Reversal of the novel oral anticoagulants dabigatran, rivoraxaban, and apixaban

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Purpose of review
We summarize the available data related to reversing the anticoagulant effect of the oral direct thrombin and factor Xa inhibitors and provide our opinion on treating patients presenting with severe and life-threatening hemorrhage related to these agents.

Recent findings
No specific antidotes are currently available for the oral direct thrombin and factor Xa inhibitors but two promising agents are under investigation in phase 3 trials. No data are available on reversing these agents in bleeding patients. Activated charcoal may be effective in reducing factor Xa inhibitor absorption up to 6 h after ingestion. Animal models suggest that unactivated 4-factor prothrombin complex concentrate may be an effective reversal agent. Recent data in warfarin-treated patients suggest that 4-factor prothrombin complex concentrate may provide more rapid and effective hemostasis than fresh frozen plasma.

Summary
In the absence of evidence in bleeding patients, animal models and ex-vivo studies suggest administration of coagulant factors in the form of hemostatic agents may be of benefit in reversing the effect of direct thrombin and factor Xa inhibitors. Specific reversal agents and clinical data in patients with hemorrhage remain an unmet need.

Keywords
direct factor Xa inhibitors, direct thrombin inhibitor, hemorrhage, hemostasis, intracerebral hemorrhage

INTRODUCTION

Since the introduction of warfarin in the United States in 1954, vitamin K antagonists (VKAs) have been the dominant option for therapeutic anticoagulation. By blocking the regeneration of vitamin K epoxide, the VKAs lead to depletion of procoagulant factors II, VII, IX, and X, reducing thrombus formation. Although the VKAs are effective in reducing mortality and morbidity from thrombotic events, they have a number of limitations: a narrow therapeutic window requires individualized dosing and frequent monitoring, several days are required for therapeutic initiation or discontinuation, and there are many drug and food interactions. The most dreaded complication of VKA use is spontaneous intracerebral hemorrhage (ICH). Although nonwarfarin-associated ICH has demonstrated a steady improvement in mortality – likely from improved systems of care and greater availability of neurologic intensive care – the in-hospital mortality of warfarin-associated ICH has remained stable at 40% [1].

The introduction of the novel oral anticoagulants (NOACs) – first the direct thrombin inhibitor dabigatran and then direct factor Xa inhibitors (rivaroxaban and apixaban) – addressed several of the limitations of VKAs. The NOACs have standardized dosing, do not require laboratory monitoring, have limited drug and food interactions, and have lower rates of ICH compared with warfarin [2–4]. However, although VKAs have well accepted and studied reversal strategies [5,6▪▪], there are currently no specific reversal agents available for NOAC-related hemorrhage and the optimal reversal strategy remains unclear. This uncertainty may be responsible for hesitancy in initiating NOACs. In this article, we provide an overview of the NOACs, review the limited evidence concerning NOAC reversal strategies, and describe our approach to

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KEY POINTS

- The oral direct thrombin and factor Xa inhibitors have many benefits over VKAs for anticoagulation including lower risk of life-threatening hemorrhage.
- There are currently no specific antidotes for the direct thrombin or factor Xa inhibitors.
- Rapidly attempting anticoagulant reversal is of utmost importance in treating life-threatening anticoagulant-related hemorrhage.
- Activated and unactivated 4-factor prothrombin complex concentrates are the preferred first-line agents for anticoagulant reversal but unactivated 3-factor concentrates and FFP are reasonable alternatives and preferable to delaying the initiation of anticoagulant reversal.

reversing the anticoagulant effects of NOACs. We also provide our opinion regarding alternative, though less preferred, reversal agents.

DABIGATRAN

Dabigatran is a direct thrombin inhibitor administered as the prodrug dabigatran etexilate (Pradaxa; Boehringer Ingelheim, Ingelheim am Rhein, Germany). After activation by plasma and hepatic esterases, dabigatran reversibly inhibits both free and fibrin-bound thrombin (activated factor II) that reduces coagulation and platelet aggregation by preventing cleavage of fibrinogen to fibrin; reducing activation of amplification phase factors V, VIII, XI, and XIII; and reducing thrombin-induced platelet aggregation. In the United States, dabigatran is approved for the treatment and secondary prevention of deep venous thrombosis and pulmonary embolism and prevention of embolic events in patients with nonvalvular atrial fibrillation. In dabigatran's landmark trial, the 150 mg twice-daily dose was superior to warfarin in preventing ischemic stroke and systemic embolization [relative risk, 0.66; 95% confidence interval (CI), 0.53–0.82; $P < 0.001$] in patients with nonvalvular atrial fibrillation while lowering rates of life-threatening bleeding and ICH [2].

