COAGULATION CONTROVERSIES:
IMPROVING CARE FOR PATIENTS IN THE
EMERGENCY DEPARTMENT AND
CRITICAL CARE ENVIRONMENT AT
RISK FOR THROMBOSIS, EMBOLUS,
AND MAJOR BLEEDING

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COAGULATION CONTROVERSIES:
IMPROVING CARE FOR PATIENTS IN THE EMERGENCY
DEPARTMENT AND CRITICAL CARE ENVIRONMENT AT RISK
FOR THROMBOSIS, EMBOLUS, AND MAJOR BLEEDING

EMCREG-International Monograph
August 2018

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Dear Colleagues,

The Emergency Medicine Cardiac Research and Education Group (EMCREG)-International was established in 1989 as an emergency medicine cardiovascular and neurovascular organization led by experts from the United States, Canada, and across the globe. We now have Steering Committee members from the US, Canada, Australia, Belgium, Brazil, France, Netherlands, New Zealand, Japan, Singapore, Sweden, and the United Kingdom. Now in our 29th year, we remain committed to providing you with the best educational programs and enduring material pieces possible. In addition to our usual Emergency Physician audience, we now reach out to our colleagues in Cardiology, Internal Medicine, Family Medicine, Hospital Medicine, and Critical Care with our EMCREG-International University of Cincinnati College of Medicine Office of Continuing Medical Education (CME) accredited symposia and enduring materials.

In this EMCREG-International Monograph, Coagulation Controversies: Improving Care for Patients in the Emergency Department and Critical Care Environment at Risk for Thrombosis, Embolus, and Major Bleeding, you will find a detailed discussion regarding the treatment of patients requiring anticoagulation and the reversal of anticoagulation for patients with severe bleeding. For emergency physicians, critical care physicians, hospitalists, cardiologists, internists, surgeons, and family physicians, the current approach and disease indications for treatment with anticoagulants such as coumadin, Factor IIa, and Factor Xa inhibitors are particularly relevant. When a patient treated with anticoagulants presents to the Emergency Department, Intensive Care Unit, or Operating Room with severe, uncontrollable bleeding, achieving rapid, controlled hemostasis is critically important to saving the patient’s life.

This EMCREG-International Monograph is divided into two sections. The first section provides a description of the current indications for treatment of patients using oral anticoagulants including coumadin, the Factor IIa (thrombin) inhibitor dabigatran, and Factor Xa inhibitors such as apixaban and rivaroxaban. In the second section of this EMCREG-International Monograph, the treatment of patients presenting to the hospital with major bleeding becomes the focus. The replacement of blood components including red blood cells, platelets, and clotting factors is the critically important initial treatment for these individuals. Reversing the anticoagulated state is also necessary. For patients treated with coumadin, infusion of vitamin K helps to initiate the process of protein synthesis for the vitamin K dependent coagulation proteins II, VII, IX, and X, as well as the anti-thrombotic Protein C and Protein S. Repletion of clotting factors for the patient with fresh frozen plasma (FFP) provides real time ability to slow bleeding. For patients treated with the thrombin inhibitor dabigatran, treatment using the highly specific antibody derived idarucizamab has been demonstrated to reverse the hypocoagulable state for the patient to allow blood clotting. In May 2018, andexanet alfa was approved by the United States (U.S.) Food and Drug Administration to reverse the Factor Xa anticoagulants apixaban and rivaroxaban in patients with major bleeding. Prior to the availability of this highly specific agent, therapy for patients treated with Factor Xa inhibitors presenting with severe bleeding usually included replacement of lost blood components including red blood cells, platelets, and clotting factors as well as prothrombin complex concentrate (PCC). The PCCs are pooled, virus-inactivated concentrates of human clotting factors. Through this EMCREG-International Monograph, clinicians can receive state of the art information which can significantly impact the care of their patients.

It is our sincere hope that you will find this EMCREG-International Monograph on the care of patients requiring anticoagulation and having associated abnormal 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 August 2018 EMCREG-International Monograph. Thank you very much for your interest in EMCREG-International educational initiatives; we hope you visit our website (www.emcreg.org) for future educational events and publications.

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ORAL ANTICOAGULANT MEDICATIONS IN THE ACUTE CARE SETTING: CHARACTERISTICS AND INDICATIONS

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Objectives
1. Discuss the types of anticoagulant agents available for preventing and treating thromboembolic disease.
2. Describe the mechanisms of action of warfarin, dabigatran, and the Factor Xa inhibitors, as well as the advantages and disadvantages of each.
3. List the primary indications for anticoagulant therapy and summarize the results of recent trials comparing oral anticoagulants for some of the major indications.

