Managing and Reversing Direct Oral Anticoagulants

A Discussion Guide

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Target Audience

This discussion guide was developed to meet the needs of pharmacists practicing in hospitals, ambulatory clinics, and other health systems, including members of ASHP.

Learning Objectives

After participating in this knowledge-based educational activity, participants should be able to:

1. Describe the differentiating characteristics of direct oral anticoagulants (DOACs), including indications and dosing requirements
2. Explain the risk factors for bleeding complications from the use of DOACs and strategies for minimizing the risk.
3. Review current and emerging approaches to reversing the effects of DOACs in patients with major or life-threatening bleeding

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Executive Summary

Direct oral anticoagulants (DOACs) have been developed to overcome the limitations of warfarin, but a risk for bleeding is associated with the use of these agents. Outcomes from DOAC therapy can be optimized by controlling modifiable risk factors for bleeding, using evidence-based approaches to provide anticoagulation, and assessing patient adherence and response to therapy. The DOACs differ in their reliance on the kidneys for elimination and frequency of administration, which should be taken into consideration in choosing therapy for a patient. Reversal of DOAC therapy may be required in patients with or at risk for bleeding because of trauma or a need for an invasive procedure (e.g., surgery). Limited data are available to guide clinical decision making about the approach used to reverse the anticoagulant effects of DOACs. The reversal strategy depends on the urgency of the situation; presence, site, and severity of bleeding; DOAC involved; and comorbid conditions. Antidotes have been developed because of the shortcomings of currently available pharmacotherapies for reversal of DOACs. The only antidote currently approved by the Food and Drug Administration, idarucizumab, reverses the anticoagulant effects of dabigatran, but it does not reverse the anticoagulant effects of other DOACs. Several other promising antidotes for use in reversing DOACs are in development. Institutional policies and procedures and standardized order sets, clinical pathways, and clinical decision support tools for the use of these products in urgent situations are critical to avoid delays that could adversely affect patient outcomes.

Warfarin and other vitamin K antagonists have been used widely for decades to prevent and treat venous thromboembolism (VTE) and prevent stroke and systemic embolism in patients with nonvalvular atrial fibrillation. These drugs were the only available oral anticoagulants until 2010 when dabigatran, the first direct oral anticoagulant (DOAC), was introduced. The currently available DOACs—dabigatran, rivaroxaban, apixaban, and edoxaban—were developed to overcome some of the shortcomings of warfarin, including the need for routine laboratory monitoring, long time to onset and offset of anticoagulant effect, numerous interactions with drugs and foods, and high incidence of bleeding complications, especially in elderly patients.[1-3]

DOACs

Vitamin K antagonists exert their anticoagulant effects by inhibiting hepatic production of and depleting vitamin K-dependent clotting factors and their depletion and recovery, especially clotting factor II (thrombin), VII, IX, and X, which disrupts the final common pathway of the clotting cascade (Figure 1). The time to onset and offset of the anticoagulant effect of warfarin is long because of the long half-lives of these vitamin K-dependent clotting factors, especially clotting factor II. Dabigatran directly inhibits activated clotting factor II (IIa), and rivaroxaban, apixaban, and edoxaban directly inhibit activated clotting factor X (Xa) activity. These anticoagulant agents have been referred to collectively as DOACs, target-specific oral anticoagulants, and non-vitamin K oral antagonists and have a rapid onset of effect.

The direct thrombin inhibitor dabigatran was approved by the Food and Drug Administration (FDA) in 2010.[4] The factor Xa inhibitors rivaroxaban, apixaban, and edoxaban received FDA approval in 2011, 2012, and 2015, respectively (Table 1).[5-7]

