

Reversing Direct Oral Anticoagulants in Acute Intracranial Hemorrhage

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Intracerebral hemorrhage is a major source of morbidity and mortality, accounting for 10% of all strokes. Oral anticoagulation therapy, while necessary to prevent thromboembolic complications, increases the risk of intracerebral hemorrhage and can potentially worsen bleeding in cases of acute hemorrhage. Before the introduction of direct oral anticoagulant agents in 2010, warfarin was the only option for oral anticoagulation. These new agents have an improved safety profile compared with warfarin but require different reversal strategies. Anticoagulation reversal in the setting of acute intracerebral hemorrhage is an evolving field. This article covers the most common direct oral anticoagulant medications, various available anticoagulant reversal strategies, and the latest guidelines for anticoagulation reversal in patients with acute intracranial hemorrhage. (*Critical Care Nurse*. 2019;39[3]:e1-e8)

Intracerebral hemorrhage (ICH) accounts for approximately 10% of all strokes and carries a high risk of mortality.¹ Oral anticoagulant use is associated with increased risk of ICH, and the incidence of disease states requiring anticoagulation, such as atrial fibrillation, is expected to increase in the next 10 to 15 years.^{1,2} The mainstay of oral anticoagulation therapy for many years has been warfarin, but since the introduction of dabigatran in 2010 the variety of anticoagulant agents has increased. This group of new anticoagulant agents has been referred to by various terms, most commonly *novel/new/non-vitamin K oral anticoagulants*, *target-specific oral anticoagulants*, and *direct oral anticoagulants* (DOACs). This shifting terminology can cause confusion and at worst may lead to medication errors if *novel oral anticoagulant* is abbreviated NOAC and interpreted as “no anticoagulation.”³ For this reason, we will refer to these agents with the term *DOAC*.

Direct Oral Anticoagulants

Five DOAC agents (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) are currently available in the United States. Other agents, such as darexaban and otamixaban, are in varying stages of development and approval. The DOAC agents are used as alternatives to warfarin for anticoagulation treatment of venous thromboembolic events and prevention of stroke in patients with nonvalvular atrial fibrillation. Dabigatran, rivaroxaban, and apixaban also carry Food and Drug Administration (FDA) indications for postoperative use to prevent venous thromboembolic events after knee and hip replacement operations.⁴⁻⁷ Off-label use of DOAC medications has also been reported.

One of the benefits of using a DOAC agent instead of warfarin is elimination of the need to frequently monitor the international normalized ratio (INR), although renal function should be assessed periodically. Studies have demonstrated reductions in major bleeding events

with the use of DOAC agents as compared with warfarin in both the clinical trial

The anticoagulant effect is typically proportional to the agent's plasma concentration.

setting and in “real-world” retrospective evaluations.⁸⁻¹⁰ However, these agents do still carry a risk of anticoagulant-associated ICH, especially when dosed inappropriately.¹¹ Understanding the mechanism of action of DOAC agents and their pharmacokinetic and pharmacodynamic parameters can help guide assessment and anticoagulant reversal decisions for patients with ICH.

Direct Thrombin Inhibition

Dabigatran is a competitive direct thrombin inhibitor that prevents thrombin-induced platelet aggregation and

binds to both clot-bound and free thrombin, thus decreasing conversion of fibrinogen into fibrin (see Figure).⁷ Dabigatran has the lowest protein-binding affinity of the DOAC agents, with only 35% bound to plasma proteins. Dabigatran is predominately cleared by the kidneys, and 80% is excreted as unchanged drug.¹² The elimination half-life is 12 to 17 hours in healthy patients. The elimination half-life and overall drug exposure are increased in patients with renal dysfunction. This effect is more pronounced in patients with severe renal impairment (creatinine clearance ≤ 30 mL/min), with dabigatran exposure 6.8 times greater than that of healthy patients and an elimination half-life of 27.5 hours.¹³ For this reason, dose adjustments are recommended for patients with renal impairment who are taking dabigatran. For example, for prevention of stroke in patients with nonvalvular atrial fibrillation, a dose reduction from 150 mg twice daily to 75 mg twice daily is recommended for patients with creatinine clearance of 15 to 30 mL/min.⁷

Factor Xa Inhibition

The factor Xa inhibitor agents are rivaroxaban, apixaban, and edoxaban. A helpful way to remember agents in this class is that the generic names all contain xa, which alludes to their mechanism of action. These drugs are competitive inhibitors of both free and prothrombinase complex-bound factor Xa (Figure). Thrombin generation and thus thrombus development are decreased by these agents. All 3 of these agents have varying degrees of metabolism by both renal and hepatic systems, notably via the CYP3A4 enzyme. They all exhibit moderately high to high degrees of plasma protein binding and different rates of renal elimination.^{4-6,12} Some differences in metabolism and clearance between agents in this class should be noted.