Introduction

The coagulation cascade, resulting in a vessel-occluding thrombus, is a valuable adaptive response to direct vascular trauma and potential exsanguination. An injury that results in exposed vascular endothelium is met with a rapid chain of events culminating in a mesh of fibrin strands netting aggregated platelets. While traumatic injuries remain a leading cause of morbidity and mortality, a substantial portion of the population is at higher risk for a different form of vessel wall injury due to plaque rupture and chronic inflammation, especially in developed countries with “Western” diets and sedentary lifestyles. In these settings, the coagulation response is no longer therapeutic, but a pathologic entity in and of itself. Likewise, thromboembolism originating from impaired circulatory flow in atrial fibrillation (or in iatrogenic circumstances such as mechanical valve replacements or ventricular assist devices) can be life-threatening. Deep venous thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolic disease (VTE), as well as acute ischemic stroke (AIS), contribute substantially to both health care expenditure and human suffering.

Clinicians have an expanding pharmacologic armamentarium available to treat thromboembolic disease. The early therapies, warfarin and other vitamin K antagonists (VKA), have been joined by a new class of anticoagulants. The non-vitamin K antagonist oral anticoagulants (NOACs, formerly novel oral anticoagulants) consist of one direct thrombin inhibitor (dabigatran) and four Factor Xa inhibitors (apixaban, betrixaban, edoxaban, and rivaroxaban). In this section of the monograph, the various indications, evidence base, and distinguishing characteristics of the VKAs and NOACs will be discussed.

The Agents

Warfarin and Other Vitamin K Antagonists

A detailed discussion of the coagulation cascade is beyond the scope of this work. However, a brief review of any introductory physiology textbook, or internet search, will remind the clinician that multiple clotting factors interact in a sequence of events coalescing into a final common pathway that results in the transformation of Factor X into the active Factor Xa. Factor Xa 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 Factors II, VII, IX, and X. The VKAs impair vitamin K metabolism in the liver, resulting in greatly diminished reserves of these crucial enzymes and subsequent decreased ability to form thrombus. Of note, however, vitamin K is also required to synthesize protein C and protein S, which serve crucial roles in counterbalancing the coagulation cascade by regulating the conversion of prothrombin into thrombin. Protein C and S levels are also greatly diminished with the use of VKAs, leading to a potentially pro-thrombotic state if a VKA were to be initiated as monotherapy. As a result, bridging therapy with a parenteral anticoagulant, usually low molecular weight heparin (LMWH) or unfractionated heparin (UFH), is advised when starting a VKA until therapeutic levels of anticoagulation are achieved. For most conditions, this is represented by an International Normalized Ratio (INR) between two (2) and three (3).

Warfarin, the most common VKA in use in the United States, has a direct half-life of 36 to 42 hours. The effective half-life approaches 96 hours, and is dependent on the liver’s ability to recover synthetic function and produce prothrombin (Factor II).1 The use of supplemental vitamin K and other treatment regimens for recovering hepatic synthetic function and reversing VKA-induced coagulopathy will be discussed in the next section. The VKAs have a vast number of drug interactions with prescription medications, over the counter treatments, nutritional supplements, dietary intake, and alternative/herbal “medicines.”2 The efficacy of anticoagulation may either be potentiated or impaired, depending on the medication in question. In addition, patients with chronic liver disease, end stage renal disease, and advanced age are more sensitive to VKAs. The variability in treatment effect with VKAs is well documented, with studies demonstrating a length of time in the therapeutic range on the order of 55-66%.3,4 The need for frequent monitoring and dose adjustment, especially in the period of VKA initiation, contributes substantially to health care costs and societal burden including time off from work, travel to monitoring tests, etc.

Non-Vitamin K Antagonist Oral Anticoagulants

Dabigatran

Dabigatran is unique in the category of NOACs 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, and the effective half-life after steady state ranges from 12-17 hours. The drug is renally cleared, resulting in increased anticoagulation as renal function decreases. 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. Drug dosing varies with renal function (Table 1).

**Factor Xa Inhibitors**

This class of medications, currently consisting of apixaban, betrixaban, edoxaban, and rivaroxaban, directly inhibit Factor Xa which results in decreased conversion of prothrombin to thrombin. Dosing regimens vary by indication. These drugs are contraindicated in the setting of severe hepatic disease, and caution and dosing adjustments may be advised in patients with renal dysfunction or increased bleeding risk (Table 1). Table 2 lists times to peak effect as well as effective half-lives of the medications. The Factor Xa 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.

Each NOAC produces variable effects on the coagulation assays commonly available in the clinical setting. None have a direct linear relationship with any of the coagulation assays; at best, an abnormal test may be considered relatively specific for the ongoing presence of the anticoagulant, but the absence of abnormality is not sensitive for the absence of anticoagulant effect. In other words, one cannot rely on normal coagulation assays to exclude anticoagulation effects. The sole exception to this is the relationship between dabigatran, the direct thrombin inhibitor, and thrombin time – a normal thrombin time essentially excludes the presence of dabigatran activity.

**Oral Anticoagulant Indications in the Acute Care Setting**

Three of the multiple Food and Drug Administration (FDA) approved indications for oral anticoagulants are of particular interest to the acute care physician: acute VTE treatment, VTE prophylaxis in medical admissions, and thromboembolic prophylaxis in atrial fibrillation. Two others, post-orthopedic surgery VTE prophylaxis and long term VTE recurrence prevention, are less relevant and will not be discussed further in this manuscript.

