Emergency Department Management Of Patients On Novel Oral Anticoagulant Agents

Abstract

The era in which vitamin K antagonists were the only option for long-term anticoagulation has ended. Patients now have multiple treatment options for prophylaxis for nonvalvular atrial fibrillation and prevention and treatment for venous thromboembolism. Novel oral anticoagulants, consisting of direct thrombin inhibitors and factor Xa inhibitors, are a diverse group of agents that have reduced medication and food interactions compared to warfarin, and they eliminate the need for frequent monitoring. However, patients presenting with novel oral anticoagulant-associated bleeding emergencies represent a diagnostic and therapeutic challenge due to the lack of access to appropriate laboratory testing modalities or well-validated reversal agents. Following the treatment path appropriate for vitamin K antagonists is ineffective and potentially harmful, making novel assays and antidotes necessary. This review examines the use on the use and risks of enriched clotting factor preparations as well as the clinical and laboratory evaluation that will guide their management.
Case Presentations

Your first patient of the evening is a 78-year-old woman who had a witnessed mechanical fall at home approximately 3 hours prior to arrival. She reports a mild frontal headache, and her family reports that she is “just not acting right.” She takes dabigatran for stroke prophylaxis, given her nonvalvular atrial fibrillation. She is neurologically intact on your examination and is oriented to person, place, and time. The CT of her head, however, shows a 5-mm intraparenchymal hemorrhage. Her PTT is 64 seconds, and her INR is 1.5. You wonder about the relevance of her coagulation studies, what the risk of deterioration is, and whether there is anything available to reverse her anticoagulation.

As you leave your first patient, you are called to the resuscitation room to evaluate a 62-year-old man who was the unrestrained driver in a high-speed motor vehicle crash. He is currently taking rivaroxaban for treatment of a pulmonary embolism that was diagnosed 2 months ago. He is hemodynamically stable and has a GCS score of 15. He has scattered abrasions and tenderness without obvious deformities to his head, chest wall, or upper extremities. His abdomen is soft, but he is diffusely tender and guards his abdomen involuntarily. Your FAST exam demonstrates free fluid in Morison’s pouch, and a CT shows a grade 2 liver laceration. His INR is 1.4. You want to transfer him to a Level 1 trauma center, but you wonder what the likelihood of progression of his injury is. You also wonder what the best practice is to mitigate the potential for deterioration.

True to form, your third patient is yet another hematologic challenge: a 68-year-old man with a recent history of coronary artery disease and a distant history of gastric ulcer who was recently placed on warfarin for a deep vein thrombosis. He presents today to your ED after 6 days of progressive weakness, dyspnea on exertion, and melena stools. Immediately prior to arrival, he had a syncopal episode, but he has awoken by the time he is brought in by EMS. His triage heart rate is 100 beats/min, and his blood pressure is 92/54 mm Hg. He looks pale, and his stool is tarry and guaiac positive. His initial hematocrit is 23.1%, and his INR is 2.4. Once again, you find yourself wondering what the management options available in treating this patient are.

Introduction

Anticoagulant medications are commonly prescribed in the United States, with 4.2 million Americans taking anticoagulants in 2007. From 2002 to 2007, 3% of all patients and 9% of patients aged > 65 years presenting to trauma centers were anticoagulated. Given the aging population in the United States, the number of patients on anticoagulants is likely to continue to grow. While the risk of major bleeding in anticoagulated patients varies based on the specific agents, many of these patients will initially present to an emergency department (ED) for evaluation in the setting of a major bleeding episode. It is incumbent upon emergency clinicians to be familiar with the management and the risks of patients suffering major bleeding episodes while taking anticoagulants.

Recently, a new generation of oral anticoagulants has entered the marketplace. They provide anticoagulation that is at least noninferior to warfarin for many indications (most notably stroke prophylaxis for patients with atrial fibrillation as well as treatment of deep vein thrombosis) while avoiding the need for frequent monitoring. These agents, which include rivaroxaban, apixaban, and dabigatran, work distally on the common pathway of the coagulation cascade by directly antagonizing the action of either factor Xa or thrombin. (See Figure 1.) However, as these agents interact in a stoichiometric manner to inhibit the target clotting factors, mere replenishment of physiological levels of these clotting factors—which many physicians are used to doing in order to reverse warfarin—is an inadequate reversal strategy. Fortunately, there are agents now available that allow for replacement of clotting factors to levels that far exceed baseline physiological levels and may be capable of overcoming the inhibition caused by the novel oral anticoagulants (NOACs). However, as a function of their ability to provide supraphysiologic levels of clotting factors, these agents may also increase the risks of arterial and venous thromboembolism. This interplay between high levels of pharmacologic inhibitors and the exogenous application of replacement factors in the setting of life-threatening bleeding in the ED creates a complex balance focused on hemostasis between hemorrhage and thrombosis.

Figure 1. Clotting Cascade With Location Of Action For Major Classes Of Agents

<table>
<thead>
<tr>
<th>Clotting Cascade With Location Of Action For Major Classes Of Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>XII → XIIa</td>
</tr>
<tr>
<td>XI → Xa</td>
</tr>
<tr>
<td>IX → IXa</td>
</tr>
<tr>
<td>VIII → VIIIa</td>
</tr>
<tr>
<td>VII → VIIa</td>
</tr>
<tr>
<td>II (Prothrombin) → IIa (Thrombin)</td>
</tr>
<tr>
<td>Fibrinogen → Fibrin</td>
</tr>
<tr>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>Apixaban</td>
</tr>
<tr>
<td>Dabigatran</td>
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</tbody>
</table>
The distinction between the NOACs and warfarin is crucial. Across virtually all published studies, NOACs appear to have a 20% to 50% reduced overall risk of major bleeding when compared to warfarin. In a large industry-funded study, major bleeding events occurred at a rate of 3.09% per year in patients taking warfarin as compared to 2.13% per year in patients on apixaban. In a subset analysis, rates of hemorrhagic stroke in this study were 0.24% per year in the apixaban group and 0.47% per year in the warfarin group. Rates of major bleeding with rivaroxaban and dabigatran appear to be similar to that of apixaban when compared to warfarin. Despite their differences in bleeding rates, mortality appears to be similar between warfarin and the NOACs.

For more information about the general management of the anticoagulated patient, see the January 2011 issue of Emergency Medicine Practice, “An Evidence-Based Approach To Managing The Anticoagulated Patient In The Emergency Department.”

Note: a list of selected abbreviations used in this article is included on page 15.

Critical Appraisal Of The Literature

A search of PubMed was carried out using multiple combinations of the following keywords: anticoagulation, emergency department, reversal, hemorrhage, dabigatran, rivaroxaban, apixaban, warfarin, prothrombin complex concentrate, factor VIII inhibitor bypass activity, recombinant factor VIIa, and fresh frozen plasma. Over 200 articles as well as the Cochrane Database of Systematic Reviews were reviewed, which served as the foundation for this issue. Due to the limited availability of clinical research addressing the fundamental questions regarding the use and reversal of the NOACs, we have included basic science research, including both in vitro and small animal models, as the foundation for this review.

Pathophysiology

Control of coagulation in the human body is a delicate balance between hemorrhage and thrombosis that is mediated by an extensive number of procoagulant and anticoagulant proteins. Pathological states that lead to an increased risk of thrombosis can occur through either an imbalance in clotting activity (such as in factor V Leiden thrombophilia) or a mechanical stimulus (such as vessel injury or the presence of atrial fibrillation or a mechanical cardiac valve). Traditionally, the disproportionate risk toward thrombosis in these disease states has been mitigated by administration of vitamin K antagonists (VKAs). These agents, most notably warfarin (and, to a lesser extent, acenocoumarol and phenprocoumon, both more commonly used in Europe), inhibit the activation of vitamin K in the liver, which leads to a reduction in the production of vitamin K-dependent clotting factors II, VII, IX, and X as well as the anticoagulant proteins C and S. These VKAs are highly effective anticoagulants that inhibit the intrinsic and extrinsic pathways as well as the common distal pathway in the coagulation cascade. Importantly, while VKAs reduce the quantity of circulating vitamin K-dependent clotting factors, those factors that are present are fully active, and reversal of the effect of these VKAs simply requires restoration of physiological levels of these clotting factors. Unfortunately, VKAs are plagued by a host of complicating attributes, including many drug and herbal interactions (see Table 1) and narrow therapeutic windows, the combination of which necessitates frequent monitoring.