FIGURE 1. Mode of Action of Anticoagulants

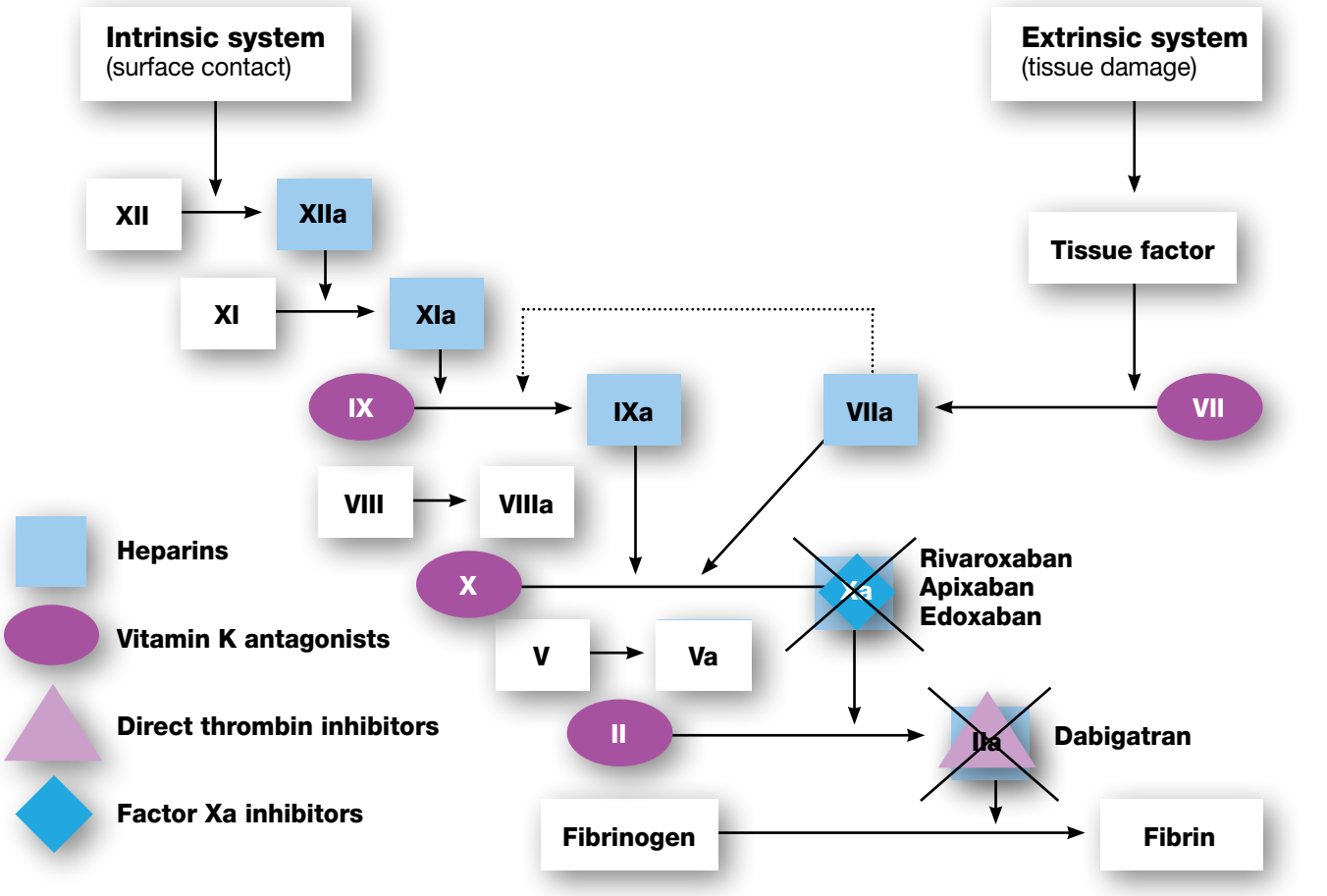

TABLE 1

Direct Oral Anticoagulant FDA-approved Indications and Dosing[4-9]

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
VTE treatment and prevention of recurrence	CrCl > 30 mL/min: 150 mg twice daily	15 mg twice daily with food for first 21 days for initial treatment of VTE, then 20 mg once daily with food[a]	*Treatment:* 10 mg twice daily for 7 days, followed by 5 mg twice daily *Prevention of recurrence:* 2.5 mg twice daily	*VTE treatment only:* 60 mg once daily[b] *CrCl 15–50 mL/min, body weight ≤60 kg, or use of certain P-gp inhibitors[c]: 30 mg once daily*
VTE prophylaxis	*CrCl > 30 mL/min after hip replacement surgery:* 110 mg on first day, then 220 mg once daily	10 mg once daily with or without food after hip or knee replacement surgery[a]	2.5 mg twice daily after hip or knee replacement surgery	Not approved by FDA for this indication[b]
Stroke/systemic embolism prophylaxis in nonvalvular atrial fibrillation	*CrCl > 30 mL/min:* 150 mg twice daily *CrCl 15–30 mL/min:* 75 mg twice daily	*CrCl > 50 mL/min:* 20 mg once daily with evening meal *CrCl 15–50 mL/min:* 15 mg once daily with evening meal	5 mg twice daily, or 2.5 mg twice daily in patients with at least 2 of the following characteristics: age ≥ 80 yr, body weight ≤ 60 kg, or SCr ≥ 1.5 mg/dL	*CrCl > 95 mL/min:* do not use[d] *CrCl > 50–95 mL/min:* 60 mg once daily *CrCl 15–50 mL/min:* 30 mg once daily

CrCl (using total body weight) = creatinine clearance, FDA = Food and Drug Administration, P-gp = P-glycoprotein, SCr = serum creatinine; VTE = venous thromboembolism

[a] Rivaroxaban use for VTE treatment and prophylaxis should be avoided in patients with CrCl <30 mL/min because of an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population.

[b] Edoxaban is approved by FDA for VTE treatment and stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation, but not for prevention of VTE recurrence or VTE prophylaxis.

[c] In the Hokusai study of edoxaban, a reduced dosage of 30 mg once daily was used for patients receiving verapamil, quinidine, or short-term azithromycin, clarithromycin, erythromycin, oral itraconazole, or oral ketoconazole therapy.

[d] Edoxaban should not be used for stroke or systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation and CrCl >95 mL/min because of an increased risk of ischemic stroke from edoxaban 60 mg once daily compared with warfarin in the ENGAGE AF-TIMI 48 study (Giugliano R et al. *N Engl J Med.* 2013; 369:2093-104).

Pharmacokinetic and pharmacodynamic differences may be important when choosing among the DOACs, especially for patients with renal insufficiency. All four DOACs are eliminated by the kidneys and can accumulate in patients with renal impairment, although the agents differ in the extent to which they rely on the kidneys for elimination (Table 2). The DOACs that are most and least dependent on the kidneys for elimination are dabigatran and apixaban, respectively. The protein binding of dabigatran is low, and it is the only DOAC that is dialyzable.[11] As the creatinine clearance decreases (i.e., as renal function declines), the half-life of each DOAC, its anticoagulant effects, and the potential for bleeding complications increase because of possible drug accumulation.[12] The magnitude of the effects is largest for dabigatran and smallest for apixaban.