Apixaban. Apixaban is 87% bound to plasma proteins. Its major metabolic pathway is hepatic, although 27% of the drug is eliminated by the kidneys. Its terminal half-life in healthy patients is 8 to 14 hours. Apixaban exposure is elevated in patients with low body weight (≤ 50 kg) and in elderly patients (≥ 80 years old), which may affect dosing of this agent.^{12,14} Dose reductions based upon age, weight, and serum creatinine level are indicated for patients with nonvalvular atrial fibrillation, but these reductions do not apply to manufacturer-recommended doses for treatment of deep vein thrombosis

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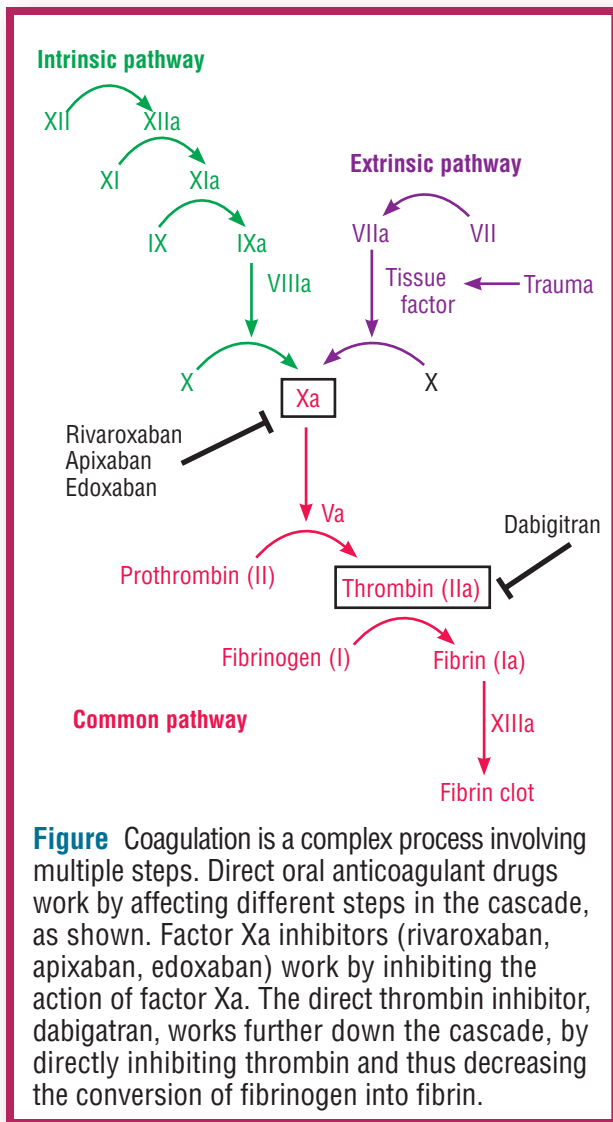


Figure Coagulation is a complex process involving multiple steps. Direct oral anticoagulant drugs work by affecting different steps in the cascade, as shown. Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) work by inhibiting the action of factor Xa. The direct thrombin inhibitor, dabigatran, works further down the cascade, by directly inhibiting thrombin and thus decreasing the conversion of fibrinogen into fibrin.

and pulmonary embolism as patients with severe renal impairment were excluded from initial trials.⁶ For patients with end-stage renal disease receiving hemodialysis, data are limited to small and single-dose trials. Manufacturer dose recommendations suggest no change to apixaban dose or frequency for patients receiving dialysis, although close monitoring would be prudent.^{6,12}

Rivaroxaban. Rivaroxaban exhibits a relatively high degree of binding, 92% to 95%, to plasma proteins.⁵ Rivaroxaban is primarily metabolized by the liver, but approximately one-third is excreted unchanged in the urine. The overall terminal half-life is 11 to 13 hours in healthy patients. Rivaroxaban's kinetics are not markedly affected by age or weight, but dose adjustments should be considered when treating nonvalvular atrial

fibrillation in patients with creatinine clearance between 15 and 50 mL/min. Data are limited regarding patients with end-stage renal disease because dose assessment data evaluate exposure to single-dose administration.^{5,12}