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Clinical Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Inhibits CYP2C9</td>
<td>NA</td>
</tr>
<tr>
<td>Sweet clover</td>
<td>Increases anticoagulation</td>
<td>Contains warfarin derivatives</td>
</tr>
<tr>
<td>Ginger</td>
<td>Reduces platelet aggregation</td>
<td>Inhibits thromboxane</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Reduces platelet aggregation</td>
<td>Increases the risk of serious bleeding</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Decreases anticoagulation</td>
<td>Increases the risk of thrombotic complications</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Increases anticoagulation</td>
<td>No effect if &lt; 400 U/day</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Decreases anticoagulation</td>
<td>Decreases INR by approximately half</td>
</tr>
</tbody>
</table>

Abbreviations: CYP2C9, cytochrome P450 2C9; INR, international normalized ratio; NA, not applicable.
Mechanisms And Comparison Of Anticoagulants

Warfarin
While not the focus of this article, warfarin merits a brief mention. It is a direct VKA and prevents the synthesis of vitamin K-dependent clotting factors in the liver. The factors II, VII, IX, and X, as well as the anticoagulant proteins C and S, are significantly reduced after warfarin administration. The important distinction between warfarin and the NOACs discussed here is that warfarin-induced coagulopathy results from a significant reduction in clotting factors, while the levels of clotting factors present after administration of the NOACs is normal; their activity is being limited in a stoichiometric relationship with their inhibitors. Restoration of physiological levels of clotting factors through administration of fresh frozen plasma and vitamin K is sufficient to reverse warfarin-induced coagulopathy, but this is inadequate for patients taking NOACs. However, due to the current paucity of data available regarding the NOACs, we often rely on studies conducted in patients taking warfarin to make management recommendations. While this may generally hold true for risk stratification, it is important to note that the mechanism of these agents (and therefore the management of these patients) is different and to avoid the risk of overgeneralization.

Direct Thrombin Inhibitors
The direct thrombin inhibitors prevent conversion of fibrinogen into fibrin by thrombin. Working at the distal end of the coagulation cascade, these agents are highly effective anticoagulants. Dabigatran, the model oral agent in this class, has a time of onset of 2 hours, has an elimination half-life of 12 to 14 hours, and is principally excreted unchanged by the renal system. (See Table 2.) There is no P450 metabolism, and there are no known food interactions. Although there is no age-specific decrease in metabolism, age-associated decreases in renal function will potentiate dabigatran’s effects. Dabigatran does cause a linear elevation in prothrombin time (PT) and thrombin clotting time (thrombin time) and a nonlinear elevation in activated partial thromboplastin time (aPTT), although none of these tests display sufficient accuracy for determination of therapeutic levels.7

In the Re-Ly (Randomized Evaluation of Long-term Anticoagulant Therapy) Trial, which was a randomized double-blind noninferiority study of 18,113 patients published in 2009, dabigatran demonstrated dose-dependent clinical equipoise or superiority in the prevention of stroke in patients with atrial fibrillation.5 Rates of major bleeding were reduced at the lower dabigatran dose and equivalent at the higher dose. There were dose-independent reductions in hemorrhagic stroke risk. Mortality rates in patients taking dabigatran and warfarin were similar.

Although still relatively new on the market, much more is known about the complications of dabigatran use as compared to the Xa inhibitors. It appears that patients aged > 70 years as well as patients with renal insufficiency are more likely to have major bleeding events while on dabigatran for atrial fibrillation and that these events are more likely to be related to gastrointestinal bleeding than intracranial hemorrhage.8,9 While the incidence of major bleeding is reduced (compared to warfarin) when dabigatran is taken for atrial fibrillation, it appears, from early reports, that mortality rates are similar.8 Furthermore, surviving patients with major bleeding on dabigatran for atrial fibrillation appear to have a more benign clinical course with lower transfusion requirements and shorter hospital length of stay (potentially related to the shorter biological half-life of dabigatran as compared to warfarin).

Notably, these data apply only to patients on dabigatran for atrial fibrillation. A recent phase II manufacturer-sponsored study evaluating the use of dabigatran in patients with mechanical heart valves was halted prematurely after enrollment of only 252 patients when an interim analysis demonstrated that the patients on dabigatran had an increased incidence of ischemic or unspecified strokes (5% vs 0) and major bleeding (4% vs 2%) than patients on warfarin.10 Thus, dabigatran’s noninferiority to warfarin in patients with atrial fibrillation should not be extrapolated to other indications.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade Name</th>
<th>Mechanism</th>
<th>FDA-Approved Indications</th>
<th>Time to Maximum Onset (h)</th>
<th>Half-Life (h)</th>
<th>% Protein Binding</th>
<th>% Renal Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Pradaxa®</td>
<td>Direct thrombin inhibitor</td>
<td>NVAF</td>
<td>2</td>
<td>12-15</td>
<td>35</td>
<td>80</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xarelto®</td>
<td>Xa inhibitor</td>
<td>NVAF, VTE prophylaxis and treatment</td>
<td>3</td>
<td>6-9</td>
<td>94</td>
<td>66</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Eliquis®</td>
<td>Xa inhibitor</td>
<td>NVAF</td>
<td>3</td>
<td>9-14</td>
<td>87</td>
<td>66</td>
</tr>
</tbody>
</table>

Abbreviations: FDA, United States Food and Drug Administration; NVAF, nonvalvular atrial fibrillation; VTE, venous thromboembolism.
Direct Factor Xa Inhibitors

Factor Xa inhibitors prevent the conversion of prothrombin to thrombin, working a step prior to the direct thrombin inhibitors in the coagulation cascade. There are currently 2 oral Xa inhibitors available in the United States: rivaroxaban and apixaban. (See Table 2.) This class of medications is a new entrant into the armamentarium of anticoagulants, with rivaroxaban being the first to obtain United States Food and Drug Administration (FDA) approval (in 2011) for stroke prophylaxis from nonvalvular atrial fibrillation.

Rivaroxaban

FDA approval of rivaroxaban was expanded in 2012 to include venous thromboembolism treatment and prophylaxis. The initial approval was supported by data from the ROCKET-AF study, a randomized double-blind trial of 14,264 patients with nonvalvular atrial fibrillation, which demonstrated the noninferiority of rivaroxaban as compared to warfarin for the prevention of stroke in nonvalvular atrial fibrillation. Rates of major bleeding were similar between groups; however, there were fewer intracranial hemorrhage and fatal bleeding episodes in patients taking rivaroxaban as compared to those taking warfarin. Rivaroxaban dosing is 10 to 20 mg by mouth 1 time per day, depending on the indication.

Rivaroxaban has a time to maximum onset of 3 hours, after dosing, and a terminal half-life of 6 to 9 hours. Clearance is, by roughly equal parts, hepatic and renal metabolism as well as renal excretion of the remaining unmetabolized drug, and diminished renal function does reduce clearance. However, patients with moderate renal failure taking renal doses of rivaroxaban (15 mg vs the 20 mg oral standard dose) still appear to have lower rates of fatal bleeding compared to patients taking warfarin. Rivaroxaban increased the PT and PTT in healthy adults and patients undergoing orthopedic surgery; however, the results are variable and reagent-dependent, making monitoring of therapeutic levels with these assays unreliable.