---

**TABLE 01**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Venous Thromboembolism Treatment</th>
<th>Non-Valvular Atrial Fibrillation Embolism Prophylaxis</th>
<th>Venous Thromboembolism Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Blocks synthesis of vitamin K-dependent factors</td>
<td>Variable, titrated by INR</td>
<td>Variable, titrated by INR</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>CrCl &gt;30 mL/min: 150 mg BID after 5-10 days of parenteral anticoagulation</td>
<td>CrCl &gt; 30 mL/min: 150 mg BID</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Factor Xa inhibitor</td>
<td>10 mg BID for 7 days, then 5 mg BID</td>
<td>5 mg BID</td>
<td>Increased bleeding risk: 2.5 mg BID</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>Factor Xa inhibitor</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>160 mg initial dose, then 80 mg daily CrCl 15-30 mL/min; dose reduction advised</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Factor Xa inhibitor</td>
<td>60 mg daily after 5-10 days of parenteral anticoagulation Increased bleeding risk: 30 mg daily after 10 days of parenteral anticoagulation</td>
<td>60 mg daily CrCl 15-50 mL/min: 30 mg daily</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Factor Xa inhibitor</td>
<td>15 mg BID for 21 days, followed by 20 mg daily CrCl&lt;30 mL/min: do not use</td>
<td>CrCl &gt;50 mL/min: 20 mg daily CrCl 15-50 mL/min: 15 mg daily</td>
<td>Not indicated</td>
</tr>
</tbody>
</table>

* Dose decrease recommended for patients with two of three factors: age ≥ 80 years, body weight ≤ 60 kg, or Cr ≥ 1.5 mg/dL
† 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; INR: International Normalized Ratio.
Betrixaban is the only oral anticoagulant currently in use that is indicated for the prevention of venous thromboembolism (VTE) in medically hospitalized patients. In the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) study, 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. Patients had to be at least 40 years of age and at risk for VTE as a complication: age > 75 years, age > 60 years with a d-dimer twice the upper limit of normal, or age > 40 and elevated d-dimer with a history of either cancer or prior VTE. Patients were randomized to fixed dose enoxaparin during the hospitalization or betrixaban during hospitalization and after discharge for a total treatment course of 35 to 42 days. There were a host of hierarchical and prespecified subgroup analyses; however, the primary outcome of silent or symptomatic VTE occurred in 7% of the overall enoxaparin cohort versus 5.3% of the betrixaban cohort (relative risk, 0.76; 95% confidence interval [CI], 0.63 – 0.92). This absolute risk reduction resulted in a number needed to treat of 59 patients being treated with betrixaban instead of enoxaparin to prevent one primary outcome. The incidences of 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%; relative risk, 1.97; 95% CI, 1.44-2.68).

### Treatment of Acute Venous Thromboembolism

Apixaban, dabigatran, edoxaban, and rivaroxaban have all been studied against VKA for the treatment of acute deep venous thrombosis (DVT) or pulmonary embolism (PE) in a number of trials. The collective experience with these agents is that the NOACs 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 NOACs over VKAs in the treatment of non-cancer associated VTE. Table 3 provides a summary of the landmark trial results for each NOAC. In the U.S., the preferred

<table>
<thead>
<tr>
<th>Drug</th>
<th>Peak Onset</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Peak serum concentration 4 hours after dose, anticoagulant effect noted within 24 hours of first dose</td>
<td>Dependent on time to resynthesize clotting factors (48-72 hours for Factor X)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>2 hours</td>
<td>12 - 14 hours</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.5 - 3.3 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>3 - 4 hours</td>
<td>19 - 27 hours</td>
</tr>
<tr>
<td>Endoxaban</td>
<td>1.5 hours</td>
<td>10 - 14 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2 - 4 hours</td>
<td>5 - 9 hours</td>
</tr>
</tbody>
</table>

* may increase to 11-13 hours in elderly patients

### Comparison of Non-Vitamin K Antagonist Oral Anticoagulants to Vitamin K Antagonists for the Treatment of Venous Thromboembolism*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary Efficacy Endpoint Result</th>
<th>Efficacy Interpretation</th>
<th>Primary Safety Result</th>
<th>Safety Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>RR 0.84; 95% CI, 0.60 – 1.18</td>
<td>Non-inferior</td>
<td>RR 0.44; 95% CI, 0.36 – 0.55</td>
<td>Superior</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>HR 1.09; 95% CI, 0.76 – 1.57</td>
<td>Non-inferior</td>
<td>HR 0.73; 95% CI, 0.49 – 1.11</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>HR 0.89; 95% CI, 0.7 – 1.13</td>
<td>Non-inferior</td>
<td>HR 0.81; 95% CI, 0.71 – 0.94</td>
<td>Superior</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>HR 0.89; 95% CI, 0.66 – 1.19</td>
<td>Non-inferior</td>
<td>HR 0.93; 95% CI, 0.81 – 1.06</td>
<td>Non-inferior</td>
</tr>
</tbody>
</table>

* Relative risks (RR) and hazard ratios (HR) represent non-vitamin K antagonist oral anticoagulants compared to vitamin K antagonists as the reference group.

