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Drug Update

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Anticoagulation Reversal Management

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Anticoagulants are commonly used in clinical practice for a variety of indications, including treatment of deep vein thrombosis and pulmonary embolism, prevention of acute ischemic stroke in patients with atrial fibrillation, management of clotting disorders, and treatment of patients with heart valve replacement.[1] Currently available oral anticoagulants include vitamin K antagonists (warfarin), direct thrombin inhibitors (dabigatran), and factor Xa inhibitors (eg, direct-acting oral anticoagulants [DOACs] such as apixaban, rivaroxaban, betrixaban, and edoxaban).[2,3] Parenteral anticoagulation agents include heparin, low-molecular-weight heparin (LMWH) (enoxaparin), pentasaccharide (fondaparinux), and direct thrombin inhibitors (argatroban and bivalirudin).[2,3] Anticoagulation use, particularly the use of DOACs, has increased over the years. Troy and Anderson[1] analyzed national trends in oral anticoagulant use among US Medicare beneficiaries from 2011 to 2019. The percentage of Medicare Part D beneficiaries using oral anticoagulants increased from 9.2% to 11.5% during this time. The percentage of these beneficiaries using DOACs increased from 7.4% to 66.8%, whereas the number of beneficiaries using warfarin decreased from 2.48 million to 1.74 million.[1] Additionally, in a study of 436 864 patients with atrial fibrillation in community practice, the percentage of patients using DOACs increased from 4.7% in 2011 to 47.9% in 2020.[4]

Anticoagulation and anticoagulation reversal management are centered on the clotting cascade.[2,3] The clotting cascade creates a stable fibrin clot via the intrinsic and extrinsic pathways. The intrinsic pathway contains factors XII, XI, IX, and VIII. Spontaneous internal damage to the vascular endothelium activates the intrinsic pathway. The extrinsic pathway contains factors III and VII. The extrinsic pathway is activated secondary to a traumatic event. These pathways merge at factor Xa to form the common pathway, which includes the remaining factors. Anticoagulants target various substrates of this clotting cascade. Vitamin K antagonists inhibit factors II, VII, IX, and X and proteins C and S. Direct oral anticoagulants and fondaparinux inhibit factor Xa. Heparin inhibits factors IIa (thrombin) and Xa. Like heparin, direct thrombin inhibitors inhibit factor IIa, but they do not inhibit factor Xa.[2,3] Reversal agents also target the clotting cascade, limiting the effects of anticoagulants or rendering them ineffective.

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The goal of anticoagulation reversal is to achieve hemostasis and preserve organ function.[3] As the use of anticoagulants increases, health care professionals should be familiar with options available for anticoagulation reversal.

Anticoagulation Reversal Agents

Anticoagulation reversal agents can be categorized as nonspecific reversal agents or specific reversal agents. Fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), activated PCC, and recombinant factor VIIa are nonspecific anticoagulation reversal agents. Specific anticoagulation reversal agents include protamine, vitamin K, idarucizumab, and andexanet alfa.[3]

Nonspecific Anticoagulation Reversal Agents

Fresh frozen plasma contains all coagulation factors, fibrinogen, protein C, and von Willebrand factor.[3,5,6] It is derived from donor plasma and then rapidly frozen and stored. Each unit of FFP has a volume of 200 to 250 mL and is dosed at 10 to 15 mL/kg (averaging 4-5 units per dose). The onset of action for restoration of clotting factors is 13 to 48 hours. Limitations of FFP include potential delays in administration due to ABO blood typing and thawing of the plasma. Because FFP is a blood product, ABO blood typing is required to prevent hemolysis caused by incompatible blood types. The use of FFP requires infusion of a large volume of fluid, which is not ideal in patients who have a preexisting comorbidity (eg, heart failure or end-stage renal disease) that makes fluid balance a challenge. Fresh frozen plasma can be associated with pathogen transmission and transfusion-related acute lung injury, but these are not common.[3,5,6]

Prothrombin complex concentrate is also derived from human plasma.[3,5,7] The main PCCs used in clinical practice are 3-factor PCC and 4-factor PCC. Three-factor PCC contains factors II (prothrombin), IX, and X. Four-factor PCC contains factors II, VII, IX, and X. Onset of anticoagulation reversal for PCCs is approximately 10 to 30 minutes, and half-life is 4 to 6 hours for factor VII and 60 hours for factor II.[8] These agents work quickly, but their continued action affects the time at which anticoagulation therapy can be restarted. Prothrombin complex concentrates are highly effective for hemostasis restoration but carry a risk of thrombosis due to their procoagulant effects. Four-factor PCC is preferred over 3-factor PCC because it contains factor VII.[3,5,7,8]

