Management of Bleeding With Non–Vitamin K Antagonist Oral Anticoagulants in the Era of Specific Reversal Agents

ABSTRACT: Vitamin K antagonists are commonly used by clinicians to provide anticoagulation to patients who have or are at risk of having thrombotic events. In addition to familiarity with the dosing and monitoring of vitamin K antagonists, clinicians are accustomed to using vitamin K if there is a need to reverse the anticoagulant effect of vitamin K antagonists. There are now 4 new non–vitamin K antagonist oral anticoagulants (NOACs) that are attractive alternatives to vitamin K antagonists. Despite similar or lower rates of serious bleeding with NOACs in comparison with warfarin, there is a pressing need for strategies to manage bleeding when it does occur with NOACs and to reverse the pharmacological effect of these agents if needed. Important steps in minimizing bleeding risks with NOACs include dose adjustment of the agents in the setting of renal dysfunction and avoidance of the concomitant use of other antithrombotic agents if feasible. Laboratory measurement of the anticoagulant effect of NOACs is best accomplished with specialized assays, although some of the more widely available coagulation tests can provide information that is potentially useful to clinicians. Nonspecific hemostatic agents such as prothrombin complex concentrates and recombinant factor VIIa can be used to reverse the effect of NOACs. More specific reversing agents include the approved humanized monoclonal antibody fragment idarucizumab for reversing the effects of dabigatran, the investigational factor Xa decoy andexanet alfa, and the synthetic small molecule ciraparantag. Both andexanet and ciraparantag have been reported to reverse the effects of the anti-Xa NOACs (rivaroxaban, apixaban, and edoxaban), and a number of other anticoagulant agents in common clinical use, as well.

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For more than half a century warfarin and other vitamin K antagonists (VKAs) were the only oral anticoagulants available for clinical use. Although VKAs are highly effective in the prevention of thromboembolism, their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and inconvenience. Since 2010, 4 new non–vitamin K antagonist oral anticoagulants (NOACs) have been approved by the US Food and Drug Administration (FDA) and regulated in Europe and Asia. They inhibit either thrombin (dabigatran) or activated factor X (FXa; rivaroxaban, apixaban, and edoxaban) and offer potential advantages over VKAs, such as rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. Their predictable pharmacokinetic and pharmacodynamic effects enable administration of fixed doses without the need for routine coagulation monitoring.

Approximately 100 000 patients were enrolled in the phase 3 trials comparing the NOACs with warfarin for stroke prevention in atrial fibrillation (AF)[1–5] and the treatment and prevention of venous thromboembolism.[6–9] As a class, NOACs have a favorable risk-benefit profile in comparison with warfarin. NOAC efficacy in reducing thromboembolic events is at least similar to warfarin, but these agents are notably safer with respect to serious bleeding, in particular, intracranial hemorrhage, the most feared and devastating complication of anticoagulant therapy.[10,11] Clinical registries and large retrospective database studies, including an FDA analysis on >134 000 Medicare patients with AF, demonstrate consistent results with the clinical trial findings.[12–16]

Despite the considerable data demonstrating that NOACs cause less serious bleeding than VKAs, and that patients who experience a bleed while taking a NOAC have similar or better outcomes in comparison with patients on warfarin,[17,18] many physicians and patients have been reluctant to embrace NOACs because of their perception that, without a specific reversal agent, they will not be able to effectively manage patients who present with serious bleeding or who require urgent procedures.[19]

With the approval of the first NOAC-specific reversal agent and the late-stage clinical development of several others, it is useful to summarize the evidence regarding the management of NOAC-related bleeding, including: (1) prevention of bleeding, (2) general principles and supportive measures, (3) nonspecific hemostatic agents, and (4) NOAC-specific reversal agents.

GENERAL PRINCIPLES AND SUPPORTIVE MEASURES

Minimize the Risk of Bleeding

The most important first step to minimize bleeding risk is selecting the right dose of the NOAC for a specific patient, which requires awareness of the different dose adjustment criteria across NOACs and even with the same NOAC across indications (AF versus venous thromboembolism). All anticoagulants, even when used in the appropriate patient at the right dose, increase the risk of bleeding, so additional efforts should be made to minimize excess risk. Concomitant administration of antiplatelet drugs and nonsteroidal anti-inflammatory drugs should be avoided when possible. Because all NOACs have some degree of clearance by the kidney, assessment of renal function (creatinine clearance, preferably using the Cockcroft-Gault formula because this was used in most clinical trials to determine dosing) at the initiation of NOAC therapy and periodically during follow-up is critical. The 2015 update of the European Heart Rhythm Association's practical guide recommends that renal function be monitored yearly in patients with creatinine clearance ≥60 mL/min, and at an interval in months that is equal to the creatinine clearance /10 for patients with renal dysfunction (eg, every 3 months for creatinine clearance 30 mL/min).[20] Renal function is also an important factor when deciding when to discontinue NOAC therapy before a planned surgery or intervention. In general, the FXa inhibitors can be stopped 24 to 48 hours before the procedure, although a longer duration is required for patients on dabigatran with significant renal dysfunction (dabigatran has 80% renal clearance) who are undergoing an intervention with a high bleeding risk.[20]

Prescribing information for all NOACs includes dose reduction criteria to avoid excess bleeding in patients anticipated to have increased drug exposure (primarily because of impaired renal function). Although lowering the NOAC dose in patients who do not meet dose reduction criteria but have experienced a bleed or require concomitant antiplatelet therapy occurs in clinical practice, the efficacy and safety of such an approach has not been prospectively tested.