† Pooled results for RE-COVER and RE-COVER II; ‡ Pooled results for EINSTEIN-PE and EINSTEIN-VTE; CI: confidence interval
agent for an individual patient may depend on which drug is covered by the patient’s insurance (if any). However, one key aspect of drug selection is that 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 reflect this. 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 NOAC therapy for these patients. Likewise, there is insufficient evidence to date with regards to cancer-associated VTE and NOAC therapy; as a result, the standard for this patient population remains long-term LMWH treatment.

Atrial Fibrillation and Stroke Prophylaxis

The incidence and prevalence of atrial fibrillation (AF) increases with age, which also greatly increases the risk of embolic stroke. Anticoagulation decreases the risk of subsequent stroke, and is recommended for patients with atrial fibrillation and risk factors for stroke. The American Heart Association/American College of Cardiology guidelines for atrial fibrillation management recommend risk stratification with a validated tool such as CHADS₂ or CHA₂DS₂VASc (Table 4) and anticoagulation for those patients found to be at risk. A recent large meta-analysis (94,656 patients) examined the composite results of the NOACs versus VKAs for AF prophylaxis and concluded that the balance of the evidence for both safety and efficacy favored NOACs over VKAs, although comparisons could not be directly drawn between individual NOACs. It is clear that there is an opportunity for acute care physicians to initiate anticoagulation in patients presenting with AF and an increased risk profile, although this opportunity is frequently missed.

Conclusion

As a class, the NOACs have shown consistent advantages in safety and efficacy, as well as require less monitoring and have fewer drug interactions and dietary restrictions than VKAs. These advantages are relevant for VTE treatment, VTE prophylaxis, and stroke prophylaxis for AF. Access questions remain, especially in the United States, since payor plans and follow up resources may constrain the ability of the acute care physician to provide these evidence-based therapies.

References


<table>
<thead>
<tr>
<th>Condition</th>
<th>CHADS₂ Score</th>
<th>CHA₂DS₂VASc Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic heart failure</td>
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<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>1</td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
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</tr>
<tr>
<td>Diabetes Mellitus</td>
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<td>1</td>
</tr>
<tr>
<td>Stroke / Transient ischemic attack</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disease (prior myocardial infarction, peripheral artery disease, aortic plaque)</td>
<td>—</td>
<td>1</td>
</tr>
</tbody>
</table>


MANAGEMENT OF BLEEDING COMPLICATIONS ASSOCIATED WITH ORAL ANTICOAGULANTS

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Objectives

1. Discuss the benefits of oral anticoagulation versus risk of bleeding.
2. Discuss the difference between repletion of factors for warfarin-related bleeding and reversal of anticoagulant effect for non-vitamin K antagonist oral anticoagulant-related bleeding.
3. Describe the mechanism of action of the anticoagulant reversal agents, idarucizumab and andexanet alfa.
4. Summarize the specific approaches to the emergency management of bleeding related to warfarin, dabigatran, and Factor Xa inhibitors.

Introduction

There are multiple common indications for chronic oral anticoagulation in contemporary medical practice, including treatment and prevention of venous thromboembolic disease (VTE, inclusive of deep vein thrombosis [DVT] and pulmonary embolism [PE]), prevention of stroke and systemic embolism in atrial fibrillation (AF), and protection against thromboembolic events in patients with mechanical heart valves. As clear as these indications are from an efficacy perspective, it is manifestly impossible to provide anticoagulation to a patient without raising that patient’s risk of bleeding. Even properly prescribed, well-controlled anticoagulation results in a non-physiologic state in which spontaneous bleeding is more likely, and in which the briskness of blood loss from vessel injury or rupture is accelerated. This means that the decision to initiate oral anticoagulation always requires a risk/benefit analysis that is unique to each patient. Often the decision seems one-sided: DVT must be treated; pulmonary embolism must be treated; patients with mechanical heart valves must be protected. There are validated risk scores for AF-related stroke that demonstrate the vast majority of patients with AF will benefit from well-controlled anticoagulation. Still, inhibition of one or more of the body’s intrinsic clotting factors creates a situation where harm may ensue when only benefit is intended.

