MANAGEMENT OF SEVERE BLEEDING IN PATIENTS TREATED WITH ORAL ANTICOAGULANTS

Proceedings Monograph from the EMCREG-International Multidisciplinary SEVERE BLEEDING CONSENSUS PANEL
October 20, 2018
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Proceedings Monograph from the
EMCAREG-International Multidisciplinary SEVERE BLEEDING CONSENSUS PANEL
October 20, 2018

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Dear Colleagues,

The Emergency Medicine Cardiac Research and Education Group (EMCREG)-International was established in 1989 as an emergency medicine cardiovascular and neurovascular organization led by experts from the United States, Canada, and across the globe. We now have Steering Committee members from the US, Canada, Australia, Belgium, Brazil, France, Netherlands, New Zealand, Japan, Singapore, Sweden, and the United Kingdom. Now in our 30th year, we remain committed to providing you with the best educational programs and enduring material pieces possible. In addition to our usual Emergency Physician audience, we now reach out to our colleagues in Cardiology, Internal Medicine, Family Medicine, Hospital Medicine, and Critical Care with our EMCREG-International University of Cincinnati College of Medicine Office of Continuing Medical Education (CME) accredited symposia and enduring materials.

In this EMCREG-International Proceedings Monograph from the October 20, 2018 EMCREG-International Multidisciplinary Consensus Panel on Management of Severe Bleeding in Patients Treated with Oral Anticoagulants held in Orlando, Florida, you will find a detailed discussion regarding the treatment of patients requiring anticoagulation and the reversal of anticoagulation for patients with severe bleeding. For emergency physicians, critical care physicians, hospitalists, cardiologists, internists, surgeons, and family physicians, the current approach and disease indications for treatment with anticoagulants such as coumadin, Factor IIa, and Factor Xa inhibitors are particularly relevant. When a patient treated with anticoagulants presents to the Emergency Department, Intensive Care Unit, or Operating Room with severe, uncontrollable bleeding, achieving rapid, controlled hemostasis is critically important to saving the patient’s life.

This EMCREG-International Proceedings Monograph contains multiple sections reflecting critical input from experts in Emergency Cardiovascular Care, Pre-hospital Emergency Medical Services, Emergency Medicine Operations, Hematology, Hospital Medicine, Neurocritical Care, Cardiovascular Critical Care, Cardiac Electrophysiology, Cardiology, Trauma and Acute Care Surgery, and Pharmacy. The first section provides a description of the current indications for treatment of patients using oral anticoagulants including coumadin, the Factor IIa (thrombin) inhibitor dabigatran, and Factor Xa inhibitors such as apixaban and rivaroxaban. In the remaining sections, the treatment of patients presenting to the hospital with major bleeding becomes the focus. The replacement of blood components including red blood cells, platelets, and clotting factors is the critically important initial treatment for these individuals. Reversing the anticoagulated state is also necessary. For patients treated with coumadin, infusion of vitamin K helps to initiate the process of protein synthesis for the vitamin K dependent coagulation proteins II, VII, IX, and X as well as the anti-thrombotic Protein C and Protein S. Repletion of clotting factors for the patient with Four-Factor Prothrombin Complex Concentrate (4FPCCs), which includes Factors II (prothrombin), VII, IX, and X and therapeutically effective concentrations of the regulatory proteins (Protein C and S), provides real time ability to slow bleeding. For patients treated with the thrombin inhibitor dabigatran, treatment using the highly specific antibody derived idarucizumab has been demonstrated to reverse the hypocoagulable state for the patient to allow blood clotting. In May 2018, andexanet alfa was approved by the US Food and Drug Administration to reverse the Factor Xa anticoagulants apixaban and rivaroxaban in patients with major bleeding. Prior to the availability of this highly specific agent, therapy for patients treated with Factor Xa inhibitors presenting with severe bleeding usually included replacement of lost blood components including red blood cells, platelets, and clotting factors as well as 4FPCCs, or if not available fresh-frozen plasma (FFP). The evaluation and treatment of the patient with severe bleeding as a complication of oral anticoagulant therapy is discussed from the viewpoint of the emergency physician, neurocritical and cardiovascular critical care intensivist, hematologist, trauma and acute care surgeon, hospitalist, cardiologist, electrophysiologist, and pharmacist in an approach we hope the reader will find extremely practical and clinically useful. The clinician learner will also find the discussion of the resumption of oral anticoagulation for the patient with severe bleeding after effective treatment important as returning the patient to an anticoagulated state as soon as feasible and safe prevents thrombotic complications. Finally, an EMCREG-International Severe Bleeding Consensus Panel algorithm for the approach to management of patients with life-threatening oral anticoagulant-associated bleeding is provided for the clinician and can be expanded in size for use in a treatment area such as the Emergency Department or Critical Care Unit.

Through this EMCREG-International Multidisciplinary Severe Bleeding Consensus Panel Monograph, clinicians can receive state of the art information which can significantly impact the care of their patients. It is our sincere hope that you will find this EMCREG-International Proceedings Monograph on the care of patients requiring anticoagulation and having associated severe bleeding useful to you in your daily practice as an emergency physician, intensive care physician, hospitalist, cardiologist, internist, and family physician. Instructions for obtaining CME credit from the University of Cincinnati College of Medicine Office of Continuing Medical Education are available at the conclusion of this January 2019 EMCREG-International Multidisciplinary Severe Bleeding Consensus Panel Proceedings Monograph. Thank you very much for your interest in EMCREG-International educational initiatives; we hope you visit our website (www.emcreg.org) for future educational events and publications.

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LEARNING OBJECTIVES

1. Discuss the difference between repletion of factors for warfarin-related bleeding and reversal of anticoagulant effect for direct oral anticoagulant-related bleeding.

2. Describe the mechanism of action and dosing of pharmacologic agents used to manage severe bleeding in patients receiving oral anticoagulation.

3. Describe risk stratification for patients with anticoagulant-related bleeding and discuss appropriate management strategies based on the actual anticoagulant.

4. Describe the prehospital, Emergency Department, and peri-operative approaches to hemorrhage control in the anticoagulated trauma patient.

5. Discuss the urgency and time-sensitive need for anticoagulation reversal in the setting of acute intracranial hemorrhage.

6. Outline a stepwise approach to the management of upper and lower gastrointestinal bleeding in anticoagulated patients.

7. Describe the patient-, procedure-, and anticoagulant-based factors that contribute to bleeding complications in patients who undergo invasive cardiac procedures or cardiac surgery and summarize the key considerations for management of bleeding in these patients.

8. Discuss the approach to restarting anticoagulant therapy after severe bleeding to prevent thrombotic complications.
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INTRODUCTION

There are multiple indications for chronic oral anticoagulation in contemporary medical practice, including treatment and prevention of venous thromboembolic disease (VTE, inclusive of deep vein thrombosis and pulmonary embolism), primary and secondary prevention of stroke and systemic embolism in atrial fibrillation (AF), protection against thromboembolic events in patients with mechanical heart valves, and secondary prevention of major cardiac events in patients with coronary artery disease or peripheral artery disease. As clear as these indications are from an efficacy perspective, it is manifestly impossible to provide anticoagulation to a patient without raising that patient’s risk of bleeding. Even properly prescribed, well-controlled anticoagulation results in a non-physiologic state in which spontaneous bleeding is more likely, and in which the briskness of blood loss from vessel injury is accelerated.

Management of severe bleeding in patients taking oral anticoagulants is complicated. Acute care physicians must be knowledgeable about the individual oral anticoagulant agents, the general management of anticoagulant-associated bleeding, and the strategies for effective use of factor repletion and specific reversal agents. With any oral anticoagulant, minor or “nuisance” bleeding is most common and can be managed without repletion or reversal. For major oral anticoagulant-associated bleeding, class-specific approaches should be used and the necessary treatment agents made readily available in the Emergency Department (ED), the Intensive Care Unit (ICU), and the surgical suite. Because the reversal agents for the thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban and rivaroxaban are expensive, acute care physicians should be prudent in using these important new therapies.

In this monograph, the available oral anticoagulant agents and the current options for repletion or reversal of their anticoagulant effects are reviewed. An algorithm for reversal of severe bleeding in patients taking factor Xa inhibitors and other anticoagulants is presented. Strategies for management of the patient with anticoagulant-associated bleeding are discussed, beginning with prehospital care and continuing through the ED and inpatient critical care settings. Finally, the approach to restarting anticoagulant therapy after severe bleeding to prevent thrombotic complications is discussed.

ORAL ANTICOAGULANTS

Warfarin and Other Vitamin K Antagonists

In the coagulation cascade, multiple clotting factors interact in a sequence of events that converge into a final common pathway that results first in the transformation of factor X into the active factor Xa (FXa). Factor Xa then enzymatically converts prothrombin (factor II) into thrombin (Factor IIa), which serves both to activate platelets and to convert fibrinogen into fibrin. Vitamin K metabolism is essential to the hepatic synthesis of carboxylated (functionally active) coagulation factors II, VII, IX, and X that, in turn, can bind calcium and phospholipid-containing surfaces. The vitamin K antagonists (VKAs) impair vitamin K metabolism, resulting in greatly diminished reserves of these specifically configured zymogen enzymes and subsequent decreased ability to form thrombus. Of note, however, vitamin K is also required to synthesize protein C and protein S, which serve crucial roles in counterbalancing the coagulation cascade by regulating the conversion of prothrombin into thrombin.

Warfarin, the most common VKA in use in the United States, has a direct circulating plasma half-life of 36 to 42 hours. However, the effective half-life approaches 96 hours, and is dependent on the liver’s ability to recover synthetic function and produce prothrombin (factor II).¹ There is significant variability in treatment effect with VKAs based on individual metabolism, drug interactions, and comorbid conditions; therefore treatment with a VKA requires frequent monitoring and dose adjustment.

Direct Oral Anticoagulants

Dabigatran is unique in the category of direct oral anticoagulants (DOACs) in that it is a direct thrombin inhibitor, binding to the active site of thrombin and preventing downstream thrombin-mediated platelet activation and fibrinogen conversion. Peak effect occurs within three hours of an oral dose,² and the effective half-life after steady state ranges from 12-17 hours (Table 1).³ The drug is primarily cleared by renal-dependent mechanisms, resulting in increased anticoagulation as renal function decreases; therefore, drug dosing varies with renal function.⁴ It is the only DOAC cleared by hemodialysis, although it remains unclear whether hemodialysis has an impact on the clinical effect. Dabigatran is potentiated by drugs that inhibit P-glycoprotein (P-gp) metabolism, such as amiodarone, ketoconazole, clarithromycin, and verapamil, and is inhibited by rifampin and other P-gp inducers.⁴
MANAGEMENT OF SEVERE BLEEDING IN PATIENTS TREATED WITH ORAL ANTICOAGULANTS

The FXa inhibitors (currently consisting of apixaban, betrixaban, edoxaban, and rivaroxaban) directly inhibit FXa, which results in decreased conversion of prothrombin to thrombin. All FXa inhibitors undergo renal and hepatic elimination. The FXa inhibitors (other than edoxaban) are metabolized by both the P-gp and the CYP3A4 systems. Potent inhibitors of both of these systems, such as ketoconazole, itraconazole, ritonavir, and clarithromycin, will potentiate their effects, while inducers of CYP3A4 and P-gp (such as rifampin, phenytoin, and carbamazepine) will inhibit their anticoagulant efficacy. DOACs should be used with caution in patients with kidney impairment and are not recommended in patients with severe liver disease.