Although routine coagulation studies are not necessary with dabigatran or the other NOACs, certain laboratory tests can help the physician assess the presence of a dabigatran effect. The Hemoclot Thrombin Inhibitor assay (Hyphen BioMed, Neuville-Sur-Oise, France) and the Ecarin clotting time (ECT) assay are two options for quantitative assessment of dabigatran plasma activity [7]. Thrombin time (TT) is very sensitive to the presence of dabigatran with a linear dose–response curve in the therapeutic range that becomes more variable at supratherapeutic levels [7]. Activated partial thromboplastin time (aPTT) is elevated in the presence of dabigatran but lacks the linear dose–response seen in TT, particularly at higher plasma levels, and becomes less sensitive as the patient approaches 12 h from the last dose [7]. Prothombin time (PT) and international normalized ratio are minimally affected by dabigatran [7]. Although the Hemoclot and ECT assays may provide the most accurate assessment of dabigatran effect, these assays are of limited use in clinical practice because of limited availability. For the clinician treating the bleeding patient, a yes/no qualitative assessment of dabigatran activity using assays with wider availability is likely to be more helpful, in which case an elevated TT suggests active dabigatran effect and an elevated aPTT suggests recent (approximately last 12 h) drug administration.

RIVAROXABAN AND APIXABAN

Rivaroxaban (Xarelto; Janssen Pharmaceuticals, Beerse, Belgium) and Apixaban (Eliquis; Pfizer and BristolMeyers Squibb, New York, USA) are the two oral direct factor Xa inhibitors available in the United States. Edoxaban (Lixiana; Daiichi Sankyo, Tokyo, Japan) belongs to this class but is not available in the United States. These drugs reversibly inhibit the role of factor Xa in the formation of functional prothrombinase complexes and effectively reduce the conversion of prothrombin to thrombin with resulting reduced conversion of fibrinogen to fibrin and reduced platelet activation. In the United States, rivaroxaban and apixaban are approved for treatment and secondary prevention of deep venous thrombosis and pulmonary embolism, prevention of embolic events in patients with nonvalvular atrial fibrillation, and thromboprophylaxis after knee or hip replacement surgery. In the Rivaroxaban Once-daily oral factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation trial, rivaroxaban was equivalent to warfarin for prevention of ischemic stroke and systemic embolism in nonvalvular atrial fibrillation with equivalent clinically relevant bleeding but lower rates of ICH (hazard ratio, 0.67; 95% CI, 0.47–0.93; $P = 0.02$) [3]. In its landmark trial, apixaban was found to be superior to warfarin for the prevention of ischemic stroke and systemic embolization in nonvalvular atrial fibrillation (hazard ratio, 0.79; 95% CI, 0.66–0.95; $P = 0.01$ for superiority) with lower rates of major bleeding and reduced ICH (hazard ratio for

ICH, 0.51; 95% CI, 0.35–0.75; $P < 0.001$) [4]. Apixaban is unique among the NOACs in that it had equivalent gastrointestinal bleeding risk compared with warfarin. Rivaroxaban and dabigatran demonstrated higher rates of gastrointestinal bleeding than warfarin in their respective trials.

The factor Xa inhibitors have no effect on TT and little effect on aPTT. Chromogenic anti-Xa assays with specialized calibrations are able to accurately quantify the plasma levels of both rivaroxaban and apixaban over their therapeutic ranges; however, this assay is of limited clinical use in the acutely bleeding patient because the turnaround time can be prohibitively long [8▪]. Rivaroxaban prolongs the PT in a linear dose–response manner over the therapeutic range of the drug but only qualitative assessment is possible at supratherapeutic drug concentrations. Quantification of therapeutically dosed rivaroxaban using PT requires standardization at individual laboratories because, while the relationship remains linear, the numeric results vary depending on the batch of thromboplastin reagent [8▪]. Apixaban has little effect on the PT at approved doses. A modified PT assay using diluted thromboplastin agent correlates well with apixaban plasma levels but unfortunately the assay is not widely available in practice [8▪]. Therefore, acute qualitative assessment of factor Xa inhibitor presence is only practical and widely available for rivaroxaban.

