EMERGENCY MEDICINE REPORTS

Practical, Evidence-Based Reviews in Emergency Care

SEPTEMBER 1, 2016 VOL. 37, NO. 17

AUTHORS

Abhi Mehrotra, MD, MBA, FACEP, Vice Chair, Strategic Initiatives & Operations, Medical Director, Hillsborough Campus ED, University of North Carolina Department of Emergency Medicine.

Timothy D. Buff, MD, Emergency Medicine, University of North Carolina, Chapel Hill.

Leah M. Hatfield, PharmD, BCPS, Lead Clinical Pharmacist Specialist, Emergency Medicine, University of North Carolina Medical Center, Chapel Hill.

Chad S. Kessler, MD, MHPE, Clinical Associate Professor, Emergency Medicine and Internal Medicine, Duke University, Durham, NC.

PEER REVIEWER

Charles V. Pollack, MD, FACEP, FAAEM, Professor and Senior Advisor for Interdisciplinary Research and Clinical Trials, Department of Emergency Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia.

STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Farel (CME question reviewer) owns stock in Johnson & Johnson. Dr. Stapczynski (editor) owns stock in Pfizer, Johnson & Johnson, Walgreens Boots Alliance Inc., GlaxoSmithKline, Bristol Myers Squibb, and AxoGen. Dr. Hatfield (author) is a retained (nonpromotional) consultant for a product under development for Portola Pharmaceuticals. Dr. Mehrotra (author) is a stockholder and board member for MedScribes. Dr. Pollack (peer reviewer) has received grant/research support and is a retained consultant for: Boehringer Ingelheim, Daiichi Sankyo; retained consultant for Janssen Pharma, BMS/Pfizer Alliance. Dr. Schneider (editor), Ms. Fessler (nurse planner), Dr. Buff (author), Dr. Kessler (author), Ms. Mark (executive editor), Ms. Coplin (executive editor), and Mr. Landenberger (editorial and continuing education director) report no financial relationships with companies related to the field of study covered by this CME activity.

AHC Media

Oral Anticoagulation Reversal

Case: *A 73-year-old female presented to the emergency department (ED) after she tripped and fell, striking her head. On arrival, she appeared to be in no acute distress, was alert and oriented, and was neurologically intact with a Glasgow Coma Scale score (GCS) of 15. Vital signs: blood pressure 162/87 mmHg, heart rate 80/min and irregularly irregular, respiratory rate 16/min, and pulse oximetry 96% on room air. She did have a scalp hematoma but without overlying laceration or palpable bony abnormality. She was currently taking warfarin for atrial fibrillation and her international normalized ratio (INR) in the ED was 3.9. A head CT was obtained rapidly and was negative for acute intracranial bleed or skull fracture.*

Introduction

Five oral anticoagulants are available in the United States: warfarin (Coumadin®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®), apixaban (Eliquis®), and edoxaban (Savaysa®). Warfarin has been in clinical use since 1954, and for more than 55 years, it was essentially the only oral anticoagulant available. In the past five years, new or novel oral anticoagulants (NOACs) have been released for use. Alternatively, these agents also are known as non-vitamin K antagonist oral anticoagulants, indicating that their mechanism of activity does not involve antagonism of the synthesis of the vitamin K-dependent coagulation factors, or direct oral anticoagulants (DOACs), reflecting that they directly inhibit one of the factors involved in the coagulation cascade. In the United States, four NOACs or DOACs currently are available: dabigatran, rivaroxaban, apixaban, and edoxaban.

Indications for Anticoagulation Reversal

The primary indication for emergency reversal of oral anticoagulation is ongoing major or life-threatening bleeding. A secondary indication is when an emergent surgical or invasive procedure is required and reversal is indicated to prevent periprocedural bleeding. For both warfarin and the DOACs, a primary reversal strategy for emergent reversal is replacement of the deficient or inhibited coagulation factor(s).[1] This is most intuitive in cases of warfarin-related bleeding, in which multiple coagulation factors are deficient. DOAC-treated patients have only one factor inhibited, and replacement strategies involve administration of enough factor to overcome inhibition induced by the DOAC present in the circulation. Many institutions have developed standardized anticoagulation reversal protocols to streamline patient care and minimize potential for errors.[2]

In many circumstances, the challenge is not the method of reversal, but rather the decision of whether to initiate reversal. Temporary withholding of anticoagulation is almost always generally advisable. It should be inherently obvious that any life-threatening bleed should be reversed promptly with the

EXECUTIVE SUMMARY

- Emergency warfarin reversal is best accomplished by IV bolus of 4-factor prothrombin complex concentrate (PCC) and vitamin K1.
- The specific emergency reversal agent for dabigatran is idarucizumab.
- The specific emergency reversal agent for FXa inhibitors (rivaroxaban, apixaban, and edoxaban) is andexanet alfa, which is awaiting FDA approval.
- If specific reversal agents for direct oral anticoagulants are not available, consider activated prothrombin complex concentrate or 4-factor prothrombin complex concentrate for life-threatening bleeding associated with these agents.

best available agent. This is typified by a patient on anticoagulation who presents with non-compressible bleeding (e.g., intracranial hemorrhage, severe gastrointestinal bleed, multi-system trauma), or hemodynamic instability secondary to exsanguination. The debate arises when a patient has the propensity to decompensate but is currently hemodynamically stable or presents with non-life-threatening bleeding. (*See Table 1.*) When possible, the provider can have a discussion with the patient or caregiver regarding the risks and benefits of immediate anticoagulation reversal. The major risk of anticoagulation reversal is primarily in patients who are on therapeutic anticoagulation to prevent recurrent thromboembolism; urgent reversal exposes the patient to occurrence of such an event. Physicians should always consider the alternatives, such as manual, balloon, or tampon compression; topical pro-hemostatic therapy (tranexamic acid, oxymetazoline); and/or supplementing with phytonadione (warfarin-induced bleeding only).[3-6]

Warfarin

As noted, warfarin was the first oral anticoagulant developed. It was the agent used almost exclusively in studies that identified the benefits and risks of treating thromboembolic conditions, as well as studies that investigated the duration of treatment necessary to reduce the risk of thromboembolic recurrence. Warfarin is the agent with which the DOACs were compared in Phase III studies evaluating their efficacy and safety.

Pharmacology

Warfarin is readily absorbed and metabolized, with elimination primarily by the liver. (*See Table 2.*) Warfarin is an antagonist for the vitamin K-dependent carboxylation of several of the proteins involved in the coagulation system: four thrombotic and two antithrombotic.[7] (*See Table 3.*)

Upon initiation of warfarin therapy, the serum levels of the prothrombotic factors drop according to their half-lives: initially factor VII (FVII), followed by factor IX (FIX), factor X (FX), and then prothrombin (FII). The levels of protein C also decrease, and because its half-life is shorter than three of the prothrombotic coagulation factors, there is an initial increase in thrombotic activity at the start of warfarin therapy. This transient hypercoagulable state usually is counteracted by the use of bridging therapy with a non-vitamin K-dependent parenteral anticoagulant, such an unfractionated heparin (UFH) or low molecular-weight heparin (LMWH), initiated concurrently with warfarin and continued until the INR is within the therapeutic range: 2.0 to 3.0 for stroke prevention in atrial fibrillation and treatment of venous thromboembolism (VTE).

Warfarin has several drug and dietary interactions that can either potentiate or reduce its anticoagulant effects. (*See Table 4.*) In clinical practice, routine monitoring is required to establish the daily dose necessary to achieve the therapeutic goal. Some patients have a difficult time achieving a stable level of anticoagulation, perhaps due to differences in the time of day when the drug is ingested, proximity to meals, variations in diet, and interaction with drugs that are either initiated, adjusted, or discontinued.[8]

Warfarin Reversal

A benefit of using warfarin is having the ready availability of agents that can correct the anticoagulant effect by replenishing the deficient coagulation factors, a mechanism properly termed "repletion" rather than "reversal." Phytonadione helps naturally replenish factors II, VII, IX, X, proteins C and S by supporting epoxide reductase in the liver. On average, oral phytonadione takes 6-24 hours and intravenous (IV) phytonadione takes two to six hours for demonstrable action, with maximal effect at 12-24 hours to decrease the risk of bleeding.[3,6,9] Because of the prolonged onset, both oral and IV dosing are more helpful in correcting an asymptomatic supratherapeutic INR and are less relevant for rapid reversal, but are used as an adjunct medication in conjunction with emergent repletion agents. The anticoagulant effect of warfarin can be more readily reduced by using agents that replace the reduced coagulation cascade factors: fresh frozen plasma (FFP), recombinant factor VIIa, and prothrombin complex concentrate (PCC) products.

