Pathology Consultation on Monitoring Direct Thrombin Inhibitors and Overcoming Their Effects in Bleeding Patients

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ABSTRACT

Objectives: Direct thrombin inhibitors (DTIs), a relatively new class of anticoagulants, present several challenges regarding monitoring of their anticoagulant effects and overcoming bleeding associated with their use. The aim of this article is to (1) briefly present the pharmacologic properties of currently available DTIs, (2) discuss approaches to laboratory assessment of these drugs, and (3) review management of bleeding associated with their use.

Methods: Published literature on DTIs, including clinical trials, case reports, and experimental animal models, was reviewed. The primary authors also reviewed their first-hand experiences with DTI anticoagulation.

Results: Based on the literature review and the practical experiences of the authors, suggestions for the monitoring of DTIs and algorithmic approaches for the management of DTI-associated bleeding were developed.

Conclusions: Routine coagulation assays (eg, the prothrombin time) show a relatively poor correlation with the degree of anticoagulation and DTI drug concentrations. Newer assays, such as the ecarin clotting time and dilute thrombin time, may be more useful in assessing DTI anticoagulation, but these assays are not yet widely available. Low-grade DTI-associated bleeds are best managed with cessation of the drug and supportive care, while higher-grade and/or life-threatening bleeds may best be reversed by active drug removal (eg, via the administration of activated charcoal or hemodialysis).

At present there is little evidence to suggest that transfusion products such as factor concentrates or thawed plasma are of any particular benefit in DTI reversal; however, these products may play a supportive role in the management of bleeding.

Upon completion of this activity you will be able to:
• outline the mechanism of action of direct thrombin inhibitor (DTI) anticoagulants.
• describe laboratory assays available for monitoring the anticoagulant effects of DTIs.
• apply strategies to reverse the effects of DTIs in the setting of bleeding or drug overdose.

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Case Report

A 67-year-old woman with a history of atrial fibrillation on dabigatran etexilate (150 mg twice per day) presents to the emergency department (ED) after a fall. She is complaining of a mild headache and hip pain. She notes that she had just taken her daily medications, including dabigatran and 81 mg of aspirin, when she slipped on her kitchen floor, violently striking her head. Her husband brought her directly to the hospital for evaluation. Basic coagulation studies (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) are ordered, and the patient is sent for an urgent computed tomography (CT) scan of her head. The CT scan reveals an extra-axial fluid collection suspicious for a subdural hemorrhage. Shortly thereafter, the laboratory reports a prolonged PT (26.4 seconds; reference range, 10.4-12.7 seconds) and aPTT (40.1 seconds; reference range, 23.6-37.6 seconds).
Concerned about the possibility of expansion of the subdural hemorrhage, the ED physician contacts the on-call laboratory medicine physician seeking advice on the laboratory assessment of dabigatran in this setting and asks about approaches to managing bleeding with blood or other products.

Questions
• What are the pharmaceutical properties of the most commonly used direct thrombin inhibitors (DTIs)?
• How can the anticoagulant effects of DTIs be appropriately assessed by hematology and coagulation laboratories?
• What therapeutic interventions are available to overcome DTI-associated coagulopathy in the setting of acute bleeding or an overdose?

Background
Thrombin is a serine protease responsible for the conversion of soluble fibrinogen to insoluble fibrin; it catalyzes additional coagulation reactions, including platelet activation. It can be inhibited directly or indirectly through binding of an anticoagulant to the active site, fibrin-binding site (exosite 1), and/or heparin-binding domain (exosite 2).1,2 Unlike the more traditional anticoagulants, such as unfractionated or low-molecular-weight heparins that inhibit thrombin indirectly through the intermediate antithrombin, the DTIs are a class of anticoagulants that bind directly to thrombin. As recombinant derivatives or synthetic analogues of hirudin, a naturally occurring peptide isolated from the salivary gland of the medicinal leech Hirudo medicinalis, DTIs bind thrombin via the active site and/or exosite 1, thereby inhibiting both free and clot-bound thrombin.3,4 Additional advantages of the DTIs include a more predictable anticoagulant response because of lack of plasma protein binding, an indirect antiplatelet effect via thrombin-induced platelet activation, and absence of an association with an immune thrombocytopenia such as heparin-induced thrombocytopenia (HIT).1 Currently, three parenteral DTIs (argatroban, bivalirudin, and desirudin) and one oral DTI (dabigatran etexilate) are available for use in the United States. Production of lepirudin (Refludan) was discontinued by Bayer HealthCare (Morristown, NJ) in May 2012, and currently its availability is limited. Pharmacologic properties of and clinical uses for each of the DTIs will be discussed and are summarized in Table 1. Because lepirudin production has been halted and ximelagatran is not available in the United States, discussion of these DTIs will be limited.
Winkler and Tormey / Direct Thrombin Inhibitors