PHARMACOKINETICS OF THE NOVEL ORAL ANTICOAGULANTS

Knowledge of NOAC pharmacokinetics may help the clinician tailor treatment to individual patients. Table 1 summarizes key pharmacokinetic data for each of the NOACs and warfarin. After addressing hemodynamic stability, the first consideration in the treatment of NOAC-associated hemorrhage is stopping the agent and preventing further drug absorption. Because the NOACs are rapidly absorbed following administration, activated charcoal can be considered for overdose or hemorrhage if administered shortly after drug consumption. In healthy subjects taking a single dose of apixaban, the area under the plasma concentration–time curve decreased by 50 and 28%, respectively, when activated charcoal followed apixaban by 2 and 6 h [9].

An important pharmacokinetic consideration when faced with possible NOAC-associated hemorrhage is determining if an anticoagulant effect is likely present. As discussed previously, TT, aPTT, and PT may be useful qualitative measures depending on the NOAC but knowledge of drug elimination and half-life can also be helpful. In patients with normal renal function, the effect of NOAC administration would be expected to completely resolve by four to five drug half-lives or approximately 48 h after the last dose. Because the NOACs depend on renal excretion (apixaban to a lesser extent), however, individuals with chronic or acutely acquired renal insufficiency will experience more prolonged therapeutic effects after the last NOAC dose. On the basis of the available half-life data, patients with creatinine clearance less than 50 ml/min undergoing surgery with high bleeding risk are currently advised to stop NOAC therapy at least 4 days prior to surgery [10]. As an extension of this recommendation, we consider those presenting with significant renal insufficiency and acute hemorrhage to be at risk for a NOAC effect if the last dose was within the prior 96 h.

Table 1. Pharmacokinetic properties of the novel oral anticoagulants and warfarin

	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Dosing frequency	Daily	Twice daily	Once daily	Twice daily
Absorption, percentage bioavailability	Rapid, 90	Rapid, 4–10	Rapid, 60–80	Rapid, 50
Time to therapeutic effect (h)	Onset 24–72; full effect 120–168	0.5–2	1–4	3–4
Percentage protein bound	99	35	~92–95	87
Half-life (h)	20–60, highly variable	12–17; 14–17 in elderly; 15–28 with renal impairment	5–9; 11–13 in elderly	12
Route of excretion	Liver	80% urine; 20% fecal	66% urine; 33% fecal	~27% urine; ~70% fecal
Potential to lower plasma levels by dialysis	No	Yes	No	No
Potential to lower plasma levels by plasma exchange	Yes	No	Yes	Yes

Dabigatran is primarily eliminated by the kidneys and has low protein binding. These properties make hemodialysis a feasible consideration for reducing plasma levels of dabigatran and the manufacturers report that 49–57% of dabigatran can be cleared with a 4-h dialysis session [11]. Rivaroxaban and apixaban have substantially greater protein binding than dabigatran and as such hemodialysis will not effectively clear the direct factor Xa inhibitors; however, therapeutic plasma exchange has been proposed as a potential strategy for clearing rivaroxaban and apixaban. We consider hemodialysis and plasma exchange potential adjunctive measures in the management of acute NOAC-associated hemorrhage, especially in suspected overdose. Hemodialysis and plasma exchange, however, probably should not be considered first-line interventions for acute NOAC reversal because of the time required to initiate therapy and the potential complications in placing the catheter in an anticoagulated patient. Data in warfarin-associated ICH suggest that rapid anticoagulant reversal may result in less hematoma growth and improved outcome [12,13]. Since both hemodialysis and plasma exchange take several hours to initiate and administer, patients could suffer ongoing hemorrhage while awaiting the effect of these interventions.

