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Bleeding and antidotes in new oral anticoagulants

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In the past decade, several new oral anticoagulants (NOACs) have been studied and approved for the prophylaxis and treatment of arterial and venous thromboembolism. These agents were shown to be as effective as or better than warfarin and resulted in comparable or lower bleeding rates than warfarin. Specific antidotes for the reversal of the anticoagulant effect of these drugs, such as monoclonal antibodies against the direct thrombin inhibitor dabigatran or recombinant Xa-analog in the case of factor Xa inhibitors, are still being investigated in early clinical trials. In certain situations, as in case of emergency surgery or life-threatening major bleeding, a rapid reversal strategy is needed. Several non-specific prohemostatic agents or coagulation factor concentrates have been suggested as potential candidates for the reversal of NOACs, but the evidence supporting these agents was mainly derived from small animal studies, or is based on partial or complete correction of laboratory parameters in healthy volunteers treated with these agents. Activated prothrombin complex concentrate seems promising for the reversal of dabigatran, while non-activated prothrombin complex concentrates have potential for the reversal of anti-factor Xa. The risk of thromboembolic complications requires careful evaluation. In this article, the evidence- or the lack of it – supporting the use of the different prohemostatic agents for the management of bleeding and for reversal of the different classes of NOACs is discussed.

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Introduction

Vitamin K antagonists (VKA) have been the only orally administered anticoagulant for more than 50 years. Together with unfractionated heparin and low molecular weight heparins, they have been the main alternatives for the prevention and treatment of arterial and venous thromboembolism. During the last ten years, several new oral anticoagulants (NOACs) have emerged in clinical trials and on the market. These new agents act through specifically blocking the activity of either thrombin or activated factor X (Figs. 1A and 2A). They have several advantages over VKA including more predictable pharmacokinetics and pharmacodynamics, and fewer food and drug interactions allowing for fixed-dosing regimens without the need for regular coagulation monitoring.