Warfarin reversal can be achieved in a number of ways. (*See Table 5.*) The simplest is to stop the daily dose. (*See Table 6.*) Since warfarin is a competitive vitamin K antagonist, pharmacologic doses of phytonadione or vitamin K1 will overcome the anticoagulant effect of excess warfarin, but it takes time to synthesize new factors. Historically, FFP has been the preferred agent for rapid reversal, but the rapidity of reversal is slower than desired and the completeness of reversal is variable.[10] A more rapid and thorough response is seen with 3- and 4-factor PCC.[9,11,12] Recombinant FVIIa also may be effective,[13-15] although it is not FDA approved for warfarin reversal.[16] For life-threating hemorrhage due to warfarin-induced coagulopathy, a combination approach is recommended. (*See Table 7.*)

Fresh Frozen Plasma. For many

Table 1. Stratification of Anticoagulation Reversal in Bleeding Patients

Bleeding Risk	Low-risk Bleeding	Moderate-risk Bleeding	Life-threatening Bleeding
Examples	Simple laceration, abrasion/ skin tear, anterior nasal bleed, hematuria, occult gastrointestinal bleeding	Posterior nasal bleed, compressible bleed not well controlled with pressure	Intracerebral hemorrhage, severe/unstable GI bleed, retroperitoneal hemorrhage, hemodynamic instability
Treatment	Manual, balloon, or tampon compression; withholding anticoagulation; topical pro-hemostatics; oral phytonadione (warfarin-induced bleeding only)	Gray zone: topical therapy vs. reversal agents	Rapid reversal

Table 2. Warfarin[17]

Oral Absorption	100%, peak serum concentration achieved at 90 min (range 20-240 min)
Serum Protein Binding	98%
Metabolism	Hepatic cytochrome P450: primarily isoenzyme CYP2C9, secondary CYP1A2 and CYP3A4
Elimination	Almost entirely hepatic metabolism
Elimination Half-life	36-42 h (variable based on rate of clotting factor catabolism)
Pharmacologic Action	Competitively inhibits vitamin-K carboxylation of factors II, VII, IX, and X, and proteins C and S
Typical Initial Dosing	2-5 mg PO daily
Monitoring Test	PT with calculated INR Dose adjusted to maintain INR between 2.0 and 3.0 in most circumstances, e.g., stroke prevention in atrial fibrillation and treatment of VTE

Table 3. Vitamin K Dependent Factors Affected by Warfarin

Prothrombotic Coagulation Factors	Biologic Half-life (Approximate)
Factor X	24-40 h
Factor IX	20-30 h
Factor VII	4-6 h
Factor II (Prothrombin)	60-72 h
Antithrombotic Proteins	**Biologic Half-life (approximate)**
Protein C	8-10 h
Protein S	40-60 h

years, FFP was the standard therapy for coagulation factor repletion because it provides multiple factors (although not in concentrated amounts) and is widely available. It does, however, require cross-matching, thawing time, and consideration of the patient's volume status.[6,12,18] Each unit of FFP is roughly 200-250 mL, and 10-15 mL/kg is recommended in an adult patient to reverse the effects of warfarin anticoagulation in cases of life-threatening bleeding. This can be a significant intravenous volume, leading to side effects such as transfusion associated circulatory overload (TACO) and immunogenic complications of transfusion-related acute lung injury (TRALI).[18,19]

Coagulation Factor VIIa (recombinant). Coagulation factor VIIa (recombinant) or rFVIIa administration initially gained traction in the early 2000s because of its targeted approach. Factor VII has the shortest biological half-life of all coagulation factors, so it is often the rate-limiting reagent in patients with multiple coagulation factor deficiencies. Significant reduction in both INR and bleeding time occurs after rFVIIa administration to patients taking warfarin who present with life-threatening bleeding.[13,14,20] Studies comparing rFVIIa to PCC found no significant difference in the short-term anticoagulation reversal as assayed by laboratory analysis.[14,20]

In addition, rFVIIa does have some drawbacks. It received an FDA black-box warning because of an increase in arterial thromboembolism when given to patients with hemophilia.[16,20] Evidence regarding the thrombosis risk of rFVIIa in anticoagulation reversal is mixed; some studies show no difference in thrombosis risk,[15] while others show an increased risk.[14,21] This risk is thought to be secondary to rFVIIa's short half-life, potentially creating a rebound increase in coagulability.[13] The current consensus is that rFVIIa is a second- or third-line agent for emergent warfarin or dabigatran reversal. This is because rFVIIa is only one of the depressed factors in warfarin therapy, it is not the inhibited factor in dabigatran therapy, better reversal agents are available, and it has the associated risk of thrombosis.

Prothrombin Complex Concentrates. Prothrombin complex concentrates (PCCs) are freeze-dried preparations of the vitamin K-dependent coagulation factors involved in assembly of the prothrombin complex: factors X, IX, VII, and

Table 4. Clinically Relevant Warfarin Interactions

Increases Anticoagulation, PT, and INR	Decreases Anticoagulation, PT, and INR
Decreased dietary vitamin K	Increased dietary vitamin K
Reduced gut bacteria due to oral antibiotics	Parenteral vitamin K
Drug-induced reduction on hepatic cytochrome P450 isoenzyme activity: such as cotrimoxazole, fluconazole, metronidazole, acyclovir, ciprofloxacin, famotidine, norfloxacin, oral contraceptives, phenylpropanolamine, propranolol, verapamil, alprazolam, clarithromycin, diltiazem, erythromycin, ketoconazole, ranitidine	Drug-induced increase in hepatic cytochrome P450 isoenzyme activity: such as phenobarbital, phenytoin, carbamazepine, primidone, dicloxacillin, nafcillin, rifampin, omeprazole, prednisone Botanicals: Coenzyme Q10, St. John's wort, ginseng
Drugs That Increase Risk of Bleeding Independent of an Increased PT and INR	
Other parenteral or oral anticoagulants: such as unfractionated heparin (UFH), LMWH, dabigatran, rivaroxaban, and apixaban	
Antiplatelet agents: such as aspirin, clopidogrel, and prasugrel	
Nonsteroidal anti-inflammatory drugs	
Serotonin reuptake inhibitors: such as citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine	

thrombin. These products are commercially available in three variations: 3-factor, 4-factor, and activated 4-factor versions.[18,22-24] (*See Table 8.*) Three-factor versions contain small amounts of FVII, whereas 4-factor versions contain clinically relevant amounts of FVII. The activated 4-factor version contains thrombin, FIX, and FX in primarily inactivated form, and FVII mainly in the active form. Four-factor PCCs contain variable amounts of protein C, protein S, and antithrombin. Since PCCs are derived from human plasma, there is variation in the amounts of each factor in individual vials. The vials are assayed for FIX activity and dosing usually is according to the degree of FIX activity desired.

PCC products carry a small risk of inducing thrombosis, estimated to be between 1% and 2%.[25] Because of variation in the clinical conditions for which these agents are used, it is not possible to precisely compare risk among the different PCC products.