HEMOSTATIC AGENTS FOR MANAGEMENT OF NOVEL ORAL ANTICOAGULANT-ASSOCIATED HEMORRHAGE

Currently, there are no commercially available antidotes to the NOACs; however, a recombinant protein that mimics factor Xa and sequestors the direct factor Xa inhibitors [14] and a humanized antibody fragment directed against dabigatran [15] both have shown the ability to restore hemostasis in animal models. The direct factor Xa inhibitor antidote (clinical trials NCT02220725 and NCT02207725) and the dabigatran antidote (clinical trial NCT02104947) are both in phase III clinical trials.

In the absence of a specific reversal agent, the widely accepted first-line approach to severe and life-threatening bleeding from anticoagulation by NOACs has been to administer supplemental coagulation factors. It is hypothesized that administration of a hemostatic agent provides excess coagulant factors that saturate the NOAC-binding sites leaving sufficient residual unbound factor to restore homeostasis in the coagulation cascade and allow for normal thrombus formation. Unfortunately, this hypothesis has not been studied in bleeding patients and the only available data are ex-vivo coagulation studies of healthy volunteers or in-vivo and ex-vivo studies using animal models. The major hemostatic agents that have been studied are summarized in Table 2 and include fresh frozen plasma (FFP), activated recombinant factor VII (rFVIIa), and either activated or unactivated prothrombin complex concentrates (PCCs). It should be noted that since patients treated with NOACs are not actually factor deficient, unlike warfarin-treated patients, vitamin K is not expected to be effective.

Zhou *et al.* [16] investigated the reversal of high-dose and moderate-dose dabigatran in a mouse ICH model by measuring 24 h hematoma volumes after treatment with unactivated 4-factor PCC [Beriplex P/N, US brand name Kcentra (CSL Behring, King of Prussia, Pennsylvania, USA)], mouse FFP, or human rFVIIa versus isotonic saline. They demonstrated that unactivated 4-factor PCC resulted in significantly smaller hematomas regardless of dabigatran dose whereas FFP demonstrated a beneficial trend with high-dose dabigatran and significantly smaller hematoma volumes with moderate-dose dabigatran. Hematoma volumes were not affected by rFVIIa and only 4-factor PCC demonstrated a mortality benefit. In a kidney incision model of a rabbit, Beriplex/Kcentra 4-factor PCC reduced blood loss in a dose-dependent manner with full normalization of blood loss at 50 IU/kg [17]. In a dabigatran porcine model, Beriplex/Kcentra 4-factor PCC resulted in improved clotting times and clot formation times on thromboelastometry although aPTT did not improve [18]. In healthy human volunteers, an unactivated 4-factor PCC (Cofact; Sanquin, Amsterdam, Netherlands) failed to improve aPTT, ECT, or TT in subjects treated with dabigatran [19].

In healthy human rivaroxaban-treated subjects, neither unactivated 4-factor PCC (Beriplex/Kcentra) nor unactivated 3-factor PCC (Profilnine; Grifols Biologicals, Los Angeles, California, USA) showed superiority in reversing coagulation assay abnormalities, and the authors concluded that both agents demonstrate potential to partially reverse rivaroxaban [20]. In a mouse model of rivaroxaban-associated ICH, rFVIIa, FFP, and Beriplex/Kcentra 4-factor PCC were equally effective in preventing excess hematoma expansion but only rFVIIa was associated with an improvement in PT [21].

The seemingly conflicting findings in these data raise several considerations: coagulation assay results may not be representative of effective reversal, the coagulation cascades in animal models may be intrinsically different than humans, or different PCCs may have different effectiveness.

OUR APPROACH TO NOVEL ORAL ANTICOAGULANT REVERSAL

In all cases of severe and life-threatening hemorrhage, addressing hemodynamic stability is the first

