



EDUCATIONAL OBJECTIVE: Readers will manage bleeding complications in patients on the new oral anticoagulants

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Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban

ABSTRACT

The new oral anticoagulants dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis) have predictable pharmacokinetic and pharmacodynamic profiles and are alternatives to warfarin. However, many physicians are wary of these drugs, since there is limited evidence on how to manage bleeding in patients taking them, and since no specific antidote is known to reverse their anticoagulant effect. Management requires careful adherence to first principles of bleeding care. Unapproved and untested reversal strategies may be required in patients with life-threatening bleeding.

KEY POINTS

Thromboprophylaxis with anticoagulants is an important aspect of managing patients at risk of systemic or pulmonary embolization.

Dabigatran is a direct inhibitor of thrombin (factor IIa); rivaroxaban and apixaban inhibit factor Xa.

Monitoring of coagulation function is not routinely necessary with the new drugs but may be useful in emergencies.

Nonspecific hemostatic agents that have been suggested for off-label use in reversing excessive bleeding in patients taking the new oral anticoagulants include recombinant factor VIIa, three-factor and four-factor prothrombin complex concentrate, and activated prothrombin complex concentrate.

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IN THE PAST SEVERAL YEARS, three new oral anticoagulants—dabigatran etexilate (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis)—have been approved for use in the United States. These long-awaited agents are appealing because they are easy to use, do not require laboratory monitoring, and have demonstrated equivalence, or in some cases, superiority to warfarin in preventing stroke or systemic embolism in at-risk populations.¹⁻⁴ However, unlike warfarin, they have no specific reversal agents. How then should one manage spontaneous bleeding problems and those due to drug overdose, and how can we quickly reverse anticoagulation if emergency surgery is needed?

For these reasons, physicians and patients have been wary of these agents. However, with a systematic approach based on an understanding of the properties of these drugs, the appropriate use and interpretation of coagulation tests, and awareness of available therapeutic strategies, physicians can more confidently provide care for patients who require urgent reversal of anticoagulant effects.

Here, we review the available literature and suggest practical strategies for management based on an understanding of the pharmacokinetic and pharmacodynamic effects of these drugs and our current knowledge of the coagulation tests.

NEED FOR ANTICOAGULANTS

Anticoagulants are important in preventing systemic embolization in patients with atrial fibrillation and preventing pulmonary embolism in patients with venous thromboembolism.