Clinical Usefulness and Pharmacologic Properties of the DTIs

Desirudin

Desirudin (Iprivask, Canyon Pharmaceuticals, Hunt Valley, MD) is a recombinant hirudin that irreversibly binds to both the thrombin active site and exosite 1, making desirudin one of the most potent DTIs alongside lepirudin. Desirudin differs from natural hirudin by the absence of a sulfate group on the tyrosine at position 63.1,5 Desirudin is 80% to 90% metabolized and eliminated renally, with 40% to 50% of the drug excreted unchanged in the urine.5,6 When administered subcutaneously, desirudin reaches its maximum concentration in 1 to 3 hours and has a half-life of 2 to 3 hours; however, this half-life can be increased up to 12 hours in patients with severe renal impairment.5 As a result, dose adjustment is required in patients with moderate (creatinine clearance [CrCl] 31 to 60 mL/min) and severe renal impairment (CrCl <31 mL/min) and is contraindicated in patients with a CrCl less than 15 mL/min. Currently, desirudin is approved by the Food and Drug Administration (FDA) for prevention of deep vein thrombosis (DVT) in patients undergoing elective total hip replacement at a subcutaneous dose of 15 mg every 12 hours. Data to support this approval originated from randomized controlled trials comparing desirudin to both unfractionated heparin (5,000 U given subcutaneously three times daily) and enoxaparin (40 mg subcutaneous daily).7,8 In both clinical trials, desirudin demonstrated superior efficacy in preventing total and proximal DVT without an increased risk of bleeding. Desirudin has also been evaluated in clinical trials for managing anticoagulation in HIT, as well as acute coronary syndrome with or without percutaneous coronary intervention (PCI).9-12 Routine laboratory monitoring is not necessary in patients who receive desirudin for DVT prophylaxis; however, daily monitoring with the aPTT is recommended in patients with moderate to severe renal insufficiency (CrCl < 60 mL/min).9

Argatroban

Argatroban (GlaxoSmithKline, Research Triangle Park, NC) is a synthetic, univalent DTI derived from L-arginine, which binds reversibly to the thrombin active site and consists of a mixture of R and S stereoisomers, each with differing anticoagulant potencies.13 Argatroban is administered intravenously with or without a bolus and reaches steady state levels within 1 to 3 hours. On discontinuation of the infusion, the half-life ranges from 39 to 51 minutes.14 Unlike the other DTIs, argatroban can be distinguished by its hepatic clearance via metabolism through the hepatic cytochrome P450 enzymes 3A4/5 and excretion in the feces. As a result, argatroban should be used with caution in patients with hepatic impairment and the dosage adjusted. Alternatively, DTIs not dependent on hepatic metabolism, such as bivalirudin, may also be useful for patients with liver disease. Given that no dosage adjustment is required for patients with renal impairment, argatroban is the preferred agent for patients with renal dysfunction.15 Argatroban is FDA approved for prophylaxis and treatment of thrombosis in patients with HIT at an initial dose of 2 μg/kg per minute and for anticoagulation in patients with or at risk for HIT undergoing PCI at an initial bolus dose of 350 μg/kg followed by a continuous infusion of 25 μg/kg per minute. Data to support the approval for HIT was obtained from two multicenter clinical trials that demonstrated a benefit of argatroban for a composite outcome of death, amputation, and occurrence of a new thrombosis compared with historic controls.16,17 A number of studies have evaluated the usefulness of argatroban for anticoagulation during PCI in patients with and without HIT. Compared with historic heparin controls, argatroban demonstrated comparable efficacy, supporting the FDA approval for its use during PCI.18,19 The clinical usefulness of argatroban has also been evaluated as an adjunctive therapy to alteplase in myocardial infarction and acute ischemic stroke.20,21 Routine coagulation monitoring with aPTT is recommended to guide the treatment of argatroban therapy; aPTT monitoring should begin 2 hours after the start of infusion, with each dose change, and at minimum daily.14

