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American Journal of Health-System Pharmacy<sup>™</sup>

VOLUME 70 | NUMBER 10 | SUPPLEMENT 1

MAY 15, 2013

## S U P P L E M E N T

New approaches to reversing oral  
anticoagulant therapy

Official journal  
of the  
American Society  
of Health-System  
Pharmacists<sup>®</sup>

[www.ajhp.org](http://www.ajhp.org)

Supported by an educational grant from CSL Behring

May 15, 2013



Coden: AHSPEK  
ISSN: 1079-2082

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## New approaches to reversing oral anticoagulant therapy

GUEST EDITOR, EDITH A. NUTESCU

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Articles based on the proceedings of a symposium held December 3, 2012, during the 47th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from CSL Behring.



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# New approaches to reversing oral anticoagulant therapy

## Introduction

EDITH A. NUTESCU

Am J Health-Syst Pharm. 2013; 70(Suppl 1):S1-2

Oral anticoagulant therapy is used to prevent thromboembolism in patients with a variety of conditions, including nonvalvular atrial fibrillation and venous thrombosis, and in patients undergoing knee or hip replacement surgery. Excessive anticoagulation can lead to bleeding (e.g., intracranial hemorrhage), whereas inadequate anticoagulation can allow thromboembolism to occur. The successful use of oral anticoagulant therapy requires achieving a balance that minimizes both the risk for thromboembolism and the risk for bleeding. The introduction of several target-specific oral anticoagulants—dabigatran, rivaroxaban, and, most recently, apixaban—has been welcomed by both patients and health care providers because the routine laboratory monitoring required during warfarin use is generally not needed during

the use of these agents. However, thromboembolic and bleeding complications can still occur during use of these novel agents.<sup>1</sup>

The prevalence of thromboembolic and bleeding complications during oral anticoagulant therapy in the United States is expected to rise in the coming years because the population is aging, many of the conditions for which therapy is used are age-related, and use of these drugs to manage these conditions is widespread.<sup>2-4</sup> Although tools are available to predict the risk for thromboembolism and bleeding in patients requiring oral anticoagulant therapy, clinicians' awareness of these risks and use of these tools may be inadequate.<sup>5-10</sup>

Prompt reversal of the effects of oral anticoagulants sometimes is needed for patients who have active bleeding or a high risk for active

bleeding or have an urgent need for an invasive procedure or surgery. Pharmacologic intervention—fresh frozen plasma, various clotting factor concentrates, and, in warfarin-treated patients, phytonadione—may be needed to provide more prompt reversal of anticoagulation than can be achieved by withholding the anticoagulant, because of the delay before anticoagulant effects diminish when therapy is discontinued. Experience to date with pharmacologic interventions to reverse the effects of target-specific oral anticoagulants is limited. Adverse events, especially thromboembolism, are associated with certain anticoagulant reversal therapies, and clinician awareness and reporting of these events may be inadequate.<sup>11</sup> A comprehensive plan is needed for prompt intervention to reverse the effects of oral anticoagulants and optimize out-

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Dr. Nutescu received an honorarium for participating in the symposium and preparing this article. Dr. Nutescu reports that she has served as a consultant for Daiichi-Sankyo Inc. and has received a research grant and served as a consultant for Janssen Pharmaceuticals, Inc.

The assistance of Carla J. Brink, M.S., B.S.Pharm., and Susan R. Dombrowski, M.S., B.S.Pharm., in developing the manuscript is acknowledged. Ms. Brink and Ms. Dombrowski have declared no potential conflicts of interest.

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DOI 10.2146/ajhp120039

comes in patients with bleeding or an urgent need for surgery or invasive procedures.

The first article in this supplement provides an overview of the mechanisms of action, pharmacokinetics, and rate of bleeding complications from warfarin and target-specific oral anticoagulants, as well as methods for assessing the risk for thromboembolism and bleeding in patients receiving oral anticoagulants or temporarily interrupting such therapy to undergo elective invasive procedures or surgery. Therapeutic strategies for balancing these risks and coagulation assays used to monitor oral anticoagulation therapy also are described. The second article describes the pharmacologic agents and strategies used for urgent reversal of the effects of warfarin and the target-specific oral anticoagulants. Finally, the third article addresses components of a plan for promptly evaluating and managing patients with or at high risk for bleeding who are receiving

oral anticoagulants or interrupting such therapy for an urgent invasive procedure or surgery.

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# Oral anticoagulant therapies: Balancing the risks

EDITH A. NUTESCU

**F**ibrin clot formation (i.e., clotting) is the result of the conversion of fibrinogen to fibrin, the last step in the final common pathway of the clotting cascade, which is catalyzed by factor Xa (FXa) and then factor IIa (thrombin).<sup>1</sup> The intrinsic and extrinsic pathways both lead to activation of factor X and the final common pathway. Currently available oral anticoagulants in the United States differ in their mechanisms of action (Figure 1).

The vitamin K antagonist warfarin has multiple targets in the intrinsic and extrinsic pathways; it inhibits hepatic production of the vitamin K-dependent clotting factors II, VII, IX, and X. Newer oral anticoagulants have more specific activity on a single clotting factor. These agents include the direct thrombin inhibitor dabigatran and direct FXa inhibitors (rivaroxaban and apixaban and the investigational agent edoxaban).

## Warfarin

Warfarin has been available for more than 60 years, and until recently it was the only oral anticoagulant available in the United States.<sup>1</sup> The drug is widely used to prevent and

**Purpose.** To describe the mechanisms of action, pharmacokinetics, and rate of bleeding complications from warfarin and target-specific oral anticoagulants; methods for assessing the risk for thromboembolism and bleeding in patients receiving oral anticoagulants or temporarily interrupting such therapy to undergo elective invasive procedures or surgery; therapeutic strategies for balancing these risks; and coagulation assays used to monitor oral anticoagulation therapy.

