OPTIMAL MANAGEMENT OF THE ANTICOAGULATED PATIENT WITH LIFE-THREATENING BLEEDING IN THE EMERGENCY DEPARTMENT AND INTENSIVE CARE UNIT:

A CASE-BASED APPROACH

JANUARY 2021

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EMCREG International

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Dear Colleagues,

JANUARY 2021

This is an EMCREG-International Proceedings Monograph based on the two day October 13 & 14, 2020 VIRTUAL EMCREG-International Symposiums titled **Optimal Management of the Anticoagulated Patient with Life-Threatening Bleeding in the Emergency Department and Intensive Care Unit: A Case-Based Approach**. You will find a detailed discussion regarding the current treatment of critically ill or injured patients with life-threatening bleeding who present to the ED or intensive care unit. This discussion is highlighted by the presentation of cases managed by experts in emergency medicine, critical care medicine, and trauma surgery. For emergency physicians, critical care physicians and hospitalists, 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, uncontrolled bleeding, the achievement of rapid controlled hemostasis is extremely important to saving the patient's life.

This EMCREG-International Monograph is divided into multiple sections. The first section provides a clinician-based 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 second section of this EMCREG-International Monograph, the treatment of anticoagulated 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 major initial therapy for these individuals. Repletion or reversal of the anticoagulated state is also necessary. For patients treated with coumadin, infusion of vitamin K helps to initiate the process of protein synthesis. The repletion of vitamin K dependent coagulation proteins II, VII, IX, and X, as well as the anti-thrombotic protein C and protein S with four factor prothrombin complex concentrate (4F-PCCs) is the critical next step. For patients treated with the thrombin inhibitor dabigatran, therapy using the highly specific antibody derived idarucizumab has been demonstrated to reverse the hypocoagulable state for the patient. For patients receiving anticoagulation therapy using the Factor Xa inhibitors rivaroxaban and apixaban with life-threatening bleeding, andexanet alfa reverses the effect of these agents allowing hemostasis. Prior to the availability of andexanet alfa, therapy for patients treated with Factor Xa inhibitors presenting with severe bleeding typically included replacement of lost blood components including red blood cells, platelets, and clotting factors. A section is also included in this Proceedings Monograph discussing an algorithm developed by the EMCREG-International Severe Bleeding in the Anticoagulated Patient Consensus Panel in October 2018 which can serve as a model for clinicians to develop care algorithms at their own hospitals. The final sections of this EMCREG-International Monograph provide multiple case studies and management approaches for patients with life-threatening bleeding from the perspectives of the emergency physician, neurocritical and cardiovascular intensivists, and trauma/surgical critical care specialists.

Our organization, 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 Australia, Belgium, Brazil, Canada, Czech Republic, France, Germany, Greece, Italy, Japan, Netherlands, New Zealand, Poland, Singapore, Spain, Sweden, Turkey, United Kingdom, and the United States. Now in our 32nd 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, critical care, internal medicine, family medicine, hospital medicine, emergency nursing, pharmacy, and allied health with our EMCREG-International University of Cincinnati College of Medicine Office of Continuing Medical Education (CME), and the University of Cincinnati Colleges of Nursing, Pharmacy, and Allied Health accredited symposiums and enduring materials.

It is our sincere hope that you will find this EMCREG-International Proceedings Monograph, based on our **VIRTUAL** EMCREG-International Symposiums held on October 13 and 14, 2020 focusing on the care of patients requiring anticoagulation having life-threatening 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 2021 EMCREG-International Monograph. Thank you very much for your interest in EMCREG-International educational initiatives. We hope you visit EMCREG-International On the Go (www.emcreg.org/emcreg-on-the-go) as well as our EMCREG-International website (www.emcreg.org) for future educational events and publications.

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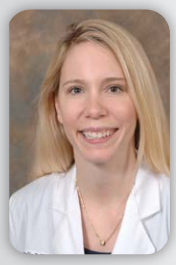

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Learning Objectives:

1. Describe the various oral anticoagulant agents and the indications for using oral anticoagulant therapy.
2. Discuss the general approach to treating life-threatening bleeding in anticoagulated patients in the emergency department, including the ways that anticoagulation is treated by repletion and reversal.
3. Define the role of an institution-wide critical pathway to aid in the management of anticoagulated patients with life-threatening bleeding.
4. Outline the decision-making process for reversal of anticoagulation in an anticoagulated patient with life-threatening gastrointestinal bleeding.
5. Identify the urgency of and indications for anticoagulation reversal in the setting of acute intracranial hemorrhage.
6. Discuss intraspinal hemorrhage, and particularly the indications for anticoagulation reversal in anticoagulated patients with intraspinal hemorrhage.
7. Identify the factors that make management of bleeding particularly difficult in patients on ECMO, and describe the approach to management of these patients.
8. Describe the critical care management of the anticoagulated blunt trauma patient in the emergency department.
9. Describe the approach to management of traumatized anticoagulated patients who require surgical care.

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INDICATIONS FOR USE OF ORAL ANTICOAGULANTS

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Adapted from: Heistand B. Indications for Use of Anticoagulants. In Life-Threatening Bleeding in the Anticoagulated Patient, Proceedings Monograph from the ACEP 2019 EMCREG-International Satellite Symposium.

Warfarin and Other Vitamin K Antagonists

In the clotting cascade, multiple clotting factors interact in a sequence of events that converge into a final common pathway resulting in the transformation of Factor X into the active Factor Xa (FXa). FXa then enzymatically converts prothrombin (Factor II) into thrombin, which serves both to activate platelets and to convert fibrinogen into fibrin. Vitamin K metabolism is essential to the hepatic synthesis of coagulation Factors II, VII, IX, and X. The vitamin K antagonists (VKAs) impair vitamin K metabolism, resulting in greatly diminished reserves of these crucial enzymes and subsequent decreased ability to form thrombus. 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. This becomes relevant when initiating anticoagulation in a patient with a current thrombus (acute venous thromboembolism [VTE]) or at high risk for thromboembolic stroke. In these cases, bridging therapy with a parenteral anticoagulant, generally low molecular weight heparin (LMWH) or unfractionated heparin (UFH), is advised due to the potential for transient hypercoagulability. The need for bridging therapy in initiating a VKA agent for atrial fibrillation is less clear, especially if cardioversion is not planned. Although it is not directly addressed in the literature, the Effectiveness of Bridging Anticoagulation for Surgery (BRIDGE) study provides some guidance.[1] Patients with atrial fibrillation undergoing an invasive procedure were randomized to a LMWH bridge or no anticoagulation, with no resulting difference in the rate of thromboembolic events - 0.4% without anticoagulation versus 0.3% in those receiving LMWH. Warfarin, the most common VKA in use in the United States, has a direct half-life of 36 to 42 hours (Table 1). 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).[2] There is significant variability in treatment effect with VKAs based on 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,[5] and the effective half-life after steady state ranges from 12-14 hours (Table 1).[7] The drug is primarily renally cleared, resulting in increased anticoagulation as renal function decreases; therefore, drug dosing varies with renal function.[8] It is the only DOAC cleared by hemodialysis, although it remains unclear as to 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, ticagrelor, and verapamil, and is inhibited by rifampin and other P-gp inducers.[8]

FXa inhibitors, including apixaban, betrixaban, edoxaban, and rivaroxaban, directly inhibit FXa which results in decreased conversion of prothrombin to thrombin.[3,9-11] All FXa inhibitors undergo renal and hepatic elimination. The FXa inhibitors are metabolized by both the P-gp and the CYP3A4 systems. Strong inhibitors of both 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. The DOACs are contraindicated in patients with severe liver and kidney impairment.

TABLE 01 Time to Peak Onset and Effective Therapeutic Half-life for Oral Anticoagulants [3-5]

Drug	Peak Onset	Half-life
Warfarin	Peak serum concentration 4 hours after dose, anticoagulant effect noted within 24 hours of first dose	Dependent on time to resynthesize clotting factors (48-72 hours for Factor X)
Dabigatran	2 hours	12 - 14 hours
Apixaban	1.5 - 3.3 hours	12 hours
Betrixaban	3 - 4 hours	19 - 27 hours
Edoxaban	1.5 hours	10 - 14 hours
Rivaroxaban	2 - 4 hours	5 - 9 hours ** may increase to 11-13 hours in elderly patients*[6]

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 assays commonly available in the clinical setting.[5,12] None of the DOACs has a direct linear relationship with any of the readily available coagulation assays. 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.[13] One therefore cannot rely on normal coagulation assays to exclude anticoagulation effects with the DOACs. 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 an immediate basis in the Emergency Department (ED).[5]

Anti-FXa assays exist, although they are not readily available in most hospitals and necessitate that the assay be calibrated specifically for each of the different FXa agents.[14] If an anti-FXa level is negative, it might obviate the need for reversal in a patient with life-threatening bleeding. There is currently no accurate, rapidly available test to make that decision. A FXa level should not be used to guide therapy at this time. Thromboelastography (TEG) is still under investigation as an option to assess the anticoagulated trauma patient.[15,16]

Oral Anticoagulant Indications in the Acute Care Setting

Of the multiple Food and Drug Administration (FDA) approved indications for oral anticoagulants, three are important to the acute care physician – acute venous thromboembolism (VTE) treatment, VTE prophylaxis in medical admissions, and thromboembolic prophylaxis in atrial fibrillation (Table 2). Three others – post-orthopedic surgery VTE prophylaxis, long-term VTE recurrence prevention, and risk mitigation for coronary artery disease – are less relevant and will not be discussed here.

Venous Thromboembolism Prophylaxis in Medical Admissions

Of the oral anticoagulants currently in use, only betrixaban and rivaroxaban are currently indicated for the prevention of VTE in medically hospitalized patients. Betrixaban gained FDA approval for this indication in 2017, after the publication of the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) study. In this trial, betrixaban was compared to enoxaparin in patients hospitalized for a variety of medical indications, with expected hospitalization of at least three days and immobilization (i.e., bed rest) for at least 24 hours.[17] Patients had to be at least 40 years of age and at risk for VTE as a complication. Patients were randomized to fixed dose enoxaparin during the hospitalization versus betrixaban during hospitalization and after discharge for a total treatment course of 35 to 42 days. The primary outcome of silent or symptomatic VTE occurred

TABLE 02 Dosing of Oral Anticoagulants by Indication and Renal Function [3, 8-11, 16]

Drug	Mechanism	VTE Treatment	NVAF Embolism Prophylaxis	VTE Prophylaxis (medical admissions)
Warfarin	Blocks synthesis of vitamin K-dependent factors	Variable, titrated by INR	Variable, titrated by INR	Not indicated
Dabigatran	Direct thrombin inhibitor	CrCl >30 mL/min: 150 mg BID after 5-10 days of parenteral anticoagulation	• CrCl > 30 mL/min: 150 mg BID • CrCl 15-30 mL/min: 75 mg BID	Not indicated
Apixaban	Factor Xa inhibitor	10 mg BID for 7 days, then 5 mg BID	• 5 mg BID • Increased bleeding risk:[a] 2.5 mg BID	Not indicated
Betrixaban	Factor Xa inhibitor	Not indicated	Not indicated	• 160 mg initial dose, then 80 mg daily • CrCl 15-30 mL/min: 80 mg initial dose, then 40 mg daily
Edoxaban	Factor Xa inhibitor	• 60 mg daily after 5-10 days of parenteral anticoagulation • Increased bleeding risk:[b] 30 mg daily after 10 days of parenteral anticoagulation	• 60 mg daily • CrCl 15-50 mL/min: 30 mg daily	Not indicated
Rivaroxaban	Factor Xa inhibitor	• 15 mg BID for 21 days, followed by 20 mg daily • CrCl<30 mL/min: do not use	• CrCl >50 mL/min: 20 mg daily • CrCl 15-50 mL/min: 15 daily	10 mg daily through discharge and up to 31-39 days total duration of treatment

[a] Dose decrease recommended for patients with two of three factors: age ≥ 80 years, body weight ≤ 60 kg, or Cr ≥ 1.5 mg/dL
[b] Dose decrease recommended for patients with body weight ≤ 60 kg, CrCl 15-50 mL/min, or concomitant P-gp inhibitor use
BID: twice daily; CrCl: creatinine clearance; VTE: venous thromboembolism; NVAF: non-valvular atrial fibrillation; INR: International Normalized Ratio.

in 7% of the overall enoxaparin cohort versus 5.3% of the betrixaban cohort (relative risk [RR]) 0.76; 95% confidence interval [CI] 0.63 – 0.92). This absolute risk reduction resulted in a number needed to treat of 59 patients to prevent one primary outcome. Major and fatal bleeding were equivalent between groups, although the rate of major or clinically significant non-major bleeding was higher in the betrixaban cohort (3.1% versus 1.6%; RR 1.97; 95% CI 1.44-2.68).