Assessment of Anticoagulant Activity
The degree of anticoagulation with VKAs like warfarin can be quickly measured with a prothrombin time (PT) and international normalized ratio (INR). On the other hand, each DOAC produces variable effects on the coagulation measurement assays commonly available in the clinical setting. None have a direct linear relationship with any of the readily available coagulation assays; at best, an abnormal test may be considered relatively specific for the ongoing presence of the anticoagulant, but the absence of abnormality is not sensitive for the absence of anticoagulant effect. In other words, one cannot rely on normal coagulation assays to exclude anticoagulation effects. The sole exception to this is the relationship between dabigatran (the direct thrombin inhibitor) and thrombin time and ecarin clotting time, which do offer quantitative assessment of dabigatran’s activity but are not usually available on a “stat” basis.

Anti-FXa assays exist; however, they are not readily available in most hospitals and necessitate that the assay be calibrated specifically for each of the different FXa agents. If an anti-FXa level calibrated to a specific DOAC is negative, it might obviate the need for reversal in a patient with life-threatening bleeding. Since there is currently no widely available test to make that decision, FXa levels are generally not useful in the emergency setting. Thromboelastography (TEG) is still under investigation as an option to assess the anticoagulated trauma patient.

ORAL ANTICOAGULANT-ASSOCIATED BLEEDING
Many patients with non-valvular AF who are treated with anticoagulants are older and frequently carry more than one comorbid diagnosis, such as renal insufficiency, that increases bleeding risk. The risk of a major bleeding event in AF patients treated with warfarin is 2-3% per year. Above age 75, the risk of intracranial hemorrhage (ICH) in patients taking warfarin increases significantly. Use of a DOAC may decrease bleeding risk by 30% or more overall, may decrease ICH by as much as 60%, and significantly decreases the risk of fatal hemorrhage, in comparison to warfarin. Currently, there are no randomized trials that compare one DOAC to another. Only gastrointestinal (GI) hemorrhage is more common in DOAC-treated patients (with the exception of apixaban and the dabigatran 110 mg twice daily dose) than in those treated with warfarin, but these events are rarely fatal. On the other hand, mortality from warfarin-related ICH is around 40% within a month of the event. Significant

### TABLE 01

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Onset</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Peak serum concentration 4 hours after dose, anticoagulant effect noted within 24 hours of first dose</td>
<td>Dependent on time to resynthesize clotting factors (48-72 hours for Factor X)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>2 hours</td>
<td>12 - 14 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.5 - 3.3 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>3 - 4 hours</td>
<td>19 - 27 hours</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1.5 hours</td>
<td>10 - 14 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2 - 4 hours</td>
<td>5 - 9 hours; * may increase to 11-13 hours in elderly patients</td>
</tr>
</tbody>
</table>
bleeding events in patients treated with anticoagulants for VTE are less common because the patients tend to be younger and have fewer comorbidities. Given the aging demographics of the United States population, more patients require anticoagulation therapy for non-valvular AF each year. Similarly, the prevalence of VTE continues to rise, as does the acceptance of more aggressive VTE prophylaxis protocols. Oral anticoagulation-related bleeding is a regular occurrence in the ED, and its incidence will only continue to increase.

**Prevention of DOAC-Associated Bleeding**

Prevention of DOAC-associated bleeding requires appropriate dosing based on 1) the particular DOAC being prescribed, 2) whether it is being used as a therapeutic or prophylactic therapy, and 3) the underlying comorbidities of the patient.

Renal insufficiency requires reduction of the DOAC dose to mitigate bleeding risk. The RE-LY, ROCKET, ARISTOTLE, and ENGAGE trials, which evaluated dabigatran, rivaroxaban, apixaban, and edoxaban, respectively, versus warfarin all excluded patients with a reduced creatinine clearance (CrCl; RE-LY, ROCKET, and ENGAGE: < 30 mL/min, ARISTOTLE: <25 mL/min or Cr > 2.5 mg/dL). For AF patients, rivaroxaban should be used at 15 mg/day with CrCl < 50mL/min, and apixaban should be used at 2.5 mg twice daily with two of three criteria: age ≥80, weight ≤ 60 kg, or creatinine ≥ 1.5mg/dL. Edoxaban should be used at 30 mg/day with CrCl ≤ 50mL/min. Dabigatran dose should be reduced to 75 mg twice daily in patients with CrCl 15-30mL/min.

Other strategies to avoid the risk of bleeding include blood pressure control, shortening the duration of concomitant antiplatelet or non-steroidal anti-inflammatory drug (NSAID) therapy, and minimizing alcohol use while on DOACs. In addition, it is important to assess, treat, and normalize causes of anemia in patients on DOACs.

### TABLE 02

<table>
<thead>
<tr>
<th>Warfarin-Related Bleeding Management Based on Urgency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reversal needed in 24-48 hours</strong></td>
</tr>
<tr>
<td>INR 4.5-8 without bleeding:</td>
</tr>
<tr>
<td>• Hold warfarin dose</td>
</tr>
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### TABLE 03

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<thead>
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<th>Approaches to the Emergency Management of Warfarin-Related Bleeding</th>
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<tr>
<td><strong>Mechanism</strong></td>
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<td>Synthesize new vitamin K-dependent factors</td>
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<td>Repletion</td>
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<td>Repletion</td>
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PCC: prothrombin complex concentrate
REVERSING THE ANTICOAGULANT EFFECT

Repletion of Vitamin K-Dependent Factors

A patient who is therapeutically anticoagulated on a VKA has impaired physiologic activity at the multiple steps in the cascade that require participation of the vitamin K-dependent factors. Vitamin K administration merely allows the resumption of production of carboxylated Gla-domain and functionally active factors, and it takes hours to several days to re-establish physiologic levels. Although necessary, this is certainly not a sufficient response to management of ICH or other life-threatening hemorrhage. In fact, warfarin-related anticoagulation cannot be reversed. Instead, the levels of deficient factors must be repleted, and clinicians must not view vitamin K as a “reversal agent.”

Repletion can be accomplished in several ways. Traditionally, fresh-frozen plasma (FFP) was the direct repletion method of choice, but its use is limited by time requirements for thawing and cross-matching, concern for volume overload, and limited efficacy. The superior alternative for repleting vitamin K-dependent factors quickly is administration of prothrombin complex concentrate (PCC). The PCCs are pooled, virus-inactivated concentrates of human clotting factors. Four-factor PCCs (4FPCCs) contain the vitamin K-dependent coagulation factors (II [prothrombin], VII, IX and X), as well as therapeutically effective concentrations of coagulation regulatory proteins (Proteins C and S). Three-factor PCCs (3FPCCs) do not contain factor VII. In the past, some authorities recommended combining 3FPCCs with recombinant factor VIIa (rFVIIa), though the need for this approach has not been specifically studied. The PCCs are indicated and most commonly used for warfarin reversal. There are suggestive data that in warfarin-associated ICH, PCCs reduce hematoma expansion more than FFP does, and PCCs are preferentially recommended in professional society guidelines.

Repletion of vitamin K-dependent factors in warfarin-associated hemorrhage and reversal of anticoagulation effect as in the case of DOAC treatment strategies discussed below should be reserved for life-threatening events, such as exsanguinating blood loss and ICH (Tables 2 and 3). Two immediate concerns arise from precipitous removal of anticoagulation. The first is that patients who are therapeutically anticoagulated are treated for a good clinical reason, such as high risk of stroke associated with atrial fibrillation, previously demonstrated pathologic clot (e.g., venous thromboembolic disease), or mechanical heart valve (warfarin only). When anticoagulation “protection” is suddenly removed, these patients immediately return to their baseline pro-thrombotic state. It is important to note that the patient should be left “unprotected” for as short a time as is clinically possible. The second concern is intuitive - a patient might receive more repletion than is needed. The “overshoot” thromboembolic complications are unusual after repletion, but are more common after PCC administration than with FFP. There is lower risk with FFP simply because less factor is being administered. Such events are still uncommon (5-10%) after use of PCCs and are dose-dependent. For that reason it is usually recommended that 4FPCC be given in two separate 25 IU/kg doses, with a clinical evaluation performed after the first infusion and consideration of omitting the second if the patient is stabilizing.

Reversal of Direct Oral Anticoagulants

Reversal agents for the direct thrombin inhibitor, dabigatran, and the FXa inhibitors, apixaban and rivaroxaban, are now approved in the United States. These agents are not hemostatic; rather, they reverse the effect of anticoagulants and are not dependent on repletion of factors, which is a critical distinction as compared to PCCs. In therapeutic anticoagulation with dabigatran, there is no deficiency of thrombin. Native thrombin is instead inhibited by the anticoagulant. Removing the effects of dabigatran frees up previously inhibited thrombin to participate meaningfully once again in coagulation. Likewise, patients treated with apixaban, betrixaban, edoxaban, or rivaroxaban have normal circulating levels of FX, but Xa is inhibited by the therapy.

Dabigatran Reversal

Idarucizumab is a humanized monoclonal Fab fragment antibody to which dabigatran has 350 times higher affinity than to thrombin. It has no intrinsic activity in the coagulation system and it provides immediate, complete, and sustained reversal of the dabigatran effect. Idarucizumab is eliminated quickly, allowing early resumption of dabigatran therapy in clinically stable patients. The dose is 5 grams total, administered intravenously as two vials of 2.5 grams in rapid succession. Patients with very high dabigatran levels may show evidence of a recurrence of anticoagulation activity between 12 and 24 hours after reversal, due to drug re-entering the circulation from the extravascular space, but a repeat dose should probably only be given if there is concomitant increased bleeding.

The safety and efficacy of idarucizumab as a reversal agent specifically for dabigatran was demonstrated in the Reversal
Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial of 503 patients, 301 of whom had serious or life-threatening hemorrhage. The median maximum percentage reversal of dabigatran, on the basis of either the diluted thrombin time or the ecarin clotting time, was 100% (95% confidence interval [CI], 100 to 100). Nearly half of these patients had GI bleeding and one-third presented with ICH. The median time to the cessation of bleeding was 2.5 hours, but this must be viewed in the context of multi-modal hemorrhage management. Idarucizumab (like andexanet alfa) is not a hemostatic agent. It merely neutralizes iatrogenic anticoagulation so that bleeding can be managed promptly, with mechanical and other pharmacologic means as appropriate and with support from transfusion of blood products as needed.

At 90 days in RE-VERSE AD, thromboembolic events had occurred in 6.3% of the patients reversed for hemorrhage. Over 90% of these complications occurred in patients who did not have re-initiation of anticoagulant therapy. There were no serious adverse safety signals. Idarucizumab was also studied for, and approved for, reversal of dabigatran anticoagulation prior to an intervention that required good hemostasis.

Factor Xa Inhibitor Reversal

A class-specific antidote, andexanet alfa, has been evaluated in several pivotal studies (ANNEXA-A and ANNEXA-R and with interim results from ANNEXA-4, a large clinical study in patients with major bleeding). These trials resulted in FDA approval for this therapy in patients with major bleeding associated with use of the FXa inhibitors apixaban or rivaroxaban.

Andexanet alfa is a decoy FXa that lacks biologic activity in the coagulation cascade because of removal of the Gla-domain. It also has a mutation in the catalytic domain that removes its intrinsic procoagulant activity. The agent competitively binds to the Xa inhibitor, but the dose of andexanet must be tailored to the molar concentration of the anticoagulant, and an infusion must be maintained to continue the competitive blockade of the anticoagulant. In an ongoing clinical study, ANNEXA-4, the bolus dose of andexanet is followed immediately with a 2-hour infusion, in order to avoid rebound of Xa activity that otherwise occurs. The recommended dosing of andexanet alfa is based on the specific FXa inhibitor, the dose of FXa inhibitor, and time since the patient’s last dose of FXa inhibitor (Tables 4 and 5).