Supportive Measures

Given the short half-lives of these medications (≈12 hours), especially in patients with normal renal function, minor bleeds only require temporary discontinuation of anticoagulation for several doses. More significant bleeds may require additional supportive measures that include: local management (mechanical/surgical); volume resuscitation; and consideration of red blood cell and platelet transfusion, if appropriate.[20–22] In cases of overdose or in patients who took NOAC within 2 to 4 hours, oral activated charcoal may attenuate absorption of drug.[23–26] Hemodialysis can be considered in patients on dabigatran who have severe bleeding in the setting of renal failure,[27–30] but it is not an option for the FXa inhibitors because they are highly protein bound.[31,32]

Laboratory Measurements

In the setting of serious bleeding or the need for emergency surgery there is often a desire to assess residual anticoagulant activity. With respect to common coagulation

tests, a prolonged activated partial thromboplastin time indicates an anticoagulant effect of dabigatran, and a prolonged prothrombin time indicates an anticoagulant effect of the FXa inhibitors.[21] However, the clinical utility of these common tests is limited, because a normal activated partial thromboplastin time or prothrombin time does not exclude clinically relevant plasma levels of dabigatran and FXa inhibitors, respectively. In particular, there is considerable variability in the sensitivity of the prothrombin time across the FXa inhibitors, and this test is less sensitive to apixaban than rivaroxaban and edoxaban. The thrombin time is the most sensitive test for dabigatran; even low levels of dabigatran will prolong the thrombin time, so a normal thrombin time excludes clinically relevant dabigatran concentrations. The dilute thrombin time (dTT) can be used to quantify dabigatran drug levels because it has good correlation across a wide range of dabigatran concentrations.[33] Chromogenic anti-FXa assays are recommended for rivaroxaban, apixaban, and edoxaban with calibration for the specific agent.[21] However, validation of these specialized coagulation tests is required, they are not universally available, and they often have a delayed turnaround time that diminishes their usefulness in emergent situations. Asking patients when they last took a NOAC is often the most practical method for quickly assessing residual anticoagulant activity.

NONSPECIFIC HEMOSTATIC AGENTS

Hemostatic factors that have been studied as potential nonspecific NOAC reversal agents are prothrombin complex concentrates (PCCs), activated PCCs (aPCCs), recombinant activated factor VII, and fresh-frozen plasma (FFP).

Prothrombic Complex Concentrates/Activated Prothrombic Complex Concentrates

PCCs are plasma-derived products that contain 3 (factors II, IX, and X) or 4 (addition of factor VII) clotting factors in addition to variable amounts of heparin and the natural coagulation inhibitors protein C and protein S. aPCC (also known as factor VIII inhibitor bypassing activity) contains mostly activated factor VII along with mainly nonactivated factors II, IX, and X.

Animal studies have demonstrated that PCCs have variable ability to normalize anticoagulation parameters and to prevent or attenuate bleeding across the NOACs.[22,34–40] Limited data in humans are restricted to healthy volunteers. In 3 small (12–93 patients) randomized, placebo-controlled studies, PCCs reversed the anticoagulant effect of rivaroxaban and edoxaban but not dabigatran.[23,41–43] There was a dose-dependent relationship with complete reversal with 50 U/kg and partial reversal with 25 U/kg. In vitro studies in healthy volunteers demonstrated that aPCCs corrected more coagulation parameters than PCCs alone.[44,45] Based on these data, a dose of 50 U/kg of PCC or aPCC is recommended for reversal of the anticoagulant effect of NOACs in patients with severe of life-threatening bleeding if a specific reversal agent(s) is not approved or available.[20] A second dose may be necessary in patients with supratherapeutic levels of dabigatran and severe renal failure.

Recombinant Activated Factor VII

In vitro and ex vivo studies demonstrate variable efficacy of recombinant activated factor VII to reverse coagulation parameters attributable to NOACs.[44,46–52] Although a dose of 90 U/kg has been proposed to reverse serious NOAC-related bleeding,[20] there are no clinical trials investigating NOAC reversal with recombinant activated factor VII.

Fresh-Frozen Plasma

FFP should not be used to reverse the anticoagulant effects of NOACs,[53–56] although it may be used as a plasma volume expander in patients with severe bleeding with significant transfusion requirements.[20–22] PCC is preferred over FFP if replacement of coagulation factors is required, because FFP has a lower concentration of clotting factors (limiting its effectiveness), has a higher risk of transfusion reactions, and is administered with an increased volume load that may precipitate heart failure.[57]

Vitamin K

Vitamin K has no role in the management of NOAC-related bleeding.[20]

Efficacy Results to Date

It is important to underscore that there are limited data supporting the efficacy and safety of using these nonspecific hemostatic agents in bleeding patients taking NOACs. It is unclear that normalizing coagulation parameters in healthy volunteers translates to improved outcomes in patients who are actively bleeding. Furthermore, the use of these agents in managing bleeding caused by VKA or in hemophiliac patients has been associated with an increased risk of thrombotic complications.[58–60] This risk may be higher when activated factors are used. For these reasons, hemostatic agents should be reserved for patients taking NOACs who present with life-threatening bleeding despite general supportive measures or patients who require emergency surgery before expected clearance of the NOAC.[20–23]

Neither nonspecific nor specific reversal agents are recommended in cases of elective procedures (to foreshorten the time to an elective procedure) or when procedures can be delayed until the anticoagulant is cleared. Moreover, these agents should not be used in patients with a gastrointestinal hemorrhage who is responding to supportive measures, or in patients with supratherapeutic drug levels without bleeding.[61]

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SPECIFIC REVERSAL AGENTS

Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment developed as a specific reversal agent for dabigatran (Figure 1, Table 1). It binds with high affinity (350 times higher than thrombin) to free and thrombin-bound dabigatran[62] and binding is effectively irreversible.[63] In healthy volunteers with normal renal function, peak plasma concentrations were achieved at the end of a 5-minute infusion, and idarucizumab had an initial half-life of 47 minutes.[64] Despite its short plasma half-life, idarucizumab binds all the dabigatran in plasma within minutes.[63] Idarucizumab is primarily eliminated renally,[64,65] so drug exposure is increased in patients with impaired renal function. However, such