Rivaroxaban was established for VTE prophylaxis after a post-hoc re-analysis[18] of the VTE Prophylaxis in Medically Ill Patients (MAGELLAN) trial[19] was performed, with supporting data from the Study of Rivaroxaban on the VTE Risk in Post-Hospital Discharge Patients (MARINER study) also considered.[20] The MAGELLAN trial randomized patients requiring acute medical admission with VTE risk to rivaroxaban versus enoxaparin. In the subsequent MARINER study, patients who had been medically hospitalized and were at risk for VTE were randomized to rivaroxaban 10 mg daily (reduced to 7.5 mg daily for creatinine clearance of 30-50 mL / min) or placebo at discharge. MAGELLAN met pre-specified non-inferiority criteria for VTE / VTE-associated death (2.7% rate in both groups, rivaroxaban RR 0.97; 95% CI 0.71 – 1.31) at 10 days, while MARINER demonstrated a decrease in the rate of symptomatic VTE after discharge (0.18% versus 0.42% favoring rivaroxaban, HR 0.44; 95% CI 0.22 – 0.89), although there were no differences in VTE-associated mortality. There was a substantially decreased rate of bleeding complications in the rivaroxaban arms of MARINER versus MAGELLAN (0.28% versus 2.8%), attributable to the fact that MARINER excluded a number of categories of risk that were allowed in the earlier MAGELLAN study: known gastric ulcers, concomitant dual anti-platelet therapy, active cancer, or pulmonic cavitary lesions. This observation led to a re-analysis of the MAGELLAN data with post-hoc exclusion of the above risk groups, resulting in an improved risk-benefit profile.[18] Based on these data, rivaroxaban was approved for VTE prophylaxis in acutely ill medical patients that are at high risk for VTE and not at high risk for bleeding.[10]

Treatment of Acute VTE

Apixaban, dabigatran, edoxaban, and rivaroxaban have all been studied against VKAs for the treatment of acute deep venous thrombosis/pulmonary embolism (DVT/PE) in a number of trials.[21-27] The collective experience with these agents is that the DOACs are consistently superior, or at least non-inferior, to VKAs for both efficacy and safety outcomes in the setting of VTE. As a result, the American College of Chest Physicians recommends the use of DOACs over VKAs in the treatment of non-cancer associated VTE.[28] Table 3 provides a summary of the landmark trial results for each DOAC. Although, at least in the United States, the preferred agent for an individual patient may come down to which drug is covered by the individual patient's insurance (if any), one key aspect of drug choice is of substantial importance to physicians providing the initial care for these patients. Apixaban and rivaroxaban were both studied, and therefore approved, without lead-in anticoagulation. Both edoxaban and dabigatran were studied with a 5-10 day parenteral anticoagulation (LMWH or inpatient UFH) period prior to the initiation of oral treatment, and the FDA label requirements for each drug reflect this.[4] In addition, all index studies were quite conservative with regards to the presence of hepatic and renal insufficiency, either requiring dose adjustment with impaired creatinine clearance, or excluding patients completely. Caution should be exercised when considering DOAC therapy for these patients. With regards to cancer-associated VTE, based on direct comparisons, guidelines now recommend either rivaroxaban monotherapy[29] or edoxaban (with parenteral anticoagulation as lead in)[30] as viable treatment options in patients with normal renal function.[31,32]

Atrial Fibrillation and Stroke Prophylaxis

The incidence and prevalence of atrial fibrillation increases with age, which also greatly increases the risk of embolic stroke. Anticoagulation decreases the risk of acute ischemic stroke (AIS) and is recommended for patients with atrial fibrillation and risk factors for AIS. The Ameri-

TABLE 03 Comparison of DOACs to VKAs for the Treatment of Venous Thromboembolism
Relative risks and hazard ratios represent DOAC compared to VKA as the reference group.[4]

Drug	Primary Efficacy Endpoint Result	Efficacy Interpretation	Primary Safety Result	Safety Interpretation
Apixaban	RR 0.84 95% CI, 0.60 – 1.18	Non-inferior	RR 0.44 95% CI, 0.36 – 0.55	Superior
Dabigatran[a]	HR 1.09 95% CI, 0.76 – 1.57	Non-inferior	HR 0.73 95% CI, 0.49 – 1.11	Non-inferior
Edoxaban	HR 0.89 95% CI, 0.7 – 1.13	Non-inferior	HR 0.81 95% CI, 0.71 – 0.94	Superior
Rivaroxaban[b]	HR 0.89 95% CI, 0.66 – 1.19	Non-inferior	HR 0.93 95% CI, 0.81 – 1.06	Non-inferior

[a] Pooled results for RE-COVER and RE-COVER II
[b] Pooled results for EINSTEIN-PE and EINSTEIN-VTE
RR: relative risk ratio; HR: hazard ratio; CI: confidence interval

can Heart Association / American College of Cardiology guidelines for atrial fibrillation management recommend risk stratification with a validated tool such as CHADS2 or CHA2DS2VASc and subsequent anticoagulation for those patients found to be at risk.[33] A recent large meta-analysis (94,656 patients) examined the composite results of the DOACs versus VKAs for atrial fibrillation prophylaxis and concluded that the balance of the evidence for both safety and efficacy favored DOACs over VKAs, although comparisons could not be directly drawn between individual DOACs.[34] It is clear that there is an opportunity for emergency physicians and other acute care physicians such as hospitalists and critical care physicians to initiate anticoagulation in patients presenting with atrial fibrillation and an increased risk profile.[35]

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THERAPEUTIC APPROACH TO THE ANTICOAGULATED PATIENT WITH LIFE-THREATENING BLEEDING

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Adapted in part from: Pollack C. Treatment of Severe Bleeding in the ED: 4-Factor PCCs, Idarucizumab, and Andexanet Alfa. In Life-Threatening Bleeding in the Anticoagulated Patient, Proceedings Monograph from the ACEP 2019 EMCREG-International Satellite Symposium.

General Approach

The initial evaluation and treatment of a patient experiencing a hemorrhage while taking an oral anticoagulant (OAC) should focus on resuscitation. Management of airway, oxygenation and ventilation should occur simultaneously with consideration of volume resuscitation and delivery of blood products, such as whole blood, packed red blood cells (RBCs), plasma and platelets as indicated. A subpopulation of these patients will benefit from a massive transfusion protocol. Source control of the site of hemorrhage may include some of the following maneuvers: tourniquet application, packing, direct pressure, endoscopy, cautery, ligation, embolization, or management in the operating room or interventional radiology suite. Some patients with major hemorrhage who can be managed with definite source control, such as arterial ligation or embolization, may require stabilization with blood products alone rather than reversal.

In conjunction with initial stabilization, several historical features should be gathered to determine the degree of anticoagulation. The timing of the last dose of medication and the patient's renal function are particularly germane to the direct oral anticoagulant (DOAC) class. Gastric lavage can aid in gastrointestinal (GI) decontamination in selected patients. Although some guidelines suggest the use of activated charcoal, the DOACs are rapidly absorbed after oral administration and activated charcoal can make airway management extremely difficult should the patient become unstable with emesis. Therefore, the use of activated charcoal should be limited to and used with caution in acute overdose situations. Hemodialysis can be deployed in patients taking dabigatran, but now that the reversal agent idarucizumab is available to bind dabigatran there is likely no longer a role for dialysis in these patients. Laboratory assessment using prothrombin time (PT)/partial thromboplastin time (PTT), thrombin time (TT), and Factor Xa levels may help guide therapy in select stable patients, but should not delay resuscitation or reversal in those who are unstable or have significant neurological impairment from suspected intracranial hemorrhage.

Vitamin K Antagonist Repletion

A patient who is therapeutically anticoagulated on a vitamin K antagonist (VKA) has impaired clotting 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 hepatic synthesis of functionally active factors, though it takes many hours to several days to re-establish physiologic levels. Although necessary, administration of vitamin K is certainly not a sufficient response to management of intracranial hemorrhage (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 should 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 (4F-PCCs) contain the vitamin K-dependent coagulation factors (II [prothrombin], VII, IX and X), as well as therapeutically effective concentrations of coagulation regulatory proteins, protein C and protein S. Three-factor PCCs (3F-PCCs) do not contain Factor VII. In the past, some authorities recommended combining 3F-PCCs 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.[1] There are suggestive data that in warfarin-associated intracranial hemorrhage (ICH), PCCs reduce hematoma expansion more than FFP does,[2] and PCCs are preferentially recommended in professional society guidelines.[3]

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. 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 (venous thromboembolic disease), or mechanical heart valve (warfarin only). When anticoagulation "protection" is suddenly removed, these patients immediately return to their baseline prothrombotic 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, though 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 for repletion, 4F-PCC should 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.[4]

Reversal of Direct Oral Anticoagulants

Reversal agents for the direct thrombin inhibitor, dabigatran, and the Factor Xa inhibitors, apixaban and rivaroxaban, are now approved in the United States. These agents are not hemostatic; rather, they reverse the effect of anticoagulants by restoring thrombin generation. These agents 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 Factor X, 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.[5] 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.

RE-VERSE AD Trial Summary

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.[6] 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.[6]

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.[6]

Factor Xa Inhibitor Reversal

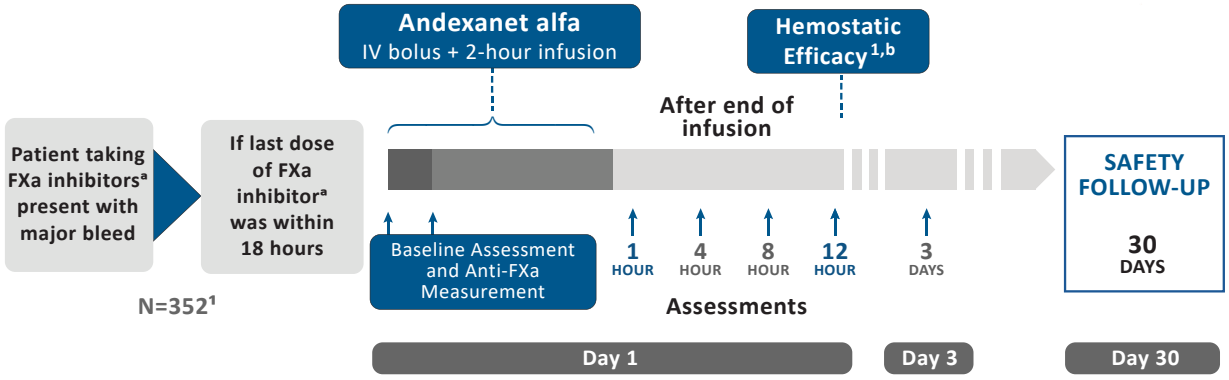
A class-specific antidote, andexanet alfa is a decoy FXa synthetic protein that lacks biologic activity in the coagulation cascade because of removal of the Gla- domain. It also has a mutation in the catalytic domain that removes its intrinsic procoagulant activity. The agent competitively binds to the Factor Xa inhibitor, must be tailored to the molar concentration of the anticoagulant, and an infusion must be maintained to continue the competitive blockade of the anticoagulant. The bolus dose of andexanet alfa is followed immediately with a two-hour infusion. 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.[7]

ANNEXA-4 Trial Summary

The ANNEXA-4 trial of andexanet alfa was designed as a multicenter, prospective, single-arm, open-label study with two co-primary outcomes: 1) the percent change from baseline anti-Factor Xa activity after andexanet alfa administration, and 2) the percentage of subjects with excellent or good hemostatic efficacy 12 hours after treatment as assessed by an independent adjudication committee based on prespecified criteria.[8] Subjects were included in ANNEXA-4 if they presented with acute major bleeding and had taken their last dose of Factor Xa inhibitor within 18 hours of presentation (Figure 1). The sites of bleeding were intracranial (64%), gastrointestinal (26%), or other (10%), and subjects had a mean age of 77 years. In subjects taking apixaban and rivaroxaban, there was a 92% reduction of median anti-Factor Xa activity from baseline to the end of the bolus (15-30 minutes). Excellent or good hemostatic efficacy occurred in 204 (82%) of the 249 evaluable subjects at 12 hours. All-cause mortality within 30 days occurred in 49 (14%) subjects and a thrombotic event occurred in 34 (9.7%) subjects.