Edoxaban. Edoxaban is approximately 55% bound to plasma proteins. Like other factor Xa inhibitors, edoxaban is a substrate for hepatic metabolism, but it has a higher proportion of renal clearance (approximately 50%) than other agents in this class. Its terminal half-life is 10 to 14 hours.⁴ Data are limited to support the use of edoxaban for patients with end-stage renal disease requiring dialysis, although there are dose adjustment recommendations for those with creatinine clearance of 15 to 50 mL/min. Edoxaban is a rare example of a drug whose use is cautioned in patients with a high calculated creatinine clearance. Edoxaban is contraindicated for use in patients with nonvalvular atrial fibrillation if the creatinine clearance is greater than 95 mL/min.^{4,12}

Laboratory Monitoring

The DOAC agents were largely developed for use in clinical practice without the need for routine laboratory monitoring, although they can cause alterations in coagulation assays commonly used in clinical practice. The anticoagulant effect of all DOAC agents is typically proportional to the agent's plasma concentration as measured by liquid chromatography/tandem mass spectrometry.¹⁵ Although available in some markets, this concentration assessment method is not widely available in all clinical practice settings.

At many institutions, clot-based assays such as thrombin time, prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) are readily available. Dabigatran has a more marked effect on the clot-based assays of aPTT and thrombin time than on PT. Thrombin time is typically very sensitive to dabigatran therapy. The result often exceeds the upper limit of the assay even with low dabigatran concentrations, according to current clinical data.¹⁵ Dabigatran can also cause prolongation of aPTT, although the degree of prolongation does not correlate well with drug concentration and varies with the reagent used for the aPTT test. An aPTT result within the reference range does not rule out the presence of dabigatran because low "troughlike" concentrations of dabigatran may yield a normal aPTT measurement. The presence of dabigatran may alter the PT/INR, but results

may be variable.^{15,16} The factor Xa inhibitor agents have a more marked effect on PT/INR than on aPTT and have no clinical effect on thrombin time. However, the degree of PT prolongation depends on both drug concentration and agent. Both rivaroxaban and edoxaban affect PT/INR, although the reagent used in the assay may affect the degree of prolongation. Apixaban does not have a marked effect on PT/INR, so a test result within the reference range does not rule out drug anticoagulation effect.¹⁶

At some institutions, chromogenic tests, such as the anti-factor Xa assay, are also available. Chromogenic anti-factor Xa testing is typically used to monitor agents such as heparin and low-molecular-weight heparin but can also be used to assess DOAC agents with factor Xa activity. Ideally anti-Xa assays would be standardized with drug-specific calibration, but this is not feasible or available in many laboratories and hospital settings. Anti-Xa assays calibrated to unfractionated or low-molecular-weight heparins may be used as qualitative assessments of anticoagulation activity. If these assays show no anti-Xa activity, then the presence of an oral factor Xa inhibitor can be excluded.^{15,16} Agent-specific assays to measure DOAC activity and plasma levels are available in some institutions and countries and would aid in reversal decision-making, but these assays are not yet widely available for clinical use.

In patients with emergency reversal needs, such as those with ICH, there may be limited time to evaluate laboratory data before using an acute reversal agent. However, laboratory testing should be done when possible to evaluate the patient and to help make clinical decisions regarding reversal therapy. Elevated thrombin time is a strong indicator of dabigatran concentration. Prolongation of aPTT is also suggestive of dabigatran exposure, but may be within the reference range at low serum dabigatran

Reversal of DOAC agents may be indicated with critical or life-threatening bleeding. concentrations. If available,

anti-Xa testing may be used to determine the presence of factor Xa inhibitor activity. Although most clinical laboratories use calibrated testing for unfractionated or low-molecular-weight heparin, a measurable anti-Xa level is indicative of factor Xa inhibitor presence. However, correlation to drug concentration without agent-specific calibration may be limited. The PT/INR may be elevated in the presence of factor Xa inhibitors, but this test should

be interpreted with caution because the PT/INR may be within the reference range in patients with drug concentrations within or below therapeutic ranges. The test result also depends on the sensitivity of the PT/INR reagent used.^{15,16}