Apixaban

The second of the oral factor Xa inhibitors to be approved by the FDA was apixaban. In a large prospective study published in 2011 of patients with chronic atrial fibrillation, apixaban 5 mg twice per day reduced the rate of stroke or systemic embolism over warfarin (target INR: 2-3) from 1.6% to 1.27% (median follow-up, 1.8 years). Furthermore, this same study demonstrated a mortality benefit for patients on apixaban, with all-cause mortality for patients on apixaban being 3.54% as compared to 3.94% for patients on warfarin. Apixaban has an onset time of approximately 3 hours and a terminal half-life of 12 to 13 hours. The drug is excreted in the feces and the urine, and approximately half of it is excreted unchanged. Apixaban, like rivaroxaban, prolongs the PT and aPTT; however, the effect is not consistent or predictable enough to be used to monitor the therapeutic range of the drug or its propensity for causing bleeding complications.

Edoxaban

The most recently developed factor Xa inhibitor is edoxaban, which was approved in Japan in 2011 for deep vein thrombosis prophylaxis and is currently being evaluated by the FDA. A recently published large phase III randomized double-blind trial demonstrated that edoxaban 60 mg daily (or 30 mg daily in patients with reduced creatinine clearance or weight < 60 kg) was noninferior to warfarin for the treatment of patients with deep vein thrombosis and pulmonary embolism. The primary outcome of recurrent symptomatic thromboembolism occurred in 3.2% of the edoxaban group and 3.5% of the warfarin group. The patients taking edoxaban also had a significantly lower incidence of major or clinically relevant nonmajor bleeding (8.5% in the edoxaban group vs 10.3% in the warfarin group). Edoxaban has an onset time of 1 to 2 hours, has a terminal half-life of 6 to 11 hours, and prolongs the PT and aPTT. However, at the time of this article’s publication, edoxaban is not approved for use in the United States.

Prehospital Evaluation And Management

Prehospital evaluation and management of patients with bleeding associated with NOACs are based on general principles of hemorrhage control and triage to the appropriate receiving facility that are commensurate with the patient’s increased risk of complications and potential need for advanced surgical or hematological consultation. Current emergency medical services (EMS) protocols reflect the increased risk profile for anticoagulated patients, with some systems recommending triage to a trauma center for these patients independent of their clinical presentation or mechanism of injury. EMS recognition of the patient’s use of NOACs is, however, a necessary prerequisite for the appropriate treatment of patients with hemorrhage using NOACs, so medical directors should incorporate education regarding the latest NOACs into their curricula.

Emergency Department Evaluation

History And Physical Examination

The initial evaluation of patients taking NOACs involves an enhanced history and physical exami-
nation. (See Table 3.) Beyond the traditional ED workup, particular attention should be given to questions that allow for risk stratification and, potentially, the opportunity to change the management of the anticoagulated patient. The initial focus should be on identifying areas of potential occult hemorrhage. This should include a discussion about the location of pain and the injury mechanism (if applicable) as well as an examination for signs of bleeding or supratherapeutic coagulopathy, which include tenderness on physical examination, presence of bruising that may be suggestive of internal injury, and stool guaiac testing. Testing for fecal occult blood should be performed with a very low threshold, as dabigatran use is associated with an increased risk of gastrointestinal bleeding. Patients with guaiac-positive brown stool should be monitored closely, and reversal of anticoagulation should be considered if the gastrointestinal bleeding becomes life threatening. In a recent relatively small but well-performed ED-based prospective observational study of 138 patients with bleeding complications of either dabigatran or warfarin, 80% of patients presenting with major bleeding episodes while on dabigatran had presented with gastrointestinal bleeding as the site of hemorrhage.

For all patients taking NOACs, it is crucial for the emergency clinician to consider factors that affect the pharmacokinetics and clearance of the NOACs, principally the timing of the last dose and factors affecting renal function, including baseline hydration status, nonsteroidal anti-inflammatory drug (NSAID) use, and underlying renal disease. Finally, it is important to question the patient about factors that may help to dictate the appropriate reversal strategy if one is indicated. These questions primarily center on the risk of thrombosis from concentrated coagulation factors or volume overload from fresh frozen plasma (which is rarely indicated) and should include discussion of any underlying malignancy, previous venous thromboembolism, hypercoagulable state, or congestive heart failure.

### Diagnostic Studies

#### Imaging Studies

**Computed Tomography**

There are currently no good data to guide imaging studies in the workup of patients taking NOACs in whom intracranial hemorrhage is suspected. Until such data exist, emergency clinicians must extrapolate appropriate management pathways from studies focused on warfarin and antiplatelet agents (such as clopidogrel). In the setting of trauma, emergency clinicians should image anticoagulated patients following even minor head injury, current head computed tomography (CT) imaging guidelines (such as the Canadian CT Head Rule or the New Orleans Criteria) are inadequate in the evaluation of the anticoagulated patient, and no alternative criteria exist that have sufficient sensitivity to identify truly low-risk patients who do not need advanced imaging when presenting immediately after injury. Further complicating the ED evaluation, there is a small subset of anticoagulated patients who will have negative initial CT scans, only to present with a clinically significant delayed intracranial hemorrhage in the following hours or days. While some have suggested a protocolized approach (including admission and repeat imaging at 24 hours for all of these patients), this is neither feasible nor cost-effective. A more realistic approach is to obtain head CT imaging on all patients with blunt head injury who are on NOACs and, for those patients with normal imaging, to have a provider make a follow-up phone call in 24 hours to reassess for symptomaticity.

Liberal application of initial neuroimaging in anticoagulated patients following even minor head injury remains the appropriate approach, and we believe that this should be the standard in patients taking NOACs until more data are available to resolve this issue.

In addition to traumatic intracranial hemorrhage, patients on anticoagulants are at an elevated risk of spontaneous intracranial hemorrhage, and emergency clinicians should image anticoagulated patients presenting with signs or symptoms suggestive of intracranial hemorrhage (including severe headache or systolic blood pressure > 220 mm Hg). Despite an absence of evidence regarding the timing of repeat head CT in patients with intracranial hemorrhage, the authors’ practice is to obtain repeat imaging 6 hours after the initial CT that demonstrated intracranial hemorrhage (sooner in cases

<table>
<thead>
<tr>
<th>Table 3. Key Elements From The History And Physical Examination Of Patients On Novel Oral Anticoagulants</th>
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<tbody>
<tr>
<td><strong>History</strong></td>
</tr>
<tr>
<td>• Time and dose of last NOAC</td>
</tr>
<tr>
<td>• Use of additional anticoagulants or antiplatelet agents</td>
</tr>
<tr>
<td>• Use of any nephrotoxins, particularly NSAIDs</td>
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<tr>
<td>• History of renal insufficiency</td>
</tr>
<tr>
<td>• Recent urine output</td>
</tr>
<tr>
<td>• History of venous thromboembolism, malignancy, hypercoagulable state</td>
</tr>
<tr>
<td>• Mechanism of trauma / estimated blood loss (if applicable)</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
</tr>
<tr>
<td>• Vital signs</td>
</tr>
<tr>
<td>• Hydration status (tachycardia, jugular venous pressure, mucous membranes)</td>
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<tr>
<td>• Site of bleeding and presence of active hemorrhage</td>
</tr>
<tr>
<td>• Presence of bruising or epistaxis</td>
</tr>
<tr>
<td>• Stool guaiac testing</td>
</tr>
</tbody>
</table>

Abbreviations: NOAC, novel oral anticoagulant; NSAIDs, nonsteroidal anti-inflammatory drugs.
of neurological decline), in consultation with the neurosurgical service.