Although some patients did not demonstrate complete reversal of anti-Xa activity, the interim clinical data supported a hemostatic effect after reversal of “good” or “excellent” in 79% of the 47 evaluable cases. There were 12 thrombotic complications (18%) during the follow-up of 30 days, 4 of which occurred during the first three days, but only 1 of those 12 patients had resumed anticoagulation before the event. In an update at the March 2018 American College of Cardiology Scientific Session, data that supported the previous interim analysis were presented on the ANNEXA-4 trial through October 20, 2017. In 132 adjudicated severe bleeds, 109 achieved “excellent” or “good” hemostasis (83%; 95% CI, 76-89%). From a safety perspective, thrombotic events occurred in 6 patients (2.6%) by three days and in 24 (11%) by 30 days. Therapeutic anticoagulation had resumed in only 9 patients before a thrombotic event occurred. Andexanet is not currently being studied for reversal prior to invasive procedures.

<table>
<thead>
<tr>
<th>Dose*</th>
<th>Initial IV Bolus</th>
<th>Follow-On IV Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose</td>
<td>400 mg at a target rate of 30 mg/min</td>
<td>4 mg/min for up to 120 minutes</td>
</tr>
<tr>
<td>High Dose</td>
<td>800 mg at a target rate of 30 mg/min</td>
<td>8 mg/min for up to 120 minutes</td>
</tr>
</tbody>
</table>

*The safety and effectiveness of more than one dose have not been evaluated. The recommended dosing of andexanet alfa is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient’s last dose of FXa inhibitor (see Table 5).
TABLE 05

<table>
<thead>
<tr>
<th>FXa Inhibitor</th>
<th>FXa Inhibitor Last Dose</th>
<th>&lt; 8 Hours or Unknown</th>
<th>≥ 8 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>≤ 10 mg</td>
<td>Low Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&gt; 10 mg / Unknown</td>
<td>High Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>≤ 5 mg</td>
<td>Low Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>&gt; 5 mg / Unknown</td>
<td>High Dose</td>
<td>Low Dose</td>
</tr>
</tbody>
</table>

Until andexanet alfa became available, PCCs served as a possible alternative for the management of life-threatening bleeding associated with anti-Xa treatment. The PCCs reverse abnormal laboratory parameters (PT and endogenous thrombin potential) in human volunteers after taking high doses of rivaroxaban and apixaban.\textsuperscript{33-35} This is not an intuitive approach in managing patients who do not have deficient levels of FXa or any of the other constituents of PCC. For this reason, treatment of anti-Xa-related bleeding with PCCs may be associated with a risk of post-repletion thromboembolic complications. Treatment with the combination of a specific reversal agent and PCCs can increase the risk of thrombotic complications; therefore, if a patient will be treated with andexanet alfa or idarucizumab, PCCs should only be administered using extreme caution while balancing the risk versus benefit ratio in the patient with severe bleeding.

APPRAOCH TO MANAGEMENT OF ORAL ANTICOAGULANT-ASSOCIATED BLEEDING

Management of DOAC-associated bleeding involves four steps: Review, Repair, Reverse or Replete, and Resume (Figure 1).\textsuperscript{36}

**Step 1.** Review requires one to stop the anticoagulation, determine the time of the last dose, review concomitant medications, evaluate the patient’s comorbidities, assess for cardiac decompensation, order baseline labs, investigate the source of bleeding, maintain organ perfusion, and evaluate for transfusion. It is also important to remember that a conservative approach may be all that is needed because DOACs have short half-lives,\textsuperscript{37,38} so stopping therapy may be sufficient in patients with minor bleeds. Removal of the oral anticoagulant with gastric lavage, oral charcoal, or dialysis (for dabigatran) has been suggested as an additional step in the management of these patients.\textsuperscript{36} The DOACs are rapidly absorbed after oral administration, however, and activated charcoal can make airway management extremely difficult should the patient become unstable and makes endoscopy nearly impossible in patients with GI bleeding. Therefore, the use of activated charcoal should be limited to and used with caution in acute overdose situations. Because dabigatran is primarily renally excreted, dialysis has been suggested as part of the treatment strategy for dabigatran-related bleeding, but now that idarucizumab is available to bind dabigatran there is likely no longer a role for dialysis.
**Step 2.** Repair involves assessing the need for endoscopy, interventional radiology or surgery and performing the appropriate procedure to stop the bleeding. These definitive measures to control the bleeding source should be initiated in parallel with repletion or reversal in patients with severe bleeding.

**Step 3.** Reverse includes use of reversal agents. The specific reversal agents, idarucizumab for dabigatran and andexanet alfa for apixaban and rivaroxaban, may be used for life-threatening bleeding, emergency surgery, and delayed clearance and bleeding. Replete includes use of PCCs or FFP for severe VKA-associated bleeding.

**Step 4.** Resume involves making an informed clinical decision about when to resume anticoagulant therapy based on the nature of the bleeding episode and the patient’s risk for a thromboembolic event.

Specific management of bleeding associated with DOAC use varies according to the severity of bleeding.

**Minor bleeding** includes ecchymosis, most epistaxis, mucosal bleeding, hematuria and menorrhagia. Management of minor DOAC-associated bleeding consists of temporarily discontinuing the DOAC, using local measures to control the source of bleeding, providing supportive care and maintaining hemodynamic status, and then consideration of restarting the DOAC when the bleeding has subsided and the risk for thrombosis exceeds the risk of bleeding.

**Moderate bleeding** includes most upper and lower GI bleeding. The DOAC should be discontinued at least temporarily and the patient monitored closely. The underlying bleeding source should be investigated and definitively treated. Extended DOAC withdrawal should be considered, and utilization of low-dose parenteral anticoagulant for patients at particularly high risk of thrombosis may be necessary to allow healing. Transfusion therapy with packed red blood cells (PRBCs) for symptomatic anemia and monitoring of renal function are essential.

**Major bleeding** is defined by the International Society of Thrombosis and Hemostasis as fatal bleeding, bleeding involving a critical area (brain, spinal cord, pericardial, intraocular, retroperitoneal, intra-articular, or intramuscular with compartment syndrome), any bleeding that results in a net drop of hemoglobin of at least 2 g/dL, or bleeding that requires the transfusion of at least 2 units of PRBCs. Major bleeding requires immediate withdrawal of any anticoagulant and antiplatelet drugs. Aggressive clinical monitoring and transfusion of PRBCs in response to proven/anticipated severe anemia are required. Interventions to identify and treat the bleeding source include endoscopy, interventional radiology, and/or surgery. Life-saving therapies, including inotropes, ventilation, and ICU admission, should be considered as needed. Reversal or repletion should be administered as appropriate.

It should be noted that transfusing platelets in the face of thrombocytopenia is different from giving platelets to overcome antiplatelet agent effects. For patients taking antiplatelet agents, the decision to transfuse platelets will vary with the actual platelet antagonist being used as well as the site of the bleeding. Transfusion of pooled platelets can mitigate the effects of clopidogrel and prasugrel; however, it has less effect on platelet inhibition from ticagrelor and its active circulating metabolite. There is evidence that platelet transfusion in patients taking antiplatelet agents may cause harm, particularly in patients with GI bleeding and ICH. Platelet transfusions in GI bleeding patients on antiplatelet therapy are associated with increased mortality without improvement in recurrent GI bleeding, major adverse cardiovascular events or length of hospital stay. Platelet transfusions have also been associated with worse outcomes in patients with ICH who have been taking antiplatelet therapy. Platelets are immune cells that release inflammatory markers, bioactive lipids and cytokines. Transfusion may contribute to transfusion-related lung injury, and also carries an increased risk of thrombosis due to platelet activation in stored product, possibly leading to recurrent events such as acute coronary syndrome, ischemic stroke, and deep vein thrombosis. Therefore, platelet transfusion should be reserved for life-threatening bleeding.

An algorithm for the approach to management of patients with life-threatening oral anticoagulant-associated bleeding is presented in Figure 2.

**PREPARATION AND ADMINISTRATION OF REVERSAL AGENTS AND ROLE OF THE PHARMACIST**

Pharmacists can assist with appropriate patient selection and reversal agent administration. Specifically, they can aid in estimating the half-life of an anticoagulant, interpreting available coagulation tests, and/or identifying drug interactions that
MANAGEMENT OF SEVERE BLEEDING IN PATIENTS TREATED WITH ORAL ANTICOAGULANTS

**FIGURE 02**
Management of Life-Threatening Bleeding in Anticoagulated Patients

**Supportive Care**
- Hemodynamic support
- ICP management
- Blood product transfusion
- Transfer for tertiary care

**Uncertain anticoagulation status**
Assess anticoagulation status (PT, aPTT, TT, Factor Xa level)
Consider hematology consult

**Life-threatening* bleeding**
- Warfarin
- Dabigatran
- Idarucizumab: 5 g IV

**Factor Xa Inhibitor**

**Andexanet alfa**
If prolonged delay to andexanet or idarucizumab consider 4FPCC or FFP

- ≥ 8 hrs from last dose
- < 8 hrs from last dose

**Rivaroxaban ≤10 mg**
- Apixaban ≤5 mg
- **Low dose andexanet alfa**
  - Initial IV bolus: 400 mg at 30 mg/min
  - Follow-on IV infusion: 4 mg/min up to 120 min

**Rivaroxaban >10 mg**
- Apixaban >5 mg
- **High dose andexanet alfa**
  - Initial IV bolus: 800 mg at 30 mg/min
  - Follow-on IV infusion: 8 mg/min up to 120 min

* Life-threatening bleeding including intracerebral hemorrhage and exsanguinating gastrointestinal bleeding
** FDA approved for rivaroxaban and apixaban only, but mechanism of action suggests it may be equally effective for edoxaban and betrixaban
ICP, intracranial pressure; 4FPCC, four-factor prothrombin complex concentrate

Algorithm available online at: http://www.emcreg.org/bleeding-reversal.pdf

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may prolong anticoagulant clearance. Finally, pharmacists can indirectly assist in patient selection and reversal administration by providing education for hospital staff about the importance of documenting vital data such as anticoagulant dose, body weight and drug levels, and about specifics of drug administration, such as the fact that andexanet alfa and idarucizumab require special care to ensure that the entire dose is administered rather than having residual drug remaining in the tubing.

Anticoagulant reversal agents need to be available around-the-clock and should be available to the departments most likely to need them without undue delay. Assuring “timely” availability of reversal agents, however, requires the consideration of multiple logistical matters such as agent storage (idarucizumab and andexanet need to be refrigerated), admixture (i.e., 9 or 18 andexanet vials each needing 3-5 minutes for reconstitution, although larger vials will soon be available), “proper reconstitution technique,” and transport requiring hand delivery. As a result, although many reversal agents provide rapid normalization of bleeding times once the agent is infused, the time from order to administration may be substantial at upwards of 30-45 minutes.

Anticoagulant reversal agents are expensive and their cost-effectiveness has not been established. An analysis of the drug cost in the context of the overall cost of ED and intensive care as well as patient outcomes has not yet been performed. The high cost of many of these reversal agents may drive hospitals to create policies that mandate these agents be dispensed by the pharmacy. What impact pharmacy-based dispensing may have on the time to reversal agent administration is unclear, but it is worth noting that this was likely how many of the agents were handled during clinical trials as investigational drugs and how many time-sensitive agents, such as alteplase for acute ischemic stroke, are currently handled. If the decision is made to stock reversal agents outside of pharmacy, a mechanism to ensure the pharmacy is informed when they are utilized is of the utmost importance to assure an uninterrupted supply is available for patients.