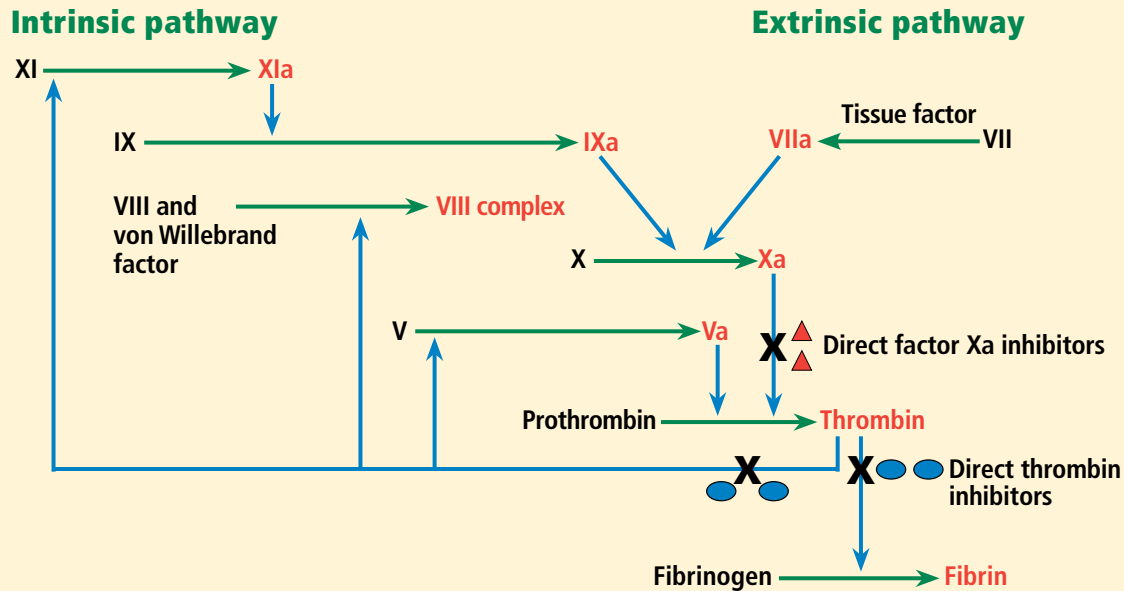


FIGURE 1. The coagulation cascade and how the new oral anticoagulants block it.

Coagulation assays are not routinely necessary with the new drugs but may be useful in emergencies

And the numbers are staggering. The estimated prevalence of atrial fibrillation in the United States was 3.03 million in 2005 and is projected to increase to 7.56 million by 2050.⁵ Ischemic stroke is the most serious complication of atrial fibrillation, which accounts for 23.5% of strokes in patients ages 80 through 89 according to Framingham data.⁶ Venous thromboembolism accounts for 900,000 incident or recurrent fatal and nonfatal events in the United States yearly.⁷

■ HOW THE NEW AGENTS BLOCK COAGULATION

Thrombin (factor IIa), a serine protease, is central to the process of clot formation during hemostasis. It activates factors V, VIII, and XI (thus generating more thrombin), catalyzes the conversion of fibrinogen to fibrin, and stimulates platelet aggregation. Its role in the final steps of the coagulation cascade has made it a target for new direct thrombin inhibitors such as dabigatran.

Factor Xa is a serine protease that plays a central role in the coagulation cascade. It is a desirable target for anticoagulation because it is the convergence point for the extrinsic and the intrinsic coagulation pathways. It converts prothrombin to thrombin. Rivaroxaban

and apixaban are direct factor Xa inhibitors (FIGURE 1).

Dabigatran, a direct thrombin inhibitor

Dabigatran etexilate is a synthetic, orally available prodrug that is rapidly absorbed and converted by esterases to its active form, dabigatran, a potent direct inhibitor of both free thrombin and clot-bound thrombin.⁸

Plasma levels of dabigatran peak within 2 hours of administration, and its half-life is 14 to 17 hours.⁹ Dabigatran is eliminated mainly via the kidneys, with more than 80% of the drug excreted unchanged in the urine (TABLE 1).

Rivaroxaban, a factor Xa inhibitor

Rivaroxaban is a potent, selective, direct factor Xa inhibitor.

Plasma levels of rivaroxaban peak 2 to 3 hours after administration, and it is cleared with a terminal half-life of 7 to 11 hours.^{10,11}

Rivaroxaban is eliminated by the kidneys and in the feces. The kidneys eliminate one-third of the active drug unchanged and another one-third as inactive metabolites. The remaining one-third is metabolized by the liver and then excreted in the feces. Rivaroxaban has a predictable and dose-dependent pharmacodynamic and pharmacokinetic profile that is not affected by age, sex, or body weight (TABLE 1).¹²

TABLE 1

Pharmacokinetic profiles and metabolism of the new oral anticoagulants

Feature	Dabigatran	Rivaroxaban	Apixaban
Prodrug	Yes	No	No
Mode of action	Thrombin inhibition	Factor Xa inhibition	Factor Xa inhibition
Bioavailability	6%–8%	80%	50%
Time to peak	1.5–2 hours	2–3 hours	3 hours
Half-life	14–17 hours	7–11 hours	8–14 hours
Excretion	Renal (unchanged) > 80% Bile 5%–10%	Renal (half inactive) 66% Feces 33%	Renal 25%–30% Feces 56%
Plasma protein binding	35%	95%	87%

DATA FROM REFERENCES 13, 16, AND 18.