**Summary.** The target-specific oral anticoagulants have a more specific mechanism of action and shorter elimination half-lives than warfarin, but the half-lives of these target-specific agents may be prolonged in patients with renal impairment or elderly patients, resulting in the potential for drug accumulation and bleeding complications. The rate of bleeding complications in the community setting may be higher than in the clinical trial setting. In patients receiv-

ing oral anticoagulants or temporarily interrupting oral anticoagulant therapy to undergo elective invasive procedures or surgery, the risks for thromboembolism and bleeding should be assessed by using validated risk scoring systems and patient stratification schemes. The time during which an oral anticoagulant should be withheld before an invasive procedure or surgery and the time until resumption of therapy after the procedure depend on the drug, risk of thrombosis, type of procedure (i.e., risk for bleeding), and patient-specific variables, especially renal function for the target-specific agents. New coagulation assays are in development for use in monitoring oral anticoagulant therapy.

**Conclusion.** An individualized approach is needed to balance the risks for thromboembolism and bleeding in patients receiving oral anticoagulants.

**Am J Health-Syst Pharm.** 2013; 70(Suppl 1):S3-11

treat arterial and venous thromboembolism, but it requires frequent laboratory monitoring because of its narrow therapeutic index, and it also interacts with numerous drugs and foods.

Warfarin is the most commonly implicated medication in emer-

gency hospitalizations of elderly Americans.<sup>2</sup> Bleeding is more likely to occur within the first month of therapy than later in treatment.<sup>3</sup> Risk factors for bleeding include a high intensity of anticoagulation (International Normalized Ratio [INR] >4.0), age 65 years or older,

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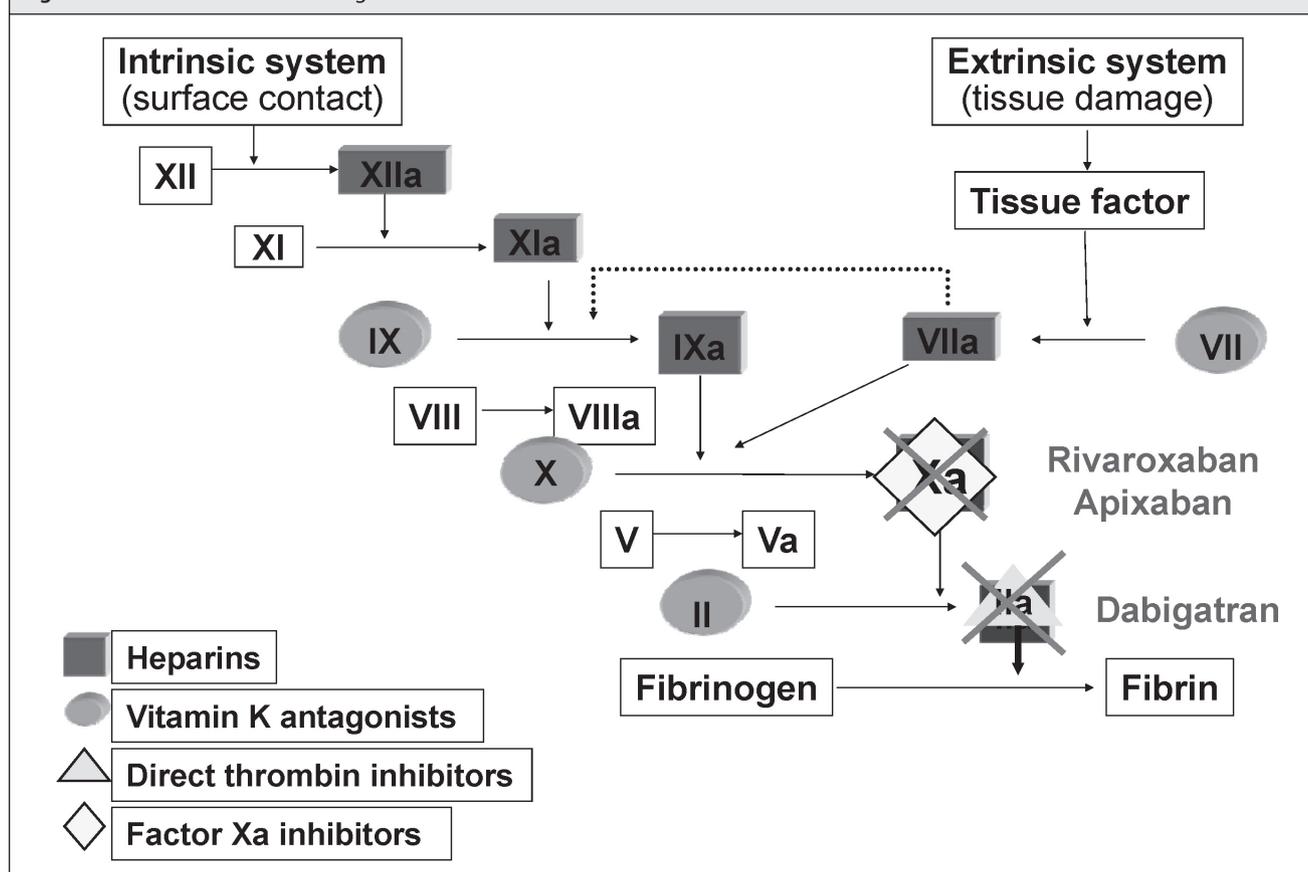
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DOI 10.2146/ajhp130040