Oral Anticoagulation and Bleeding Risk

The typical patient with AF likely to benefit from anticoagulation is older and frequently carries more than one comorbid diagnosis, such as renal insufficiency, that increases bleeding risk. The risk of a major bleeding event in AF patients treated with warfarin is 2-3% per year. Above age 75, the risk of intracranial hemorrhage (ICH) in patients taking warfarin increases significantly. Use of a non-vitamin K antagonist oral anticoagulant (NOAC), either the oral antithrombin dabigatran or one of the oral anti-Xa anticoagulants apixaban, edoxaban, or rivaroxaban may decrease bleeding risk by 30% or more overall, and significantly decreases the risk of fatal hemorrhage, in comparison to warfarin. Currently there are no randomized trials that compare one NOAC to another. Only gastrointestinal hemorrhage is more common in NOAC-treated AF patients (with the exception of apixaban) than in those treated with warfarin, but these events are rarely fatal. On the other hand, mortality from warfarin-related ICH is around 40% within a month of the event. Significant bleeding events in patients treated with anticoagulants for VTE are less common because the patients tend to be younger and have fewer comorbidities, but they still occur. Given the aging demographics of healthcare in the United States, more and more patients are on anticoagulation therapy for AF. Similarly, the prevalence of VTE continues to rise, as does the acceptance of more aggressive VTE prophylaxis protocols. Oral anticoagulation-related bleeding is a regular occurrence in the Emergency Department (ED). Fortunately, most episodes are not life-threatening, and the intensity of anticoagulation with warfarin can readily be measured with the International Normalized Ratio (INR) test. Although the INR results can generally be used to guide therapy (Table 1), it should be noted that patients can have significant bleeding, including ICH, with INR values that are not particularly high and are sometimes still in the therapeutic range. Patients taking warfarin who present with complications related to their care are likely to have a supratherapeutic INR without bleeding, abnormal bruising or bleeding gums, or guaiac-positive stools without hemodynamic instability. Epistaxis on warfarin therapy may be a bit more challenging to manage, but typically does not present as a life threat. The usual treatment for such a presentation involves temporary discontinuation of warfarin therapy, often for just a day or two, and local care. With more significant gastrointestinal hemorrhage, transfusion may be required. With severe bleeding cases and with ICH, the need to “reverse” the anticoagulant effects of warfarin is indicated.

Repletion of Vitamin K Dependent Factors

It is a common misperception that vitamin K is an “antidote” for warfarin. Recall that the mechanism of action of warfarin anticoagulation is the prevention of synthesis of effective levels of the coagulation cascade components that require vitamin K, namely Factors II, VII, IX, and X, plus Protein C and Protein S. A patient who is therapeutically anticoagulated on warfarin has basically no activity at the multiple steps in the cascade that require participation of those...
factors. Vitamin K administration merely allows the resumption of production of the factors (Table 1). It takes hours to several days to rebuild physiologic levels of the vitamin K-dependent factors. This is certainly not an adequate response to ICH or other life-threatening hemorrhage. In fact, warfarin-related anticoagulation cannot be reversed. Instead, the levels of deficient factors must be repleted.

Repletion can be accomplished in several ways (Table 2). Traditionally, fresh-frozen plasma (FFP) was the direct repletion method of choice. The FFP approach is limited by four concerns: 1) time for thawing in the acute hemorrhagic situation; 2) patients must be ABO cross-matched before infusion; 3) volume overload, especially in elderly patients who might have limited cardiac reserve and in whom rapid infusion of colloid can cause pulmonary edema; and 4) limited efficacy, for example in a 70 kg patient, one unit of FFP increases most factor concentrations by around 2.5%. An increase in factor levels of at least 10% is usually needed for any significant change in coagulation status, so four units FFP (around 1 liter colloid) is needed for benefit.

The better approach in repleting vitamin K-dependent factors is prothrombin complex concentrate (PCC). The PCCs are pooled, virus-inactivated concentrates of human clotting factors. Four-factor PCCs (4FPCC) contain the vitamin K-dependent coagulation factors (II [prothrombin], VII, IX and X), as well as therapeutically effective concentrations of thrombininhibitors (Proteins C and S). Three-factor PCC (3FPCC) does not contain Factor VII, and in the past some authorities recommended combining 3FPCC with recombinant Factor VIIa, though the efficacy of this approach has not been specifically studied and the combination is expensive. The PCCs are most commonly indicated and used for warfarin reversal. In Europe they are also indicated for treatment and perioperative prophylaxis of bleeding in patients with acquired deficiency of the prothrombin complex coagulation factors (II, VII, IX and X).

A meta-analysis of randomized trials and observational studies demonstrated that PCCs reduced all-cause mortality in warfarin-related hemorrhage compared to FFP, without any significant difference in post-repletion thromboembolic complications. There are suggestive data that in warfarin-associated ICH, PCCs reduce hematoma expansion more than FFP does. The PCCs are preferentially recommended in professional society guidelines.