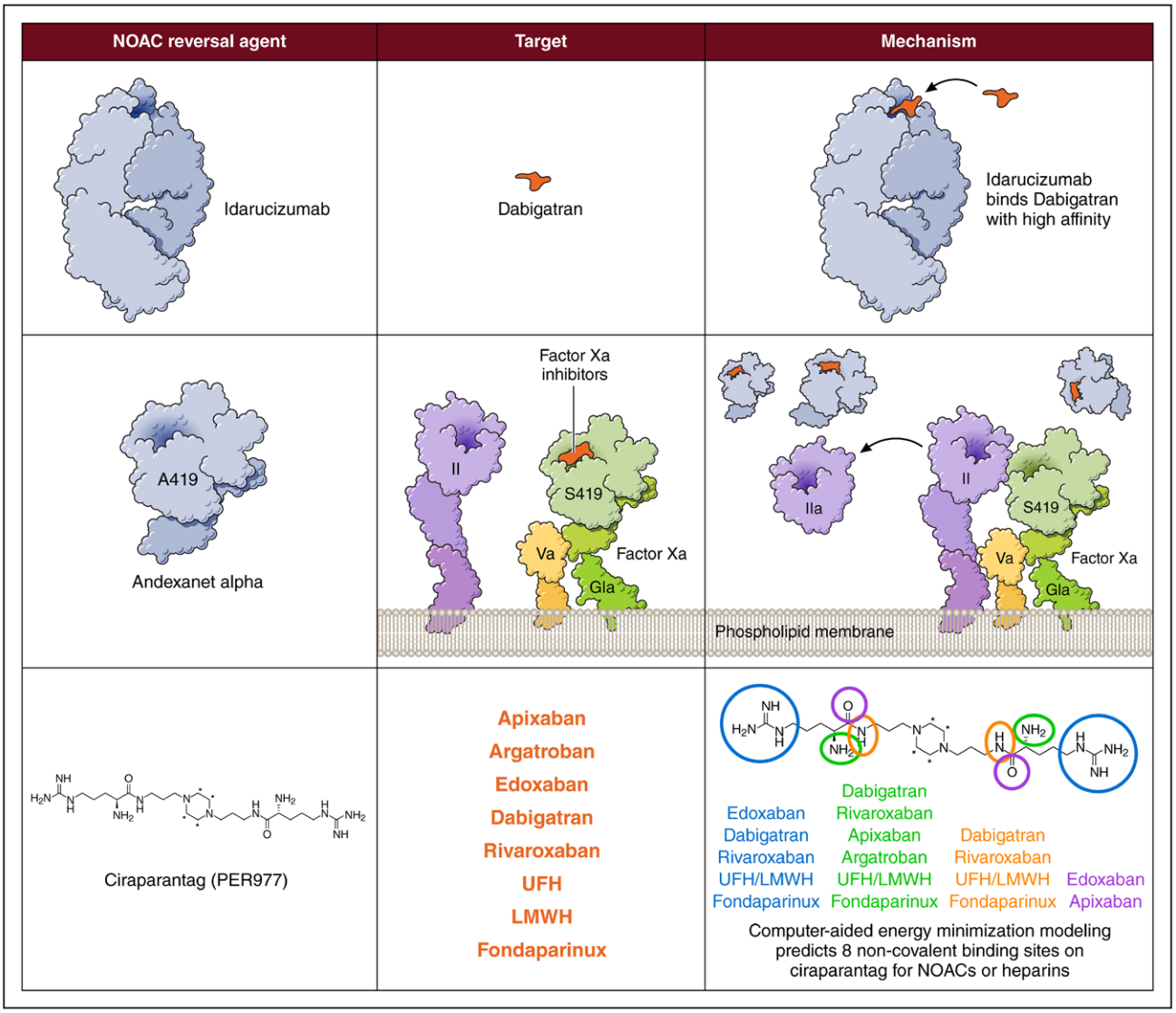

Figure 1. Specific NOAC reversal agents.
Dabigatran binds with high affinity to the fragment antigen-binding (Fab) cavity of idarucizumab which prevents dabigatran from binding to factor IIa (thrombin). Andexanet alpha is a modified human recombinant factor Xa decoy that binds the direct factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. Andexanet alpha is catalytically inactive because of the replacement of active-site serine (S419) with alanine (A419) and the deletion of the γ-carboxyglutamic acid–rich (GLA) membrane-binding domain, which eliminates the ability to assemble the prothrombinase complex comprising factor Xa and factor Va. The factor Xa inhibitors are thereby sequestered within the vascular space allowing the restoration of endogenous factor Xa activity and thrombin generation. Ciraparantag is a small synthetic water-soluble molecule that binds to a wide range of anticoagulants through noncovalent hydrogen bonding and charge-charge interactions preventing the anticoagulants from binding to their endogenous targets. II indicates factor II; IIa, activated factor II (thrombin); Va, activated factor V; antagonist GLA, γ-carboxyglutamic acid-rich; factor Xa, activated factor X; LMWH, low-molecular-weight heparin; NOAC, non–vitamin K antagonist oral anticoagulant; and UFH, unfractionated heparin.

Table 1. Comparison of Specific NOAC Reversal Agents

	Idarucizumab	Andexanet alfa	Ciraparantag
Alternate names	aDabi-Fab, BI655075	PRT064445	Aripazine, PER977
Company	Boehringer Ingelheim	Portola Pharmaceuticals	Perosphere Inc.
Chemical structure	Humanized monoclonal antibody fragment	Recombinant truncated human factor Xa variant (decoy)	Synthetic water-soluble cationic small molecule consisting of 2 L-arginine units connected with a piperazine-containing linker chain
Molecular mass	47 766 Da	39 000 Da	512 Da
Binding	Noncompetitive binding to dabigatran	Competitive binding to direct factor Xa inhibitors or to indirect factor Xa inhibitor–activated antithrombin	Covalent hydrogen bonding
Target affinity	≈350× greater affinity for dabigatran than factor IIa	Affinity for direct factor Xa inhibitors similar to that of native factor Xa	Not reported
Onset	<5 min	2 min	5–10 min
Half-life	Initial: 47 min	Terminal: ≈6 h	Duration of action 24 h
	Terminal: 10.3 h		
Elimination	Kidney (protein catabolism)	Not reported	Not reported
Anticoagulant(s) reversed	Dabigatran	Direct and indirect factor Xa inhibitors*	Dabigatran
			Argatroban
			Low-molecular-weight heparins
			Unfractionated heparin
			Oral and parenteral factor Xa inhibitors
Route and dose in clinical studies	5 g administered as 2 doses of 2.5 g IV over 5–10 min, 15 min apart (repeat dosing can be considered if recurrent bleeding or require second emergent procedure if elevated coagulation parameters)	400–800 mg intravenous bolus (30 mg/min) followed by infusion of 4–8 mg/min†	100–300 mg intravenous bolus
Storage	Refrigerated	Refrigerated	Room temperature

NOAC indicates non-vitamin K oral anticoagulant.

