An Evidence-Based Approach To Managing The Anticoagulated Patient in The Emergency Department

**Abstract**

As the population ages and an increasing number of patients are placed on anticoagulation, many more anticoagulant-related emergencies can be expected. Spontaneous intracerebral hemorrhage in anticoagulated patients has an annual risk of 0.5% to 1%. A thorough medication history including herbal supplements is imperative due to warfarin’s narrow therapeutic index and interactions with commonly used medications. During primary hemostasis, a platelet plug forms at the site of vascular injury. Secondary hemostasis stabilizes the platelet plug with fibrin. Antithrombotic drugs are divided into 3 classes: anticoagulants, antiplatelet agents, and fibrinolytic agents. Anticoagulants primarily prevent and treat venous thromboembolic disease because fibrin is the main component of venous thrombi. Antiplatelet therapy targets arterial thrombus due to the predominance of platelets in arterial thrombi. There is no expert consensus advising which patients receiving anticoagulation or antiplatelet therapy with mild head injury require a head computed tomography (CT) scan, and there is no consensus on the disposition of these patients. The best protocol to reverse coumadin-associated coagulopathy is controversial; options include various combinations of vitamin K, fresh frozen plasma (FFP), and more recently prothrombin complex factors (PCCs). The best protocol to reverse heparin-associated coagulopathy is controversial; options include protamine sulfate, PCCs, and fresh frozen plasma. Recognize the significance of minor head trauma in the anticoagulated patient.

**CME Objectives**

Upon completion of this article, you should be able to:

1. Describe the life-threatening complications of anticoagulation and how they may present.
2. Recognize the significance of minor head trauma in the anticoagulated patient.
3. Be aware of the significant risk of drug interactions especially with warfarin.
4. Discuss the controversies in reversing the anticoagulated patient.

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Prior to beginning this activity, see “Physician CME Information” on the back page.
concentrate and recombinant factor VIIa. Protamine, desmopressin, platelet transfusions, and cryoprecipitate are other agents utilized to reverse hemorrhaging patients.

**Case Presentation**

You start another busy shift with a double row of charts waiting to be seen. Your first patient is an elderly man who fell 1 hour prior to presentation. He did not lose consciousness, but he was dazed for a few minutes. He complains of a mild headache but denies any neck pain. He takes warfarin for valvular heart disease. He looks good and has no focal neurological complaints. His mental status is normal, he has a negative head CT scan, and his INR is 3.9. His family wants to take him home, which would help relieve some of the congestion in the ED, but you wonder what would be best. To observe and repeat imaging? Reverse his anticoagulation? Change his dosing regimen of warfarin?

In the next room, you quickly evaluate a 51-year-old obese woman with nonspecific back and abdominal pain that started 24 hours before and has slowly progressed to become intolerable. She denies fever, chills, nausea, or vomiting. She is on the last day of a 5-day course of ciprofloxacin for a UTI. She takes warfarin for a pulmonary embolus that occurred 2 months prior. Her hematocrit is mildly decreased, and her white blood count is normal; however, the INR is 6.8. You wonder if her abdominal pain is related to the UTI, or if it could be somehow related to the prolonged INR. In fact, you wonder why her INR is so prolonged . . .

**Introduction**

There is rarely a shift in the emergency department (ED) in which the emergency clinician does not encounter an anticoagulated patient who poses a management dilemma, including asymptomatic but supratherapeutic anticoagulated patients sent to the ED for repeat blood work. The question of whether to observe, discharge, or image is addressed with each encounter, yet there is considerable variation in the approach to these problems among practicing emergency clinicians. An additional challenge when managing patients on warfarin is that many medications can interact with its metabolism, thus impacting the therapeutic effect. Also, many patients are taking antiplatelet agents, which may impact their emergency care. While patients on antiplatelet agents are not technically anticoagulated, they are at risk of having bleeding complications.

Anticoagulation status affects the evaluation of many medical and traumatic complaints. In a prospective observational cohort of 300 ED patients on warfarin, Newman et al found that 43% were subtherapeutic and 29% were supratherapeutic; however, no correlation with outcome was reported. In a retrospective review of a trauma registry, Wojcik et al did not find any significant effect on mortality in 1916 trauma patients who were on warfarin, though most other studies report the opposite. For example, in a retrospective study of 2791 anticoagulated elderly patients who fell from standing, the anticoagulated patients had a higher mortality rate than patients who were not anticoagulated. The emergency clinician is charged with the task of quickly identifying the subset of anticoagulated patients at risk for serious complications, which is particularly important when managing a patient with a head injury. The approach to reversing an anticoagulant depends on the drug involved as well as the risk/benefit ratio of reversal.

This issue of *Emergency Medicine Practice* focuses on the challenge of evaluating and managing the anticoagulated patient using the best available evidence from the literature. The main complication of this therapy is hemorrhage, which can be life-threatening, depending on its location. This issue also addresses the patient taking antithrombotic or antiplatelet agents and includes discussions of prothrombin complex concentrates and the off-label use of recombinant activated factor VII (rFVIIa). While published guidelines exist to help the emergency clinician navigate some of these dilemmas, it
is the appropriate application of such guidelines that constitutes the art of emergency medicine.

Abbreviations And Acronyms

ABCs: Airway, breathing, circulation  
ACCP: American College of Chest Physicians  
ACEP: American College of Emergency Physicians  
CADP: Collagen/adenosine diphosphate membrane  
CBC: Complete blood count  
CEPI: Collagen/epinephrine membrane  
CT: Computed tomography  
DVT: Deep vein thrombosis  
ED: Emergency department  
FDA: US Food and Drug Administration  
FFP: Fresh frozen plasma  
GCS: Glasgow Coma Scale  
INR: International normalized ratio  
ISI: International sensitivity index  
LMWH: Low-molecular-weight heparin  
PCC: Prothrombin complex concentrate  
PT: Prothrombin time  
PTT: Partial thromboplastin time  
RBC: Red blood cell  
rFVIIa: Recombinant activated factor VII  
STEMI: ST-segment elevation myocardial infarction  
TBI: Traumatic brain injury  
TPA: Tissue plasminogen activator  
UTI: Urinary tract infection  
vWF: von Willebrand factor

Critical Appraisal Of The Literature

The literature review was launched with Ovid MEDLINE® and PubMed searches for articles on anticoagulation emergencies published between 1966 and 2010. A combination of keywords included warfarin, anticoagulation, head injury, retroperitoneal hematoma, international normalized ratio, INR, prothrombin complex concentrate, fresh frozen plasma, coagulopathy, factor VIIa, low-molecular-weight heparin, and LMWH. The articles obtained provided for further manual literature searches. Over 150 total articles were reviewed, and of these, 104 are referenced here. A search of the Cochrane Database of Systematic Reviews produced a guideline on the use of hemostatic drugs for acute traumatic brain injury.6 In addition, a 2008 American College of Emergency Physicians (ACEP) clinical policy on mild traumatic brain injury (TBI) was identified.7

The literature basis for management of the ill or injured anticoagulated patient consists primarily of retrospective studies, case reports, review articles, and case series. Also, many of the issues with the anticoagulated patient are either not addressed or minimally addressed by most guidelines.6-10 This literature, overall, is fairly weak. The most notable areas of research in the recent literature deal with new techniques of reversing anticoagulation.