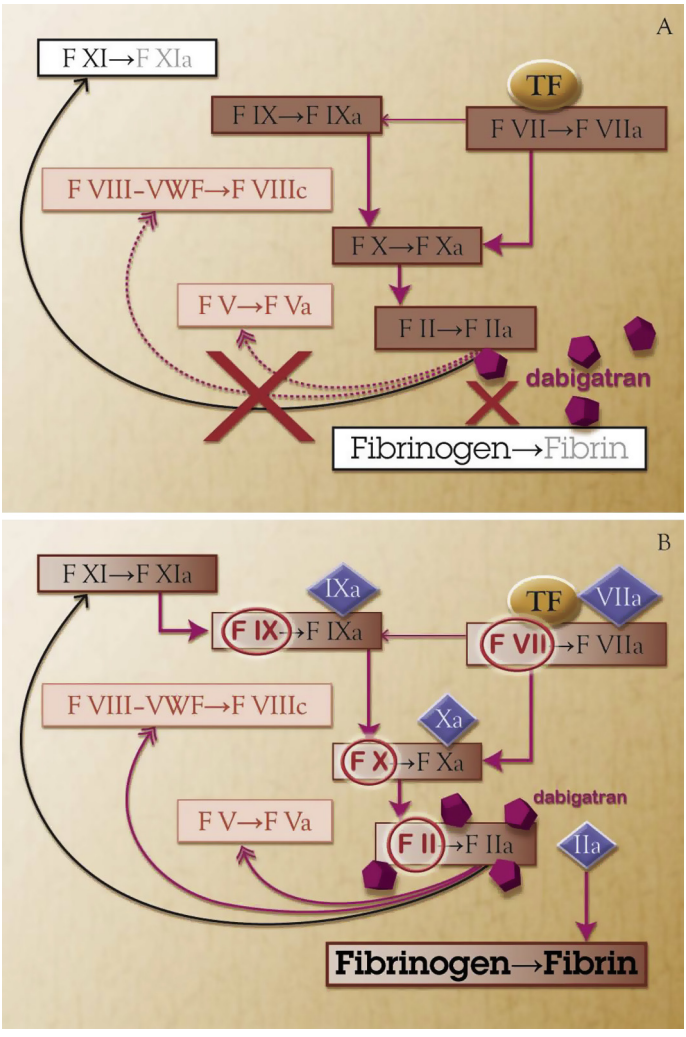

Fig. 1. Mechanism of action of a direct thrombin inhibitor (dabigatran) (1A), and reversal with activated prothrombin complex concentrate (1B). Originally published in *Blood*. [Schulman S, Crowther C. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012;119:3016–3023. ©the American Society of Hematology.].

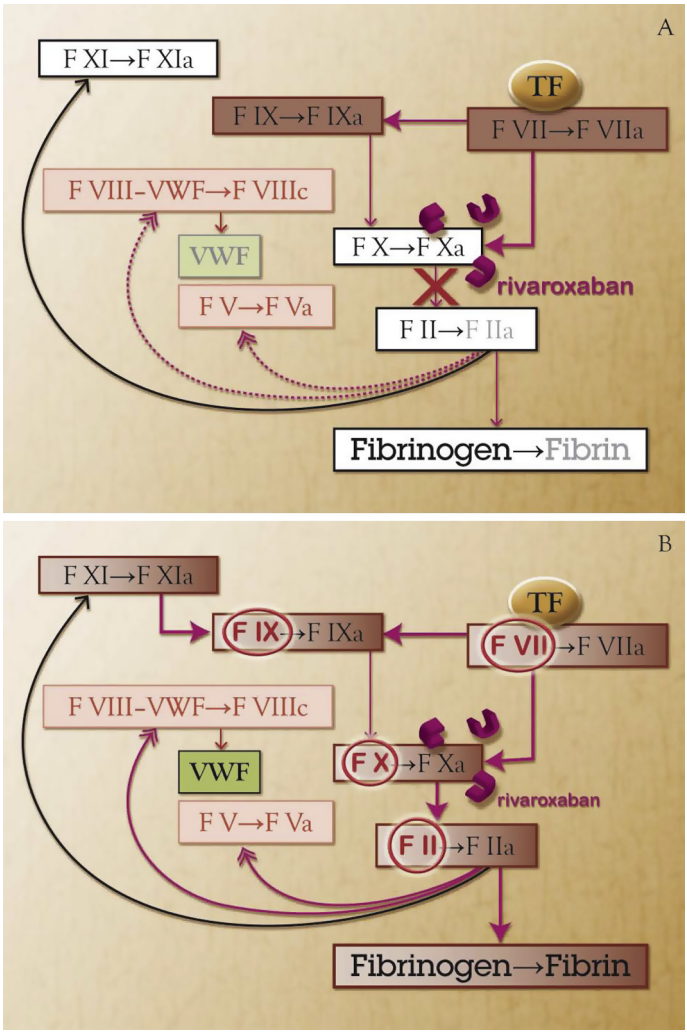

Fig. 2. Mechanism of action of a direct factor Xa inhibitor (rivaroxaban) (2A), and reversal with non-activated prothrombin complex concentrate (2B). Originally published in *Blood*. [Schulman S, Crowther C. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. Blood. 2012;119:3016–3023. ©the American Society of Hematology.].

Oral direct thrombin inhibitors

Thrombin has a central role in the coagulation system, and direct oral thrombin inhibitors (DTI) were hence the first to be developed. These DTIs block thrombin reversibly at the active site. Ximelagatran was the first orally available agent in this family, with promising results in phase III studies [1]. It was, however, withdrawn from the market due to serious hepatic adverse events. Dabigatran etexilate is a pro-drug with a bioavailability of 6.5%. The maximum serum concentration is reached 1.5–3 h after ingestion and it has a half-life of 12–17 h in patients with normal renal function. Thirty-five percent of the drug is protein bound, and 80% is eliminated unchanged by the renal route [2].