The number of daily doses may be a consideration in choosing among the DOACs because of patient adherence and resulting outcomes. Apixaban requires two daily doses.[6] Edoxaban is taken once daily.[7] Dabigatran and rivaroxaban are taken once or twice daily depending on the indication.[4,5]

Dabigatran and edoxaban are substrates for the efflux transporter P-glycoprotein (P-gp), and these drugs can interact with P-gp inhibitors and inducers.[4,7] Concomitant use of these DOACs with potent P-gp inhibitors can increase systemic exposure to the DOAC and the risk of bleeding, especially in patients with renal impairment taking dabigatran.[4] This property may influence other P-gp influenced agents.

Rivaroxaban and apixaban are substrates for P-gp and cytochrome P-450 (CYP) 3A4, and these DOACs can interact with inhibitors and inducers of P-gp and CYP3A4. Concomitant use of these DOACs with potent inhibitors of P-gp or CYP3A4 can increase systemic exposure to the DOAC and the risk for bleeding.[5,6]

TABLE 2

Properties of Direct Oral Anticoagulants[4-7,10]

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target for activity	Factor IIa (thrombin)	Factor Xa	Factor Xa	Factor Xa
Prodrug	Yes	No	No	No
Bioavailability (%)	3–7 (increased by 75% if capsules broken, chewed, or opened)	66–100[a]	~50	62
Time to peak plasma concentration (hr)	1–3 (delayed by food)	2–4 (delayed by food)	3–4	1–2
Half-life (hr)	12–17	5–9 (11–13 elderly)	12	10–14
Dosing frequency	Once or twice daily	Once or twice daily	Twice daily	Once daily
Renal elimination of unchanged drug (%)	80	36	27	50
Dialyzable	Yes	No	No	No
Protein binding (%)	35	92-95	87	55
Key drug interactions	Potent inhibitors and inducers of P-gp	Potent inhibitors and inducers of P-gp or CYP3A4	Potent inhibitors and inducers of P-gp or CYP3A4	Potent inhibitors and inducers of P-gp

CYP = cytochrome; FDA = Food and Drug Administration; P-gp = P-glycoprotein; VTE = venous thromboembolism

[a] The bioavailability of rivaroxaban is dose-dependent (80%-100% for the 10-mg dose and 66% for the 20-mg dose) and increased by food for the 20-mg dose.

Weighing Risks

A risk for bleeding is associated with the use of all oral anticoagulants, including DOACs, and this risk must be balanced with the risk for thromboembolism when making decisions about use of the drugs. Efforts to minimize the risk for or manage bleeding may increase the risk for thromboembolism.

Clinical trials comparing the efficacy and safety of DOACs with warfarin for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation or prevention or treatment of VTE revealed differences in the risk for gastrointestinal (GI) bleeding and intracranial hemorrhage (ICH).[8,9,13-16] The results of real-world studies comparing the risk of bleeding from warfarin and DOACs have been mixed, with a higher rate associated with warfarin than DOACs in some but not all studies.[17-21] Clinical experience with DOACs in special patient populations, including pediatric patients, morbidly obese patients, patients with hypercoagulable conditions, and patients with mechanical devices (e.g., nonnative cardiac valves), is limited.

An individualized approach is needed to balance the risks for bleeding and thromboembolism in patients receiving oral anticoagulants. Excessive anticoagulation during DOAC therapy may be the result of drug interactions, disease states (especially renal, liver, or cardiac impairment, which are common in the elderly), and the use of excessive anticoagulant dosages. Figure 2 lists risk factors for bleeding during oral anticoagulant therapy. Controlling modifiable risk factors for bleeding, using evidence-based approaches to provide anticoagulation, and assessing patient adherence and response to anticoagulant therapy are recommended to optimize patient outcomes.

Various scoring systems are available to quantify the risk for thromboembolism and bleeding. In patients with atrial fibrillation, the $CHADS_2$ and CHA_2DS-Vasc scores are predictive of the risk for stroke, and the $HEMORR_2HAGES$ and HAS-BLED scores are predictive of the risk for bleeding during oral anticoagulant therapy.[24-28] In patients with atrial fibrillation undergoing surgery, the risk for perioperative thromboembolism during temporary interruption of oral

FIGURE 2.

Risk Factors for Bleeding During Oral Anticoagulant Therapy[22-26]

- Undergoing an invasive procedure
- History of stroke or bleeding
- Falling or trauma (or elevated risk for falling or trauma)
- Excessive anticoagulation
- Poor understanding of or nonadherence to the anticoagulation regimen
- Use of antiplatelet agents or nonsteroidal anti-inflammatory drugs
- Advanced age
- Impaired organ (i.e., kidney, liver) function
- Low body weight
- Female sex
- Ethanol abuse
- Uncontrolled hypertension
- Diabetes mellitus
- Anemia
- Thrombocytopenia
- Pancytopenia
- Malignancy
- Genetic factors (e.g., thrombophilias)
- Rheumatic heart disease

anticoagulant therapy can be predicted based on the $CHADS_2$ score and other characteristics (e.g., presence of active cancer, rheumatic valvular heart disease, thrombophilias, mechanical heart valve; history of VTE, stroke, or transient ischemic attack).[23]