Activated PCC is a factor VIII inhibitor–bypassing agent.[3,5,7] It primarily contains the activated form of factor VII and inactive forms of vitamin K–dependent coagulation proteins. It also has smaller quantities of factors II, IX, and X. Activated PCC has an onset of peak thrombin generation within 15 to 30 minutes and a half-life of 2 to 3 hours for factor VIIa and 60 hours for factor II.[3,8] Compared with other nonspecific anticoagulation reversal agents, activated PCC is more expensive and associated with more thromboembolic complications. Activated PCC has been used off label for the reversal of DOACs.[3,5,7,8]

Recombinant factor VIIa is commercially available.[5] It binds to the tissue factor at sites of injury and initiates coagulation via the extrinsic pathway. Factor VIIa has an onset of action of 15 minutes and a half-life of 2 to 3 hours.[9,10] Thrombotic events are the most common and serious adverse reactions associated with factor VIIa use. Factor VIIa can be used off label for DOAC reversal.[5]

Specific Anticoagulation Reversal Agents

Protamine sulfate serves as the reversal agent for heparin and LMWH.[8,11-13] It works by binding to heparin to form a stable salt that will interfere with anticoagulation. Unlike its action on heparin, protamine will not completely neutralize the anti–factor Xa activity of LMWH (maximum neutralization effect is about 60% to 75%). The incomplete neutralization is thought to be due to poor binding of protamine to the molecular moieties of LMWH and to the longer half-life of LMWH.[14] Protamine has an onset of action of about 5 minutes and a half-life of around 7 minutes. Adverse effects of protamine include hypotension, bradycardia, flushing of skin, and possible anaphylactic reactions.[13] The dosing of protamine depends on the timing of the last dose of heparin or LMWH, as illustrated in Table 1.[6,7,11,12]

Vitamin K is indicated for the reversal of vitamin K antagonists.[3,7] Vitamin K allows for the synthesis of vitamin K–dependent clotting factors by serving as a cofactor to produce factors II, VII, IX, and X and proteins C and S.[8] Vitamin K overcomes vitamin K antagonists in a dose-dependent manner to restore the activity of vitamin K–dependent clotting

Table 1: Protamine Sulfate Dosing[a]

Agent	Half-Life	Time of Last Dose of Agent	Recommended Dose
Heparin	60-90 min	≤30 min ago	1 mg protamine for every 100 units heparin administered (maximum 50 mg protamine)
		30 min to 2 h ago	0.5 mg protamine for every 100 units heparin administered (maximum 50 mg protamine)
		>2 h to <4 h ago	0.25 mg protamine for every 100 units heparin administered (maximum 50 mg protamine)
		≥4 h ago	Protamine likely not required
Enoxaparin	4.5-7 h	≤8 h ago	Protamine dose (mg) is equal to the enoxaparin dose (mg) administered (maximum 50 mg protamine)
		>8 h to <12 h ago OR if a second dose is indicated[b]	Protamine dose (mg) is equal to 50% of the enoxaparin dose (mg) administered (maximum 50 mg protamine)
		≥12 h or 3-5 half-lives have lapsed	Protamine likely not required

[a] Data were derived from Yee and Kaide,[6] Baugh et al,[7] Lamperti et al,[11] and the enoxaparin sodium package insert.[12]
[b] A second dose of protamine may be indicated if the activated partial thromboplastin time remains prolonged 2 to 4 hours after the first protamine dose has been given.

factors. Vitamin K is dosed at 1 to 10 mg via the oral, subcutaneous, intramuscular, or intravenous routes. Vitamin K should never be administered as an intravenous push; rather, it should be given as a slow intravenous infusion (diluted in 50 mL normal saline and given over 15 to 30 minutes).[3] Patients can have infusion reactions to vitamin K. If a patient experiences a reaction or has a history of a reaction, the vitamin K infusion time should be extended longer than the standard 15 to 30 minutes. Anaphylactic reactions to vitamin K have been reported; however, the preparations currently on the market do not appear to carry the same risk.[3] Subcutaneous and intramuscular administration are not recommended due to erratic absorption and the risk of hematoma development.[8] After intravenous administration of vitamin K, the international normalized ratio will begin to decrease within 1 to 2 hours, with a peak effect at 4 to 6 hours. If administered orally, the onset of action is 6 to 10 hours and the peak effect occurs around 24 to 48 hours after administration.[7,8]