ANNEXA-4 employed a single-arm trial design. However, as part of the accelerated approval program, there are now plans for a Phase 3b/4 trial with a usual care comparator arm (ClinicalTrials.gov number NCT03661528). Although ANNEXA-4 represents the largest dataset of DOAC-related major hemorrhage subjects, practical considerations not directly addressed by the study have arisen since its accelerated approval by the FDA in August 2018. Intraoperative use, re-dosing, and extended infusion were not explicitly studied so no official direction from the sponsor or regulatory agency is available. Although trauma patients with major hemorrhage were enrolled in ANNEXA-4, they were a small fraction of the overall cohort and require more targeted study. Likewise, patients without major hemorrhage but who have an indication for an acute operation that cannot be safely delayed, such as acute necrotizing soft tissue infection or ischemic/necrotic bowel, were not evaluated in ANNEXA-4 and are subjects for future study.

FIGURE 01 Phase 3b/4 Confirmatory Study in Patients with Acute Major Bleeding



Limitations of Use: Andexanet alfa has not been shown to be effective for, and is not indicated for, bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

[a] Patients enrolled were taking apixaban, rivaroxaban, edoxaban, or enoxaparin.

[b] The independent adjudication committee reviewed each case to determine hemostatic efficacy on the basis of predetermined criteria, to provide a rating of excellent or good (effective hemostasis) or poor/none (ineffective hemostasis).[1]

Accelerated approval of Andexanet alfa was based on percent change in anti-FXa activity, rather than hemostatic outcome.

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TABLE 01 Comparison with Other Studies on Management of Anticoagulant-Associated Bleeds

Study (Ref.) Characteristic or Outcome	Sarode et al.[15] (N=104)	Sarode et al.[15] (N=98)	ANNEXA Full Study[8] Efficacy Population (N=254)	ANNEXA Full Study[8] Safety Population (N=352)	Majeed et al.[13] (N=84)	Schulman[14] (N=66)
Anticoagulant	Warfarin	Warfarin	Xa inhibitors		Xa inhibitors	Xa inhibitors
Reversal agent	Plasma	PCC	Adexanet alfa		PCC	PCC
Exclusion for poor prognosis	Expected survival < 3 days	Expected survival < 3 days	Expected survival < 1 month		DNR order given	DNR order given
Age, mean (SD)	69.8 (13.9)	69.8 (12.8)	77.1 (11.1)	77.4 (10.8)	75 (10.9)	76.9 (10.4)
Male sex	51 (49)	50 (51)	129 (51)	187 (53)	48 (57)	42 (67)
ICH	12 (12)	12 (12)	171 (67)	227 (64)	59 (70)	36 (55)
GI Bleed	64 (62)	63 (64)	62 (24)	90 (26)	13 (16)	16 (24)
Time last dose Xa inhibitor to REV, median (IQR)	NA	NA	(Mean ± SD) rivaroxaban: 12.3 ± 5.1 apixaban: 12.1 ± 4.6		12.5 (9-16)	16.9 (12-21)
Effectiveness assessment according to Sarode et al.[15] for CNS bleeds						
Excellent or Good	7 (58)	5 (42)	135 (80)		Not done	25 (76)[†]
Effectiveness assessment according to ISTH [16] criteria for CNS bleeds						
Excellent or Good	Not done	Not done	Not done		43 (73)	25 (69)
Safety outcomes during 30 days						
Thromboembolism	7 (6)	8 (8)	34 (10)		3 (4)	5 (8)
Death	5 (5)	6 (6)	49 (14)		27 (32)	9 (14)

[†] Only patients with repeat tomography (n=30) or with large CNS bleeds resulting in early death (n=3) were included in this analysis.
Results are in *n* (%).
Adapted with permission from Schulman et al. Thromb Haemost 2018;118(05): 842-851

Prothrombin Complex Concentrate

Prothrombin complex concentrates have served as a possible alternative for the management of life-threatening bleeding associated with anti-Factor Xa treatment. The PCCs reverse abnormal laboratory parameters (PT and endogenous thrombin potential) in human volunteers after taking high doses of rivaroxaban and apixaban. [9-11] However, giving high doses of prothrombin concentrates to patients who do not have deficient levels of Factor Xa or any of the other constituents of PCC is not an intuitive approach. In terms of clinical data, only a few small series have looked at the clinical use of PCCs in the treatment of DOAC-related major hemorrhage and thus none of the PCCs have regulatory approval for use in this scenario (Table 1). In a retrospective cohort analysis of intracranial hematoma expansion, Gerner et al.[12] reported on 146 subjects with DOAC-related ICH; 103 were treated with PCCs and 43 received no PCCs. The primary outcome was hematoma enlargement, defined as volume increase of >33%. Secondary outcomes were in-hospital mortality, three-month mortality and functional outcome at three months. No significant differences were seen between the two groups for the primary and secondary outcomes. Systolic blood pressure control <160mmHg at four hours post-admission was the only finding associated with a lower risk of hematoma expansion in DOAC-related ICH. Majeed et al.[13] found that PCC use resulted in effective hemostasis in 58/84 (69%) of DOAC-related acute major bleeding subjects, 70% of whom had ICH. In the cohort with ineffective hemostasis (n=26), a similar percentage (61.5%), had ICH. In a prospective registry cohort study at nine Canadian hospitals, Schulman et al.[14] reported on 66 subjects with DOAC-related major bleeding (36 with ICH) who were treated with a fixed dose of 2,000 units of PCC. For the ICH subpopulation, 67% of treated subjects were described as having good hemostasis, 17% moderate and 17% poor/none. In the 36 patients with ICH who had repeat brain imaging or who died early, 31% died or had hematoma expansion of greater than 35%.

Since patients who are taking DOACs are doing so because they are at a high risk of thrombosis, removing the anticoagulant exposes them to their baseline thrombotic risk. In addition, patients with major hemorrhage, particularly ICH, are often critically ill in the intensive care unit. These patients are immobilized with lines and catheters, and thus at increased risk for thromboembolic events. In the study by Schulman et al., 9/66 (14%) patients died by day 30 and 5/66 (8%) patients had a thromboembolic event.[14] In Majeed's study, mortality at 30 days was 32% and three (3.6%) patients had thrombotic events. In a randomized comparison of 4F-PCCs versus FFP in VKA-associated major hemorrhage, Sarode et al. found thromboembolic adverse event rates of 7.8% for PCC and 6.4% for FFP.[15] Overall, available studies suggest that thromboembolic rates of 2.4-10% are expected in this subject population and may vary depending on the severity of hemorrhage, baseline thromboembolic risk and comorbidities. Thus, treatment of anti-Factor Xa related bleeding may be associated with a risk of post-treatment thromboembolic complications. Importantly, treatment with the combination of a specific reversal agent AND PCCs would be expected to 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.

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DEVELOPMENT OF A SEVERE BLEEDING TREATMENT ALGORITHM FOR ANTICOAGULATED PATIENTS

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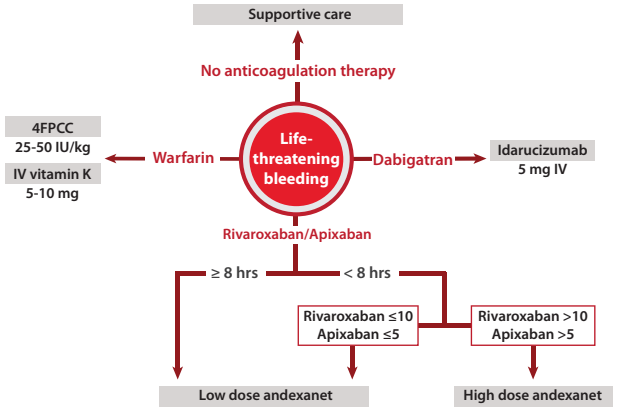
Because the administration of repletion and reversal agents is usually time-dependent and often costly, it is important for institutions to have predefined guidelines for determining which patients qualify for the administration of specific agents. Ideally, these guidelines should be developed by a multidisciplinary team, with subject matter experts who can interpret the available data and make informed decisions as to which patients are most likely to benefit from reversal. In addition, it is important that individual institutions work to identify and overcome any site-specific barriers to the appropriate administration of anticoagulation reversal agents.

In late 2018, a group of specialists with expertise in emergency cardiovascular care, prehospital emergency medical services, emergency medicine operations, hematology, hospital medicine, neurocritical care, cardiovascular critical care, cardiac electrophysiology, cardiology, trauma and acute care surgery, and pharmacy, convened at an EMCREG-International consensus panel to discuss the management of severe bleeding in patients taking oral anticoagulants.[1] At the meeting, an algorithm was developed (Figure 1) for clinician use in treatment areas such as the emergency department or critical care unit.

Many institutions, both academic and community based, have pathways or algorithms for the treatment of severe bleeding in patients taking oral anticoagulants. These pathways have been updated in light of the prevalence of the DOAC oral anticoagulants and the emergence of new agents to reverse them. For example, shortly after Food and Drug Administration (FDA) approval of andexanet alfa, and following several requests to have this agent available at hospitals within Partners Healthcare, a Boston-based nonprofit healthcare organization consisting of 15 hospitals and physicians' networks, the Partners Center for Drug Policy (CDP) conducted a clinical and economic review.[2] Experts from hematology, cardiology, neurosurgery, orthopedic surgery, emergency medicine, general surgery, neurology, and pharmacy were consulted to develop recommendations with the goal of ensuring appropriate and cost-effective use of andexanet alfa. Clinical trials and FDA filings were summarized, and after consulting with clinical leaders from all relevant Partners' hospitals, practical recommendations for use were generated (Figure 2). Guidelines were developed by the CDP with the understanding that recommendations could be tailored to meet the needs of particular hospitals and any clinical decision would ultimately be made by a qualified, licensed, healthcare provider based on his or her own professional judgment of all the facts involving a specific patient. A key feature of these guidelines is a focus on life-threatening and critical site bleeding. Specifically, the appropriateness of reversal is to be determined based upon an assessment by the treating provider that failure to reverse could result in death or permanent disability. For example, in a patient on an oral Factor Xa inhibitor, stable gastrointestinal bleeding would not be eligible for treatment with andexanet alfa, while the same patient with hemorrhagic shock unresponsive to conventional measures would be eligible.

FIGURE 01 EMCREG Algorithm for the Management of Life-Threatening Bleeding in Anticoagulated Patients



An accompanying pharmacoeconomic analysis projected the annual drug budget impact of adding andexanet alfa to formularies across the Partners Healthcare system, using assumptions about the number of individuals in the system on apixaban or rivaroxaban, annualized rates of life-threatening bleeding as estimated from large clinical trials, and wholesale acquisition costs of both standard-dose and high-dose regimens. A summary of one Partners hospital's initial experience with andexanet alfa was published last year.[3]

Recently, the American College of Cardiology (ACC) provided updated guidance for managing patients with bleeding related to anticoagulation in the form of an Expert Consensus Decision Pathway (ECDP).[4] The ACC ECDP took an approach similar to the algorithms described above, emphasizing the appropriateness of reversal agents specifically in cases of critical site or life-threatening bleeding (Table 1) and endorsing andexanet alfa as the preferred Factor Xa reversal strategy. A multidisciplinary group recently published an Anticoagulant Reversal Strategies manuscript which confirmed the findings of the EMCREG-International Multidisciplinary publication on Management of Severe Bleeding in the Patients Treated with Oral Anticoagulants published in Critical Pathways in Cardiology in September 2019.[1,5]

FIGURE 02 Brigham and Women's Hospital Guidelines for Management of Life-Threatening Bleeding in Patients on Factor Xa Inhibitors

Criteria	Critical life-threatening bleeding and rivaroxaban/apixaban ingested < 18 hours ago
Indications	For critical life-threatening bleeding defined as bleeding that causes hemodynamic compromise, threatens a vital organ, or may result in disability, that does not respond to conventional measures and did not receive prior 4PCC
Approval Required	No approval required for rivaroxaban or apixiban for critical life-threatening major bleeding if dose < 18 hours prior
Laboratory Monitoring	Baseline CBC, Anti-Xa (UFH/LMWH): • Draw prior to adminsitration • Don't wait for results

		Timing of Factor Xa Inhibitor Last Dose Before Coagulation Factor Xa (Andexanet)	
FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg / Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg / Unknown	High Dose	

Dose	Initial IV Bolus	Follow-on IV Infusion
Low Dose/Standard Dose	400 mg: target rate of 15-30 min	4 mg/min for 120 min (480 mg)
High Dose	800 mg: target rate of 15-30 min	8 mg/min for 120 min (960 mg)

Hematology approval required:
- > 18 hours since last ingested dose
- Alternate reversal agent already administered (e.g., 4PCC)
- Reversal of betrixaban, edoxaban, enoxaparin, or fondaparinux
- Less severe bleeding
- Emergency surgery/procedure (in absence of critical life-threatening bleeding)

Adapted with permission from Culbreth SE, Rimsans J, Sylvester K, Pallin DJ, Connors JM. Andexanet alfa – the first 150 days. 2019, Am J Hematol. 94(1):E21-E24.