Bivalirudin

Bivalirudin (Angiomax, The Medicines Co, Parsippany, NJ) is a synthetic, bivalent DTI that binds to both the active site and exosite 1 of thrombin. Unlike the other hirudin derivatives, binding of bivalirudin is reversible because of proteolytic cleavage at an arginine-proline bond on bivalirudin that allows for restoration of enzymatic activity at the thrombin active site.1,22 Therefore, compared with the recombinant hirudins (desirudin, lepirudin), bivalirudin is associated with a decreased bleeding risk and thereby an improved safety profile. Bivalirudin is cleared by a combination of plasma proteolytic cleavage (20%) and renal elimination (80%).22,23 The half-life of bivalirudin in a patient with normal renal function is 25 minutes; however, clearance is decreased by 20% with a CrCl less than 60 mL/min and by 80% in a dialysis-dependent patient. As a result, renal dose adjustment is required. Bivalirudin is FDA approved for use in patients with unstable angina undergoing PCI with or without provisional use of a glycoprotein IIb/IIIa inhibitor or in patients with or at risk for HIT undergoing PCI. Dosing typically follows the manufacturer’s recommendations, with an initial bolus of 0.75 mg/kg followed by a continuous infusion of 1.75 mg/kg per hour during the procedure and for up to 4 hours after the procedure; a decreased infusion rate of 0.2 mg/kg per hour can be considered for an additional 20 hours. The clinical efficacy of bivalirudin has been extensively reviewed elsewhere, and clinical trials have demonstrated similar efficacy and improved clinical outcomes with bivalirudin compared with heparin-based strategies.23,24
The activated clotting time is the recommended test to assess the anticoagulant effect of bivalirudin, primarily because of the accessibility to laboratory testing in the cardiac catheterization laboratory that meets turnaround time requirements; however, nomograms have been published for monitoring bivalirudin outside the setting of PCI with aPTT.

**Dabigatran Etxilate**

Dabigatran etxilate (Pradaxa, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT) is currently the only available oral DTI; only one other oral IIa inhibitor has been developed, ximelagatran, but was removed from European markets after 20 months and never approved in the United States because of hepatotoxicity.1 Dabigatran etxilate is the prodrug of dabigatran, which binds reversibly to thrombin’s active site. The bioavailability of dabigatran etxilate after oral absorption is low (6%-7%), and it is more consistently absorbed in an acidic environment. As a result, the capsule formulation of dabigatran etxilate is unique and composed of pellets containing a tartaric acid core and coated with dabigatran etxilate so that it brings its own acidic microenvironment to the site of absorption.25,26 After oral administration, peak plasma concentrations are achieved within 1.5 to 2 hours, which decreases by more than 70% over 4 to 6 hours. With a single dose of dabigatran, the terminal half-life is 9 hours, and with repeated dosing, this half-life reaches 12 to 17 hours. However, because dabigatran is primarily excreted through the kidneys (85%) with the remainder excreted in the bile after conjugation with glucuronic acid, dose adjustment is required for patients with a CrCl of 15 to 30 mL/min. Dabigatran etxilate is currently FDA approved for anticoagulation to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; this is based on data from phase II and III clinical trials demonstrating that dabigatran was not inferior to warfarin.27,28 Other potential clinical uses for dabigatran have been evaluated and reviewed extensively elsewhere including its use for prevention and treatment of venous thromboembolism, myocardial infarction, and anticoagulation during PCI.1,24,26,29 Routine monitoring is not required for dabigatran etxilate; however, some advocate for the use of testing to assess drug compliance, in the evaluation of the bleeding patient, in the perioperative setting, or in patients with renal impairment.

Although DTIs offer many advantages over traditional anticoagulants, such as unfractionated and low-molecular-weight heparins and warfarin, several questions remain unanswered regarding their usage. From the standpoint of laboratory monitoring, the optimal laboratory test to assess the anticoagulant effect of the DTIs continues to remain an issue. Moreover, in the absence of specific antidotes, management of bleeding due to DTIs can be challenging. Therefore, both of these issues will be discussed in greater detail.

**Laboratory Assessment of the DTIs**

With the exception of desirudin and dabigatran etxilate, the remaining parenteral DTIs (argatroban, bivalirudin, and lepirudin) require routine laboratory monitoring of their therapeutic effect while balancing the risk of bleeding with that of clinical efficacy. The key features of an optimal test for monitoring a DTI should include standardization, specificity, automation, cost-effectiveness, a desirable turnaround time, wide accessibility, and most importantly, correlation with clinical outcomes. However, none of the currently recommended laboratory tests or dedicated assays under investigation meet all of these criteria; there is currently an unmet need of an optimal test to monitor the DTIs. The recommended tests, expected changes in laboratory results, and recommendations for dose adjustments are summarized in Table 2 for each of the DTIs and discussed in detail in the following section.