A final role for pharmacy is to assure any adverse events associated with reversal agents be reported to the manufacturers and the Food and Drug Administration’s Safety Information and Adverse Event Reporting Program.

**INSTITUTIONAL PROCESSES FOR THE ADMINISTRATION OF ANTICOAGULANT REVERSAL AGENTS**

Because administration of specific anticoagulation reversal agents is costly and time-consuming, institutions should develop their own predefined objective guidelines for determining which patients qualify for administration of a reversal agent. Ideally, these guidelines should be developed by a multidisciplinary team, and there should be at least one subject matter expert who can interpret the available data and make informed decisions for patients who may benefit from reversal but do not fit the institution’s standard guidelines. Although this model may work well at large academic institutions, it is not possible at all community hospitals. Therefore, each institution must work on their own process improvements to identify and mitigate barriers to proper and efficient administration of anticoagulation reversal agents. Furthermore, in each individual case, the decision to treat relies on the determination by the treating clinician that 1) there is life-threatening hemorrhage, 2) the hemorrhage is likely due to drug-related coagulopathy, and 3) the case is not futile.

Timely administration of the reversal agent requires that the processes involved in drug preparation and patient care occur in a parallel, rather than serial, fashion. For example, as soon as a patient is identified as being a possible candidate for DOAC reversal, the caregivers that will be involved, such as the pharmacy, nursing, ED and critical care teams, should be notified so when the decision to treat is made, all are prepared for efficient execution of care. Involvement of a pharmacist on the clinical team can facilitate communication with central pharmacy and ensure prompt admixture and delivery of drug. As the drug is being prepared, the pharmacist can verify proper administration by double checking the patient’s DOAC dose, weight, and creatinine clearance, and the medical team can begin to gather equipment and prep the patient for control of the bleeding source. Finally, it should be noted that the time to obtain the drug from central pharmacy may be prohibitive in some cases, such as with pericardial tamponade, in which the decision to take the patient to the OR must be made very quickly.

**PREHOSPITAL MANAGEMENT OF THE ANTICOAGULATED PATIENT WITH SEVERE BLEEDING**

Hemorrhage control is a key life-saving intervention expected of every level of Emergency Medical Services (EMS) providers, and
identification of life-threatening bleeding is a component of the prehospital “primary survey.” This focus is especially relevant in trauma, where almost half of trauma-related prehospital deaths are due to hemorrhage and transfusion delays as short as 10 minutes are associated with increased mortality. Rapid reversal of anticoagulation in traumatic brain injury patients decreases ICH growth, which may improve outcomes. Life-threatening non-traumatic hemorrhage is also common, with spontaneous ICH and GI bleeding being most prevalent.

Increased availability of coagulation factor concentrates has created an attractive option for bleeding patients known to be on anticoagulant medications or with trauma-induced coagulopathy. European case reports have shown efficacy when administered prior to hospital arrival, with improved access to this therapy for patients served by rural hospitals. A single-center trial that compared the efficacy of first-line therapy using FFP versus coagulation factor concentrates for the reversal of trauma-induced coagulopathy was stopped early because the FFP group had significantly increased risk of rescue therapy and massive transfusion.

Published experience and evidence of prehospital treatment of non-traumatic hemorrhage is sparse and primarily limited to case reports and single-institution experiences. Blood and plasma transfusion are used most often for critical GI bleeding, with improvements in hemodynamics and demonstrated reversal of coagulopathy. Mobile stroke units have been able to reverse anticoagulation prior to administration of tissue plasminogen activator (tPA) or to treat ICH.

**Barriers to Prehospital Hemorrhage Control**

Several barriers prevent advancement in prehospital hemorrhage control options. Although the scope of practice varies among states, a prehospital provider’s education is the most limiting factor. Basic Emergency Medical Technicians are primarily limited to the fundamental techniques of bandages and tourniquets. Paramedics, with roughly 1,000 additional hours of initial training, can obtain vascular access and administer a wide variety of medications from a locally determined pharmacopeia. However, even today, large parts of the United States do not have access to paramedic-level care. Even where trained providers are available, operational barriers impact treatment options. Use of plasma may be evidence-based, but the choice of plasma source, plasma preparation, and logistics including stock management require consideration. Not all emergency vehicles have temperature-controlled storage for medications or blood products, and agencies distant from trauma centers may not have ready-access to a blood bank. Freeze-dried or lyophilized plasma may extend access in the future but are not current options.

Recognition of external traumatic bleeding and some non-traumatic hemorrhage, such as gastrointestinal hemorrhage, is straightforward and only requires a physical exam. Widespread availability of advanced diagnostics, such as ultrasound or mo-
bile computed tomography, is not realistic, limiting detection of other types of life-threatening hemorrhage. Prehospital identification of patients taking anticoagulant medications, especially DOACs, is poor[2] and prehospital point-of-care testing of coagulation profiles is not widespread.

Presuming technological and educational advancements allow betterprehospital recognition of hemorrhage in anticoagulated patients, the adoption rate of potential therapies will be driven by cost. Prehospital emergency medical care is primarily reimbursed at a fixed rate, with minor adjustments for patient acuity and geographic region. Care episodes that do not result in patient transportation are not reimbursed. Unlike hospitals, EMS agencies generally cannot itemize or separately bill for medications or procedures. Thus, effective treatments may not be economically feasible.

**EMERGENCY EVALUATION AND TREATMENT OF THE ANTICOAGULATED PATIENT WITH SEVERE BLEEDING**

**Emergency Medicine Perspective on the Trauma Patient**

Injured patients who present to EDs and are taking oral anticoagulants account for 4% of all trauma patients. This subset of patients tends to be older, has more comorbidities, and has higher mortality than those not on anticoagulants. The structured approach to the evaluation of a traumatized patient who is taking an oral anticoagulant begins with assessment of hemodynamic stability and the location of the hemorrhage.69,70 Control of the hemorrhage source using direct manual compression, tourniquet application, intravascular embolization or surgical intervention should be attempted. Intravenous administration of vitamin K 5-10 mg should be given to those patients on VKAs. Supportive care with the administration of blood products, either whole blood or PRBCs, should proceed according to institutional policy and patient stability. Oral anticoagulants should clearly be stopped while a patient is being resuscitated, and consideration toward reversal and/or factor repletion should proceed in trauma patients with major or critical site hemorrhage. In mild or moderate bleeding, source control may be sufficient for hemostasis and obviates the need for factor replacement or reversal.

For patients taking VKAs who are compliant as evidenced by an elevated INR, 4FPCCs 25-50 units/kg should be given to replete key proteins in the coagulation cascade. FFP may be useful in factor repletion and plasma expansion in this scenario with careful attention to volume status and left ventricular function. For patients taking FXa inhibitors or dabigatran, the specific reversal agent should be administered if available. Other factors contributing to the decision to give specific reversal agents to a trauma patient with major bleeding are patient comorbidities. Uremia, chronic liver disease, thrombocytopenia, and the use of antiplatelet agents, including aspirin and PG2Y12 inhibitors such as clopidogrel and prasugrel, contribute to coagulopathy. In such cases, a more aggressive resuscitation and reversal strategy may include platelet administration, with the caveats mentioned previously. It is noteworthy to consider that treatment with factor replacement and reversal therapy carries significant expense, exposes the patient to their baseline or even increased risk of thromboembolism, and is not definitive therapy if the source of the hemorrhage is left unsecured.

**Intracranial Hemorrhage**

Traumatic brain injury (TBI) accounts for 2.5 million ED visits, 282,000 hospitalizations and 56,000 deaths annually in the United States.71 The increased use of oral anticoagulants among older adults has led to an increased number of patients presenting to ED with suspected TBI.72 These patients may appear well and present with low mechanisms of injury, such as ground level falls, yet still have traumatic ICH that may require neurosurgical intervention.73,74 Efforts to develop clinical decision rules to identify a subpopulation of this group that is at low risk of injury, such that no neuroimaging is required, have met with limited success. Most patients with a suspected TBI who are taking anticoagulants should undergo neuroimaging.72 Delayed traumatic ICH, defined as blunt head injury with initially normal neuroimaging followed by interval development of ICH on repeat imaging, has been reported.75 The incidence of delayed traumatic ICH is unknown, although a recent retrospective review found that among patients taking DOACs who were at risk for traumatic ICH but had a negative brain CT on admission (n=249), the incidence of delayed ICH was 0.8%.76 Evidence-based guidance to assist clinicians in establishing protocols for observation and repeat neuroimaging in TBI patients taking anticoagulants is limited.77,78 Some studies suggest that the subset of patients taking DOACs who have blunt traumatic ICH have lower mortality than those taking VKAs.79

Intracranial hemorrhages, consisting of TBI, non-traumatic subarachnoid hemorrhages (SAH), and spontaneous intracerebral hemorrhages, are neurologic emergencies that can lead to
significant morbidity and mortality. Although these three broad categories of ICH are managed somewhat differently, almost all of them require immediate reversal of anticoagulation in addition to initial resuscitation that includes hemodynamic management, airway stabilization as needed, a neurologic exam, and a head CT. Patients who are on anticoagulants and sustain an ICH have a higher risk of death and hematoma expansion compared to those who are not anticoagulated, making anticoagulation reversal an important component of care for these patients. Rapid reversal of anticoagulation is usually necessary for even small, relatively asymptomatic hemorrhages to prevent hemorrhage expansion and to allow for completion of neurosurgical procedures or surgeries when indicated. Unlike patients with GI or retroperitoneal bleeding, those with isolated ICH do not require significant volume resuscitation, and even small increases in the amount of hemorrhage may lead to increased disability or mortality.

Prompt and aggressive anticoagulation reversal is important for long-term outcomes in patients with anticoagulant-related ICH. Time spent waiting on subspecialty consultation, transfer to another facility, or waiting on reversal after admission can impact long-term morbidity and mortality. A retrospective study of patients with intracerebral hemorrhage who were taking oral anticoagulants demonstrated that those who achieved a combination of INR reversal to < 1.3 and systolic blood pressure reduction to < 160 mm Hg within four hours had a significantly lower rate of hematoma enlargement (18.1% versus 44.2%). The mainstays of anticoagulant reversal include FFP or PCCs combined with vitamin K. The 2015 American Heart Association guidelines for intracerebral hemorrhage (as measured by the size of the hematoma) was 2.2±1.9 at baseline, with an average presenting GCS of 14. Patients with a GCS of < 7 were excluded. Good or excellent neurologic presentation at baseline, with an average presenting GCS of 7 or better and a Glasgow Coma Scale of 15/15 at presentation, was strongly associated with improved outcomes. Patients with a GCS of < 7 had a significantly higher mortality rate (45%) than those with a GCS of 7 or better (20%). The risk of rebleeding was also higher in patients with a GCS of < 7 (30%) than in those with a GCS of 7 or better (15%).

**Vitamin K Antagonist-Associated Intracranial Hemorrhage**

Based on years of clinical practice and research, there are more data to support anticoagulation reversal practices in the setting of VKAs as compared to newer oral anticoagulants, particularly in the care of patients with ICH. Patients who experience an intracerebral hemorrhage while taking warfarin have a higher mortality than those who are not anticoagulated. The mainstays of reversal include FFP or PCCs combined with vitamin K. The 2015 American Heart Association guidelines for intracerebral hemorrhage state that “PCCs may have fewer complications and correct the INR more rapidly than FFP and might be considered over FFP (Class IIb, Level of Evidence B).” Based on available evidence, it is reasonable to assume that nearly all ICHs in the setting of VKA therapy represent a life threat and PCCs should be used for reversal. One criticism of PCC is that there has not been a large randomized controlled trial comparing it to FFP in the setting of intracranial hemorrhages. Smaller studies do support that PCCs reverse coagulopathy, defined as elevated INR, in patients with VKA-associated anticoagulation faster than FFP in the setting of both extracranial and intracranial bleeding.