Figure 1. Mode of action of anticoagulants.



history of highly variable INRs, history of gastrointestinal (GI) bleeding, hypertension, cerebrovascular disease, anemia, malignancy, trauma, renal impairment, certain genetic factors (e.g., activity of cytochrome P-450 isozymes 2C9 and 4F2 and vitamin K oxide reductase complex subunit 1), certain concomitant drugs, and a long duration of warfarin therapy.<sup>3</sup>

The time to onset and offset of the anticoagulant effect of warfarin is influenced by the elimination half-life of the *R*- and *S*-isomers of the drug (45 hours and 29 hours, respectively) and the four vitamin K-dependent clotting factors:<sup>4</sup>

- II: 42–72 hours
- VII: 4–6 hours
- IX: 21–30 hours
- X: 27–48 hours

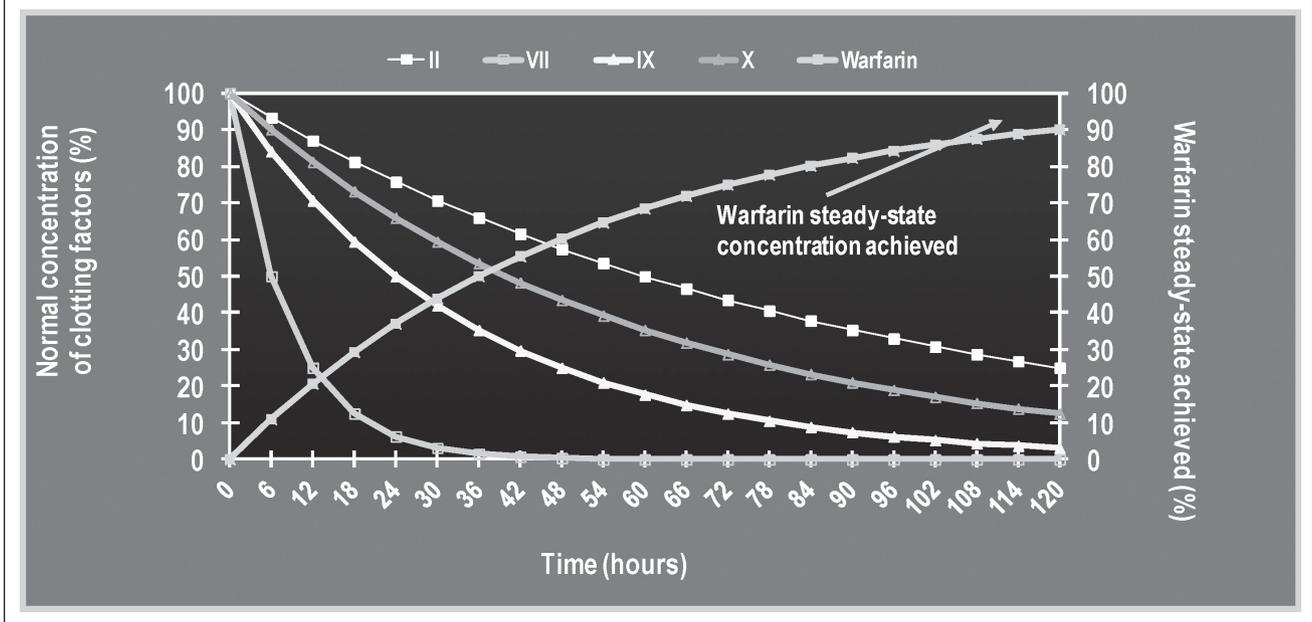
The half-life of factor II is considerably longer than those of the other three vitamin K-dependent factors and the two isomers of the drug. This long half-life contributes to the lag between the time when the drug is initiated, the dosage is changed, or the drug is discontinued and the time when a clinical effect is observed. It can take up to 120 hours after the initiation of warfarin (or longer in slow metabolizers of the drug) to achieve a steady-state concentration of the drug (Figure 2).<sup>5</sup> Conversely, it can take up to five days after warfarin discontinuation before the drug is completely eliminated.

The anticoagulant effect of warfarin is measured by the prothrombin time (PT), which reflects reduced hepatic production of factors II, V, VII, and X.<sup>1</sup> Because the reagents used for PT and their sensitivity vary

among clinical laboratories, the INR is used to standardize and express the PT results.<sup>6</sup>

The resumption of a normal INR value after warfarin discontinuation requires the production of active vitamin K-dependent clotting factors. Several variables can cause a delay in recovery of a normal INR. In a retrospective cohort study of 633 ambulatory patients with an INR greater than 6.0 and various indications for warfarin therapy, 232 patients (37%) had an INR of 4.0 or higher after two doses were withheld.<sup>7</sup> Risk factors for this delay in reduction of INR included advanced age (odds ratio [OR] per decade of life, 1.18; 95% confidence interval [CI], 1.01–1.38; *p* = 0.04), a high index INR (OR per unit, 1.25; 95% CI, 1.14–1.37; *p* < 0.001), decompensated congestive heart failure (OR, 2.79; 95%

Figure 2. Pharmacokinetics of warfarin and vitamin K-dependent clotting factors. Reproduced, with permission, from reference 5.



CI, 1.30–5.98;  $p = 0.009$ ), and active cancer (OR, 2.48; 95% CI, 1.11–5.57;  $p = 0.03$ ). A high weekly maintenance warfarin dose was associated with a low risk for delay in reduction of INR (adjusted OR per 10 mg of warfarin, 0.87; 95% CI, 0.79–0.97;  $p = 0.009$ ).