**Ultrasound**

According to currently available guidelines, a focused assessment with sonography for trauma (FAST) examination should be included in any setting where abdominal injury is suspected or abdominal trauma has occurred. However, a negative FAST examination should not be completely reassuring, as a prospective observational study demonstrated that anticoagulated patients are at an elevated risk for processes that would be unlikely to be detected by ultrasonography, such as spontaneous or traumatic retroperitoneal hemorrhage. Follow-up testing should include CT when severe injury is suspected. However, it is important to realize that even whole-body CT is only about 85% sensitive for intracranial, thoracic, and abdominal injuries following traumatic injury and that these data are typically derived from populations of patients who were not specifically anticoagulated and, therefore, not at an elevated risk for acute or delayed bleeding. As always, close monitoring and serial evaluations of patients taking NOACs should take precedence over a single negative radiology study obtained early in the ED evaluation.

**Laboratory Studies**

**Prothrombin Time/International Normalized Ratio**

Dabigatran, rivaroxaban, and apixaban generally cause increases in PT to levels of 13 to 17 seconds (INR 1.1-1.5) in otherwise healthy adults. (See Table 4.) This increase in PT is reversible in rivaroxaban-mediated coagulopathy following the administration of 4-factor prothrombin complex concentrate (PCC). With the appropriate standardization, PT may be used to monitor rivaroxaban peak plasma levels; however, this level of standardization using rivaroxaban calibrators is not yet commonly performed.

**Partial Thromboplastin Time**

Dabigatran significantly increases the PTT, leading some authors to suggest obtaining a PTT level in all suspected cases of dabigatran-associated bleeding or overdose. Based on a blinded 16-center in vitro study of dabigatran-mediated coagulopathy, a normal PTT (with a normal INR) can generally be interpreted as an absence of clinically significant levels of dabigatran in the patient. However, a recent study in 35 patients taking dabigatran demonstrates that there remains a small population of patients who will have therapeutic levels of dabigatran with normal PT and PTT. Rivaroxaban also prolongs the PTT in animal models. Importantly, a normal PTT (in conjunction with a normal INR) virtually excludes supratherapeutic plasma levels of NOACs when measured at least 3 hours after the last oral dosing.

**Anti-Factor Xa Activity Levels**

The anti-factor Xa chromogenic assay, frequently used to monitor low-molecular-weight heparins, can also be used to accurately determine the concentration of both rivaroxaban and apixaban. This has led some groups to recommend obtaining anti-factor Xa levels in all cases of suspected rivaroxaban and apixaban-mediated bleeding, with normal values being interpreted as an absence of activity of these agents. Although access to this assay is relatively widespread, long turnaround times may limit the utility for ED patients.

**Ecarin Clotting Time**

Ecarin clotting time (ECT) is an effective means of monitoring dabigatran activity; however, access to this assay is currently limited. No therapeutic range based on ECT has been established to date, but the utility of ECT testing is that a normal value can be interpreted as negligible or absent dabigatran activity.

**Creatinine Clearance**

Assessment of renal function is particularly important for agents cleared significantly by renal excretion (eg, dabigatran, apixaban, and rivaroxaban). Acute kidney injury is heavily associated with major bleeding while on dabigatran, appearing in as many as 53% of patients. Importantly, the biological half-life of dabigatran increases from 13 hours to 18 hours as creatinine clearance decreases from 80 to 30 mL/min.

**Thrombin Time**

Thrombin time is extremely sensitive to dabigatran and is maximally elevated in patients taking dabiga-

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**Table 4. Laboratory Marker Abnormalities Of Novel Oral Anticoagulant Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Laboratory Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prothrombin Time/INR</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Minor elevation</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Minor elevation</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Minor elevation</td>
</tr>
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</table>

Abbreviation: INR, international normalized ratio.
trant at therapeutic levels, making it a poor predictor of overdose; however, an absence of an elevation of thrombin time virtually excludes the medication as a cause of bleeding.7,37,40 Although generally available in tertiary referral centers, access to this assay may be limited in community EDs. Novel thrombin time-based studies are currently in development to address the oversensitivity of the traditional thrombin time assay.

Platelet Count
Although none of the NOACs inhibit platelet function, proper platelet quantity is essential to clot formation. Close monitoring of platelet level is essential, along with consideration of any decrease in platelet function that may be secondary to antiplatelet medications such as aspirin or clopidogrel or underlying medical comorbidities such as severe renal disease.

**Emergency Department Management**

**General Principles**
Management of NOAC-associated bleeding in the ED follows a common pathway independent of the class of the offending agent. (See Clinical Pathway, page 10.) The general principles of hemorrhage management always take priority, including preventing further doses of any anticoagulant or antiplatelet agents and site-specific bleeding control. This includes all of the basic management options well known to emergency clinicians (direct pressure for bleeding at compressible sites, intravenous proton-pump inhibitors for suspected upper gastrointestinal bleeding, etc). Emergency clinicians should obtain a baseline hematocrit and a type and screen for potential packed red blood cell infusion, in case it becomes necessary later in the patient’s management. Furthermore, it is appropriate to order coagulation studies, including PT, PTT, and thrombin time (if dabigatran) or anti-Xa inhibitor studies (if Xa inhibitor). Due to the higher rates of renal clearance of the NOACs, supporting renal function is critical. Obtain baseline renal function studies, and support renal function with judicious use of intravenous fluids (or blood, as indicated by patient status) to maintain systolic blood pressure > 90 mm Hg. Avoid hypertension, particularly in cases of intracranial hemorrhage, by maintaining systolic blood pressure < 140 mm Hg. Close monitoring of hemodynamics is crucial, as these patients have the ability to decompensate quickly.

For persistent external bleeding, management should be directed to the quantity of bleeding and the hemodynamic state of the patient. Unstable patients with extremity bleeds should receive pressure dressings, with tourniquet application in refractory cases. There is no evidence as to whether commercial hemostatic dressings are of use in NOAC-mediated coagulopathy. While kaolin-based products activate factor XII (and thus act upstream of the sites of action of the NOACs),41 other products are composed of lyophilized chitosan and may not have this issue.42 Regardless, their use is not contraindicated, and they may prove useful as normal coagulation function returns through administration of reversal agents or clearance of NOACs.

In cases of major, potentially life-threatening bleeding, establish intravenous access (preferably 2 large-bore peripheral intravenous lines) in the event that aggressive resuscitation is required, due to the risks of bleeding associated with central access attempts in an anticoagulated patient. If central access is required, an ultrasound-guided femoral approach is preferred due to the reduced complications and compressible nature of the site. Patients should be transfused to maintain hematocrit > 21% and platelets > 50 x 10^9/L.43,44

Management of patients with major bleeding associated with NOAC use is a multidisciplinary effort, and early consultation (or transfer if consultative services are unavailable) should be the rule. Emergency clinicians should consider consultation by a hematologist (or the use of a multidisciplinary institutional protocol developed in conjunction with the hematology service) for consideration of reversal agents and should consider the appropriate interventional service for management of the hemorrhage. Interventional service may include general or trauma surgery, interventional radiology, gastroenterology, or neurosurgery, depending on the patient’s needs. In patients taking dabigatran, nephrology consultation for hemodialysis should also be considered.