Etiology

Warfarin is the most commonly used anticoagulant to treat and prevent the complications of thromboembolic disease. As the population ages, there is a concomitant increase in the number of patients eligible for anticoagulation. Indications for warfarin are presented in Table 1 along with the associated target international normalized ratio (INR) for the disorder.

Because of the increasing number of patients on anticoagulants, coupled with a more active elderly population, an increased number of patients with anticoagulant-related emergencies can be expected.11-12 Chronic anticoagulation is associated with a rate of 1% to 3% of major bleeds and 6% to 10% of minor bleeds per year.14 The risk of hemorrhage is directly related to the degree of prolongation of the INR in patients taking warfarin.9,15 This risk increases significantly when the INR exceeds 4.16 In the anticoagulated patient, minor head trauma may result in a fatal, delayed intracranial bleed.17 For these reasons, some authorities have recommended a lower intensity of anticoagulation (INR greater than 1.5 but less than 2.5) although this may not be adequate to protect against thromboembolic events.18 A case-controlled study of 179 patients suggests that this level is not associated with an increase in intracerebral hemorrhage.19

Pathophysiology

A brief review of hemostasis is necessary in order to provide perspective on the management of anticoagulation-related emergencies. Normal hemostasis involves the formation of a platelet plug at the site of injury to the vascular endothelium. Primary hemostasis requires platelets, plasma coagulation factors, and the vascular endothelium. Primary hemostasis involves the formation of a platelet plug at the site of injury to the vascular endothelium. The release of von Willebrand factor from the injured endothelium recruits platelets. (See Figure 1, page 4.) Disorders of primary hemostasis produce mucocutaneous bleeding, eg, epistaxis, hematuria, petechiae. Medications such as aspirin and clopidogrel act at this level.

Table 1. Target INRs For The Anticoagulated Patient

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis, pulmonary embolus</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Mechanical heart valve</td>
<td>3.0 (2.5-3.5)</td>
</tr>
<tr>
<td>Mitral valve stenosis</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Ischemic cerebrovascular disease</td>
<td>2.5 (2.0-3.0)</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.
Secondary hemostasis is the stabilization of the platelet plug with a fibrin cap. As a result of the coagulation cascade, fibrinogen is converted to fibrin. Disorders of this phase of coagulation result in delayed bleeding such as intracranial hemorrhage, retroperitoneal hematoma, and hemarthrosis.

Antithrombotic drugs are used for the prevention and treatment of thrombosis. These medications are divided into 3 categories: anticoagulants, antiplatelet drugs, and fibrinolytic agents. Anticoagu-

Anticoagulants interfere with the coagulation cascade at one or multiple steps. Anticoagulants block the synthesis and activation of clotting factors. Warfarin prevents the synthesis of the vitamin K-dependent factors (II, VII, IX, and X). Heparin and LMWH act to facilitate the actions of antithrombin III. Through this facilitation, heparin inactivates both activated factor X and thrombin equally. Low-molecular-weight heparins inactivate activated factor X 2 to 4 times more than they inhibit thrombin.20 Anticoagulants are the essential drugs for the prevention and treatment of venous thromboembolic disease because fibrin is the main component of venous thrombi.

Antiplatelet agents exert their effect on the platelets to prevent thrombus formation by interfering with platelet activation or aggregation. Aspirin prevents platelet aggregation by inhibiting cyclooxygenase-1 irreversibly. Clopidogrel inhibits platelet aggregation through antagonism of the adenosine diphosphate receptor. Strategies to prevent or treat arterial thrombosis focus mainly on antiplatelet agents due to the predominance of platelets in arterial thrombi.

Fibrinolytic agents induce fibrin degradation. These medications are generally given in the hospital, so patients would not present to the ED with complications, but rather develop such complications with treatment in the hospital.

**Differential Diagnosis**

The presentation of patients with complications of anticoagulation will depend on the anatomical areas involved. (See Table 2.) The most common complications of anticoagulants are hemorrhagic, and the most serious complication is intracerebral hemorrhage. Anticoagulated patients with back pain may need to be evaluated for spinal epidural hematoma or retroperitoneal hemorrhage, depending on the nature of their presentation. Any type of bleed will be more difficult to manage in the anticoagulated patient.

**Table 2. Hemorrhagic Complications Of Anticoagulation**

- Intracerebral/intracranial hemorrhage
- Spinal epidural hematoma
- Retroperitoneal hemorrhage
- Rectus sheath hematoma
- Hemothorax
- Gastrointestinal bleeding
- Hemopericardium
- Compartment syndrome
- Hematuria
**Prehospital Care**

Prehospital management of the anticoagulated patient depends on the chief complaint; there are no unique prehospital treatments applicable to these patients. Prehospital personnel should follow standard guidelines for transport to a trauma center versus transportation to the closest facility. All anticoagulated patients with head injury should be transported to a facility with 24-hour diagnostic imaging, and there should be a low threshold for transporting to a trauma center with neurosurgical capabilities.

With any external bleeding, direct pressure at the bleeding site is recommended. Universal precautions should be followed, including gloves, mask, and eye protection or face shield. Hand-washing should be performed after touching blood, body fluids, and contaminated items, even if gloves are worn. Tourniquets are not routinely indicated to control bleeding. In any case, the most significant hemorrhagic complications are internal.

**Emergency Department Evaluation**

**History**

In addition to exploring the appropriate questions for the patient’s specific presentation, it is essential to identify the reasons why the patient is anticoagulated and when the INR was last checked. It is also important to ascertain the target degree of anticoagulation. Depending on the clinical circumstances, the risk versus benefit of reversing anticoagulation must be considered.

A history of medications taken and any recent changes in the medication regimen are extremely valuable, since warfarin has both a narrow therapeutic index and interacts with many commonly used medications. 

(See Table 3.) In particular, many antibiotics and analgesics will potentiate the effect of warfarin. In a prospective study of 289 patients, Hylek et al found that acetaminophen is an underrecognized cause of excessive anticoagulation in patients on warfarin. Despite this risk, acetaminophen is still cautiously recommended as the analgesic of choice in patients on warfarin. The mechanism of interaction between acetaminophen and warfarin has not been elucidated, but it is generally limited to high doses or prolonged (>2 weeks) courses of acetaminophen.

Some medications, such as rifampin, lopinavir, and ritonavir, decrease the effect of warfarin by inducing the CYP2C9 enzyme system. An INR should be checked within several days of the addition of a new medication that potentially interacts with warfarin.