Temporary interruption of anticoagulant therapy usually is needed for patients undergoing surgery or invasive procedures because of the risk of bleeding. The type of surgery affects the risk for perioperative bleeding.[29] Major orthopedic, cardiac, vascular, neurosurgical, cancer, and urologic surgery is associated with a high risk for bleeding (a 2% to 4% 2-day risk of major bleeding).[30,31] Minor procedures are associated with a low risk for bleeding (a 2-day risk for major bleeding of 0 to 2%).[30,31] The timing of discontinuation of the DOAC before surgery depends on the type of surgery, DOAC, and renal function. The DOAC should be discontinued earlier in patients undergoing invasive procedures associated with a high risk of bleeding complications than in patients undergoing minor procedures and in patients with renal impairment than patients with normal renal function because of the reduced renal clearance of the drug in patients with renal impairment.[29] Withholding DOAC therapy for several days may be required before procedures associated with a very high risk for bleeding.

In assessing a patient receiving anticoagulant therapy who presents with trauma or for surgery or an invasive procedure, the presence and site of bleeding (i.e., risk for complications), urgency of the situation, and level of anticoagulation based on medication administration history (i.e., time elapsed since the last DOAC dose), laboratory assays, and use of antiplatelet agents should be taken into consideration, keeping in mind the need for resumption of anticoagulation after the surgery or invasive procedure. Bleeding into vital closed spaces, such as the eye or spinal region, can have long-term consequences.

Deciding whether and when to restart anticoagulation in a patient who required interruption or reversal of anticoagulant therapy because of bleeding, surgery, or an invasive procedure requires weighing the risks for thromboembolism and bleeding. These risks may change over time during the postoperative period, requiring reevaluation. Resuming warfarin after GI bleeding or ICH has been associated with improved long-term survival and a reduced incidence of thrombosis, with minimal risk of recurrent bleeding events compared with not resuming warfarin therapy.[32-35] The timing of resumption of warfarin affected the risk for recurrent bleeding.[33] Similar relationships are likely between the resumption of DOACs after resolution of bleeding and survival and the risk for thromboembolism and recurrent bleeding, although these relationships remain to be confirmed.

Lab Tests

Although routine laboratory monitoring is not required during DOAC therapy, laboratory tests may provide valuable insight about the level of anticoagulation during treatment with these agents or after interruption of therapy in patients with or at risk for bleeding.[10] Laboratory assays may be used to support decisions about when anticoagulation effects are low enough for a patient to undergo surgery or restart anticoagulant therapy. The response to therapeutic interventions

to reverse anticoagulation (e.g., hemodialysis for dabigatran reversal) also may be monitored using laboratory tests.

The results of many coagulation tests commonly used to measure the intensity (i.e., level) of anticoagulation can vary among the DOACs for several reasons, including differences in the site of action (i.e., inhibition of factor IIa or factor Xa) and how each specific reagent may respond.[36] The thrombin time (TT) is a commonly available test that can be used as a sensitive qualitative test to detect the presence of dabigatran.[37] The chromogenic ecarin clotting time (ECT) or dilute thrombin time (dTT) are methods for quantifying the amount of dabigatran present.[36]

Chromogenic anti-factor Xa assays can be used to provide qualitative and quantitative information about rivaroxaban, apixaban, and edoxaban.[36,38] The ECT and TT are not useful for monitoring coagulation during treatment with these factor Xa inhibitors. The international normalized ratio (INR) is not consistently reliable for routine monitoring of coagulation during treatment with factor Xa inhibitors because the assay would need to be calibrated for the specific DOAC, and differences in available assays may influence the results.[36,39]

The prothrombin time (PT) is a more sensitive test than the activated partial thromboplastin time (aPTT) for assessing the level of coagulation during treatment with rivaroxaban, apixaban, and edoxaban, although the aPTT is a more sensitive test than the PT during therapy with direct thrombin inhibitors (i.e., dabigatran).[37,40] The INR is derived from the PT, and point-of-care INR test results during dabigatran therapy tend to be higher than INR results obtained from clinical laboratories.[41] Therefore, the use of point-of-care INR tests to measure coagulation in patients receiving dabigatran is not recommended.[41]

The PT, INR, and aPTT can be important tools to use in screening for excessive DOAC plasma concentrations. Although these tests are relatively insensitive and results may be normal at commonly observed DOAC plasma concentrations, elevated values may be a signal that excessive DOAC plasma concentrations are present. In such situations, the patient should be evaluated for other causes of elevated PT, INR, or aPTT values. If none is identified, causes of excessive DOAC plasma concentrations (e.g., renal dysfunction; excessive DOAC administration; breaking, chewing, or opening dabigatran capsules, which increases the oral bioavailability; drug interactions; organ failure) should be explored. Prevention of the situation recurring should be explored should excessive anticoagulation effects be present.

Reversal

Reversal of the anticoagulant effects of DOACs may be needed for patients with or at risk for bleeding, including patients undergoing emergent or elective surgery or invasive procedures. The anticoagulant reversal strategy depends on the setting (e.g., emergency department, operating room, intensive care unit) and urgency (Table 3). The presence, site, and severity of bleeding are important considerations. Anticoagulant therapy typically is withheld in patients with or at risk for bleeding. Strategies for managing bleeding may involve mechanical intervention (e.g., surgery) or pharmacologic intervention using topical agents (e.g., recombinant human thrombin), agents that neutralize the drug (i.e., antidotes), or agents that reverse the effects of the drug by independently promoting hemostasis. Replacement of substantial blood losses may be needed (i.e. concentrated clotting factors). Because blood products contain citrate, which can deplete calcium, calcium supplements also may be needed. The management of comorbid conditions should be optimized during reversal of anticoagulant therapy.