### Target-specific oral anticoagulants

The shortcomings of warfarin prompted research to develop new oral anticoagulants. Dabigatran was approved by the Food and Drug Administration (FDA) for stroke prevention in atrial fibrillation (AF) in October 2010.<sup>8</sup> Rivaroxaban was approved for this indication in November 2011 after first receiving FDA approval in July 2011 for prophylaxis of venous thromboembolism (VTE) in patients undergoing knee or hip replacement surgery.<sup>9</sup> Rivaroxaban was also approved by FDA for treatment of VTE (deep venous thrombosis [DVT] and pulmonary embolism [PE]) in November 2012. An application for the indication of acute coronary syndrome (ACS) has been submitted to FDA; approval is

pending, as the agency requested additional data from the manufacturer.<sup>10</sup>

Apixaban is the newest target-specific anticoagulant to become available. It was approved by FDA in December 2012 for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.<sup>11</sup> Edoxaban has been evaluated for stroke prevention in AF, prevention of VTE in patients undergoing hip replacement surgery, and treatment of VTE.<sup>12–14</sup> It has been approved in Japan for VTE prevention after major orthopedic surgery, but plans for submission of a new drug application to FDA have not yet been announced.

All four of these target-specific oral anticoagulants are eliminated by the kidneys and can accumulate in patients with renal impairment, although the agents differ in the extent to which they rely on the kidneys for elimination (Table 1). Dabigatran is the drug that is most dependent on renal function for elimination, and apixaban is the least dependent. Dabigatran is dialyzable; the other three target-

specific agents are unlikely to be removed by dialysis. As creatinine clearance decreases (i.e., as renal function deteriorates), the half-life of each drug and its anticoagulant effect increase because of drug accumulation, and this increases the potential for bleeding complications. The magnitude of the effect is largest for dabigatran and smallest for apixaban. These differences are important in the choice among the target-specific oral anticoagulants for patients with renal impairment.

Clinical trials comparing dabigatran, rivaroxaban, or apixaban with warfarin for stroke prevention in AF revealed important differences in the safety profiles of these agents. In the RELY and ROCKET-AF studies, there was no significant difference in major bleeding, the primary safety endpoint, between dabigatran (the larger [150 mg] of two dosages evaluated) or rivaroxaban and warfarin ( $p = 0.31$  and  $p = 0.44$ , respectively).<sup>17,18</sup> In the ARISTOTLE study, the rate of major bleeding was 31% lower with apixaban than warfarin, a difference that is significant ( $p < 0.001$ ).<sup>19</sup>

Table 1.  
Properties of Target-Specific Oral Anticoagulants<sup>15,16,a</sup>

Property	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Direct factor inhibition	Ila	Xa	Xa	Xa
Renal clearance (%)	80	33	25	40
Half-life in renal impairment (hr)				
CL <sub>cr</sub> >80 mL/min	14–17	5–9	8–15	9–11
CL <sub>cr</sub> 50–79 mL/min	16.6	8.7	14.6	<sup>b</sup>
CL <sub>cr</sub> 30–49 mL/min	18.7	9.0	17.6	<sup>b</sup>
CL <sub>cr</sub> <30 mL/min	27.5	9.5	17.3	<sup>b</sup>
Dialyzable	Yes	Unlikely	Unlikely	Unlikely

<sup>a</sup>CL<sub>cr</sub> = creatinine clearance.

<sup>b</sup>Data not available.

Table 2.  
Selected Scoring Systems for Stroke Risk Assessment in Patients with Atrial Fibrillation<sup>21,22,a</sup>

Risk Factor	Points
<i>CHADS<sub>2</sub></i>	
Congestive heart failure	1
Hypertension	1
Age ≥75 years	1
Diabetes	1
History of stroke or transient ischemic attack	2
Maximum score	6
<i>CHA<sub>2</sub>DS<sub>2</sub>-Vasc</i>	
Congestive heart failure/left ventricular dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes	1
History of stroke, transient ischemic attack, or thromboembolism	2
Vascular disease	1
Age 65–74 years	1
Female sex	1
Maximum score	9

<sup>a</sup>Patients with atrial fibrillation are considered at low, intermediate, or high risk for stroke if their CHADS<sub>2</sub> score or CHA<sub>2</sub>DS<sub>2</sub>-Vasc score is 0, 1, or 2 or higher, respectively.

The rate of intracranial hemorrhage (ICH) was significantly lower with all three oral anticoagulants compared with warfarin in these three studies ( $p < 0.001$ ,  $p = 0.02$ , and  $p < 0.001$ , respectively). However, the rate of major GI bleeding was significantly higher with dabigatran 150 mg and rivaroxaban than with warfarin ( $p < 0.001$  for both comparisons), although it was not significantly different between apixaban and warfarin ( $p = 0.37$ ). There appeared to be a tradeoff between the reduced risk for ICH and the increased risk for

major GI bleeding when dabigatran or rivaroxaban was used instead of warfarin.

In 2011, dabigatran and warfarin were the most common prescription drugs associated with serious, disabling, or fatal injury reported to the FDA MedWatch adverse event reporting program.<sup>20</sup> Dabigatran accounted for 3781 serious adverse events, including 2367 cases of hemorrhage and 542 deaths. Warfarin accounted for 1106 serious adverse events, including 731 cases of hemorrhage and 72 deaths. The unex-

pectedly large number of reports of hemorrhage in patients receiving dabigatran could reflect differences between the clinical trial setting and the community setting, including differences in monitoring and perhaps heightened reporting because of a perception of greater safety issues with the newer target-specific oral anticoagulants than with warfarin and differences in patient populations. Most complications from dabigatran use reported to FDA occurred in elderly patients, many of whom have impaired renal function. Dabigatran dosage reduction is recommended for patients with renal impairment, and failure to make this reduction could explain hemorrhagic complications in these patients.<sup>8</sup>

The use of any oral anti-coagulant to reduce the risk for thromboembolism—whether it is warfarin or one of the target-specific agents—is accompanied by a risk for bleeding. Efforts to reduce the risk for bleeding may increase the risk for thromboembolism. An individualized approach is needed to balance these risks and minimize related morbidity and mortality.

