Series Editor: Lewis S. Nelson, MD

# Oral Anticoagulation
## Striking the Perfect Balance

**Betty Chen, MD, and Lewis S. Nelson, MD**

Though anticoagulants are life-saving drugs, cases in which reversal is imperative due to uncontrolled bleeding are not uncommon. How can the effects of anticoagulants be safely reversed, and what potential hazards does this corrective effort present?

A 77-year-old man taking an oral anticoagulant for atrial fibrillation presents to the emergency department after falling at home. On arrival, he complains of abdominal pain. His vital signs are as follows: blood pressure, 67/42 mm Hg; heart rate, 102 beats/min; respiratory rate, 20 breaths/min; temperature, 97.9°F. His oxygen saturation is 95% on room air. On physical examination, the patient appears uncomfortable. He is pale and weak and has a tachycardic, irregular rhythm. His lungs are clear, but his abdomen is diffusely tender with rebound.

Large-bore intravenous access is obtained, and his blood pressure improves to 110/76 mm Hg after 3 L of normal saline are administered. Initial lab test results are significant for a hemoglobin of 10 g/dL, an international normalized ratio (INR) of 3.4, and an activated partial thromboplastin time (aPTT) of 45 seconds. His basic metabolic panel is notable for a creatinine level of 1.3 mg/dL. A CT scan of his abdomen shows a mesenteric hematoma and a retroperitoneal hematoma.

### Which anticoagulants can be administered orally?

The vitamin K antagonist warfarin is the most frequently prescribed anticoagulant for prevention and treatment of thromboembolic diseases. The vitamin K antagonists inhibit vitamin K 2,3-epoxide reductase and vitamin K quinone reductase. Inhibition of these enzymes hinders the conversion of inactive vitamin K to vitamin K quinol, the active form of vitamin K. Without active vitamin K, activation of factors II, VII, IX, and X is interrupted. Because genetics, diet, and drug interactions affect the action of warfarin, patients must undergo frequent surveillance of coagulation parameters and dose titration to ensure therapeutic consistency.[1] As a result, maintaining therapeutic dosing with warfarin is complicated and inconvenient.

Newer synthetic oral anticoagulants are now available that target different clotting factors and inhibit the coagulation cascade in a manner distinct from that of warfarin. A benefit of these new anticoagulants is the convenience of fixed-dose administration without the requirement for frequent laboratory surveillance of anticoagulant effect. Although these agents have few drug interactions and no dietary interactions, the absence of an adequate mechanism to monitor effect may underlie the lack of an apparent need to monitor.

The oral direct thrombin inhibitor dabigatran etexilate binds bound and free thrombin and interrupts both conversion of fibrinogen to fibrin and platelet activation.[2] Dabigatran is approved in the United States for prevention of systemic thromboembolism and stroke in patients with nonvalvular atrial fibrillation. Dabigatran has few drug interactions, and hypersensitivity reaction to dabigatran and active pathologic bleeding are the only abso-

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lute contraindications. Dose adjustment may be required in patients with renal dysfunction since dabigatran is largely excreted by the kidneys.[3]

Rivaroxaban, another synthetic oral anticoagulant, inhibits factor Xa and thereby interrupts the coagulation cascade at the intersection of the intrinsic and extrinsic pathways. In addition, this medication interrupts tissue factor–induced platelet aggregation.[4] Rivaroxaban is approved for the prophylaxis of deep vein thrombosis and pulmonary embolism following orthopedic surgery and for prevention of stroke or systemic thromboembolism in patients with nonvalvular atrial fibrillation. Although not yet available in the United States, apixaban, another synthetic factor Xa inhibitor, is used for anticoagulation. Apixaban is eliminated both renally and fecally, which might increase safety for patients with renal dysfunction.[2]

**Table**
Recommendations for Management of Elevated INR in Patients Requiring Chronic Anticoagulation With Warfarin

| INR | Recommendation |
|---|---|
| ≥4.5-10; no evidence of bleeding | Omit next dose of warfarin<br>No role for vitamin K or factor replacement |
| >10; no evidence of bleeding | Give oral vitamin K |
| Bleeding at any INR | Give vitamin K by slow intravenous injection<br>Factor replacement with prothrombin complex concentrate or fresh frozen plasma |

Adapted from Guyatt et al.[6]

## How do you measure the anticoagulation effect of these medications?

The effect of the vitamin K antagonists is most frequently measured using prothrombin time (PT) and the INR. The PT is a measure of the extrinsic pathway as well as the common pathway of the coagulation cascade. The extrinsic pathway depends largely on factor VII, the vitamin K–dependent factor with the shortest half-life. However, because variations in reagents and laboratory equipment may change the PT result, the INR is more useful since it reports the PT as a ratio, comparing it to an international standard.[1] Factors II, IX, and X, part of the intrinsic or final common pathway, are also vitamin K–dependent. Therefore, warfarin may also increase aPTT, especially with supratherapeutic dosing.

There are no readily available tests to measure the degree of anticoagulation with the newer oral anticoagulants. Although the PT and aPTT increase with dabigatran use, there is not a linear relationship with the degree of anticoagulation.[5] The thrombin clotting time (TT) and the ecarin clotting time (ECT) do exhibit a linear relationship with the degree of anticoagulation achieved with dabigatran. The TT measures the time required for fibrinogen to convert into fibrin in a plasma sample, a surrogate for thrombin activity. ECT is a measure of the time required for a clot to form in the presence of ecarin, an extract derived from the venom of *Echis carinatus*, a viper found in the Middle East and Asia. Neither of these tests is widely and immediately available. The manufacturer of dabigatran has developed a test to rapidly determine the serum dabigatran concentration, but it has not yet been approved for clinical use and it does not necessarily reflect the degree of anticoagulation.