Repletion of vitamin K-dependent factors in warfarin-associated hemorrhage should be reserved for legitimate life threats, such as exsanguinating blood loss and ICH. There are two immediate con-

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**TABLE 01**  
Warfarin-Related Bleeding Management Based on Urgency

<table>
<thead>
<tr>
<th>Reversal needed in 24-48 hours</th>
<th>Reversal needed in 6-24 hours</th>
<th>Reversal needed emergently</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR 4.5-10 without bleeding:</td>
<td>INR &gt; 10 without bleeding OR</td>
<td>INR &gt; 1.5 AND major bleeding including intracranial hemorrhage:</td>
</tr>
<tr>
<td>• Hold warfarin dose</td>
<td>INR 4.5-10 and minor bleeding:</td>
<td>• Hold warfarin dose</td>
</tr>
<tr>
<td></td>
<td>• Hold warfarin dose</td>
<td>• Give intravenous vitamin K 10mg</td>
</tr>
<tr>
<td></td>
<td>• Give oral vitamin K or intravenous vitamin K 2.5mg</td>
<td>• Clotting factor repletion (see Table 2)</td>
</tr>
</tbody>
</table>

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**TABLE 02**  
Approaches to the Emergency Management of Warfarin-Related Bleeding

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Agent dose</th>
<th>Time to correction of coagulopathy</th>
<th>Best-use scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesize new vitamin K-dependent factors</td>
<td>Intravenous vitamin K 5-10 mg</td>
<td>6-24 hours</td>
<td>Adjunct in life-threatening hemorrhage</td>
</tr>
<tr>
<td>Repletion</td>
<td>Fresh Frozen Plasma - typically 4 units</td>
<td>4-24 hours</td>
<td>Life-threatening hemorrhage: if PCC unavailable</td>
</tr>
<tr>
<td>Repletion</td>
<td>4-Factor PCC Weight-dependent dosing, 25-50 IU/kg</td>
<td>10-30 minutes</td>
<td>Life-threatening hemorrhage: HIGHLY RECOMMENDED if available</td>
</tr>
<tr>
<td>Repletion</td>
<td>3-Factor PCC + recombinant Factor VIIa</td>
<td>10-30 minutes</td>
<td>Life-threatening hemorrhage: more expensive</td>
</tr>
</tbody>
</table>

PCC: prothrombin complex concentrate
cerns that arise from precipitous removal of anticoagulation, whether by repletion in the case of warfarin-related bleeds or by reversal as in the case of NOAC treatment strategies discussed below. The first is that patients who are therapeutically anticoagulated are treated for a good clinical reason, such as high stroke risk, previously demonstrated pathologic clot, or mechanical heart valves. When anticoagulation “protection” is suddenly removed, these patients immediately return to their native (or iatrogenic) prothrombotic state. Although resumption of anticoagulation after repletion/reversal is beyond the scope of this monograph, 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. “Overshoot” thromboembolic complications are unusual after repletion, but are more common after PCC administration than with FFP. There is lower risk with FFP simply because less factor is being administered. Such events are still rare (5-10%) after use of PCCs but are clearly dose-dependent. For that reason it is usually recommended that 4FPC 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.12

Reversal of Non-Vitamin K Antagonist Oral Anticoagulants

The NOACs, as a class, represent a pharmacologic advance over warfarin, which is burdened by inter- and intra-patient variability in effect, multiple drug-drug and drug-diet interactions, and a need for regular monitoring because of its narrow therapeutic index.13 Developed to overcome these limitations, the NOACs have a predictable anticoagulant response that allows for fixed doses without routine coagulation monitoring. In Phase 3 trials including more than 150,000 patients, NOACs were at least as effective as warfarin for stroke prevention in AF and for VTE management, while providing safety advantages. Ongoing observational studies support the efficacy and safety of these agents in routine practice.

Still, bleeding events can occur in patients being treated with NOACs. Recall the initial propositus of this review - it is manifestly impossible to anticoagulate a patient without raising that patient’s risk of bleeding. The perception that the management of bleeding events may be more difficult in patients taking a NOAC than in those taking warfarin is sometimes cited as the reason why some physicians have been slow to incorporate NOAC use into their practices. These concerns have been addressed in the case of dabigatran with the specific reversal agent idarucizumab, which is now approved in the United States. Andexanet alfa has also been recently approved by the U.S. Food and Drug Administration (FDA) as a specific reversal agent for the anti-Xa anticoagulants apixaban and rivaroxaban (Table 3). Please note this change in terminology - these agents reverse the effect of anticoagulants and are not dependent on repletion of factors. This is a critical distinction, because 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 the coagulation cascade. Likewise, patients treated with apixaban, betrixaban, edoxaban, or rivaroxaban have normal circulating levels of Factor X, but Xa is inhibited by the therapy. Andexanet alfa removes the effects of anti-Xa therapy. Repletion in such cases is nonspecific (because “pure” Factor IIa or Factor Xa cannot be administered) and suboptimal, and by definition creates an “overshoot” concern and a risk of thromboembolic complications.

Dabigatran Reversal

Prior to development of a reversal agent, major bleeding among patients treated with dabigatran in Phase 3 randomized trials in AF or VTE was managed at least as successfully as among the patients treated with warfarin; dabigatran-treated patients with major bleeds on therapy had shorter ICU lengths of stay and nominally lower mortality.14 Nonetheless, a specific reversal agent for dabigatran was desirable. Idarucizumab (Figure 1) is a monoclonal Fab fragment antibody to which dabigatran has 350 times higher affinity than to thrombin.15 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 5g, administered intravenously as two vials of 2.5g in rapid succession. Patients with very high dabigatran levels may show evidence of a recurrence of anticoagulation activity between 12 and 24 hours after reversal, due to drug re-entering the circulation from the extravascular space, but a repeat dose should probably only be given if there is concomitant increased bleeding.