TABLE 01 Critical Site Bleeds

TYPE OF BLEED	INITIAL SIGNS AND SYMPTOMS	POTENTIAL CONSEQUENCES OF BLEED
Intracranial hemorrhage: Includes intraparenchymal, subdural, epidural, and subarachnoid hemorrhages	**Unusually intense headache, emesis** **Neurological signs:** e.g., reduced LOC, vision changes, numbness, weakness, aphasia, ataxia, vertigo, seizures	Stupor or coma Permanent neurological deficit Death
Other central nervous system hemorrhage: Includes intraocular, Intra- or extra-axial spinal hemorrhages	**Intraocular:** monocular eye pain, vision changes, blindness, **Spinal:** back pain, bilateral extremity weakness or numbness, bowel or bladder dysfunction, respiratory failure	**Intraocular:** permanent vision loss **Spinal:** permanent disability, paraplegia, quadriplegia, death
Pericardial tamponade	Shortness of breath, tachypnea Hypotension, jugular venous distension Tachycardia, muffled heart sounds, rub	Cardiogenic shock Death
Airway, including posterior epistaxis	**Airway:** hemoptysis, shortness of breath, hypoxia **Posterior epistaxis:** profuse epistaxis, hemoptysis, hypoxia, shortness of breath	Hypoxemic respiratory failure Death
Hemothorax, intra-abdominal bleeding, and RPH	**Hemothorax:** tachypnea, tachycardia, hypotension **Intra-abdominal (nongastrointestinal):** abdominal pain, distension, hypotension, tachycardia **RPH:** Back/flank/hip pain, tachycardia, hypotension	**Hemothorax:** respiratory failure **RPH:** femoral neuropathy **All:** hypovolemic shock, death
Extremity bleeds: includes intramuscular and intra-articular bleeding	**Intramuscular:** pain, swelling, pallor, paresthesia, weakness, diminished pulse **Intra-articular:** joint pain, swelling, decreased range of motion	**Intramuscular:** compartment syndrome, paralysis, limb loss **Intra-articular:** irreversible joint damage

LOC = loss of consciousness; RPH = retroperitoneal hematoma. Reprinted with permission from Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight CommitteeJ Am Coll Cardiol. 2020 Aug 4;76(5):594-622.

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INTRACRANIAL BLEEDING IN THE ANTICOAGULATED PATIENT

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Intracranial hemorrhages may occur for many reasons, such as traumatic brain injuries (TBIs), primary intracerebral hemorrhages (ICHs), or subarachnoid hemorrhages (SAHs). TBIs include subdural hematomas, epidural hematomas, contusions, and traumatic subarachnoid hemorrhages. Primary ICHs in the brain parenchyma most commonly occur due to long-standing hypertensive changes.[1] Lastly, subarachnoid hemorrhages occur when an intracranial aneurysm ruptures. Although each of these intracranial hemorrhages has distinct imaging findings and requires specific approaches to management, all of them represent life-threatening neurologic emergencies.[2] In particular, nearly all patients with an intracranial hemorrhage who are anticoagulated require reversal as early as possible in their course to reduce the risk of hematoma expansion and to facilitate the safety of potentially necessary neurosurgical procedures.[3]

Anticoagulation reversal in a patient with an intracranial hemorrhage poses unique challenges compared to reversal for other life-threatening causes of hemorrhage. Cessation of bleeding in intracranial hemorrhage can be hard to assess in real-time, and evidence of continued bleeding may only be noted by changes in the neurologic exam, or worsening of findings on head CT. Patients who have sustained an intracranial hemorrhage may be unable to provide an accurate medication history due to suppressed mental status. This is concerning if a patient is anticoagulated with a direct oral anticoagulant (DOAC), since standard laboratory results obtained in the emergency department (ED) do not readily provide insight into important information such as the agent, dose, or timing of the medication. Lastly, whereas patients with ongoing bleeding due to other causes may display signs of hemorrhagic shock, increases in bleeding due to intracranial hemorrhage are not significant enough to require volume resuscitation.

Because the population is aging and the use of oral anticoagulants is expanding, anticoagulation-associated intracranial hemorrhages represent a growing problem that emergency physicians may face. In general, nearly all patients with an intracranial hemorrhage who are anticoagulated should be provided reversal agents in order to avoid limiting care when there is the impression of a likely poor outcome.[4] On a case by case basis, there may be certain patients, such as those who are elderly or have large hemorrhages, in whom reversal is withheld. For the purpose of this review, specific antidote-based reversal and repletion strategies for cases comprising the three common types of intracranial hemorrhages are presented.

CLINICAL CASE #1

A 67-year-old male presented to the ED with a TBI after falling off a ladder. On examination, he had a total Glasgow Coma Score (GCS) of 7 and required endotracheal intubation immediately. His initial international normalized ratio (INR) value was 3.0, and prior documentation in the electronic medical record (EMR) indicated that he was taking warfarin for atrial fibrillation. His initial non-contrast head CT demonstrated diffuse areas of contusion and traumatic subarachnoid hemorrhage (Figure 1). He received a dose of intravenous vitamin K and four factor prothrombin complex concentrate (4F-PCCs), and his repeat INR was 1.2. The patient was admitted to the neurologic intensive care unit (ICU) and an intracranial pressure monitor was placed.

FIGURE 01 Non-contrast head CT demonstrates multifocal traumatic subarachnoid hemorrhage, bilateral frontal intraparenchymal contusions, and evidence of sulci effacement.

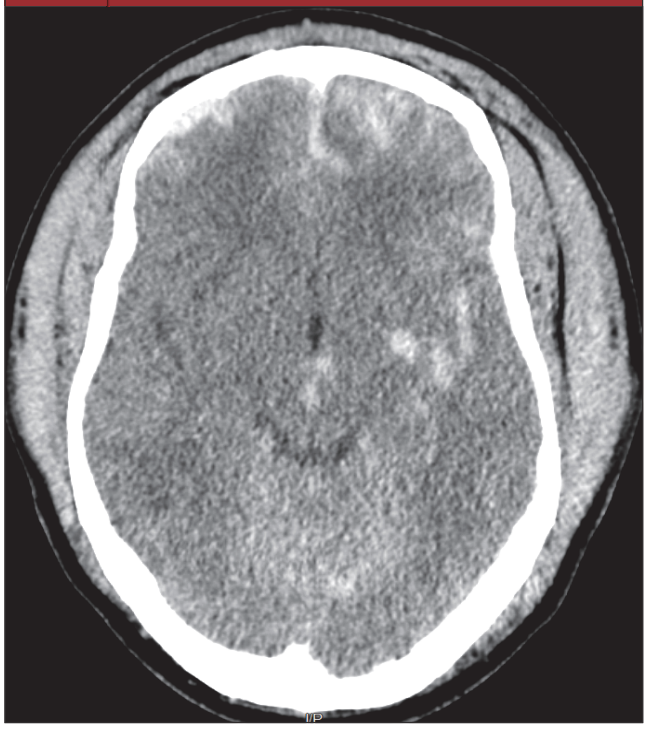

Image courtesy of Natalie P. Kreitzer, MD

This patient taking warfarin with a severe TBI represents a common traumatic injury with a high potential for morbidity and mortality. In patients with TBI, the odds of mortality and need for neurosurgical intervention are greater in patients taking warfarin than in patients who are not anticoagulated when controlling for other factors.[5] It is imperative to rapidly reverse coagulopathy in this setting. In warfarin associated ICH, the odds of hematoma expansion decrease significantly when INR is reversed to ≤ 1.3.[6] INR reversal can be completed significantly faster with administration of PCCs as opposed to fresh frozen plasma (FFP) in these patients.[7]

CLINICAL CASE #2

A 42-year-old male presented to the ED with the worst headache of his life. A head CT demonstrated a diffuse subarachnoid hemorrhage (Figure 2). His neurologic exam was initially intact, with a GCS of 15 on presentation. He reported that he took dabigatran for atrial fibrillation, and his last dose was four hours prior to presentation. He received two 2.5-gram boluses of idarucizumab prior to an external ventricular drain (EVD) placement and coiling of an anterior communicating artery aneurysm.

FIGURE 02 Non-contrast head CT demonstrates diffuse aneurysmal subarachnoid hemorrhage.

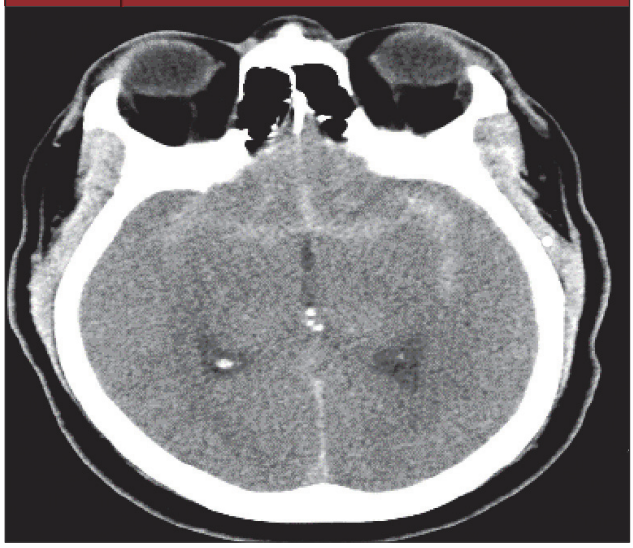

Image courtesy of Natalie P. Kreitzer, MD

Subarachnoid hemorrhage (SAH) secondary to a ruptured aneurysm represents a common form of intracranial hemorrhage. Patients who are anticoagulated and incur a SAH require reversal medications prior to undergoing neurosurgical procedures to relieve intracranial pressure secondary to noncommunicating hydrocephalus and to secure the ruptured aneurysm.[8] Idarucizumab, a non-competitive monoclonal antibody fragment, binds to dabigatran and inhibits direct thrombin inhibition anticoagulation effects. In the REVERSE-AD trial, a total of 98 subjects presented with an ICH. Of these 98 subjects, the median level of unbound dabigatran was reduced from 110ng/ml to 20ng/ml, indicating complete reversal for 24 hours. However, repeat head CTs were not mandated in the REVERSE-AD cohort, so objective findings regarding hematoma expansion were not consistently documented.[9,10]

CLINICAL CASE #3

A 58-year-old male presented to the ED with the acute onset of confusion and left-sided weakness. His family reported that he had a history of atrial fibrillation. The patient was taking 10 mg of rivaroxaban daily and last received a dose six hours prior to his ED presentation. Head CT demonstrated a right basal ganglia spontaneous ICH (Figure 3). Based on his rivaroxaban dose, he was given the low dose bolus and two-hour infusion of andexanet alfa. He was admitted to the ICU and a repeat head CT demonstrated no significant changes.

FIGURE 03 Non-contrast head CT shows a large right-sided basal ganglia hemorrhage.

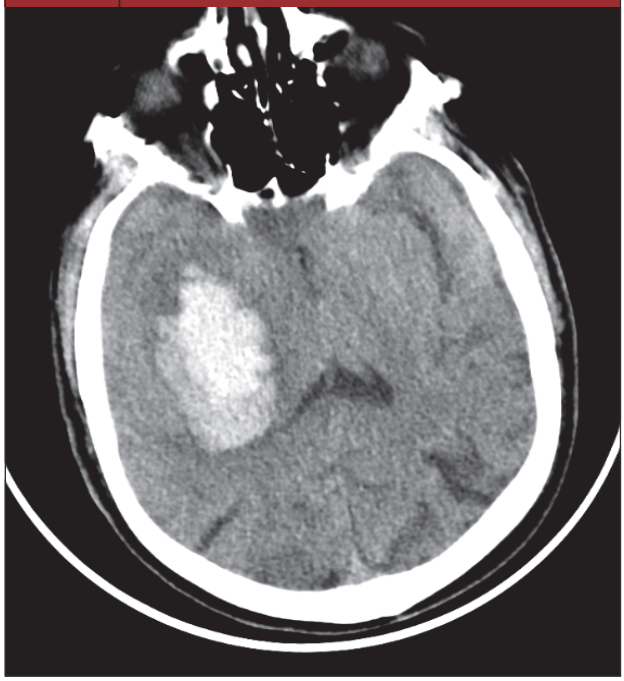

Image courtesy of Natalie P. Kreitzer, MD

Spontaneous ICH, sometimes referred to as a hemorrhagic stroke, accounts for 15% of all strokes, and as such, is much less common than ischemic stroke.[1,11] Although less common, morbidity and mortality from ICH is much higher, particularly in patients with anticoagulation-associated ICH, as they tend to be older, have higher volumes of hemorrhage, and are at higher risk of hematoma expansion.[6] Although there are decades of literature describing warfarin-associated ICH, newer DOACs such as Factor Xa inhibitors are rapidly rising in use as anticoagulants. These agents represent a critical component of reversal practices for the emergency physician. Andexanet alfa, a specific decoy molecule that binds to anti-Factor Xa drugs such as rivaroxaban or apixaban, was approved by the Food and Drug Administration in May 2018 for reversal in life-threatening hemorrhages. The ANNEXA-4 study, a prospective, multicenter open-label trial of its use in life-threatening hemorrhages enrolled 227 patients with an intracranial hemorrhage. Of those, 71 presented with a primary ICH and were evaluated for hemostatic efficacy (HE), defined as an increase in volume of < 30% (good efficacy) or <20% (excellent efficacy). The overall HE rate in ANNEXA-4 was 22%, consistent with patients who receive reversal or repletion therapy in ICH associated with other anticoagulants such as dabigatran or warfarin.[12]

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INTRASPINAL BLEEDING IN THE ANTICOAGULATED EMERGENCY DEPARTMENT PATIENT

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Intraspinal hemorrhage is exceedingly rare. The estimated incidence is 0.1 per 100,000 population per year.[1] These estimates are derived mainly from case reports/case series and there are little organized data available in published literature to inform clinicians. Therefore for appropriate, timely diagnosis in the emergency department (ED) setting, a high index of suspicion is warranted.