### Risk assessment

Several validated stroke risk assessment tools are available for use in patients with AF (Table 2). Use of the CHADS<sub>2</sub> score is advocated in the 2012 guidelines from the American College of Chest Physicians

(ACCP).<sup>21,23</sup> Points are assigned to individual risk factors, then added to determine the CHADS<sub>2</sub> score. Patients with AF are categorized as low, intermediate, or high risk for stroke if their CHADS<sub>2</sub> score is 0, 1, or 2 or higher, respectively. No anticoagulation is recommended by ACCP for patients at low risk for stroke.<sup>23</sup> The use of dabigatran instead of warfarin is suggested when oral anticoagulation is recommended in patients at intermediate or high risk for stroke (i.e., a CHADS<sub>2</sub> score of 1 or higher). No recommendations are made in the ACCP guidelines for the use of rivaroxaban or apixaban for stroke prevention in AF because these drugs were not approved by FDA for this indication at the time the guidelines were being developed. It is expected, however, that future updates in the guidelines will encompass these agents.

Guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA) call for aspirin therapy for patients with no risk factors for stroke, aspirin or oral anticoagulant therapy for patients with one stroke risk factor, and oral anticoagulant therapy for patients with two or more risk factors.<sup>24,25</sup> Dabigatran is an alternative to warfarin for oral anticoagulant therapy in patients without contraindications to its use, according to ACC and AHA. As with the ACCP guidelines, the ACC/AHA guidelines were published in 2011 and thus do not mention rivaroxaban or apixaban.

Updated guidelines released by the European Society of Cardiology (ESC) in August 2012 recommend use of the CHA<sub>2</sub>DS<sub>2</sub>-Vasc score (Table 2), another point-based system for predicting stroke in patients with AF that takes into consideration the presence of vascular disease, history of thromboembolism, age 65–74 years (as well as 75 years or older), and female sex as well as the risk factors assessed in the CHADS<sub>2</sub> scoring system.<sup>22,26</sup> The CHA<sub>2</sub>DS<sub>2</sub>-Vasc score

was developed to improve upon the predictive value of the CHADS<sub>2</sub> score and better identify patients truly at low risk for stroke.<sup>26</sup> Patients with AF are considered at low, intermediate, or high risk for stroke if their CHA<sub>2</sub>DS<sub>2</sub>-Vasc score is 0, 1, or 2 or higher, respectively. No anticoagulant therapy is recommended by ESC for patients with a CHA<sub>2</sub>DS<sub>2</sub>-Vasc score of 0 (i.e., patients less than 65 years of age with lone AF). In patients with a CHA<sub>2</sub>DS<sub>2</sub>-Vasc score of 1, warfarin, a direct thrombin inhibitor (i.e., dabigatran), or an oral FXa inhibitor (i.e., rivaroxaban, apixaban) should be considered after assessing the risk of bleeding complications and considering patient preferences. Anticoagulant therapy is recommended unless contraindicated for

patients with a CHA<sub>2</sub>DS<sub>2</sub>-Vasc score of 2 or higher.

Point-based scoring systems for assessing the risk for bleeding from the use of oral anticoagulants in patients with AF have also been developed and validated (Table 3).<sup>27,28,30</sup> None of these scoring systems have yet been recommended by ACCP, ACC, or AHA, although the lack of a recommendation does not suggest that assessment of bleeding risk is not needed. The ESC recommends use of the HAS-BLED scoring system instead of the HEMORR<sub>2</sub>HAGES and Anticoagulation and Risk Factors in Atrial Fibrillation scoring systems because of the greater simplicity of HAS-BLED.<sup>26,28</sup> A formal bleeding risk assessment is recommended by ESC for all patients with AF who

Table 3.

**Selected Scoring Systems for Bleeding Risk Assessment in Patients with Atrial Fibrillation Receiving Oral Anticoagulant Therapy<sup>27-29,a</sup>**

Risk Factor	Points
<i>HEMORR<sub>2</sub>HAGES<sup>b</sup></i>	
Hepatic or renal disease	1 for each
Ethanol use	1
Malignancy	1
Age >75 years	1
Reduced platelet count or function	1 for each
Re-bleeding	2
Hypertension, uncontrolled	1
Anemia	1
Genetic factors	1
Elevated fall risk ± neuropsychiatric disease	1
Stroke	1
Maximum score	14
<i>HAS-BLED<sup>c</sup></i>	
Hypertension, systolic blood pressure >160 mm Hg	1
Abnormal renal or liver function	1 for each
Stroke	2
Bleeding history or predisposition	1
Labile INRs	2
Age >65 years	1
Antiplatelet or NSAID use	1
Alcohol use >8 servings/week	1
Maximum score	11

<sup>a</sup>INR = International Normalized Ratio, NSAID = nonsteroidal antiinflammatory drug.

<sup>b</sup>The risk for bleeding in patients with a HEMORR<sub>2</sub>HAGES score of 0–1, 2–3, or 4 or more is low, moderate, or high, respectively.