The factor Xa inhibitors increase the PT and aPTT in a dose-dependent fashion. A point-of-care assay that measures anti-Xa activity correlates well with factor Xa inhibitor dose. The factor Xa inhibitors have no effect on ECT or TT.

If the identity of an oral anticoagulant is unknown in the setting of abnormal coagulation parameters, it may be helpful to perform a mixing study. In this study, pooled plasma is mixed 1:1 with a sample of the plasma in question. If the INR, PT, or PTT are prolonged due to a deficiency in vitamin K–dependent clotting factors, the addition of an equal amount of normal plasma should lead to correction of these values, even in cases of severe vitamin K–dependent factor deficiency. Failure to correct in a mixing study suggests the presence of a coagulation inhibitor such as heparin or the lupus anticoagulant.[1]

## How do you reverse anticoagulation in the setting of bleeding complications?

Vitamin K administration repletes the deficiency caused by the vitamin K antagonists. To assist in correction and prevent overcorrection of the INR, the American College of Chest Physicians published guidelines for management of elevated INRs in patients receiving vitamin K antagonists (Table).[6] To decrease the incidence of anaphylactoid reactions associated with intravenous administration of vitamin K, the medication should be administered no faster than 1 mg/min, with close monitoring. Regardless of the route of administration, there is a delay of several hours in the onset of action of vitamin K.[7]

> ➤➤ ***Fast Track***
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> *Because of the delay in vitamin K's effect, patients who are unstable or bleeding, or who have severe vitamin K deficiency, should receive direct factor replacement.*

Because of the delay in vitamin K's effect, patients who are unstable or bleeding, or who have severe vitamin K deficiency, should receive direct factor replacement. Fresh frozen plasma, cryoprecipitate, recombinant factor VIIa, and prothrombin complex concentrate (PCC) are all methods of replacing deficient factors. Infusion of 15 mL/kg of fresh frozen plasma should be sufficient to reverse coagulopathy from the vitamin K antagonists, with the caveat that each unit of fresh frozen plasma does not have a standard amount of clotting factors. Repeat dosing of fresh frozen plasma may be required due to the short half-life of some of the clotting factors. In addition, fresh frozen plasma may cause volume overload, which can be problematic for patients with intracranial hemorrhage, renal failure, or congestive heart failure. PCCs are small-volume replacements for factors II, VII, IX, and X. Recombinant factor VIIa can also be used to reverse coagulation from the vitamin K antagonists, but thrombosis is a possible adverse effect.[1]

The direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban have no definitive antidotes to reverse their anticoagulant effects. Dabigatran's manufacturer recommends fresh frozen plasma for volume resuscitation in cases of severe bleeding. PCC is also suggested, despite lack of substantial proof of efficacy. A study in mice given a single supratherapeutic dose of dabigatran noted a dose-dependent benefit from PCC in limiting surgically induced intracranial hematoma expansion. However, tail vein bleeding time remained prolonged despite PCC administration.[8] In healthy humans administered dabigatran for 2 days, there were no changes in aPTT, TT, or ECT after administration of PCC, as anticipated, since dabigatran inhibits thrombin, which is located at the end of the coagulation cascade. Upstream factor replacement should not change these measurements because the final common pathway is still interrupted.[9] Recombinant factor VIIa does not appear to be effective as an antidote, as measured in mice studies.[8]

Hemodialysis as a means to remove dabigatran has been suggested, although the data are limited. Preclinical studies show that hemodialysis extracts 62% to 68% of a single subtherapeutic dose of dabigatran administered to hemodialysis-dependent patients immediately prior to hemodialysis.[3] There have been no studies to evaluate the use of hemodialysis in overdose or the actual effect on coagulation parameters, bleeding, morbidity, or mortality. Hemodialysis may be risky in severely coagulopathic and unstable patients since catheter placement may cause bleeding.

Rivaroxaban is not amenable to dialysis due to its high protein binding. Appropriate volume resuscitation with factor replacement is the mainstay of care. Few studies have evaluated the efficacy of PCC in reversing rivaroxaban-induced anticoagulation. However, a single study suggests that PCC may be helpful. In healthy volunteers given rivaroxaban, administration of PCC normalized PT at a standard dose of 50 U/kg.[9]

Packed red blood cells can replace lost volume in hemorrhagic shock. However, red blood cells do not correct the underlying coagulopathy. In fact, transfusion of red blood cells alone can exacerbate coagulopathy by causing hypocalcemia due to the citrate anticoagulant they contain and by worsening factor dilution. Therefore, close monitoring of serum calcium and repletion of vitamin K–dependent factors are imperative.

## Case Conclusion

The patient was intubated and admitted to the intensive care unit. He developed recurrent hypotension and was

given 8 units of packed red blood cells as well as fresh frozen plasma after serial labs showed a falling hemoglobin. The surgery team did not take him to the operating room because he had been anticoagulated with dabigatran. Instead, the nephrologist performed hemodialysis based on the degree of coagulopathy and the severe nature of his illness. After two hemodialysis sessions, his hemoglobin stabilized. His INR and aPTT improved but did not normalize. The patient remained intubated for 3 days due to poor respiratory function, but he was subsequently extubated and discharged home. **EM**

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