Intraspinal hemorrhage may be spontaneous, traumatic or iatrogenic. Over half of cases have no identified risk factors, and these are classified as "spontaneous" intraspinal hemorrhage. Risk factors for spontaneous intraspinal hemorrhage are ill-defined but may include arteriovenous malformations and anticoagulant use. Some of these "spontaneous" hemorrhages may also be due to unrecognized minor trauma.[2]

Like intracranial hemorrhage (ICH), intraspinal hemorrhage may involve the subdural space, epidural space or parenchyma of the cord.[3] Given the typical slow and progressive clinical presentation, the source of bleeding is thought to be venous most of the time. Rapid progression of neurological deficits may indicate arterial bleeding or rapid venous bleeding in the context of anticoagulant use.[3]

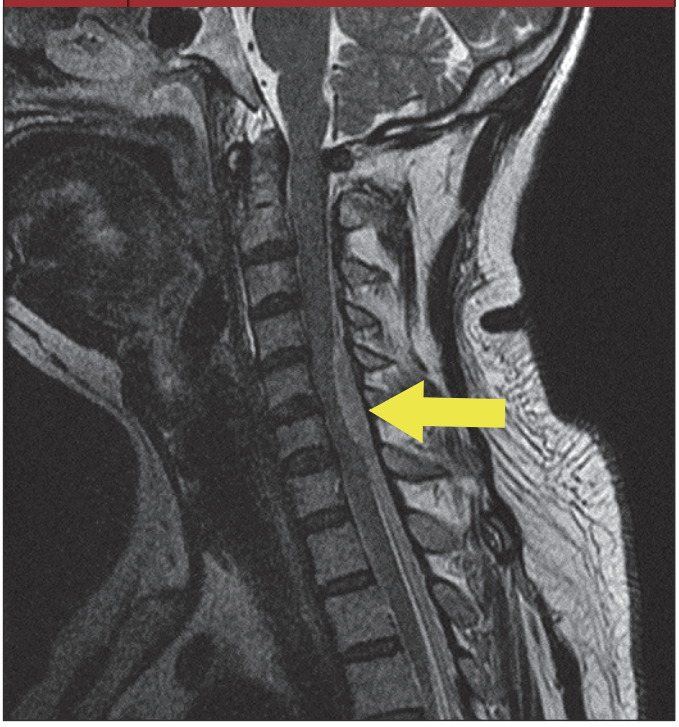
CLINICAL CASE

A 63-year-old male with no significant past medical history presented to the ED complaining of bilateral clumsy hands three days after a fall. His exam was "normal" and he had good strength in his bilateral upper and lower extremities. The patient denied any neck or back pain. His screening labs were normal and a CT of the head and cervical spine was normal. The patient was then discharged home. Three days later, he returned with complaints of worsening and persistent "clumsiness" and his exam clearly revealed right greater than left bilateral upper extremity weakness. An MRI of the cervical spine demonstrated an epidural hematoma in the level of C4-C7 (Figure 1).

Clinical Management

In this clinical case, it was not unreasonable to discharge the patient initially from the ED following the negative evaluation and workup. However, the clinical situation may have been different if the patient was on anticoagulant therapy. The clinician's index of suspicion may have been greater, the patient's symptoms/deficits could have progressed differently or more rapidly, and the neurologic exam may not have been normal three days after the injury. The CT findings may have been indicative of hemorrhage. Once an intraspinal hemorrhage is identified, urgent surgical intervention within 12-48 hours is recommended.[2] Patients who progress rapidly due to arterial bleeding or venous bleeding in the context of anticoagulant use may require more timely surgery. Prognostication is not reliable, and patients with a poor exam may still have a reasonable recovery. There are no established data or clinical guidance for the management of intraspinal hemorrhage in the setting of anticoagulant use. To extrapolate from guidance on ICH, the 2017 Emergency Neurological Life Support states: "A general principle is that any ICH occurring in a patient on antithrombotic medications should be considered life-threatening due to the risk of hematoma expansion. Interventions to treat coagulopathy are based on this history and laboratory information more than on size or location of the hematoma or clinical scores."[4] Thus, intraspinal bleeding in the setting of anticoagulant use should be considered very high risk for permanent paralysis with resultant disability for the patient. All patients with intraspinal hemorrhage need surgery. Reversal of coagulopathy is crucial prior to surgery. As such, anticoagulated patients with intraspinal hemorrhage require rapid anticoagulant reversal to facilitate timely surgical management.

FIGURE 01 MRI of cervical spine shows an epidural hematoma at the level of C4-C7 (arrow).



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Summary

Intraspinal hemorrhage may present with slow, progressive symptoms. A high index of suspicion in the right clinical context is warranted for timely diagnosis. Surgery, such as laminectomy/hemilaminectomy and decompression, is the ultimate treatment. Prognostication is not reliable, thus all patients with intraspinal hemorrhage require surgery to provide the best chance of recovery. In anticoagulated patients, rapid reversal is needed to facilitate timely surgery.

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REVERSAL OF ORAL ANTICOAGULANT THERAPY IN THE PATIENT WITH SEVERE GASTROINTESTINAL BLEEDING

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Gastrointestinal bleeding remains a relatively common presentation to the emergency department (ED). The care of patients with gastrointestinal bleeding includes recognition of the bleeding, clarification of an upper versus lower gastrointestinal bleeding source, volume resuscitation, and termination of the bleeding. One of the most important aspects of the care of patients with gastrointestinal bleeding is assuring that the patient has an adequate coagulation system, including both sufficient platelets and an adequate coagulation cascade. If that patient is being treated with a parenteral or oral anticoagulation agent such as heparin, low molecular weight heparin, warfarin, or a direct oral anticoagulant (DOAC), repletion or reversal of the anticoagulant effects of the involved agent is imperative to terminate the gastrointestinal bleed. Use of oral anticoagulants like warfarin or the newer DOACs is becoming much more common, especially in the elderly patient population with a history of recent surgery, deep venous thrombosis/pulmonary embolism, or atrial fibrillation. Emergency physicians should be familiar with these agents, their mechanisms of action, and their reversal agents or in the case of warfarin, repletion therapy. Often rapid reversal of warfarin or DOACs in the ED may be the most important first step to termination of a severe gastrointestinal bleed, especially when surgical or endoscopic therapy is not readily available.

CLINICAL CASE

Initial Presentation: A 66-year-old male presented to the ED by Emergency Medical Services (EMS) with a history of vomiting blood and weakness. EMS reported a large bright red vomiting spell that happened just prior to arrival. On arrival, the patient was alert and cooperative, but appeared pale and sweaty. His blood pressure was 80/40 mmHg with an irregular pulse of 140 beats per minute (bpm). The paramedic had started an 18-gauge IV in the field and the patient had received 500cc of normal saline en route.

History of Present Illness: The patient was well until about three hours prior to arrival when he started feeling "sick to his stomach" and was having constant epigastric pain, nausea, and some lower abdominal cramping. He had a large, loose, black bowel movement and felt like he was going to "pass out" on the toilet. Shortly thereafter, he vomited a large amount of bright red blood. He continued to feel very weak and short of breath.

Past Medical History: Hypertension, type II diabetes, and atrial fibrillation (intermittent), but no history of peptic ulcer disease or cirrhosis.

Medications: Simvastatin, diltiazem, hydrochlorothiazide, metformin, aspirin, and rivaroxaban.

Family History: Unremarkable

Social History: History of daily alcohol use, no tobacco use.

Physical Exam: Vital Signs: blood pressure 80/40 mmHg, pulse 130 bpm and irregular, respirations 20 per minute, and oxygen saturation 97%. The head and neck exam was unremarkable except for dried blood around the mouth. No nosebleed was noted. His chest was clear and no cardiac murmurs were noted. His abdomen was nontender, without guarding, masses, or rebound. His rectal exam revealed melenic stool that was heme positive. His extremities and neurologic exam were unremarkable.

Critical Actions:

The patient was placed on a continuous cardiac monitor. A second IV was started and he was given 2 liters of lactated Ringer's solution intravenously and was typed and crossed for two units of packed red blood cells. Basic laboratory tests were drawn and sent including a complete blood count (CBC), platelets, and coagulation studies. He was administered a proton pump inhibitor intravenously. A nasogastric (NG) tube was placed to wall suction, revealing bright red blood, which continued flowing over time. An electrocardiogram (ECG) revealed atrial fibrillation with a rapid ventricular response, but there were no ischemic changes noted when compared to an old ECG. Gastroenterology was consulted. Reversal of anticoagulation was considered.

The decision to reverse the effects of oral anticoagulation requires consideration of three basic questions. First, what is the oral anticoagulant? Options include warfarin, which is a vitamin K synthesis inhibitor, the direct oral anticoagulants rivaroxaban, apixaban, betrixaban, or edoxaban, which are Factor Xa inhibitors, or dabigatran, which is a Factor II direct thrombin inhibitor. Knowledge of the drug dosage and timing of the last dose can also guide reversal therapy in the ED. In the case of warfarin, the international normalized ratio (INR) is important to assess anticoagulation and guide therapy. Second, the degree of bleeding must be assessed. Is there no bleeding (and perhaps just an elevated INR)? Is the bleeding mild or moderate? Or is the bleeding life- or limb-threatening? The degree of bleeding guides the rapidity and aggressiveness of anticoagulant reversal (see page 10 of this EMCREG-International monograph for a list of Critical Site Bleeds). Life-threatening gastrointestinal bleeding requires rapid and aggressive reversal of anticoagulation. Third, what is the appropriate reversal agent and dosage to reverse the oral anticoagulant effects? If the patient has been taking warfarin, a vitamin K antagonist, for anticoagulation, repletion of the patient's Factors II, VII, IX, and X as well as protein C and protein S is necessary to stop bleeding. The different agents have different mechanisms of

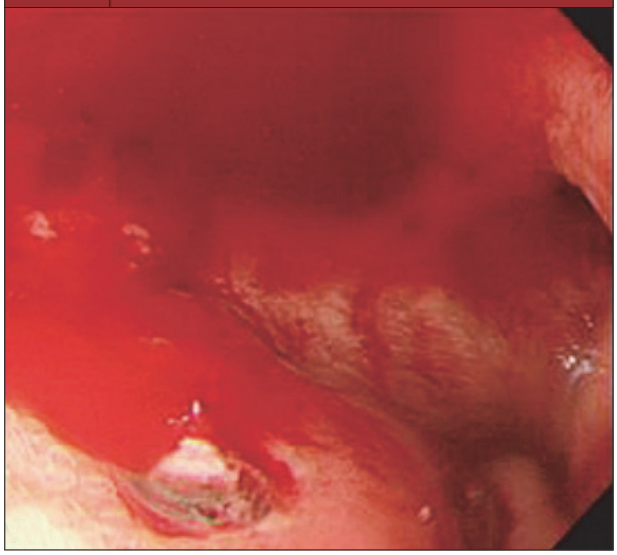
anticoagulation, and therefore require different reversal agents. Memorizing these agents is difficult. Having a pre-approved guideline or protocol for anticoagulant reversal is imperative to guide these decisions. See page 9 of this EMCREG-International monograph for a description of institutional guidelines and pages 5, 6 and 10 for a discussion of the various repletion and reversal agents and their dosing information.

