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Practical, Evidence-Based Reviews in Trauma Care

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AHC Media

Anticoagulation in the Trauma Patient

The number and variety of anticoagulants have expanded greatly during the past decade. No longer is warfarin the only anticoagulant medication encountered in the trauma bay. Because of the large number of individuals on anticoagulation for various conditions, anticoagulated patients assuredly will present as trauma patients. Knowing how to and, more importantly, when to reverse these agents is critical to successful resuscitation. The reasons for anticoagulation vary widely. Pulmonary embolism, artificial heart valves, vascular stents, and deep vein thrombosis (DVT) are perhaps the most common reasons for anticoagulation. When a patient sustains a traumatic injury, rapid reversal of these anticoagulants may become necessary. Although historically physicians could simply use fresh frozen plasma (FFP) and vitamin K to reverse warfarin, or protamine to partially reverse low molecular weight heparin (LMWH), there now are four novel anticoagulants (NOACs) that potentially may need to be reversed, with more new agents in the pipeline. Antiplatelet agents that act on a completely different part of the clotting system also can be complicating factors in trauma patients. This article reviews methods of anticoagulation reversal for warfarin, LMWHs, the NOACS, and antiplatelet agents and presents a strategy for managing patients appropriately.

Case

A 68-year-old woman with a history of atrial fibrillation is brought in by emergency medical services (EMS) after she was the restrained driver in a motor vehicle accident. Her vital signs are: heart rate 105 beats per minute, respiratory rate 16 breaths per minute, and blood pressure 102/75 mmHg. She has a past medical history of hypertension and atrial fibrillation and is taking lisinopril and rivaroxaban (Xarelto®). She is complaining of abdominal pain. The primary and secondary trauma survey are conducted, and the patient has a positive Focused Abdominal Sonography in Trauma (FAST) exam showing fluid in Morison's pouch. What reversal agents or blood products should be considered in the management of this patient?

Introduction

Bleeding rates vary based on the type of anticoagulant. It is estimated that for warfarin the incidence of bleeding is approximately 15-20% per year, and the incidence of life-threatening bleeding is 1-3% per year.[1] Approximately 2.6 million people have atrial fibrillation and many are taking warfarin for stroke prophylaxis. In 2010 about 30 million prescriptions for warfarin were written just for patients with atrial fibrillation, with many other clinical indications for anticoagulation. In addition, many doctors are turning to new anticoagulants such

EXECUTIVE SUMMARY

- Thromboelastography is a functional test of coagulation of whole blood that takes into account the interaction of clotting factors, fibrinogen, and platelets by determining the viscoelasticity of the clot during formation and breakdown. Although not a substitute for standard tests of coagulation, it can augment the understanding of the patient's overall coagulation picture and help guide the need for transfusion of various blood products.
- There are two components for warfarin reversal: sustained reversal with vitamin K administration, and a more immediate reversal with products like prothrombin complex concentrates or fresh frozen plasma.
- Although heparin is completely reversed using protamine sulfate, low molecular weight heparin reversal with protamine is only partial. The algorithm for reversal is not as easy to follow as the algorithm for unfractionated heparin reversal.
- In the fall of 2015, idarucizumab (PraxBind®) was introduced for dabigatran reversal. It is a monoclonal antibody to dabigatran with an affinity 350 times higher than factor II for the dabigatran molecule, reversing the effects of dabigatran within minutes.
- According to expert panel recommendations from the Hemostasis and Thrombosis Research Society, Thrombosis and Hemostasis Summit of North America, the use of 4-factor PCCs is the preferred reversal agent for Xa inhibitors. This is likely to change as new agents for reversal become FDA approved.

as factor Xa and factor II inhibitors.

The combination of trauma and anticoagulation may be significant. One study estimated that about 3% of patients presenting to a level 1 trauma center were using warfarin, with a threefold increase in mortality.[2] A working knowledge of reversal of anticoagulation induced by any number of older and newer agents is essential for the treating clinician.

Normal Hemostasis

Hemostasis is a complex process, but a few basic principles can guide the understanding of anticoagulants and their reversal. Hemostasis is a tightly regulated balance between clot formation and clot breakdown and occurs as the result of two independent systems.

Primary hemostasis involves the attachment of platelets to damaged, exposed endothelium via von Willebrand factor. Platelets subsequently are activated and release substances into the blood (serotonin, platelet activating factor, platelet factor 4, thromboxane A2, etc.), which act to attract, activate, and facilitate aggregation of other platelets. In primary hemostasis, the integrity of this system depends on both the number of platelets available (platelet count) and platelet function. The function can be affected by many factors, including medications such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and other specific antiplatelet agents, along with additional factors such as uremia. While platelet function testing can be performed, it is rarely done in the emergency setting.

Table 1. Testing the System

Test	Range	Components Tested	Medications
Prothrombin Time (PT/INR)	12-13 sec/0.8-1.2	Extrinsic and common pathways (II, VII, X)	Warfarin, anti-Xa agents (rivaroxaban*, apixaban*, edoxaban*)
Partial Thromboplastin Time (PTT)	30-60 sec	Intrinsic and common pathways (all factors except factor VII)	Heparin, factor II inhibitors (dabigatran**)
Anti-Xa Levels		Factor X	LMWHs, Anti-Xa agents (rivaroxaban*, apixaban*, edoxaban*)

*PT is frequently elevated with these agents, but a prediction as to the degree of anticoagulation is unreliable with these agents.
**PTT is useful in determining the presence of an anti-factor II activity; however, it cannot be used to monitor the degree of anticoagulation produced by these medications.