<sup>c</sup>The risk for bleeding in patients with a HAS-BLED score of 0, 1–2, and 3 or more is low, moderate, or high, respectively.

are receiving oral anticoagulant (or antiplatelet) therapy. In patients with a HAS-BLED score of 3 or higher, who by definition are considered at high risk, the use of caution, periodic monitoring, and efforts to correct reversible risk factors for bleeding (e.g., uncontrolled hypertension, labile INR values, concomitant non-steroidal anti-inflammatory drug or alcohol use) are recommended by ESC. A high HAS-BLED score alone is not necessarily an absolute contraindication to use of oral anticoagulant therapy.

The risk scoring systems in Table 2 and Table 3 were developed for patients with AF and are based on clinical data from this patient population. A similar process should be used to assess the risk for thromboembolism and bleeding in patients receiving oral anticoagulants for other indications (e.g., VTE), with tools developed for those specific indications.

### Perioperative management

Oral anticoagulant therapy should be temporarily discontinued in patients undergoing an elective invasive

procedure or surgery who have a high bleeding risk, for the purpose of avoiding bleeding complications; however, the risk for perioperative thromboembolism is also a major concern when anticoagulation therapy is interrupted. The risk for perioperative thromboembolism (Table 4) and bleeding (Table 5) should be evaluated in such patients to determine the appropriate time to discontinue and resume oral anticoagulant therapy. Although VTE is a postoperative concern in patients without indications for anticoagulation prior to surgery, arterial and venous thromboembolism is the primary concern during interruption of oral anticoagulation in patients with indications for such therapy before surgery (e.g., AF, mechanical heart valve, VTE).<sup>31</sup>

A residual anticoagulant effect is acceptable at the time of minor invasive procedures or surgery with a low risk of bleeding, but minimal or no anticoagulant effect is desired at the time of major procedures with a high risk of bleeding or where the consequences of bleeding are particularly dire (Table 5). Aggressive anticoagulation is needed for patients at high risk for thromboembolism (Table 4), and therapy with a short half-life (e.g., a low molecular weight heparin or target-specific oral anticoagulant instead of warfarin) should be considered in such patients so that it has a rapid offset of effect before the procedure and rapid onset after the procedure (i.e., minimal interruption of anticoagulation). The rate of decline in plasma concentration of a drug after discontinuation depends on the half-life. The percentage of the plasma concentration remaining after one, two, three, four, and five half-lives have elapsed is 50%, 25%, 12.5%, 6.25%, and 3.125%, respectively. When therapeutic concentrations are present and the drug is discontinued, at least four or five half-lives must elapse before the plasma concentration becomes

Table 4.

### Patient Risk Stratification for Perioperative Thromboembolism when Oral Anticoagulant Therapy Is Temporarily Interrupted<sup>31</sup>

*High Risk (>10% annual risk for thromboembolism)*

Atrial fibrillation

- Recent (within past three months) stroke or transient ischemic attack
- CHADS<sub>2</sub> score 5 or 6
- Rheumatic valvular heart disease

Mechanical heart valve

- Any caged-ball or tilting disc valve in mitral or aortic position
- Any mitral valve prosthesis
- Recent (within past six months) stroke or transient ischemic attack

Venous thromboembolism

- Recent (within past three months) venous thromboembolism
- Severe thrombophilia
  - Deficiency of protein C, protein S, or antithrombin
  - Antiphospholipid antibodies
  - Multiple thrombophilias

*Moderate Risk (5–10% annual risk for thromboembolism)*

Atrial fibrillation

- CHADS<sub>2</sub> score 3 or 4

Mechanical heart valve

- Bileaflet aortic valve prosthesis with major risk factors for stroke

Venous thromboembolism

- Venous thromboembolism within past 3–12 months
- Recurrent venous thromboembolism
- Non-severe thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation)
- Active cancer (treated within past six months or palliative)

*Low Risk (<5% annual risk for thromboembolism)*

Atrial fibrillation

- CHADS<sub>2</sub> score 0–2 (without prior stroke or transient ischemic attack)

Mechanical heart valve

- Bileaflet aortic valve prosthesis without atrial fibrillation and major risk factors for stroke

Venous thromboembolism

- Venous thromboembolism more than 12 months ago with no other risk factors for thromboembolism

sufficiently low to minimize the therapeutic effects. Variables that can cause a delay in recovery of a normal INR in patients receiving warfarin may increase the amount of time before surgery during which the drug should be withheld to avoid bleeding complications. Impaired renal function, which is common in the elderly, may require discontinuation of oral anticoagulants further in advance of surgery than would be necessary in patients with normal renal function to minimize the risk for bleeding.

Postoperative considerations in determining when to resume oral anticoagulant therapy include the effect of the surgery, risk of bleeding, and bowel motility. Therapy may be resumed once hemostasis has been achieved.

Warfarin should be discontinued five days before surgery and resumed approximately 12–24 hours after surgery when there is adequate hemostasis.<sup>31</sup> To minimize the risk of over-anticoagulation, generally the preoperative warfarin dose should be used instead of a larger dose when therapy is resumed. An alternative approach is to give a mini-loading dose for the first few days when therapy is reinitiated to cause more rapid anticoagulation, and then transition to the preoperative maintenance dose.<sup>31</sup>

The number of doses of target-specific oral anticoagulants that should be withheld before invasive procedures depends on the type of procedure and the patient's renal function (Table 6), especially for dabigatran because of the importance of the kidneys in elimination of the drug.<sup>34,35</sup> A larger number of doses of dabigatran should be withheld before invasive procedures in patients with moderate or severe renal impairment than in patients with mild renal impairment or normal renal function. A larger number of doses of dabigatran, rivaroxaban, and apixaban should be withheld before major surgery than before a minor procedure because of the greater risk

Table 5.