Case Resolution

The patient's lab results came back with a hemoglobin of 8.2, normal platelet count, and an INR of 1.2. His glucose was elevated at 171. Because of the patient's hypotension and uncontrolled bleeding, it was determined that anticoagulation reversal was indicated. Although andexanet alfa would have been the drug of choice for the Factor Xa anticoagulant rivaroxaban in this situation due to its specificity and evidence for its efficacy, it was not on formulary at this hospital. Therefore, the patient received four factor prothrombin complex concentrate (4F-PCC) 5,000 units intravenously. Subsequently, the patient underwent emergent upper endoscopy. A briskly bleeding gastric ulcer was identified (Figure 1), which was cauterized and clipped to terminate the bleeding. The patient was admitted to the intensive care unit, where he was transfused and monitored over 48 hours. Cardiology was consulted to address his atrial fibrillation and coagulation status. He was discharged on day 4 in stable condition.

Gastrointestinal bleeding, complicated by the use of oral anticoagulants, remains a common medical emergency. Emergency physicians should be familiar with warfarin and the DOACs, their mechanisms of action, and their reversal agents. Often rapid reversal of warfarin or DOACs in the ED may be the most important first step to termination of a severe gastrointestinal bleed.

FIGURE 01 Bleeding Gastric Ulcer



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CONTROL OF MASSIVE BLEEDING IN PATIENTS ON ECMO: MANAGEMENT CHALLENGES

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Over half of patients who bleed while on extracorporeal membrane oxygenation (ECMO) circuits post-cardiotomy require redo-thoracotomy to control mediastinal hemorrhage.[1] Overall, more than one-third of all patients on ECMO circuits will suffer a bleeding event while on circuit irrespective of the rate of thrombosis or circuit failure, and many will bleed even without systemic anticoagulation. Exposure to ECMO itself is a risk for bleeding, and the interplay between pump physics and ex-vivo biologic interactions with the circuits and the patient's blood products yields a complicated milieu of thrombosis and hemostasis which combine to create management challenges when patients on ECMO circuits have significant bleeding.

CLINICAL CASE

A 70-year-old white female presented to her cardiologist's office with a complaint of decreased exercise tolerance over the preceding six months. She had a history of well-controlled arterial hypertension and atrial fibrillation for which she was anticoagulated with a direct oral anticoagulant (DOAC). Workup included a transthoracic echocardiogram which demonstrated preservation of left ventricular function with extensive calcifications of the mitral annulus and leaflets with moderate mitral stenosis and significant regurgitation. No evidence of coronary artery disease was discovered. The patient was scheduled for mitral valve replacement surgery and anticoagulation was discontinued preoperatively.

On the day of surgery, mitral valve replacement (MVR) with a 25 mm bioprosthetic valve was planned via sternotomy under cardiopulmonary bypass (CPB) with cardioplegia. CPB was established without difficulty and the patient underwent MVR after decalcification of the mitral annulus. Intraoperative transesophageal echocardiogram (Figure 1) confirmed the preoperative diagnosis and correct placement of the MVR was confirmed post-implantation. Upon discontinuation of CPB, extensive bleeding was noted in the operative field in the area of the posterior mediastinum. The patient was restarted on CPB and the chest was explored, revealing an atrioventricular (AV) groove rupture. Standard surgical repair of the AV groove rupture was performed with opposing Teflon strips with preservation of the circumflex marginal vessel.

After surgical repair of the AV groove, the decision was made to centrally cannulate for venoarterial (VA) ECMO and add a left ventricular (LV) vent to the return circuit (https://thoracickey.com/venting-and-clearing-of-the-heart/). The LV vent is a catheter inserted through the LV apex to drain blood from the LV into the venous return side of the ECMO circuit, thereby decompressing the LV and decreasing the wall stress on the repair, increasing the likelihood of successful reapproximation of the myocardium. Left ventricular venting also allows for unloading of the LV and limits the stroke volume, thereby decreasing the force of contraction via inhibition of the Starling mechanism. Once successful placement of the ECMO cannulae and vent were confirmed, ECMO was started and protamine was given to reverse the activated clotting time (ACT) to 180 seconds. After reversal, mild continued bleeding in the operative field was noted, but no coagulopathy was identified by classical or viscoelastic assay and the chest was temporarily closed and the patient returned to the intensive care unit (ICU) under full ECMO support with the goals of correcting medical bleeding, ongoing resuscitation, and effective decompression of the LV.

FIGURE 01 Intraoperative transesophageal echocardiogram confirms mitral regurgitation as demonstrated by retrograde blood flow (blue) from the left ventricle back into the left atrium.

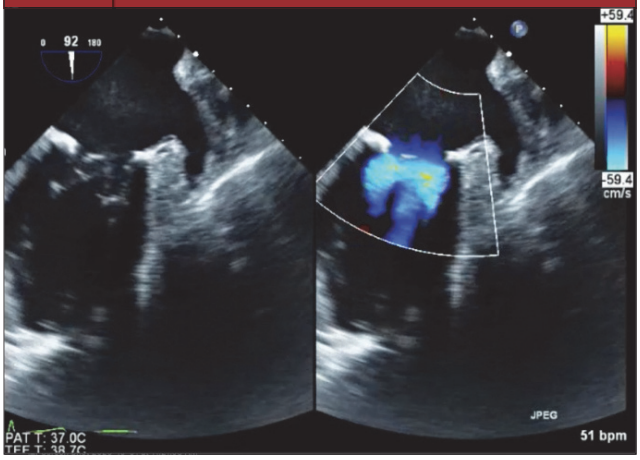

Image courtesy of Jordan B. Bonomo, MD

Upon return to the ICU, ongoing bleeding from the mediastinal and chest tubes was noted at a rate of nearly 250 mL/hr. Thromboelastogram was noted to be normal with no evidence of accelerated clot lysis or hyperfibrinolysis and the international normalized ratio (INR) was measured at 1.1. Fibrinogen levels were > 200 mg/dL, yet bleeding continued. Resuscitation with component blood products was undertaken and a total of five units of packed red blood cells, five units of fresh frozen plasma, two units of platelets and one unit of cryoprecipitate were given in accordance with recent evidence supporting balanced transfusion strategies in ongoing surgical and traumatic bleeding. Additionally, the ECMO circuit was optimized to limit the pump revolutions per minute (RPM) to attain a cardiac index (CI) of 2.2 and thereby decrease shear forces experienced by erythrocytes, thrombocytes and von Willebrand factor (vWF). Of note, a Type II vWF

syndrome can be induced by high velocity ECMO flow, which leads to uncoiling of high molecular weight multimers of vWF, making it susceptible to proteolytic cleavage by the metalloproteinase ADAMTS-13 and thereby disrupting primary hemostasis. The goals of hemostatic optimization for patients bleeding while on ECMO are listed in Table 1.

TABLE 01 Targets for Hemostasis Optimization

- Acidosis [pH > 7.2]
- Hypothermia [T > 36˚C]
- Correct hypocalcemia
- Platelets > 50,000
- Hematocrit > 24%
- Fibrinogen > 100 mg/dL
- TEG normalized
- Lowest RPM for CI 2.2 – 2.8

Despite effective resuscitation and optimization of hemostatic targets, the patient continued to bleed and the decision was made to treat with recombinant FVIIa (rFVIIa). Dosing in the literature varies from low dose (20 mcg/kg) in surgical and neurosurgical patients to higher dose (90 mcg/kg) in trauma patients to highest dose in severe traumatic bleeding (120 mcg/kg). Reported dosing in prior experience with patients on ECMO circuits has varied from 20-220 mcg/kg. The balance between effective hemostasis and major thrombotic events should be weighed carefully when assessing the potential benefit of rFVIIa in patients undergoing ECMO therapy. Major adverse cardiac events including myocardial infarction and ventricular thrombus formation have been reported, as have major ischemic strokes and ECMO pump/oxygenator failure necessitating emergent circuit changes. In most published series regarding the use of rFVIIa in patients bleeding while undergoing ECMO therapy, mortality rates have approached 50%, and pediatric thrombosis rates are notably higher than those seen in adults. In 2016, a 10-year single-center cohort experience with 30 patients on ECMO with bleeding requiring rFVIIa was reported. The center treated with a single dose of 60 mcg/kg of rFVIIa and reported no catastrophic circuit failures, only five patients requiring circuit changes which may not have been the direct result of the rVIIa, and an overall mortality of nearly 50%.[2] In a smaller series of 15 patients reported in 2013, the mortality of those patients requiring rFVIIa for persistent severe bleeding while on ECMO was 60% and the dose used was 60 mcg/kg with a repeat dose as needed per discretion of the treating physician.[3] In this series, the authors reported two required circuit changes within 48 hours and one of the 15 patients progressing to brain death from a presumed ischemic stroke.

Outcome

In this case, despite optimization of hemostatic targets, bleeding continued and the decision to administer rFVIIa was made. Due to the low flow of the LV vent drainage cannula, a lower initial dose of rFVIIa was thought to represent a balanced approach to attempted hemostasis and circuit protection. The patient was given 20 mcg/kg with a repeat dose two hours later. After the second dose, chest tube output was dramatically reduced and repeat chest imaging demonstrated clear lung fields and mediastinal contours within limits (Figure 2). Hemostasis was maintained for the next 48 hours and the patient returned to the operating room for peripheralization of ECMO cannulae and mediastinal washout. Intraoperatively, multiple clots in the LV, mitral annulus and LV vent were noted and the patient was transitioned to a direct thrombin inhibitor (DTI) for a potential diagnosis of heparin induced thrombocytopenia corresponding to a drop in platelets and concern for a new hypercoagulable state. Despite ongoing efforts to maintain anticoagulation with a DTI, the patient developed a worrisome neurologic exam and on cranial CT scanning was found to have an acute ischemic stroke in the left middle cerebral artery territory. Additional body imaging via CT demonstrated multiple thrombotic events including multiple organ infarcts and necrosis. At the behest of the family, the patient was transitioned to comfort care, interventions were de-escalated, and life-sustaining therapies were withdrawn.

The Future: Anticoagulation-Free ECMO?

Despite years of effort to understand the mechanisms that underlie the balance between coagulopathy and thrombosis in patients receiving ECMO therapy, much remains unknown. The risk of bleeding while on ECMO is high enough that some authors have advocated the use of heparin-free, anticoagulation-free ECMO for some patients. In the largest systematic review of this practice, the authors report that even without anticoagulation, the rate of major bleeding remained over 30%.[1] Currently, there are suggestions that with heparin bonded circuitry, as long as ECMO flow rates remain greater than four liters per minute, the rate of thrombosis is acceptably low. In patients with extreme risk of bleeding or active hemorrhage, the withholding of anticoagulation may be a reasonable practice.

FIGURE 02 Anteroposterior chest x-ray demonstrates clear lung fields and mediastinal contours within limits.

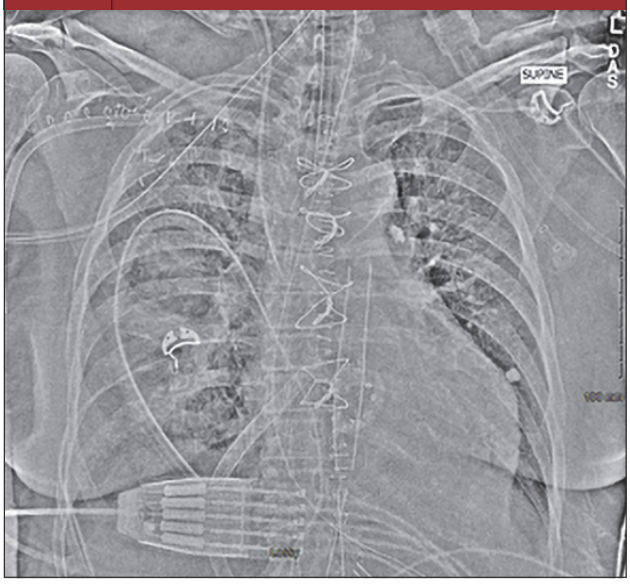

Image courtesy of Jordan B. Bonomo, MD

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ANTICOAGULATION IN THE TRAUMATICALLY INJURED PATIENT

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Emergency trauma care is challenging due to the wide variety of traumatic injuries that can present to the emergency department (ED). Outside of the primary survey and lifesaving stabilization, medical optimization and resuscitation quickly take priority in severely injured patients. Therapeutic anticoagulation as well as the acute coagulopathy of trauma both pose life-threatening risks for traumatically injured patients. Both conditions require emergency correction to optimize patient outcomes. Up to 40% of traumatic deaths are a result of hemorrhage, and this is the leading preventable cause of trauma-related death.[1] One priority is to identify any therapeutic anticoagulant in order to determine if a specific plan or agent is available for reversal or repletion of clotting factors. Resuscitation with crystalloid and factor-poor blood products leads to dilution of clotting factors. If a patient's medications are unknown, or they exhibit signs of the coagulopathy of trauma, the team must have tests to identify the presence of coagulopathy and a plan to treat and restore normal coagulation. The optimal approach is cognizant of the "lethal triad" of trauma and the importance of concomitant correction of hypothermia and acidosis to prevent worsening of coagulopathy.