Secondary hemostasis involves activation of the clotting cascade, resulting in the catalysis of fibrinogen to fibrin. Fibrin acts to cross link and thereby strengthen the primary platelet plug. The integrity of the system depends on the quantity of functional clotting factors and their successful activation. In addition, the subsequent components of the cascade must be present in adequate quantities, be functional, and be successfully activated. Secondary hemostasis is tested by measuring the prothrombin time (PT) and the partial thromboplastin time (PTT). (*See Table 1.*)

Impact of Anticoagulation Agents and Other Factors on Normal Hemostasis

The practicing clinician does not need to understand the nuances and complexities of the coagulation cascade. A basic familiarity with five coagulation factors (II, VII, VIII, IX, and X) can explain almost all of the clinically relevant aspects of anticoagulation and its reversal. Factor VIII is included here because of its relevance to inherited clotting disorders: factor VIII deficiency (hemophilia A) and factor IX deficiency (hemophilia B). Patients with either of these diseases can present as trauma patients. (*See Figures 1-3; see also Table 1.*) Although anti-factor Xa activity can be tested to evaluate the effectiveness of anti-Xa agents, it is rarely useful in the emergency setting. PT can be prolonged with the use of rivaroxaban, an anti-Xa agent; however, the degree of PT/INR abnormality is not an effective measure of anticoagulation.

Figure 1. Where Warfarin Acts

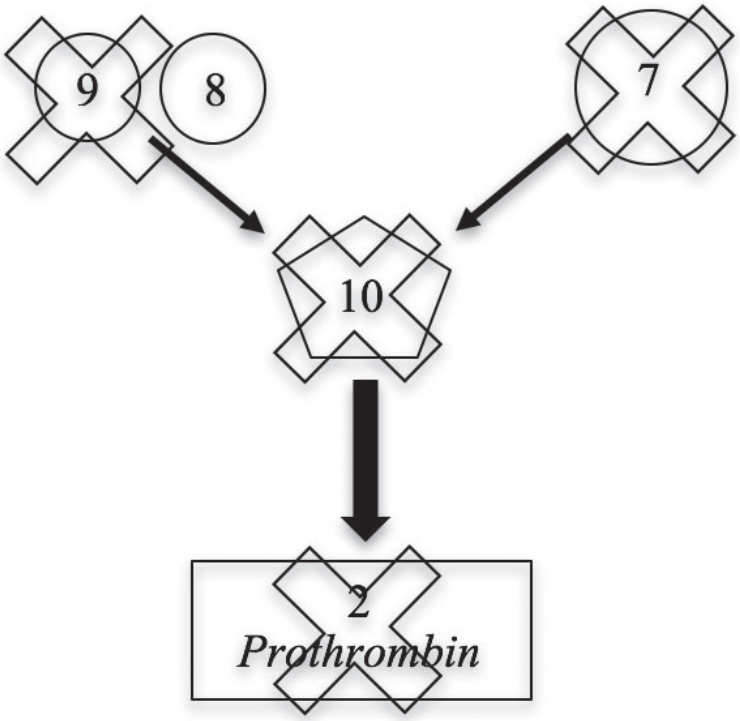
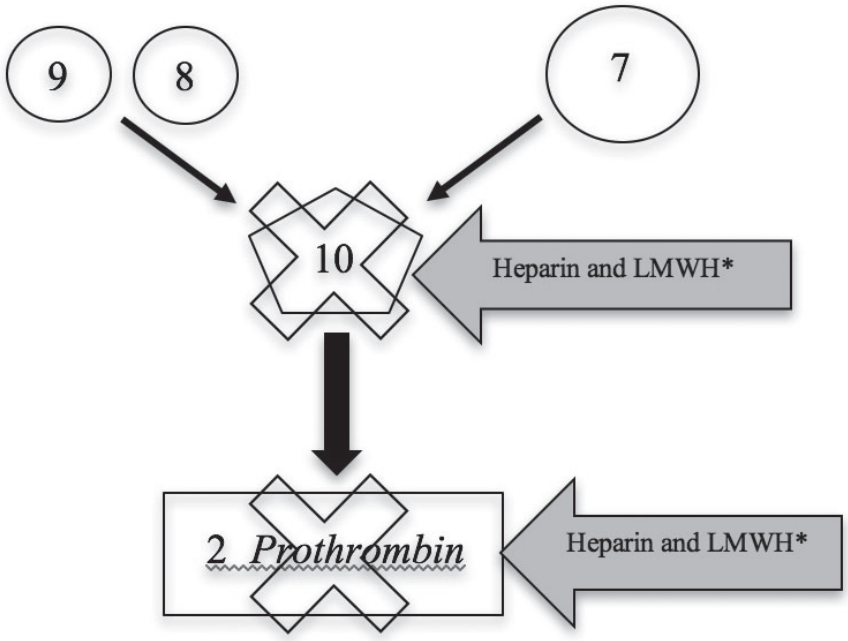


Figure courtesy of Colin Kaide, MD

Figure 2. Where Heparins Act



Heparin acts on factor X and factor II equally. LMWH acts primarily on factor X, with varying ratios of anti-X/anti-II activity.
Figure courtesy of Colin Kaide, MD

With rivaroxaban, a normal PT/INR does effectively exclude significant drug levels. PT/INR is very insensitive for detecting or predicting anticoagulation with apixaban (Eliquis®) or edoxaban (Savaysa®).[3,4] The aPTT will be prolonged in patients who are taking the factor II inhibitor dabigatran (Pradaxa®), and a normal aPTT excludes any significant level of the drug.[3] In addition to medications that can affect coagulation, malnutrition and severe liver disease can have a significant effect on the production of functional clotting factors.