Reversal of coagulopathy should be guided by balancing the risk of bleeding with the risk of thrombosis from reversal. In general, 4-factor PCC is the preferred reversal agent for all NOACs, although emergency clinicians should expect greater benefit for the Xa inhibitors than for dabigatran (see the discussion in the “Treatment Strategies” section that follows). Regardless, 4-factor PCC is likely to provide more benefit than any other reversal agent for dabigatran-mediated bleeding, and it should be provided based on the clinical scenario. If 4-factor PCC is not available, emergency clinicians should order either 3-factor PCC in combination with rFVIIa or factor VIII inhibitor bypassing activity (FEIBA). The distinction between these agents is negligible; they both have increased risks of thrombosis and approximately equivalent efficacy, based on currently available data. As a final option, when all other agents are unavailable, emergency clinicians may choose to use fresh frozen plasma alone, but they must realize that this may be futile and lead to complications associated with volume overload.
Treatment Strategies
Due to the relatively short half-life of the NOACs, traditional supportive measures applied early in the course of bleeding are extremely important in the management of NOAC-associated hemorrhage. Initial general management strategies include withholding additional anticoagulants, avoiding nephrotoxins, supporting urine output with intravenous fluids, and managing bleeding by providing packed red blood cells in single units (or according to institutional massive transfusion protocols), with simultaneous fresh frozen plasma and platelets as indicated by the level of hemorrhage. Additional management strategies depend on the site of bleeding but include intravenous proton-pump inhibitors for upper gastrointestinal bleeding, blood pressure control for intracranial hemorrhage, tamponade for bleeding at compressible sites, and intervention by surgery or interventional radiology as appropriate for internal bleeding.

Guidelines for the reversal of the NOACs are sparse, with many groups withholding formal recommendations until more data are available. The Working Group on Perioperative Haemostasis has circulated a proposal in 2013 that recommends treating serious bleeding in a critical organ due to dabigatran and rivaroxaban with activated PCC (aPCC) 30-50 U/kg or PCC 50 U/kg.

Recommendations from the Thrombosis and Hemostasis Summit of North America published in 2012 regarding major bleeding associated with the NOACs include use of oral activated charcoal for recent ingestion of all agents. They further recommend hemodialysis and hemoperfusion with activated charcoal for dabigatran-mediated bleeding. They cite a possible benefit to 4-factor PCC and an unclear benefit to 3-factor PCC for bleeding mediated by all agents. Interestingly, they recommend against the use of fresh frozen plasma for bleeding mediated by dabigatran, rivaroxaban, and apixaban, with the rationale that fresh frozen plasma is only capable of replenishing clotting factors whose production is diminished by the VKAs and that it does not provide sufficient levels to overwhelm the inhibition provided by NOACs.

While not addressing the NOACs, the American College of Chest Physicians recommended in 2012 that patients without major bleeding with supratherapeutic INR levels (> 4) should have their warfarin held and should only be treated with 2 mg of oral vitamin K if their INR is > 10. Patients with major bleeding while on VKAs should be reversed with 4-factor PCC rather than fresh frozen plasma. Additionally, these patients should be given vitamin K 5 to 10 mg intravenously.

The American Heart Association and American Stroke Association 2010 guidelines for the management of spontaneous intracerebral hemorrhage do not address the NOACs. However, they do express a preference for PCCs over fresh frozen plasma in the management of VKA-associated intracerebral hemorrhage. They make this recommendation based on a reduction in complications associated with PCC over fresh frozen plasma, noting that there is no clear outcome benefit to PCC. They further recommend against recombinant activated factor VII (rFVIIa) both in unselected patients and as a single reversal agent in selected patients (specifically those at low baseline risk for thrombosis).

In terms of monitoring, a multispecialty group of German physicians representing their individual specialty societies (including cardiologists, neurologists, and hematologists) produced a statement regarding optimal laboratory testing in the setting of suspected bleeding due to NOACs. They recommend follow-dabigatran levels with thrombin time, HEMO-CLOT® thrombin inhibitors assay, or ecarin clotting time. For the Xa inhibitors rivaroxaban and apixaban, they recommend anti-factor Xa testing.

Activated Charcoal For Oral Agents
Recommendations from the Thrombosis and Hemostasis Summit of North America published in 2012 advocate for the use of activated charcoal for recent (< 2 h) ingestions of dabigatran, rivaroxaban, and apixaban, as this is considered by some to be a “low side-effect” treatment option. However, it is important to note that this suggestion is based on feasibility data gathered in vitro in a single study presented only in abstract. Since the publication of these recommendations, a single case report has been published documenting the successful treatment of a patient with activated charcoal concurrent with other modalities (including gastric lavage) following intubation to reduce risk of charcoal aspiration.

While activated charcoal is an effective antidote for a wide variety of agents, concern over lack of efficacy as well as airway complications and risk of aspiration pneumonitis limit its widespread use. It may be an effective agent for the treatment of patients who are intubated prior to administration or in carefully selected patients who have taken their NOAC within the last 1 to 2 hours and have an anticipated clinical course that does not include any expected mental status decline or airway collapse.

Fresh Frozen Plasma
Data regarding the efficacy and appropriateness of fresh frozen plasma for NOAC-mediated bleeding is conflicting. Fresh frozen plasma has shown efficacy in an animal model of dabigatran-associated intracranial hemorrhage when given with PCC. However, some groups recommend against the routine use of fresh frozen plasma in bleeding mediated by all NOACs due to the absence of compelling data supporting benefit and with clear risks associated
Clinical Pathway For Management Of Hemorrhage In Patients Using Novel Oral Anticoagulants

**Abbreviations:** CBC, complete blood count; Cr, creatinine; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; FEIBA, factor VIII inhibitor bypassing activity; FFP, fresh frozen plasma; GI, gastrointestinal; ICH, intracranial hemorrhage; IV, intravenous; NOAC, novel oral anticoagulant; PCC, prothrombin complex concentrate; PT, prothrombin time; PTT, partial thromboplastin time; rFVIIa, recombinant activated factor VII; SBP, systolic blood pressure; TT, thrombin time.

**Minor Bleed (extremity bleed in hemodynamically stable patient, stable GI bleeding, etc):**
- Continue basic hemorrhage management
- Support clearance with judicious IV fluids (unless contraindications exist)
- Monitor closely until confirmation that bleeding has ceased

**Major Bleed (any ICH, life-threatening GI bleeding, or unstable patient):**
- Establish large-bore IV access
- Maintain SBP 90-120 mm Hg (support renal function but avoid hypertension)
- Maintain hematocrit > 21% and platelets > 50 x 10^9/L
- Get consults from:
  - Hematology (prior to reversal for all agents)
  - Surgery / interventional radiology / gastroenterology / neurosurgery (depending on the site of bleeding)
  - Nephrology for dialysis (for dabigatran)
- Reversal: 4-factor PCC (if not available, 3-factor PCC + rFVIIa > FEIBA > 3-factor PCC + FFP > FFP alone). Recheck coagulation studies 30 min after administration and reconsider redosing until normalized
- Administer tranexamic acid (1 g IV bolus, then 1 g over 8 h)

**General Measures**
- Prevent additional doses of NOAC, anticoagulants, and nephrotoxins and inquire about timing of last dose
- Begin basic principles of hemorrhage management based on the site of bleeding
- Obtain CBC, Cr, CrCl, eGFR, type and screen, PT/PTT, TT (if dabigatran), and anti-Xa (if Xa inhibitor)

(Class III)

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Class Of Evidence Definitions

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Indeterminate</th>
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<tbody>
<tr>
<td>• Always acceptable, safe</td>
<td>• Safe, acceptable</td>
<td>• May be acceptable</td>
<td>• Continuing area of research</td>
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<td>• Definitely useful</td>
<td>• Probably useful</td>
<td>• Possibly useful</td>
<td>• No recommendations until further research</td>
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<td>• Proven in both efficacy and effectiveness</td>
<td>Level of Evidence:</td>
<td>• Considered optional or alternative treatments</td>
<td>Level of Evidence:</td>
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<tr>
<td>Level of Evidence:</td>
<td>• One or more large prospective studies are present (with rare exceptions)</td>
<td>• Generally higher levels of evidence</td>
<td>• Evidence not available</td>
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<tr>
<td>• High-quality meta-analyses</td>
<td>• Nonrandomized or retrospective studies: historic, cohort, or case control studies</td>
<td>• Less robust randomized controlled trials</td>
<td>• Higher studies in progress</td>
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<tr>
<td>• Study results consistently positive and compelling</td>
<td>• Results consistently positive</td>
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<td>• Results inconsistent, contradictory</td>
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with fresh frozen plasma administration. However, in large-volume and life-threatening hemorrhage (traumatic exsanguination, gastrointestinal bleeding, etc) in a patient taking a Xa or direct thrombin inhibitor, the use of fresh frozen plasma in a massive transfusion protocol is appropriate due to the need to replete coagulation factors along with packed red blood cells and platelets.