**Routine Assays**

As an expected result of thrombin inhibition, the conventional thrombin time (TT) displays a dose-dependent prolongation with administration of DTIs; however, the TT is overly sensitive to low levels, often exceeding maximum measurement times (>200 seconds) at therapeutic drug levels, thereby rendering it unsuitable for routine monitoring.30 Likewise, the variability of the PT and international normalized ratio (INR) to the DTIs also make the PT/INR an unsuitable monitoring tool. This is in part because of the high concentrations of tissue factor in PT reagents that allows for generation of high concentrations of factor Xa and activation of factor V and prothrombinase formation.31 Furthermore, this variable responsiveness often complicates the transition from a DTI to a vitamin K antagonist such as warfarin and interpretation of laboratory results in a bleeding patient. A greater prolongation of the PT is more common with argatroban than with the DTIs with greater thrombin affinity, such as lepirudin; this paradoxical effect results from the high molar concentrations of argatroban required to achieve therapeutic drug levels.31 As a result, other tests, such as the chromogenic factor X assay, have provided a more reliable way to predict the INR in patients making a transition from argatroban to warfarin.32

Because of the unreliability of the TT and PT/INR, aPTT has become the most commonly recommended routine coagulation assay to monitor the DTIs with the exception of the PT setting, which requires point-of-care testing with activated clotting time. DTIs prolong the aPTT in a dose-dependent fashion because of the inhibition of thrombin-mediated feedback activation of factors V and VIII. However, these clotting time prolongations are not linear and are highly dependent on the sensitivity of the reagent and instrumentation used in the absence of standardization of the aPTT; this has been most extensively investigated for argatroban and dabigatran etxilate.33-36 Recently, two
Illustrative cases were published in a review of HIT that demonstrated confounding of the aPTT as a result of an acquired consumptive coagulopathy in the critically ill patient. In both cases, the argatroban infusion was started and stopped because of supratherapeutic aPTT prolongations despite subtherapeutic argatroban dosing, which has the potential to lead to thrombosis progression. Because of the lack of standardization and nonspecific prolongations of the aPTT despite DTI therapy, either resulting from an underlying factor deficiency or a lupus anticoagulant, many have started to advocate for dedicated, more specific tests for monitoring DTIs; this has been especially true with the introduction of dabigatran etexilate.

### Dedicated Assays

Highly specific assays, such as ultra performance liquid chromatography coupled with tandem mass spectrometry, have been developed for the direct quantification of the...
Overcoming the Effects of DTIs in the Setting of Acute Hemorrhage or Overdose

Because of their inhibition of thrombin activity, overcoming adverse bleeding events in patients taking DTIs can be challenging for treating clinicians and transfusion services. In the absence of a specific antidote to the action of commonly used DTIs (ie, equivalent to the action of protamine sulfate on heparin), strategies have been developed to promote hemostasis with a cocktail of coagulation factors or via removal of the active form of the drug. The aim of this section is to (1) review data obtained from animal models of correction of bleeding with DTIs, (2) discuss in vivo/ex vivo clinical studies and anecdotal cases that have been reported regarding DTI reversal, and (3) develop a practical algorithm incorporating data from animal models and human studies that may be useful in treating the bleeding patient receiving DTI therapy.