Clotting factor concentrates, fresh frozen plasma (FFP), activated charcoal, and hemodialysis (for dabigatran only) are among the pharmacologic interventions that have been used to reverse the anticoagulant effects of DOACs.[44] Activated charcoal may be administered orally if the last DOAC dose was taken within the past few hours.[12]

FFP is obtained from human blood and contains all of the vitamin K-dependent clotting factors in plasma. The large volume of fluid administered is a potential disadvantage of using FFP.[10,44] Limited data suggest that FFP alone is not beneficial for reversing DOACs.[38]

Concentrated clotting factor products include three- and four-factor prothrombin complex concentrate (PCC) products, recombinant factor VIIa (rFVIIa), and activated PCC (aPCC, also known as antiinhibitor factor complex, factor VIII inhibitor bypassing activity, or FEIBA).[10] The PCC products vary in their clotting factor content. Three-factor PCC (PCC3) products contain inactivated clotting factors II, IX, and X and only small amounts of factor VII in an inactivated form. Four-factor PCC (PCC4) products contain a larger amount of inactivated clotting factor VII than PCC3 products as well as clotting factors II, IX, and X in an inactivated form. Activated PCC contains clotting factor VII in an activated form and clotting factors II, IX, and X primarily in an inactivated form. The risk for thrombosis is a concern with the use of clotting factor concentrates, especially as the dose increases. This

TABLE 3

Therapeutic Interventions to Reverse Direct Oral Anticoagulants[10,42,43,a]

Degree of Urgency (time frame for action) or Severity of Bleeding	Dabigatran	Rivaroxaban, Apixaban, or Edoxaban
No rush (> 24 hr), minor bleeding	Withhold drug, monitor clinical status, and recheck lab tests	Withhold drug, monitor clinical status, and recheck lab tests
Expedited (1–24 hr), major bleeding	Withhold drug, give activated charcoal if last dose taken within past few hours, and give idarucizumab 5 g i.v. If idarucizumab not available, consider prolonged hemodialysis (> 2 hr). If active bleeding persists after idarucizumab administered[b] or idarucizumab not available, consider low-dose[c] aPCC 8-12 units/kg i.v. or PCC4 (or PCC3 if PCC4 not available) 25 units/kg i.v., with titration using additional doses to desired effect.[d]	Withhold drug and give activated charcoal if last dose taken within past few hours. For active bleeding, consider PCC4 (or PCC3 if PCC4 not available) 25 units/kg i.v. or low-dose aPCC 8-12 units/kg i.v., with titration using additional doses to desired effect.[d]
Emergent (<1 hr), major bleeding (including noteworthy ICH[e])	Withhold drug, give activated charcoal if last dose taken within past few hours, and give idarucizumab 5 g i.v. Consider use of prolonged hemodialysis (> 2 hr) if idarucizumab not available. If active bleeding persists after idarucizumab administered[b] or idarucizumab not available, consider adding aPCC 25-50 units/kg i.v. (with a second dose ready if 25 units/kg used initially[d]), PCC4 25-50 units/kg i.v., or in patients with major trauma, TXA (1 g i.v. bolus, then 1 g i.v. over 8 hr).	Withhold drug, give activated charcoal if last dose taken within past few hours, and consider PCC4 (or PCC3 if it is the only concentrated clotting factor product available) or aPCC 25-50 units/kg i.v.

a PCC = activated prothrombin complex concentrate; ICH = intracranial hemorrhage; i.v. = intravenous; PCC4 = four-factor prothrombin complex concentrate; PCC3 = three-factor prothrombin complex concentrate; TXA = tranexamic acid

[a] Comorbid conditions and risk factors for bleeding should be managed to the extent possible, regardless of the degree of urgency or severity of bleeding.

[b] In patients with dabigatran overdoses or excessively high serum concentrations, 5 g of idarucizumab may not fully reverse the anticoagulant effects.

[c] Low-dose aPCC (8 units/kg) has been used successfully prior to insertion of a dialysis catheter in patients receiving dabigatran to prevent bleeding from the procedure.

[d] If bleeding can be assessed and the patient is not exsanguinating, a titration strategy using incremental doses can be considered until bleeding management goals are achieved because the onset of the hemostatic effects of PCC products is rapid.

[e] In patients receiving dabigatran with ICH, authoritative guidelines recommend 5g idarucizumab. If idarucizumab is not available, 50 units/kg of aPCC or PCC4 is suggested. Hemodialysis may be considered in patients with a high dabigatran serum concentration (e.g., patients with renal failure or an overdose). If clinically significant bleeding persists after treatment with idarucizumab, aPCC, or PCC4, a repeat dose of idarucizumab, hemodialysis, or both can be considered. Use of recombinant factor VIIa is not recommended. In patients receiving factor Xa inhibitors with ICH, PCC4 or aPCC 50 units/kg is suggested if the ICH occurred within 3 to 5 terminal half-lives after drug exposure or in a patient with liver failure.

risk must be weighed against the potential benefit of using these products for anticoagulant reversal. The choice among concentrated clotting factor products may depend on what is available.