Vitamin K
Oral vitamin K (2.5 mg) is recommended for patients on warfarin with INR ≥ 9 and no evidence of bleeding, while intravenous vitamin K is recommended for all patients with major bleeding, regardless of INR. Interventions for management of supratherapeutic INR levels are included in Table 5. The role of intravenous vitamin K in patients with major bleeding is to continue the effect of short-acting agents (such as fresh frozen plasma and PCC), as intravenous and oral vitamin K only begin to significantly reduce INR at 6 and 12 hours, respectively. There are no data to support the routine use of vitamin K with NOACs, due to differences in mechanism of action as well as the long time to effect of vitamin K when compared to the short half-life of the NOACs.

Tranexamic Acid
Tranexamic acid (TXA) is a procoagulant molecule with demonstrated efficacy in reducing mortality associated with significant hemorrhage, particularly when given in the first 3 hours of bleeding. There are no primary data addressing the role of TXA in the setting of NOAC use; however, the absence of major side effects has led some authors to recommend the use of TXA (1 g, intravenously) for major bleeding attributed to dabigatran use.

Prothrombin Complex Concentrate

3-Factor Prothrombin Complex Concentrate
In a small retrospective analysis of 17 patients, 3-factor PCC (marketed in the United States as Profilnine SD and Bebulin VH and containing factors II, IX, and X as well as trace amounts of factor VII) was shown to reduce INR faster than fresh frozen plasma in patients with intracranial hemorrhage while on warfarin. The increased speed of reversal as compared to fresh frozen plasma has been repeated in subsequent studies and demonstrated to be as low as 1 minutes for 3-factor PCC compared to 115 min for fresh frozen plasma under ideal conditions (although it is extremely rare to accomplish this in clinical practice). PCC is particularly effective at quickly reducing INR to < 1.5 in patients who are supratherapeutic on warfarin and this can be achieved in approximately 75% of patients. Importantly, this reduction in INR is preserved for at least 96 hours when given in conjunction with a single intravenous dose of 10 mg vitamin K. However, reversal of warfarin-induced coagulopathy with 3-factor PCC is incomplete and may be associated with major adverse thrombotic

Table 5. Managing Supratherapeutic INRs For Patients Taking Warfarin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
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<tbody>
<tr>
<td>INR &gt; therapeutic range but &lt; 5; no significant bleeding</td>
<td>Lower dose or omit dose; monitor more frequently and resume at lower dose when INR is therapeutic; if only minimally above therapeutic range, no dose reduction may be required (Grade 1C).</td>
</tr>
<tr>
<td>INR ≥ 5, but &lt; 9; no significant bleeding</td>
<td>Omit next 1 or 2 doses, monitor more frequently; resume at an appropriately adjusted dose when INR is in therapeutic range. Alternatively, omit dose and give vitamin K (1-2.5 mg orally), particularly if at increased risk of bleeding (Grade 1C). If more rapid reversal is required because the patient requires urgent surgery, vitamin K (≤ 5 mg orally) can be given with the expectation that a reduction of the INR will occur in 24 hours. If the INR is still high, additional vitamin K (1-2 mg orally) can be given (Grade 2C).</td>
</tr>
<tr>
<td>INR ≥ 9; no significant bleeding</td>
<td>Hold warfarin therapy and give higher dose of vitamin K (2.5-5 mg orally) with the expectation that the INR will be reduced substantially in 24-48 hours (Grade 1B). Monitor more frequently and use additional vitamin K, if necessary. Resume therapy at an appropriately adjusted dose when INR is therapeutic.</td>
</tr>
<tr>
<td>Serious bleeding at any elevation of INR</td>
<td>Hold warfarin therapy and give vitamin K (10 mg by slow IV infusion), supplemented with PCC, FFP, or rFVIIa, depending on urgency; vitamin K can be repeated every 12 hours (Grade 1C).</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>Hold warfarin therapy and give PCC, FFP, or rFVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR (Grade 1C).</td>
</tr>
</tbody>
</table>

In patients with mild to moderately elevated INRs without major bleeding, give vitamin K orally rather than subcutaneously (Grade 1A).

Abbreviations: FFP, fresh frozen plasma; INR, international normalized ratio; IV, intravenous; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII.

events (including ischemic stroke and pulmonary embolism) in patients with an underlying elevated risk of thrombosis. In a study of 70 patients receiving 3-factor PCC for treatment of warfarin-associated intracranial hemorrhage, 10% of patients had a presumed or confirmed thromboembolic event, which included a 3% rate of both ischemic stroke and pulmonary embolism. Importantly, this study demonstrated that there appears to be no additional benefit with concomitant administration of fresh frozen plasma in patients receiving PCC, although there is a theoretical benefit to supplementing the low levels of factor VII in 3-factor PCC with the factor VII contained in fresh frozen plasma.

4-Factor Prothrombin Complex Concentrate
4-factor PCC (which contains purified factor VII in addition to II, IX, and X as well as the anticoagulant proteins C and S) is also a useful adjunct for correcting bleeding in patients on warfarin and the NOACs. The FDA recently approved Kcentra™ (known as Beriplex™ outside of the United States) as the first inactive 4-factor PCC available in the United States. Kcentra™ is approved by the FDA only for reversal of VKA-induced coagulopathy in patients with major bleeding, and is not for patients taking NOACs. Risks identified on the package insert for 4-factor PCC include thrombosis and heparin-induced thrombocytopenia (as it contains heparin). Because of this, its use in patients with a history of heparin-induced thrombocytopenia or thrombophilia is relatively contraindicated and must be considered carefully in the context of the clinical situation.

In patients with intracranial hemorrhage on warfarin, a 13-patient randomized controlled trial demonstrated that 4-factor PCC provides a faster and greater magnitude of correction when given with fresh frozen plasma as compared to patients receiving fresh frozen plasma alone. As a result of the faster time to goal, less fresh frozen plasma was given to patients receiving PCC, leading to a complete absence of fluid-overload related complications in this group (as compared to 63% in the group receiving fresh frozen plasma alone). While many studies have demonstrated impressive clinical efficacy with 3-factor PCC, the need for factor VII appears to be greater in patients with greater coagulopathy, leading some to suggest that the addition of factor VII is important to correct bleeding in patients with INR > 4.5.

The use of PCC with dabigatran-induced bleeding is controversial. A well-conducted study of 4-factor PCC demonstrated that there was no effect on the PTT, ECT, or thrombin time in healthy volunteers taking dabigatran. However, while there are no high-quality studies of patients with major bleeding on dabigatran, there are basic science reports and case studies supporting the efficacy of PCC in dabigatran-associated bleeding, although the studies may not be generalizable to humans, and PCCs take days to reduce coagulopathy in a meaningful way and have no effect on mortality. Importantly, the lack of efficacy noted in these studies may have been related to the dose of PCC provided.

The data on the use of 4-factor PCC in rivaroxaban (and by extension, apixaban) is much more supportive. In a well-designed randomized placebo-controlled crossover study of 12 healthy volunteers, PCC rapidly and completely reduced rivaroxaban-induced elevations in PT and reduced endogenous thrombin potential. These changes occurred within 15 minutes, appeared to last for at least 24 hours, and are thought to be due to the PCC either bypassing or overwhelming the activity of the NOAC.