Head-to-head trials have shown 4-factor PCC to have equal anticoagulation reversal to 3-factor but overall lower thrombosis risk.[26,27] Experimental literature indicates that 4-factor PCC can reverse the anticoagulant effects of warfarin, dabigatran, and rivaroxaban.[9] The benefits of either PCC formulation compared to FFP are small volume, no need for cross-matching, and quick therapeutic response. The reversal duration with warfarin-induced hemorrhage often is temporary because the half-life of infused factors can be shorter than the elimination half-life of warfarin, but coadministration of IV vitamin K can help replenish intrinsic production of coagulation factors to extend anticoagulation reversal.[1,11,12]

For reversal of warfarin-induced coagulopathy, the current strategy is a PCC dose based on the estimated depletion of coagulation factors as determined by the pretreatment INR and body weight; with greater depletion as noted by a higher INR and increasing body weight, a larger dose is used. The manufacturer's prescribing information for 4-factor PCC has dosing recommendations based on reversal of the coagulopathy to an INR < 1.3.[23] (*See Table 9.*) Normalization of the coagulopathy to this degree may not be necessary in many cases, and it is primarily reserved for life-threatening hemorrhage. In addition, a systematic review of PCC protocols using 8 to 50 units FIX/kg to reverse warfarin-induced coagulopathy found no superior dosing regimen, suggesting that smaller doses may be just as effective as those currently recommended.[28]

Direct Thrombin Inhibitor: Dabigatran

Dabigatran initially was approved in the United States in 2010 for preventing atrial thromboembolism (e.g., embolic stroke) in patients with non-valvular atrial fibrillation. With time, approved uses of dabigatran have expanded to include deep venous thrombosis (DVT) and pulmonary embolism (PE).[29,30]

Pharmacology

Dabigatran is a direct-acting inhibitor of thrombin, activated FII or FIIa. (*See Table 10.*) This drug is administered as dabigatran etexilate mesylate, which is absorbed as dabigatran etexilatre ester and subsequently hydrolyzed to form the active agent dabigatran. The purported advantages of dabigatran compared with warfarin are reduced dietary and drug interactions, the lack of a need for routine monitoring tests, and the reduced incidence of serious bleeding (especially intracranial).[31-35] These advantages also have been demonstrated in real-world experience.[36-41] The one adjustment with dabigatran dosing is for patients with impaired renal function as determined by a calculated creatinine clearance (CrCL) below 30 mL/min.

Dabigatran has some drug interactions of concern. The most important of these interactions are with verapamil and amiodarone, both of which increase the serum concentration of dabigatran. This effect can be minimized by a two-hour gap between ingestion of dabigatran and the other agents.

Dabigatran Reversal

Because dabigatran is predominately excreted unchanged by the kidneys, maintaining a robust urine flow or initiating hemodialysis will hasten removal. Idarucizumab is a specific antibody Fab fragment that binds dabigatran and renders it inactive. For life-threatening hemorrhage due to dabigatran-induced coagulopathy, idarucizumab is the most effective treatment. (*See Table 11.*) Clinical reports describe apparent reversal of the dabigatran-induced

Table 5. Warfarin Reversal Agents[1,9,11,12,18,20,49]

Agent	Contents (Factors)	Onset of Action	Peak Effect	Duration	Major Side Effects
Phytonadione (Vitamin K1)		IV: 2-6 h Oral: 6-12 h	IV: 12-24 h Oral: 24-48 h		IV extravasation
Fresh Frozen Plasma (FFP)	All coagulation factors, albumin, and vWF	Immediate	60 min	Variable	Volume load, TRALI*, TACO**, anaphylaxis
Coagulation Factor VIIa (recombinant)	Factor VII in activated form	Immediate	10 min	6-8 hours	Thrombosis
Prothrombin Complex Concentrate (PCC)	3-factor: II, IX, and X 4-factor: II, VII, IX, X, C, S, AT, and albumin Activated: FVIIa, II, IX, and X	Immediate	10-15 min	6-8 hours	Thrombosis

*TRALI: transfusion-related acute lung injury
**TACO: transfusion-associated circulatory overload

Table 6. Approximate Time Course for Warfarin Reversal

Approach	Median Time to Achieve INR < 1.6
Stop daily drug	2-3 days
Oral phytonadione or vitamin K1	24-36 h
Intravenous phytonadione or vitamin K1	8-16 h
Fresh frozen plasma	60 min, limited by volume concerns
4-factor PCC	10-15 min
Coagulation factor VIIa (recombinant)	10 min

Table 7. Recommendations for Warfarin-induced Life-threatening Hemorrhage

Vitamin K replacement	Phytonadione or vitamin K1 10 mg IV
Factor replacement	4-factor PCC 50 units/kg IV [*see Table 9 for additional information] or 3-factor PCC 50 units/kg plus one unit (about 250 mL) fresh frozen plasma

coagulopathy with both rFVIIa and aPCC, whereas FFP has no demonstrable effect.[6,18,20,42-45]

Idarucizumab. Idarucizumab is a humanized monoclonal antibody fragment (MW 47.8 kDa) that binds dabigatran with a much higher affinity, about 350-fold, than dabigatran's binding to thrombin.[46] (*See Table 12.*) Therefore, idarucizumab will bind and neutralize both free and thrombin-bound dabigatran. Idarucizumab has no demonstrable procoagulant or anticoagulant effects, no endogenous targets, and no Fc receptor binding, all of which result in a low risk of adverse effects.[47] Studies in healthy young volunteers, older volunteers, and volunteers with renal insufficiency found that IV idarucizumab has a rapid onset of action, with reversal of the anticoagulant effect of therapeutic doses of dabigatran in a few minutes after completion of the IV infusion and an elimination half-life of about 47 minutes.[47] Like other small proteins, idarucizumab is filtered into the urine with a portion that is excreted unchanged and a portion undergoing catabolism in the renal tubules.

A Phase III study found that idarucizumab 5 g IV completely reversed the anticoagulant effect of dabigatran in patients with serious bleeding or who required an urgent procedure.[48] The majority of patients had laboratory evidence of an anticoagulated state, and the reversal effect from idarucizumab was evident within minutes and was sustained for up to 72 hours. In those patients in the group with serious bleeding who could be evaluated for continued hemorrhage, cessation of bleeding was noted after a mean of 11.4 hours.

Following publication of this study, idarucizumab underwent expedited FDA review and was approved on Oct. 16, 2015. Based on its ability to bind to dabigatran (Pradaxa), the registered trademark name for idarucizumab is Praxbind®.

Factor Xa Inhibitors: Rivaroxaban, Apixaban, and Edoxaban

Rivaroxaban and apixaban initially were released for use in the United States in 2011 and 2012, respectively. In January 2015, the FDA approved an additional drug in this class, edoxaban, for treatment of DVT and PE, and stroke prevention in patients with nonvalvular atrial fibrillation.[7] A difference with edoxaban compared to rivaroxaban and apixaban is its minimal metabolism

Table 8. Approximate Composition of Prothrombin Complex Concentrates

	3-factor PCC (Profilnine®) 500 unit vial (20 mL)	4-factor PCC (Kcentra®) 500 unit vial (20 mL)	Activated 4-factor PCC (FEIBA®) 500 unit vial (20 mL)
Thrombin (FII)	24-38 units/mL	20-48 units/mL	1.3 unit/U FEIBA
Factor VII	< 5 units/mL	10-25 units/mL	FVIIa 1.5 unit and FVII 0.9 unit per U FEIBA
Factor IX	24-38 units/mL	20-31 units/mL	1.4 unit/U FEIBA
Factor X	24-38 units/mL	22-60 units/mL	1.1 unit/U FEIBA
Protein C	0	15-45 units/mL	1.1 unit/U FEIBA
Protein S	0	12-38 units/mL	0
Antithrombin	0	0.2-1.5 units/mL	0
FDA approval	Prevention and control of bleeding episodes in adult patients with hemophilia B	Urgent reversal of warfarin-induced coagulopathy in adult patients with acute major bleeding or needing urgent surgery or invasive procedure	Spontaneous bleeding episodes or to cover surgical interventions in hemophilia A or B patients with inhibitors

Table 9. 4-Factor PCC Dosage for Urgent Reversal of Warfarin-induced Severe Bleeding

Pre-treatment INR	2-4	4-6	> 6
4-Factor PCC dose (FIX units/kg)	25	35	50
Not to exceed (units)	2500	3500	5000

Table 10. Dabigatran[29]