In addition to medications, the emergency clinician should ask all patients whether they use any herbal supplements, since it is reported that up to one-third of adults use alternative therapies, and patients may be reluctant to tell a physician about their use of herbal supplements. Not only are adverse effects possible, but some herbal supplements have been reported to interact with warfarin. (See Table 4.) In a longitudinal analysis of 171 patients, Shalansky et al demonstrated an increased risk of bleeding in patients using complementary and alternative medicine while taking warfarin.

Patients should also be asked about recent falls or trauma. Coagulopathic patients are at risk for delayed hemorrhage. In a retrospective review of 159 anticoagulated patients in a trauma registry, Cohen et al reported an abrupt neurological deterioration in 45 patients who were admitted for observation. Unfortunately, for reasons not explained in their article, 30% of these patients did not have an initial computed tomography (CT) scan prior to their clinical deterioration. The majority of the patients who deteriorated had subdural hematomas, cerebral contusions, or intracerebral hemorrhage. Age

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**Table 3. Drugs That Potentiate Warfarin**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>Strongest effect of all antibiotics; inhibits CYP2C9</td>
</tr>
<tr>
<td></td>
<td>(hepatic microsomal metabolism)</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Including levofloxin, initially thought not to interact.</td>
</tr>
<tr>
<td></td>
<td>Inhibits CYP2C9 and decreases vitamin K-producing bacteria</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Inhibits warfarin metabolism</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Inhibits warfarin metabolism</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Inhibit CYP2C9</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Interferes with vitamin K cycle</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Inhibits warfarin metabolism. Decreases vitamin K-producing</td>
</tr>
<tr>
<td></td>
<td>bacteria</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Inhibits CYP2C9</td>
</tr>
</tbody>
</table>

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**Table 4. Herbal Supplement Interactions With Warfarin**

<table>
<thead>
<tr>
<th>Herb</th>
<th>Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<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 risk of serious bleeding</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Decreases anticoagulation</td>
<td>Increases risk of thrombotic complications</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Increased 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 in approximately half</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.
greater than 65 years and a supratherapeutic INR (> 5 in 50% of patients) were the most common predictors of delayed clinical deterioration.9

Physical Examination
Because anticoagulated patients are at such high risk, the physical examination should target essential concerns, yet remain systematic and comprehensive. These concerns will vary with the presenting complaint or complication. For instance, the patient with head injury will need an appropriate neurological examination. After an assessment of the airway, breathing, and circulation (ABCs), the patient’s level of consciousness should be recorded using the Glasgow Coma Scale (GCS). The pupillary response, motor examination, and sensory examination are important. A careful cranial nerve examination may identify an acute 3rd nerve palsy, suggesting herniation in the setting of decreased level of consciousness and the need for immediate neurosurgical evaluation and intervention. A 6th nerve palsy may be falsely localizing, because this nerve has the longest intracranial course of any cranial nerve. In addition, a detailed physical examination for other traumatic injuries will be required.

If an anticoagulated patient presents with flank, back, or abdominal pain, the diagnosis of retropitoneal hemorrhage must be considered. The abdomen may be relatively benign. Given the retropitoneal location of the hemorrhage, tenderness may be mild or absent. Paresthesias and pain may radiate along the lumbar plexus or femoral nerve distribution due to compression of these nerves.33 There are 4 eponyms that describe different patterns of ecchymosis associated with retropitoneal hemorrhage. The best-known of these signs are Cullen’s sign and Turner’s sign. Cullen’s sign is the presence of periumbilical ecchymosis, while Turner’s Sign is the presence of flank ecchymosis.34 Fox’s sign is ecchymosis of the upper thigh with a sharply demarcated border inferior to the inguinal ligament.35 The fourth sign is the blue scrotum sign of Bryant. (See Table 5.) Unfortunately, these signs are often late manifestations of retropitoneal hemorrhage.36

The anticoagulated patient with back pain may have a spinal epidural hematoma. In a patient with midline back pain, a neurological examination should include motor, reflexes, sensation, and a rectal examination for tone. The sensory examination will have variable deficits, depending on the level of the compression from the hematoma. In cauda equina syndrome, the classic sensory finding is saddle anesthesia. Bilateral leg weakness may be present, which results in gait abnormalities. Rectal tone may be decreased. Normally, a gentle stroke of the skin near the anus should produce an anal wink. With compression of the spinal cord, this may be absent. Overflow incontinence due to urinary retention is usually present.

For other complaints, the physical examination must be tailored to the complaint. With extremity pain, the involved extremity must be evaluated while considering the possibility of a compartment syndrome or a hemarthrosis. Bleeding complications, especially internal bleeding, must be considered anatomically.

Diagnostic Studies
Laboratory Testing
Chemistry Panel
The chemistry panel demonstrates the hydration status, renal function, and acid-base status of the patient. Acidosis must be corrected before the use of rFVIIa in order for it to be maximally effective.37

Complete Blood Count
In general, a CBC reflects the presence or absence of an anemia, especially when combined with an assessment of the patient’s hydration status and vital signs. Unfortunately, the initial hemoglobin and hematocrit may not accurately reflect the degree of blood loss, due to delayed redistribution. Serial measurements may be required.

The CBC also includes a platelet count. The platelet count does not reflect platelet function, which can be measured by the closure time. An adequate number of functional platelets must be present for proper coagulation.

International Normalized Ratio
The INR provides a measurement of the extrinsic pathway of clotting cascade. This measurement replaced the prothrombin time (PT) ratio and is more reproducible from laboratory to laboratory. The INR was devised to standardize results that varied previously due to the reagent or tissue factor used. Each manufacturer gives an International Sensitivity Index (ISI) for any tissue factor. The value of the ISI is used to calculate the INR from the measured PT, which accounts for different tissue factors that may be used. The reference range for prothrombin time is 7-10 seconds, and the reference range for the INR is 0.8-1.2. The INR is used to monitor the effectiveness of warfarin

<table>
<thead>
<tr>
<th>Sign</th>
<th>Location of ecchymosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cullen’s</td>
<td>Periumbilical</td>
</tr>
<tr>
<td>Turner’s</td>
<td>Flank</td>
</tr>
<tr>
<td>Fox’s</td>
<td>Upper thigh, inferior to inguinal ligament</td>
</tr>
<tr>
<td>Bryant’s</td>
<td>Scrotum</td>
</tr>
</tbody>
</table>

Table 5. Clinical Signs Of Retroperitoneal Hemorrhage
therapy. The risk of bleeding increases substantially when the INR is greater than 4.\textsuperscript{38}

**Partial Thromboplastin Time**
The partial thromboplastin time (PTT) is a measurement of the intrinsic and common pathway of the clotting cascade. This test is used to assess adequacy of treatment with unfractionated heparin. Low-molecular-weight heparins do not require monitoring and produce a reliable anticoagulant effect. In rare cases, antifactor Xa assays can be used to monitor the effect of LMWHs because they do not reliably affect the PTT.