Limited clinical data are available for the use of concentrated clotting factor products for reversal of the anticoagulant effects of DOACs. The available clinical data, which are derived from in vivo and ex vivo assessments, are inconsistent. Randomized comparisons of various concentrated clotting factor products have not been performed in patients with bleeding. A wide range of clotting factor concentrate doses, including very large doses, have been used, but uncertainty remains about the optimal dose and whether to repeat the dose if anticoagulant effects persist.[38] Whether experience with concentrated clotting factor products for DOAC reversal in patients without bleeding is relevant for patients with bleeding is unknown. Experience with use of these products for DOAC reversal in patients with bleeding is limited to case reports and case series. The use of aPCC has been preferred over PCC4 for reversal of dabigatran but how the efficacy of aPCC compares with PCC4 for reversal of factor Xa inhibitors is unclear.[10] Thrombosis has been reported in patients receiving aPCC for reversal of dabigatran, rivaroxaban, or apixaban.[45] Small, single clotting factor concentrate doses have been effective for DOAC reversal in patients with GI bleeding that is readily observed and assessed, with a rapid onset of effect and no need for repeat dosing, but some therapeutic failures have been reported.[38] Some PCC4 products and aPCC contain the natural regulatory anticoagulant protein C, protein S, or both, which can affect the reversal effect.[36] Some PCC3 and PCC4 products (but not aPCC or rFVIIa) contain heparin, which is a concern in patients with recent heparin-induced thrombocytopenia or heparin allergy.[36]

Antidotes

Although concentrated clotting factor products have been used to reverse the anticoagulant effects of DOACs, they do not remove the DOAC. These products are associated with a risk for thrombosis, prevention of which presumably was the reason for using the DOAC. Antidotes have been developed as a more specific approach to reversing DOACs because of the shortcomings of concentrated clotting factor products and other currently available pharmacotherapies and strategies for reversal.

Idarucizumab

Idarucizumab is a fully humanized monoclonal antibody fragment that binds specifically to dabigatran and inhibits its anticoagulant effects.[46] It has no known effects on other anticoagulants. Idarucizumab does not independently cause hemostasis. It has structural features similar to thrombin but it does not activate clotting. The affinity of idarucizumab is approximately 350 times greater for dabigatran than for thrombin.[47] Idarucizumab is eliminated renally, but renal impairment does not affect the reversal of the anticoagulant effects of dabigatran by idarucizumab.[46]

Idarucizumab was approved by FDA in October 2015 for use when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery, an urgent procedure, or life-threatening or uncontrolled bleeding.[46] In phase 1 studies of idarucizumab in 145 humans, the drug was well-tolerated and provided an immediate and complete reversal of dabigatran-induced anticoagulation in a dose-dependent manner that was sustained for more than 24 hours.[48,49] There was no evidence of immunogenicity.

A phase 3 prospective cohort study known as RE-VERSE AD currently is under way to explore the use of intravenous (i.v.) idarucizumab 5 g to reverse dabigatran in patients with serious bleeding or requiring an urgent invasive procedure. The results of an interim analysis of 51 patients with serious bleeding and 39 patients requiring an urgent procedure were released in 2015.[50] Most of the patients had atrial fibrillation and were taking dabigatran 110 mg twice daily for stroke and systemic embolism prophylaxis, with a median time since the last dose of approximately 15 hours. Roughly one in three patients had a creatinine clearance less than 50 mL/min, but no patients had a creatinine clearance less than 11 mL/min. Plasma concentrations of dabigatran were therapeutic prior to administration of idarucizumab, which reduced the measured active concentration to less than 20 ng/dL (i.e., a level associated with little or no anticoagulant activity) within minutes. This level was maintained for 24 hours in 62 (79%) of the 78 patients for whom blood samples were available. Clotting test results were promptly normalized by idarucizumab in 88% to 98% of patients. Hemostasis was restored in the subset of patients receiving the drug for serious bleeding after a median of 11.4 hours. This median is based on the time when follow-up assessments were performed, so the time to restoration of hemostasis probably is shorter. Acceptable intraoperative

hemostasis was provided in the patients undergoing urgent procedures. No safety issues were identified with the use of idarucizumab. One thrombotic event was reported within 72 hours after idarucizumab administration in a patient who had not restarted anticoagulant therapy.

Updated results from the REVERSE-AD study were presented in 2016 for 123 patients receiving idarucizumab for dabigatran reversal, including 66 patients with serious bleeding and 57 patients undergoing an emergent procedure.[51] The mean time to incision was 1.7 hours after the idarucizumab infusion in patients undergoing surgery. Normal intraoperative hemostasis was observed in 48 of 52 assessable patients, and no major bleeding occurred post-operatively. In 48 assessable patients with serious bleeding, the median time to bleeding cessation after idarucizumab administration was 9.8 hours. Thrombotic events occurred in five patients between 2 and 24 days after the idarucizumab infusion. None of these patients were anticoagulated at the time of the thrombotic event. Twenty-six (21%) of the 123 patients died due to worsening of the emergency situation or comorbidities.

These findings underscore the importance of addressing the patient's entire clinical situation. Follow-up assessment of the risk for thrombosis to determine whether and when to resume anticoagulation also is needed.