Thromboelastography

Thromboelastography (TEG) is a functional test of coagulation of whole blood that takes into account the interaction of clotting factors, fibrinogen, and platelets by determining the viscoelasticity of the clot during formation and breakdown. There is growing interest in the use of TEG in trauma patients to assess the patients' entire clotting process.[5]

TEG works by measuring the physical properties of clot formation in whole blood. The sample is placed in a cup in which a pin is suspended from a torsion wire. The wire is connected to a mechanical-electrical transducer. As clotting progresses, an increased tension in the coagulating blood alters the rotation of the pin. These changes are converted into electrical signals that the software converts into a graphi representation. Measurements of the different phases of clotting and subsequent fibrinolysis are shown as changing of the shape of the graphic.[6]

Although not a substitute for standard tests of coagulation, TEG can augment the understanding of the patient's overall coagulation picture and help guide the need for transfusion of various blood products. Varying patterns of the TEG tracing can be used to identify anomalies in the coagulation process.

Anticoagulation Drugs and Strategies for Reversal

Warfarin

Warfarin is a vitamin K antagonist that blocks the production of active vitamin K-dependent coagulation factors II, VII, IX, X, and antithrombotic proteins C and S. In the case of serious trauma or hemorrhage, any warfarin effect resulting in an INR greater than 1.4 should be reversed. In patients with

Figure 3. Where NOACs Act

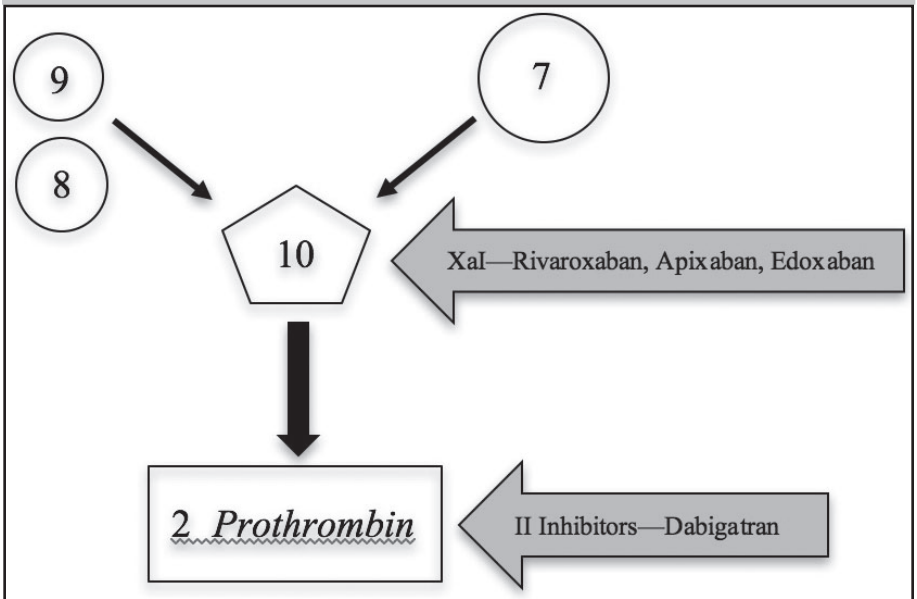


Figure courtesy of Colin Kaide, MD

Table 2. Recommendations for Managing Increased INRs or Bleeding in Patients Receiving Vitamin K Antagonists

Condition	Description
INR above therapeutic range but < 5.0; no significant bleeding	Lower dose or omit dose, monitor more frequently, and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required.
INR ≥ 5.0 but ≤ 10.0; no significant bleeding	Omit next one or two doses, monitor more frequently, and resume at lower dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K1 (1-2.5 mg orally), particularly if at increased risk of bleeding. If more rapid reversal is required because the patient requires urgent surgery, vitamin K1 (2-4 mg orally) can be given with the expectation that the INR will decrease in 24 hours. If the INR is still high, additional vitamin K1 (1-2 mg orally) can be given.
INR > 10.0; no significant bleeding	Hold warfarin therapy and give higher dose of vitamin K1 (5-10 mg orally) with the expectation that the INR will be reduced substantially in 24-48 hours. Monitor more frequently, and use additional vitamin K1 if necessary. Resume therapy at lower dose when INR therapeutic.
Serious or life-threatening bleeding at any elevation of INR	Hold warfarin therapy and give vitamin K1 (10 mg by slow IV infusion), supplemented with 4-factor prothrombin complex concentrate, or fresh frozen plasma. Vitamin K1 can be repeated every 12 hours.

Adapted from Holbrook A, et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis 9th Edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:e152S-184S.

minor bleeding, reversal of anticoagulation is likely unnecessary, especially if the patient is anticoagulated for life-sustaining reasons (LVAD, mechanical heart valves, active venous thromboembolism, etc.). See Table 2 for recommendations for managing increased INRs or bleeding in patients receiving vitamin K antagonists.

There are two components for warfarin reversal: sustained reversal with vitamin K administration and a more immediate reversal with products like prothrombin complex concentrates (PCC) or FFP. (*See Table 3.*) INR reversal normally is seen within these time frames, as long as the patient has liver function and the patient is dosed appropriately.

