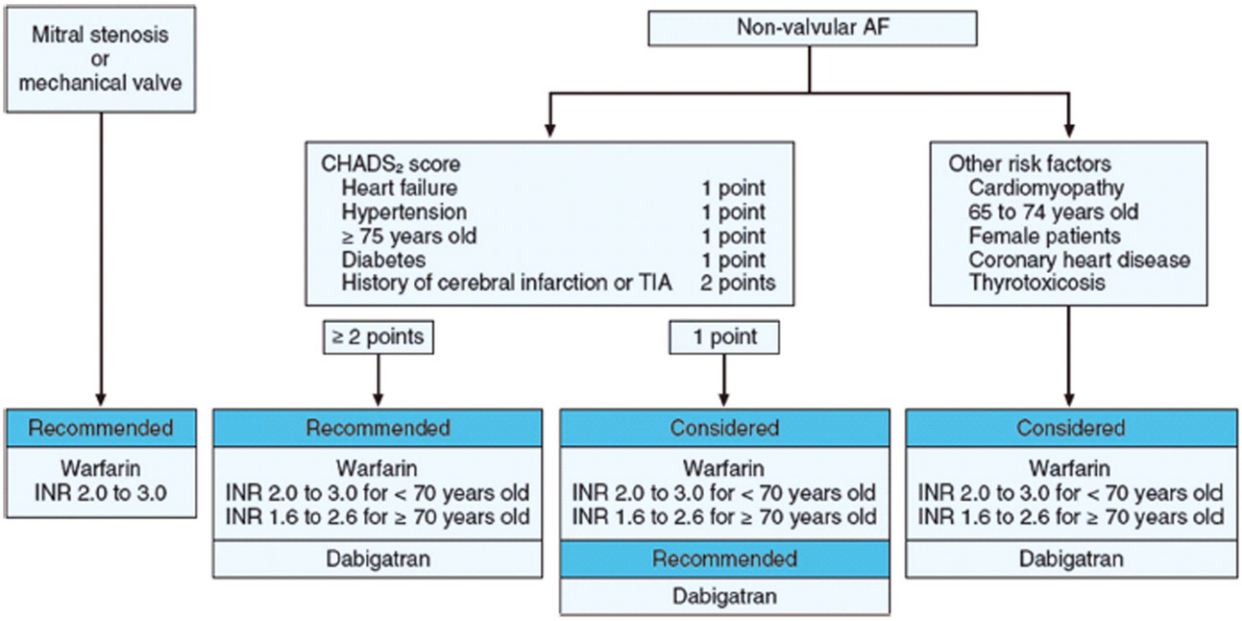

Fig. 3. A schematic representation obtained from the Japanese Circulation Society illustrating anticoagulation use in patients non-valvular arterial fibrillation, taken from (5).

regarding the incidence of stroke and systemic embolism for dabigatran (150 mg dose) and apixaban. Moreover, dabigatran (110 mg dose) and apixaban were shown to be superior to warfarin in preventing major bleeding. The incidence of hemorrhagic stroke and intracranial hemorrhage in patients treated with the novel anticoagulants was significantly lower than that in patients treated with warfarin (Fig. 2). The incidence of ischemic stroke was lower in patients treated with dabigatran (150 mg) than in patients treated with warfarin. Gastrointestinal bleeding was frequently seen in patients treated with dabigatran (150 mg) and rivaroxaban. Compared to patients treated with warfarin, patients treated with dabigatran showed withdrawal more frequently and those treated with apixaban showed withdrawal less frequently.

3. Use of different anticoagulants according to risk stratification

The CHADS2 score is used to estimate the risk of stroke in patients with NVAF and to help determine whether anticoagulant therapy is required. This score is based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack (TIA) and 1 point each is assigned for congestive heart failure, history of hypertension, an age of at least 75 years, and diabetes. When the CHADS2 score is 2 or more, the annual risk of stroke is 4% or more. Therefore, a CHADS2 score of 2 or more is considered a high risk for stroke and is an indication for warfarin treatment. When the CHADS2 score is 1, warfarin treatment is not immediately recommended, but the benefits of reducing stroke incidence are considered against the risk of major bleeding. A previous study showed that compared to warfarin, dabigatran is associated with lower rates of stroke, systemic embolism, major bleeding, and intracranial bleeding in patients with low (0–1), medium (2), and high (≥ 3) CHADS2 scores [5]. Given the small number of patients with a CHADS2 score of 0 in that study (only 2.5% of the patients were in the low-risk group), the Japanese Circulation Society released an urgent statement recommending dabigatran for patients with CHADS2 scores of 1 [6] (Fig. 3).