**Closure Time**
Closure time, measured by a platelet function analyzer (PFA-100\textsuperscript{®}) device has replaced bleeding time to assess platelet function. Assessing the bleeding time was more time-intensive and more operator-dependent. To perform a closure time, citrate-anticoagulated blood is placed in a cartridge with a membrane and time-to-clot is assessed. Two membranes are used: collagen/epinephrine (CEPI) membrane and collagen/adenosine diphosphate (CADP) membrane. Aspirin will prolong the CEPI but not the CADP. Thrombocytopenia (platelet count < 100,000/mm\textsuperscript{3}) may also prolong the closure time.\textsuperscript{39} A closure time is indicated to assess platelet function when there is a history of easy bruising or bleeding or in cases of critical, life-threatening bleeding. A normal closure time is 80-184 seconds for the CEPI and 56-102 seconds for the CADP, although these ranges may vary slightly between laboratories. In some institutions, the prolonged turnaround time for this test precludes its use in the ED.

**Type And Screen/Crossmatch**
The type test determines ABO and Rh-type compatibility. The type and screen allows type-specific blood products to be used relatively early. A crossmatch is performed to ensure compatibility between the donor’s red blood cells (RBCs) and the recipient’s plasma in a more complete search for antibodies.

**Urinalysis**
The clinical significance of gross hematuria in anticoagulated patients must not be downplayed as simply a side-effect of medications. A substantial portion of these patients will have underlying pathology. In one series, malignant tumors were found in 24% of patients and other treatable etiologies in half of the patients.\textsuperscript{43} In addition, the urinalysis is the initial test to rule out an infectious etiology.

**Imaging**

**Head Computed Tomography**
The head CT scan is an essential component of the evaluation of head trauma (even seemingly minor trauma) in the anticoagulated patient.\textsuperscript{9,40,41} (See Figure 2.) One small, retrospective study suggested that anticoagulated patients with head injury, normal GCS scores, and no focal neurological deficits may not require head CT scan.\textsuperscript{42} This retrospective study had a total of 89 anticoagulated patients, only 7 of whom had an intracranial hemorrhage, and all of these patients had either a focal deficit or decreased GCS (average 12). The authors’ recommendation may be overly bold for such a small study, since other studies disagree with this conclusion and recommend a more conservative approach. Unfortunately, despite the
The use of intravenous vitamin K does have a black box warning related to reports of severe anaphylactoid reactions and cardiac or respiratory arrest despite using precautions such as slow infusion rates and dilution. When using intravenous vitamin K, do not infuse faster than 1 mg/minute. Intravenous vitamin K may be diluted with either normal saline or D5W. Because of these potential reactions, the oral route of replacement is preferred except in cases of serious or life-threatening bleeding.

The oral form is well-absorbed except in cases of altered absorption, such as with gastrointestinal bleeding.

Fresh Frozen Plasma
Fresh frozen plasma (FFP) should be used for any patient with an elevated INR and serious or life-threatening bleeding. A type and screen must be sent to ensure compatibility of FFP. Fresh frozen plasma is available at most hospitals, but if kept frozen, it must be thawed before use. The thawing time is usually 30 to 45 minutes. Some hospitals have developed protocols for emergency reversal of warfarin using universal FFP in order to avoid delays in initiating management. Other hospitals maintain thawed plasma, which is kept at 1° to 6°Celsius for up to 5 days. Even with such protocols, the time until correction of the INR is substantial due to thawing and time required to administer the appropriate volume of FFP. The dose of FFP is 10-15

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>Replaces factors II, VII, IX, and X</td>
<td>· Markedly elevated INR</td>
<td>· Slow onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>· Elevated INR with bleeding</td>
<td>· May not be effective in liver failure</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Restores clotting factors</td>
<td>· Elevated INR with bleeding</td>
<td>· Large volume required</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>· Thawing time</td>
</tr>
<tr>
<td>Prothrombin complex concentrate</td>
<td>Restores factors II, VII, IX, and X</td>
<td>· Elevated INR with life-threatening bleeding</td>
<td>· Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>· Thrombotic complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>· Only to be used for warfarin reversal</td>
</tr>
<tr>
<td>rFVIIa*</td>
<td>Activates coagulation cascade</td>
<td>· Elevated INR with life-threatening bleeding</td>
<td>· Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>· Short duration of effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>· Thrombotic complications</td>
</tr>
<tr>
<td>Protamine</td>
<td>Reverses heparin and partially LMWH</td>
<td>· Bleeding in patients on heparin or LMWH</td>
<td>· Maximum dose 50 mg</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Increases vWF levels and activity</td>
<td>· Bleeding in patients on antiplatelet agents</td>
<td>· May cause vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>· Repeated doses decrease sodium</td>
</tr>
<tr>
<td>Platelets</td>
<td>Supplies platelets</td>
<td>· Bleeding in patients on antiplatelet agents or with thrombocytopenia</td>
<td>· Variable response</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Provides vWF, factor VII, and fibrinogen</td>
<td>· Low fibrinogen level</td>
<td>· Pooled plasma product</td>
</tr>
<tr>
<td></td>
<td></td>
<td>· Bleed after thrombolytics</td>
<td></td>
</tr>
</tbody>
</table>

*Off-label usage.

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin; rFVIIa, recombinant activated factor VII; vWF, von Willebrand factor.
ml/kg, which can be a substantial fluid load in these patients, many of whom are elderly and have significant comorbidities. In addition, substantial time may be required to administer this volume.14

Despite these drawbacks, FFP is still the most widely used agent (besides vitamin K) to reverse the anticoagulant effects of warfarin. The time delays and risks associated with the use of FFP have led to a search for alternative approaches to the correction of supratherapeutic INRs. Prothrombin complex concentrate (PCC) and rFVIIa have been proposed as alternatives.

**Prothrombin Complex Concentrate**

Prothrombin complex concentrate is a pooled plasma product. Prothrombin complex concentrate replaces the vitamin K-dependent clotting factors, II, VII, IX, and X. Unlike FFP, PCC is reconstituted quickly, given in a small volume, and can be given rapidly.46 Fresh frozen plasma is used as adjunctive therapy since PCC provides only low levels of factor VII.46 Prothrombin complex concentrates that only have a low level of factor VII are known as 3-factor PCCs and are the only types currently available in the US.46 (See Table 7.) In a retrospective case series of 40 patients, Holland et al showed an increase in adequate correction of elevated INRs from 55% with 3-factor PCC alone to 89% with 3-factor PCC with the addition of 2 units of FFP.46 In Europe, 4-factor PCCs are available and provide adequate levels of factor VII. Prothrombin complex concentrate provides faster — and perhaps even more complete — correction of anticoagulation when compared with FFP alone.47-49 In trauma patients with intracranial hemorrhage, a protocol using PCC, FFP, and vitamin K normalized the INR in half the time required to do the same with FFP.47 In addition, PCC avoids the excessive fluid load that is associated with FFP.49,50

PCC has an 8-hour duration of effect.47 While PCC rapidly corrects the anticoagulation profile, there is a concern for thrombotic complications. In a 58-patient study, PCC was very successful in correcting the INR, but 4 patients had suspected thromboembolic complications, 2 patients had deep vein thromboses (DVTs), and 2 patients had non-ST segment elevation myocardial infarction (non-STEMI), although it is difficult to definitively attribute the cause to the PCC treatment.50 In light of the potential for both venous and arterial thrombotic complications, PCC should only be administered in the setting of immediately life-threatening bleeding.