Animal Models

One of the earliest animal studies involved use of an activated prothrombin complex concentrate (APCC; a prothrombin complex concentrate with an activated factor VII component) in rabbits treated with recombinant hirudin.45 APCC at 3 mg/kg overcame the effects of hirudin as measured by bleeding and whole blood coagulation times. A number of more recent animal studies have explored the reversal of dabigatran. One of the first such studies comparing four-factor prothrombin complex concentrate (4FPCC), fresh frozen plasma (FFP), and recombinant factor VIIa (rFVIIa) showed that 4FPCC was most efficacious in promoting survival, preventing intracerebral hematoma expansion, and reducing tail vein bleeding in mice anticoagulated with dabigatran.46 FFP and rFVIIa showed little benefit. A later study of 4FPCC in a rabbit kidney injury model also demonstrated that this product was capable of reducing blood loss and improving hemostasis in a dose-dependent manner.47 Unfortunately, there is no complete agreement regarding the efficacy of 4FPCC or APCC for dabigatran reversal. A recent extensive study examined the effects of four approaches (4FPCC alone, rFVIIa alone, 4FPCC + rFVIIa, and APCC) on peripheral blood loss in a murine model with dabigatran. Although some of the aforementioned regimens were associated with improvements in coagulation test parameters, none significantly reduced blood loss in comparison with untreated controls.48 Despite the lack of consensus regarding the potential efficacy of 4FPCC or APCC, the animal model data from most studies suggest that rFVIIa and FFP are mostly ineffective as solo therapies for reversal of DTI anticoagulation. Moreover, and as noted by virtually all of the studies reviewed herein, animal models of hemorrhage are at best approximations of the bleeding that occurs in humans.

Of note, some early animal studies examined the efficacy of 1-deamino-8-d-arginine vasopressin (DDAVP) for...
reversing the effects of hirudin. Investigators found that large increases in factor VIII levels associated with DDAVP administration appeared to correct bleeding times and other measures of coagulation.49-51 However, moderate to high doses of hirudin could not be overcome by DDAVP in some of these animal studies, and these initial reports have been followed up with little to no clinical investigation of the usefulness of DDAVP for DTI-associated bleeding.

Human Studies: Clinical Trials and Ex Vivo Experiments

To date, clinical trials examining the effects of a blood product or factor concentrate administration on reversal of DTIs have been limited. One of the first studies by Wolzt et al52 involved recruitment of healthy volunteers who were administered melagatran followed by either a dose of rFVIIa (90 μg/kg) or placebo. The end point of the study was thrombin generation and platelet activation as measured by in vitro assays. The authors found that rFVIIa had no appreciable effect on thrombin generation or platelet granule secretion compared with placebo.52 More recently, Eerenberg et al53 enrolled 12 healthy volunteers who received dabigatran and then were administered 4FPCC. The primary end point was correction of several in vitro coagulation tests, including aPTT and TT. The investigators demonstrated that 4FPCC dosed at 50 U/kg had no significant effect on any of the coagulation parameters tested. Based on this result, the authors concluded that there is no evidence to support 4FPCC for DTI reversal.

Several ex vivo experiments have also been performed to examine the efficacy of procoagulant factor concentrates on the DTIs dabigatran, argatroban, and bivalirudin. Recently, Marlu et al54 tested the thrombin generation potential of several doses of 4FPCC, APCC, and rFVIIa added to extracted plasma samples of healthy volunteers who had been administered dabigatran. In this study, all three agents were associated with increases in thrombin generation and reduced clot formation lag time kinetics. However, the authors were concerned that the doses of rFVIIa and APCC needed to achieve these corrections may be unsafe for patients. As a result, the authors ultimately concluded that PCC and lower doses of APCC were likely the most reasonable considerations for dabigatran reversal, but further in vivo clinical trials were warranted. Finally, another group using thromboelastography on samples treated with argatroban and bivalirudin demonstrated that rFVIIa was effective in improving clot formation.55

The data from the aforementioned studies provide little in the way of clear guidance for DTI reversal with factor concentrates. Although the clinical trials showed no benefit for rFVIIa or APCC with two unique DTIs, they were somewhat limited. First, neither specifically assessed cessation of bleeding but rather correction of surrogate in vitro assays of coagulation. It is possible that clinical benefits pertaining to in vivo hemostasis may be obtained in the absence of a significant change in coagulation test parameters. Secondly, those studies only examined single fixed doses of either rFVIIa or 4FPCC. It is conceivable that an alternative dosing strategy or combination of coagulation factor products might have yielded different results. Therefore, in the absence of a clinical trial specifically examining bleeding outcomes and/or survival with any of these products, it is likely premature to dismiss their potential usefulness for DTI-associated bleeding, particularly in light of some of the positive findings generated in ex vivo studies and animal models.