Warfarin Reversal Agents

Vitamin K1 (Phylloquinone)

Vitamin K is available in oral and intravenous forms. (*See Table 4.*) The oral form is preferentially used whenever possible because it has a lower risk of anaphylaxis. The IV doses must be given over at least 20 minutes, and some hospitals require 30-60 minutes to decrease the risk of adverse reaction. The IV preparation can be given orally.[7] True anaphylaxis to IV vitamin K is rare and should not preclude its use when treating significant bleeding. The subcutaneous administration of vitamin K is no longer recommended because of erratic absorption.[8]

Fresh Frozen Plasma

The second component of warfarin reversal is replacing the missing factors. Historically, FFP has served this purpose, but with the advent of factor concentrates like PCC, there now are other options.[9,10] FFP is created by separating the plasma from the cellular components of a single-donor whole blood, followed by rapid freezing to at least 18° C. Freezing is essential to preserve the soluble coagulation factors. FFP contains fibrinogen and is easier to store when compared to platelets, with a shelf life of up to one year.[11] (*See Table 5.*) The disadvantage of FFP is the large volume that is needed for successful reversal. In addition, there may be a delay in administration after ordering FFP related to the time it takes to cross-match and thaw. PCCs can be administered quickly and in a very low volume. When compared to FFP, PCCs correct the INR faster.[9] Unfortunately, studies have failed to show significant benefits in terms of patient survival.

Transfused plasma should be

Table 3. Summary and Dosage of Reversal Agents for Warfarin

Agent	Dose	Additional Information
Vitamin K	1-10 mg PO or IV	SC delivery is no longer used
PCC 3-factor (Profilnine) 4 factor (Kcentra†)	**Strategy 1: INR and Weight-Based Dosing** • INR 2-4: 25 IU/kg by IV push • INR ≥ 4-6: 35 IU/kg by IV push • INR > 6: 50 IU/kg by IV push **Strategy 2: INR-Based Dosing** • INR < 5: 500 units; INR ≥ 5: 1,000 units **Strategy 3: Fixed Dose** • 1,500 IU	INR-based dosing is most effective with 3-factor preparations. Absolute dosing strategies should not be used with 3-factor PCCs. Any of the three strategies can be used with 4-factor PCCs.

† FDA approved for the reversal of warfarin-related bleeding.

Table 4. Vitamin K Onset of Action

- Oral vitamin K: Onset 6-10 hours, peak in 24-48 hours[8]
- IV vitamin K: Onset 1-2 hours, peak in 12-24 hours[8]

Table 5. Fresh Frozen Plasma Facts[15]

- One unit has a volume of 200-250 mL.
- INR of a unit of FFP = 1.5. Transfusion of large volumes of FFP into a patient with elevated INR will not correct it to below 1.5.
- When using FFP for warfarin reversal, the dosing is very important. The starting dose should be 10-15 mL/kg or about 4 units of FFP minimum in an emergency situation.[15]
- Plasma stored for three months has about 60% of normal factor VII activity.
- FFP should be infused rapidly after thawing.
- In an average sized adult, one unit of FFP increased levels of all coagulation factors by 2-3%.

Table 6. Prothrombin Complex Contentrate Types

- Kcentra® (US)/Beriplex® (Europe) – 4-factor plus protein C+S
- Profilnine SD® – 3-factor
- Bebulin VH® – 3-factor

compatible with recipient's ABO group, but Rh compatibility is not essential.[12] Reactions and side effects to FFP are similar to those with whole blood, including fever, allergic responses, and blood-borne infections. One concern clinicians should keep in mind when admininstering blood products that contain plasma is transfusion-related acute lung injury (TRALI), which is a serious complication thought to be an immune-mediated process that can result from the administration of blood products. It has a prevalence of 1/5,000 transfusions containing plasma and has a mortality of 6-9%.[13,14]

Massive blood transfusions may result in clotting deficiencies even if a patient is not taking an anticoagulant. Although the ratio may vary, many institutions use 1 unit of FFP for every 2 units pRBCs, but some institutions may have more aggressive formulas for replacement in their massive transfusion protocols.[16,17]

Prothrombin Complex Concentrate

PCC is a plasma product with non-activated clotting factors II, VII, IX, and X. (*See Table 6.*) To reduce the risk of viral transmission, PCC preparations undergo a viral inactivation process. There are two types of PCCs: 3-factor or 4-factor preparations. They both contain four factors, but the 3-factor PCC has very low amounts of factor VII. There are some PCCs that contain proteins C and S to balance any procoagulant effect.

PCCs are used most often in the emergency department (ED) for the reversal of warfarin. Several studies have shown that there is a small risk of prothrombotic events with use of Kcentra®, but results also have shown that the risk is similar when compared to FFP.[18-21]

The most recent analysis of 4-factor PCCs compared to FFP has shown that the risk of inappropriate thrombosis is roughly the same in each group.[21]

Activated Recombinant Factor VII (rFVIIa)

Recombinant factor VII, rVIIa (NovoSeven®) has been used as a reversal agent for warfarin-associated bleeding. It was created initially for use in patients with hemophilia A or B who have inhibitors to factors VIII or IX and is only FDA approved for that indication. There have been investigations of off-label use, including several studies for trauma such as intracranial hemorrhage (ICH), although most have been inconclusive or have found no significant difference when compared to placebo.[22-24] Although rVIIa rapidly corrects an elevated INR, recent studies have called into question the clinical effectiveness, and it is no longer recommended as a reversal agent.[25,26] In addition to not being recommended for warfarin reversal, it is not recommended as a general hemostatic agent in patients who have sustained trauma.