**Recombinant Factor VIIa**

Recombinant factor VIIa is a synthetic factor initially approved to treat bleeding in hemophiliacs who had developed inhibitors to factor concentrates. Circulating factor VIIa binds with tissue factor to trigger coagulation.14 It directly stimulates thrombin production, activates factor X, and converts fibrinogen to fibrin to form a stable clot. Despite its early promise, there are no studies that demonstrate rFVIIa definitively improves outcomes compared with standard therapy for warfarin reversal. (See Controversies/Cutting Edge section, page 15.) There was a reduction in intracerebral hematoma expansion in patients treated with rFVIIa in one promising study.51 The duration of effect for rFVIIa is only 2-3 hours. In addition to its high cost, there is also concern for potential thrombotic complications with the administration of rFVIIa. In fact, a recent analysis of 35 clinical trials on the off-label use of rFVIIa demonstrated an increased risk of arterial thrombotic complications, particularly in elderly patients.52

**Protamine**

Protamine can be used to reverse the anticoagulation effects of heparin and to partially reverse the anticoagulation effects of the LMWH. The dose of protamine is based on the amount of heparin or LMWH received over the past 4 hours. For every 100 units of heparin or each mg of LMWH, 1 mg of protamine should be given.14 Protamine only reverses about 60% of the anticoagulant effect of LMWH.14 The maximum dose is 50 mg intravenously over 10 minutes. For reversal of LMWH, the above dosing applies to enoxaparin; the protamine dose will be different for dalteparin and fondaparinux.

**Desmopressin**

Desmopressin increases platelet adherence at the site of vessel injury by promoting the release of von Willebrand factor (vWF). It is the treatment of choice for many patients with von Willebrand disease and mild hemophilia A. Clinical studies are lacking to determine whether it is effective in acquired bleeding disorders, uremic platelet dysfunction, or

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**Table 7. Prothrombin Complex Concentrate Brands Available In The US**16

<table>
<thead>
<tr>
<th>Brand</th>
<th>Dose</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profilnine-SD®</td>
<td>Low-dose therapy (25 U/kg)</td>
<td>Contains 150 U factor II,</td>
</tr>
<tr>
<td></td>
<td>High-dose therapy (50 U/kg)</td>
<td>35 U factor VII, 100 U factor X for every 100 U factor IX.</td>
</tr>
<tr>
<td>Bebulin-VH®</td>
<td>Can be dosed by body weight (35 U/kg) or with a formula based on desired factor increase, hematocrit, INR, and body weight (preferred)</td>
<td>· Also contains factor II and factor X</td>
</tr>
<tr>
<td>(factor IX Complex)</td>
<td></td>
<td>· Contains low amounts of factor VII</td>
</tr>
<tr>
<td>Proplex-T®</td>
<td>Withdrawn from US market</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: INR, international normalized ratio; U, units.
Clinical Pathway For Management Of Supratherapeutic INR

Supratherapeutic INR

Bleeding?

YES

If serious or life-threatening, administer all of the following:
• Vitamin K 10 mg IV slowly (Class II)
• FFP (Class II)
• PCC or rFVIIa* (Class III)

NO

Adjust treatment according to INR

INR = 3 to < 5
1. Omit next dose
2. Recheck INR (Class II)

INR = 5 to < 9
1. Omit next 1 or 2 doses
2. Recheck INR
3. Consider oral vitamin K (1-2.5 mg) (Class II)

INR = ≥ 9
1. Omit next 1 or 2 doses
2. Administer oral vitamin K (2.5–5 mg)(Class II)

*If PCC or rFVIIa is unavailable, proceed with vitamin K and FFP.

Adapted from ACCP Guidelines 2008

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

Class Of Evidence Definitions

Each action in the clinical pathways section of Emergency Medicine Practice receives a score based on the following definitions.

Class I
• Always acceptable, safe
• Definitely useful
• Proven in both efficacy and effectiveness

Level of Evidence:
• One or more large prospective studies are present (with rare exceptions)
• High-quality meta-analyses
• Study results consistently positive and compelling

Class II
• Safe, acceptable
• Probably useful

Level of Evidence:
• Generally higher levels of evidence
• Non-randomized or retrospective studies: historic, cohort, or case control studies
• Less robust RCTs
• Results consistently positive

Class III
• May be acceptable
• Possibly useful
• Considered optional or alternative treatments

Level of Evidence:
• Generally lower or intermediate levels of evidence
• Case series, animal studies, consensus panels
• Occasionally positive results

Indeterminate
• Continuing area of research
• No recommendations until further research

Level of Evidence:
• Evidence not available
• Higher studies in progress
• Results inconsistent, contradictory
• Results not compelling

Clinical Pathway For Management Of Minor Head Injury In The Anticoagulated Patient

Minor head trauma while anticoagulated

Elevated INR?

YES

Perform head CT scan

NO

Standard head injury management (Class II)

Intracranial hemorrhage?

YES

• Observe 6-12 hours, depending on hospital protocol (Class III)
• Repeat CT scan (Class II)
• Correct INR (Class III)

NO

If serious or life-threatening, administer all of the following:
• Vitamin K 10 mg slow IV (Class II)
• FFP (Class II)
• PCC or rFVIIa* (Class III)

See class of evidence descriptions, page 10.

*If PCC or rFVIIa is unavailable, proceed with vitamin K and FFP.

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

patients on antiplatelet therapy. Desmopressin is relatively inexpensive and does not carry blood-borne viruses. The dose is 0.3 mcg/kg intravenously. Commonly encountered adverse effects include facial flushing, tachycardia, hypotension, and cephalgia. Its role in the management of the head-injured patient on antiplatelet therapy is undefined.

Platelet Transfusion
Platelet transfusion has been suggested as a possible treatment for the patient with platelet dysfunction who has an intracranial bleed or some other hemorrhagic life-threatening complication. There are little data in this area.

Cryoprecipitate
Cryoprecipitate is a concentrate of plasma that contains fibrinogen, factor VIII, and vWF. It is used in conjunction with FFP to treat hemorrhage caused by fibrinolytic therapy. The biggest advantage of cryoprecipitate is more fibrinogen per volume.