Dabigatran has been shown to be as effective as enoxaparin for thromboprophylaxis after knee [3] and hip [4,5] arthroplasty. It was also similar effective as warfarin for the acute management [6] and extended maintenance therapy [7] of VTE. Dabigatran was non-inferior (110 mg bid) or superior (150 mg

bid) to warfarin for stroke prevention in atrial fibrillation (SPAF) [8]. The drug is currently approved for SPAF (North America, Europe) and for VTE prevention after major orthopedic surgery (Canada, Europe).

Oral factor Xa inhibitors

Several direct anti-Xa agents have been evaluated in large clinical trials for the prevention and treatment of arterial and VTE (rivaroxaban, apixaban, edoxaban). These drugs act by reversibly blocking factor X at the active site. Compared to DTI, these drugs demonstrate higher bioavailability (rivaroxaban: 80%, apixaban: 60%, edoxaban: 50%), comparable time to peak concentration (1–4 h), somewhat shorter half-life (6–14 h) and are less dependent on renal excretion (apixaban: 25%, rivaroxaban: 66%, edoxaban 35%).

Rivaroxaban was superior to enoxaparin for VTE prevention after hip [9] and knee [10] arthroplasty. It was non-inferior to warfarin for SPAF [11] and for the acute [12,13] and extended management [12] of VTE. It is now marketed for thromboprophylaxis after major orthopedic surgery, SPAF, and the treatment of VTE (North America, Europe). Similar results were shown with apixaban for VTE prevention in orthopedic patients [14,15] and SPAF [16]. Apixaban is now approved for SPAF (North America, Europe) and VTE prevention after major orthopedic surgery (Canada, Europe).

Bleeding complications of the new oral anticoagulants

The use of anticoagulants is associated with an increased bleeding risk, regardless of the choice of anticoagulant agent. In the phase III clinical trials evaluating the NOACs, patients were selected according to strict inclusion and exclusion criteria and they were followed intensively during the study. The studies generally reported rates of non-major, major and life-threatening bleeding; however different definitions were used in the different studies. Although the incidence of bleeding generally was similar or lower with the NOACs than with standard therapy, it is not clear to what extent this reflects the real world [17]. Early regulatory reports indicate, however, similar major bleeding rates for dabigatran in patients with atrial fibrillation as those reported from the phase III trial [18].

Risk factors for bleeding on anticoagulants

The use of VKA is associated with an annual increase in major bleeding risk of 0.3–0.5% and intracranial hemorrhage of 0.2% [19]. Several determinants of major bleeding during treatment with VKA have been identified, including the intensity of anticoagulation, and patient's characteristics (age, comorbid conditions including treated hypertension, cerebrovascular disease, ischemic stroke, serious heart disease, diabetes, renal insufficiency, alcoholism, liver disease or the presence of malignancy) [19]. Other important risk factors include pharmacogenetic factors, the concomitant use of drugs that interfere with hemostasis (antiplatelet drugs, nonsteroidal antiinflammatory drugs, or cyclooxygenase type 2 inhibitor), and the length of therapy [19].

Theoretically, the same factors could be considered to predict the increased bleeding risk in patients on NOACs. Since these agents are more dependent on renal excretion than VKA, renal impairment seems to be an important predictive factor of bleeding on the new agents. However, in a post-hoc analysis of the major bleeding events from the RE-LY trial, only age was an independent risk factor for major bleeding on dabigatran [20]. Another study showed that combination of dabigatran with antiplatelet agents was also a risk factor for bleeding on dabigatran [21], which has already been shown for VKA [22]. The concomitant use of NSAID was also found to be associated with an increased risk of bleeding in dabigatran treated patients, especially GI bleeding. Several phase III studies have shown a dose dependent increase in the bleeding risk [8,23].

In another subgroup analysis of the RE-LY trial, higher $CHADS_2$ scores were associated with an increased risk of dabigatran related major bleeding and intracranial hemorrhage [24]. An analysis of data from the ARISTOTLE trial showed similar results, with increased rates of apixaban-related major bleeding with increased $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores. However, the rates of intracranial hemorrhage were relatively lower in patients with high $CHADS_2$ scores compared to those with lower scores, and the relative risk reduction in intracranial bleeding with apixaban as compared to warfarin tended to be greater in patients with HAS-BLED scores of 3 or higher [25].