Idarucizumab is available in 2.5-g vials and given as two consecutive infusions when the recommended 5-g dose is used to reverse the anticoagulant effects of commonly encountered serum concentrations of dabigatran. As with many antidotes, additional idarucizumab doses may be required to fully reverse the anticoagulant effects of dagibatran when excessively high concentrations are present (e.g., in overdose situations), although the safety and effectiveness of repeat treatment with idarucizumab have not been established.[46]

Andexanet Alfa

Andexanet alfa (also known as PRT4445 or PRT064445), a recombinant protein that is structurally similar to factor Xa, was developed for use as an antidote to factor Xa inhibitors. It acts as a decoy, binding to factor Xa inhibitors, thereby limiting their anticoagulant effects.[52] Andexanet alfa may neutralize the activity of other factor Xa inhibitors, including low molecular weight heparin.[53] Andexanet alfa does not cleave prothrombin to thrombin.

In studies of animals treated with rivaroxaban, andexanet alfa provided dose-dependent reversal of factor Xa inhibition, and it corrected clotting times in ex vivo assays of anti-factor Xa activity in human plasma.[53] Andexanet alfa also restored hemostasis in an animal model involving rivaroxaban and liver laceration.[53]

The efficacy of andexanet alfa administered as an i.v. bolus alone and as an i.v. bolus followed by a 2-hour infusion for reversal of apixaban 5 mg twice daily for 3.5 days or rivaroxaban 20 mg once daily for 4 days was evaluated in two parallel randomized placebo-controlled studies of healthy older volunteers known as ANNEXA-A and ANNEXA-R.[54] In ANNEXA-A, andexanet alfa was given 3 hours after the last apixaban dose (at or near the peak plasma concentration) to 24 subjects as a 400-mg bolus alone, then as a 400-mg bolus followed by a 4-mg/min infusion over 2 hours. In ANNEXA-R, andexanet was given 4 hours after the last rivaroxaban dose (at or near the peak plasma concentration) to 27 subjects as an 800-mg i.v. bolus alone, then as an 800-mg bolus followed by an 8-mg/min infusion over 2 hours. Anti-factor Xa activity was reduced by more than 90%, and the thrombin generation that had been inhibited by treatment with apixaban or rivaroxaban was fully restored within 2 to 5 minutes after administration of the andexanet alfa i.v. boluses. These effects were sustained when andexanet alfa was administered as a bolus followed by an infusion. Rebound increases in endogenous thrombin potential (ETP) above baseline values were observed approximately 1 hour after administration of bolus andexanet alfa alone, with a peak in ETP 3 hours after the bolus, which suggests that a bolus followed by continuous infusion may be needed to provide sustained reversal of anti-factor Xa activity for more than 1 hour. No thrombotic events or serious or severe adverse events were reported by subjects treated with andexanet alfa. A phase 3 trial of andexanet alfa for reversal of rivaroxaban, apixaban, edoxaban, or enoxaparin in patients with acute major bleeding is under way.[55]

These findings suggest that andexanet alfa will reverse the anticoagulant effects of factor Xa inhibitors, with a rapid onset and offset of effect, and prolonged infusion may be needed if concerns about bleeding persist. A rapid onset of effect can be advantageous for patients with impending surgery, and a rapid offset can facilitate resumption of anticoagulation. Whether currently available laboratory assays are useful for determining when the anti-factor Xa activity of the DOAC has decreased to a safe level during andexanet alfa therapy is unclear.

Ciraparantag

Ciraparantag (also known as PER977and aripazine) is an investigational factor Xa and IIa inhibitor developed for use as a "universal" antidote to reverse the anticoagulant effects of both factor Xa inhibitors and factor IIa inhibitors. The synthetic small molecule binds directly to and reverses the anticoagulant effects of factor Xa and IIa inhibitors. It also binds to fondaparinux and heparins but it does not bind to blood clotting factors, albumin, or other blood proteins.[56] In a placebo-controlled study of animals given overdoses of rivaroxaban, apixaban, or dabigatran, ciraparantag appeared to reverse the anticoagulant activity of these DOACs within 30 minutes after i.v. administration in a dose-dependent manner based on ex vivo assays of rivaroxaban and apixaban anti-factor Xa activity in human plasma.[57] Ciraparantag decreased bleeding by more than 90%. There was no evidence of prothrombotic effects.

In a phase 1 double-blind, placebo-controlled study, escalating single i.v. doses of ciraparantag (5 mg to 300 mg) were given 3 hours after a single, oral, 60-mg dose of edoxaban or placebo to 80 healthy individuals.[56] In the subjects receiving edoxaban, the whole-blood clotting time returned to baseline (i.e., hemostasis was restored) within 10 minutes after administration of 100 mg to 300 mg of ciraparantag. The effect of ciraparantag was dose-dependent and sustained for 24 hours. By contrast, the time to restoration of hemostasis in subjects given placebo was approximately 12-15 hours. There was no evidence of prothrombotic effects from use of ciraparantag. Transient mild perioral and facial flushing, dysgeusia, and headache were reported by subjects treated with ciraparantag.

Currently available data suggest that the effects of ciraparantag have a rapid onset and last for a long period that remains to be determined and will affect its clinical use. Because ciraparantag reverses both factor Xa and IIa inhibitors, its use may be problematic if resumption of anticoagulation is needed on an emergent basis. However, the reversal of both factor Xa and IIa inhibitors can be advantageous in patients with emergent bleeding caused by an unknown DOAC. Further clinical research is needed to determine the role of ciraparantag and other antidotes in reversing DOACs.