In a prospective observational study that compared treatment with PCCs and FFP in the setting of VKA-associated ICH, patients who received PCCs had a lower risk of death or severe disability at three months (p = 0.039) when compared to FFP alone. A randomized controlled trial comparing FFP to PCCs in the setting of VKA-associated ICH suggested that PCCs reversed INR faster than FFP; however, the trial was stopped early because of safety concerns due to greater hematoma expansion in the FFP group. Regardless of whether FFP or PCCs are used in the acute setting, patients also need to receive intravenous vitamin K to allow for the endogenous production of clotting factors.

**DOAC-Associated Intracranial Hemorrhage**

Intracranial hemorrhages comprise only 13% of all major bleeds in all DOAC-treated patients. Of all DOAC bleeding complications, ICHs have the highest mortality at 45%. The risk of ICH is significantly lower in patients anticoagulated with a DOAC than with warfarin. In the RE-VERSE AD study, in which idarucizumab was evaluated for dabigatran reversal, 98 (32.3%) of the patients presented with ICH, including intracerebral hemorrhage, SAH, and subdural hematoma (SDH). The 30-day mortality rate was 16.4% among patients with ICH, which was lower than previously described rates of warfarin-associated ICH.

The interim publication of the ongoing ANNEXA-4 study of andexanet alfa enrolled 28 (42% of total) patients with intracranial hemorrhage. These constituted a mixture of intracerebral hemorrhage, SAH, and SDH, similar to the Phase 3 idarucizumab study. The study population overall had a more favorable neurologic presentation at baseline, with an average presenting GCS of 14. Patients with a GCS of < 7 were excluded. Good or excellent hemostasis (as measured by the size of the hematoma) was achieved in 80% of patients. The mean modified Rankin scale for global disability and handicap score was 2.2±1.9 at baseline and 2.0±2.0 at 30 days among survivors.

For anticoagulated patients with ICH, several issues complicate the decision to treat with a specific reversal agent. First, the treating physician should strongly consider the goals of care. With the limited accuracy of ultra-early prognosis, patients with pre-injury functional independence, even with major traumatic
ICH, should be treated aggressively for the first 24 to 48 hours to try to preserve the opportunity for recovery. Similarly, an anticoagulated patient with a rim subdural hematoma and a GCS of 15 may be an excellent target for intervention to preserve their neurologic status. Contrary to historical practice, a decline in neurologic exam during serial exams should not be the requirement for a decision to treat, since clinical changes likely represent cerebral compression from progression of intracranial pathology. Although patients with GCS < 7 were excluded from treatment in the ANNEXA trial, there is no clear reason to exclude patients with low GCS from treatment withandexanet alfa. Currently, there are no data on the natural progression of different types of ICH in patients taking DOACs, so risk stratification as a guide to decision-making is not reliable. Despite recommendations for early aggressive care, there are patients with a poor baseline quality of life with persistent neurologic deficits who may not receive meaningful benefit from intervention with a reversal agent. Finally, there are currently no data regarding re-dosing or extended infusion of andexanet alfa in patients with ICH; therefore, monitoring of TEG and repeating an anti-Xa level after initial dosing may be helpful, especially in patients with renal insufficiency.

**Abdominal and Chest Trauma**

The evaluation and resuscitation of a patient with blunt thoracoabdominal trauma in the setting of anticoagulation are similar to that of a non-anticoagulated patient in that evaluation of the site and severity of hemorrhage is paramount. Initial concern that patients taking DOACs would have higher mortality than those taking VKA in the setting of severe blunt traumatic injury, defined as an injury severity score (ISS) > 15, was not supported in recently published registry data. After excluding patients with severe head injuries, the authors found significantly lower mortality in the DOAC group versus the warfarin group (8.3% versus 29.5%, respectively; p<0.015). No difference in mean ISS, hospital or ICU length of stay, or complications was noted. Units of blood product transfused per patient was lower in the DOAC group (2.8 ± 1.8 units per patient in the DOAC group versus 6.7 ± 6.4 units per patient in the warfarin group; p = 0.001). Initial imaging evaluation with Focused Assessment with Sonography in Trauma (FAST) followed by cross-sectional imaging to identify the site and severity of bleeding is recommended. Repeat evaluation and observation as an inpatient or in a clinical decision or observation unit are prudent for patients for whom there is concern for bleeding in the setting of anticoagulation.

**Gastrointestinal Bleeding**

In anticoagulated patients, GI bleeding is a common clinical problem that results in significant morbidity and cost. By some estimates, it accounts for up to 2% of hospital admissions with a mortality rate of 5%. Risk factors for DOAC-related GI bleeding include concomitant use of ulcerogenic agents (NSAIDs), older age, renal impairment, previous H. pylori infection and history of GI bleed. Unlike warfarin, aspirin and NSAIDs where upper GI bleeding (UGIB) predominates, lower GI bleeding (LGIB) accounted for 53% of GI bleeding with dabigatran. The most frequent sources of anticoagulant-associated GI bleeding are peptic ulcer disease for UGIB and colonic diverticuli for LGIB.

**Evaluation of GI Bleeding**

Determination of the location of the GI bleed is important in patients who are anticoagulated in terms of how aggressively and urgently one must consider discontinuation of the anticoagulant and/or correction of the coagulopathic state, especially since LGIB stops spontaneously in 80-85% of patients. Factors predictive of an upper GI source include a patient-reported history of melena, melanotic stools on examination, blood or coffee-ground emesis during nasogastric lavage, and blood urea nitrogen (BUN) to serum creatinine ratio > 30. Up to 60% of patients with a history of UGIB are bleeding from the same lesion as a previous event; therefore, past history can help identify bleeding sources. Hematochezia suggests a lower GI source, but can be seen in patients with massive UGIB or small bowel bleeding.

Whether all patients with suspected acute GI bleeding require nasogastric (NG) tube placement and lavage remains controversial. Studies have failed to demonstrate a reduction in mortality, hospital length of stay, need for surgery or transfusion requirement. However, NG tube lavage is associated with shorter time to GI endoscopy and assists in ruling out an upper GI source of bleeding. In anticoagulated patients, this additional information may be helpful in deciding whether reversal and push for urgent endoscopy are appropriate when UGIB is suspected.

Frank red blood during nasogastric lavage, tachycardia, orthostatic dizziness, cold/clammy extremities and hemoglobin less than 8 g/dL suggest severe bleeding, as do confusion, angina and palpitations. Serious hypovolemia is signaled by resting tachycardia (less than 15% blood volume loss), orthostatic hypotension (15-40% volume loss) and supine hypotension (at least 40%
blood loss). Severe abdominal pain, rebound, and involuntary guarding raise one’s concern for perforation.

**Emergent Management**

General emergency management includes triaging to an appropriate level of care, obtaining adequate intravenous access, and supportive measures. Non-major GI bleeding involves cessation of drug and delayed endoscopic management. If the bleeding is limited or slow, replacing lost fluid and blood products, if necessary, may be the best course of action while one waits for the anticoagulant effect to abate. Acute management of serious bleeding focuses on aggressive resuscitation, strategic drug reversal, and prompt endoscopy to control the bleeding source. Besides fluid and blood replacement, intermediate steps include the use of antifibrinolytic agents (TXA, DDAVP). The role of non-specific reversal agents such as PCCs remains controversial. One study suggests that use of PCC is associated with a 7% risk of thromboembolism.

Patients with hypovolemia and active bleeding require red cell transfusion, even with an apparently normal hemoglobin at the onset. This is especially true if the patient remains hemodynamically unstable despite appropriate fluid resuscitation. Many guidelines recommend transfusion if hemoglobin falls below 9 g/dL; a more restrictive approach, however, using a hemoglobin of less than 7 g/dL has been shown to be safe with improved mortality. Given the risk of continued bleeding in anticoagulated individuals, a more robust transfusion threshold is appropriate. Equally important, one should avoid over transfusing patients with suspected variceal bleeding, as this can precipitate worsening hemorrhage. Thrombocytopenia should be corrected when platelets fall below 50,000/microL. Since packed red blood cells do not contain coagulation factors, giving FFP for every 1-2 units of packed cells as part of a massive transfusion protocol is currently the standard of care for massively bleeding patients.

With life-threatening bleeding in hemodynamically unstable patients, complete reversal is appropriate while seeking emergent endoscopy. Intervention with antifibrinolytic agents, non-specific repletion agents (PCCs), and specific reversal agents such as idarucizumab and andexanet alfa is warranted. This occurs more often with UGIB since a large percentage of LGIB stops spontaneously.

**Ancillary Therapeutic and Diagnostic Intervention**

Acid suppression is paramount with upper GI bleeding. Proton pump inhibitors (PPI) should be started at presentation. Whereas pre-endoscopy histamine (H2) receptor antagonists and acid suppressive therapy have not been shown to significantly lower the rate of ulcer rebleeding, high dose antisecretory therapy with intravenous PPI infusion significantly reduces the rate of rebleeding compared to standard treatment in patients with bleeding ulcers. The PPIs also decrease length of stay, rebleeding rate, and need for blood transfusion post-endoscopic intervention. Radiographic imaging such as CT scan, angiography and radionuclide studies are sensitive but often less accurate for localizing the bleeding site. These studies are considered secondary to endoscopy, which has both diagnostic and therapeutic potential. Use of newer endoscopy techniques allows successful endoscopic management even in the setting of brisk bleeding.

**Mucosal Bleeding**

Mucosal bleeding, such as epistaxis and post-dental extraction, can be quite unnerving to the patient and frustrating for the physician, but rarely results in substantial morbidity or mortality. Bleeding can be more impressive, recurrent, and difficult to manage in patients with impaired hemostasis due to treatment with antiplatelet or anticoagulation medications. For mucosal bleeding, the risk/benefit ratio for systemic anticoagulation reversal or factor replenishment versus the underlying condition warranting anticoagulation would argue for local hemorrhage control as the first line treatment. There is a limited base of quality evidence to inform management strategies.

**Epistaxis**

Epistaxis can be characterized as anterior or posterior, with most nosebleeds originating from Kisselbach’s plexus in the anterior nasal septum where they are easily controlled. Posterior nosebleeds, while infrequent, do have a greater likelihood of blood loss, difficulty in achieving hemostasis, and need for hospitalization and potential surgical intervention.

Direct pressure is the cornerstone of local bleeding control. For most nosebleeds, simply pinching and holding the nasal alae will, within a few minutes, prove sufficient for hemostasis. Failing that measure, nasal tampons allow for pressure to be directly applied against the offending vessel. Various devices are commonly available in the ED, including fluid-expandable...
sponge nasal tampons and inflatable nasal balloons. There has been no demonstrated advantage of one over the other, although patient comfort has been reported to be improved with the inflatable nasal balloons.\textsuperscript{98} Posterior epistaxis can be controlled via nasal tampon deployment as well, although a device of sufficient length is required. The classical solution to posterior epistaxis in the ED that is refractory to tampon placement is the use of a Foley catheter, which is advanced in a similar fashion to a nasogastric tube, inflated, and then pulled back into the nasal passages until lodging, which provides tamponade of the bleeding. Bilateral posterior packing may be required to achieve control. Despite this approach, bleeding may persist and surgical or interventional radiology consultation may be required for arterial ligation or embolization.