Bleeding rates in the phase III clinical trials

The reported bleeding rates with NOACS according to treatment indications are shown in Table 1. In view of the differences in outcome definitions and population characteristics head-to-head comparisons should be avoided. Two indirect comparisons of the efficacy and safety of three novel anticoagulants using network meta-analysis have been published recently [26,27]. The results of these indirect comparisons must be interpreted with caution and have been criticized [28]. In one analysis the bleeding rates from the 12 phase II and phase III trials enrolling patients treated with the NOACs for SPAF showed a trend towards reduced major bleeding (relative risk [RR], 0.86; 95% confidence interval [CI], 0.72–1.02) with a significant reduction of intracranial hemorrhage (RR, 0.46; 95% CI, 0.39–0.56) [29]. In the same population, major gastrointestinal bleeding was more common with dabigatran or rivaroxaban compared to VKA. Another meta-analysis in the VTE population concluded that rivaroxaban reduced the risk of major bleeding compared with conventional VKA treatment (RR, 0.57; 95% CI, 0.39–0.84), whereas other NOACs did not (dabigatran: RR, 0.76; 95% CI, 0.49–1.18; apixaban: RR, 2.95; 95% CI 0.12–71.8) [26]. It should be noted that also phase II trials were included, in which the doses could have differed from those used in the phase III regimens. In general, the bleeding rates with the new anticoagulants are similar or lower than those of VKA.

Management of bleeding complications of new anticoagulants

There are currently no clinically evaluated or approved specific antidotes against the NOACs. Management of bleeding should be individualized mainly according to the severity of bleeding but also to the patient characteristics, indication of anticoagulation, the specific anticoagulant the patient is using, dosage, timing of the last dose, other interacting or concomitant anti-hemostatic therapy, comorbidities, and the site of bleeding. The management options can be divided into supportive measures and more specific reversal strategies.

Table 1
Major bleeding rates in the phase III trials with the new oral anticoagulants.

Indication	Agent	Trial	Dose	Number of patients	Duration (mean)	Major bleeding (%)
VTE prophylaxis after knee or hip arthroplasty	Dabigatran	RE-NOVATE	150 mg o.d	1174	33 d	1.3
			220 mg o.d	1157	33 d	2.0
		RE-MOBILIZE	150 mg o.d	857	14 d	0.6
			220 mg o.d	871	14 d	0.6
		RE-MODEL	220 mg o.d	679	8 d	1.5
			150 mg o.d	703	8 d	1.3
	Rivaroxaban	RECORD-1	10 mg o.d	2209	35 d	0.3
		RECORD-2	10 mg o.d	1252	35 d	0.1
		RECORD-3	10 mg o.d	1254	12 d	0.6
		RECORD-4	10 mg o.d	1526	12 d	0.7
	Apixaban	ADVANCE-1	2.5 mg b.i.d	1599	12 d	0.7
		ADVANCE-2	2.5 mg b.i.d	1528	12 d	0.6
		ADVANCE-3	2.5 mg b.i.d	2708	34 d	0.8
VTE treatment	Dabigatran	RE-COVER	150 mg b.i.d	1273	6 m	1.6
		RE-COVER II	150 mg b.i.d	1279	6 m	1.2
		RE-MEDY	150 mg b.i.d	1430	18	0.9
		RE-SONATE	150 mg b.i.d	681	12	0.3
	Rivaroxaban	EINSTEIN-DVT	15 mg b.i.d	1731	3 m, 6 m, 12 m	0.8
		EINSTEIN-PE	then 20 mg o.d	2419	3 m, 6 m, 12 m	1.1
		EINSTEIN-Ext	20 mg o.d	602	6 m, 12 m	0.7
	Apixaban	AMPLIFY-Ext	2.5 mg b.i.d	840	12 m	0.2
			5 mg b.i.d	813	12 m	0.1
Atrial fibrillation	Dabigatran	RE-LY	150 mg b.i.d	6015	24 m	6.2
			110 mg b.i.d	6076	24 m	5.4
	Rivaroxaban	ROCKET-AF	20 mg o.d	7131	20 m	5.6
	Apixaban	ARISTOTLE	5 mg b.i.d	9120	22 m	3.6