Oral bioavailability	3-7%, not affected by food, but bioavailability increased if capsule shell is not intact (e.g., broken, opened, or chewed) Peak serum concentration 1-2 h
Serum protein binding	35%
Metabolism	About 20% metabolized to four different acryl glucuronides with similar pharmacologic activity as the parent compound
Elimination	Up to 80% excreted unchanged in the urine
Elimination half-life	12-17 h (in the setting of normal renal function)
Pharmacologic action	Competitively inhibits thrombin (FIIa)
Typical initial dosing	150 mg PO BID (CrCL > 30 mL/min) 75 mg PO BID (CrCl between 15-30 mL/min)
Monitoring test	No established monitoring test Prothrombin time (PT) and activated clotting time (ACT) insensitive to the anticoagulant effect of dabigatran at therapeutic doses Activated partial thromboplastin time (aPTT) prolonged by therapeutic doses, but commercial reagents differ widely in their sensitivity to dabigatran Thrombin time (TT) is sensitive to anticoagulant effect of dabigatran at therapeutic doses Plasma diluted thrombin time (dTT) and the Ecarin Clotting Time (ECT) possess linear correlation with serum dabigatran levels over therapeutic range

and elimination primarily unchanged in the urine. In a trial comparing edoxaban with warfarin, an increased rate of ischemic stroke was seen in patients with a creatinine clearance > 95 mL/min receiving edoxaban. The obvious but unverified assumption is that patients with robust renal function excrete the drug more rapidly, producing a diminished anticoagulant effect. Thus, edoxaban is not recommended for patients with a creatinine clearance > 95 mL/min.[7]

Pharmacology

Rivaroxaban, apixaban, and edoxaban are direct inhibitors of activated factor X (FXa). (*See Table 13.*) They inhibit not only free FXa, but also FXa already incorporated into the prothrombinase complex, composed of FXa, FVa, plasma membrane phospholipids, and calcium ion.

These FXa inhibitors have drug interactions so there should be at least a two-hour gap between administration of these agents and ingestion of verapamil, amiodarone, HIV protease inhibitors, and azone antifungals.

The factor Xa inhibitors have effects on routine coagulation tests that vary according agent, test, and assay reagent used.[50-54] There is no value using the standard PT, aPTT, or TT to monitor therapeutic effect of oral FXa-inhibitors. With careful choice of reagents and analyzers using the

Table 11. Recommendations for Dabigatran-induced Life-threatening Hemorrhage

Agent	Dose
Idarucizumab (Praxbind®)	5 g IV, either bolus injection or infusion
If idarucizumab is not available, consider	
Activated Prothrombin Complex Concentrate (aPCC)	50 units/kg IV, may repeat in 2-4 hours if bleeding continues OR emergency hemodialysis
OR (less preferred)	
Coagulation Factor VIIa (recombinant) (rFVIIa)	90 micrograms/kg IV, may repeat in 2 hours if bleeding continues

Table 12. Idarucizumab

Metabolism	Several pathways contribute to the metabolism of antibodies
Elimination	Renal (about 60%)
Elimination half-life	47 min initial half-life (dependent on renal function)
Pharmacologic action	Binds to dabigatran and its acylglucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, neutralizing their anticoagulant effect
Typical initial dosing	5 g IV infusion or bolus (provided as two separate vials each containing 2.5 g/50 mL)
Monitoring test	Ecarin Clotting Time (ECT)
FDA approval	When reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures or if life-threatening or uncontrolled bleeding is present

PT, it is possible to determine if an anticoagulative effect is present with rivaroxaban and apixaban, but such testing modifications need to be requested specifically and are not routinely available.[54] Since rivaroxaban, apixaban, and edoxaban competitively inhibit FXa, the chromogenic anti-FXa activity assay can be used to measure their anticoagulant effect, and with calibration for the specific drug, the serum level.[50] Such a measurement may be useful to assess the degree of drug-induced anticoagulation before either invasive procedures or initiation of fibrinolytic therapy in order to avoid excessive hemorrhage.

Factor Xa Inhibitor Reversal

The specific reversal agent for the FXa inhibitors is andexanet alfa, currently under FDA review. On Aug. 18, 2016, the FDA sent a Complete Response Letter to Portola Pharmaceuticals, the developer of andexanet alfa, requesting additional information related to the manufacturing process and additional data supporting inclusion of edoxaban and enoxaparin in the prescribing information. Because andexanet alfa is an FDA-designated Breakthrough Therapy, approval for use in the United States is anticipated within the next few months.

Until then, there is a paucity of data regarding which agent consistently reverses rivaroxaban, apixaban, or edoxaban.[55] Limited studies suggest that aPCC would be expected to have greater effectiveness than 4-factor PCC or rFVIIa at reversing the hemorrhagic state producing serious bleeding associated with rivaroxaban, apixaban, or edoxaban.[55,56] (*See Table 14.*)

Andexanet alfa. Andexanet alfa is a truncated version of FXa produced by recombinant protein technology that is enzymatically inactive because it lacks a 34-amino acid fragment required for assemblage into the prothrombinase-complex. Andexanet alfa acts as a decoy, binding and competitively sequestering oral and parenteral FXa inhibitors away from active native FXa. In Phase II studies with healthy volunteers taking therapeutic range doses of rivaroxaban or apixaban, andexanet alfa reduced anti-FXa activity by more than 90% and restored thrombin generation within two to five minutes.[57] Because the half-life of andexanet alfa is about an hour, the drug is administered as a bolus plus an infusion for two additional hours.

Andexanet alfa doses used in clinical trials have varied and a recommended effective dose awaits further analysis and FDA approval. It is anticipated that the recommended dose of andexanet alfa will vary according to the specific FXa inhibitor agent being reversed because of the differences in therapeutic doses for these drugs. Andexanet alfa is currently undergoing a Phase III trial to determine efficacy and safety in bleeding patients.[58] This study does not include an evaluation of FXa-inhibitor-treated patients who need reversal to undergo a procedure.

Andexanet alfa also reverses the effect of the anti-FXa parenteral anticoagulants heparin, LMWH, and fondaparinux.[59,60] Dose recommendations, and understanding of efficacy and safety, await additional studies.

Protocol for Oral Anticoagulant-induced Hemorrhage

A stepwise approach should include:

- Assess the severity of bleeding and its effect on the patient's hemodynamic function.
- Determine the timing and amount of any antithrombotic medication, including oral anticoagulants and antiplatelet agents.
- Establish necessary IV access and initiate volume resuscitation with isotonic saline and red cell transfusions as needed to maintain tissue oxygen delivery.
- Consider agents that reverse antiplatelet medications, such as desmopressin, or inhibit fibrinolysis, such as tranexamic acid.[61]

In life-threatening bleeding, such as intracranial hemorrhage, administer

Table 13. Factor Xa Inhibitors[7,62,63]

	Rivaroxaban	Apixaban	Edoxaban
Oral bioavailability	Dose dependent: 10 mg tablets: 80-100% not affected by food 15 mg and 20 mg tablets: about 66% without food and increases > 90% with food Peak serum concentrations 2-4 h	Approximately 50%, not affected by food Peak serum concentrations 3-4 h	Approximately 62%, not affected by food Peak serum concentrations 1-2 h
Serum protein binding	92-95%	87%	55%
Metabolism	Oxidative degradation by hepatic cytochrome P450 isoenzymes CYP3A4, CYP3A5, and CYP2J2	About 25% with O-methylation and hydroxylation by hepatic cytochrome P450, primarily isoenzyme CYP3A4	Minimal, < 15% via hydrolysis, conjugation, or oxidation
Elimination	About one-third excreted unchanged in the urine, about one-third excreted as inactive metabolites in the urine, and one-third excreted as inactive metabolites in feces	About 30% in urine and 70% in feces	50% in urine and 50% in feces
Elimination half-life	5-9 h	12 h	10-14 h
Typical initial dosing (normal renal function)	Treatment of DVT and PE: 15 mg PO BID for daily for 21 days, then transition to 20 mg PO once daily with food for remaining treatment Reduction in risk or recurrent DVT or PE: 20 mg PO once daily with food Stroke prevention in non-valvular AF: 20 mg PO once daily with evening meal	Treatment of DVT and PE: 10 mg PO BID for daily for 7 days, then transition to 5 mg PO BID for remaining treatment Reduction in risk or recurrent DVT or PE: 2.5 mg PO BID Stroke prevention in non-valvular AF: 5 mg PO BID	Treatment of DVT and PE: 60 mg PO once daily following 5-10 days of initial therapy with a parenteral anticoagulant (for CrCL > 50 mL/min) Stroke prevention in non-valvular AF: 60 mg PO once daily (for CrCL between 50 and 95 mL/min)