Case Reports on Blood Product/Coagulation Factor Dosing for Dabigatran

The most extensive case report/case series literature on overcoming bleeding associated with DTIs exists for dabigatran. Reports of excessive bleeding with dabigatran were noted in numerous clinical scenarios including intracranial hemorrhage after trauma or surgery, postoperative hemorrhage (eg, following cardiac and orthopedic procedures), cardiac tamponade after cardiac ablation, spontaneous upper and lower gastrointestinal hemorrhage, and epistaxis.56-69 Given the dearth of evidence-based approaches for bleeding in these settings, the strategies outlined by the authors were all somewhat different. For cases in which treatment strategies were discussed, some authors elected to simply hold dabigatran doses and treat patients supportively.56-57 In other more severe cases, a number of approaches were used, including rFVIIa administration (in dosages ranging from 30-90 μg/kg), three-factor PCC (3FPCC, in dosages ranging from 25-50 U/kg), APCC (in dosages ranging from 36-40 U/kg), APCC (in dosages ranging from 16-26 U/kg), and plasma product transfusions (including FFP and cryoprecipitate) given alone or in combination with the previously mentioned coagulation factor concentrate therapies.58-69

In sorting through the various transfusion approaches reported, most authors providing FFP or cryoprecipitate (either alone or in combination with other therapies) concluded that these products had little to no direct effect on DTI-related bleeding.58-69 The picture becomes less clear, however, for the other products. Regarding rFVIIa, only one of five reports reviewed definitively attributed successful reversal of dabigatran to its administration.59 Four of the remaining studies found no clinical benefit to rFVIIa administration, whereas the fifth found a reduction in blood loss only (the authors of this study opted against firmly recommending the use of rFVIIa given the potential for thrombotic complications).58,59,61,62 Three studies described the use of 3FPCC. Of these, two studies found stabilization of hemoglobin levels or reduced bleeding after the administration of 3FPCC, whereas 3FPCC was thought to have no effect on hemostasis in the third study (in this case, the patient died of probable hemorrhagic shock).56 One case series details
two patients who received 4FPCC, which the authors concluded had no clinical benefit. To date, only a single case report has described the use of APCC to reverse the effect of dabigatran. The authors noted cessation of bleeding within minutes of APCC administration and no further hemorrhage and further concluded that APCC was useful in overcoming the anticoagulant effects of dabigatran.

Case Reports on Blood Product/Coagulation Factor Dosing for Bivalirudin

Four case reports on uncontrolled bleeding in the setting of bivalirudin therapy during cardiac surgery have been published. In three of all four of these cases, rFVIIa was administered in doses ranging from 15 to 90 μg/kg to establish hemostasis. In three of the four cases, the authors reported reduced bleeding, although one of the patients also underwent hemodialysis, as discussed more fully later in this article. Complications reported included DVT in one of the cases, likely attributable to rFVIIa administration. In the fourth report, rFVIIa administration to reverse bivalirudin resulted in the immediate development of a left atrial thrombus, necessitating prolonged anticoagulation in the postoperative period. The patient did survive this event and was ultimately discharged.

Case Reports on Blood Product/Coagulation Factor Dosing for Argatroban

Several cases of excessive bleeding after argatroban treatment have also been reported, and all were associated with poorly controlled hemostasis during or immediately after major cardiac surgery. In two cases, moderate bleeding was treated with supportive infusions of RBCs, FFP, and platelets. The authors of these reports comment that these supportive transfusions did not necessarily cause an immediate reversal of the coagulopathy. In the remaining three cases, massive hemorrhage was encountered. In the first of these reports, a patient was given massive transfusions of RBCs, platelets, and FFP to support large blood losses. These blood products did not appear to have definitive effects on the reversal of the coagulopathic state induced by argatroban. In the second case, the authors used a single dose of rFVIIa at a dose of 75 μg/kg as a component of massive transfusion support. In this case, the benefit was unclear because the patient continued to bleed, requiring large volumes of RBC, platelet, and FFP transfusions even after rFVIIa administration. The third case involving massive bleeding occurred in the setting of a pediatric cardiac surgery. In addition to large numbers of whole blood–derived components, the treating clinicians used two doses of rFVIIa at a dose of 90 μg/kg and concluded that rFVIIa was of no benefit in controlling hemostasis. Lastly, there is a case report of a patient undergoing anticoagulation for thrombosis prophylaxis in the setting of HIT who had accidentally received an overdose of argatroban. The authors note that coagulation parameters corrected with the administration of several units of FFP over time. However, because this is a single case, it is also unclear if the coagulation parameter correction simply resulted from clearance of the drug, given its short half-life.