Assessment of drug effect

Unless coagulation screening has already been obtained together with blood count on arrival of the patient at the Emergency Department, this should be ordered when it becomes evident that the patient is being treated with any anticoagulant agent. For patients on dabigatran the activated partial thromboplastin time (aPTT) has a linear response to the drug concentration up to the therapeutic range, above which the response flattens out. Therefore, aPTT is useful to assess if there is any significant concentration of dabigatran in the circulation but not to understand the extent of intoxication. A normal aPTT essentially excludes dabigatran as the cause of bleeding. Similarly, a normal prothrombin time (PT) essentially excludes factor Xa inhibitors as the cause of bleeding. For better understanding of therapeutic versus excessive levels of dabigatran a dilute thrombin time (Hemoclot) is required and for the factor Xa inhibitors an anti-Xa level using a test with the suspected drug as standard is useful. This laboratory evaluation should be initiated simultaneously with the supportive measures discussed below. In addition, a serum creatinine must be obtained even if the patient previously had normal renal function. Acute disease or hypovolemia can profoundly affect the renal function and reduce the elimination of the NOAC.

Supportive measures

Patients presenting with bleeding should receive general supportive measures as outlined in Table 2. Enhancement of diuresis will not have any effect on reduction of drug exposure. The diuretics will reduce tubular fluid absorption but will not increase glomerular filtration of the drug. The coagulation mechanism is disturbed by hypocalcemia, acidosis and hypothermia, all of which must be avoided.

Due to the relatively short half-life of the NOACs, simply discontinuing the drug might be sufficient in patients with mild bleeding and normal renal function. Similarly, treatment with any drug that inhibits platelet function should be temporarily withheld. In patients with more severe bleeding, discontinuing the drug, supporting the patient hemodynamically with transfusions and administration of specific or non-specific hemostatic agent should be considered.

Oral activated charcoal should be administered in case of drug intoxication or if the intake of the drug occurred within the past 2 h. Gastric lavage, maybe also be used in case of intoxication and recent

Table 2
Supportive measures in NOAC-associated bleeding.

Support for blood circulation and oxygenation
Secure intravenous access
Volume expanders
Other hemodynamic support
Oxygen on mask or nasal prongs
Red cells concentrates
Correct acidosis
Counteract hypothermia
Reduction of drug exposure
Delay next dose of NOAC or discontinue drug
Hold also antiplatelet therapy
Active charcoal orally if last dose of NOAC <3 h ago
Hemodialysis – only for dabigatran
Improvement of hemostasis
Compression of accessible bleeding source
Injection of adrenalin topically
Correct hypocalcemia
Apply topical thrombin or fibrin glue
Antifibrinolytic agents
Desmopressin – if platelet inhibition has occurred
Platelet transfusion – for thrombocytopenia or if clopidogrel or prasugrel has been given
Fresh frozen plasma for dilution coagulopathy
Coiling or regional embolization
Surgical intervention

intake. Local measures to mechanically control the bleeding should be utilized when possible, including mechanical compression of the bleeding vessels, endoscopic therapy for gastrointestinal bleeding, angiographic coiling, or, as a last resort, surgical intervention to stop bleeding.

Tranexamic acid and epsilon-aminocaproic acid are synthetic antifibrinolytic agents that competitively block the lysine binding site of plasminogen, thereby preventing its conversion to plasmin. Tranexamic acid is also a non-competitive inhibitor of plasmin. There is a wealth of evidence suggesting that antifibrinolytic agents can reduce blood loss caused by trauma [30], during orthopedic [31] and non-orthopedic surgery [32] without an increase in the risk of vascular occlusion. There is no published experience on the use of antifibrinolytic agents in the setting of bleeding complications of the new anticoagulants, but their demonstrated safety should encourage their use in the bleeding patient receiving these new agents.