Although the CHADS2 score is useful for evaluating the risk of stroke in NVAF patients, about half of all NVAF patients have a score

of 0 or 1 [7]. There are no clear guidelines on whether warfarin should be administered or not, to these patients because the risk of annual incidence of stroke is so low for such patients that the benefits of anticoagulation therapy do not clearly exceed the increased risk of major bleeding. The CHA2DS2-VASc score has been proposed as a complement for the CHADS2 score, since it uses additional risk factors to predict stroke risk in NVAF patients [8]. The scoring system of the CHA2DS2-VASc score ranges from 0 to 9; 1 point each is assigned for congestive heart failure, hypertension, an age of 65–74 years, diabetes mellitus, vascular disease, and female gender, and 2 points are assigned for an age of at least 75 years and a previous incidence of stroke or TIA.

A nationwide cohort study conducted in Denmark demonstrated that at 1-year follow-up, the rate of thromboembolism per 100 people per year was 1.67 (95% confidence interval, 1.47–1.89) in patients with a CHADS2 score of 0 and 0.78 (0.58–1.04) in patients with a CHA2DS2-VASc score of 0 [7]. This rate was found to rise to 4.75 (4.45–5.07) and 2.01 (1.70–2.36) in patients with a CHADS2 and CHA2DS2-VASc scores of 1, respectively, and to 7.34 (6.88–7.82) and 3.71 (3.36–4.09) in patients with a CHADS2 and CHA2DS2-VASc scores of 2, respectively. Patients were categorized as low- (score of 0), intermediate- (score of 1), or high-risk (score of 2 or more), and the *C* statistics at the 10-year follow-up was 0.812 (0.796–0.827) when patients were categorized according to the CHADS2 score and 0.888 (0.875–0.900) when categorized according to the CHA2DS2-VASc score. Thus, the CHA2DS2-VASc score performed better than the CHADS2 score in predicting thromboembolism. Furthermore, these results indicate that patients categorized as low-risk by CHA2DS2-VASc are truly at a low risk for thromboembolism and that anticoagulation should be recommended for NVAF patients with a CHA2DS2-VASc score of 2 or more and considered for NVAF patients with a CHA2DS2-VASc score of 1.

Although the CHA2DS2-VASc score was found to be superior to the CHADS2 score in predicting patients at risk for thromboembolism, it is more complicated than CHADS2. Therefore, we typically perform CHADS2 scoring for all NVAF patients, and recommend dabigatran, rivaroxaban, or warfarin treatment for patients with a score of 2 or more and dabigatran treatment for patients with a score of 1. For patients who have a CHADS2 score of 0 or have a CHADS2 score of 1 but develop renal dysfunction or other adverse effects after dabigatran treatment, CHA2DS2-VASc scoring is performed for more precise stratification. Dabigatran, rivaroxaban, or warfarin are recommended for patients with a CHA2DS2-VASc score of 2 or more and considered for patients with a CHA2DS2-VASc score of 1. Patients with a CHA2DS2-VASc score of 0 have a low risk for thromboembolism and may not benefit from anticoagulants; however, dabigatran or rivaroxaban may be considered as these anticoagulants have a low risk of inducing intracranial bleeding. This strategy is depicted in Fig. 4.

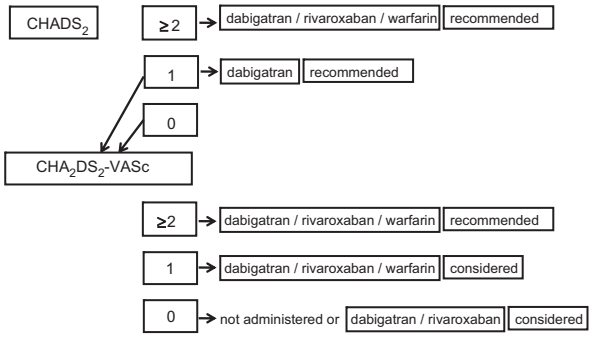

Fig. 4. A schematic representation showing the strategy of anticoagulant use according to CHADS2 and CHA2DS2-VASc scores.

4. Prevention of intracranial and major bleeding

History of stroke or TIA is as a major risk factor for intracranial hemorrhage and recurrent stroke [9–11]. Therefore, it is necessary to pay attention to preventing intracranial bleeding and recurrent stroke in NVAF patients with a history of stroke or TIA. Compared to warfarin, the aforementioned novel anticoagulants show the same efficiency in suppressing stroke and systemic embolism and are associated with a much lesser incidence of intracranial bleeding [1–4]; therefore, the novel anticoagulants should be the first choice for preventing stroke recurrence in NAVF patients with a history of stroke or TIA. To avoid brain hemorrhage, it is essential to manage risk factors such as blood pressure, blood glucose, smoking, and excess alcohol consumption. Of these, management of blood pressure is the most important, and the lower the blood pressure the better for reducing the risk of brain hemorrhage or brain infarction [12]. High blood pressure is associated with intracranial bleeding, and the optimal cut-off value for preventing intracranial bleeding is 130/81 mmHg, as determined by receiver–operating characteristic curve analysis [13]. In patients treated with antithrombotic agents, blood pressure can be controlled to values below 130/80 mmHg in a manner similar to the one used for patients with kidney disease, past history of myocardial infarction, and diabetes mellitus [14].