Clinical Trials and Case Reports on Active Drug Removal

Attempts at overcoming the anticoagulant activity of DTIs using transfusion therapy are unreliable; therefore, an alternative approach involves reducing the DTI from circulation via dialysis or absorption. This strategy, including both one-time venous hemodialysis and continuous venovenous hemofiltration, has been reported as a means to prevent or control bleeding in patients taking bivalirudin and lepirudin. Accumulating evidence suggests that hemodialysis may be an effective approach for removal of dabigatran. A small clinical study performed on patients with chronic renal failure showed that hemodialysis over 2 to 4 hours was effective in removing about two-thirds of an initial dose of dabigatran. Moreover, at least seven cases have been reported of dabigatran-associated bleeding being reversed, in part, by hemodialysis.

In addition to removal by hemodialysis, some reports have also found that activated charcoal can reduce dabigatran absorption after acute ingestion. The earliest data, in the form of in vitro studies of dabigatran suspended in water and pooled plasma, showed impressive decreases in drug levels after the addition of activated charcoal to the aforementioned mixtures. Moreover, a recent case report involving an intentional overdose of dabigatran involved gastric lavage as recommended by a national guidance and administration of activated charcoal. In this case, no blood products or factor concentrates were administered, and the patient did not undergo hemodialysis. Despite marked prolongations of baseline TT, the patient did not manifest any signs of overt bleeding and survived the overdose. It is important to note that because of its action in the gut, activated charcoal is likely only to be a useful therapy if used within 1 to 2 hours of a dose (or overdose) of dabigatran.

A Reasonable Approach to DTI Reversal

For a patient who experiences untoward bleeding during DTI therapy, several practical concerns should be initially assessed: (1) What DTI was administered, when was it administered, and what is its half-life? (2) What is the severity of the patient’s bleeding? (3) Does the patient have renal or hepatic impairment or other causes for prolonged DTI half-life? (4) What is the availability of hemodialysis, and is the patient stable enough to have a catheter placed? (5) What coagulation factor product(s) is available in your hospital’s blood bank, transfusion service, or pharmacy?
These questions will help guide the initial approach to therapy. For instance, in the case of an oral DTI taken recently as part of an intentional overdose, the initial approach may involve gastric lavage and activated charcoal therapy. It is also critical to be aware of the coagulation factor products available in your particular institution. For example, many experimental studies provide protocols or approaches based on providing a 4FPCC. However, a single commercial 4FPCC (Kcentra, CSL Behring, Marburg, Germany) was only recently approved by the FDA for use in the US market for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist therapy in adult patients with acute major bleeding (not yet available for general clinical use at the time of this writing).89 There are virtually no extensive, US-based clinical data for this product in the setting of DTI-related bleeding. Therefore, familiarity with dosing 4FPCCs for DTI-related bleeding is limited. Finally, virtually all strategies for dealing with DTI therapy will center on the severity or risk of bleeding. Although many scales exist for estimating bleeding severity, in this review, we use the World Health Organization (WHO) and National Cancer Institute (NCI) scale/grading system for triaging bleeding severity.90 In general, the grading system is applied on a per organ system basis and will be used herein as follows: grade 0, no evidence of bleeding; grade I, mild or asymptomatic bleeding but not requiring intervention; grade II, moderate bleeding with medical intervention needed but not requiring transfusion support; grade III, severe blood loss with medical intervention needed and requiring transfusion support; grade IV, severe life-threatening blood loss or bleeding (eg, into a closed space) requiring major, urgent interventions and transfusions.

Low-Grade Hemorrhage (WHO Grade 0/I/II) in a Patient Taking a DTI

For the patient who has no bleeding (ie, grade 0 on the NCI/WHO scale) but has a potential risk for bleeding, holding future doses of the DTI and watchful waiting is likely the reasonable approach. If the patient has received an overdose of an oral DTI such as dabigatran, performance of gastric lavage and administration of activated charcoal may be warranted to attempt to prevent drug absorption if the drug had been given within 2 hours of presentation.86-88 As noted in Figure 1, for patients with WHO/NCI grade I/II bleeding, holding the next dose should be the first step. Beyond this, providing supportive transfusions as needed (eg, to correct anemia), addressing bleeding sites locally/topically (if applicable), and observing the patient closely until coagulation parameters normalize is a prudent approach. At this time, there is no evidence to suggest that administration of coagulation factor concentrates or use of dialysis is warranted for lower-grade, non–life-threatening bleeding, particularly because some of these interventions carry risks that may outweigh the benefits in the setting of DTI-associated hemorrhage.