Plasma products (fresh frozen plasma and cryoprecipitate) are generally useful in patients with acquired deficiency of coagulation factors. In patients with major trauma or massive bleeding due to any other cause combined with initial vigorous volume replacement there is often consumption- and/or dilution coagulopathy that requires adequate transfusion with plasma [33,34]. The NOACs act, however, by reversibly and competitively blocking activated factor X or thrombin, and the transfusion of plasma in patients on these agents is therefore unlikely to be effective in reversing their anticoagulant effect.

There is no reason to believe that vitamin K or protamine would have any reversal effect in patients on NOACs.

Direct thrombin inhibitors

In a post hoc analysis of major bleeding events from five phase III trials, the time in the intensive care unit and the 30 day mortality rate in the dabigatran arm were lower than those in the warfarin arm, despite most of the patients with major bleeding were treated only with general supportive measures [35]. This suggests that dabigatran-associated bleeding can often be treated without the need for specific reversal agents or factor concentrates.

Activated charcoal

Activated charcoal has been shown, in vitro, to absorb 99.9% of dabigatran suspended in acidic water [36]. Considering the rapid intestinal absorption and quick onset of action of dabigatran, the adminstration of activated charcoal to adsorb dabigatran should be done within 1–2 h after intake of the drug. This treatment option is especially useful in case of intoxication. It should however be mentioned that the efficacy of activated charcoal has not been tested in clinical practice.

Desmopressin and von Willebrand factor concentrates

Desmopressin (D-arginine-deamino-vasopressin, DDAVP) is a synthetic vasopressin analog that stimulates the release of factor VIII and von Willebrand factor (VWF) from the vascular endothelium, resulting in an increase in the coagulation activity. One study in healthy individuals demonstrated that DDAVP infusion caused significant dose dependent reduction in the hirudin (another DTI) induced prolongation of the aPTT in vivo [37]. Similarly, animals anticoagulated with hirudin showed a reduction in skin bleeding time when treated with a combined factor VIII (FVIII) and VWF concentrate but not if treated with FVIII alone, suggesting a corrective effect of VWF. No clinical trials have evaluated the effect of VWF concentrates in bleeding patients on DTI.

Prothrombin complex concentrates

Prothrombin complex concentrates (PCCs) contain inactive factor II, IX, X and VII. There is also an activated PCC (APCC) that in addition contains small amounts of these factors in active form (Fig. 1B).

APCC given at a dose of 50 IU/kg or 100 IU/kg caused a reduction in bleeding time in a dabigatran treated model after tail incision. APCC also shortened the prolonged bleeding time induced by other thrombin inhibitors such as melagatran [38] and hirudin [39]. An ex-vivo study showed good effect of

APCC in reversing the impaired thrombin generation in healthy individuals treated with dabigatran [40], and the authors concluded that out of PCC, APCC and rFVIIa, APCC was the most reasonable alternative for reversing dabigatran effect. Another study showed good effect of APCC in correcting thrombin generation ex-vivo in samples from patients on dabigatran [41]. In a case report a patient with ablation-induced and dabigatran-associated pericardial tamponade was managed successfully with APCC [42]. Well-designed clinical trials are still needed to confirm the effect of APCC in reversing the anticoagulant effect of dabigatran. APCC should only be given after careful consideration because of the associated increased risk of thromboembolic complications [43].