*For the indirect factor Xa inhibitors, andexanet alfa likely to completely reverse fondaparinux, which only inhibits factor Xa, but not low-molecular-weight heparins that also inhibit factor IIa.

†Lower dose to reverse apixaban, higher dose to reverse rivaroxaban.

patients also have elevated dabigatran concentrations because this agent is also predominantly renally cleared.

In preclinical studies, idarucizumab reduced blood loss in animal models in a dose-dependent fashion.[66–68] In phase I and II clinical trials, idarucizumab reversed the anticoagulant effect (activated partial thromboplastin time, thrombin time, dTT, ecarin clotting time , and activated clotting time) in a dose-dependent manner in both young and older healthy volunteers, and in individuals with mild to moderate renal impairment, as well.[64,69,70] Idarucizumab was well tolerated without any thrombotic or other serious side effects. In addition, idarucizumab administered without dabigatran had no effect on coagulation parameters or endogenous thrombin generation.[64]

The RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) study is an ongoing phase 3, global, prospective, cohort study (http://www.clinicaltrials.gov. Unique identifier: NCT02104947) investigating the safety and efficacy of 5 g idarucizumab (administered as 2 rapid 2.5 g intravenous boluses) in dabigatran-treated patients who present with uncontrolled or life-threatening bleeding (group A) or nonbleeding patients who require emergent surgery or intervention (group B). There is planned enrollment of ≈500 patients to be completed in 2016.[63] The primary end point is maximum percentage reversal of the anticoagulant effect of dabigatran within

4 hours of completion of the idarucizumab infusions on the basis of central laboratory measurement of the dTT or ecarin clotting time. Key secondary end points include time to cessation of bleeding in group A, and assessment of hemostasis during interventions in group B.

An interim analysis of the first 90 patients in RE-VERSE AD (51 in group A and 39 in group B) has been reported.[71] Overall, 22 (24%) and 9 (10%) patients had normal coagulation tests at baseline as assessed by dTT or ecarin clotting time, respectively (assays performed at a central laboratory later). Idarucizumab rapidly (within minutes) normalized the coagulation assays in 88% (ecarin clotting time) to 98% (dTT) of patients who had elevated levels at baseline (Figure 2). By 24 hours, 79% of patients had plasma concentrations of active dabigatran that were <20 ng/mL, a level that produces little or no anticoagulant activity.

In group A patients with severe bleeding, the investigator reported the median time to cessation of bleeding