CLINICAL CASE

A 65-year-old male was involved in a high-speed motor vehicle accident. He was the unrestrained driver of a vehicle that was struck by another automobile on a rural highway. There was a prolonged extrication. He subsequently received spinal motion restriction and was transported to the trauma center ED by ground Emergency Medical Services (EMS). His past medical history included hypertension, poorly controlled diabetes (hemoglobin A1c 8.2%), obesity (body mass index 32), chronic obstructive pulmonary disease, atrial fibrillation, and coronary artery disease. His past surgical history was notable for coronary artery bypass grafting five years ago and a knee arthroplasty two years ago. Pertinent medications for the patient included apixaban and aspirin, in addition to an anti-hypertensive. He also was on medications for glycemic control, and took inhalers and lipid-lowering agents.

Initial evaluation in the ED revealed an ill-appearing and diaphoretic male with a rapid respiratory rate. He was on a spinal immobilization backboard and had a soft Philadelphia cervical collar applied. The patient was tachycardic (128 beats per minute), hypotensive (blood pressure 84/48 mmHg), tachypneic (respiratory rate 30 breaths per minute), and had a normal pulse oximetry of 100% on a non-rebreather mask. The primary survey revealed a patent airway without blood or obstruction. He was protecting his airway. Although the patient was tachypneic, his breathing was not labored, and he was able to speak in full sentences. He had weak but palpably present distal pulses in the radial and dorsal pedis arteries, with delayed capillary refill. The extremity exam revealed an open, displaced fracture of the right distal lower extremity, but the patient was able to move all four extremities.

The patient was exposed in the trauma bay and two 18-gauge intravenous lines were established by the nursing staff in his upper extremities. He was awake and alert and followed commands. While he was able to answer questions, he was noted to be confused and oriented only to person and time, but not location or situation. His lungs were clear with symmetric excursion and without wheezing. His chest wall did not have crepitus or subcutaneous emphysema. The patient's abdomen was tender to palpation with voluntary guarding; he had diffuse ecchymosis on his abdominal wall, consistent with a "seatbelt sign." His pelvis was stable and he did not have any spinal tenderness from the first cervical vertebrae to the sacrum. The open fracture of his right lower leg was not actively bleeding, and there were good pulses distal to the fracture.

Laboratory profiling revealed a white blood cell count of 23,000, hemoglobin 11.8 g/dL, platelets 225,000, and evidence of acute kidney injury with a mildly increased serum creatinine (1.7 mg/dL), blood urea nitrogen (BUN, 30 mg/dL), and glucose (400 mg/dL). The coagulation studies were also abnormal with a prothrombin time (PT) of 20.2 seconds, international normalized ratio (INR) of 1.7, and an activated partial thromboplastin time (aPTT) of 42 seconds. A venous blood gas demonstrated a metabolic acidosis with a pH 7.27, normal partial pressure of carbon dioxide (40 mmHg), a bicarbonate of 19 mEq/L and an elevated lactate (6 mmol/L). A chest x-ray was obtained that was normal. A Focused Assessment with Sonography for Trauma (FAST) was performed by the emergency physician. It was technically adequate and negative for free fluid in the abdomen or pericardial effusion. The patient was transfused with one unit of packed red blood cells and one unit of fresh frozen plasma due to his hemodynamic instability and initial laboratory derangements. His heart rate improved to 100 beats per minute, and his blood pressure increased to 108/74. A CT series for trauma was obtained, including the head, cervical spine, abdomen and pelvis, with reconstruction images of the thoracic and lumbar spines. The non-contrast head CT demonstrated scattered traumatic subarachnoid hemorrhage and small cerebral contusions of the right frontal and left parietal lobes (Figure 1). The abdomen CT demonstrated a grade V liver laceration (Figure 2) without significant hemoperitoneum. Apixaban and aspirin therapies were confirmed as was administration of that day's dose in the morning preceding the accident.

FIGURE 01 Non-contrast head CT demonstrates hemorrhagic contusions (arrows).

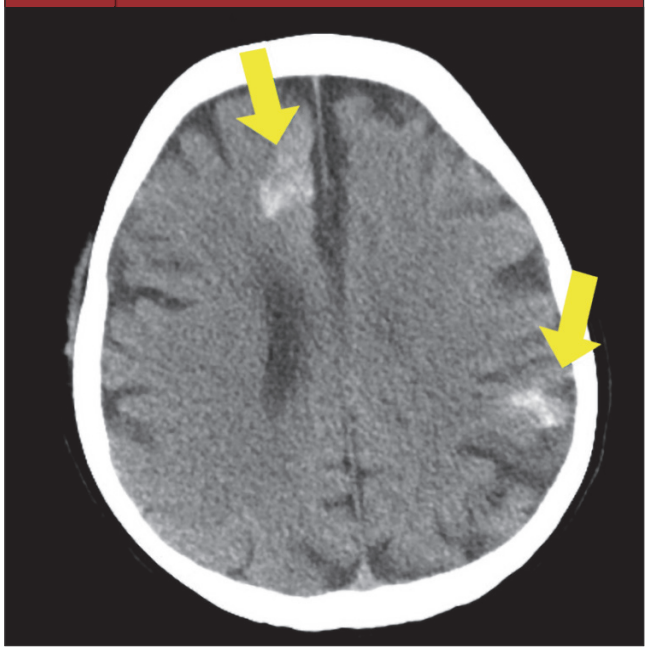
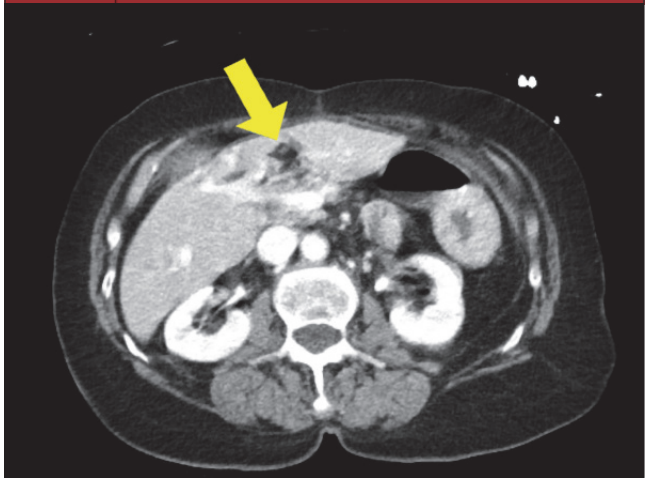


Image courtesy of William A. Knight, MD

FIGURE 02 Abdominal CT with intravenous contrast shows a Grade V liver laceration (arrow).



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Emergency Medicine Trauma Resuscitation Priorities

The anticoagulated and traumatically injured patient should be evaluated as any other trauma patient with a consistent and systematic approach. This approach should include a methodical primary survey focusing on Airway, Breathing, Circulation, Disability and Exposure (ABCDE), identifying and treating immediate life-threatening injuries. The secondary survey occurs after initial stabilization of the patient, and is a rapid and thorough head-to-toe examination in order to identify all significant injuries and critical sites for hemorrhage (see page 10 of this EMCREG monograph for a list of Critical Site Bleeds). Pertinent patient medical history, medications, and information about the injury should be obtained during the secondary survey. Trauma is often dynamic, and frequent reassessment is mandatory. In the event of an exsanguinating injury, with or without anticoagulation, source control is critical. This can include direct compression, tourniquet application, embolization with interventional radiology, and/or surgery such as exploratory laparotomy, thoracotomy, craniotomy, and open reduction/internal fixation of orthopedic injuries.

Assessment of Anticoagulation Status

A complete past medical and surgical history, including a complete and accurate medication reconciliation, is often not possible during the acute resuscitation of a critically injured trauma patient. Any medication that a patient is prescribed and takes on a regular basis is important, but it is critical to identify anticoagulant or antiplatelet medications as they particularly impact the hemorrhagic nature of trauma injuries. When a patient's mental status permits sharing current prescriptions, anticoagulation is generally easy to identify, even if the patient does not know the indication or dosing. When the patient's mental status is altered or obtunded this becomes more challenging, and the provider must rely on communicating with EMS, family, the electronic health record (EHR), or communicating with outside health systems for information.

Routine laboratory testing may reveal clues that link to a particular therapeutic anticoagulant, but this is often unreliable. Vitamin K antagonists such as warfarin cause predictable increases in PT and INR. Factor Xa inhibitors and direct thrombin inhibitors do not have reliable or efficient tests available in the ED, but can give clues to their presence with changes in the anti-Xa level for Factor Xa inhibitors as well as PTT and dilute thrombin time for direct thrombin inhibitor levels. Thromboelastography can be helpful in identifying disorders of coagulation attributed to pharmacology or trauma. Platelet function assays can be used to determine activity of agents such as aspirin or clopidogrel. With the direct-acting oral anticoagulants (DOACs), it is important to determine the time from when the patient took their last dose as well as the patient's renal function.

Coagulopathy of Trauma

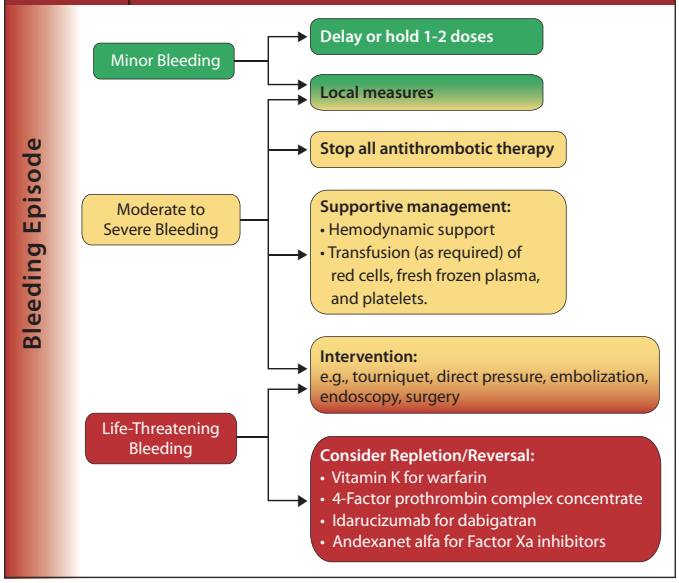
There is a unique coagulopathy of trauma that can confound or contribute to a patient's pharmacologically anticoagulated state. In a hemorrhaging patient, coagulopathy develops due to consumption of coagulation factors and dilution. Hyperfibrinolysis further contributes to this coagulopathic state. The combination of the dilution/consumption of coagulation factors with acidosis and hypothermia creates the "lethal triad of trauma." The evidence has changed significantly over the past 20 years, and medical management has progressed from the initial resuscitation with crystalloid fluids to early and aggressive blood product resuscitation, particularly with coagulation factor-rich

products. It is important for a system to have a multidisciplinary and collaborative approach to identify the best protocol for evidence-based blood product resuscitation. Options include packed red blood cells, whole blood, fresh frozen plasma, platelets, and various ratios of combining these products to ensure factor-rich resuscitation.

The mantra of treating any coagulopathy in trauma should include "resuscitation, reversal and repletion." One must approach each patient with a critical analysis regarding the benefits (and risks) of reversing anticoagulation versus the risk of thromboembolism (Figure 3). In addition to blood product resuscitation, specific reversal agents must be considered as well. These include vitamin K replacement for those taking vitamin K antagonists as well as fresh frozen plasma. Four factor prothrombin complex concentrates (4F-PCCs) containing vitamin K dependent Factors II, VII, IX, and X as well as protein C and protein S are another low volume option with excellent efficacy for vitamin K inhibitors, and weaker efficacy for DOACs. It is important for the clinician to note that it will take multiple hours to days for vitamin K to return hepatic synthesis of vitamin K dependent coagulation factors to normal circulating levels. Andexanet alfa is approved for reversal of Factor Xa inhibitors, and the monoclonal antibody fragment idarucizumab has been approved for the reversal of the direct thrombin inhibitor dabigatran. There is some evidence to support the use of desmopressin or platelet transfusion when platelet function is affected.

The severity and location of the bleed, as well as surgical options and availability of the surgeon must be considered during any reversal of anticoagulation decision. The availability of a specific reversal agent versus off-label use of PCCs can also impact a clinician's resuscitation options and decision-making.