Table 14. Suggestions for Rapid Reversal of Rivaroxaban-, Apixaban-, or Edoxaban-induced Life-threatening Hemorrhage

Agent	Dose
Andexanet alfa*	400 mg IV bolus at 30 mg/min followed by continuous infusion at 8 microgram /min for 120 min* (low-dose regimen)
OR	
Activated Prothrombin Complex Concentrate (aPCC)	50 units/kg IV, may repeat in 2-4 hours
OR	
4-Factor Prothrombin Complex Concentrate (4-factor PCC)	25 units/kg IV, may repeat in 2-4 hours
OR	
Coagulation Factor VIIa (recombinant) (rFVIIa)	90 micrograms/kg IV every 2 hours until hemostasis is achieved
*Proposed dose suggested by Phase III trials	

the emergency reversal agent without waiting for coagulation test results. In non-life-threatening bleeding, obtain the appropriate test to determine if there is a clinically relevant anticoagulant effect from the reported oral anticoagulant and to guide therapy.[50,56,61] (*See Table 15.*)

Future Directions

Many of the studies supporting anticoagulation reversal are based on ability to correct abnormal coagulation tests. Although the different coagulation tests are a good measurement of coagulability, more research needs to be directed toward patient-centered outcomes, such as duration of hospitalization and mortality. Intracranial bleeding is the most devastating complication from oral anticoagulants, and research needs to target neurological outcomes, both short- and long-term, of patients who present with a bleed while on anticoagulation and receive rapid reversal.

There is a targeted therapy for DOAC reversal under study that has the potential to reverse multiple agents.

Table 15. Screening Tests to Assess for Clinically Relevant Anticoagulant Effects

Drug	Best Test	Comment
Warfarin	PT and INR > 1.7	An INR of 1.7 corresponds to approximately 30% of normal coagulation activity[66]
Dabigatran	TT > 15-19 seconds	Sensitive to therapeutic levels of dabigatran[67]
Rivaroxaban	Anti-FXa activity > 0.1 unit/mL	Must be calibrated for rivaroxaban
Apixaban	Anti-FXa activity > 0.1 unit/mL	Must be calibrated for apixaban
Edoxaban	Anti-FXa activity > 0.1 unit/mL	Must be calibrated for edoxaban

Ciraparantag or aripazine is a nonspecific binder of multiple anticoagulants, including dabigatran and the factor Xa inhibitors as well as unfractioned heparin and low-molecular weight heparin.[64]

Conclusion

Warfarin long has been the primary agent for outpatient anticoagulation. The DOACs have several FDA-approved indications, but their use has been somewhat impeded by the lack of a rapid reversal agent.[3,5] Over the past five years, 4-factor PCC has been found useful for rapid reversal of both supratherapeutic INR in warfarin use and laboratory hemostasis in use of DOACs,[1,12,49] but more research needs to be done on patient-centered outcomes.

Case: *There are no established guidelines on whether the provider should rapidly reverse the warfarin-induced anticoagulation in this patient. This is different from hemophilia, for which there are guidelines that "all significant head trauma, with or without hematoma, must be treated promptly with the major dose of factor replacement before any diagnostic tests."*[65] *This patient does not have indications for a life-threatening bleed at the moment, but her chances of deterioration are high given her age and supratherapeutic INR. In this case, she was observed and started to deteriorate and she became obtunded. A repeat head CT showed an intracranial bleed three hours after arrival. Four-factor PCC and IV vitamin K1 were given with rapid correction in her INR. There was no further neurologic deterioration, and subsequent CT scans showed stabilization in the size of the hematoma. The patient made a slow recovery over two weeks and was discharged to a rehabilitation facility.*

References

1. Johansen M, Wikkelsø A, Lunde J, et al. Prothrombin complex concentrate for reversal of vitamin K antagonist treatment in bleeding and non-bleeding patients. *Cochrane Database Syst Rev* 2015;7:CD010555.
2. UNC Health Care. UNC Health Care Guideline: Emergent Anticoagulation Reversal. Available at: www.med.unc.edu/emergmed/files/emergent-anticoagulation-reversal-guideline-unc-healthcare.
3. Gonsalves WI, Pruthi RK, Patnaik MM. The new oral anticoagulants in clinical practice. *Mayo Clin Proc* 2013;88:495-511.
4. Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. *Best Pract Res Clin Haematol* 2013;26:191-202.
5. Siegal DM, Cuker A. Reversal of target-specific oral anticoagulants. *Drug Discov Today* 2014;19:1465-1470.
6. Baumann Kreuziger LM, Keenan JC, Morton CT, Dries DJ. Management of the bleeding patient receiving new oral anticoagulants: A role for prothrombin complex concentrates. *Biomed Res Int* 2014;2014:583794.
7. Savaysa® (edoxaban) Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf.
8. Schein JR, White CM, Nelson WW, et al. Vitamin K antagonist use: Evidence of the difficulty of achieving and maintaining target INR range and subsequent consequences. *Thromb J* 2016;14:14.
9. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: A randomized, plasma-controlled, phase IIIb study. *Circulation* 2013;128:1234-1243.
10. Demeyere R, Gillardin S, Arnout J, Strengers PF. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: A randomized study. *Vox Sang* 2010;99:251–260.
11. Klein L, Petters J, Milner J, Gorlin J. Evaluation of fixed dose 4-factor prothrombin complex concentrate for emergent warfarin reversal. *Am J Emerg Med* 2015;33:1213-1218.
12. Goldstein JN, Refaai MA, Milling TJ Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: A phase 3b, open-label, non-inferiority, randomised trial. *Lancet* 2015;385:2077-2087.
13. Nishijima DK, Dager WE, Schrot RJ, Holmes JF. The efficacy of factor VIIa in emergency department patients with warfarin use and traumatic intracranial hemorrhage. *Acad Emerg Med* 2010;17:244-251.
14. Levi M, Levy JH, Andersen HF, Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med* 2010;363:1791-1800.
15. Dager WE, King JH, Regalia RC, et al. Reversal of elevated international normalized ratios and bleeding with low-dose recombinant activated factor VII in patients receiving warfarin. *Pharmacotherapy* 2006;26:1091-1098.
16. NovoSeven® RT (coagulation Factor VIIa recombinant) Prescribing Information. Available at: http://www.novo-pi.com/novosevenrt.pdf.
17. Coumadin® (warfarin sodium) Prescribing Information. Available at: http://package-inserts.bms.com/pi/pi_coumadin.pdf.
18. Babilonia K, Trujillo T. The role of prothrombin complex concentrates in reversal of target specific anticoagulants. *Thromb J* 2014;12:8.
19. Milling TJ Jr., Refaai MA, Goldstein JN, et al. Thromboembolic events after vitamin K antagonist reversal with 4-factor prothrombin complex concentrate: Exploratory analyses of two randomized, plasma-controlled studies. *Ann Emerg Med* 2016;67:96-105.
20. Lee FM, Chan AK, Lau KK, Chan HH. Reversal of new, factor-specific oral anticoagulants by rFVIIa, prothrombin complex concentrate and activated prothrombin complex concentrate: A review of animal and human studies. *Thromb Res* 2014;133:705-713.
21. Kaatz S, Crowther M. Reversal of target-specific oral anticoagulants. *J Thromb Thrombolysis* 2013;36:195-202.
22. Bebulin® (Factor IX Complex) Nanofiltered and Vapor Heated

Prescribing Information. Available at: http://www.baxalta.com/assets/documents/bebulin_pi.pdf.