Table 7. Dosage of Reversal Agents for Heparin and Low Molecular Weight Heparin

Agent	Dose	Additional Information
Protamine for Heparin	**Time Elapsed From Last Heparin Dose:** **Dose of Protamine (mg) to Neutralize 100 units of Heparin** Immediate: 1-1.5 mg/100 units heparin 30-60 min: 0.5-0.75 mg/100 units Heparin > 2 h: 0.25-0.375/100 units heparin	Doses should not exceed 50 mg at a time.
Protamine for LMWH	Dalteparin (Fragmin®): 1 mg protamine neutralizes 100 units dalteparin • If bleeding continues or PTT remains prolonged 2-4 hours after protamine, may give a second protamine dose of 0.5 mg per 100 units dalteparin. Enoxaparin (Lovenox®): If < 8 hours after last dose of enoxaparin, give 1 mg protamine per 1 mg enoxaparin. • If 8-12 hours after last dose of enoxaparin, give 0.5 mg protamine per 1 mg enoxaparin. • If > 12 hours after last dose of enoxaparin (when enoxaparin administered q12h), protamine not required. • If bleeding continues or PTT remains prolonged 2-4 hours after protamine, may give a second protamine dose of 0.5 mg per 1 mg enoxaparin.	Protamine may have some effect on LMWH. Only 60-75% of the anti-Xa activity of LMWH is neutralized by protamine. Effectiveness depends on which LMWH is used. There is a real concern when using protamine with LMWH — protamine when given by itself has anticoagulant effects. If there is reversal of the non-Xa activity and only partial (but not enough) reversal of the Xa activity, the net vector will point to anticoagulation. DO NOT EXCEED 50 mg per dose. Protamine only partially neutralizes anti-factor Xa activity (~60%). Fondaparinux (Arixtra®): Has only anti-Xa activity, and protamine will have only minimal reversal effect overall.

Table 8. Cryoprecipitate Facts

- Each unit of cryoprecipitate = 100-250 mg fibrinogen, 80-100 units factor VIII, and 50-60 mg of fibronectin
- Volume of each bag = 15-18 mL
- Must give a large amount of cryoprecipitate to increase factor VIII level to 50% of normal; for example, in a 70 kg patient that would be 14 bags.
- von Willebrand factor degrades during storage and has variable amounts in each bag.

Low Molecular Weight Heparin

Heparin and the LMWHs are both indirect inhibitors in that they require binding first to antithrombin and in turn to factors II and X. While heparin binds both factor II and factor X with equal affinity, the LMWHs bind mostly to factor X with an anti-X to anti-II ratio varying from as low as 1.6 to as high as 9.7.[27] Binding of the heparin/antithrombin complex to factor X and II inactivates the factor. The LMWHs include enoxaparin (Lovenox®), dalteparin (Fragmin®), tinzaparin (Innohep®), and nadroparin (Fraxiparine®). Fondaparinux (Arixtra®) is an ultra-short, synthetic pentasaccharide anticoagulant (PSA). Because of the short length of the molecule and the way it binds to antithrombin, it only has inhibitory effects on factor X.[28]

LMWH Reversal

While heparin is completely reversed using protamine sulfate, LMWH reversal with protamine is only partial. The algorithm for reversal is not as easy to follow as is the one for unfractionated heparin reversal. The general approach is a 1:1 ratio; for example, 1 mg protamine per 1 mg of enoxaparin. If bleeding continues, a second dose of 0.5 mg/1 mg enoxaparin can be given. The maximum protamine dose is limited by its weak anticoagulant effects. As the dose of protamine increases, it has an inhibitory effect on factor V, causing a mild anticoagulant effect that may offset the benefit of its reversal potential.[27,29]

It is important to understand the risks of protamine administration, including cardiovascular collapse and allergic reaction. Protamine was derived from fish sperm, and although now it is made by a recombinant process, people with fish allergies are at a higher risk for these serious reactions.[29] (*See Table 7.*)

Novel Anticoagulants (NOACs)

There are many new anticoagulants on the market now, and these medications are popular with patients because they do not require INR checks. There are two types on the market currently: direct factor II inhibitors such as dabigatran, and direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). Clinicians have struggled with initiating these medications because of the lack of availability of a consistent strategy to reverse the effects quickly if a patient suffered trauma or hemorrhage.

Direct Factor II Inhibitors (Dabigatran)

The definitive way to remove dabigatran is dialysis, but that is often not practical in a trauma setting with an acutely bleeding patient.

Initially there were many case reports and studies in healthy

Table 9. Dosage of Reversal Agents for Anti-Factor II Agents, Dabigatran

Agent	Dose	Additional Information
aPCC (FEIBA)	50 U/kg	May be more thrombogenic than non-activated PCC
Antibodies to dabigatran (Idarucizumab)	5 g provided as two separate vials each containing 2.5 g/50 mL	The only FDA approved "antidote" to dabigatran-related bleeding
Cryoprecipitate	2 pools	If fibrinogen is < 200 mg/dL, give 2 pools cryoprecipitate

Table 10. Dosage of Reversal Agents for Anti-Factor Xa Anticoagulants (Rivaroxaban, Apixaban, Edoxaban)

Agent	Dose	Additional Information
4-factor PCC (Kcentra)	25-50 units/kg	Not to exceed 5,000 units. Repeat dosing is not recommended. This is generally considered the preferred agent for reversing anti-Xa Inhibitors
aPCC (FEIBA)	25 units/kg	If still clinically significant bleeding, consider re-dosing, but no sooner than 6 hours.