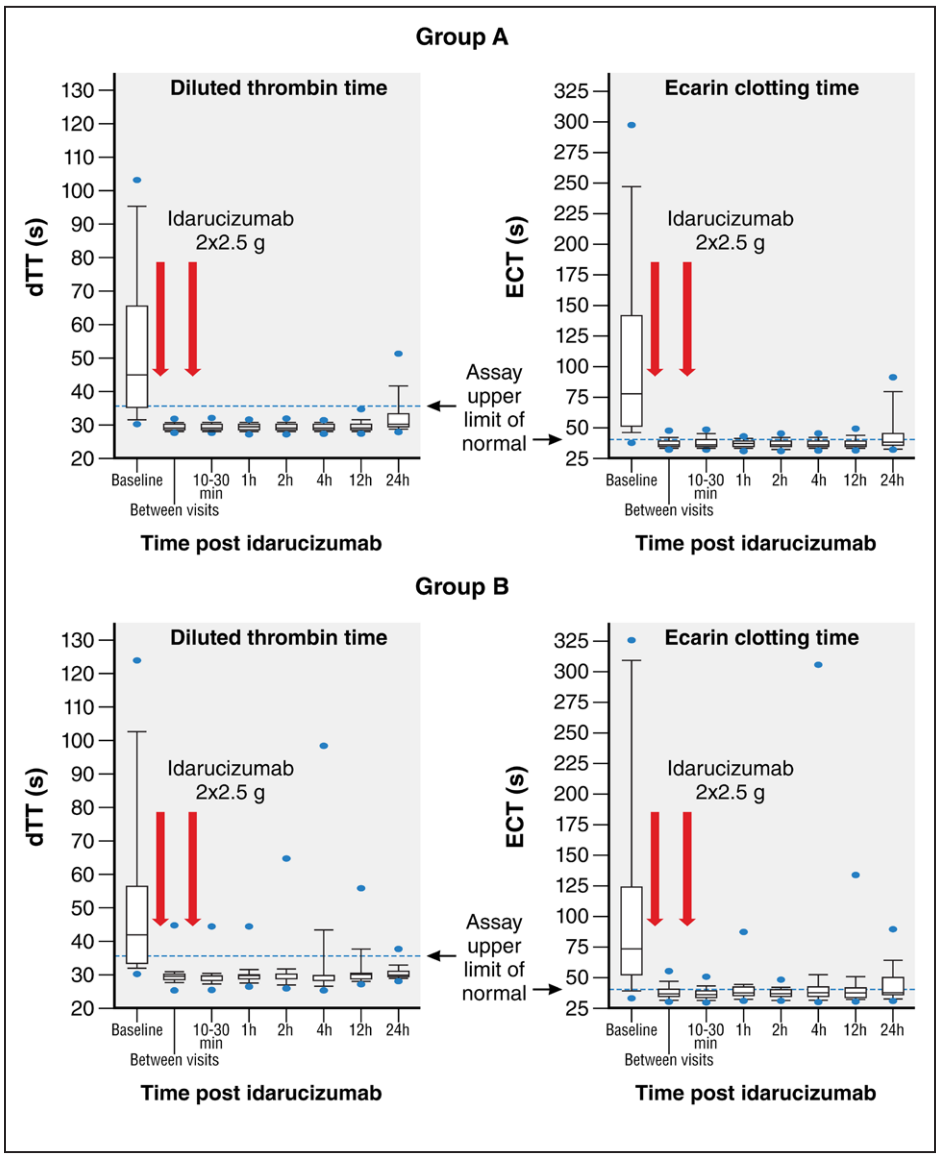

Figure 2. RE-VERSE AD: reversal of dabigatran with idarucizumab.
Time course of the dilute thrombin time and ecarin clotting time before and after the administration of idarucizumab: The analyses included 51 patients who had serious bleeding (group A) and 39 who required urgent surgery or intervention (group B). Idarucizumab was administered in 2 infusions. Blood samples were obtained at baseline, after the first infusion, at 10 to 30 minutes after the administration of the second infusion, and at 1, 2, 4, 12, and 24 hours. Data are presented as box-and-whisker plots, in which the top and bottom of the rectangles indicate the 75th and 25th percentiles, respectively; the horizontal lines within the rectangles indicate the 50th percentile; the lines above and below the rectangles indicate the 90th and 10th percentiles, respectively; and the dots above and below the lines indicate the 95th and 5th percentiles, respectively. The dashed lines indicate the upper limit of the normal range for the tests. dTT indicates dilute thrombin time; and ECT, ecarin clotting time. Adapted from Pollack et al[71] with permission of the publisher. Copyright © 2015, Massachusetts Medical Society.

was 11.4 hours, although assessment was not possible in 13 of the 51 patients because of inaccessibility of bleeding sites. In group B, normal intraoperative hemostasis was achieved in 92% of the 36 patients who underwent procedures after receiving dabigatran. There were 5 thrombotic events but only 1 within 72 hours of administration of idarucizumab, supporting the interpretation that these events were not secondary to an increased thrombotic state postreversal. The mortality rate was 20% (18 deaths, 9 in each group) over approximately 3 months follow-up, and all deaths appeared to be associated with preexisting medical conditions. The majority of deaths (n=10) were attributable to vascular causes.

In October 2015, the FDA granted accelerated approval to idarucizumab for use in patients who are taking dabigatran during emergency situations when there is a need to reverse the anticoagulant effects of dabigatran. This approval was based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers. Idarucizumab also received approval from the European Medicines Agency in November 2015. More widespread approval and availability is expected through 2016.

Andexanet Alfa

Andexanet alfa (andexanet) is a specific reversal agent for direct (apixaban, rivaroxaban, and edoxaban) and indirect (low-molecular-weight heparins and fondaparinux) FXa inhibitors that act through antithrombin. It is a modified human recombinant FXa decoy protein that is catalytically inactive because of replacement of an active-site serine with alanine and with deletion of the membrane-binding domain, which eliminates the ability to assemble the prothrombinase complex (Figure 1, Table 1). Andexanet retains the ability to bind to NOACs with high affinity and a 1:1 stoichiometric ratio.[72,73] By sequestering FXa inhibitors within the vascular space, endogenous FXa activity is restored as evidenced by the increase in thrombin generation and the reduction in anti-FXa activity.[73]

Andexanet corrected abnormal anti-FXa activity in vitro attributable to rivaroxaban, apixaban, edoxaban, and betrixaban[73,74] and corrected coagulation assays, reduced blood loss, and restored hemostasis in animal bleeding models.[75–77] In phase 2 studies, andexanet demonstrated rapid, dose-dependent reversal of anticoagulant effects (anti-FXa activity, unbound FXa concentrations, restoration of thrombin potential) in healthy volunteers administered apixaban, rivaroxaban, or enoxaparin.[74,78–80] Because of its pharmacodynamic half-life of 1-hour, andexanet was administered as a bolus followed by an infusion with anti-FXa activity returning to placebo levels within 2 hours of the end of infusion. There were no thrombotic or other adverse events reported and no antibodies to FX or FXa were observed. However, andexanet administration has been associated with transient increases in prothrombin fragments 1.2, D-dimer, and thrombin-antithrombin levels, the latter mediated by binding of andexanet to tissue factor pathway inhibitor, an endogenous inhibitor of factor Xa, forming a nonproductive complex.[80]

Based on these preliminary findings, 2 parallel randomized, double-blind, placebo-controlled trials (ANNEXA [Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors trials]) were performed in healthy older volunteers 50 to 75 years of age pretreated with apixaban (ANNEXA-A, http://www.clinicaltrials.gov. Unique identifier: NCT02207725) and rivaroxaban (ANNEXA-R, http://www.clinicaltrials.gov. Unique identifier: NCT02220725).[72] A total 145 participants were randomly assigned in a 3:1 ratio in ANNEXA-A (48 andexanet, 17 placebo) and 2:1 in ANNEXA-R (53 andexanet, 27 placebo). Each trial was performed with a part 1 in which andexanet was given as an intravenous bolus followed by a part 2 with an intravenous bolus followed by a continuous 120-minute infusion. Based on the phase 2 studies that demonstrated different stoichiometric requirements for different NOACs, a higher dose of andexanet was used for rivaroxaban than for apixaban because of higher plasma concentrations and a larger volume of distribution. For ANNEXA-A with apixaban, andexanet was given as a 400-mg intravenous bolus (30 mg/min) in part 1 and an 400-mg bolus followed by a continuous infusion of 4 mg/min for 120 minutes (480 mg total) in part 2. For ANNEXA-R with rivaroxaban, andexanet was given as an 800-mg bolus in part 1 and an 800-mg bolus followed by a continuous infusion of 8 mg/min for 120 minutes (960 mg total) in part 2. The primary end point for both studies was the percent change in anti-FXa activity from baseline to nadir.

