Reversal of Warfarin

Case-Based Practice Recommendations

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Case Presentation: A 74-year-old woman presents to the emergency department with bruising. She takes warfarin for atrial fibrillation. She has recently begun taking trimethoprim/sulfamethoxazole. Her international normalized ratio (INR) is reported as 8.6.

Supratherapeutic INR values are common in warfarin-treated patients. In this case, the antibiotic is the likely cause, but it is not unusual for an INR measurement to exceed 3.0 without explanation. Irrespective of whether a cause for the INR increase can be identified, the patient should be interviewed and examined to ensure she is not bleeding. For an asymptomatic patient whose INR is >5, warfarin should be withheld for at least 1 dose, and close follow-up monitoring should be arranged. This patient's INR will return to the therapeutic range more quickly if she receives low-dose oral vitamin K (as opposed to simple warfarin withdrawal).[1] Low-dose oral vitamin K is often considered in such situations because INR elevations like the one described here can be quite alarming to both the patient and the

clinician. However, there is uncertainty about the short-term risk of major bleeding in such a patient. In one observational cohort of 1104 warfarin-treated asymptomatic patients with a single INR value between 5.0 and 9.0 (90% of whom were managed with simple warfarin withdrawal), only 0.96% experienced major hemorrhage within 30 days.[2] However, an earlier observational study of 114 asymptomatic patients taking warfarin with an INR >6.0 managed without vitamin K reported major bleeding in 5 patients (4.4%; 95% confidence interval, 1.4%–9.9%) during 14 days of follow-up.[3] To address this uncertainty, we randomized 355 nonbleeding warfarin-treated patients whose INR was >5.0 and <9.0 to receive either 1.25 mg of oral vitamin K or placebo. Although INR correction was more robust for the vitamin K–treated patients, the rate of major bleeding was low in both groups at 7 days (no major bleeds in either group) and at 90 days (2.5% with vitamin K versus 1.1% in the placebo group, $P=0.22$).[1] On the basis of these results, we suggest that for asymptomatic warfarin-treated pa-

tients whose INR is >5.0 and <9.0, low-dose oral vitamin K will more quickly lower the INR (and possibly allow earlier resumption of treatment) but would not be expected to lower the risk of major bleeding. Advanced age, decompensated heart failure, low weekly warfarin dose, and active malignancy are independent predictors of slow INR decay[4]; patients with these characteristics or clinical features to suggest a higher-than-average bleeding risk may benefit the most from a more rapid INR correction because they may be exposed to a higher risk of bleeding.[5]

Although the patient is asymptomatic, the treating physician decides to administer vitamin K. What dose and route of administration should be used?

For most warfarin-treated patients who are not bleeding and whose INR is >4.0, oral vitamin K (in doses between 1 and 2.5 mg) will lower the INR to between 1.8 and 4.0 within 24 hours.[6] Intravenous vitamin K can lower the INR more quickly than oral vitamin K, but at 24 hours, intravenous and oral vitamin K produce similar

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degrees of INR correction.[7] Subcutaneous vitamin K should not be used because it is less effective than oral or intravenous vitamin K; at 24 hours after treatment with low-dose subcutaneous vitamin K, fewer than 50% of patients will achieve an INR between 1.8 and 4.0.[6,8] We suggest 2 options for administering oral vitamin K: Either give one quarter to one half of a 5-mg tablet or add 1 to 2 mg of the intravenous preparation to a cup of orange juice. There is high-quality evidence that either method is effective for INR correction.[1,9]

An 86-year-old man is hospitalized with choledocholithiasis and biliary obstruction. He is scheduled to undergo endoscopic retrograde cholangiopancreatography with attempted stone retrieval in ≈24 hours. He takes warfarin for atrial fibrillation. His INR is currently 2.3, and his hepatic synthetic function appears to be normal. What is the optimal strategy to normalize his INR?

