Reversal of Warfarin
Case-Based Practice Recommendations
David A. Garcia, MD; Mark A. Crowther, MD

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). 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. 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. 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, \( P = 0.22 \)). On the basis of these results, we suggest that for asymptomatic warfarin-treated patients 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; 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.

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. Intravenous vitamin K can lower the INR more quickly than oral vitamin K, but at 24 hours, intravenous and oral vitamin K produce similar...
degrees of INR correction. 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. 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.

An 86-year-old man is hospitalized with cholecdocholithiasis 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. 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. Thus, if the endoscopic retrograde cholangiopancreatography can be safely performed the next day, this patient should receive 1 to 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).

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.”

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. 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. 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).

Figure. A suggested algorithm for the management of a warfarin-treated patient whose international normalized ratio (INR) exceeds 4. IV indicates intravenously; Conc, concentrate.
Table 1. Characteristics of Therapies for Warfarin Reversal

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

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

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

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>Factor II, IU/mL</th>
<th>Factor VII, IU/mL</th>
<th>Factor IX, IU/mL</th>
<th>Factor X, IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Available in the United States PCCs, 3-factor (II, IX, X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin SD (Grifols)</td>
<td>$\leq 150$</td>
<td>$\leq 25$</td>
<td>$\leq 100$</td>
<td>$\leq 100$</td>
</tr>
<tr>
<td>Bebulin VH (Baxter)</td>
<td>24–38</td>
<td>$&lt; 5$</td>
<td>24–38</td>
<td>24–38</td>
</tr>
<tr>
<td>Prothromplex HT (Baxter)</td>
<td>30</td>
<td>. . .</td>
<td>30</td>
<td>130</td>
</tr>
<tr>
<td>Available outside the United States PCCs, 4-factor (II, VII, IX, X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beriplex (CSL Behring)</td>
<td>20–48</td>
<td>10–25</td>
<td>20–31</td>
<td>22–60</td>
</tr>
<tr>
<td>Octaplex (Octapharma)</td>
<td>14–38</td>
<td>9–24</td>
<td>25</td>
<td>18–30</td>
</tr>
<tr>
<td>Cofact (Sanguin)</td>
<td>14–35</td>
<td>7–20</td>
<td>25</td>
<td>14–35</td>
</tr>
<tr>
<td>Prothromplex T (Baxter)</td>
<td>30</td>
<td>25</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

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.

References:
1. 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.
2. 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. Two case series have reported thromboembolism rates ≥10% among patients who received recombinant factor VIIa for intracerebral hemorrhage.

Sources of Funding
Dr Crowther holds a Career Investigator Award from the Heart and Stroke Foundation of Canada and also holds the Leo Pharma Chair in Thromboembolism Research. No other funding source supported this work.

Disclosures
Within the past 2 years, Dr Garcia has served as an advisor to CSL Behring, Boehringer Ingelheim, Bristol Meyers Squibb, and Daiichi Sankyo. Dr Crowther discloses that he has served on advisory boards and/or prepared educational materials for...
Crowther has provided expert testimony for Bayer.

References


Reversal of Warfarin: Case-Based Practice Recommendations
David A. Garcia and Mark A. Crowther

Circulation. 2012;125:2944-2947
doi: 10.1161/CIRCULATIONAHA.111.081489
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/23/2944

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/