Supratherapeutic INRs
Elevated INRs are commonly encountered in the ED. In 2008, the American College of Chest Physicians (ACCP) published evidence-based guidelines directing the management of such patients. (See Table 8, page 12.) These guidelines critically review the management of thromboembolic disorders. The strength of their recommendations depends on the trade-off between benefits, risks, and costs and the level of confidence in these estimates. A strong recommendation receives a grade 1 designation while a less-certain benefit will receive a grade 2 designation. Support for these recommendations are labeled A, B, or C depending on the quality of the evidence. Advanced age and extreme elevation of INR are clinical predictors of prolonged delay of normalization of INR, so these patients may be at greater risk of hemorrhagic complications until their INR is corrected. In a prospective study of 979 anticoagulated patients, Garcia et al demonstrated that when the INR is greater than 5 but less than 9, patients have a risk of major hemorrhage of 1.3% (confidence
interval 0.6-2.1%) within 30 days.\textsuperscript{36}

For patients with no significant bleeding and markedly elevated INR (\textgreater 9), oral vitamin K is recommended in a dose of 2.5-5 mg, which will be expected to decrease the INR over 24-48 hours.\textsuperscript{34} For serious or life-threatening bleeding, intravenous vitamin K is recommended in a dose of 10 mg infused slowly, plus FFP and either PCC or rFVIIa.\textsuperscript{34}

**Head Trauma**

The anticoagulated patient with head trauma is at risk of harboring a life-threatening lesion and must be carefully assessed and reassessed.\textsuperscript{55} In a retrospective study, Mina et al demonstrated a mortality 5 times that of non-anticoagulated patients with similar head injuries.\textsuperscript{56} Falls were the leading mechanism for such injuries. In fact, there was a 39\% (7/18) death rate in patients who fell on a level surface and were taking either anticoagulants or antiplatelet agents.\textsuperscript{56} Unfortunately, there were no clinical predictors for subsequent mortality in this study.\textsuperscript{56} The degree of anticoagulation predicts adverse outcomes in elderly patients after head injury.\textsuperscript{57,58} Age over 70 years and anticoagulation with warfarin were both independent predictors of mortality after head trauma in a retrospective study of 1493 patients.\textsuperscript{59} In this study, anticoagulated patients were assigned to 4 different groups based on their INR: less than 1.9, 2 to 2.9, 3 to 3.9, and greater than or equal to 4. There was a progressive increase in both mortality and incidence of an intracranial hemorrhage as the INR increased.\textsuperscript{59} A retrospective study of 166 patients by Fortuna et al questioned this increase in mortality; however, his study involved patients receiving only antiplatelet medications and/or warfarin, thus potentially decreasing the impact of therapeutic anticoagulation.\textsuperscript{60} Ninety-one of the study patients were on aspirin alone, while only 29 patients were taking warfarin, with a mean INR of only 2.3.\textsuperscript{60}

Head injury remains the fifth leading cause of death in patients over 65 years of age.\textsuperscript{58} The risk of death increases when the patient is anticoagulated; consequently, practice guidelines directing management of mild TBI patients generally exclude patients on anticoagulants.\textsuperscript{55,58} There are no historical or physical criteria that can safely screen which anticoagulated patients with mild TBI harbor a potentially lethal injury. Expedited head CT is a necessity in the anticoagulated patient with head trauma.\textsuperscript{44,59} If the CT scan reveals an intracranial hematoma, the patient must be provided aggressive reversal of their anticoagulation. On the other hand, there is no consensus on how to manage the disposition of the anticoagulated patient with minor head trauma and a negative head CT scan.\textsuperscript{9,44} Some have advocated admitting these patients for observation while others have recommended repeat head CT scan at an 8- or 12-hour interval.\textsuperscript{9,61} Despite the fact that this is a common clinical scenario, there is a distinct lack of outcomes data.\textsuperscript{9}

Head-injured patients on antiplatelet agents

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**Table 8. Managing Supratherapeutic INRs**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR more than therapeutic range but &lt; 5.0; no significant bleeding</td>
<td>Lower dose or omit dose; monitor more frequently and resume at lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required (Grade 1C).</td>
</tr>
<tr>
<td>INR ( \geq 5.0 ), but &lt; 9.0; no significant bleeding</td>
<td>Omit next 1 or 2 doses, monitor more frequently; resume at an appropriately adjusted dose when INR in therapeutic range. Alternatively, omit dose and give vitamin K (1–2.5 mg po), 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 po) can be given with the expectation that a reduction of the INR will occur in 24 h. If the INR is still high, additional vitamin K (1–2 mg po) can be given (Grade 2C).</td>
</tr>
<tr>
<td>INR ( \geq 9.0 ); no significant bleeding</td>
<td>Hold warfarin therapy and give higher dose of vitamin K (2.5–5 mg po) with the expectation that the INR will be reduced substantially in 24–48 h (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 FFP, PCC, or rFVIIa, depending on urgency; vitamin K can be repeated every 12 hours if persistent INR elevation (Grade 1C).</td>
</tr>
<tr>
<td>Life-threatening bleeding</td>
<td>Hold warfarin therapy and give FFP, PCC, or rFVIIa supplemented with vitamin K (10 mg by slow IV infusion). Repeat, if necessary, depending on INR (Grade 1C).</td>
</tr>
</tbody>
</table>

Abbreviations: FFP, fresh frozen plasma; h, hours; INR, international normalized ratio; IV, intravenously; PCC, prothrombin complex concentrate; po, by mouth; rFVIIa, recombinant activated factor VII.

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

Adapted from "Pharmacology and Management of the Vitamin K Antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)." Published in Chest. Copyright 2008 by AM COLLEGE OF CHEST PHYSICIANS. Reproduced with permission of AM COLLEGE OF CHEST PHYSICIANS in the format Journal via Copyright Clearance Center.
such as clopidogrel or aspirin also demand caution, yet they are even less studied. In a prospective study of 231 elderly patients (age > 60) who fell, Spektor et al reported that low-dose aspirin prophylaxis did not increase the frequency of intracranial bleeding. A retrospective study by Mina et al of 74 patients with intracranial injuries suggested that even aspirin increases the risk of death in patients with an intracranial injury. Obviously, more studies are needed to clarify this clinical situation.

Non-Traumatic Intracranial Bleeding
The anticoagulated patient with an intracerebral hemorrhage has an acutely life-threatening emergency. This is the most-feared complication of anticoagulation, with an annual risk of 0.5% to 1%. For more information on current guidelines on management of intracerebral hemorrhage, see the January 2011 issue of EM Practice Guidelines Update at www.ebmedicine.net/ICH. Warfarin use is associated with 5% to 24% of non-traumatic intracranial hemorrhage cases. There are no universal guidelines for the management of oral anticoagulant therapy-associated intracerebral hemorrhage. Most warfarin-associated intracerebral hemorrhages occur with the INR in the therapeutic range. In patients on warfarin, 50% of spontaneous intracerebral hemorrhages will expand in the first 24 hours, compared to 20% of traumatic intracerebral hemorrhages.

Risk Management Pitfalls For Management Of Anticoagulated Patients In The ED

1. “His head CT was negative and his neuro examination was normal. Of course I sent him home.”
   Delayed intracranial bleeds have been reported in anticoagulated patients with mild head injury. Although there is not universal agreement on the management of these patients, both observation and repeat CT scan have been suggested in the neurosurgical and trauma literature.