Idarucizumab is the reversal agent for dabigatran.[5,7] Dabigatran functions as a direct thrombin inhibitor to inhibit thrombin that is free or fibrin bound. Idarucizumab binds to dabigatran more strongly than dabigatran binds to thrombin, so it neutralizes dabigatran's anticoagulant effect.[15] Idarucizumab rapidly (within minutes) normalizes activated partial thromboplastin time, diluted thrombin time, and ecarin clotting time. Idarucizumab is dosed at 5 g intravenously for 1 dose, and it is supplied and administered as two 2.5-g doses given about 15 minutes apart. Limited evidence supports giving additional doses of idarucizumab. However, an additional dose could be considered if bleeding continues, if laboratory tests demonstrate a continued anticoagulant effect of dabigatran, or if a continued anticoagulant effect is suspected before a second invasive procedure is performed. The initial half-life is 25 minutes, and the terminal half-life is 10.3 hours. Adverse responses to idarucizumab include increased thromboembolic risk and hypersensitivity reactions. Additionally, patients with a hereditary fructose intolerance may be at an increased risk of serious adverse events due to the sorbitol excipient in idarucizumab.[15] Dabigatran can be restarted 24 hours after idarucizumab administration in appropriate patients.[5,7]

Andexanet alfa is a reversal agent for factor Xa inhibitors such as DOACs.[3] Andexanet alfa has US Food and Drug Administration approval to reverse apixaban and rivaroxaban; however, it is often also used off label to reverse betrixaban and edoxaban.[3,16] It is a

recombinant modified variant of factor Xa that acts as a decoy protein. It reversibly binds to and sequesters factor Xa inhibitors. It also neutralizes the anticoagulant effects of factor Xa inhibitors by decreasing free plasma concentrations of apixaban and rivaroxaban. Additionally, it competes with factor Xa for binding to the heparin-antithrombin complex, neutralizing the effect of LMWH and unfractionated heparin. However, it is currently approved only for reversal of DOACs. Andexanet alfa decreases anti–factor Xa activity by more than 90% within 5 minutes and restores thrombin generation to normal levels within 10 minutes. The half-life of andexanet alfa is 1 hour. Andexanet alfa dosing is either low dose or high dose.[6,16] The low dose is for patients who have taken apixaban at a dose of 5 mg or less or rivaroxaban at a dose of 10 mg or less within the previous 8 to 18 hours or who have taken apixaban or rivaroxaban with an unknown time of last dose. The low dose is a 400-mg intravenous bolus given over 15 minutes, followed immediately by a 480-mg intravenous infusion over 2 hours. The high dose is indicated for patients who have taken apixaban at a dose greater than 5 mg or rivaroxaban at a dose greater than 10 mg within the previous 8 hours. The high dose is an 800-mg intravenous bolus given over 30 minutes, followed immediately by a 960-mg intravenous infusion over 2 hours. Andexanet alfa requires refrigeration for storage and a filter for administration.[3,16]

The most recent trial evaluating the safety and efficacy of andexanet alfa was the ANNEXA-I (Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage) trial.[17] The purpose of the ANNEXA-I trial was to compare andexanet alfa with usual care for limiting hematoma expansion in patients with an intracerebral hemorrhage. In this trial, andexanet alfa achieved greater hemostatic efficacy than did usual care in patients who had taken factor Xa inhibitors within 15 hours before having an intracerebral hemorrhage (150 of 224 patients [67.0%] receiving andexanet alfa vs 121 of 228 patients [53.1%] receiving usual care; adjusted difference per 100 patients, 13.4; 95% CI, 4.6-22.2; $P = .003$). However, more patients in the andexanet alfa group than in the usual-care group experienced at least 1 thrombotic event (27 of 263 patients [10.3%] receiving andexanet alfa vs 15 of 267 patients [5.6%] receiving usual care; increase per 100 patients, 4.6; 95% CI, 0.1-9.2; $P = .048$). Additionally, ischemic stroke occurred in 17 of 263 patients (6.5%) who received andexanet alfa versus 4 of 267 patients (1.5%) who received usual care. Currently, no evidence supports using andexanet alfa to reverse anticoagulation before surgical procedures.[18] The ANNEXA-RS (A Study of Andexanet Alfa in Patients Requiring Urgent Surgery or Procedure) trial (NCT05926349) is comparing andexanet alfa use with usual care in patients who take a factor Xa inhibitor and require an urgent surgery or procedure. This phase 3 trial is expected to be completed by November 2026.[15,17]