23. Kcentra® (Prothrombin Complex Concentrate (Human)) Prescribing Information. Available at : http://labeling.cslbehring.com/PI/US/Kcentra/EN/Kcentra-Prescribing-Information.pdf.
24. Feiba NF (Anti-Inhibitor Coagulant Complex), Nanofiltered and Vapor Heated Prescribing Information. Available at: http://www.feiba.com/us/forms/feiba_nf_pi.pdf.
25. Dentali F, Marchesi C, Pierfranceschi MG, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost* 2011;106:429-438.
26. Holland L, Warkentin TE, Refaai M, et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. *Transfusion* 2009;49:1171-1177.
27. Levi M, Moore KT, Castillejos CF, et al. Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. *J Thromb Haemost* 2014;12:1428-1436.
28. Khorsand N, Kooistra HA, van Hest RM, et al. A systematic review of prothrombin complex concentrate dosing strategies to reverse vitamin K antagonist therapy. *Thromb Res* 2015;135:9-19.
29. Pradaxa® (dabigatran etexilate mesylate) Prescribing Information. Available at: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf.
30. Hankey GJ, Eikelboom JW. Dabigatran etexilate. A new oral thrombin inhibitor. *Circulation* 2011;123:1436-1459.
31. Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: A subgroup analysis of the RE-LY trial. *Ann Intern Med* 2011;155:660-667, W204.
32. Adam SS, McDuffie JR, Ortel TL, Williams JW Jr. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: A systematic review. *Ann Intern Med* 2012;157:796-807.
33. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet* 2014;383:955-962.
34. Tun NM, Oo TH. Prevention and treatment of venous thromboembolism with new oral anticoagulants: A practical update for clinicians. *Thrombosis* 2013;2013:183616.
35. Fox BD, Kahn SR, Langleben D, et al. Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: Direct and adjusted indirect meta-analysis of randomised controlled trials. *BMJ* 2012;345:e7498.
36. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 2015;131:157-164.
37. Camm AJ, Amarenco P, Haas S, et al. XANTUS Investigators. XANTUS: A real-world prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;37:1145-1153.
38. Larsen TB, Rasmussen LH, Skjoth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with strial fibrillation: A prospective nationwide cohort study. *J Am Coll Cardiol* 2013;61:2264-2273
39. Hernandez I, Baik SH, Pinera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Intern Med* 2015;175:18-24.
40. Graham DJ, Reichman ME, Wernecke M, et al. Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. *Circulation* 2015;131:157-164.
41. Romanelli RJ, Nolting L, Dolginsky M, et al. Dabigatran versus warfarin for atrial fibrillation in real-world clinical practice. A systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes* 2016;9:126-134.
42. Eerenberg EE, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: A randomized, placebo-controlled, crossover study in health subjects. *Circulation* 2011;124:1573-1579.
43. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: A randomised crossover ex vivo study in healthy volunteers. *Thromb Haemost* 2012;108:217-224.
44. Khoo TL, Weatherburn C, Kershaw G, et al. The use of FEIBA® in the correction of coagulation abnormalities induced by dabigatran. *Int J Lab Hematol* 2013;35:222–224.
45. van Ryn J, Ruehl D, Priepki H, et al. Reversibility of the anticoagulant effect of high doses of the direct thrombin inhibitor dabigatran by recombinant factor VIIa or activated prothrombin complex concentrate. *Haematologica* 2008;93:A0370.
46. Praxbind® (idarucizumab) Prescribing Information. Available at: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Praxbind/Praxbind.pdf.
47. Glund S, Moschetti V, Norris S, et al. A randomized study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thromb Haemost* 2015;113:943-951.
48. Pollack CV, Reilly PA, Eikelboom J, et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015;373:511-520.
49. Suryanarayan D, Schulman S. Potential antidotes for reversal of old and new oral anticoagulants. *Thromb Res* 2014;133 Suppl 2:S158-S166.
50. Blann AD, Lip GYH. Laboratory monitoring of the non-vitamin K oral anticoagulants. *J Am Coll Cardiol* 2014;64:1140-1142.
51. Murck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. *Clin Pharmacother* 2014;53:1-16.
52. Frost C, Nepal S, Wand J, et al. Safety, pharmacokinetics and pharmacodynamics of multiple oral doses of apixaban, a factor Xa inhibitor, in healthy subjects. *Br J Clin Pharmacol* 2013;76:776-786.
53. Yamahira N, Forst C, Fukase H, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of apixaban in healthy Japanese male subjects. *Int J Clin Pharmacol Ther* 2014;52:564-573.
54. Cuker A, Husseinzadeh H. Laboratory measurement of the anticoagulant activity of edoxaban: a systemic review. *J Thromb Thrombolysis* 2015;39:288-294.
55. Smythe MA, Trujillo T, Fanikos J. Reversal agents for use with direct and indirect anticoagulants. *Am J Health Syst Pharm* 2016;73(Suppl 2):S27-S48.
56. Crowther M, Crowther MA. Antidotes for novel oral anticoagulants. Current status and future potential. *Arterioscler Thromb Vasc Biol* 2015;35:1736-1745.
57. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med* 2015;373:2413-2424.
58. ClinicalTrials.gov. NCT02329327. A study in patients with acute major bleeding to evaluate the ability of andexanet alfa to reverse the anticoagulation effect of direct and indirect oral anticoagulants. Available

at: https://clinicaltrials.gov/ct2/show/NCT02329327?term=andexanet&rank=3.

59. Lu G, Lin J, Curnutte JT, Conley PB. Reversal of heparin-induced anticoagulation by andexanet alfa, a universal antidote for factor Xa inhibitors. Presented at the American Society of Hematology 57th Annual Meeding and Exposition, Dec. 6, 2015. Available at: https://ash.confex.com/ash/2015/webprogram/Paper81760.html.
60. Crowther M, Levy G, Lu G, et al. Reversal of enoxaparin-induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), an antidote for direct and indirect fXa inhibitors — a phase 2 randomized, double-blind, placebo controlled trial. Available at: file:///C:/Users/User/Downloads/ISTH2014%20PTLA%20P2%20Andexanet%20Enox.pdC.
61. Siegel DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacologic reversal agents. *J Thromb Thrombolysis* 2015;39:395-402.
62. Xarelto® (rivaroxaban) Prescribing Information. Available at: https://www.xarelto hcp.com/shared/product/xarelto/prescribing-information.pdf.
63. Eliquis® (apixaban) Prescribing Information. Available at: http://package-inserts.bms.com/pi/pi_eliquis.pdf.
64. Hu TY, Vaidya VR, Asirvatham SJ. Reversing anticoagulant effects of novel oral anticoagulants: Role of ciraparantag, andexanet alfa, and idarucizumab. *Vasc Health Risk Manag* 2016;12:35-44.
65. Emergency Care of Patients with Hemophilia. Available at: https://athn.org/files/resources/athnready/Emergency%20Care%20for%20Patients%20with%20Hemophilia%20FINAL.pdf.
66. Gulati G, Hevelow M, George M, et al. International normalized ratio versus plasma levels of coagulation factors in patients on vitamin K antagonist therapy. *Arch Pathol Lab Med* 2011;135:490-494.
67. Hawes EMN, Deal AM, Funk-Adcock D, et al. Performance of coagulation tests in patients on therapeutic doses of dabigatran: A cross-sectional pharmacodynamic study based on peak and trough plasma levels. *J Thromb Haemost* 2013;11:1493-1502.