Non-activated PCCs are either 4-factor PCCs commonly used in Europe and Canada, or 3-factor PCCs with very low levels of FVII, which until recently were the only ones approved in the United States. Studies on efficacy of PCC in the reversal of the anticoagulant effect have shown inconsistent results. Animal models, including a mice model for intracerebral hemorrhage [44] and a rabbit model for kidney injury [45], showed good effect of PCC in limiting hematoma expansion and blood loss. Another ex-vivo study using plasma samples from dabigatran-treated healthy individuals failed to show correction of impaired thrombin generation after treating the samples with PCC. [46]. A small case series reported failure of PCC to manage massive dabigatran-associated bleeding [47]. These agents are also associated with thromboembolic complications. In the absence of evidence from clinical trials supporting their efficacy in patients with bleeding, the use of PCC for the reversal of dabigatran effect should be questioned.

Recombinant activated factor VII

Recombinant factor VIIa (rFVIIa) was developed mainly for the treatment of patients with hemophilia and antibodies to FVIII, but the off-label use of rFVIIa has rapidly increased. No clinical trials have evaluated the effect of rFVIIa in reversing dabigatran, but it was not effective in reversing the effect of melagatran in healthy volunteers [48], nor the effect of argatroban in a cardiopulmonary bypass setting [49]. It was not effective either in limiting the bleeding in a trauma + dabigatran-induced intracerebral hemorrhage model in mice [44]. In a series of 4 case reports, rFVIIa failed to control dabigatran induced bleeding in the three patients [47]. Similar results were seen in ex-vivo treated plasma samples form healthy volunteers on dabigatran [46]. Warkentin et al. reported a case undergoing coronary by-pass surgery two days after stopping dabigatran, resulting in massive post-operative bleeding. The patient was treated with five doses of rFVIIa and finally hemodialysis [50]. The authors presented the case as supportive for the effect of high dose rFVIIa in the setting of dabigatran bleeding, but the data should be interpreted carefully as the patient received other treatments, including massive transfusions of platelets, erythrocytes and plasma, and the bleeding did not stop until the patient was hemodialyzed.

None of the treatments with factor concentrates normalized the prolonged thrombin time, even when effective in bleeding models. This demonstrates that dabigatran is still in circulation.

Hemodialysis and hemoperfusion

Dabigatran has a relatively low plasma protein binding (35%), implying that the drug can be dialyzed in case of intoxication, life-threatening bleeding or before emergency surgery. Animal models have demonstrated the efficacy of dialysis and the use of activated charcoal perfusion, reducing the circulating dabigatran levels by 75–80% after 1 h of such treatment [36]. In one study including patients on hemodialysis receiving a single dose of dabigatran, 62% of the drug was removed after 2 h and 68% after 4 h of dialysis [51]. Several case reports have indicated the successful and safe use of hemodialysis for the removal of dabigatran [47,50,52,53]. This method is however limited by the difficulty of inserting central dialysis catheters in a patient who is fully or excessively anticoagulated, inducing the risk of additional bleeding.

Monoclonal antibodies against dabigatran

A humanized, highly selective and specific monoclonal antibody fragment (Fab) against dabigatran is currently in development, with clinical studies expected to start later this year. This would be the

only specific reversal agent for dabigatran [54]. The antibody has tight binding to dabigatran and is highly specific with no effect on other molecules, rapid dose-dependent decrease in experimentally-induced blood loss using a rat tail injury model, with sustained effect for up to 6 h after intravenous injection resulting in complete reversal of the anticoagulation effect of dabigatran as demonstrated by ex vivo clotting tests.

Activated factor X inhibitors

Activated charcoal

In one study, apixaban was found to undergo entero-enteric recirculation and intestinal re-absorption of apixaban could be interrupted by activated charcoal even at 3 h after drug administration in dogs (late charcoal effect) [55]. To our knowledge, no studies on the use of activated charcoal with other anti-Xa agents have been published.