Potential Challenges

The use of antidotes to reverse DOACs can present difficulties in clinical decision making because of limited clinical experience with and availability of these products. The pharmacokinetic and pharmacodynamic properties of both the DOAC and the antidote need to be taken into consideration. Use of an antidote to reverse a DOAC with a longer duration of activity than the antidote can result in a rebound increase in the anticoagulant effects of the DOAC (i.e., risk for bleeding) when the effects of the antidote terminate. Conversely, the effects of an antidote with a long duration of activity could create challenges in resuming anticoagulant therapy.

In emergent situations with life-threatening bleeding in a patient who has taken a DOAC, it can be difficult to determine whether to use a hemostatic agent. The use of these agents in conjunction with antidotes may optimize the management of acute bleeding. The specific product, dose, and risk for thrombosis are considerations in choosing among hemostatic agents. Whether a PCC product, aPCC, or antifibrinolytic agent (e.g., tranexamic acid) is necessary or may be given using a reduced dose in a patient receiving an antidote for DOAC reversal is unclear. The use of reduced doses of reversal agents and titrating administration to the desired effect is a strategy that may be used under certain circumstances (i.e., when time is available) to meet therapeutic goals and minimize costs and risks associated with therapy.

The best strategy for accurately measuring the response to antidote administration and ascertaining when the antidote is no longer necessary remains to be determined. Patients who have exceedingly high DOAC plasma concentrations that may persist for several days after discontinuation of the DOAC (e.g., patients who have taken an overdose or in whom the dosage was not reduced to account for reduced elimination due to renal impairment) may present a challenge to clinicians. Repeated doses of the antidote (e.g., idarucizumab, ciraparantag) or prolonged infusion (e.g., andexanet alfa) may be needed until the bleeding stops.

Management Considerations

Because the prompt availability of antidotes and other reversal agents is important in urgent situations, institutional policies and procedures and standardized order sets, clinical pathways, and clinical decision support tools for use of these products should be developed to expedite the process and avoid delays that could adversely affect patient outcomes. Order sets, pathways, and clinical decision support tools should address the choice among formulary agents, dosing, and reliable laboratory testing based on the urgency of

the situation and comorbid conditions. Standardizing the approach to reversing DOACs is challenging because of the wide variability in DOAC serum concentrations due to differences in dosing (especially overdoses), organ dysfunction, drug interactions, and body weight.

Therapeutic decision making may depend on the situation. For example, optimal timing of DOAC reversal before an invasive procedure is needed to minimize the risks of bleeding and thrombosis. In patients with acute bleeding, clinical decisions may depend on the urgency of the situation and whether adequate time is available to permit titration of the antidote and addition of a hemostatic agent. Titration of a hemostatic agent may be easier in situations where bleeding can be easily measured or assessed (e.g., patients with trauma or GI bleeding) than in patients with ICH.

Small initial doses of reversal agents with optional repeat doses may be feasible in situations that are not life-threatening. Additional doses may be necessary in situations involving large DOAC overdoses or very high DOAC plasma concentrations. The reassessment of coagulation status and adjustment of reversal therapy as needed should be addressed in policies and procedures. The long-term risk for thromboembolism and need for resumption of anticoagulation should be taken into consideration. In patients with excessive anticoagulation, the cause should be identified and corrected to the extent possible to prevent recurrence. Supportive management should be included in institutional policies and procedures and standardized order sets, clinical pathways, and clinical decision support tools. The Appendix provides resources related to oral anticoagulation.

Conclusion

A risk for bleeding is associated with DOACs, and the use of reversal strategies may be needed if bleeding occurs or surgery or an invasive procedure is required in a patient receiving DOAC therapy. Antidotes may be an option for use as an alternative to or in conjunction with concentrated clotting factors and other strategies for reversal of the anticoagulant effects of DOACs. Additional clinical experience with antidotes is needed to determine the optimal approach to using these products to reverse DOACs. Institutional policies and procedures and standardized order sets, clinical pathways, and clinical decision support tools are needed to optimize outcomes in patients requiring reversal of DOACs.

Appendix. Oral Anticoagulation Resources

American College of Chest Physicians

VIEW RESOURCE Evidence-based guidelines for antithrombotic therapy and prevention of thrombosis

VIEW RESOURCE Evidence-based guidelines for antithrombotic therapy for VTE disease

American Heart Association/American College of Cardiology/ Heart Rhythm Society

VIEW RESOURCE Evidence-based guideline for the management of patients with atrial fibrillation

American Society of Clinical Oncology

VIEW RESOURCE Evidence-based clinical practice guideline for venous thrombo-embolism prophylaxis and treatment in patients with cancer

ASHP

VIEW RESOURCE ASHP therapeutic position statement on the role of pharmacotherapy in preventing venous thromboembolism in hospitalized patients

European Heart Rhythm Association

VIEW RESOURCE Updated practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

VIEW RESOURCE Practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation.

The Joint Commission

VIEW RESOURCE National Patient Safety Goal 03.05.01 effective January 1, 2016

VIEW RESOURCE Venous thromboembolism measures as of January 8, 2016

VIEW RESOURCE Sentinel Event Alert issue 41: Preventing errors relating to commonly used anticoagulants (from September 24, 2008)

Neurocritical Care Society and Society of Critical Care Medicine

VIEW RESOURCE Guideline for reversal of antithrombotics in intracranial hemorrhage

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