The distinction between correction of laboratory parameters and more important outcomes (such as reductions in bleeding and mortality) is critical. Recent animal data demonstrate that it is possible to show correction of laboratory values with PCC and factor VIIa without a reduction in bleeding. Thus, one should be careful about overinterpreting studies with only laboratory value corrections as principle outcomes, as additional human trials evaluating the impact of PCC on clinical outcomes are needed. However, given the current state of the literature, PCC appears to be the most effective modality for the reversal of NOAC-associated bleeding currently available.

Activated PCC (Factor VIII Inhibitor Bypassing Activity)
aPCC, also known as FEIBA, is a 4-factor PCC that contains activated factor VII as well as lesser amounts of factors II, IX, and X and protein C. The name FEIBA refers to its principle use, which is reversing bleeding in hemophiliac patients with antibodies to factor VIII through activated factor X and II activity. In a retrospective review of 141 patients with life-threatening bleeding, FEIBA reversed warfarin-induced coagulopathy in patients with major bleeding faster and more completely than fresh frozen plasma when given in conjunction with vitamin K and dosed at 500 U for INR < 5 and 1000 U for INR > 5. This study demonstrated no mortality benefit with FEIBA or fresh frozen plasma, although the study was not adequately powered to make this distinction.

Conceptually, FEIBA should perform similarly to 4-factor PCC, with preferential success in reversing activity of the Xa inhibitors rivaroxaban and apixaban over the direct thrombin inhibitor dabigatran. At this time, there are few clinical data to support the use of FEIBA with major bleeding induced by the NOACs, although case reports are beginning to emerge with dabigatran. A critical consider-
ation includes the greater theoretical risk of induced thrombosis with FEIBA as compared to PCC, since the clotting factors are activated. Additionally, it is important to recheck an INR 30 minutes following infusion to determine the need for additional FEIBA.

Recombinant Factor VIIa If Using 3-Factor Prothrombin Complex Concentrate

In the absence of 4-factor PCC or FEIBA, an alternative approach is to use rFVIIa or to supplement 3-factor PCC with rFVIIa. rFVIIa (marketed in the United States as NovoSeven\textsuperscript{®}) activates factors IX and X, resulting in a rapid increase in thrombin.\textsuperscript{68} The ability of rFVIIa to produce sufficient quantities of thrombin to overwhelm dabigatran-mediated inhibition is unclear, as it has had mixed results in animal models.\textsuperscript{50} A single case report documented correction of dabigatran-mediated bleeding in a patient administered rFVIIa in conjunction with hemodialysis.\textsuperscript{69} An animal model of apixaban-mediated bleeding demonstrated reversal of laboratory parameters but no reductions in bleeding.\textsuperscript{60} It is important to consider the risk of thrombosis with rFVIIa, as this product is associated with a high risk of arterial thrombotic complications and adverse events, particularly in patients aged > 65 years.\textsuperscript{70} The risk of thrombosis likely results from the high levels of the procoagulant factor VIIa without any balance from anticoagulant molecules such as protein C or S.

Hemodialysis

Due to the low rate of protein binding, hemodialysis is an effective modality for removing dabigatran from the circulation.\textsuperscript{71} Four hours of hemodialysis will reduce the levels of circulating drug by approximately half, which is uniquely useful in cases of overdose. Case reports support the use of hemodialysis for patients with hemorrhage while on dabigatran are emerging.\textsuperscript{69} Furthermore, hemodialysis is the only treatment modality with demonstrated efficacy in the management of dabigatran-associated bleeding. This has led some to recommend hemodialysis for dabigatran-associated bleeding, although it is wise to anticipate challenges in obtaining hemodialysis catheter access in a patient with major bleeding.\textsuperscript{50} Due to higher levels of protein binding, hemodialysis is unlikely to be helpful for bleeding associated with the Xa inhibitors rivaroxaban and apixaban.

Hematology Consultation /Transfer

Timely access to expert hematology advice is critical for the management of patients receiving blood products or clotting factors for the management of bleeding attributed to NOACs. If this expertise is not available in your facility, consideration of transfer is appropriate.

Disposition

There are no studies addressing which patients taking NOACs are safe to discharge and which are at risk for delayed complications. However, due to the extremely short half-life of the medications, it is reasonable to consider discharge of appropriately selected patients. These patients may include those who: (1) are reliable, (2) have normal mental status and renal function, (3) are not significant fall risks, (4) have bleeding in a compressible site that is controlled, (5) are at least 12 hours past their last dose of oral anticoagulant, and (6) have had coagulation studies that are within normal limits. Due to the potential for complications and need for close monitoring, all patients who receive pharmacological reversal of coagulopathy for anticoagulant-associated major bleeding should be admitted to the hospital with consideration of intensive care unit placement if bleeding and coagulopathy are not definitively controlled.

Controversies And Cutting Edge

Bedside/ Point-Of-Care

Thromboelastography

One of the key dilemmas associated with the evaluation of patients taking NOACs is the inability to rapidly determine the presence of an anticoagulant. Rapid thromboelastography (rTEG) is a point-of-care assay that combines multiple distinct dynamic measurements to provide information about clot formation, stability, and lysis kinetics, and it is elevated following dabigatran administration.\textsuperscript{72} By measuring the clot formation and degradation in vitro, the graphical output of real-time clot stability may be analyzed and extrapolated to derive functional measurements of clot formation such as the activated clotting time.

There are case reports of patients presenting with fatal dabigatran-mediated bleeding where the activated clotting time measurement in the rTEG may be the only coagulation study that is abnormal.\textsuperscript{73} Furthermore, there are reports demonstrating the utility of rTEG for rapid evaluation of coagulopathy correction following FEIBA administration in the setting of dabigatran-associated subdural hemorrhage when verification of coagulopathy reversal is essential prior to life-saving surgical intervention.\textsuperscript{57} In vitro and animal model data exist that demonstrate rivaroxaban and apixaban-mediated elevations in clotting times as measured by rTEG, although detailed human data are lacking.\textsuperscript{36,63,74}

r-Antidote

A recombinant form of factor Xa, called r-Antidote, that may be an effective reversal agent for factor Xa inhibitors is currently being studied. In animal trials,
Risk Management Pitfalls For Novel Oral Anticoagulant Agents

1. “I didn’t think I needed to order coagulation studies.”
   Obtain coagulation studies in patients with suspicion for major bleeding who are taking NOACs or whose medication history is unclear. This information may help to guide management as well as to identify the causative agent in an obtunded patient.

2. “I didn’t think that I needed to recheck coagulation studies after treating the patient.”
   Remember to recheck coagulopathy studies 30 minutes after the administration of PCC or 30 minutes after the administration of FEIBA to determine the need for additional doses.

3. “She didn’t appear to be at an elevated risk for thrombosis.”
   Consider the baseline risk of thrombosis due to medical comorbidities (including malignancy or thrombophilia) before administering PCC or FEIBA or for patients aged > 65 years receiving rFVIIa.

4. “We always give fresh frozen plasma for coagulopathy.”
   Aggressively administering fresh frozen plasma when PCC is available (and is the preferred treatment) can lead to slower reversal, unnecessary volume overload, and respiratory failure.

5. “We gave charcoal, and then he started to vomit.”
   Remember to perform endotracheal intubation prior to administration of activated charcoal in patients with recent overdose of NOACs who are at an elevated risk for alterations in mental status, vomiting, or aspiration. Video laryngoscopy improves first-pass success in these patients who may be at an elevated risk for bleeding during intubation.

6. “I didn’t think that I needed to document the discussion of risks regarding NOAC reversal.”
   The use of reversal agents is associated with an increased risk of thromboembolic complications; therefore, always discuss the risks and benefits with patients and their families and document the discussions regarding risks and benefits of using this treatment. Document that the patients and/or family understood and were in agreement with their use.