**Procedure Risk Stratification for Perioperative Bleeding<sup>32,33</sup>***High Risk (two-day risk of major bleeding 2–4%)*

- Major cardiac surgery (heart valve replacement/coronary artery bypass grafting)
- Major neurosurgical procedures
- Major cancer surgery (head and neck/abdominal/thoracic)
- Major orthopedic surgery (joint replacement/laminectomy)
- Major urologic surgery (prostate/bladder resection)
- Major vascular surgery
- Kidney biopsy
- Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation
- Endoscopically guided fine-needle aspiration
- Any major operation (procedure duration >45 minutes)

*Low Risk (two-day risk of major bleeding 0–2%)*

- Cholecystectomy
- Abdominal hernia repair
- Abdominal hysterectomy
- Coronary angiography/percutaneous coronary intervention/electrophysiologic testing
- Pacemaker/cardiac defibrillator insertion<sup>a</sup>
- Gastrointestinal endoscopy ± biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endonosonography without aspiration
- Minor plastic surgery (carpal tunnel repair)
- Minor orthopedic surgery/arthroscopy
- Minor gynecologic surgery (dilation and curettage)
- Minor dental procedures (extractions)
- Minor skin procedures (cancer excision)
- Minor eye procedures (cataract)

<sup>a</sup>Delayed initiation of bridging to minimize risk for pocket hematoma.

Table 6.

**Interruption of Target-Specific Oral Anticoagulant Therapy for Invasive Procedures and Surgery<sup>8,9,11,34,35,a</sup>**

Drug (Creatinine Clearance)	Time of Last Dose before Minor Procedure (days) <sup>b</sup>	Time of Last Dose before Major Surgery (days) <sup>b</sup>
Dabigatran (>50 mL/min)	1	2
Dabigatran (31–50 mL/min)	2	4
Dabigatran (≤30 mL/min)	4	6
Rivaroxaban or apixaban (>50 mL/min)	1	2
Rivaroxaban or apixaban (30–50 mL/min)	1–2	3–4
Rivaroxaban or apixaban (<30 mL/min)	2	4

<sup>a</sup>Therapy should generally be resumed 24–48 hours after a minor procedure and 48–72 hours after major surgery. If unfractionated heparin (UFH) or low molecular weight heparin (LMWH) is used as bridging therapy in patients with atrial fibrillation, mechanical heart valve, or venous thromboembolism who are at high risk for thromboembolism, oral anticoagulant therapy with a target-specific agent should be resumed at the time when the UFH infusion is discontinued and at the time when the next scheduled dose of LMWH would have been given.

<sup>b</sup>See Table 5 for procedure risk stratification for perioperative bleeding (minor procedures are associated with a low risk of perioperative bleeding, and major surgery is associated with a high risk for perioperative bleeding).

of bleeding associated with major surgery (Table 5).

Dabigatran, rivaroxaban, and apixaban should be resumed 24–48 hours after a minor procedure and 48–72 hours after major surgery, assuming that hemostasis has been achieved. In patients at high thrombosis risk in whom adequate hemostasis is achieved shortly after the end of the procedure and postoperative bleeding risk is standard, it may be reasonable to resume anticoagulation within 24 hours after surgery. Some clinicians suggest resuming therapy in a stepped dosing approach. For dabigatran, this would start with a half dose (75 mg) for the first dose and thereafter increase to the usual maintenance dose. For rivaroxaban, it would start with 10 mg then increase to the usual maintenance dose.<sup>35</sup> In patients with postoperative bowel paralysis, bridging with an injectable anticoagulant may be required until the patient is able to take oral anticoagulants. The rivaroxaban prescribing information contains a boxed warning that discontinuing rivaroxaban in the absence of adequate alternative anticoagulation increases the risk of thrombotic events and that if anticoagulation with rivaroxaban must be discontinued for a reason other than pathological bleeding, another anticoagulant should be administered.<sup>9</sup>

### Measurement of anticoagulant effect

The lack of a need for routine laboratory monitoring is an advantage of the target-specific oral anticoagulants over warfarin. Nevertheless, measurement of anticoagulant activity during therapy with the target-specific agents is potentially useful in patients undergoing invasive procedures or surgery and certain other patients and scenarios, such as the following:

- Active bleeding,
- Progressive renal insufficiency,

- Possible excessive or inadequate dosing,
- Drug interactions,
- Suspected nonadherence,
- Elderly or very young,
- Overweight or underweight, and
- Receiving thrombolytic or triple anti-thrombotic therapy.

Various hematologic tests have been used to assess coagulation status, and the usefulness of these coagulation assays differs among the target-specific oral anticoagulants. The ecarin clotting time (ECT), a direct measure of thrombin generation (ecarin activates prothrombin), is the most useful laboratory test for monitoring coagulation during dabigatran therapy, but this test is not widely available in the clinical setting.<sup>6</sup> The thrombin time (TT), a measure of the activity of thrombin in plasma, is less useful than the ECT, but it is more widely available. The PT and INR are less useful than the TT for assessing coagulation during dabigatran therapy. The activated partial thromboplastin time (aPTT, a measure of the intrinsic and final common pathways in coagulation) is frequently used in most institutions and is sensitive to the effects of dabigatran; thus, this assay is a potential alternative until ECT becomes more widely available.