CME/CE Questions

1. Which statement regarding warfarin therapy is *not* correct?
   a. Warfarin inhibits the production of four factors involved in the coagulation cascade.
   b. 4-factor Prothrombin Complex Concentrate contains the four factors inhibited by warfarin.
   c. Fresh frozen plasma restores an elevated INR due to warfarin more rapidly than 4-factor PCC or coagulation factor VIIa (recombinant).
   d. Ciprofloxacin prescribed on discharge from the ED has the potential to increase the level of anticoagulation induced by warfarin.
2. Which statement regarding dabigatran is true?
   a. Dabigatran is inhibits factor VIIa.
   b. Activated prothrombin complex concentrate reverses the dabigatran-induced coagulopathy.
   c. Dabigatran is primarily eliminated by hepatic metabolism.
   d. The anticoagulant effect of dabigatran can be monitored by the prothrombin time.
3. Which agent specifically reverses the anticoagulant effect of dabigatran?
   a. Idarucizumab
   b. Phytonadione
   c. Fondaparinux
   d. Adalimumab
4. Which factor is inhibited by rivaroxaban, apixaban, and edoxaban?
   a. Thrombin (factor IIa)
   b. Factor VIIa
   c. Factor VII
   d. Factor Xa
5. Which coagulation factor product is recommended to reverse the anticoagulation effect induced by rivaroxaban?
   a. Fresh frozen plasma
   b. Activated prothrombin complex concentrate
   c. 3-factor prothrombin complex concentrate
   d. None of the above
6. Which of the following would be considered an appropriate circumstance for emergency reversal of rivaroxaban anticoagulation?
   a. Posterior nasal hemorrhage
   b. Orthopedic fixation of fractured tibia in two days
   c. Intracerebral hemorrhage
   d. Lower GI bleed with normal pulse and blood pressure

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the references for further research.
2. Scan the QR code at right or log onto AHCMedia.com and click on My Account. *First-time users must register on the site.*
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

EMERGENCY MEDICINE REPORTS

CME/CE Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

EDITORS

Sandra M. Schneider, MD
Professor, Emergency Medicine
Hofstra North Shore–LIJ School of Medicine
Manhasset, New York
John Peter Smith Hospital
Fort Worth, Texas

J. Stephan Stapczynski, MD
Clinical Professor of Emergency Medicine
Scholarly Projects Advisor
University of Arizona College of Medicine - Phoenix
Emergency Department, Maricopa Integrated Health System

NURSE PLANNER

Paula A. Fessler, RN, MS, NP
Vice President Emergency Medicine Service Line, Northwell Health
New Hyde Park, New York

EDITORIAL BOARD

Paul S. Auerbach, MD, MS, FACEP, FAWM
Redlich Family Professor
Department of Emergency Medicine
Stanford University School of Medicine
Stanford, California

William J. Brady, MD, FACEP, FAAEM
Professor of Emergency Medicine and Medicine, Medical Director, Emergency Preparedness and Response, University of Virginia Operational Medical Director, Albemarle County Fire Rescue, Charlottesville, Virginia; Chief Medical Officer and Medical Director, Allianz Global Assistance

Michael L. Coates, MD, MS
Professor
Department of Family and Community Medicine
Wake Forest University School of Medicine
Winston-Salem, North Carolina

Alasdair K.T. Conn, MD
Chief of Emergency Services
Massachusetts General Hospital
Boston, Massachusetts

Charles L. Emerman, MD
Chairman
Department of Emergency Medicine
MetroHealth Medical Center
Cleveland Clinic Foundation
Cleveland, Ohio

Chad Kessler, MD, MHPE
Deputy Chief of Staff, Durham VAMC
Chairman, VHA Emergency Medicine Field Advisory Committee
Clinical Associate Professor, Departments of Emergency Medicine and Internal Medicine
Duke University School of Medicine
Durham, North Carolina

Kurt Kleinschmidt, MD, FACEP, FACMT
Professor of Surgery/Emergency Medicine
Director, Section of Toxicology
The University of Texas Southwestern Medical Center and Parkland Hospital
Dallas, Texas

Frank LoVecchio, DO, FACEP
Vice-Chair for Research
Medical Director, Samaritan Regional Poison Control Center
Emergency Medicine Department
Maricopa Medical Center
Phoenix, Arizona

Larry B. Mellick, MD, MS, FAAP, FACEP
Professor, Department of Emergency Medicine and Pediatrics
Augusta University
Augusta, Georgia

Paul E. Pepe, MD, MPH, FACEP, FCCM, MACP
Professor of Medicine, Surgery, Pediatrics, Public Health and Chair, Emergency Medicine
The University of Texas Southwestern Medical Center and Parkland Hospital
Dallas, Texas

Charles V. Pollack, Jr., MA, MD, FACEP, FAAEM
Associate Provost for Innovation in Education, Thomas Jefferson University, Director, Jefferson Institute of Emerging Health Professions, Associate Dean for CME and Strategic Partner Alliances, Thomas Jefferson University, Professor and Senior Advisor for Interdisciplinary Research and Clinical Trials, Department of Emergency Medicine, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania

Robert Powers, MD, MPH
Professor of Medicine and Emergency Medicine
University of Virginia
School of Medicine
Charlottesville, Virginia

David J. Robinson, MD, MS, MMM, FACEP
Professor and Vice-Chairman of Emergency Medicine
University of Texas Medical School at Houston
Chief of Emergency Services, LBJ General Hospital, Harris Health System
Houston, Texas

Barry H. Rumack, MD
Professor Emeritus of Pediatrics and Emergency Medicine
University of Colorado School of Medicine
Director Emeritus
Rocky Mountain Poison and Drug Center
Denver, Colorado

David Sklar, MD, FACEP
Professor of Emergency Medicine
Associate Dean, Graduate Medical Education
University of New Mexico School of Medicine
Albuquerque, New Mexico

Gregory A. Volturo, MD, FACEP
Chairman, Department of Emergency Medicine
Professor of Emergency Medicine and Medicine
University of Massachusetts Medical School
Worcester, Massachusetts

Steven M. Winograd, MD, FACEP
St. Barnabas Hospital
Clinical Assistant Professor, Emergency Medicine
New York College of Osteopathic Medicine
Old Westbury, New York

Allan B. Wolfson, MD, FACEP, FACP
Program Director,
Affiliated Residency in Emergency Medicine
Professor of Emergency Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

CME Question Reviewer

Roger Farel, MD
Retired
Newport Beach, CA

© 2016 AHC Media LLC. All rights reserved.

EMERGENCY MEDICINE REPORTS™
(ISSN 0746-2506) is published twice per month by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Editorial & Continuing Education Director: Lee Landenberger

Executive Editor: Shelly Morrow Mark

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Emergency Medicine Reports,*** P.O. Box 550669, Atlanta, GA 30355.

Copyright © 2016 by AHC Media LLC, Atlanta, GA. All rights reserved. Reproduction, distribution, or translation without express written permission is strictly prohibited.

Back issues: $31. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

AHC Media

SUBSCRIBER INFORMATION

CUSTOMER SERVICE: (800) 688-2421

Customer Service Email Address:
Customer.Service@AHCMedia.com

Editorial E-Mail Address:
Shelly.Mark@AHCMedia.com

Online:
AHCMedia.com

SUBSCRIPTION PRICES

1 year with 66 ACEP/72 AMA/36 AAFP Category 1/Prescribed credits: $564

1 year *without* credit: $419
Add $19.99 for shipping & handling

MULTIPLE COPIES:
Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

ACCREDITATION

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 72 *AMA PRA Category 1 Credits™*. Each issue has been designated for a maximum of 3.0 *AMA PRA Category 1 Credits™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Approved by the American College of Emergency Physicians for a maximum of 66.00 hour(s) of ACEP Category I credit.

This Enduring Material activity, Emergency Medicine Reports, has been reviewed and is acceptable for up to 36.00 Prescribed credit(s) by the American Academy of Family Physicians. Term of approval begins 01/01/2016. Term of approval is for one year from this date. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

The American Osteopathic Association has approved this continuing education activity for up to 60 AOA Category 2-B credits.

AHC Media is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 3.0 nursing contact hours using a 60-minute contact hour. Provider approved by the California Board of Registered Nursing, Provider # CEP14749, for 3.0 Contact Hours.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME/CE activity is intended for emergency and family physicians and nurses. It is in effect for 36 months from the date of the publication.