Anticoagulant Reversal Considerations for ICH

Underlying hemostatic abnormalities, such as acquired or congenital coagulation factor disorders or deficiencies, should be addressed in patients with acute ICH and in those taking oral anticoagulant therapies (eg, DOAC agents or vitamin K antagonists like warfarin). Patients taking oral anticoagulants are more likely than those not taking anticoagulants to have secondary hematoma expansion and increased risk of death or poor functional outcomes. Recent data suggest that these outcomes are similar for DOAC-associated and vitamin K antagonist-associated ICH.¹⁷⁻¹⁹ Patient history, especially the specific oral anticoagulant agent and time of the last known ingestion, can be critical for deciding if anticoagulant reversal is indicated. The time of the last dose and the current renal function, measured by creatinine clearance at the time of hospital presentation, can help establish the expected duration of anticoagulant activity because agents have varying degrees of renal elimination.

Although data are limited regarding the relationship between anticoagulant reversal and clinical outcome, reversal of DOAC agents may be indicated in patients with critical or life-threatening bleeding.¹⁹ The choice of DOAC reversal agents has shifted over the past few years from nontargeted therapies, such as coagulation factors, to targeted drug- or class-specific DOAC reversal agents. The Table presents a summary of reversal strategies and recommendations of the Neurocritical Care Society and Society of Critical Care Medicine.²⁰

Nontargeted Reversal

Activated Charcoal. Activated charcoal is frequently used in cases of accidental or intentional overdose to bind drugs and prevent their absorption by the gastrointestinal tract. Although activated charcoal does not reverse the effects of DOAC drugs, it may be used to minimize absorption if the time of the last ingested dose is known. Administration of 50 g of activated charcoal, either orally or via nasogastric tube, within 2 hours of the last dose of apixaban or dabigatran, has been shown to

Table Anticoagulant reversal recommendations for patients with critical bleeding²⁰

	Preferred reversal agent	Alternate reversal agent	Additional considerations
Oral direct thrombin inhibitors Dabigatran	Idarucizumab 5-g IV bolus If dabigatran was administered within past 3-5 half-lives If renal insufficiency is present and has led to exposure beyond typical 3-5 half-lives	Use if idarucizumab is unavailable Activated PCC (50 U/kg) If dabigatran was administered within past 3-5 half-lives If renal insufficiency is present and has led to exposure beyond typical 3-5 half-lives	Activated charcoal (50 g) Within 2 hours of dabigatran ingestion If patient is intubated with enteral access and/or low risk for aspiration Hemodialysis If idarucizumab is unavailable If critical bleeding continues after use of other treatment modalities
Oral factor Xa inhibitors Apixaban Rivaroxaban Edoxaban	4-factor PCC (50 U/kg) If ICH occurred within 3-5 half-lives of drug exposure (longer if renal failure is present) Andexanet alfa Low dose: 400 mg IV bolus at rate of 30 mg/min followed by infusion of 4 mg/min for up to 2 hours High dose: 800 mg IV bolus at rate of 30 mg/min followed by infusion of 8 mg/min for up to 2 hours	Activated PCC (50 U/kg) If ICH occurred within 3-5 half-lives of drug exposure (longer if renal failure is present) and 4-factor PCC is unavailable	Activated charcoal (50 g) Within 2 hours of agent ingestion If patient is intubated with enteral access and/or low risk for aspiration

Abbreviations: FDA, Food and Drug Administration; ICH, intracerebral hemorrhage; IV, intravenous; PCC, prothrombin complex concentrate.

reduce drug exposure.^{21,22} Activated charcoal may be effective for up to 6 hours after apixaban ingestion, although its effect may be diminished.²² Rivaroxaban is rapidly absorbed from the gastrointestinal tract. Activated charcoal may inactivate rivaroxaban, but the optimal time for administration is not clear and may be too short for activated charcoal to be a feasible means of reversal.²³ The time of the last drug dose is frequently unknown in patients with acute ICH, limiting the utility of charcoal as a reversal agent. Additionally, following acute ICH, patients may be unable to safely ingest activated charcoal, necessitating the use of nasogastric or orogastric tubes.