In addition to mechanical compression, there are pharmacologic adjuncts available in the form of topical vasoconstrictors or TXA. Commonly used topical vasoconstrictors include cocaine, phenylephrine, epinephrine, and oxymetazoline. TXA is a fibrin stabilizer that enhances hemostasis by blocking the activity of plasminogen.\textsuperscript{99} Recently, the use of topical TXA has been described in the setting of epistaxis using an atomizer, nebulizer, or saturating a nasal tampon with the injectable preparation (100 mg/mL solution).\textsuperscript{100-103} The use of chemical cautery allows for desiccation of a bleeding vessel in the anterior septum, as long as the vessel can be visualized and the field is dry. Silver nitrate is typically used, with the caveat that it is applied only for a few seconds and not on both sides of the septum. In the anticoagulated patient, a prolonged period of observation prior to discharge from the ED may be warranted, as the re-bleed rate is higher in anticoagulated patients.\textsuperscript{97}

**Oral Bleeding**

The randomized controlled trial literature for oral bleeding (typically post-dental extraction) in the ED is non-existent at this time, with no available evidence in the anticoagulated patient cohort.\textsuperscript{104} The principles for controlling post-extraction bleeding in the anticoagulated patient are similar to epistaxis – direct pressure remains critical. Rarely, arterial bleeding may require direct ligation with a figure-of-eight or purse-string stitch.

Hemostatic control of an extraction site can be accomplished by having the patient bite down on a small gauze roll after the pre-existing clot and debris have been gently irrigated away. Direct pressure may be facilitated with local injection of lidocaine with epinephrine into the surrounding gingiva, both for vasoconstriction as well as pain relief from direct pressure onto a recent oral surgery site. Cohort data suggest an association with improved hemostasis when the gauze used for compression is saturated with TXA.\textsuperscript{105} Routine post-operative topical TXA mouthwash is associated with decreased oral bleeding in patients on VKAs such as warfarin; however, this regimen has not been prospectively studied in the setting of acute bleeding.\textsuperscript{106} Packing the socket with surgical gelatin foam may be an option for hemostasis, especially if TXA is not available.

**CRITICAL CARE MANAGEMENT OF THE ANTI-COAGULATED PATIENT WITH SEVERE BLEEDING**

**Management of the Anticoagulated Patient in the Perioperative Setting**

Patients who are severely injured rapidly develop a “coagulopathy of trauma” due to significant tissue damage.\textsuperscript{107} The current standard of care is to treat this coagulopathy by minimizing infusion of crystalloid and transfusing PRBCs and plasma (FFP) in a 1:1 ratio.\textsuperscript{108} Obtaining immediate hemorrhage control is critical to prevent the “lethal triad of trauma”: worsening coagulopathy, acidosis, and hypothermia. Hemorrhage control may involve use of tourniquets,\textsuperscript{109} aortic balloon occlusion,\textsuperscript{110} embolotherapy, or operative exploration. However, such a strategy does not address patients who have pharmacologic inhibition of the coagulation system in addition to the inherent coagulopathy of trauma. Such patients frequently require specific reversal agents to restore their innate clotting ability and decrease risk of fatal exsanguination related to the operation.

The PCCs have been shown to very rapidly and effectively reverse coagulopathy due to vitamin K antagonists, most commonly warfarin, in patients who require emergency surgery.\textsuperscript{111,112} More recently, they have also been shown to improve time to correction of coagulopathy and to decrease the need for blood product transfusion when given in addition to a 1:1 transfusion strategy in hemorrhaging trauma patients.\textsuperscript{113} Although PCCs are costly, they are less likely than plasma to result in transfusion-associated circulatory overload and are associated with a lower overall transfusion need, both of which can offset the cost of the drug. Moreover, PCCs are now commonly available in most hospitals, making their use in the perioperative setting practical and feasible. However, PCCs should not be used alone for
treatment of the exsanguinating patient because such patients require ongoing volume repletion, which is best carried out using plasma to replete ongoing consumption of coagulation factors and minimize the risk of hemodilution of these factors associated with crystalloid infusion.

Whereas treatment of bleeding patients who have coagulopathy due to the presence of warfarin is somewhat straightforward, management of severely injured bleeding patients who are taking DOACs is challenging. First, as previously mentioned, there is no readily available laboratory test that can measure for the presence or activity level of these agents in the serum. As such, the surgeon/intensivist must consider the severity of the bleed, time since the patient last ingested a dose of the drug, and the pharmacokinetics of the drug in the setting of the patient’s renal and liver function when determining whether or not to administer a reversal agent. Moreover, specific reversal agents for DOACs, especially andexanet alfa, are expensive. Waiting to evaluate whether the amount of hemorrhage is increasing may be a reasonable option in many instances, unless the patient presents in extremis where there is no physiologic reserve left or the patient has a significant hemorrhage in a closed space, such as the cranium. Also, the physician may be able to use secondary signs, such as the presence of blood clots on the stretcher or in the operative field, to determine coagulation status and inform the decision on use of DOAC-specific reversal agents. Ultimately, the surgeon must make a subjective assessment of the risk/benefit ratio regarding the patient’s likely anticoagulation status, the urgency of the surgery, and the ability to perform intra-operative reversal if necessary. Lastly, the surgeon/intensivist should consider the duration of the reversal agent to determine the likelihood of rebound coagulopathy. Rebound coagulopathy may occur with andexanet alfa due to its short half-life and weak covalent bond to the FXa inhibitor, but is much less likely to occur with idarucizumab, which irreversibly binds dabigatran.29,88

Following operation, various endpoints should be used to determine coagulation ability. In addition to conventional coagulation parameters, TEG can be used to determine both clotting ability as well as clot stability (degree of fibrinolysis),114 but this modality is not predictive of the presence of DOACs. In addition to monitoring hemoglobin and lactic acid/base deficit levels, the amount and character of output from surgically placed drains can be used to assess for ongoing coagulopathy and possible need for (additional) doses of reversal agents.

The decision to resume anticoagulation post-operatively or following severe injury is challenging, and there are no set standards to follow. Delay to resumption of anticoagulation is associated with the risk of thromboembolic or occlusive disease,88 whereas early resumption is associated with recurrent hemorrhage. Although one may be able to restart anticoagulation earlier in patients who have definitive control of hemorrhage, such as post-splenectomy, delay to resumption of anticoagulation may be necessary in patients in whom inherent clotting ability is needed for days to weeks to prevent worsening injury, such as with brain trauma.

**Evaluation and Treatment of Post-Procedural Bleeding in the Anticoagulated Cardiac Patient**

**Anticoagulation During Cardiovascular Procedures**

The introduction of a non-biologic material or surface into the circulation represents a nidus for thrombus formation. This teleological response to “non-self” is the result of triggering the contact activation pathway, beginning with FXIIa, FXIα, pre-kallikrein and high molecular weight kininogen. The insertion of catheters and stents and the performance of tissue ablation for the purpose of disrupting reentry circuits in atrial fibrillation and atrial flutter stimulate tissue factor-based coagulation.

The underlying mechanisms of thrombus formation, coupled with the risk for bleeding with anticoagulant therapy in an acute setting, have led to the development and wide-scale use of anticoagulants that have a rapid onset of action and short plasma half-life. The most commonly employed agent is unfractionated heparin (UFH); however, other parenteral anticoagulants such as bivalirudin, lepirudin, enoxaparin and argatroban may also be used, particularly for percutaneous coronary intervention (PCI) and in cases where UFH is contraindicated, such as in patients with heparin-induced thrombocytopenia.

DOACs, while increasingly used worldwide, are not a common first-line consideration in cardiovascular procedures; however, patients receiving DOACs who undergo pacemaker or internal cardioverter-defibrillator (ICD) placement or direct-current cardioversion are increasingly kept on treatment. Accordingly, a keen understanding of these agents and their pharmacological profiles is an absolute requirement for clinicians in case bleeding complications occur.
Bleeding Complications During Cardiovascular Procedures

Coronary angiography and PCI are among the most common diagnostic procedures and interventions, respectively, in patients with cardiovascular disease. The complications associated with coronary angiography are influenced by a variety of factors, including access site, sex, age, body weight, urgency of the procedure and associated comorbidities. The most common complication is bleeding as a result of vascular trauma. This is particularly common among women of low body weight with small caliber peripheral vessels (femoral artery access site). In response to observed trends, there has been increasing use of the radial artery for access and use of ultrasound-guided arterial puncture (in the femoral and radial arteries). In the Minimizing Adverse hemorrhagic events by TransRadial access site and systemic Implementation of angioX (MATRIX) study, 8,404 patients with acute coronary syndrome undergoing invasive management were randomly assigned to either radial or femoral access. The rates of major bleeding were significantly lower with the radial as compared with the femoral approach (relative risk 0.58; 95% CI, 0.53-0.67).

Close attention to the dosing of anticoagulants has also reduced the likelihood of peri-procedural bleeding localized to the access site or the retroperitoneal space. Bleeding at a distance, including the gastrointestinal tract, urinary tract or central nervous system, is less common but certainly can occur. In addition, the coronary arteries themselves may bleed if perforation occurs. Although coronary arterial perforation is not a common event (0.2% of all cases), it causes cardiac tamponade in up to 30% of patients, a need for emergent surgery in 8 to 10% of patients and death in up to 8% of patients in whom it occurs.

Hospitalized patients with cardiovascular disease may undergo a variety of procedures, including pacemaker or ICD placement, left ventricular assist device insertion, radiofrequency ablation, and peripheral arterial angioplasty, that can be associated with bleeding complications. As mentioned previously, UFH represents the most commonly used parenteral anticoagulant; however, DOACs are rapidly entering the picture since many electrophysiologists feel increasingly comfortable continuing these agents during procedures, at times with UFH given during the procedure to minimize the risk of thrombosis and thromboembolism. This approach will likely become more prevalent, and clinicians must take all anticoagulants and antithrombotic agents into consideration should serious bleeding ensue.

Management of Bleeding Complications

The approach to managing bleeding complications in an anticoagulated patient should be stepwise, drug(s)-specific and tailored to the site of bleeding and overall clinical status of the patient. An assessment of risk and benefit for stopping or reversing anticoagulation must be undertaken and, whenever possible, patient and family values and preferences must be factored into the equation. The initial treatment of anticoagulant-related bleeding is supportive with a focus on maintaining blood pressure and perfusion pressure, controlling the site of bleeding through either manual means when the site is readily accessible, vascular embolization or surgical intervention, blood product administration and, for serious, life-threatening or uncontrollable bleeding, replacement or reversal agents. Minor bleeding can often be addressed by employing supportive means or, in the case of access site bleeding, local measures including manual or device compression. Moderate bleeding may require monitoring in a step-down unit or its equivalent and catheter-based (embolization, cauterization, clipping) or minor surgical (vascular repair) intervention. Life-threatening bleeding events require immediate discontinuation of the anticoagulant, reversal of its anticoagulant effects and specific interventions. UFH can be readily reversed with protamine following a standard institution-based protocol, which is recommended for all hospitals performing invasive cardiac procedures. There are potential complications associated with this agent that include myocardial suppression, hypotension, and paradoxical anticoagulation if overdosed and, rarely, anaphylactic shock. Supportive measures with volume expansion and PRBCs may also be required. Careful consideration of the potential impact of concomitant platelet antagonists and the possibility of transfusion of pooled platelets is essential. In patients receiving warfarin, 4FPCCs and vitamin K are recommended. If a patient is receiving a DOAC, a targeted approach that incorporates the use of specific reversal agents should be taken in addition to supportive care.