volunteers trying to determine the easiest and safest reversal strategy. The American Society of Hematology recommended activated PCC for first-line treatment in life-threatening bleeding.[30] Factor Eight Inhibitor-Bypassing Activity (FEIBA®), also called activated PCC (aPCC), which is a pooled plasma product containing mostly non-activated factors II, IX, X, and activated factor VII, enables the clotting cascade to bypass factors VIII and IX. Effective for treating bleeding episodes in hemophilic patients with antibodies to factor VIII, it also may reverse coagulopathy induced by some antithrombotic agents. Unfortunately FEIBA carries a risk of thrombotic complications, and common minor adverse reactions include headache, fevers, flushing, gastrointestinal upset, and allergic reactions.[31]

In the fall of 2015, idarucizumab (PraxBind®) was introduced for dabigatran reversal. It is a monoclonal antibody to dabigatran with an affinity 350 times higher than factor II for the dabigatran molecule,[32] reversing the effects of dabigatran within minutes.[33] Data proving improved outcomes in patients still are lacking unfortunately. Clear indications for when to use idarucizumab, such as degree of bleeding, severity and controllability of bleeding, timing since last dose of anticoagulant, etc., are still being studied and validated.

Cryoprecipitate

Cryoprecipitate contains fibrinogen, factor VIII, and fibronectin. It is derived by thawing single-donor plasma and requires ABO compatibility. (*See Table 8.*) It is indicated for treatment of patients with fibrinogen deficiency, congenital afibrinogenemia, dysfibrinogenemia, and factor VIII deficiency (only when factor VIII products are not readily available). In bleeding patients on dabigatran, a low fibrinogen level prompts administration of cryoprecipitate. It is also indicated for life-threatening bleeding that can occur after the administration of tissue plasminogen activator (tPA). Fibrinogen levels should be measured and if fibrinogen is < 200 mg/dL, two pools of cryoprecipitate should be given. See Table 9 for the dosage of reversal agents for anti-factor II agents, including dabigatran.

Direct Factor Xa Inhibitors (Rivaroxaban, Apixaban, Edoxaban)

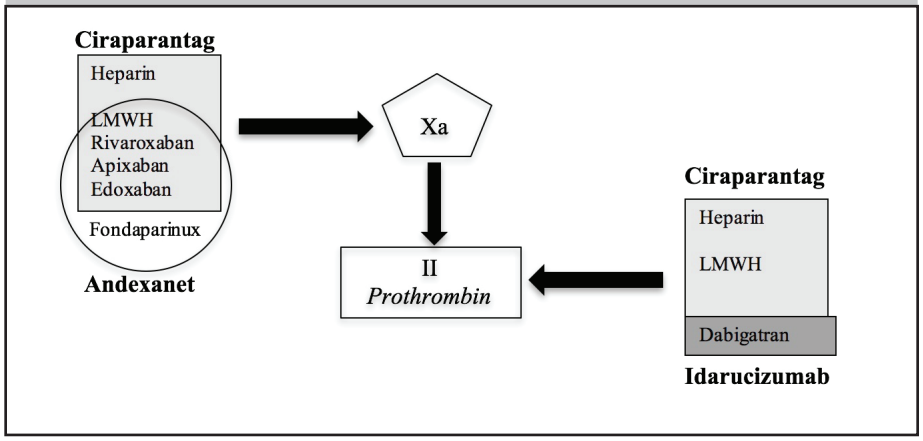
Many different approaches have been studied and tried for reversing factor Xa inhibitors, including rVIIa, 4-factor PCCs, and activated PCC (FEIBA®). More recently, andexanet-alfa, a recombinant and modified factor Xa decoy molecule, is undergoing the final phase of study and awaiting FDA approval.

According to the expert panel recommendations of the Hemostasis and Thrombosis Research Society, Thrombosis and Hemostasis Summit of North America, the use of 4-factor PCCs is the preferred reversal agent for Xa inhibitors until a definitive antidote is available.[34] Four-factor PCCs appear to be effective at reversing abnormal coagulation parameters in healthy human volunteers dosed with factor Xa inhibitors; however, there have been no studies evaluating the effect of PCCs on clinical bleeding in humans receiving factor Xa inhibitors. Studies and case reports have shown that FEIBA also is capable of reversing the effects of Xa inhibitors, but it still carries an increased risk of thrombotic complications.[35,36] Both of these strategies essentially involve "bombing" the coagulation system with clotting factors to quickly supply factor X that has not yet been bound to the anti-Xa agent. (*See Table 10.*) While potentially effective, there is a risk for inappropriate thrombosis.

In the spring of 2017, andexanet alfa may be available for clinical use.[37] This medication works on both direct Xa inhibitors and indirect factor Xa inhibitors (heparin, LMWHs, and fondaparinux). Andexanet alfa is an inactive factor Xa decoy that binds the factor Xa inhibitors, which then makes them unable to bind to factor Xa in the bloodstream. This novel approach for reversal was described recently in an article in the *New England Journal of Medicine*. After administration of andexanet, thrombin generation was found to increase above the lower limit of the normal range in 100% of patients in one study.[37]

One potential benefit of andexanet is that about 1-3 hours after the drug was administered, levels of anticoagulation returned to pre-andexanet levels. Even though the reversal effect lasted for a short period of time, it is believed that this is long enough to allow for an effective hemostatic plug to develop.[38]

Figure 4. Actions of Reversal Agents



This short duration could be useful in patients who require brief anticoagulation reversal for a procedure or surgery.