Apixaban, an oral factor Xa inhibitor

Apixaban is a selective, direct oral factor Xa inhibitor.

Plasma levels of apixaban peak about 3 hours after administration, and its terminal half-life is 8 to 14 hours.¹³ Apixaban is eliminated by oxidative metabolism, by the kidney, and in the feces. It has predictable pharmacodynamic and pharmacokinetic profiles and has the least renal dependence of the three agents (TABLE 1).

■ THE NEW ORAL ANTICOAGULANTS AND BLOOD COAGULATION ASSAYS

Assessment of the anticoagulant activity of the new oral anticoagulants is not necessary in routine clinical practice, but it may be useful in planning intervention in patients with major bleeding, those with drug overdose, or those who need emergency surgery.

The activated partial thromboplastin time

The activated partial thromboplastin time (aPTT) is a measure of the activity of the intrinsic pathway of the coagulation cascade.

Dabigatran. There is a curvilinear relationship between the aPTT and the plasma concentration of dabigatran and other direct thrombin inhibitors, although the aPTT prolongation appears to vary with different reagents and coagulometers.^{9,14,15} However,

Stangier et al⁹ found a linear relationship between the aPTT and the square root of the dabigatran plasma concentration.

Rivaroxaban prolongs the aPTT in a dose-dependent manner, but there is no standard for calibration of this assay. Hence, the aPTT is not recommended for monitoring rivaroxaban in clinical practice.

Apixaban may also prolong the aPTT, but there are limited data on its reactivity with different reagents.

The prothrombin time and international normalized ratio

The prothrombin time and international normalized ratio (INR) are measures of the extrinsic pathway of the coagulation cascade.

Dabigatran. The INR has a linear response to the dabigatran concentration, but it is insensitive.⁹ Hence, it is not suitable for monitoring the anticoagulant effects of direct thrombin inhibitors.

Rivaroxaban. The prothrombin time correlates strongly with the plasma concentration of rivaroxaban in healthy trial participants¹¹ and in patients undergoing total hip arthroplasty or total knee arthroplasty.¹⁶ Samama et al¹⁷ noted that, unlike with vitamin K antagonists, the INR cannot be used to monitor patients on rivaroxaban because the prothrombin time results varied with different reagents. They used a standard calibration curve to ex-

Management of bleeding from these novel agents should begin with preventing bleeding in the first place

press the prothrombin time results in plasma concentrations of rivaroxaban rather than in seconds or the INR.

Apixaban increases the INR in a dose-dependent manner.¹⁸ Its effect on different reagents remains unknown.

The thrombin time

The thrombin time reflects the activity of thrombin in the plasma. The amount of thrombin and the concentration of thrombin inhibitors in the plasma sample determine the time to clot formation.

Dabigatran. The thrombin time displays a linear dose-response to dabigatran, but only over the range of therapeutic concentrations. At a dabigatran concentration greater than 600 ng/mL, the test often exceeds the maximum measurement time of coagulometers.⁹ Hence, this test is too sensitive for emergency monitoring, especially in cases of drug overdose. However, it is well suited for determining if any dabigatran is present.

Rivaroxaban and apixaban have no effect on the thrombin time.

The Hemoclot direct thrombin inhibitor assay and dabigatran

The Hemoclot direct thrombin inhibitor assay (Hyphen BioMed, France) is a sensitive diluted thrombin time assay that can be used for quantitative measurement of dabigatran activity in plasma. This test is based on inhibition of a constant amount of highly purified human alpha-thrombin by adding it to diluted test plasma (1:8 to 1:20) mixed with normal pooled human plasma.^{19,20}

Stangier et al¹⁹ found that the Hemoclot assay was suitable for calculating a wide range of dabigatran concentrations up to 4,000 nmol/L (1,886 ng/mL). Although this finding has not been confirmed in larger studies, this test may provide a rapid and accurate assessment of dabigatran's anticoagulant activity in cases of emergency surgery or overdose.