For warfarin-treated patients who need to undergo a semiurgent (within 24–36 hours) procedure, low-dose oral vitamin K, given the day before the intervention, will often achieve sufficient INR correction and avoid the need for transfusion. In a study of 2 parallel cohorts of patients assessed in a perioperative anticoagulation management clinic, all patients had their warfarin held 5 days before surgery. For patients whose INR was 1.4 to 1.9 the day before surgery, 1 mg of oral vitamin K was given. Thirty-nine (90.7%) of the 43 individuals in this cohort had an INR <1.5 the next day, and there was no difficulty reestablishing anticoagulation with warfarin after the procedure.[10] A study of anticoagulated patients who were planning to discontinue warfarin yielded similar findings. One milligram of oral vitamin K, given on the day of discontinuation, produced an INR <1.4 in 10 of 15 patients 24 hours later.[11] Thus, if the endoscopic retrograde cholangiopancreatography can be safely performed the next day, this patient should receive 1 to

Figure. A suggested algorithm for the management of a warfarin-treated patient whose international normalized ratio (INR) exceeds 4. IV indicates intravenously; Conc, concentrate.

2.5 mg of oral vitamin K as soon as possible, with plans to administer fresh frozen plasma at the time of the procedure only if the INR has not corrected. However, low-dose vitamin K should not be used as a substitute for careful perioperative management. A recent small trial found that low-dose oral vitamin K, when given at noon on the day before surgery, failed to achieve adequate INR correction in >60% of patients who had discontinued their vitamin K antagonist 2 days before elective surgery; most of these patients were using fluindione or acenocoumarol (vitamin K antagonists not available in the United States).[5]

A 52-year-old woman with a mechanical mitral valve presents with minor epistaxis. Her INR is 15.7. She is otherwise stable; the epistaxis resolves quickly with direct pressure, and a thorough review of systems and physical examination reveal no other evidence of bleeding.

The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines state, "For patients with INRs >9.0 and no significant bleeding, we recommend holding warfarin therapy and administering a higher dose of vitamin K (2.5 to 5 mg) orally, with the expectation that the INR will be reduced substantially in 24 to 48 h. Clinicians should monitor the INR more frequently, administer additional vitamin K if necessary, and resume therapy at an appropriately adjusted dose when the INR

reaches the therapeutic range."[12] There is moderate-quality evidence to support this recommendation; several studies indicate that a large proportion of patients with extreme INR elevation (eg, >10) will have their INR return to a safer range within 24 hours after 2 to 5 mg of oral vitamin K is administered.[13,14] Although some clinicians express concern that active anticoagulant reversal may place a patient with a prosthetic heart valve at high risk for thrombotic complications, we have conducted a small study that suggests low-dose oral vitamin K can be used in such patients without a high risk of overcorrection.[15] Additionally, thrombotic events have been very uncommon in the studies of low-dose oral vitamin that have been presented to date. We recommend that all nonbleeding patients with an INR >10 should receive 2.5 to 5 mg of oral vitamin K. The INR should be measured 24 to 48 hours later to guide the use of additional therapy. Any sign of bleeding should prompt a thorough clinical evaluation with admission and consideration of transfusion therapy (Figure).

A 37-year-old man receiving warfarin for secondary prevention of venous thromboembolism presents to the emergency department with a 2-day history of melena and new massive hematemesis. His INR is 7.3.

Up to 10% of patients with warfarin-associated major bleeding will die within 30 days. The most lethal form of warfarin-associated bleeding is in-
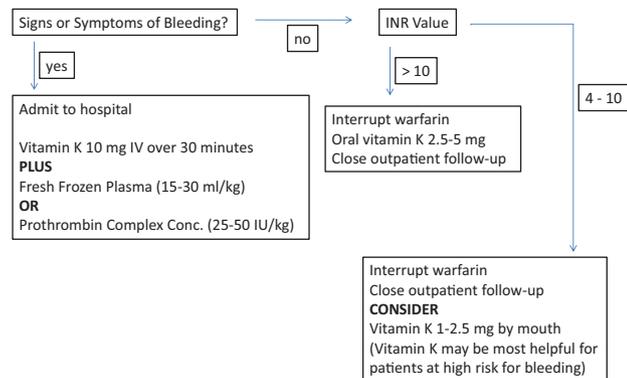
Table 1.   Characteristics of Therapies for Warfarin Reversal