Anti-FXa activity was rapidly (within 2–5 minutes) reduced by 92% to 94% with andexanet bolus in comparison with 18% to 21% for placebo ($P<0.001$for both studies; Figure 3). The reversal of anti-FXa activity persisted for 2 hours after completion of the bolus, although increases were detected within 15 minutes. The reversal was sustained when andexanet was administered as a bolus plus an infusion. Thrombin generation was also rapidly and fully restored in 96% to 100% of participants who received andexanet in comparison with 7% to 11% who received placebo ($P<0.001$ for both studies). Similar decreases were observed for unbound plasma concentrations of apixaban and rivaroxaban. No thrombotic or serious adverse events were reported, and there were no neutralizing antibodies against andexanet or antibodies to FX or FXa detected. However, transient increases in levels of D-dimer and prothrombin fragments 1.2 were observed in a subgroup of participants. The clinical significance of these transient elevations is uncertain.

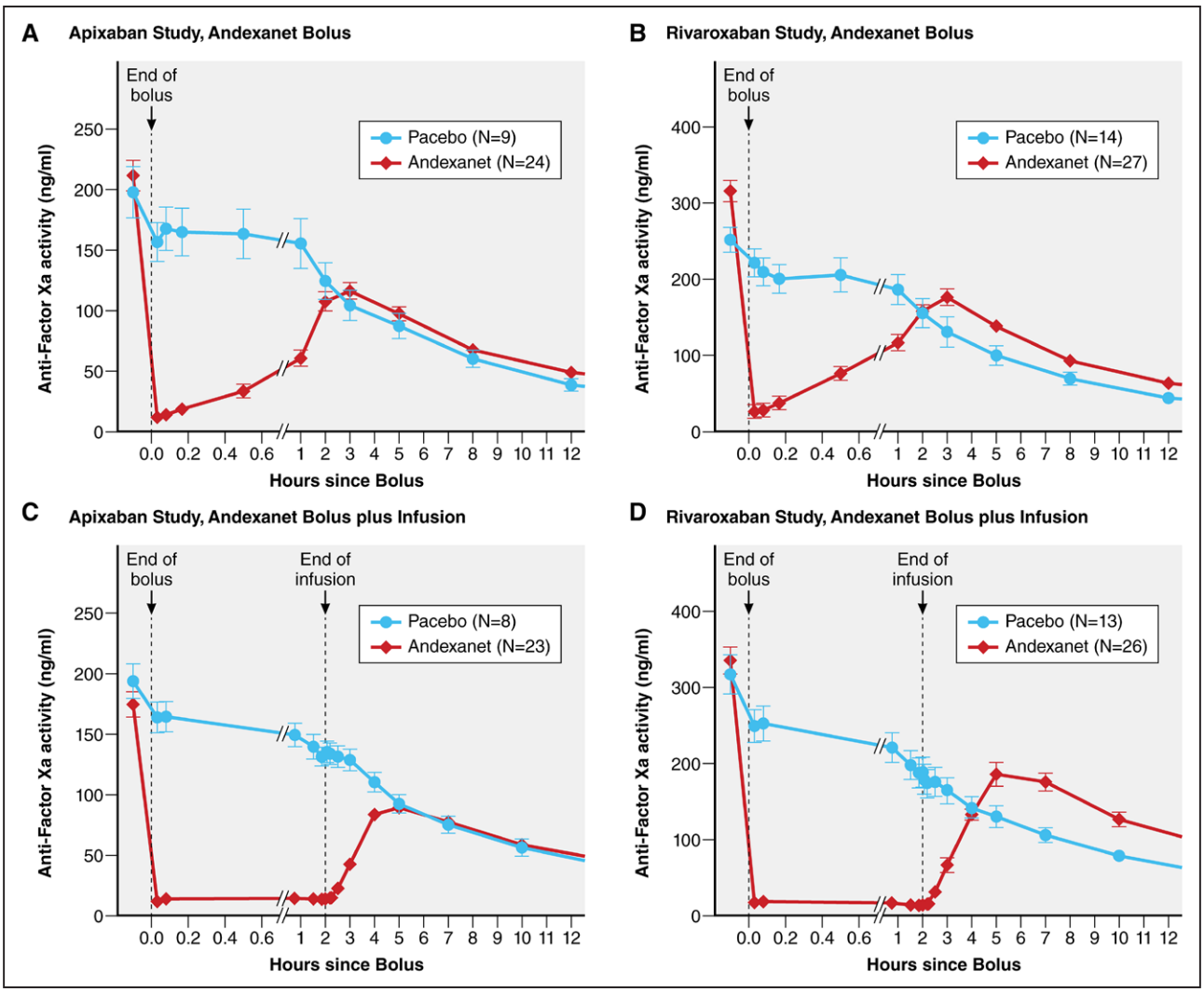

Figure 3. ANNEXA-A and -R: reversal of factor Xa inhibitors with andexanet.
Time courses of anti–factor Xa activity before and after administration of andexanet. Anti–factor Xa activity among persons who had received anticoagulation treatment with apixaban or rivaroxaban was measured before and after the administration of andexanet or placebo on study day 4. Dashed lines indicate the end of administration of the bolus or infusion. **A**, Data from participants in the apixaban study (ANNEXA-A) who received andexanet, as a 400-mg intravenous bolus, or placebo. **B**, Participants in the rivaroxaban study (ANNEXA-R) who received andexanet, as an 800-mg intravenous bolus, or placebo. **C**, Participants in the apixaban study who received andexanet, as a 400-mg intravenous bolus plus a 4-mg-per-minute infusion for 120 minutes, or placebo. **D**, Participants in the rivaroxaban study who received andexanet, as an 800-mg intravenous bolus plus an 8-mg-per-minute infusion for 120 minutes, or placebo. Different scales along the x axis in each graph are used to enable visualization of the immediate, short-term dynamics as well as the longer-term dynamics of anti–factor Xa activity after andexanet treatment. The points on the graph represent the mean anti–factor Xa activity level, and I bars indicate the standard error. There was a significant difference ($P<0.05$) in the percent change in anti–factor Xa activity (relative to the prebolus activity level) between andexanet and placebo until 2 hours after administration of the bolus or infusion. Adapted from Siegal et al[72] with permission of the publisher. Copyright © 2015, Massachusetts Medical Society.