Ciraparantag (PER977) is an oral anticoagulant reversal agent that is still in development.[3,18] Ciraparantag binds to inhibitors of factor Xa and thrombin. It can bind noncovalently to heparin, LMWH, and DOACs. Once bound, it inhibits the anticoagulant from binding to its endogenous target. It works within minutes after intravenous administration and has a relatively short half-life of 12 to 19 minutes. Two phase 2 studies of the use of ciraparantag to reverse apixaban (NCT03288454) and rivaroxaban (NCT03172910) have been completed; however, as of this writing the results have not yet been published. The use of ciraparantag for reversal of anticoagulation in healthy adult patients taking edoxaban, apixaban, or rivaroxaban is being studied in a phase 2 trial (NCT04593784).[3,18]

Criteria for Anticoagulation Reversal

The indication for anticoagulation reversal guides reversal agent selection. The 2 main indications for anticoagulation reversal are management of bleeding and preparation for surgical procedures or other invasive procedures.

Anticoagulation Reversal for Management of Bleeding

In 2020, the American College of Cardiology published guidance for managing bleeding in patients who take oral anticoagulants.[3] First, the patient's bleed must be categorized as major or nonmajor, as outlined in Table 2. This categorization helps determine the appropriate management strategy. After the bleed has been categorized, the patient's risk should be assessed according to the location of the bleed and whether the bleed is considered life-threatening.[3]

Table 2: Criteria for Classifying Major and Nonmajor Bleeds[a]

Major Bleed (must meet ≥ 1 criteria)	Nonmajor Bleed
Bleeding at a critical site: • Intracranial hemorrhage (intraparenchymal, subdural, epidural, or subarachnoid hemorrhage) • Other central nervous system hemorrhage (intraocular, intra- or extra-axial, spinal hemorrhages, pericardial tamponade) • Airway (posterior epistaxis) • Hemothorax • Intra-abdominal hemorrhage • Retroperitoneal hemorrhage • Extremity bleeds (intramuscular and intra-articular bleeds)	None of the major bleed criteria met
Hemodynamic instability: • Systolic blood pressure <90 mm Hg • Decrease in systolic blood pressure of >40 mm Hg • Orthostatic blood pressure changes (systolic blood pressure drop of ≥20 mm Hg or diastolic blood pressure drop of ≥10 mm Hg)	
Clinically overt bleeding with a ≥2 g/dL hemoglobin decrease or administration of ≥2 units packed red blood cells	

[a] Data were derived from Tomaselli et al.[3]

If the bleed is considered major and is at a critical site or life-threatening (ie, uncontrollable bleeding), the oral anticoagulant should be stopped, nonpharmacologic interventions should be performed, and the patient should receive a pharmacologic agent such as a reversal agent or hemostatic agent with the goal of managing the bleed and ensuring that the patient's condition becomes stable.[3] If the major bleed is not at a critical site or life-threatening, then the oral anticoagulant should be stopped and interventions to stop the bleeding should be made. If neither of these strategies control the bleeding, then a reversal agent or hemostatic agent should be administered to control bleeding and stabilize the patient. If the bleed is considered nonmajor and the patient requires hospitalization, surgical/procedural intervention, or transfusion, then the oral anticoagulant should be stopped and interventions (both pharmacologic and nonpharmacologic) to manage bleeding should be employed. If the patient's condition is stable (not requiring hospitalization, surgical or procedural interventions, or blood transfusions) and interventions successfully manage the bleeding, then it is likely safe for the patient to resume oral anticoagulant therapy.[3]

When the patient's condition is stable (bleeding appears controlled and the patient's hemodynamics have improved), the patient should be evaluated for a clinical indication for continuing oral anticoagulation.[3] If no clinical indication exists, then discontinuing the anticoagulant is suggested. A patient should not resume anticoagulation if the bleed is at a critical site, if the patient is at high risk of rebleeding (high risk factors include lobar intracranial hemorrhage secondary to amyloid angiopathy and spontaneous subdural hematomas), if the patient is at high risk of death or disability if additional bleeding occurs, if the source of the bleed is not known, if a surgical procedure or other invasive procedure is planned, or if the patient prefers not to resume anticoagulation. If none of these situations apply, then restarting the oral anticoagulant could be considered.[3]