Table 2. Hemostatic agents considered for novel oral anticoagulant reversal

	FFP	rFVIIa (Novoseven)	Unactivated 3-factor PCC (Profilnine)[a]	Activated 4-factor PCC (FEIBA)	Unactivated 4-factor PCC (Kcentra)[a]
Contents	All factors in normal serum concentrations	Activated recombinant factor VII	Unactivated: factor II; factor IX; factor X; minimal factor VII content	Unactivated: factor II; factor IX; factor X; activated factor VII	Unactivated: factor II; factor VII; factor IX; factor X; protein C; protein S; heparin; antithrombin III
Dosing	10–15 ml/kg, maximum 1500 ml	90 μg/kg	60 units/kg	50–100 units/kg, maximum 200 units/kg daily	50 IU/kg, maximum 5000 IU
Time to effect	Hours	Rapid, ~10 min	Rapid, <15 min	Rapid, peak effect in 15–30 min	Rapid, ~10 min
Advantages	Replenishes all factors; limited thrombosis risk	Directly activates thrombin on platelets; rapid; small volume; recombinant product without infection risk	Rapid; small volume; virally inactivated	Rapid; small volume; provides factor VII; virally inactivated	Rapid; small volume; provides factor VII; virally inactivated
Disadvantages	Risk of fluid overload; preparation delay due to thawing; infectious risk; ABO matching required TRALI and other transfusion reactions	Increased thrombotic complication risk greatest with activated factors	Thrombotic complications; negligible factor VII	Increased thrombotic complication risk greatest with activated factors	Thrombotic complications; contraindicated in HIT

FEIBA, factor VIII inhibitor bypassing agent; FFP, fresh frozen plasma; HIT, heparin-induced thrombocytopenia; IU, international unit; PCC, prothrombin complex concentrate; rFVIIa, activated recombinant factor VII; TRALI, transfusion-related acute lung injury.
[a]Products available in the United States. A variety of PCCs are available internationally and vary in their specific contents.

step followed by immediate discontinuation of anticoagulation. Adequate volume status is attained to support renal function and drug excretion. Activated charcoal is given, especially within 6 h of the last NOAC dose. We obtain stat PT, aPTT, and TT (an additional to the usual screening studies in ICH) to help identify patients with NOAC exposure when the history is unclear. Our hemostatic agent of choice is 50 units/kg of activated 4-factor PCC [factor eight inhibitor bypassing agent (FEIBA)] in NOAC-associated ICH. For warfarin-associated ICH, we use 50 units/kg of unactivated 4-factor PCC (Kcentra). Prior to the approval of Kcentra in the United States, we administered FEIBA for both NOAC and warfarin-associated hemorrhages. We pursue anticoagulant reversal whenever NOAC ingestion in the last 48 h (96 h for renal insufficiency) is suspected. In warfarin-associated ICH, 4-factor PCC more frequently achieves effective hemostasis with faster coagulation study normalization and fewer adverse events related to fluid overload than FFP [6▪▪,22▪]. Because FEIBA and rFVIIa both contain activated factors, some believe they have added hemostatic benefit, but this remains unproven and these agents do pose higher risk of thrombotic complications than modern unactivated PCCs [23]. After administration of FEIBA, we consider repeat dosing if ongoing hemorrhage is clinically suspected. Since factor II (24–48 h) and factor X (48–60 h) have long half-lives, we do not anticipate a need for routine redosing in NOAC-associated ICH once hemostasis is achieved. It is unclear if repeating coagulation studies help to identify an adequate hemostatic response. In cases of NOAC overdose, we consider early hemodialysis or plasma exchange but otherwise do not routinely pursue these interventions unless bleeding is refractory to PCC administration.

At this time, activated or unactivated 4-factor PCCs are likely to be the best agents currently available for reversing NOAC effect, and we recommend institutions consider adding these agents to their formularies. We recognize that in some situations, it may not be possible to obtain FEIBA or Kcentra at all times. Therefore, beginning anticoagulant reversal as early as possible with available alternative agents (3-factor PCC preferred over FFP) is likely preferable to delaying treatment while awaiting the ideal agent or worse yet failing to attempt anticoagulant reversal. We advise against rFVIIa as an alternative reversal agent because it failed to demonstrate hemostatic control in a dabigatran animal model [16], its lack of clotting factors other than VII, and of its thrombotic risk.

CONCLUSION

The NOACs have addressed several of the limitations of using VKAs for therapeutic anticoagulation and have the benefit of reduced life-threatening hemorrhage risk. However, the lack of specific reversal agents is a limitation. Until specific antidotes are available, rapid attempts at anticoagulation reversal using activated or unactivated, 4-factor PCC is our first-line therapy. Adjunctive therapies including activated charcoal, hemodialysis (dabigatran), and therapeutic plasma exchange (direct factor Xa inhibitors) should also be considered.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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