A human study conducted in in the clinical setting of potentially life-threatening bleeding was published recently in the *New England Journal of Medicine*.[38] This interim report from an ongoing study looked at 67 patients with acute major bleeding, most of which was either gastrointestinal bleeding or intracranial hemorrhage. The bleeding developed within 18 hours of the last administered dose of a factor Xa inhibitor, including rivaroxaban, apixaban, edoxaban, or enoxaparin. The patients received a bolus dose followed by infusion of andexanet. There were two different doses for both the bolus and the infusion, depending on the time since the last dose of factor Xa inhibitor.

The first arm of the study looked at efficacy and included 47 patients. Seventy-nine percent of the patients had either excellent or good hemostasis. There were 67 patients in the safety arm of the study, and 18% of the patients had a thrombotic event. It is not clear if this is because of their underlying hypercoagulable condition or related to the andexanet administration. As andexanet does not have procoagulant catalytic activity due to small changes in the amino acid structure, it seems unlikely to be a direct cause of the thrombotic events.[38] Larger studies are in process and will provide more information about efficacy and safety.

Ciraparantag

Another polyvalent reversal agent in the early investigational stages is ciraparantag. It is a synthetic and cationic molecule that binds to multiple anticoagulants through non-covalent hydrogen bonds and charge–charge interactions. These agents include direct Xa inhibitors, direct thrombin inhibitors, and unfractionated heparin and LMWH. (*See Figure 4.*) In animal bleeding studies, the drug demonstrated efficacy in reversal of anticoagulation as evidenced using TEG and by observing reduced bleeding.

A human volunteer study of 80 patients given edoxaban showed restoration of baseline hemostatsis within 10-30 minutes after administration of ciraparantag. This effect persisted for 24 hours. No procoagulant effects were observed in these studies. Additional studies, including Phase III trials, are planned.

Platelet Inhibitors and Their Reversal

Platelet Inhibitors

Many patients currently take aspirin or clopidogrel (Plavix®), and there is some controversy regarding management of these patients when they incur trauma. Although there are no established guidelines for reversal of antiplatelet agents, one study in healthy volunteers found that 2-3 pools of platelets (either random donor 4-6 packs or apheresis units) induced a normalization of platelet function.[39] Although frequently requested by neurosurgical consultants, there is not enough evidence at this time to make routine platelet transfusion a "standard of care."[40]

Platelet Concentrates

Platelet concentrates are made from blood products and there are two types: single-donor apheresis and pooled random-donor whole blood units. Single-donor apheresis platelets have an advantage over the pooled type because they only involve one donor, which reduces the risk for transfusion-transmitted diseases and minimizes exposure to potentially sensitizing plasma proteins. They both provide a similar amount of active platelets. After a platelet concentrate is prepared, it is viable for five days when kept at room temperature and intermittently agitated. They are very temperature sensitive and should not be refrigerated.

Platelets are easier to transfuse than other blood products because they do not need to be cross-matched. Platelet transfusions still should be ABO and Rh compatible; in emergency situations, unmatched platelets can be transfused. There are enough red blood cells (RBCs) in a single unit of platelets to sensitize an Rh-negative patient. Although unmatched platelets will not cause the same reaction that transfusing unmatched RBCs can, it is important to limit the amount of incompatible platelets and use matched as soon as available.[41,42]

Platelets often are ordered either by the "pack," or by "apheresis units." There is institutional variation in how many units are placed in a pack, but the most common is a "six-pack," followed by the "four-pack." A typical four- or six-pack of random donor units is equal to a single-donor apheresis unit. Each 4-6 pack contains about 250-350 mL of plasma, which is also equivalent to 1 unit FFP. Rapid transfusion of platelets is possible with specialized platelet filters. It is important to note that ordering may vary by hospital and it is important to be aware of the semantics at your institution's blood bank. It is especially confusing when hospitals refer to a four- or six-pack as a "unit." For the rest of this review of platelet concentrates, the term "unit" will be used to describe individual units, and UNIT will describe a 4-6

Table 11. Platelet Facts

- One unit of random-donor platelets should increase the platelet count by 5,000 to 10,000/mm^3.
- Usual dosing starts at 1 random-donor unit for every 10 kg of body weight.
- For example, 1 UNIT (4-6-pack) or 1 single-donor apheresis UNIT given to an average sized adult will increase the platelet count to around 50,000/mm^3.

Table 12. Summary and Dosage of Reversal Agents for Platelet Inhibitors, Aspirin, Clopidogrel, and Others

Agent	Dose	Additional Information
Platelet transfusion	2-3 UNITS of pooled platelets or 2-3 apheresis UNITS	Human studies proving the efficacy of the use of platelets in patients with antiplatelet agent-induced bleeding are lacking.
DDAVP (Desmopressin)	0.3 µg/kg IV	Promotes platelet adherence. Consider for bleeding with platelet inhibitor use along with platelet transfusion.

pack. (*See Table 11.*)

Active bleeding should be treated when the platelet count is lower than 50,000/mm^3. The idea of prophylactic treatment in trauma is controversial unless the patient has a platelet count of less than 20,000/mm^3. Additional studies also have suggested a threshold of 10,000/mm^3.[43,44]

Trauma patients who have idiopathic thrombocytopenia purpura (ITP) can present severely thrombocytopenic because of antiplatelet antibodies. Transfused platelets are consumed rapidly, only lasting minutes to hours. In the case of severe bleeding or severe head trauma, ITP patients should be given a 2-3 times the normal dose of platelets.[45] This may temporize bleeding until definitive treatment of the ITP-mediated thrombocytopenia can be initiated.