The clinical spectrum of intracranial hemorrhage is similar for patients treated with warfarin and dabigatran [10]. Absolute rates of intracranial hemorrhage across all sites and of both fatal and traumatic intracranial hemorrhages are lower with dabigatran than with warfarin [10]. Concomitant aspirin use is the most important modifiable independent risk factor for intracranial hemorrhage. In a recent report, patients with atrial fibrillation who were at risk for stroke and were aged less than 75 years showed a lower incidence of intracranial and extracranial bleeding when treated with dabigatran than when treated with warfarin [15]. In patients aged 75 years or more, compared to warfarin treatment, dabigatran treatment was associated with lower risk of intracranial bleeding risk but similar or higher risk of extracranial bleeding [15]. Bleeding risk increased with age and degree of renal dysfunction, was inversely related to body weight, and increased with concomitant administration of antiplatelet therapy [15]. Caution is, therefore, required when administering anticoagulants to a patient who is aged 75 years or older or has low body weight or renal dysfunction or if the patient is concomitantly administered antiplatelets.

A new bleeding risk index, called HAS-BLED, which is scored from 0 to 9 for several factors, namely, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly age (>65 years), and concomitant drug/alcohol use, has been proposed for NVAF patients [16]. This simple score provides a practical tool to assess the individual bleeding risk of an NVAF patient and can potentially support decision-making regarding antithrombotic therapy. The incidence of major bleeding was reported as 3.74%/year or more in patients with a HAS-BLED score of 3 or more, indicating that attention should be given to major bleeding in these patients [16].

5. Intracranial bleeding

Compared to warfarin, dabigatran, rivaroxaban, and apixaban have a much lower risk of inducing intracranial hemorrhage [2–4]. Intracranial bleeding during anticoagulation is often devastating, and the lower risk associated with these novel anticoagulants is, therefore, beneficial for patients requiring anticoagulation. The lower risk of intracranial bleeding with the novel anticoagulants may be explained

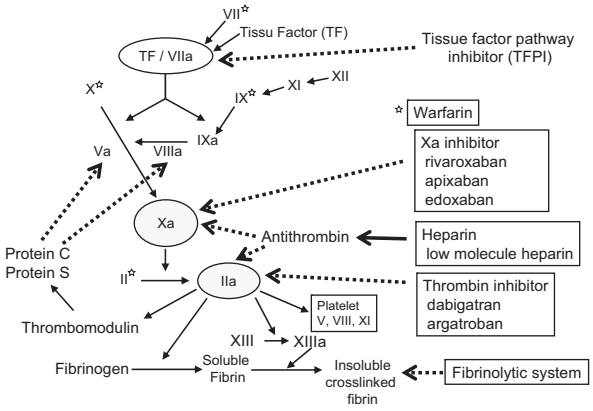

Fig. 5. A schematic representation of the coagulation cascade. TF, tissue factor.

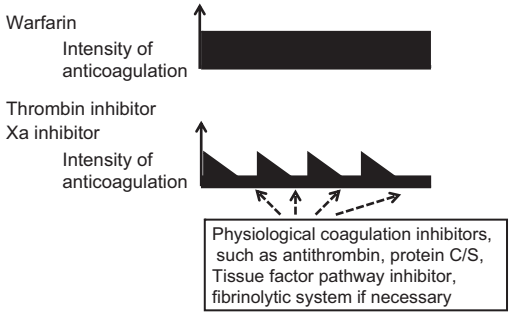

Fig. 6. A schematic representation of the intensity of coagulation with continuous (a) and intermittent anticoagulation (b). Broken arrows indicate inhibition of thrombin activity at the trough phase by physiological coagulation inhibitors.

on the basis of the tissue factor and VIIa complex formation, the first reaction in the coagulation cascade (Fig. 5). The concentration of tissue factor in the brain is same as that in the lungs and placenta and higher than that in other parts of the body [17]. However, warfarin suppresses vitamin K-dependent carboxylation of coagulation factor VII, resulting in low concentrations of VIIa and low production of tissue factor and VIIa complex. Thus, it is difficult for the coagulation cascade to start and for bleeding to stop.