The ongoing ANNEXA-4 phase 3b to 4 study (http://www.clinicaltrials.gov, NCT02329327) is evaluating the efficacy and safety of andexanet in patients taking FXa inhibitors with acute major bleeding. Unlike RE-VERSE AD, this study does not include patients without bleeding but who require emergency or urgent procedures. Whether this will impact the potential approved indications for andexanet remains to be determined. Andexanet has been granted breakthrough therapy designation by the FDA, in which expedited review is provided for therapies to treat serious or life-threatening conditions, often based on preliminary clinical evidence demonstrating substantial improvement over other therapies/existing care. The Prescription Drug User Fee Act date for andexanet is August 17, 2016, which is the target date for the FDA to complete its review and take action on the application.

Ciraparantag (PER977)

Ciraparantag is a small synthetic water-soluble molecule developed as a reversal agent for unfractionated heparin, low-molecular-weight heparins, fondaparinux, and the oral direct Xa and IIa inhibitors (Figure 1, Table 1). It binds to targets through noncovalent hydrogen bonding and charge-charge interactions, thereby preventing the anticoagulants from binding to their endogenous targets.[81] Ciraparantag is earlier in it development program than other specific reversal agents. It was granted the fast track designation by the FDA, a status that facilitates the development and expedites the review of drugs intended to treat serious or life-threatening conditions and demonstrates potential to address unmet clinical needs.

Ciraparantag reduced blood loss by >90% in an animal bleeding model in the setting of high doses of NOACs and restored global coagulation tests to baseline in 20 minutes.[81–83] When added to whole blood spiked with rivaroxaban or apixaban from healthy human volunteers, ciraparantag reversed anti-FXa activity in a dose-dependent fashion.[82]

In a phase 1 dose-ranging study in healthy volunteers (n=80) administered a single dose of edoxaban 60 mg, ciraparantag decreased whole-blood clotting times to within 10% of baseline values within 10 minutes with single intravenous doses of 100 to 300 mg.[84] Reversal was sustained for 24 hours. Clot formation was restored as assessed by scanning electron micrograph measurement of mean fibrin-fiber diameter. No procoagulant effects or adverse events were reported. An additional study investigating reinitiation of anticoagulation with edoxaban and second reversal with ciraparantag is ongoing (http://www.clinicaltrials.gov. Unique identifier: NCT02207257). Validation studies of whole-blood clotting time as a global test of coagulation that can be used to monitor the effects of ciraparantag have been completed and submitted to the FDA (Sasha H. Bakhru, PhD, Perosphere, Inc., Danbury CT, personal communication, 2016). Additional validation for an automated point-of-care coagulometer is underway.

CLINICAL PERSPECTIVE

The availability of NOACs for the treatment and prevention of thromboembolism has transformed the landscape in the management of patients with AF and venous thromboembolism. Although NOACs are as effective as, if not more effective than warfarin for the treatment and prevention of thromboembolism, the major advance in the care of patients is their improved safety profile with respect to serious bleeding, particularly intracranial hemorrhage, and reduction in mortality in patients with AF. Importantly, the dramatic reductions observed in fatal and life-threatening bleeding that have been observed repeatedly in clinical trials and patient registries have all occurred without the availability of any specific reversal agents or antidotes for the NOACs, whereas we have been able to reverse warfarin with vitamin K and replacement of coagulation factors (FFP or PCC). This underscores that the best way to manage bleeding is to prevent serious bleeding from occurring, and the safety advantage of the NOACs in comparison with warfarin is an important advance regardless of the availability of specific reversal agents.

Although severe and life-threatening bleeding is uncommon with warfarin and even rarer with NOACs, it does occur, and the perceived lack of the ability to reverse the anticoagulant effects of NOACs is a concern for many patients and physicians, which has tempered widespread adoption of these agents.[85] We now have an opportunity to recalibrate our approach to NOAC therapy and specifically the management of bleeding with the availability of the first specific reversal agent idarucizumab for dabigatran, the potential approval of andexanet for reversal of FXa inhibitors, and the continued development of the universal inhibitor ciraparantag. These agents offer an important medical advance because they are remarkably effective at rapidly reversing the anticoagulant effects of NOACs without prothrombotic side effects, although further evaluation is needed to confirm the latter.

An important question to ask is what is, or rather, what should be the impact of the reversal agents for the NOACs? Because serious bleeding is uncommon, the biggest impact will likely be reassurance that a treatment option is available if rapid reversal of a NOAC is desired clinically. With regard to their actual clinical impact in patients taking NOACs who present with bleeding, it will be important to emphasize that specific reversal agents should be used sparingly because the vast majority of bleeds can be managed conservatively with temporary discontinuation of NOACs and supportive measures; time is the only antidote required in most cases. It is helpful to have a general framework or action plan to manage NOAC-related bleeding and reversal (Table 2).[20,21,61,85] Local institution management pathways and protocols must be developed to ensure that only appropriate patients with serious or life-threatening bleeding receive the specific reversal agents. Some examples of situations that would qualify as serious or life-threatening bleeding include bleeding causing hemodynamic compromise, intracranial hemorrhage, bleeding into a critical organ or closed space, persistent bleeding despite general supportive measures and local hemostatic support, or risk of recurrent bleeding attributable to excess NOAC drug exposure because of the delayed clearance of NOAC (eg, acute renal failure) or overdose.

In a patient with serious bleeding, however, specific reversal agents (if available) should be used instead of general hemostatic agents because the nonspecific agents are less effective in reversing coagulation abnormalities,

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Table 2. Management of NOAC-Related Bleeding

	Mild	Moderate	Severe/Life Threatening*	
			Dabigatran	FXa Inhibitors
Supportive measures				
Delay or discontinue NOAC	X	X	X	X
Discontinue (or reverse) other antithrombotics	X	X	X	X
Decrease absorption-activated charcoal if last dose 2–4 h		X	X	X
Maintain diuresis/volume support (fluids)		X	X	X
Mechanical compression/intervention to establish hemostasis		X	X	X
Transfusion: PRBCs, FFP (as plasma expander), platelets		X	X	X
Dialysis			X†	
Nonspecific hemostatic agents				
PCC > aPCC > rFVIIa				X‡
Specific reversal agents				
Indarucizumab			X	
Andexanet alfa				If approved
Ciraparantag			If approved	If approved

aPCC indicates activated prothrombin complex concentrate; FFP, fresh-frozen plasma; FXa, activated Factor X; NOAC, non–vitamin K oral anticoagulant; PCC, prothrombin complex concentrate; PRBCs, packed red blood cells; and rFVIIa, recombinant activated factor VII.