The ecarin clotting time and dabigatran

The ecarin clotting time is a measure of the activity of direct thrombin inhibitors, but not the factor Xa inhibitors.

Ecarin is a highly purified metalloprotease

isolated from the venom of a snake, *Echis carinatus*, and it generates meizothrombin from prothrombin.²¹ Meizothrombin facilitates clot formation by converting fibrinogen to fibrin and, like thrombin, it can be inactivated by direct thrombin inhibitors, thereby prolonging the clotting time.

The limitations of the ecarin clotting time include dependence on the plasma levels of fibrinogen and prothrombin.

The ecarin chromogenic assay and dabigatran

The ecarin chromogenic assay is an improvement on the principle of the ecarin clotting time that can be used to measure the activity of direct thrombin inhibitors.²² In this test, ecarin is added to a plasma sample to generate meizothrombin, and the amidolytic activity of meizothrombin towards a chromogenic substrate is then determined.

Results of the ecarin chromogenic assay are not influenced by the levels of fibrinogen or prothrombin. Another advantage is that this assay can be used in automated and manual analyzers, thus enabling its use at the bedside. However, to our knowledge, it is not being regularly used to monitor direct thrombin inhibitors in the clinical setting, and there is no standard calibration of the ecarin clotting time method.

Assays of factor Xa activity

A variety of assays to monitor the anticoagulant activity of factor Xa inhibitors have been proposed.²³⁻²⁵ All measure inhibition of the activity of factor Xa using methods similar to those used in monitoring heparin levels. All require calibrators with a known concentration of the Xa inhibitor; many are easily adapted for laboratories currently providing measurement of factor Xa inhibition from heparin.²³ These assays have been suggested as a better indicator of plasma concentration of factor Xa inhibitor drugs than the prothrombin time.²⁵

CONTROLLING BLEEDING IN PATIENTS ON THE NEW ORAL ANTICOAGULANTS

Bleeding is an anticipated adverse event in patients taking anticoagulants. It is associated with significant morbidity and risk of death.^{26,27}

Many physicians still have limited experience with using the new oral anticoagulants and managing the attendant bleeding risks. Hence, we recommend that every health institution have a treatment policy or algorithm to guide all clinical staff in the management of such emergencies.

Prevention of bleeding

Management of bleeding from these agents should begin with preventing bleeding in the first place.

The physician should adhere to the recommended dosages of these medications. Studies have shown that the plasma concentration of these drugs and the risk of bleeding increase with increasing dosage.^{1,28,29}

In addition, these medications should be used for the shortest time for which anticoagulation is required, especially when used for preventing deep vein thrombosis. Prolonged use increases the risk of bleeding.^{30,31}

Most patients who need anticoagulation have comorbidities such as heart failure, renal failure, diabetes mellitus, and hypertension. Although the kidneys play a major role in the excretion of dabigatran and, to some extent, rivaroxaban and apixaban, patients with severe renal impairment were excluded from the major trials of all three drugs.¹⁻³ Hence, to avoid excessive drug accumulation and bleeding, these medications should not be used in such patients pending further studies. Further, patients taking these medications should be closely followed to detect new clinical situations, such as acute renal failure, that will necessitate their discontinuation or dose adjustment.

If surgery is needed

If a patient taking a new oral anticoagulant needs to undergo elective surgery, it is important to temporarily discontinue the drug, assess the risk of bleeding, and test for renal impairment.