If a patient has ongoing bleeding and/or hemostatic instability, employing nonpharmacologic measures (if appropriate) to help manage the bleeding is recommended.[3,19] These measures include applying pressure and packing. The patient can also receive aggressive volume resuscitation via isotonic crystalloid solution (0.9% sodium chloride or lactated Ringer solution) or blood products as directed by the health care provider. If a patient receives 3 or more units of packed red blood cells within 1 hour, the American College of Cardiology recommends that site-specific massive transfusion protocols be activated.[19] Patients who

receive a massive transfusion protocol need calcium supplementation[20] because the anticoagulant citrate, used as a preservative in blood products, will chelate calcium in the blood. It is reasonable to administer 1 g of calcium gluconate for every 3 units of packed red blood cells that a patient receives during massive transfusion.[3,20]

Anticoagulation Reversal Before Surgical Procedures or Other Invasive Procedures

Anticoagulation may also require reversal before surgical procedures or other invasive procedures. For planned procedures, oral anticoagulants should ideally be withheld during the days before the procedure to limit the need for reversal agents. However, anticoagulation reversal may be necessary for procedures that are unplanned or urgent.

Milling and Pollack[9] sought consensus among guidelines for anticoagulation reversal in various clinical scenarios. For the reversal of vitamin K antagonists before surgery or other invasive procedures, the use of 4-factor PCC with or without vitamin K is recommended. If PCC is not available, FFP can be considered. For the reversal of DOACs, andexanet alfa could be considered. However, andexanet alfa has not been approved by the US Food and Drug Administration for periprocedural reversal of factor Xa inhibitors. Alternative agents that could be used for factor Xa reversal include 4-factor PCC and activated PCC. Recombinant factor VIIa should be considered only in patients for whom other measures have been unsuccessful because recombinant factor VIIa carries a high risk of thrombosis. Idarucizumab should be used for dabigatran reversal.[9]

A study of reversal agents for DOACs was published in the *European Heart Journal* in 2023.[5] For patients receiving anticoagulation who require an intervention or surgical procedure that has an intermediate or high bleeding risk, reversing the oral anticoagulant is recommended. For patients taking a direct thrombin inhibitor (dabigatran), the reversal strategy should be idarucizumab 5 g intravenously given once. If idarucizumab is unavailable, activated PCC or PCC can be administered at a dose of 50 units/kg intravenously. For reversal of factor Xa inhibitors (including apixaban and rivaroxaban), administering PCC 50 units/kg intravenously is recommended.[5]

Anticoagulation Reversal Agent Selection

The American College of Cardiology recommends using vitamin K and 4-factor PCC to reverse bleeding in patients taking vitamin K antagonists.[3] If 4-factor PCC is unavailable, using FFP is recommended. The American College of Cardiology and the European Society of Cardiology recommend administering idarucizumab to reverse dabigatran; if idarucizumab is unavailable, PCC or activated PCC could be used.[5] The American College of Cardiology and the European Society of Cardiology recommend using andexanet alfa to reverse factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban). However, the European Society of Cardiology recommends using either andexanet alfa or PCC, whereas the American College of Cardiology recommends using PCC or activated PCC only if andexanet alfa is unavailable. Additionally, for patients with a known recent (≤4 hours before presentation) ingestion of dabigatran or a factor Xa inhibitor, activated charcoal may provide benefit. For nonurgent interventions or surgical procedures in patients receiving anticoagulants, the European Society of Cardiology recommendations are unchanged for reversal of thrombin inhibitors (dabigatran); however, for reversal of factor Xa inhibitors, the only recommended option is PCC.[5]

Conclusion

Anticoagulation reversal is common in the hospital setting. The decision to reverse anticoagulation should be personalized to the patient and made by the multidisciplinary team weighing the risks and benefits of treatment. Treatment can include the use of nonspecific or specific reversal agents, depending on the anticoagulant ingested. The results of future trials evaluating the safety and efficacy of the newer reversal agents, andexanet alfa and ciraparantag, have the potential to shape future practice.