The safety and efficacy of idarucizumab as a reversal agent specifically for dabigatran was demonstrated in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) trial of 503 patients, 301 of whom had serious or life-threatening hemorrhage.16 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, 100 to 100). Nearly half of these patients had gastrointestinal 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 removes iatrogenic anticoagulation so that bleeding can be managed in an unfeathered fashion, with mechanical and other pharmacologic means as indicated, and with support from transfusion of blood products as needed.16

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 had no antithrombotic protection on board. There were no serious adverse safety signals.16 Idarucizumab was also studied for, and approved for, reversal of dabigatran anticoagulation prior to an intervention that requires good hemostasis. The interested reader is referred to the original data.16
**Factor Xa Inhibitor Reversal**

Just as the safety of dabigatran was documented in studies versus warfarin in both VTE and AF, the anti-Xa oral anticoagulants are associated with a generally improved safety profile, especially in regard to risk of ICH on treatment. Nonetheless, a specific reversal agent could help streamline the management of those rare patients who do experience major bleeds while on therapy. A class-specific reversal agent, andexanet alfa, was evaluated in initial ANNEXA-A and ANNEXA-R studies and in ANNEXA-4, a large clinical study in patients with major bleeding. These trials have resulted in recent FDA approval for this therapy in patients with major bleeding associated with treatment using the Factor Xa inhibitors apixaban and rivaroxaban. Andexanet alfa (Figure 2) is a decoy Factor Xa 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 binds in a competitive fashion to the Xa inhibitor, but the dose of andexanet alfa must be tailored to the molar concentration of the anticoagulant, and an infusion must be maintained to continue the competitive blockade of the anticoagulant.

In the ongoing ANNEXA-4 study, the bolus dose of andexanet alfa is followed immediately with a 2-hour infusion, in order to avoid rebound of Xa activity that otherwise occurs (Table 4 and Table 5). The interim clinical data from 67 patients show immediate and complete reversal of the anti-Xa activity, although after the end of the infusion some rebound was detected. The hemostatic effect after reversal was rated by the treating clinician as “good” or “excellent” in 79% of the 47 evaluable cases. There were 12 thrombotic complications (18%) during the follow-up of 30 days, 4 of which occurred during the first 3 days, but only 1 of those 12 patients had resumed anticoagulation before the event. Andexanet is not currently being studied for reversal prior to invasive procedures. In an update at the March, 2018 American College of Cardiology Scientific Session, data were presented on the ANNEXA-4 trial through October 20, 2017 which supported the previous interim analysis. In 132 major adjudicated severe bleeds, 109 achieved “excellent” or “good” hemostasis (83%; 95%CI 76-89%). From a safety perspective, thrombotic events occurred in 6 patients (2.6%) by 3 days and in 24 (11%) by 30 days. Therapeutic anticoagulation had resumed in only 9 patients before a thrombotic event occurred. Until andexanet alfa became available, PCC served as a possible
### TABLE 03: Approaches to the Emergency Management of Non-Vitamin K Antagonist Oral Anticoagulant (NOAC)-Related Bleeding

<table>
<thead>
<tr>
<th>Bleed severity</th>
<th>Dabigatran-associated</th>
<th>Anti-Xa-associated (apixaban, rivaroxaban)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor, patient stable</td>
<td>• No specific action required, but evaluate for contributing causes (NSAIDs, correct dosing, etc)</td>
<td>• No specific action required, but evaluate for contributing causes (NSAIDs, correct dosing, etc)</td>
</tr>
<tr>
<td>Clinically relevant but not major, patient stable</td>
<td>• Hold one or more doses</td>
<td>• Hold one or more doses</td>
</tr>
<tr>
<td>Major bleed but not life-threatening</td>
<td>• Hold dose • Supportive measures</td>
<td>• Hold dose • Supportive measures</td>
</tr>
<tr>
<td>Life-threatening bleed, including any intracranial bleed</td>
<td>• Hold dose • Supportive measures • Idarucizumab 5g intravenously</td>
<td>• Hold dose • Supportive measures • Andexanet alfa - Factor Xa agent specific therapy with dosing noted in Tables 4 and 5</td>
</tr>
</tbody>
</table>

NSAIDs: non-steroidal anti-inflammatory drugs

### TABLE 04: Andexanet Alfa Dosing Regimens

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

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

### TABLE 05: Andexanet Alfa Dose Based on Rivaroxaban or Apixaban Dose (Timing of Factor Xa Inhibitor Last Dose Before Andexanet Alfa Initiation)