Hemodialysis. Because of its low degree of protein binding, dabigatran can be effectively removed by hemodialysis. Intermittent hemodialysis has been shown to effectively remove up to 77% of dabigatran; however, the drug levels may increase following cessation of therapy, causing rebound anticoagulation.^{13,24} Continuous renal replacement therapy may help attenuate this effect, although the overall rate of dabigatran removal is slower than with intermittent hemodialysis.^{24,25} The evidence is limited to small studies and case series. No data on the use of dialysis for DOAC removal in ICH patients or corresponding patient outcomes are available, likely

because of the practical difficulty in initiating emergency dialysis in this population. Because factor Xa inhibitors are highly protein bound, they are not sufficiently removed with hemodialysis.

Clotting Factor Products. Although transfusion of platelets and fresh frozen plasma may be required as part of a massive transfusion strategy in patients with polytrauma, administration of these conventional blood products will not reverse the effects of DOAC agents. Clotting factor concentrate and recombinant factor products may be used off-label in patients with life-threatening bleeding. Although data support the consideration of recombinant factor VIIa, the increased risk of thrombosis with this agent makes it less desirable for anticoagulation reversal.¹⁸ The more commonly used clotting factor products for DOAC reversal are 4-factor prothrombin complex concentrate (4f-PCC), which contains clotting factors II, VII, IX, and X, and activated prothrombin complex concentrate (aPCC), which contains clotting factors II, IX, X, and activated VII. For patients with life-threatening bleeding and ICH, data regarding the utility of these agents are mixed.

Data on 4f-PCC and aPCC use in ICH patients taking DOACs are limited because most of the initial studies

were either *ex vivo* or in healthy volunteers.^{26,27} Because of the lack of targeted reversal agents, these PCC products have been used in patients with ICH and other life-threatening bleeding with data available from retrospective and observational cohorts. The use of 4f-PCC and aPCC has been described in patients with ICH and other life-threatening bleeding in retrospective analyses and observational studies. Although studies have shown that 4f-PCC and aPCC reduce coagulopathy as measured by various coagulation assays, 1 recent observational study did not

Frequent neurological examinations are important to monitor for ICH expansion.

demonstrate that 4f-PCC prevents hematoma expansion and death in patients with ICH. However, this study included patients taking dabigatran.²⁸⁻³⁰ Administering 4f-PCC at a dose of 25 to 50 U/kg to patients taking the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban may be of clinical benefit for anticoagulant reversal. Administering aPCC to patients taking dabigatran may also be of clinical benefit. However, these PCC agents have not been directly compared with targeted reversal therapies, so further investigation is warranted.

Targeted Reversal

Idarucizumab. The humanized monoclonal antibody fragment idarucizumab was the first targeted DOAC reversal agent in the United States and was designed as an antidote for dabigatran. Since its first global approval in October 2015 by the US FDA, idarucizumab has become widely available in most markets worldwide. Idarucizumab binds to dabigatran with an affinity 350 times greater than that of dabigatran for thrombin.³¹ Idarucizumab prevents dabigatran from binding to thrombin and blocking the conversion of fibrinogen (Figure). The RE-VERSE AD trial was a prospective, open-label evaluation of the efficacy of idarucizumab to reduce dabigatran-induced coagulation abnormalities in patients with uncontrolled bleeding or need for urgent reversal. The results showed that idarucizumab could reverse coagulopathy, as defined by dilute thrombin time or ecarin clotting time, in patients taking dabigatran. Bleeding cessation, where observable, occurred a median of 1.6 or 2.5 hours (depending on patient group) after administration of idarucizumab.³² Since idarucizumab became available, several case

reports on intracranial hemorrhage have been published, but large-scale case series or prospective data in this specific patient population are lacking.³³⁻³⁵ Idarucizumab does not appear to be associated with any significant prothrombotic laboratory indicators, which is a key difference between using this reversal agent and using nontargeted therapies such as PCCs.^{26,27,36}

Idarucizumab is supplied as two 2.5 g/50 mL vials, yielding a total dose of 5 g. The solution should be administered either as 2 consecutive infusions or as consecutive bolus injections via syringe. The two 2.5 g/50 mL vials should be administered within 15 minutes of each other. Administration of a second 5-g dose may be considered in patients with ongoing bleeding if hemodialysis is not an option. Data to guide redosing are limited.¹⁸