Product	Time to Effect (After Administration)	Duration of Effect	Evidence of Efficacy for Warfarin Reveasl	Risk of Thrombosis	Relevant References
Oral vitamin K	24 h	Days	++++	NS	1, 6, 7, 8, 9, 11, 13, 14, 15
Intravenous vitamin K	8–12 h	Days	++++	NS	6, 7, 18
Fresh frozen plasma	Immediate	12–24 h	++	NS	12
PCC	Immediate	12–24 h	+++	+ (Higher with activated PCC)	19, 20, 21, 22
Recombinant factor VIIa	Immediate	2–6 h	+	++	23, 24, 25

PCC indicates prothrombin complex concentrate; NS, not significant (strategy neither significantly increases nor significantly decreases the risk of thrombosis).

tracranial hemorrhage (50% of such cases result in death), but major gastrointestinal bleeding (as described in this case) is also dangerous.[16,17] Although there is no high-quality evidence documenting the benefit of rapid INR normalization, every effort should be made to correct the coagulopathy as soon as possible; Table 1 provides information about warfarin reversal options. Intravenous vitamin K is necessary (to permit the synthesis of new, functional clotting proteins) but not sufficient; a large dose (5–10 mg administered intravenously) will normalize the INR in most patients, but its effect will take 24 hours to be fully manifest.[18] In the interim, coagulation factors should be replaced aggressively. Fresh frozen plasma is widely available and has been used for many patients with warfarin-associated coagulopathy. Unfortunately, each 250-mL

unit of plasma produces only small augmentations in the activity of individual clotting proteins. Thus, for a patient with profound coagulopathy, one might need to administer >1500 mL of fresh frozen plasma to achieve any meaningful increase in coagulation factor levels, particularly if bleeding is ongoing and coagulation factors continue to be lost. In contrast to fresh frozen plasma, prothrombin complex concentrates (PCCs) contain much higher amounts of the vitamin K–dependent clotting proteins per unit of volume (Table 2). Moderate-quality evidence suggests that 4-factor PCCs (which contain significant amounts of factors II, VII, IX, and X) reverse the anticoagulant effect of warfarin quickly.[19] Three-factor PCCs, which contain little or no factor VII and are labeled for the treatment of patients with factor IX deficiency, may also be

helpful in reversing warfarin. One study suggests that 3-factor products do not normalize the INR without concomitant plasma administration,[20] but others[21] have disputed this finding. Although the precise risk of thrombosis after PCC administration is not known, a recent meta-analysis of 27 studies suggests it is ≈1.8%.[22] This number may seem high; however, it is important to remember that (1) PCCs should only be used in patients with major or life-threatening bleeding (wherein the risk of death exceeds 1.8%), and (2) all patients receiving warfarin have an enhanced risk of thrombosis compared with patients not receiving warfarin, and thus, their risk of thrombosis after PCC will also be high. Recombinant factor VIIa has been used off-label for patients with serious warfarin-associated bleeding, but an experimental bleeding model suggests recombinant factor VIIa may not restore hemostasis as effectively as it corrects the INR.[23] Two case series have reported thromboembolism rates ≥10% among patients who received recombinant factor VIIa for intracerebral hemorrhage.[24,25]

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Table 2.   Vitamin K–Dependent Factor Amounts in Nonactivated Prothrombin Complex Concentrates Available Within and Outside the United States

Product (Manufacturer)	Factor II, IU/mL	Factor VII, IU/mL	Factor IX, IU/mL	Factor X, IU/mL
Available in the United States				
PCCs, 3-factor (II, IX, X)				
Profilnine SD (Grifols)	≤150	≤35	≤100	≤100
Bebulin VH (Baxter)	24–38	<5	24–38	24–38
Prothromplex HT (Baxter)	30	...	30	130
Available outside the United States				
PCCs, 4-factor (II, VII, IX, X)				
Beriplex (CSL Behring)	20–48	10–25	20–31	22–60
Octaplex (Octapharma)	14–38	9–24	25	18–30
Cofact (Sanguin)	14–35	7–20	25	14–35
Prothromplex T (Baxter)	30	25	30	30

PCCs indicates prothrombin complex concentrates.

The lower levels of factor VII in the 3-factor concentrates may be associated with less robust correction of the international normalized ratio; whether this correlates with a persistent risk of bleeding is unknown.

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