DDAVP

DDAVP is a synthetic analogue of pituitary vasopressin, 1-deamino-(8-D-arginine) vasopressin (DDAVP). It stimulates the release of von Willebrand factor from vascular endothelium.[46] It facilitates platelet binding to damaged endothelium. Responsiveness to DDAVP varies from patient to patient. A dose of 0.3 mg/kg intravenously over a 15-minute period may help to overcome some of the antiplatelet effect of drugs such as clopidogrel.[47] (*See Table 12.*)

General Hemostatic Agents

Tranexamic Acid

Tranexamic acid (TXA) acts as a general hemostatic agent by blocking the conversion of plasminogen to plasmin, catalyzed by tPA. This slows the breakdown of clots and tips the overall balance of the system toward a mild procoagulant state. It has been studied in a prehospital setting for use in trauma patients with life-threatening exsanguination. TXA previously had been shown to reduce blood loss in patients undergoing elective surgery, and in a large study of more than 20,000 patients, it was found to reduce the risk of death (RR 0.91, $P = 0.0035$). There were no significant complications in this study as a result of the TXA, and studies are ongoing in the prehospital setting in trauma patients.[48]

Case Conclusion

In the opening case, the patient was anticoagulated with an Xa inhibitor, rivaroxaban. She showed evidence of active bleeding. The decision to reverse anticoagulation in any patient is a balance of risks. In her case, she was anticoagulated for atrial fibrillation. The risk of reversing her anticoagulation is relatively small, considering the rate of embolic events in atrial fibrillation is small in the short term. Active bleeding in an anticoagulated trauma patient can lead to significant morbidity and an increased risk of death. Since she is awake and likely can confirm that she is taking her medication as directed, reversal is indicated. The preferred agent is a 4-factor PCC (Kcentra® is the only available agent in the United States). The dose is 25-50 units per kg, not to exceed 5,000 units. The decision to use the higher end of the dosing range depends on a number of factors, including the severity of bleeding, the likelihood of timely and definitive hemorrhage control, and the stability of the patient. An alternative agent for reversal is activated PCC (FEIBA) at the dose of 25 units/kg, which can be re-dosed after six hours if bleeding is not controlled.

Lab testing of anti-Xa activity will not happen in real-time and should not be considered in the decision to initiate immediate reversal.

Conclusion

There are many new anticoagulants and antiplatelet drugs that can complicate the course of the trauma patient. It is very important to elicit the correct and pertinent information from these patients as to what agents they are taking and why, so as to ensure the proper initiation of drug reversal when it is deemed necessary for patient care.

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CME/CE Questions

1. Which of the following anticoagulants has a specific antibody reversal agent?
   a. dabigatran
   b. rivaroxaban
   c. warfarin
   d. low molecular weight heparin
2. A patient presents after a rollover motor vehicle accident. She has a small subdural hematoma. She is on warfarin and has an INR of 1.5. Which of the following statements about the use of FFP is correct?
   a. The administration of FFP is indicated because the INR is elevated and she has bleeding.
   b. FFP is unlikely to lower the patient's INR.
   c. The correct dose of FFP to administer is 5 mL/kg.
   d. FFP is likely to correct the INR to normal.
3. Which of the following pairings between anticoagulant and factors affected is correct?
   a. Warfarin: Factor II, VII, IX, X
   b. Heparin: Factor II, VII, VIII
   c. Rivaroxaban: Factor VII, X, Xa
   d. Dabigatran: Factor VII, IX, X
4. In reversing anticoagulation induced by enoxaparin, why is the dose of protamine capped at 50 mg?
   a. Doses of protamine greater than 50 mg have no added benefit.
   b. Protamine's inherent toxicity is manifested at doses greater than 50 mg.
   c. Protamine partially reverses heparin, but at higher doses it inhibits factor V, leading to additional anticoagulation.
   d. Protamine is indicated only for use in heparin-induced anticoagulation and is not effective in reversing effects of low molecular weight heparin.
5. Platelet inhibitors such as clopidogrel might be reversed by which of the following strategies?
   a. FFP and vitamin K
   b. 4-factor PCCs
   c. FEIBA and cryoprecipitate
   d. Platelet transfusion and DDAVP
6. Which of the following is no longer recommended for the reversal of warfarin anticoagulation?
   a. FFP IV
   b. 3-factor PCC IV
   c. Vitamin K SQ
   d. 4-factor PCC IV
7. What is the commonality among the following anticoagulants: rivaroxaban, apixaban, edoxaban, fondaparinux, and low molecular heparin?
   a. They are all reversible by FFP and vitamin K.
   b. They all have their effects primarily on factor X.
   c. They all have specific antibody reversal agents.
   d. They all have their effects on factor II.
8. Which of the following does *not* have an FDA-approved reversal agent, as of publication time?
   a. dabigatran
   b. rivaroxaban
   c. unfractionated heparin
   d. warfarin
9. Which of the following is true regarding the use of recombinant factor VII?
   a. It has been shown to reduce morbidity and mortality when given to patients with non-anticoagulation related intracerebral hemorrhage.
   b. It has been shown to reduce morbidity and mortality when given to patients with warfarin-related intracerebral hemorrhage.
   c. It has been shown to reduce morbidity and mortality when given to non-anticoagulated patients with blunt trauma.
   d. It has been shown to reduce morbidity and mortality when given to patients with hemophilia and a factor VIII inhibitor.
10. Which of the following patients is *most* likely to benefit from reversal of anticoagulation?
    a. A bleeding trauma patient on warfarin with an INR of 1.4
    b. A bleeding trauma patient who received heparin for dialysis approximately three hours prior to his accident
    c. A bleeding trauma patient on warfarin with an INR of 2.3
    d. A bleeding patient on rivaroxaban who took her last dose 24 hours ago

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