High-Grade Hemorrhage (WHO Grade III/IV) in a Patient Taking a DTI

For patients experiencing major or life-threatening bleeding associated with DTI administration, the first step should be holding or discontinuing the drug. The next steps in triaging often depend on the type of DTI administered. For oral agents like dabigatran, the available literature and guidelines recommend gastric lavage and/or activated charcoal if the time frame is appropriate.86-88 If the patient can tolerate placement of an intravenous catheter, then urgent hemodialysis may be useful for a number of DTIs including dabigatran, lepirudin, and bivalirudin.72,80-82,86,87,91 Attempts should also be made at controlling the bleeding at its origin or site using interventional means as tolerated by the patient and as clinically feasible.

Beyond active removal of the DTI, transfusion or coagulation factor therapy should be considered. Based on our review of the literature and practical experience, no strong, evidence-based recommendation can be made regarding any single (or combination) approach to coagulation factor therapy. Therefore, use of any coagulation factor strategy should be reserved for cases with ongoing severe or life-threatening bleeding and when interventional measures such as hemodialysis have failed or are not possible. If coagulation factor therapy is deemed appropriate, then some animal model and ex vivo data do point to success in using particularly activated
forms. Available reports suggest 3FPCCs at a dose of 30 to 50 U/kg in combination with low-dose rFVIIa (30 μg/kg) or FFP (10-15 mL/kg) to supplement factor VII, which is lacking in 3FPCC. This combination should provide some theoretical benefit by increasing total prothrombin available without creating a very high risk for thrombotic complications. Alternatively, treating clinicians may opt for a true 4FPCC or APCC product (eg, factor eight bypassing activity concentrate). However, it is difficult to determine the appropriate dose to maximize hemostasis while minimizing thrombotic risk. At present, given the lack of clinical trials or reports for their use in reversing DTI agents, data recommending a suitable dose are limited. As noted previously, currently only a single report is available on the clinical use of APCC to reverse dabigatran, with the average dose reported to be about 20 U/kg.66 A single case series is available for 4FPCC (using doses of 36-40 U/kg).62 It is also important to note that the vast majority of the literature suggests that simple FFP or cryoprecipitate transfusions are of no specific benefit in DTI reversal. Therefore, whole blood–derived plasma components should not be considered as a first-line therapy unless indicated by some other circumstance (eg, the development of disseminated intravascular coagulation associated with hemorrhage or as part of a massive transfusion protocol).

One additional consideration is addressing other hemo-
stasis needs that may be reversible via transfusion or component therapy. Patients who are being treated with DTIs may also be receiving antiplatelet therapy (eg, aspirin or clopidogrel). Therefore, platelet transfusion may be of some benefit. If patients are demonstrating prolonged DTI exposure because of lack of renal clearance, there may also be coexisting renal insufficiency or uremia.92 In these circumstances, uremic platelet dysfunction can also contribute to the coagulopathic picture. As such, administration of DDAVP or cryoprecipitate can help to promote platelet function and overcome uremia-associated dysfunction.92 Finally, there is also evidence from human studies and animal models that maintaining hemoglobin parameters of more than 8 g/dL (or hematocrit parameters >24%) may help to promote coagulation at the microvascular level via increased platelet function.93,94 Therefore, RBC transfusions may not only help to provide oxygen-carrying capacity but also aid in hemostasis.

**Conclusions**

The use of DTIs as standard anticoagulants is increasing as they are applied in clinical settings such as HIT and for the prevention of thromboembolism in patients with atrial fibrillation. Because of their inherent pharmacologic properties and their inability to be reversed by transfusions or antidotes, DTIs are particularly problematic from the standpoint of laboratory monitoring and when patients develop bleeding while receiving therapy. The information herein should help clinicians and laboratorians better understand both laboratory studies and treatment of bleeding associated with DTIs. It is also imperative that we look to the future and integrate newly developing tests and potential antidotes into our clinical practice as they become available.95

Winkler and Tormey / Direct Thrombin Inhibitors

Case Summary

The patient, who weighs 65 kg, received a 2,000-U dose of 3FPCC and 2-mg dose of rFVIIa before dialysis catheter insertion. She then underwent emergency hemodialysis over 4 hours. Her coagulation studies ultimately normalized over the next 10 to 12 hours, she remained clinically stable, and serial imaging studies showed no worsening of her subdural hemorrhage. Dabigatran was held and she received no other blood product transfusions.

References

Rhea JM, Snyder ML, Winkler AM, et al. Development