FIGURE 03 Algorithm for the Management of Patients Experiencing Bleeding While Taking Oral Anticoagulants



Case Resolution

The patient was resuscitated by the emergency medicine and trauma surgery teams. His blood pressure decreased to 90/50 upon returning from the CT scanner. He was transfused with an additional one unit of packed red blood cells, one unit of fresh frozen plasma and a 6-pack of platelets. Given his morning dose of apixaban, he was administered andexanet alfa due to his intracranial hemorrhage and his presumed hemorrhagic shock from his grade V liver laceration. Due to the persistent hypotension, he was taken directly to the operating room with the trauma team for exploratory laparotomy and management of the liver laceration. After the patient was stabilized by the trauma team, the orthopedic surgeon performed an open reduction and internal fixation of his open tibia/fibula fracture. He was transferred to the intensive care unit (ICU) for ongoing resuscitation and management of his multiple injuries. He had a repeat head CT which was stable and without hemorrhagic expansion. The patient required ICU resuscitation and management for five days and was ultimately transferred to a long-term acute care hospital for rehabilitation on day 7. His anticoagulation for atrial fibrillation was held for two weeks given his intracranial hemorrhage, and deferred to his primary care physician for optimal timing to resume this therapy. The patient ultimately made a full recovery.

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THE ANTICOAGULATED PATIENT PRESENTING WITH LIFE-THREATENING INJURIES

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The most common cause of preventable death following injury is hemorrhage. This is the basis for the concept of "damage control" surgery and resuscitation, both of which are now standards of care in trauma surgery. However, there are no data upon which one can design the treatment strategy for injured patients on direct oral anticoagulant agents (DOACs).

Damage control surgery is centered on the philosophy that there is no need to definitively repair all injuries in the initial operation for stabilization when a patient presents to the emergency department (ED) with multisystem injury and/or in extremis. The approach is based on the United States Navy, which has "damage control" teams whose job is to make a ship seaworthy when it is damaged. This is in distinction to "repair" teams, whose job is to definitively repair a ship – a task that can take a very long time with multiple specialty teams (e.g., electricians, welders) being asked to participate at various time points.

Damage control resuscitation is based on the concept of "trauma-induced coagulopathy," which predicts that otherwise healthy individuals who experience significant traumatic injury will develop a severe coagulopathy due to the degree of tissue disruption.[1] This concept is the basis for a 1:1:1 transfusion ratio of packed red blood cells:plasma:platelets to address actual or impending coagulopathy in hemorrhaging patients. The approach has been shown to significantly lower mortality, especially mortality due to hemorrhage, in injured patients.[2] Although there are no studies validating this approach in anticoagulated patients, the general consensus is that the approach is still warranted because the associated risk is low and it might mitigate the worsening coagulopathy that may develop in addition to the pharmacologic anticoagulation already present.

The challenge in determining how to alter standard therapy for a patient who is on a DOAC prior to injury is in determining the degree of anticoagulation present. Because there are no readily available tests to assess the degree of anticoagulation, as is done using the international normalized ratio (INR) for warfarin, one has to use qualitative variables to determine the degree of anticoagulation and define management approach. Such factors include: time from last dose of DOAC to patient presentation, renal and liver function to determine clearance of the drug, the location and severity of hemorrhage present, surgical options available to arrest hemorrhage (e.g., tourniquet for extremity hemorrhage), and the availability of reversal agents for the specific DOAC ingested. There are no specific cut-points to determine when or how to intervene for any of these variables, but many authors suggest that if a DOAC was ingested more than 12-18 hours from the time of injury, the impact of the DOAC on bleeding is not likely to be significant.

Because of the initial scarcity of the DOAC-specific reversal agents, idarucizumab for dabigatran and andexanet alfa for apixaban and rivaroxaban, as well as the cost associated with these agents, many centers utilize four factor prothrombin complex concentrate to reverse anticoagulation due to DOACs.[3] However, there are no well-designed human studies upon which to base this strategy. Conversely, the studies supporting the use of andexanet alfa[4] and idarucizumab[5] do not have a control arm and also have significant limitations in assessing clinically relevant outcomes. Nonetheless, from a mechanistic perspective, use of these agents to reverse the specific DOAC for which they are designed makes logical sense.

CLINICAL CASE

An 89-year-old female nursing home patient was brought to the emergency department after being found down. She had moderate to advanced baseline dementia. The patient was confused/agitated but seemed to be complaining of left hip pain. She was on apixaban, with the last dose less than 12 hours ago, for atrial fibrillation. The patient also had a cardiac pacer with a fixed ventricular heart rate. Her initial blood pressure was 130/80 mmHg with a pulse of 60 beats per minute (bpm). Within 90 minutes, her blood pressure had dropped to 60/40 mmHg with the pulse rate of 60 bpm. She had a scalp laceration, which was bleeding. Chest x-ray, abdominal ultrasound, and pelvic x-ray were negative. Whole-body CT scan showed small bilateral subdural hemorrhages as well as a complex left acetabulum fracture with active hemorrhage (Figure 1). Emergency transfusion was started and interventional radiology was consulted for embolo-

FIGURE 01 Pelvis CT with intravenous contrast demonstrates a left acetabular fracture with an associated focus of hemorrhage (arrow).

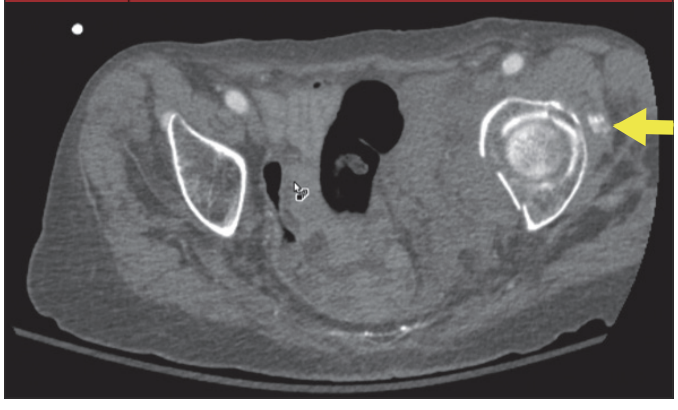

Image courtesy of Babak Sarani, MD

therapy of the pelvis. The patient was treated with andexanet alfa. On angiography, no hemorrhage was noted and the patient's blood pressure normalized and stabilized. Approximately six hours later, the patient underwent a repeat CT of the head, which showed redistribution of the subdural hemorrhage but no ongoing bleeding. The patient became progressively more somnolent over the next one to two days and was placed in a "comfort measures only" status by her family.

Should this example be considered a success or failure of andexanet alfa? The patient was ultimately transferred to hospice, but there was no ongoing or recurrent bleeding after andexanet alfa was administered. Most likely, the patient succumbed to her underlying brain injury and dementia. Thus, the drug achieved its therapeutic goal of stopping the two foci of bleeding, even though the clinical endpoint of decreased mortality was not met. This example highlights the difficulty in treating such patients. It certainly is possible that the bleeding would have stopped without the reversal agent, especially since there was no way to reliably assess how much active drug she had in the serum at the time of injury. Without a quantitative test to measure the anticoagulation associated with DOACs, the decision regarding administration of the reversal agent remains a clinical one based on the previously mentioned variables.

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CONTINUING MEDICAL EDUCATION POST-TEST ANSWER FORM AND EVALUATION

OPTIMAL MANAGEMENT OF THE ANTICOAGULATED PATIENT WITH LIFE-THREATENING BLEEDING IN THE ED AND ICU: A CASE-CASED APPROACH
LAUNCH DATE: 1/1/2021
END DATE: 1/1/2022

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 70% is needed to receive credit**.

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1. **Which of the following statements regarding the dosing of direct thrombin inhibitors or Factor Xa inhibitors is TRUE?**

   A. Renal function should always be considered and may require dose modification.

   B. Hepatic metabolism is the primary source of drug clearance.

   C. Dosing is not affected by renal or hepatic function.

   D. Dosing should be modified based on the patient's INR.

2. **In acutely hospitalized patients over the age of 40 who are at risk for venous thromboembolism (VTE), which of the following statements is TRUE?**

   A. The direct oral anticoagulants (DOACs) have been determined to be too risky for use as prophylaxis against VTE in hospitalized patients.

   B. In large studies, both betrixaban and rivaroxaban have been shown to be effective for VTE prophylaxis in hospitalized patients at risk for VTE.

   C. For the admitted patient who is at risk for venous thromboembolic disease and is being treated with anticoagulation, renal function is not a factor in dosing.

   D. Oral anticoagulation is not considered an appropriate method of preventing thromboembolic disease in acutely ill hospitalized patients.

3. **Regarding the management of oral anticoagulant related hemorrhage, which of the following statements is CORRECT?**

   A. Life-threatening hemorrhage is common.

   B. Initial management should focus on resuscitation and source control.

   C. All patients who experience oral anticoagulant related bleeding require administration of a reversal agent.

   D. In the context of blunt trauma, the mortality for patients taking direct oral anticoagulants is higher than for those taking warfarin.

4. **Which of the following reversal-repletion strategy : oral anticoagulant combination is INCORRECT?**

   A. Idarucizumab : dabigatran

   B. Andexanet alfa : apixaban

   C. 4-factor prothrombin complex concentrate (PCC) : warfarin

   D. Fresh frozen plasma : clopidogrel

5. **According to the 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants, which of the following types of hemorrhage could be considered a critical site bleed?**

   A. Pericardial tamponade

   B. Posterior epistaxis

   C. Retroperitoneal hemorrhage

   D. All of the above

6. **A 75-year-old woman with a history of hypertension and atrial fibrillation presents to the emergency department (ED) after a fall down a flight of stairs. She has a Glasgow Coma Scale (GCS) of 13 and a non-contrast head CT demonstrates an acute, moderate-sized subdural hematoma. You determine from her husband that she is on apixaban and that her last dose was approximately 6 hours ago. The reversal agent andexanet alfa is available at your institution. In addition to the administration of andexanet alfa, what additional measures should be considered?**

   A. Activated charcoal

   B. Vitamin K

   C. 4-Factor PCC

   D. Platelet transfusion

   E. None of the above

7. Which of the following is a sign that a patient's gastrointestinal bleeding is life-threatening?

A. Melenic stool

B. Hypotension not responsive to fluid resuscitation

C. Tachycardia

D. Anticoagulation due to an oral anticoagulant

8. In an 80-year-old patient who has a traumatic subdural hematoma with a GCS of 14 and last took apixaban two hours ago, when should reversal of anticoagulation take place?

A. Immediately after diagnosis of intracranial hematoma

B. Within the first 4 hours

C. Within the first 12 hours

D. If the patient's exam worsens or the subdural hematoma is larger on a repeat head CT

9. Which of the following is the best reversal strategy for a patient who presents to the ED with a warfarin-associated intracranial hemorrhage?

A. PCCs only

B. Andexanet alfa

C. PCCs and vitamin K

D. Fresh frozen plasma and vitamin K

10. All of the following statements regarding intraspinal bleeding are correct EXCEPT:

A. Intraspinal bleeding is exceedingly rare.

B. Prognostication is unreliable and decompressive surgery should be performed regardless of exam findings.

C. Risk factors may include arteriovenous malformations and anticoagulant use.

D. Given the usual rapid progression of neurologic deficits, the bleeding source is thought to be arterial most of the time.

11. For the management of bleeding in patients on ECMO, all of the following are correct hemostasis optimization targets EXCEPT:

A. pH > 7.2

B. Temperature > 36°C

C. Fibrinogen > 50

D. Platelets > 50,000

12. Even without systemic anticoagulation, case series have described bleeding rates for ECMO patients exceeding 30%.

A. True

B. False

13. Which of the following is NOT a part of the "lethal triad of trauma?"

A. Acidosis

B. Coagulopathy

C. Hemorrhage

D. Hypothermia

14. Approximately what percentage of traumatic deaths occur as a result of hemorrhage?

A. 20%

B. 40%

C. 60%

D. 80%

15. The most appropriate time to administer a pharmacologic reversal agent for a direct oral anticoagulant is:

A. Prior to emergency operation in a hemorrhaging patient

B. Prior to elective surgery in a patient with atrial fibrillation

C. During an operation if bleeding is encountered

D. In the recovery room after attempts to stop bleeding following operation have failed

(Answer sheet next page)

CME 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.

CME Expiration date: January 1, 2022
Launch Date: 1/1/2021 • End Date: 1/1/2022

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(circle correct answer)

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2.	**A**	**B**	**C**	**D**	
3.	**A**	**B**	**C**	**D**	
4.	**A**	**B**	**C**	**D**	
5.	**A**	**B**	**C**	**D**	
6.	**A**	**B**	**C**	**D**	**E**
7.	**A**	**B**	**C**	**D**	
8.	**A**	**B**	**C**	**D**	
9.	**A**	**B**	**C**	**D**	
10.	**A**	**B**	**C**	**D**	
11.	**A**	**B**	**C**	**D**	
12.	**A**	**B**			
13.	**A**	**B**	**C**	**D**	
14.	**A**	**B**	**C**	**D**	
15.	**A**	**B**	**C**	**D**	

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