7. “He was neurologically intact and his head CT was negative, so I discharged him to home.”
   We do not yet know how the risk of delayed intracranial hemorrhage with the NOACs compares to traditional anticoagulants or antiplatelet agents. Provide your patients with a good follow-up plan and return precautions.

8. “I didn’t remember how to dose the reversal agent when it came time to administer it.”
   Written protocols can facilitate care, especially when related to lifesaving interventions that are infrequently used. Proactively establish protocols with other specialties (pharmacy, blood bank, hematology) to promote management efficiency and improved patient outcomes.

9. “I didn’t think I needed to administer the guaiac stool test on her.”
   Patients on dabigatran are at an elevated risk for gastrointestinal bleeding, even beyond that conferred with warfarin use. Have a high suspicion for bleeding in patients taking NOACs.

10. “His FAST examination was negative.”
    Patients on NOACs who sustain trauma can have delayed bleeding, so serial examinations and repeat FAST examinations should be performed, with a low threshold for consideration of CT imaging if they deteriorate.
this drug reversed the inhibition of factor Xa by the NOACs in a dose-dependent fashion and restored hemostasis in a liver laceration model.\textsuperscript{75,76} Further clinical trials are currently being conducted.

**Summary**

Management of major bleeding events in patients taking NOACs is already becoming a common clinical scenario in emergency medicine. Although there are relatively few high-level data that conclusively direct our management of these patients, studies are emerging that may begin to inform our approach. There are more data regarding dabigatran than the Xa inhibitors, presumably due to its earlier approval date and higher clinical use at this time. Early studies provide mixed results of treatment of dabigatran-mediated bleeding with PCCs, FEIBA, and rFVIIa. It is likely that these agents provide some relief of major bleeding, but they are limited by the relatively distal point of inhibition of the coagulation cascade by dabigatran. Where comparisons between dabigatran and the Xa inhibitors exist, it appears that reversal of coagulopathy and major bleeding are more successful in the Xa inhibitors when using any of the available agents, likely due to their more proximal point of inhibition of the coagulation cascade.

Regardless of the NOAC in use by the patient experiencing a major bleeding episode in the ED, there appears to be a hierarchy of efficacy and risk regarding the available nonspecific reversal agents that should be employed after careful consideration of the clinical situation. Furthermore, due to the relatively short half-lives of these agents and the potential complications associated with many of the available reversal agents, the importance of general hemorrhage management approaches cannot be understated.

**Time-And Cost-Efficient Strategies**

1. Avoid the use of rFVIIa when 4-factor PCC is available. Recombinant factor VIIa is extremely expensive due to the method of production. Additionally, there appears to be a lower risk of thrombosis (with resultant decreases in medical costs and length of hospitalization) with 4-factor PCC as compared to rFVIIa.
2. Use appropriate adjunctive approaches early in the treatment course. Basic hemorrhage control approaches are generally low-cost and may have considerable impact as temporizing measures that reduce the need for higher-cost interventions.
3. Develop protocols and checklists for the management of patients with bleeding related to NOAC use. Early intradepartmental agreement on the management of these patients reduces time to definitive care and should improve outcomes.

**Case Conclusions**

The 78-year-old woman with the 5-mm intraparenchymal hemorrhage did well. You initially focused on temporizing measures, including blood pressure control and seizure prophylaxis. You verified that her creatinine clearance was normal and supported her renal function with judicious IV fluids. After a discussion about her elevated risk for thrombosis with rFVIIa and 3-factor PCC, you obtained informed consent for administration of both of these agents. She was admitted to the neurology service, and her follow-up CT demonstrated no progression of the lesion.

The 62-year-old man with the traumatic liver laceration was at risk for hemorrhagic shock if his liver laceration and hemoperitoneum progressed. You administered 2500 U of 4-factor PCC (25 U/kg, based on his weight of 100 kg) and rechecked his INR after 15 minutes, finding it to be 1.1. The patient was transported to a neighboring Level 1 trauma center for definitive management.

Because all of the 4-factor PCC that was available at your institution was used on the previous patient, you gave the 68-year-old man with coronary artery disease and a presumed upper gastrointestinal bleed 3-factor PCC, a single unit of fresh frozen plasma, vitamin K 10 mg IV, 2 units of packed red blood cells, and an IV proton pump inhibitor infusion. Fifteen minutes after the PCC and fresh frozen plasma infusion, his INR was 1.2. He was admitted to the medicine service and was found to have a single gastric ulcer that was successfully banded via endoscopy the following morning. He remained hemodynamically stable throughout his hospitalization.

**Selected Abbreviations**

- aPCC: Activated prothrombin complex concentrate
- aPTT: Activated partial thromboplastin time
- FAST: Focused assessment with sonography for trauma
- FEIBA: Factor VIII inhibitor bypassing activity
- INR: International normalized ratio
- NOAC: Novel oral anticoagulant
- NSAID: Nonsteroidal anti-inflammatory drug
- PCC: Prothrombin complex concentrate
- PT: Prothrombin time
- PTT: Partial thromboplastin time
- Re-Ly Trial: Randomized Evaluation of Long-term Anticoagulant Therapy Trial
- rFVIIa: Recombinant activated factor VII
- TXA: Tranexamic acid
- VKA: Vitamin K antagonist
References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available.


45. CRASH-2 collaborators, Roberts I, Shakur H, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011;377(9771):1096-1101. (Randomized placebo-controlled trial; 20,211 patients)
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1. The percentage of all patients presenting to trauma centers who are anticoagulated is: approximately:
   a. < 1%
   b. 3%
   c. 8%
   d. 15%

2. VKAs exert their anticoagulant effects by:
   a. Inhibiting the action of factor IIa
   b. Reducing the synthesis and, thus, the quantity of factors II, VII, IX, and X
   c. Reducing the activity of circulating factors II, VII, IX, and X
   d. Inhibiting platelet aggregation

3. The mechanism of action of dabigatran is to:
   a. Directly inhibit the conversion of fibrinogen into fibrin
   b. Directly inhibit the synthesis of thrombin
   c. Reduce the synthesis of factor X
   d. Reduce the concentration of circulating factor VIIa

4. The mechanism of action of apixaban is:
   a. To reduce the synthesis of factor X
   b. To directly inhibit the synthesis of thrombin
   c. To directly inhibit the action of thrombin
   d. The same as the mechanism of action of rivaroxaban
5. The defining feature of the pharmacokinetics of NOACs as compared to warfarin is:
   a. More cytochrome P450 interactions
   b. Reduced renal clearance
   c. Dramatically shorter half-life
   d. Slower time to maximum effect

6. Patients taking dabigatran are at a particularly increased risk for which type of bleeding?
   a. Gastrointestinal
   b. Intracranial
   c. Peripheral
   d. Pulmonary

7. Patients with suspected intracranial hemorrhage on NOACs should:
   a. Be evaluated utilizing the New Orleans Criteria
   b. Receive a head CT only if they meet the Canadian CT Head Rule criteria
   c. Be admitted and monitored for 24 hours
   d. Receive a head CT, as no current clinical guidelines or decision rules can safely exclude bleeding in patients taking NOACs

8. The test of choice for monitoring rivaroxaban activity is:
   a. PT
   b. PTT
   c. Thrombin time
   d. Anti-factor Xa

9. The role of fresh frozen plasma in the treatment of apixaban-mediated bleeding is:
   a. Primary treatment
   b. For use in conjunction with 4-factor PCC
   c. For use only if other primary therapies are not available
   d. For use with vitamin K in minor bleeding

10. Based on the best available evidence to date, the best treatment for bleeding associated with NOACs is:
    a. 3-factor PCC
    b. 4-factor PCC
    c. rFVIIa
    d. Fresh frozen plasma

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