REFERENCES

1. Troy A, Anderson TS. National trends in use of and spending on oral anticoagulants among US Medicare beneficiaries from 2011 to 2019. *JAMA Health Forum.* 2021;2(7):e211693. doi:10.1001/jamahealthforum.2021.1693
2. Opoku A, Iwuji K, Clough B, et al. Discordance between aPTT and anti-factor Xa levels and implications in patients receiving intravenous unfractionated heparin therapy. *Southwest Respir Crit Care Chron.* 2019;7(30):12-18. doi:10.12746/swrccc.v7i30.559
3. Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC expert consensus decision pathway on management of

bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2020;76(5):594-622. doi:10.1016/j.jacc.2020.04.053
4. Navar AM, Kolkailah AA, Overton R, et al. Trends in oral anticoagulant use among 436864 patients with atrial fibrillation in community practice, 2011 to 2020. *J Am Heart Assoc*. 2022;11(22):e026723. doi:10.1161/JAHA.122.026723
5. van Es N, De Caterina R, Weitz JI. Reversal agents for current and forthcoming direct oral anticoagulants. *Eur Heart J*. 2023;44(20):1795-1806. doi:10.1093/eurheartj/ehad123
6. Yee J, Kaide CG. Emergency reversal of anticoagulation. *West J Emerg Med*. 2019;20(5):770-783. doi:10.5811/westjem.2018.5.38235
7. Baugh CW, Levine M, Cornutt D, et al. Anticoagulant reversal strategies in the emergency department setting: recommendations of a multidisciplinary expert panel. *Ann Emerg Med*. 2020;76(4):470-485. doi:10.1016/j.annemergmed.2019.09.001
8. Simon EM, Streitz MJ, Sessions DJ, Kaide CG. Anticoagulation reversal. *Emerg Med Clin North Am*. 2018;36(3):585-601. doi:10.1016/j.emc.2018.04.014
9. Milling TJ, Pollack CV. A review of guidelines on anticoagulation reversal across different clinical scenarios - is there a general consensus? *Am J Emerg Med*. 2020;38(9):1890-1903. doi:10.1016/j.ajem.2020.05.086
10. Mehringer SL, Klick Z, Bain J, et al. Activated factor 7 versus 4-factor prothrombin complex concentrate for critical bleeding post-cardiac surgery. *Ann Pharmacother*. 2018;52(6):533-537. doi:10.1177/1060028017752365
11. Lamperti M, Jain A, Byrappa V. Reversal of anticoagulation in neurosurgical and neurocritical care settings. In: Prabhakar H, ed. *Essentials of Evidence-Based Practice of Neuroanesthesia and Neurocritical Care*. Academic Press; 2022:239-266. Accessed July 24, 2024. doi:10.1016/b978-0-12-821776-4.00018-4
12. Enoxaparin sodium. Package insert. Sanofi-Aventis US LLC; 2009. Accessed July 24, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020164s083lbl.pdf
13. Protamine sulfate. Package insert. Fresenius Kabi; 2024. Accessed July 15, 2024. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7a31fc4c-579f-45cc-9559-39cfad9a57b3
14. Vanderwerf JD, Kumar MA. Management of neurologic complications of coagulopathies. *Handb Clin Neurol*. 2017;141:743-764. doi:10.1016/B978-0-444-63599-0.00040-5
15. Praxbind. Package insert. Boehringer Ingelheim Pharmaceuticals Inc; 2015. Accessed July 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf
16. Andexanet alfa. Package insert. AstraZeneca Pharmaceuticals LP; 2018. Accessed June 27, 2024. https://www.fda.gov/media/113279/download?attachment
17. Connolly SJ, Sharma M, Cohen AT, et al; ANNEXA-I Investigators. Andexanet for factor Xa inhibitor-associated acute intracerebral hemorrhage. *N Engl J Med*. 2024;390(19):1745-1755. doi:10.1056/NEJMoa2313040
18. Ansell J, Laulicht BE, Bakhru SH, et al. Ciraparantag, an anticoagulant reversal drug: mechanism of action, pharmacokinetics, and reversal of anticoagulants. *Blood*. 2021;137(1):115-125. doi:10.1182/blood.2020007116
19. ACS TQIP massive transfusion in trauma guidelines. American College of Surgeons. 2014. Accessed July 2024. Accessed July 23, 2024. https://www.facs.org/media/zcjdtrd1/transfusion_guildelines.pdf
20. Robinson A, Rech MA, DeChristopher PJ, et al. Defining the optimal calcium repletion dosing in patients requiring activation of massive transfusion protocol. *Am J Emerg Med*. 2023;70:96-100. doi:10.1016/j.ajem.2023.05.017

CE Evaluation Instructions

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:

1. Discuss anticoagulation reversal agents.
2. Review criteria for anticoagulation reversal.
3. Summarize recommendations for anticoagulation reversal agent selection.

Contact hour: **1.0**
Pharmacology contact hour: **1.0**
Synergy CERP Category: **B**

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