EMERGENCY MEDICINE REPORTS

Oral Anticoagulation Reversal

Stratification of Anticoagulation Reversal in Bleeding Patients

Bleeding Risk	Low-risk Bleeding	Moderate-risk Bleeding	Life-threatening Bleeding
Examples	Simple laceration, abrasion/ skin tear, anterior nasal bleed, hematuria, occult gastrointestinal bleeding	Posterior nasal bleed, compressible bleed not well controlled with pressure	Intracerebral hemorrhage, severe/unstable GI bleed, retroperitoneal hemorrhage, hemodynamic instability
Treatment	Manual, balloon, or tampon compression; withholding anticoagulation; topical pro-hemostatics; oral phytonadione (warfarin-induced bleeding only)	Gray zone: topical therapy vs. reversal agents	Rapid reversal

Warfarin

Oral Absorption	100%, peak serum concentration achieved at 90 min (range 20-240 min)
Serum Protein Binding	98%
Metabolism	Hepatic cytochrome P450: primarily isoenzyme CYP2C9, secondary CYP1A2 and CYP3A4
Elimination	Almost entirely hepatic metabolism
Elimination Half-life	36-42 h (variable based on rate of clotting factor catabolism)
Pharmacologic Action	Competitively inhibits vitamin-K carboxylation of factors II, VII, IX, and X, and proteins C and S
Typical Initial Dosing	2-5 mg PO daily
Monitoring Test	PT with calculated INR Dose adjusted to maintain INR between 2.0 and 3.0 in most circumstances, e.g., stroke prevention in atrial fibrillation and treatment of VTE

Vitamin K Dependent Factors Affected by Warfarin

Prothrombotic Coagulation Factors	Biologic Half-life (Approximate)
Factor X	24-40 h
Factor IX	20-30 h
Factor VII	4-6 h
Factor II (Prothrombin)	60-72 h
Antithrombotic Proteins	**Biologic Half-life (approximate)**
Protein C	8-10 h
Protein S	40-60 h

Clinically Relevant Warfarin Interactions

Increases Anticoagulation, PT, and INR	Decreases Anticoagulation, PT, and INR
Decreased dietary vitamin K	Increased dietary vitamin K
Reduced gut bacteria due to oral antibiotics	Parenteral vitamin K
Drug-induced reduction on hepatic cytochrome P450 isoenzyme activity: such as cotrimoxazole, fluconazole, metronidazole, acyclovir, ciprofloxacin, famotidine, norfloxacin, oral contraceptives, phenylpropanolamine, propranolol, verapamil, alprazolam, clarithromycin, diltiazem, erythromycin, ketoconazole, ranitidine	Drug-induced increase in hepatic cytochrome P450 isoenzyme activity: such as phenobarbital, phenytoin, carbamazepine, primidone, dicloxacillin, nafcillin, rifampin, omeprazole, prednisone Botanicals: Coenzyme Q10, St. John's wort, ginseng
Drugs That Increase Risk of Bleeding Independent of an Increased PT and INR	
Other parenteral or oral anticoagulants: such as unfractionated heparin (UFH), LMWH, dabigatran, rivaroxaban, and apixaban	
Antiplatelet agents: such as aspirin, clopidogrel, and prasugrel	
Nonsteroidal anti-inflammatory drugs	
Serotonin reuptake inhibitors: such as citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine	

Warfarin Reversal Agents

Agent	Contents (Factors)	Onset of Action	Peak Effect	Duration	Major Side Effects
Phytonadione (Vitamin K1)		IV: 2-6 h Oral: 6-12 h	IV: 12-24 h Oral: 24-48 h		IV extravasation
Fresh Frozen Plasma (FFP)	All coagulation factors, albumin, and vWF	Immediate	60 min	Variable	Volume load, TRALI*, TACO**, anaphylaxis
Coagulation Factor VIIa (recombinant)	Factor VII in activated form	Immediate	10 min	6-8 hours	Thrombosis
Prothrombin Complex Concentrate (PCC)	3-factor: II, IX, and X 4-factor: II, VII, IX, X, C, S, AT, and albumin Activated: FVIIa, II, IX, and X	Immediate	10-15 min	6-8 hours	Thrombosis

*TRALI: transfusion-related acute lung injury
**TACO: transfusion-associated circulatory overload

Approximate Composition of Prothrombin Complex Concentrates

	3-factor PCC (Profilnine®) 500 unit vial (20 mL)	4-factor PCC (Kcentra®) 500 unit vial (20 mL)	Activated 4-factor PCC (FEIBA®) 500 unit vial (20 mL)
Thrombin (FII)	24-38 units/mL	20-48 units/mL	1.3 unit/U FEIBA
Factor VII	< 5 units/mL	10-25 units/mL	FVIIa 1.5 unit and FVII 0.9 unit per U FEIBA
Factor IX	24-38 units/mL	20-31 units/mL	1.4 unit/U FEIBA
Factor X	24-38 units/mL	22-60 units/mL	1.1 unit/U FEIBA
Protein C	0	15-45 units/mL	1.1 unit/U FEIBA
Protein S	0	12-38 units/mL	0
Antithrombin	0	0.2-1.5 units/mL	0
FDA approval	Prevention and control of bleeding episodes in adult patients with hemophilia B	Urgent reversal of warfarin-induced coagulopathy in adult patients with acute major bleeding or needing urgent surgery or invasive procedure	Spontaneous bleeding episodes or to cover surgical interventions in hemophilia A or B patients with inhibitors

Approximate Time Course for Warfarin Reversal

Approach	Median Time to Achieve INR < 1.6
Stop daily drug	2-3 days
Oral phytonadione or vitamin K1	24-36 h
Intravenous phytonadione or vitamin K1	8-16 h
Fresh frozen plasma	60 min, limited by volume concerns
4-factor PCC	10-15 min
Coagulation factor VIIa (recombinant)	10 min

Recommendations for Dabigatran-induced Life-threatening Hemorrhage

Agent	Dose
Idarucizumab (Praxbind®)	5 g IV, either bolus injection or infusion
If idarucizumab is not available, consider	
Activated Prothrombin Complex Concentrate (aPCC)	50 units/kg IV, may repeat in 2-4 hours if bleeding continues OR emergency hemodialysis
OR (less preferred)	
Coagulation Factor VIIa (recombinant) (rFVIIa)	90 micrograms/kg IV, may repeat in 2 hours if bleeding continues

Screening Tests to Assess for Clinically Relevant Anticoagulant Effects

Drug	Best Test	Comment
Warfarin	PT and INR > 1.7	An INR of 1.7 corresponds to approximately 30% of normal coagulation activity
Dabigatran	TT > 15-19 seconds	Sensitive to therapeutic levels of dabigatran
Rivaroxaban	Anti-FXa activity > 0.1 unit/mL	Must be calibrated for rivaroxaban
Apixaban	Anti-FXa activity > 0.1 unit/mL	Must be calibrated for apixaban
Edoxaban	Anti-FXa activity > 0.1 unit/mL	Must be calibrated for edoxaban

Suggestions for Rapid Reversal of Rivaroxaban-, Apixaban-, or Edoxaban-induced Life-threatening Hemorrhage

Agent	Dose
Andexanet alfa*	400 mg IV bolus at 30 mg/min followed by continuous infusion at 8 microgram /min for 120 min* (low-dose regimen)
OR	
Activated Prothrombin Complex Concentrate (aPCC)	50 units/kg IV, may repeat in 2-4 hours
OR	
4-Factor Prothrombin Complex Concentrate (4-factor PCC)	25 units/kg IV, may repeat in 2-4 hours
OR	
Coagulation Factor VIIa (recombinant) (rFVIIa)	90 micrograms/kg IV every 2 hours until hemostasis is achieved
*Proposed dose suggested by Phase III trials	

Supplement to *Emergency Medicine Reports*, September 1, 2016: "Oral Anticoagulation Reversal." Authors: Abhi Mehrotra, MD, MBA, FACEP, Vice Chair, Strategic Initiatives & Operations, Medical Director, Hillsborough Campus ED, University of North Carolina Department of Emergency Medicine; Timothy D. Buff, MD, Emergency Medicine, University of North Carolina, Chapel Hill; Leah M. Hatfield, PharmD, BCPS, Lead Clinical Pharmacist Specialist, Emergency Medicine, University of North Carolina Medical Center, Chapel Hill; and Chad S. Kessler, MD, MHPE, Clinical Associate Professor, Emergency Medicine and Internal Medicine, Duke University, Durham, NC.

Emergency Medicine Reports' "Rapid Access Guidelines." Copyright © 2016 AHC Media LLC, Atlanta, GA. Editors: Sandra M. Schneider, MD, FACEP, and J. Stephan Stapczynski, MD. Nurse Planner: Paula A. Fessler, RN, MA, NP. Continuing Education and Editorial Director: Lee Landenberger. Executive Editor: Shelly Morrow Mark. For customer service, call: 1-800-688-2421. This is an educational publication designed to present scientific information and opinion to health care professionals. It does not provide advice regarding medical diagnosis or treatment for any individual case. Not intended for use by the layman.