2. “I was just treating her UTI. I didn’t have time to review all her medications.”
   Many elderly patients are on warfarin, and many antibiotics interact with this drug. A few minutes reviewing medications could save you hours in court time later.

3. “She didn’t complain of abdominal pain. I didn’t even consider the possibility of a retroperitoneal hemorrhage.”
   Abdominal pain is present in less than two-thirds of these cases. The patient may also complain of hip, thigh, or groin pain. These diverse presentations need to be considered in the anticoagulated patient.

4. “I reviewed the med list. There was no mention of the supplements that interfere with warfarin.”
   Many patients don’t consider supplements drugs. They have to be specifically asked about supplement use.

5. “Of course I gave him vitamin K subcutaneously for his elevated INR. That’s how we always did it when I trained.”
   The subcutaneous use of vitamin K is unpredictable, and this route is not recommended by the ACCP guidelines.

6. “I saw the abdominal wall ecchymosis. I thought it was from his injections of LMWH.”
   Cullen’s sign is the presence of periumbilical ecchymosis and is associated with retroperitoneal hemorrhage.

7. “The liver patient was bleeding and his INR was elevated. I gave him PCC to reverse his coagulopathic state. How could I predict he was going to have a stroke?”
   PCC is only for warfarin-induced coagulopathy. It may cause thrombotic complications in all other circumstances.

8. “I gave her vitamin K before I transferred her to the tertiary center for her intracerebral bleed. I knew she was on warfarin, but I didn’t think she would expand her bleed.”
   Although treatment may be limited by what resources are available, PCC, rFVIIa, or FFP should be considered prior to transfer if it doesn’t cause undue delay.

9. “He was another patient with severe back pain. Everybody thinks their back pain is severe.”
   In the anticoagulated patient, spinal epidural hematoma must be considered.

10. “I didn’t consider compartment syndrome. It was only minor trauma.”
    With the anticoagulated patient, these volume-space problems may occur with even minor trauma. They must be anticipated, and good discharge instructions are a must.
to 30% of such bleeds in patients not on warfarin. In a retrospective study by Lee et al, 8% of 65 anticoagulated patients studied showed progression even after normalization with FFP, and almost 20% progressed before complete reversal of anticoagulation. In patients with supratherapeutic INRs, the degree of prolongation correlated with hematoma expansion and increased mortality. Surprisingly, in a retrospective study of 52 anticoagulated patients with head trauma, these patients did not show improvement with reversal of coagulopathy. Due to its retrospective nature, the rapidity of the reversal of anticoagulation was not noted. The authors mention that they did not have a protocol for reversal, implying that it may have been delayed, which may explain the patients’ lack of improvement.

There are no direct comparison studies between rFVIIa and PCC in patients with warfarin-associated intracerebral hemorrhage. The choice of reversal agents will often depend on availability and local protocols. Most authorities prefer PCCs, if available, due to their longer duration of action and apparently fewer thromboembolic events. Currently, the anticoagulated patient with an intracerebral hemorrhage has a worse outcome than other patients with intracerebral hemorrhage, regardless of treatment.

### Spinal Epidural Hematoma

Spinal epidural hematoma has been described as a clinical entity since 1867. Without rapid diagnosis and proper treatment, it often leads to permanent neurological deficits. Anticoagulation may be complicated by a spinal epidural hematoma. Spinal hematoma has been reported as a rare complication in hemodialysis patients who receive heparin during dialysis and have uremic-induced platelet dysfunction. This entity must be suspected in any anticoagulated patient with spinal pain, especially if weakness, sensory deficits, or bowel and bladder symptoms are present. Immediate correction of any coagulopathy, emergent MRI, and neurosurgical consultation are indicated.

### Retroperitoneal Hemorrhage

The anticoagulated patient with a retroperitoneal hemorrhage has a potentially life-threatening emergency. This entity is often insidious and not recognized initially. Abdominal pain is present in less than two-thirds of these cases, and the patient may also complain of hip, thigh, or groin pain. Unexplained shock is another presentation. Anticoagulation and recent femoral artery catheterization are risk factors for retroperitoneal hemorrhage. Renal patients receiving LMWH are also at risk for retroperitoneal hemorrhage. This complication has been reported after peripheral nerve blocks in the lumbar plexus region. In a study by Ivascu et al, the mortality rate was 12.5% in 112 anticoagulated patients with retroperitoneal hemorrhage.

The presentation of a retroperitoneal hemorrhage can be subtle. In a small retrospective study by Hassaan et al, anemia was almost universally present in the 19 patients with retroperitoneal hemorrhage. Five percent of patients will not be anemic, so this diagnosis must still be pursued in the right clinical situation. The CT scan of the abdomen is diagnostic of a retroperitoneal hematoma. A femoral nerve palsy may result from compression by a hematoma on the nerve as it passes below the unyielding fascia into the femoral canal. Some authorities recommend early operative decompression after reversal of the anticoagulation.

### Rectus Abdominal Sheath Hematoma

Rectus abdominal sheath hematoma complicates anticoagulation with warfarin, heparin, and LMWH. A case series reported excellent outcomes with correction of coagulopathy and observation.
Multiple Trauma

Although all trauma issues are more difficult in the anticoagulated patient, not all scenarios could be covered in this article, which focuses mainly on the most lethal complication, intracranial injury. Earlier use of plasma products and platelets will reduce the incidence of coagulopathy in the trauma patient who receives massive transfusions.85,86 A study by Williams demonstrated an association of anticoagulation with an increased mortality in trauma patients.87 In a survey of US trauma centers, Horton found that there is not a standardized approach to rFVIIa administration in the management of the severely injured trauma patient.88 A retrospective study of non-weight-based, low-dose rFVIIa for trauma patients with mild to moderate coagulopathy revealed a 15% rate of thromboembolic events although they felt that not all of these events, were related to this intervention.89 The appropriate management of coagulopathy in the multiple trauma patient has yet to be defined.

Special Circumstances In Management

Anticoagulated Patients On Antiplatelet Agents

The patient taking both anticoagulants and antiplatelet agents has deficiencies in both primary and secondary hemostasis. In a retrospective study of 109 patients, Ivascu et al showed an increased mortality from bleeding or from their comorbidities in head trauma patients who were only on aspirin or clopidogrel.90 This effect would be expected to be increased further in patients who were also anticoagulated. In fact, studies have shown an increased risk of bleeding when anticoagulation and antiplatelet agents are used together.91 Desmopressin can counteract the effects of aspirin and clopidogrel,92 but there are no studies that evaluate the effectiveness of this treatment in the trauma patient. In a case report by Ranucci et al, desmopressin partially corrected the antiplatelet effects of clopidogrel and aspirin.93 Platelet transfusions have been used in patients on antiplatelet agents although no good outcome studies exist. Reversal of coagulopathy would follow previous recommendations.