Renal impairment is particularly relevant in the case of dabigatran, since more than 80% of the unchanged drug is cleared by the kidneys. Decreasing the dose, prolonging the dosing interval, or both have been suggested as means to reduce the risk of bleeding in patients with renal impairment who are taking

TABLE 2

How long to delay elective surgery or procedures after last anticoagulant dose

Anticoagulant drug	Creatinine clearance (mL/min)	Low-risk surgery ^a	High-risk surgery ^b
Dabigatran	> 50	24 hours	2 days
	31–50	2 days	4 days
	≤ 30	4 days	6 days
Rivaroxaban	> 30	24 hours	2 days
	≤ 30	2 days	4 days
Apixaban	> 30	24 hours	2 days
	≤ 30	2 days	4 days

^a Examples include cardiac catheterization, diagnostic endoscopy, breast biopsy, and minor orthopedic procedures

^b Examples include cardiac surgery, vascular surgery, spinal or neurosurgery, and abdominal surgery

dabigatran.^{32,33} Patients with normal renal function undergoing low-risk surgery should discontinue dabigatran at least 24 hours before the surgery. If the creatinine clearance is 31 to 50 mL/min, inclusively, the last dose should be at least 48 hours before the procedure for low-risk surgery, and 4 days before a procedure that poses a high risk of bleeding.³²⁻³⁴ Some experts have given the same recommendations for rivaroxaban and apixaban (TABLE 2).³⁴

The aPTT and prothrombin time are readily available tests, but they cannot determine the residual anticoagulant effects of dabigatran, rivaroxaban, or apixaban. However, in many (but not all) cases, a normal aPTT suggests that the hemostatic function is not impaired by dabigatran, and a normal prothrombin time or an absence of anti-factor Xa activity would similarly exclude hemostatic dysfunction caused by rivaroxaban or apixaban. These tests are potentially useful as adjuncts before surgical procedures that require complete hemostasis.

Furthermore, a normal thrombin time rules out the presence of a significant amount of dabigatran. Therefore, a normal thrombin time might be particularly useful in a patient undergoing a high-risk intervention such as epidural cannulation or neurosurgery and who is normally receiving dabigatran.

Every hospital needs a policy or algorithm for managing bleeding emergencies

TABLE 3

Managing bleeding in patients receiving dabigatran, apixaban, or rivaroxaban

Strategies to minimize risk of bleeding

Review all clinical problems in the patient (eg, degree of renal impairment) before starting a patient on dabigatran, apixaban, or rivaroxaban

Prescribe drugs at recommended dosages and limit duration to the shortest time for which anticoagulation is needed

Periodically review clinical conditions (eg, acute renal failure) that may warrant abrupt discontinuation of anticoagulation or dose adjustment

Stratify bleeding risk preoperatively and discontinue anticoagulation before surgery or procedures (when appropriate)

Use commonly available anticoagulation tests before procedures with high risk of bleeding:

A normal thrombin time and normal activated partial thromboplastin time will, in many cases, imply no hemostatic dysfunction due to dabigatran

A normal prothrombin time or an undetectable anti-factor Xa activity would exclude hemostatic dysfunction due to rivaroxaban or apixaban in many cases

Suggested interventions for patients with bleeding due to new oral anticoagulants

General measures:

Assess vital signs and resuscitate as appropriate

Withdraw the anticoagulant

Periodically assess blood count and coagulation cascade

Gastric lavage and activated charcoal if within 3 hours of dose

If bleeding is severe or life-threatening:

Consider multidisciplinary team care in an intensive care unit

Mechanical compression of accessible sites

Surgical interventions as appropriate

Hemodialysis (only dabigatran)

Nonspecific prohemostatic agents^a

Activated prothrombin complex concentrate 50–100 U/kg intravenously (preferred)

Prothrombin complex concentrate 50 U/kg

Recombinant factor VIIa 120 U/kg

^aRefer to the manufacturer's recommended dosages for severe bleeding episodes.

Managing overdose and bleeding complications

Assessing the severity of bleeding is the key to managing bleeding complications.