Prothrombin complex concentrates

In a mouse model treated with high-dose rivaroxaban, PCC at a dose of 100 IU/kg prevented expansion of intracerebral hematoma although the prolonged PT was not corrected (Fig. 2B) [56]. In rat-injury models treatment with rivaroxaban increased blood loss and affected coagulation assays, whereafter PCC shortened the aPTT as well as clotting time assessed with thromboelastography but blood loss did not decrease [57]. Identical results were obtained in rabbits treated with apixaban, with correction of laboratory parameters without an effect on blood loss [58]. In a study in healthy individuals treated with rivaroxaban, PCC given at a dose of 50 IU/kg normalized the rivaroxaban induced prolongation of prothrombin time [46]. To our knowledge no study evaluated the effect of PCC in patients on rivaroxaban with active bleeding. In another animal model PCC shortened the prolonged PT induced by edoxaban, but its effect on blood loss was not reported [59].

In baboons infusion of APCC corrected the prolonged bleeding time caused by supra-therapeutic doses of rivaroxaban and PT was shortened but not corrected to baseline level [60]. In another study APCC given at 100 IU/kg shortened the PT in rats on edoxaban [59]. In both studies, the effect on blood loss was not reported.

Recombinant activated factor VII

In a rat model, rFVIIa ex vivo had the most potent effect in reversing the anticoagulant effect of edoxaban, as measured by PT, returning to normal. Similarly, the bleeding time in these rats was normalized by rFVIIa given at very high doses of 3 mg/kg, which also normalized the level of thrombin-antithrombin complex, which was initially lowered by edoxaban [59]. Baboons treated with supra-therapeutic doses of rivaroxaban showed some reduction but no normalization of the PT and the bleeding time when given high doses of rFVIIa (210 μg/kg) [60]. In rabbits treated with rivaroxaban or apixaban and using the Folts injury model, rFVIIa reduced the bleeding time and the aPTT but did not have any effect on the amount of blood loss [57].

PRT4445

PRT4445 is a universal reversal agent for factor Xa inhibitors. It is a novel recombinant protein that is similar to the native factor Xa, with structural modification causing it to be hemostatically inactive. It binds to Factor Xa inhibitors in the blood, preventing them from inhibiting the activity of the native Xa. In pre-clinical data PRT4445 reversed the effect of fondaparinux and enoxaparin. In an escalating-dose safety and tolerability study enrolling 32 volunteers, PRT4445 was well tolerated with no safety issues. Blood samples of these volunteers treated with PRT4445, were mixed with an anti-Xa agent and showed rapid (5 min) and sustained (3 h) effect on reversing the anticoagulant activity. Phase II studies are expected to conclude in 2013.

Universal NOACs reversal agent

PER977 is a synthetic small molecule developed by Perosphere Inc and it has been demonstrated to bind to several NOACs, including dabigatran, rivaroxaban, apixaban and edoxaban. Animal studies have

not shown significant adverse events. It reverses the anticoagulant activity of the above-mentioned NOACs as demonstrated by a reduction in blood loss in the rat tail injury model. This effect has also been demonstrated using aPTT and anti-Xa analysis on human blood ex-vivo. However, PER977 does not affect the normal coagulation activity in blood samples not containing NOACs, and it does not inhibit or affect microsomal metabolism in the liver. Clinical trials are expected on start during 2013.

Conclusion

The new oral direct thrombin inhibitor, dabigatran, and the factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, have shown a favorable safety and efficacy profile compared to warfarin for the prevention and treatment of thromboembolic conditions. Similar to all other antithrombotic agents, treatment with these highly specific anticoagulants causes an increased bleeding risk. There is currently only weak evidence supporting the use of activated prothrombin complex concentrate for the reversal of dabigatran, and for the use of non-activated prothrombin complex concentrates to neutralize the anticoagulant effect of rivaroxaban, apixaban and edoxaban. There is, however, mounting evidence that bleeding complications of these agents can be managed by supportive measures to keep the patient hemodynamically stable until the drug effect weans off, facilitated by the short half-life of these agents. Moreover, the lower bleeding rates seen with these agents, especially intracranial bleeding, adds to the safety profile of these agents. This can be further improved by the development of specific reversal agents to be used in case of emergency surgery or life-threatening bleeding.

Conflict of interest

Sam Schulman has received honoraria from Boehringer Ingelheim and Bayer Healthcare for work in study-related committees.

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