*Includes bleeding causing hemodynamic compromise, intracranial hemorrhage, bleeding into a critical organ or closed space, persistent bleeding despite general supportive measures and local hemostatic support, risk of recurrent bleeding because excess NOAC drug exposure attributable to delayed clearance of NOAC (acute renal failure) or overdose.

†Only consider in patients on dabigatran with renal failure if specific reversal agent not available.

‡Specific reversal agents preferred if approved.

have not been shown to improve outcomes, and are potentially prothrombotic. Although coagulation testing will identify those patients with therapeutic levels of anticoagulation who will likely benefit from specific reversal agents, and will help physicians to monitor the response to reversal, it is reasonable to administer specific reversal agents immediately without waiting for a laboratory test confirming therapeutic levels of anticoagulation in patients who present with life-threatening bleeding who are presumed to be on a NOAC.

Whether the specific reversal agents improve outcomes in bleeding patients still needs to be determined. It should be acknowledged that it may be difficult to prove such a clinical benefit. Patients with serious bleeding often have an anatomic cause for the bleeding because of a compromise in vascular integrity. Although the presence of an anticoagulant may exacerbate the problem, reversing a laboratory coagulation parameter will not address the primary sources of bleeding. Whether removing the contribution of the anticoagulant will modify the clinical course in patients who present with serious bleeding remains to be seen. The fact that the mortality rate in REVERSE AD interim analysis was 20% at 3 months, with more than half of the deaths occurring within the first 4 days,[63] underscores that such patients have a poor prognosis regardless of how they are managed.

Although the use of specific reversal agents in patients taking NOACs who present with serious bleeding fulfills an unmet need, the clinical impact of these agents will likely be greater in the management of patients who are not bleeding but require emergency or urgent procedures (Figure 4).[20,21,61] Unlike for patients presenting with life-threatening NOAC-related bleeding where immediate reversal can be initiated without waiting for a laboratory test confirming therapeutic levels of anticoagulation, it will be important to have such confirmation in nonbleeding patients requiring emergency or urgent invasive procedures. As noted, up to a quarter of patients in REVERSE AD had normal coagulation testing at baseline. Progress in this area will require further validation and implementation of coagulation tests specific for NOACs that provide results rapidly to clinicians. Patients having elective procedures should not be routinely administered specific reversal agents because the intervention can be safely performed in most cases 24 to 48 hours after the last dose of the NOAC depending on renal function and bleeding risk of surgery.

Although not the focus of this review, the logistics, storage, and cost of the reversal agents are important considerations for institutions as they develop protocols. Although these agents will likely be stored in the pharmacy, having them also directly available

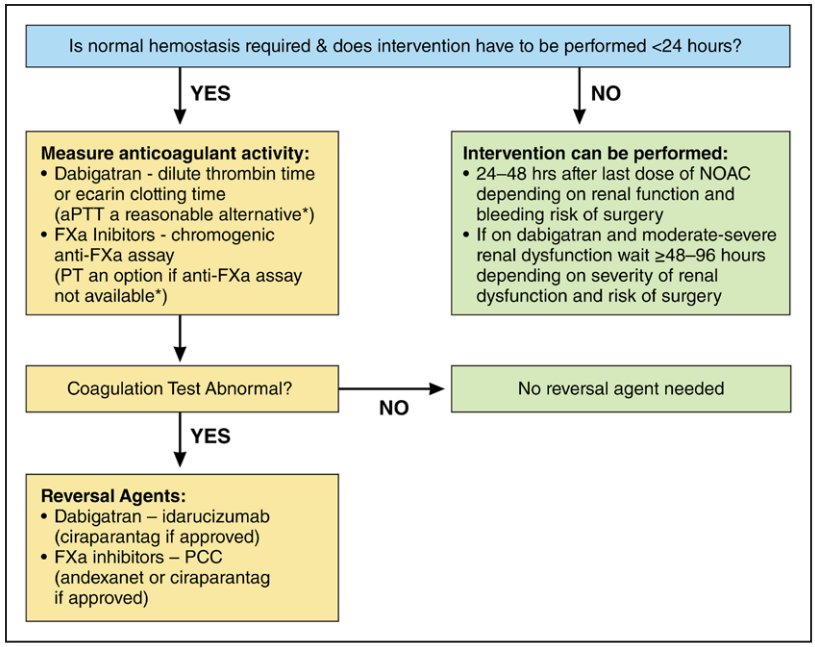

Figure 4. Management of NOAC-treated patients who require invasive procedures.
*A prolonged activated partial thromboplastin time (aPTT) indicates an anticoagulant effect of dabigatran, and a prolonged prothrombin time (PT) indicates an anticoagulant effect of the FXa inhibitors. However, the clinical utility of these common tests is limited because a normal aPTT or PT does not exclude clinically relevant plasma levels of dabigatran and FXa inhibitors, respectively. In particular, there is considerable variability in the sensitivity of the PT across the FXa inhibitors, and this test is less sensitive to apixaban than rivaroxaban and edoxaban. aPTT indicates activated partial thromboplastin time; FXa, activated Factor X; NOAC, non–vitamin K antagonist oral anticoagulants; PCC, prothrombin complex concentrate; and PT, prothrombin time.

for use in the emergency departments to treat life-threatening bleeding events may save critical time. Both andexanet and idarucizumab require refrigeration but ciraparantag is stored at room temperature. In its current formulation, andexanet also requires mixing before administration. The cost of idarucizumab is ≈$3500. The costs of andexanet (and ciraparantag) are unknown. At our institution, the cost of 4-factor PCC (Kcentra 500 U) is ≈$780 (John Fanikos, RPh, MBS, personnel communication, 2016), thus 50 U/kg PCC to reverse anticoagulation in a 70-kg person would cost $5460.

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FOOTNOTES

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