Management of the Bleeding Patient in the Cardiovascular Critical Care Unit after Surgery/Cardiopulmonary Bypass and ECMO

Bleeding in the Cardiac Surgical Patient

In clinical practice, the management of bleeding patients in the cardiovascular critical care unit (CVICU) can be divided into those with medical bleeding and those with surgical bleeding. By far the most straightforward decision to treat is for those
patients with surgical bleeding. When bleeding crosses certain accepted thresholds in the post-operative period, return to the operating room (OR) for exploration and surgical control is mandatory. Massive bleeding has been defined differently at different times, but current use of the Hemostasis Score identifies massive bleeding as operative field blood loss exceeding 600 mL/hr, chest tube output of > 300 mL/hr or 150 mL/hr for two hours. The PLASMACARD study identified excessive post-operative bleeding as >1.5 mL/kg/h for at least three hours as requiring re-exploration in the OR.120

Bleeding vessels, pericardial bleeding and valvular leakage must be fixed mechanically; however, control of post-operative “surgical bleeding” also relies on the correction of coagulopathy to allow for meticulous control of bleeding in the surgical field. Often patients are taken back to the OR for exploration for bleeding and no clear source is identified, but instead serosal oozing and leakage are noted. Controversy exists as to whether bleeding can be controlled via medical means, and multiple research studies have explored the use of antifibrinolytic therapies and pro-coagulants administered locally in the OR or systemically in an attempt to obviate the need to return to the OR.

The agents TXA, rFVIIa, protamine, FFP and PCCs have all been studied in the perioperative setting. Recently, more than 3,400 patients were included in a propensity-matched observational study investigating the effectiveness of PCCs versus FFP for coagulopathy treatment as first line therapy in patients who were bleeding after cardiac surgery.121 Although the authors found a reduction in the need for RBC transfusion and a reduction in post-operative blood loss in patients treated with PCCs, there was a trend towards higher rates of acute kidney injury. It is unclear if the use of PCCs increased the rates of post-operative thrombosis in these patients, but that possibility remains a critical risk to be explored in patients with vulnerable post-operative grafts and valves. Another key consideration is that PCCs are approved for the reversal of vitamin K antagonized coagulopathy and the use in the post-operative patient is currently off label unless specifically used to reverse the effects of warfarin taken prior to surgery.

The measurement of the extent of coagulopathy in these patients remains enigmatic as well. The use of point of care assays of coagulation, such as TEG and rotational thromboelastometry (ROTEM), remains variable even among large academic centers. It appears the use of these phenotypic tests of clotting is increasing, yet the literature base and rigor needed to draw conclusions about the effectiveness of their inclusion in algorithmic approaches to the management of perioperative coagulopathy is lacking. To date, outcomes remain unstudied, the data focusing instead on the reduction of blood product transfusion as a result of the inclusion of TEG in management strategies. In one recent publication, the authors describe a single center experience with the introduction of TEG into the post-operative management protocols and report an overall 40% reduction in the mean units of blood products used during overall hospitalizations for these patients.122 The reduction in usage of blood products seemed to return to pre-TEG levels in patients once they had progressed beyond 24 hours post-operatively.

**Bleeding After Cardiopulmonary Bypass**

Cardiopulmonary bypass requires that patients have large bore central arterial and venous cannulation performed in order to complete a CPB circuit and those cannulae require high dose systemic anticoagulation to remain patent and to prevent thromboembolic events from impacting the circuit. Each of the components of the CPB circuit are generally heparin-bonded with the exception of the oxygenator. Despite the heparin bonding, the CPB circuit is markedly thrombogenic through direct activation of the clotting cascade via contact-mediated coagulation as well as through a secondary pathway of inflammation. This inflammatory pathway also leads to a coagulopathy that closely resembles the consumptive pathology of disseminated intravascular coagulation. In addition to the consumption of thrombocytes by the CPB circuit, the priming of the circuit with crystalloid (the standard prime) creates a dilutional coagulopathy as does the use of cell-saver technologies which reintroduce collected red blood cells from the surgical field. This is done in the absence of the associated clotting factors found in serum. After CPB, there remains a coagulopathy from the use of intraoperative heparin despite heparin reversal with protamine at the end of the CPB run. Remnant heparin activity contributes to some element of post-operative bleeding in many cases. Thromboelastography, while gaining some following in the management of CPB patients, has also been reported to under-diagnose and fails to predict hypercoagulable states when present in these patients, and may not determine the underlying cause of bleeding in CPB patients. The cause of this phenomenon remains unclear and further study is underway.123

**Bleeding in Patients on ECMO**

Bleeding while undergoing extracorporeal membrane oxygenation (ECMO) support is very common, with an estimated occurrence
of over 40%. The most common site of bleeding in patients on veno-arterial ECMO is the arterial cannula site, with an average transfusion volume of > 10 units of PRBCs in most patients on circuit. Survival to discharge in patients on ECMO has been correlated with the total units of blood products required in numerous studies. Two variables that greatly affect the transfusion requirements are the efficiency of the ECMO circuit and the thresholds established by ECMO centers for blood product administration. There is no well-adopted clear threshold for ECMO patients’ transfusion targets, and most centers establish their own. Despite prior practice that established hemoglobin targets of 14 g/dL while on ECMO, including the current ELSO guidelines recommending hemoglobin levels of 12-14 g/dL, many modern ECMO teams are targeting lower hemoglobin thresholds. Long-term outcomes data are not available, but restrictive transfusion strategies in patients on veno-venous ECMO have been described without reported increases in mortality. Nonetheless, lower hemoglobin targets lead to fewer transfusions.

The ECMO circuit efficiency is another key driver of rates of transfusion. Large cannulae, well running centrifugal pumps, heparin-bonded circuits and high-efficiency oxygenators all lead to less thrombosis and in-circuit consumption. Patients are systemically anticoagulated to prevent thrombosis using an hPTT target of between 60-80 seconds in many units; lower-intensity heparinization at 40-60 seconds has also been used with similar effect in prevention of thrombosis and lower bleeding rates. Bleeding on ECMO circuits that is not easily controlled with surgical manipulation of cannulae is often catastrophic. When coagulopathy occurs due to factor consumption in the ECMO circuit, TEG and other standard measures of coagulation are used to guide reversal; however, the use of antifibrinolytics and prothrombotic agents is fraught with risk. Ultimately, coagulation of the circuit and clotting in the oxygenator lead to complement activation, consumptive coagulopathy and hemolysis that is profoundly injurious to end organ capillary beds, including the kidney and, more importantly, the brain. Therefore, the use of coagulopathy reversal agents while patients are on ECMO circuits is rare.

**RESTARTING ANTICOAGULANT THERAPY AFTER REVERSAL TO PREVENT THROMBOTIC COMPLICATIONS**

Factor Xa inhibitors are widely used in for the prevention of stroke in patients with AF. Patients with AF frequently undergo interventional procedures with attendant risks of bleeding, including catheter ablation of AF, pacemaker and defibrillator implantation, and left atrial appendage closure procedures. In the event of major life-threatening bleeding, FXa reversal may be pursued. When to again provide anticoagulation after reversal is a complicated clinical decision informed by the nature of the major bleeding event, the nature of the interventional procedure, and the underlying risk for thromboembolic events in the individual patient. Timely and optimal resumption of oral anticoagulation is essential to minimize the risk of thromboembolic events.

**Electrophysiologic Procedures**

There are many interventional electrophysiologic procedures, but in general they can be grouped into three major categories for the purpose of this discussion. These categories include catheter-based procedures, such as diagnostic electrophysiology studies, catheter ablation of AF, and catheter ablation of ventricular tachycardia; device implantation procedures, such as pacemaker, defibrillator, and cardiac resynchronization procedures; and left atrial appendage occlusion procedures, such as Watchman device implantation. The bleeding risks of each of these procedures vary but include bleeding due to access site and vessel cannulation, intrathoracic bleeding such as cardiac perforation and tamponade, and bleeding at non-instrumented sites due to systemic anticoagulation, such as ICH. These procedures also carry an increased risk of thromboembolic events, particularly in the case of left-sided ablation procedures where instrumentation and prothrombotic changes in the chambers that lead directly to the arterial circulation increase the risk of stroke. For example, the risk of transient ischemic attack or stroke is approximately 1% in the 30 days following ablation.

**Use of Reversal Agents**

The occurrence of major bleeding during or after electrophysiologic procedures in patients with therapeutic oral FXa inhibition requires cessation of DOAC therapy, provision of supportive measures, and correction of any anatomic sources of bleeding, such as femoral artery compression or pericardiocentesis. However, if bleeding continues or is life-threatening, use of reversal agents may be necessary, alone or in conjunction with definitive surgical repair. As per a recent scientific statement from the American Heart Association, all healthcare institutions should have a peri-operative bleeding management and DOAC reversal protocol.124
Resumption of Anticoagulation

Administration of hemostatic factors can result in thromboembolism through a variety of mechanisms.\textsuperscript{125,126} Given the increased risks of thromboembolic events in patients with AF and the periprocedural risks of thromboembolic events, resuming oral anticoagulation is an important priority after major bleeding, including life-threatening major bleeding. The risk of thromboembolic events was highlighted in the ANNEXA-4 trial, in which approximately one in five patients experienced a thrombotic event after administration of andexanet alfa for reversal of major, life-threatening bleeding. Similarly, at the conclusion of the major clinical trials that evaluated the use of DOACs compared with warfarin, transition off of FXa inhibitors was associated with an increased risk of stroke that correlated with prolonged time to therapeutic anticoagulation.\textsuperscript{127} The increased risks of thromboembolic events in these patient populations did not appear to be secondary to rebound phenomena. Rather, event rates increased with the duration of time off anticoagulation. Additionally, andexanet alfa may be prothrombotic due to increased thrombin generation, and this effect may contribute to some of the thrombotic events in patients who have received it.

Several conditions must be met before restarting anticoagulation can be considered. First, the major bleeding must have resolved. Second, the patient must be in an environment where reinitiating DOAC therapy and the patient’s response can be appropriately monitored. For most patients with life-threatening bleeding during or after an interventional electrophysiologic procedure, this will be in the hospital. The importance of appropriate supportive and interventional care cannot be overemphasized, and the benefit of resumption of anticoagulation must be balanced against the risk of complications. Supportive measures may include, but are not limited to, avoidance of unnecessary adjunctive antiplatelet therapy, appropriate surgical consultation and operative intervention when necessary, and transfusion of blood products when indicated.