Minor bleeding such as epistaxis and ecchymosis can be managed symptomati-

cally (eg, with nasal packing), perhaps with short-term withdrawal of the anticoagulant. Moderate bleeding such as upper or lower gastrointestinal bleeding can be managed by withdrawal of the anticoagulant, clinical monitoring, blood transfusion if needed, and treatment directed at the etiology.

Major and life-threatening bleeding (eg, intracerebral hemorrhage) requires aggressive treatment in the intensive care unit, withdrawal of the anticoagulant, mechanical compression of the bleeding site if accessible, fluid replacement and blood transfusion as appropriate, and interventional procedures. Nonspecific reversal agents might be considered in patients with major or life-threatening bleeding.

The half-life of dabigatran after multiple doses is approximately 14 to 17 hours and is not dose-dependent.⁹ Hence, if there is no active bleeding after a dabigatran overdose, stopping the drug may be sufficient. Since the pharmacodynamic effect of dabigatran declines in parallel to its plasma concentration, urgent but not emergency surgery may need to be delayed for only about 12 hours from the last dose of dabigatran.

The 2011 American College of Cardiology Foundation/American Heart Association guidelines recommend that patients with severe hemorrhage resulting from dabigatran should receive supportive therapy, including transfusion of fresh-frozen plasma, transfusion of packed red blood cells, or surgical intervention if appropriate.³⁵ However, transfusion of fresh-frozen plasma is debatable because there is no evidence to support its use in this situation. While fresh-frozen plasma may be useful in cases of coagulation factor depletion, it does not effectively reverse inhibition of coagulation factors.³⁶

Off-label use of nonspecific hemostatic agents

To date, no specific agent has been demonstrated to reverse excessive bleeding in patients taking the new oral anticoagulants. However, in view of their procoagulant capabilities, nonspecific hemostatic agents have been suggested for use in reversal of major bleeding resulting from these drugs.^{37–39} Examples are:

Recombinant factor VIIa (NovoSeven) initiates thrombin generation by activating factor X.

Four-factor prothrombin complex concentrate (Beriplex, recently approved in the United States) contains relatively large amounts of four nonactive vitamin K-dependent procoagulant factors (factors II, VII, IX, and X) that stimulate thrombin formation.

Three-factor prothrombin complex concentrate (Bebulin VH and Profilnine SD) contains low amounts of nonactive factor VII relative to factors II, IX, and X. In some centers a four-factor equivalent is produced by transfusion of a three-factor product with the addition of small amounts of recombinant factor VIIa or fresh-frozen plasma to replace the missing factor VII.⁴⁰

Activated prothrombin complex concentrate (FEIBA NF) contains activated factor VII and factors II, IX, and X, mainly in nonactivated form.³⁶ Therefore, it combines the effect of both recombinant factor VIIa and four-factor prothrombin complex concentrate.³⁷

Studies of nonspecific hemostatic agents

In a study of rats infused with high doses of dabigatran, van Ryn et al³⁸ observed that activated prothrombin complex concentrate at a dose of 50 or 100 U/kg and recombinant factor VIIa at a dose of 0.1 or 0.5 mg/kg reduced the rat-tail bleeding time in a dose-dependent manner but not the blood loss, compared with controls, even with a higher dose of recombinant factor VIIa (1 mg/kg). Recombinant factor VIIa also reversed the prolonged aPTT induced by dabigatran, whereas activated prothrombin complex concentrate did not. They suggested that recombinant factor VIIa and activated prothrombin complex concentrate may be potential antidotes for dabigatran-induced severe bleeding in humans.

In an ex vivo study of healthy people who took a single dose of dabigatran 150 mg or rivaroxaban 20 mg, Marlu et al³⁷ found that activated prothrombin complex concentrate and four-factor prothrombin complex concentrate could be reasonable antidotes to these drugs.