<table>
<thead>
<tr>
<th>FXa Inhibitor</th>
<th>FXa Inhibitor Last Dose</th>
<th>&lt; 8 Hours or Unknown</th>
<th>≥ 8 Hours</th>
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</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>≤ 10 mg</td>
<td>Low Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>&gt; 10 mg / Unknown</td>
<td>High Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>≤ 5 mg</td>
<td>Low Dose</td>
<td>Low Dose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>&gt; 5 mg / Unknown</td>
<td>High Dose</td>
<td>Low Dose</td>
</tr>
</tbody>
</table>
alternative for the management of life-threatening bleeding associated with anti-Xa treatment. PCC reverses abnormal laboratory parameters (prothrombin time and endogenous thrombin potential) in human volunteers after taking high doses of rivaroxaban and apixaban.19,20,21 This is not an intuitive approach in managing patients who do not have deficient levels of Factor Xa or any of the other constituents of PCC. For this reason, treatment of anti-Xa-related bleeding with PCC is associated with a risk of post-repletion thromboembolic complications.

Conclusion

In summary, management of severe or life-threatening bleeding complications associated with oral anticoagulation is not commonly required in the acute care setting. With the exception of major gastrointestinal bleeds, hemorrhagic risk is notably lower with NOACs than with warfarin. With any oral anticoagulation agent, minor or “nuisance” bleeding is most common and can be managed without repletion/reversal. Standard protocols exist now for the management of major bleeding associated with warfarin and dabigatran, and with FDA approval of a specific reversal agent for the anti-Xa agents apixaban and rivaroxaban, treatment pathways for reversal in patients with major bleeding will soon be available. These class-specific approaches should be instituted in hospital-level protocols and the necessary treatment agents should be readily available in the ED, the Intensive Care Unit, and the Operating Room. Since the reversal agents for the thrombin inhibitor dabigatran and the Factor Xa inhibitors apixaban and rivaroxaban are scarce and expensive resources for any hospital care environment, acute care physicians should prudently use these important new therapies.

References


Continuing Medical Education Post-Test Answer Form and Evaluation

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1. Which of the following medications is a direct thrombin inhibitor?
   A. Apixaban  
   B. Betrixaban  
   C. Dabigatran  
   D. Warfarin

2. Which of the following coagulation factors is NOT vitamin K-dependent?
   A. Factor II  
   B. Factor IX  
   C. Factor X  
   D. Factor XI

3. All of the following statements regarding Factor Xa inhibitors are true EXCEPT:
   A. The absence of abnormality on coagulation assays is not sensitive for the absence of anticoagulant effect.  
   B. Inhibition of Factor Xa directly results in decreased conversion of fibrinogen to fibrin.  
   C. Dosing regimens may vary with renal function.  
   D. Factor Xa inhibitors are at least non-inferior to vitamin K antagonists in safety and efficacy outcomes for the treatment of acute venous thromboembolism.

4. Close monitoring and dose adjustment are most important when treating with:
   A. Warfarin  
   B. Dabigatran  
   C. Betrixaban  
   D. Rivaroxaban

5. All of the following statements regarding atrial fibrillation and stroke prophylaxis are true EXCEPT?
   A. Patients with atrial fibrillation and risk factors for acute ischemic stroke (AIS) should be treated with anticoagulants.  
   B. The American Heart Association/American College of Cardiology guidelines for atrial fibrillation recommend risk stratification with a validated tool such as CHADS2.  
   C. The balance of the evidence for safety and efficacy favors vitamin K antagonists over non-vitamin K antagonist anticoagulants for AIS prophylaxis in patients with atrial fibrillation.  
   D. Atrial fibrillation and embolic stroke both increase in incidence with age.

6. A patient with warfarin-related life-threatening bleeding may be treated with all of the following EXCEPT:
   A. Vitamin K  
   B. Fresh frozen plasma  
   C. Prothrombin complex concentrate  
   D. Andexanet alfa

7. All of the following are concerns with administration of fresh frozen plasma for the repletion of clotting factors in a patient who is anticoagulated on warfarin EXCEPT:
   A. Volume overload and pulmonary edema  
   B. Hepatic failure  
   C. Time for thawing  
   D. Limited efficacy

8. In the RE-VERSE AD study, administration of idarucizumab produced a median maximum percentage reversal of dabigatran of:
   A. 50%  
   B. 75%  
   C. 90%  
   D. 100%

9. The recommended dosing of andexanet alfa is based on all of the following EXCEPT:
   A. The specific Factor Xa inhibitor  
   B. The dose of Factor Xa inhibitor  
   C. The patient’s renal function  
   D. The time since the patient’s last dose of Factor Xa inhibitor

10. All of the following statements regarding treatment with andexanet alfa are true EXCEPT:
    A. It competitively blocks the Xa inhibitor.  
    B. It lacks biologic activity in the coagulation cascade.  
    C. It is administered as two intravenous doses in rapid succession.  
    D. Some rebound anti-Xa activity may occur.

(Answer sheet next page)
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<th>3</th>
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<td>3</td>
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<td>5</td>
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