Management Of tPA-Related Hemorrhage

Thrombolytic therapy may be complicated by symptomatic intracranial hemorrhage. This complication may occur while the patient is still in the ED. The changes to the coagulation profile after fibrinolytic therapy are not well-studied. The goal is to stop the continued breakdown of fibrin. Ten units of cryoprecipitate should be administered along with FFP.93,94 If the patient had been receiving antiplatelet agents, platelets should be transfused. There are no significant studies in this area.

Controversies/Cutting Edge

Rapid Correction With Recombinant Factor VIIa

The role of rFVIIa in the management of an intracranial hemorrhage is unclear, regardless of whether or not the patient is anticoagulated. The functional and survival benefits that were demonstrated in a phase II trial were not found in the phase III trial.64 Recombinant factor VIIa was initially approved by the US Food and Drug Administration (FDA) on March 25, 1999 for use in hemophiliac (A and B) patients with inhibitors to factors VIII or IX. Since its approval, its off-label use in patients without hemophilia has been increasing.86,95,96 There is a strong interest in rFVIIa to decrease the expansion of intracerebral hemorrhage.97 A phase III trial of rFVIIa in limiting intracerebral hemorrhage demonstrated reduced growth of the hematoma; however, there was not a benefit in survival or functional outcome.98 A small prospective study showed that rFVIIa can rapidly reverse excessive anticoagulation, and in some cases with lower doses.99

Although there are 4 vitamin K-dependent coagulation factors that are depleted by warfarin, factor VII seems to be the most depleted, critical factor in the anticoagulated patient.100 Recombinant factor VIIa activates factors IX and X when complexed with tissue factor. The result is increased formation of thrombin and subsequently fibrin.88

Recombinant factor VIIa has also been used to reverse excessive anticoagulation in trauma patients much more quickly than traditional methods.89,101 To be maximally effective in these trauma patients, acidosis must be corrected before the use of rFVIIa.37 Thromboembolic adverse events seem to occur more frequently with the off-label use of rFVIIa to treat various types of bleeds in nonhemophiliacs, but the determination of these adverse events is limited by the voluntary nature of post-licensure reporting.95 In a study of 29 patients, no thromboembolic complications were reported.100 This study demonstrated a better functional outcome, although there was no change in mortality.100 In a recent pooled analysis of 35 clinical trials on the off-label use of rFVIIa, an increased risk of arterial thrombotic complications was demonstrated, most notably in elderly patients.52

Although rFVIIa is expensive, it may prove cost-effective if improved outcomes lead to shorter hospitalizations and rehabilitation times.100 The use of rFVIIa may allow the early surgical evacuation of a hematoma.68 Owen reported attempts of an academic center to standardize its use in an effort to decrease costs.102 A dose escalation study was performed to identify the lowest effective dose.103 Doses of rFVIIa greater than 80 mcg/kg increase risk of thromboembolic complications without any further benefit in limiting hematoma growth.104 Further
research is required to clarify the most appropriate and efficient use of rFVIIa.

**Disposition**

The disposition of the anticoagulated patient with a potential or actual bleeding complication must be made after cautiously weighing the risk of potential deterioration. Most asymptomatic patients can be discharged home even with markedly elevated INRs unless they have little support or they are a significant fall risk.

There is no consensus on how to manage the disposition of the anticoagulated patient with minor head trauma and a negative head CT scan. There is also no agreed-upon degree of INR that precludes concern for a delayed bleed. Some authorities have advocated admitting these patients for observation while others have recommended repeat head CT scan at an 8- or 12-hour interval. The clinical condition of the patient, associated medical problems and injuries, and support system for the patient will play a role in the decisionmaking. Most significant complications of anticoagulation will result in admission of those patients to an intensive care unit or a transfer if the specialty required is not available.

**Summary**

In summary, patients on anticoagulants are at risk for the following hemorrhagic complications:
- Intracerebral/ intracranial hemorrhage
- Spinal epidural hematoma
- Retroperitoneal hemorrhage
- Rectus sheath hematoma
- Hemothorax
- Gastrointestinal bleeding
- Compartment syndrome
- Hematuria

With the aging of the population, more and more anticoagulated patients will be presenting to ED. A protocol for rapid reversal of anticoagulation should be established, and the anticoagulated ED patient must be carefully evaluated and treated for any of the above complications. A thorough knowledge of reversal agents is necessary to optimally manage these patients. Appropriate consultation should be obtained early, and disposition of these patients must be suitably cautious. There is an increasing body of literature on reversing anticoagulation, and this will need to be followed closely for any changes and future recommendations.

**Case Conclusions**

The elderly man who “looked so good” left with his family only to return with decreased mental status just 6 hours later. A repeat head CT scan showed a large subdural with a shift. He was rapidly intubated, and he received FFP, vitamin K, and PCC. Since he received 3-factor PCC, the FFP was added to make up for the low level of factor VII in this type of PCC. The neurosurgeon took the patient to the operating room.

You decided to send the obese woman in the next room for an abdominal CT scan. This study demonstrated a large retroperitoneal hemorrhage. She received packed red blood cells, FFP, and vitamin K. She was stabilized without any operative intervention. The intensivist felt that her need for reversal was urgent but not immediately life-threatening. He planned to use PCC if she became hemodynamically unstable.

At the conclusion of another busy shift, you reflect upon the diverse presentation of patients taking anticoagulants. You realize these complications will increase in frequency. The management of these complications may be subject to change as the newer agents are further studied.

**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, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.


83. Ivascu FA, Howells GA, Junn FS, et al. Predictors of mortality in trauma patients with intracranial hemorrhage on
1. Most patients presenting to the ED on warfarin are:
   a. Supratherapeutic
   b. Therapeutic
   c. Subtherapeutic
   d. At risk of immediate hemorrhage

2. Primary hemostasis results in the formation of:
   a. Platelet plug
   b. Thrombin
   c. Fibrin cap
   d. Increased coagulation factors

3. Secondary hemostasis results in the formation of:
   a. Platelet plug at site of injury
   b. von Willebrand Factor
   c. Fibrin reinforcement of platelet plug
   d. Increased coagulation factors

4. What mechanism of injury is responsible for the majority of traumatic deaths in anticoagulated patients?
   a. Motor vehicle crashes
   b. Falls
   c. Gunshot wounds
   d. Assaults

5. Approximately what percentage of spontaneous intracerebral hemorrhages will expand in the first 24 hours in patients on warfarin?
   a. 5%
   b. 10%
   c. 30%
   d. 50%

6. Which of the following antibiotics decreases the effect of warfarin?
   a. Amoxicillin
   b. Rifampin
   c. Doxycycline
   d. Ciprofloxacin

7. Warfarin is classified as a:
   a. Vitamin K antagonist
   b. Platelet antagonist
   c. Competitive inhibitor of thrombin
   d. Antithrombin III agonist

8. Fox's sign of retroperitoneal hemorrhage is best described as
   a. Ecchymosis of the scrotum
   b. Profound abdominal distention
   c. Periumbilical ecchymosis
   d. Ecchymosis of the upper thigh

CME Questions

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