Andexanet Alfa. Andexanet alfa is a recombinant, modified, enzymatically inactive human factor Xa protein that binds the factor Xa inhibitor agents but does not potentiate thrombin generation. This competitive binding frees endogenous factor Xa to participate in the clotting cascade (Figure) and stimulates thrombin production via normal pathways. Andexanet alfa itself does not augment or produce a hypercoagulable state. Data also support the reversal effect of andexanet alfa on anticoagulation by low-molecular-weight heparins.³⁷⁻³⁹ Interim data from the ongoing ANNEXA-4 investigation focus on the co-primary end points of change in anti-factor Xa activity and rate of hemostatic efficacy 12 hours after administration of andexanet alfa in patients who were taking apixaban, rivaroxaban, edoxaban, or enoxaparin and presented with acute major bleeding. Current data show significant decreases in anti-factor Xa activity 12 hours after infusion in patients taking rivaroxaban and apixaban and achievement of excellent to good hemostasis in 79% of patients 12 hours after infusion.³⁹ Andexanet alfa was first approved in the United States by the FDA in May 2018 and is under consideration for European and Japanese approval.⁴⁰

Two dosing regimens for andexanet alfa are recommended in current approved labeling for the reversal of rivaroxaban and apixaban: a high dose of 800 mg intravenous bolus followed by intravenous infusion at a rate of 8 mg/min for up to 120 minutes, and a low dose of 400 mg intravenous bolus followed by intravenous infusion at a rate of 4 mg/min for up to 120 minutes. The selection of high-dose versus low-dose regimen

depends on anticoagulant agent, last anticoagulant dose strength, and timing of last anticoagulant dose. High-dose therapy is indicated in patients receiving more than 10 mg of rivaroxaban or more than 5 mg of apixaban within the past 8 hours. Low-dose therapy is indicated for patients who received lower doses of rivaroxaban and apixaban within the past 8 hours or those who require reversal but ingested the last anticoagulant dose more than 8 hours earlier. Andexanet alfa is supplied as 100-mg vials to be reconstituted with sterile water; the product may take 3 to 5 minutes to dissolve. Infusions are made directly from reconstituted solutions with no additional diluent or base solution needed.⁴¹ Further data are needed to direct andexanet dosing for reversal of other factor Xa inhibitors such as edoxaban and enoxaparin.

Ongoing Investigations

Ciraparantag, also known as aripazine, is a synthetic molecule designed with multiple binding sites to inactivate various anticoagulant agents. Data are currently limited in the clinical setting, but preliminary data show that ciraparantag reverses edoxaban and enoxaparin.^{42,43}

Another agent with a possible role in DOAC-associated intracranial hemorrhage is tranexamic acid. The recently published TICH-2 trial evaluated the use of tranexamic acid in patients with spontaneous ICH; this trial excluded patients receiving anticoagulation. Results for the TICH-2 study population did not show a benefit in functional status at 90 days, as measured by the modified Rankin scale, but hematoma expansion decreased in patients receiving tranexamic acid as compared with those receiving placebo.⁴⁴ Trials to assess the utility of tranexamic acid in patients with anticoagulant-associated intracranial hemorrhage are underway.⁴⁵

Postreversal Considerations

Serial laboratory monitoring of coagulation parameters may not indicate an ongoing anticoagulant effect after DOAC reversal, unlike warfarin reversal. Clinical markers of bleeding and frequent neurological examinations are important to monitor for potential rebound of anticoagulant effect and ICH expansion. It is also important to monitor for signs and symptoms of thrombosis, especially if nontargeted coagulation factor products are used. Idarucizumab does not appear to promote clot formation.⁴⁶ Risks of excessive coagulation and thrombosis

are associated with PCC products.²⁰ Clinicians should monitor patients receiving these products for signs and symptoms of pulmonary embolism or embolic stroke. Additionally, complete clearance requires 4 to 5 drug half-lives; this time may be even greater in patients with impaired renal function. Rebound anticoagulation is possible 8 to 12 hours after anticoagulant effects have been reversed, especially with nontargeted reversal agents.

Conclusion

The use of DOACs is increasing in the United States, and patients presenting with ICH may be taking these medications. Although DOACs are lifesaving drugs for many people, they can present complications in patients with acute ICH. All emergency and critical care nurses should understand DOACs and how their anticoagulant effects can be reversed in an emergency. Targeted options are preferred, when available, for DOAC reversal in patients with critical bleeding such as ICH. After anticoagulation reversal, patients should continue to be monitored for signs of reversal failure, such as hematoma expansion, and reversal agent complications, such as embolic events. **CCN**

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None reported.

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