Dabigatran-associated bleeding after cardiac surgery in humans has been successfully managed with hemodialysis and recombinant

factor VIIa, although the efficacy of the latter cannot be individually assessed in the study.⁴¹

In a randomized placebo-controlled trial aimed at reversing rivaroxaban and dabigatran in healthy participants, Eerenberg et al³⁹ showed that four-factor prothrombin complex concentrate at a dose of 50 IU/kg reversed prolongation of the prothrombin time and decreased the endogenous thrombin potential in those who received rivaroxaban, but it failed to reverse the aPTT, the endogenous thrombin potential, and thrombin time in those who received dabigatran.

However, Marlu et al reported that four-factor prothrombin complex concentrate at three doses (12.5 U/kg, 25 U/kg, and 50 U/kg)—or better still, activated prothrombin complex concentrate (40–80 U/kg)—could be a useful antidote to dabigatran.³⁷

It is important to note that the healthy participants in the Eerenberg et al study³⁹ took dabigatran 150 mg twice daily and rivaroxaban 20 mg daily for 2.5 days, whereas those in the Marlu et al study³⁷ took the same dose of each medication, but only once.

The three-factor prothrombin complex concentrate products have been shown to be less effective than four-factor ones in reversing supratherapeutic INRs in patients with warfarin overdose, but whether this will be true with the new oral anticoagulants remains unknown. Furthermore, the four-factor concentrates effectively reversed warfarin-induced coagulopathy and bleeding in patients,⁴² but to our knowledge, the same is yet to be demonstrated in bleeding related to the newer agents.

Other measures

Gastric lavage or the administration of activated charcoal (or in some cases both) may reduce drug absorption if done within 2 or 3 hours of drug ingestion (TABLE 1). Because it is lipophilic, more than 99.9% of dabigatran etexilate was adsorbed by activated charcoal from water prepared to simulate gastric fluid in an in vitro experiment by van Ryn et al.⁴³ This has not been tested in patients, and no similar study has been done for rivaroxaban or apixaban. However, use of charcoal in cases of recent ingestion, particularly with intentional overdose of these agents, seems reasonable.

Assessing the severity of bleeding is the key to managing bleeding complications

Hemodialysis may reverse the anticoagulant effects of dabigatran overdose or severe bleeding because only about 35% of dabigatran is bound to plasma proteins (TABLE 1). In a single-center study, 50 mg of dabigatran etexilate was given orally to six patients with end-stage renal disease before dialysis, and the mean fraction of the drug removed by the dialyzer was 62% at 2 hours and 68% at 4 hours.³² This study suggests that hemodialysis may be useful to accelerate the removal of the drug in cases of life-threatening bleeding.

Rivaroxaban and apixaban are not dialyzable: the plasma protein binding of rivaroxaban is 95% and that of apixaban is 87%.

FUTURE DIRECTIONS

Because the new oral anticoagulants, unlike warfarin, have a wide therapeutic window, routine anticoagulant monitoring is not needed and might be misleading. However, there are times when monitoring might be useful; at such times, a validated, widely available, easily understood test would be good to have—but we don't have it—at least not yet.

Therapeutic ranges for the aPTT have been established empirically for heparin in various indications.⁴⁴ Additional study is needed to determine if an appropriate aPTT range can be determined for the new oral anticoagulants, particularly dabigatran.

Similarly, as with low-molecular-weight heparins, anti-factor Xa activity monitoring may become a more available validated means of testing for exposure to rivaroxaban and apixaban. More promising, using concepts derived from the development of the INR for warfarin monitoring,⁴⁵ Tripodi et al⁴⁶ have derived normalized INR-like assays to report rivaroxaban levels. A standardized schema for reporting results is being developed.⁴⁶ Studies are required to determine if and how this assay may be useful. Initial trials in this regard are encouraging.⁴⁷

Finally, the thrombotic risk associated with the use of nonspecific prohemostatic agents is unknown.^{37,48} Additional studies are required to standardize their dosages, frequency of administration, and duration of action, as well as to quantify their complications in bleeding patients.

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Hemodialysis may reverse dabigatran but not rivaroxaban or apixaban

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