6. Intermittent anticoagulation

The plasma concentrations of the novel anticoagulants vary over the course of a day, with 1 or 2 peaks and troughs in their concentration vs. time curves [1–4]. In the peak phases, coagulation is suppressed by direct inhibition of thrombin or factor Xa. However, in the trough phases, it seems that the coagulation cascade is not fully inhibited. One potential explanation for the lack of thrombus formation during the trough phase is the presence of physiological coagulation inhibitors, such as antithrombin, protein C, and protein S, tissue factor pathway inhibitor, and the fibrinolytic system, which would suppress thrombus formation if they are active during the trough phase (Figs. 5 and 6). Continuous activation of thrombin may reduce the activity of physiological coagulation inhibitors and the fibrinolytic system by exhausting factors related to coagulation. Intermittent anticoagulation induced by the novel anticoagulants, as well as continuous anticoagulation induced by warfarin, is thought to suppress the continuous activation of thrombin, thus preventing thrombus formation in the cardiovascular system.

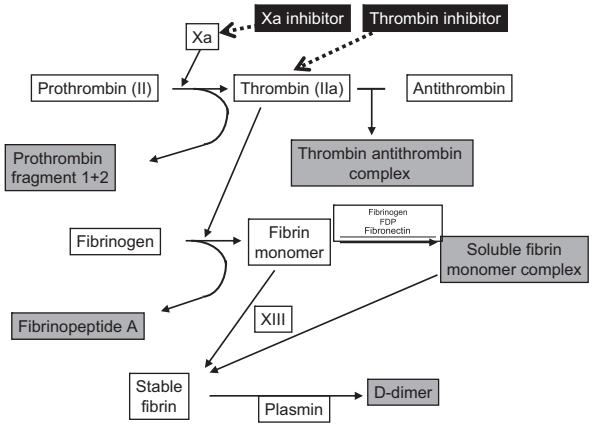

Fig. 7. A schematic representation showing the molecular markers in the coagulation cascade. The broken arrows indicate inhibition.

7. Monitoring coagulation levels

Coagulation levels can be monitored after warfarin treatment by measuring the prothrombin time (PT). However, monitoring is not needed for novel anticoagulants because these drugs have a much wider therapeutic range than warfarin. Nonetheless, in patients at high risk of major bleeding, the physician may decide to evaluate the coagulation levels. Protocols for measurement of coagulation levels in patients treated with novel anticoagulants that have peak and trough phases in their concentration curves have not been established yet. The concentrations of dabigatran and rivaroxaban are related to activated partial thrombin time (APTT) and PT, respectively [18,19], and major bleeding during treatment with these anticoagulants may be checked by measuring APTT or PT, respectively. Prolonged APTT (more than 80 s) in the trough phase is related to major bleeding during treatment with dabigatran [20,21]. The relationship between major bleeding and PT during rivaroxaban treatment has not yet been studied. Ischemic events may be assessed by measuring the plasma levels of molecular markers of the coagulation system, such as prothrombin fragment 1+2, thrombin–antithrombin complex, and soluble fibrin monomer complex (Fig. 7). Further investigation is needed to determine the optimum method for assessing major bleeding and ischemic events during treatment with novel anticoagulants.

8. Management of major bleeding

Hemorrhagic complications are the most common adverse events associated with both anticoagulants and antiplatelet agents. Patients should be aware of these risks, and physicians should have knowledge on how to manage bleeding complications. It is important to treat the bleeding as promptly and efficiently as possible. For patients with major bleeding during treatment with novel anticoagulants, oral medication should be ceased, bleeding should be stopped by mechanical compression or by surgical interventions, and circulating blood volume and blood pressure should be maintained by appropriate intravenous drip infusion [18]. As much as 80% of dabigatran is excreted from the kidney; therefore, intravenous infusion and induction of diuresis can be beneficial when managing major bleeding during dabigatran treatment. For patients with intracranial hemorrhage, treatment to suppress blood pressure should be provided. The *T*max of dabigatran, when taken with food, is 4 h. Therefore, it may be important to perform gastric lavage or oral administration of activated charcoal if bleeding occurs within 4 h of dabigatran

administration. The circulatory system may be supported by supplementation of endogenous procoagulant factors, such as fresh frozen plasma, and factor IX complex (prothrombin complex concentrate [PCC]) containing factors II, VII, IX, and X, or recombinant factor VII. Preclinical studies have reported that PCC and recombinant factor VII inhibit prolongation of bleeding time after administration of dabigatran in rats [22,23]. In a clinical study on healthy volunteers, PCC did not reverse the anticoagulant effects of dabigatran as assessed by measuring APTT, but it did reverse the anticoagulation effects of rivaroxaban [19]. Further studies are needed to verify the effects of PCC, recombinant factor VII, and fresh frozen plasma on bleeding during treatment with new anticoagulants. Hemodialysis to remove dabigatran may be useful. Finally, the development of antibodies that can neutralize dabigatran may offer an important option for patients with severe bleeding [24].

Conflict of interest

None.

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