**FIGURE 03** Management of Resumption of Oral Anticoagulation Following Major Life-Threatening Bleeding and Reversal of DOAC Therapy

- Major, life-threatening bleed and reversal of DOAC
  - Bleeding resolved? NO → No anticoagulation
  - Yes → Adequate environment to monitor patient? NO → Admit patient, escalate level of care
  - Yes → Evaluation of stroke risk
    - LOW (CHA2DS2-VASc = 0-1) → Hold DOAC 3-5 days
    - HIGH (CHA2DS2-VASc ≥ 2) → Evaluate risk and severity of potential recurrent bleeding
      - LOW → Restart DOAC
      - HIGH → Stop heparin and consider additional intervention (e.g. surgery)

- Start heparin without bolus. Target aPTT in low end of therapeutic range.
  - Bleeding recurs → Stop heparin and consider additional intervention (e.g. surgery)

- No evidence of re-bleed → Stop heparin and start DOAC
The optimal approach to re-initiation of anticoagulation will depend upon each case; however, Figure 3 illustrates an approach to resumption of anticoagulation after an electrophysiologic procedure. Primary factors to consider include: 1) the nature of the bleeding complication and anatomy, 2) the patient’s risk factors for thromboembolism (e.g., CHA2DS2-VASc score and other stroke risk factors), and 3) the specific procedure the patient underwent, such as device implantation versus left-sided ablation. For example, a patient with AF and no additional risk factors for stroke (CHA2DS2-VASc=0) who experienced a spontaneous subarachnoid bleed after an elective pacemaker implant will be approached very differently than a patient with AF and a CHA2DS2-VASc score of 6 who had pericardial tamponade at the end of a catheter ablation procedure for AF. Patients with multiple risk factors for stroke and patients undergoing left-sided catheter ablation procedures are at the highest risk of post-operative thromboembolic events. For example, all patients undergoing catheter ablation of AF must receive therapeutic anticoagulation for 2-3 months after the procedure to reduce the risk of stroke.128

Resumption of Anticoagulation After Cardiac Tamponade

A challenging and illustrative case in resumption of anticoagulation after major, life-threatening bleeding with reversal of FXa inhibition is the resumption of anticoagulation after cardiac tamponade. Patients who experience cardiac tamponade during catheter ablation require emergent pericardiocentesis. A pericardial drain is placed and drain output is carefully monitored after the procedure. If there is no significant evidence of repeat bleeding (minimal drain output), anticoagulation can be resumed. Ideally, this is done with administration of intravenous heparin without a bolus. If the patient tolerates therapeutic heparin without evidence of repeat bleeding, the pericardial drain is pulled and DOAC therapy is resumed. After 1-2 doses of DOAC therapy, an echocardiogram is usually repeated to ensure that there is no recurrence of the effusion.

Resumption of Anticoagulation After Intracranial Hemorrhage

Another challenging case is the resumption of oral anticoagulation (OAC) after the occurrence of ICH. Prophylactic subcutaneous enoxaparin may be started 24 hours after an ICH, provided at least four terminal half-lives of the anticoagulation agent used at the index time of the ICH have passed and a stability image shows no progression of bleeding. Registry data suggest that the majority of patients in clinical practice resume OAC after an ICH event within six months.129 In general, observational studies have shown that resuming OAC after prior ICH is associated with a 70% reduction in the risk of thromboembolism (relative risk 0.31; 95% CI, 0.23-0.42).130 Systematic review and meta-analysis suggest that there is no evidence of increased risk of recurrent ICH after resuming OAC (relative risk, 1.01; 95% CI, 0.58-1.77), although the highest risk patients may not have resumed OAC.131 Of course, after an ICH event, everything should be done to minimize bleeding risk, including but not limited to optimal blood pressure control, avoidance of concomitant antiplatelet therapy whenever possible, and avoidance of other medications that increase bleeding risk, such as NSAIDs. When to resume OAC after an ICH event is a controversial decision that, again, depends on the specific circumstances of the bleeding event, the risk factors for recurrent ICH, and the patient’s underlying risk for thromboembolism. Care must be used in patients with primary ICH, and a risk/benefit analysis much be performed for each patient. For example, a patient with cerebral amyloid angiopathy would likely be too high risk to be anticoagulated, but a patient without underlying vascular abnormalities and a hypertensive etiology of hemorrhage may be appropriate for anticoagulation after hypertension has been controlled. Resumption of therapeutic anticoagulation usually occurs 2-4 weeks after the bleeding event.132

Further studies are needed to clarify optimal strategies for resumption of OAC after an ICH event. Fortunately, there are several ongoing clinical trials that will help clarify best practices. For example, the APACHE-AF trial will enroll patients with AF and recent ICH and randomize them to apixaban versus avoidance of OAC.133

CONCLUSION AND FUTURE DIRECTIONS

The use of oral anticoagulants is becoming more common as the population ages, and anticoagulant-related bleeding events will continue to increase in frequency. This monograph summarizes the recommendations of the EMCREG-International Multidisciplinary Severe Bleeding Consensus Panel regarding management of severe bleeding in patients on oral anticoagulants based on currently available data. There are many areas, however, where further research is required. Most importantly, current data on the efficacy of DOAC reversal agents are based on improvement in bleeding times; there has been no randomized controlled trial to evaluate the efficacy of reversal agents based on patient outcomes. Additionally, an analysis of the pharmacoeconomics of reversal agents is necessary to evaluate the cost of the drug as
it relates to the cost of the episode of care and quality-adjusted life years. Because of the short half-life of andexanet alfa, repeat dosing may be necessary, but the strategies for repeat dosing and the measures used to drive repeat dosing have yet to be clearly defined. A time-to-treat analysis to determine the therapeutic window during which reversal agents can be used would be beneficial as well, especially for physicians who will be making the decision to transfer patients with life-threatening bleeds to institutions that have reversal agents available. The role of renal insufficiency in treatment with reversal agents, particularly as it relates to the treatment window, remains to be defined. The role of 4FPCCs in patients with DOAC-related bleeding must be evaluated as well. There are currently no studies linking clinical outcomes to the use of 4FPCCs in bleeding patients, and the upstream use of 4FPCCs may preclude use of andexanet alfa because of the risk of severe complications. And finally, it is imperative that the optimal timing for resumption of anticoagulation in order to avoid thrombotic complications be investigated.

References


Management of Severe Bleeding in Patients Treated with Oral Anticoagulants


CONTINUING MEDICAL EDUCATION POST-TEST ANSWER FORM AND EVALUATION

MANAGEMENT OF LIFE-THREATENING BLEEDING IN ANTICOAGULATED PATIENTS

Based on the information presented in this monograph, please choose one correct response for each of the following questions or statements. Record your answers on the answer sheet found on the last page. To receive Category I credit, complete the post-test and record your responses on the following answer sheet and complete the evaluation. A passing grade of 80% is needed to receive credit.

TEST ALSO AVAILABLE ONLINE: www.emcreg.org/testing

1. A patient who is prescribed apixaban for atrial fibrillation presents with a life-threatening intracranial hemorrhage, but it is unclear whether she is still taking the medication. Which of the following lab tests can confirm the ABSENCE of anticoagulant effect?
   A. Thrombin time (TT)
   B. Prothrombin time (PT)
   C. Partial thromboplastin time (PTT)
   D. None of the above

2. Currently, the only FDA-approved treatment for life-threatening bleeding associated with Factor Xa inhibitor anticoagulation is:
   A. Fresh frozen plasma (FFP)
   B. Idarucizumab
   C. Andexanet alfa
   D. Prothrombin complex concentrate (PCC)

3. All of the following statements regarding treatment with andexanet alfa are true EXCEPT:
   A. It competitively blocks the Factor Xa inhibitor.
   B. It lacks biologic activity in the coagulation cascade.
   C. It is administered as two intravenous doses in rapid succession.
   D. It is not currently being studied for reversal prior to invasive procedures.

4. All of the following are important initial steps in the management of a patient with oral anticoagulant-associated bleeding EXCEPT:
   A. Stop all oral anticoagulants.
   B. Evaluate for transfusion.
   C. Consider activated charcoal.
   D. Consider specific reversal agents.

5. Unfractionated heparin is the most commonly used parenteral anticoagulant for hospitalized patients undergoing cardiac procedures.
   A. True
   B. False

6. Assuring timely availability of reversal agents requires the consideration of which of the following factors?
   A. Storage requirements (refrigeration)
   B. Admixture
   C. Proper reconstitution technique
   D. Transport/delivery
   E. All of the above

7. Which of the following are barriers to advanced prehospital hemorrhage control?
   A. Level of training/scope of practice
   B. Logistics of medication/blood product storage
   C. Access to diagnostic tools
   D. Cost
   E. All of the above

8. All of the following are appropriate for administration to a patient with a vitamin K antagonist (VKA)-related hemorrhage EXCEPT:
   A. Idarucizumab
   B. Whole blood
   C. Vitamin K
   D. 4 Factor PCC
   E. FFP

9. Patients with oral anticoagulant-related traumatic hemorrhage tend to be older and have more comorbidities than the general trauma population.
   A. True
   B. False

10. Which of the following should be considered when deciding to give a reversal agent to a bleeding trauma patient?
    A. Hemodynamic stability
    B. Comorbidities such as kidney, heart, and liver disease
    C. Time since taking their last dose of anticoagulant
    D. Underlying thrombotic risk
    E. All of the above
11. A patient who has atrial fibrillation and congestive heart failure is taking warfarin and presents with a subdural hematoma. What should be used to manage the bleeding?
   A. PCCs only
   B. PCCs and vitamin K
   C. FFP and vitamin K
   D. Idarucizumab

12. A patient taking dabigatran for atrial fibrillation presents with a subarachnoid hemorrhage. What should be used to manage the bleeding?
   A. PCCs
   B. Idarucizumab
   C. Vitamin K
   D. Dialysis

13. In a patient with gastrointestinal bleeding, nasogastric tube placement and lavage demonstrates all of the following benefits EXCEPT:
   A. Reduction in mortality, hospital length of stay, and need for transfusion
   B. Assistance in ruling out an upper GI source of bleeding
   C. Assistance in clearing the stomach of blood, improving visualization
   D. Reduction in time to endoscopy

14. A patient taking a direct oral anticoagulant for venous thromboembolism presents with ongoing, active epistaxis. Immediate options for management include all of the following EXCEPT:
   A. Topical oxymetazoline
   B. Direct pressure clamping the nose shut
   C. Inflatable nasal balloon
   D. Silver nitrate cautery

15. Options for controlling post-extraction dental bleeding include all of the following EXCEPT:
   A. PCC garge/mouthwash
   B. Direct pressure with dry gauze
   C. Topical tranexamic acid
   D. Lidocaine/epinephrine injection into the gingiva

   A. True
   B. False

17. A surgeon is trying to determine whether or not to urgently operate on a patient who states he takes “an oral blood thinner.” Assuming this is not warfarin, what is the best way for the surgeon to determine the degree to which the patient is anticoagulated?
   A. Measure the PT/INR.
   B. Measure the PTT.
   C. Obtain a thromboelastogram (TEG) or rotational thromboelastometry (ROTEM) study.
   D. Obtain a history regarding which drug the patient takes and the timing of his most recent dose.

18. A patient who takes warfarin for a mechanical aortic valve presents with a perforated ulcer and requires urgent laparotomy. His INR is 3.0. The fastest and most efficient medication to treat the anticoagulation is to administer:
   A. Plasma
   B. PCC
   C. Factor VIIa
   D. Vitamin K

19. In surgical bleeding, the accepted threshold(s) that mandate a return to the operating room include:
   A. Chest tube output of > 100mL/hr for 3 hours
   B. Chest tube output of > 300mL/hr for 1 hour
   C. Chest tube output of > 150mL/hr for 2 hours
   D. B and C

20. Which of the following patients has the highest risk of post-procedure thromboembolism?
   A. Patient with a CHADS-VASc score of 3 undergoing defibrillator implantation
   B. Patient with a CHADS-VASc score of 5 undergoing defibrillator implantation
   C. Patient with a CHADS-VASc score of 3 undergoing ventricular tachycardia ablation
   D. Patient with a CHADS-VASc score of 5 undergoing ventricular tachycardia ablation

(Answer sheet next page)
CONTINUING MEDICAL EDUCATION POST-TEST ANSWER FORM AND EVALUATION

After you have read the monograph, carefully record your answers by circling the appropriate letter for each question on the CME ANSWER SHEET on this page and complete the evaluation questionnaire.

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6. a b c d e
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8. a b c d e
9. a b
10. a b c d e
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MANAGEMENT OF SEVERE BLEEDING IN PATIENTS TREATED WITH ORAL ANTICOAGULANTS

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