Chromogenic anti-FXa assays are useful for monitoring coagulation during rivaroxaban and apixaban therapy.<sup>6</sup> Although the aPTT and PT are less useful than chromogenic assays during rivaroxaban therapy, the availability of PT makes PT practical to use. The INR is not useful for monitoring coagulation during treatment with FXa inhibitors (i.e., rivaroxaban or apixaban).<sup>6</sup>

The aPTT and PT are widely available, although not ideal, tests for monitoring the target-specific oral anticoagulants. The extent to which these anticoagulants prolong the aPTT and PT varies.<sup>36</sup> Dabigatran prolongs the aPTT to a greater extent and the PT to a lesser extent

than do the FXa inhibitors, and the extent of the PT prolongation differs between rivaroxaban and apixaban. The extent of prolongation of these test values also depends on the reagent and coagulometer used, anticoagulant dose, and time since the last dose. The aPTT is useful for its negative predictive value. A normal aPTT suggests that little dabigatran anticoagulant activity may be present. However, a normal aPTT during dabigatran therapy and a normal PT during rivaroxaban therapy<sup>37</sup> cannot completely exclude the presence of the drug, because the tests are not sufficiently sensitive. A safe PT or aPTT value for invasive procedures in patients receiving target-specific oral anticoagulants has not been identified. The TT, since it is highly sensitive, is more appropriate for providing qualitative information about the presence of dabigatran than quantitative information about the amount of drug present. A relationship between coagulation assay results and patient outcomes has not been established.

Newer coagulation assays need to be developed, standardized, and validated. Endogenous thrombin potential (ETP), dilute prothrombin time (dPT), Heptest (American Diagnostica, Stamford, CT), prothrombinase-induced clotting time (PiCT), and chromogenic anti-factor IIa are among the assays in development.<sup>6</sup> The ETP reflects thrombin generation. The dPT is an assay with greater sensitivity than PT. The Heptest measures inhibition of endogenous FXa. The PiCT assay, which is approved by FDA for measuring the effects of unfractionated heparin and low molecular weight heparin, has been explored for use in measuring the anticoagulant effect of rivaroxaban.<sup>6</sup> Chromogenic anti-factor Xa and anti-factor IIa assays are potentially useful for monitoring coagulation during treatment with FXa inhibitors as well as the factor IIa inhibitor dabigatran.<sup>6</sup>

## Conclusion

An individualized approach is needed to balance the risks for thromboembolism and bleeding in patients receiving oral anticoagulants.

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# Pharmacologic interventions for reversing the effects of oral anticoagulants

JAMES S. KALUS

The use of oral anticoagulant medications has become quite frequent in clinical practice. Warfarin is the most common oral anticoagulant used. However, newer agents, such as the direct thrombin inhibitor dabigatran and the factor Xa antagonist rivaroxaban, are becoming more commonly used as well. A second factor Xa antagonist, apixaban, became available in December 2012. The anticoagulant effect of warfarin is mediated by inhibition of vitamin K oxide reductase, the enzyme responsible for converting oxidized vitamin K to reduced vitamin K.<sup>1</sup> The latter is vital for hepatic production of active vitamin K-dependent clotting factors II, VII, IX, and X. These clotting factors play key roles in the extrinsic and intrinsic pathways of the clotting cascade (Figure 1), the end result of which is the generation of thrombin (factor IIa), conversion of fibrinogen to fibrin, and clot formation and stabilization. Inhibition of vitamin K oxide reductase by warfarin interferes with clotting by decreasing the availability of vitamin K-dependent clotting factors and thrombin formation. The

**Purpose.** To describe the pharmacologic agents and strategies used for urgent reversal of warfarin and the target-specific oral anticoagulants dabigatran, rivaroxaban, and apixaban.

**Summary.** To reverse the anticoagulant effects of warfarin in patients who are bleeding or need surgery, exogenous vitamin K (phytonadione) may be used in combination with another, shorter-acting intervention, such as fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), recombinant factor VIIa, or activated PCC (aPCC). Three-factor PCC contains factors II, IX, and X in an inactivated form, and four-factor PCC also includes factor VII in an inactivated form. No four-factor PCC products are available in the United States, but aPCC, which contains the same four factors with factor VII provided in an activated form, is available. The intervention depends on the International Normalized Ratio, presence of bleeding, and need for and timing of surgery. Research suggests

that clotting factor concentrates are more effective than FFP alone for warfarin reversal. These products also may be useful for reversing the effects of target-specific oral anticoagulants, but limited efficacy and safety data are available to support their use. The risks and benefits associated with these products need to be weighed before their use for reversal of dabigatran, rivaroxaban, or apixaban. Additional clinical data are needed to clearly define the role of concentrated clotting factor products in reversal and to determine the optimal clotting factor concentrate product and dose for urgent reversal of oral anticoagulation.

**Conclusion.** Phytonadione and clotting factor concentrates appear to have a role for reversal of warfarin, and limited evidence suggests that clotting factor concentrates could have a role in reversal of target-specific oral anticoagulants in an emergency situation.

**Am J Health-Syst Pharm.** 2013; 70(Suppl 1):S12-21

anticoagulant effect of dabigatran is mediated through direct inhibition of the action of thrombin, and rivaroxaban and apixaban produce anticoagulation through direct inhibition of factor Xa.

Although these agents are safe and effective, anticoagulant reversal is sometimes required in the setting of bleeding or if an urgent surgical procedure is needed. Reversal can be achieved by interruption of antico-

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Based on the proceedings of a symposium held December 3, 2012, during the 47th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from CSL Behring.

Dr. Kalus received an honorarium for participating in the symposium and preparing this article. Dr. Kalus has declared no potential conflicts of interest.

The assistance of Carla J. Brink, M.S., B.S.Pharm., and Susan R. Dombrowski, M.S., B.S.Pharm., in developing the manuscript is acknowledged. Ms. Brink and Ms. Dombrowski have declared no potential conflicts of interest.

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DOI 10.2146/ajhp130041

agulant therapy. Interruption (i.e., withholding) of oral anticoagulant therapy is followed by a gradual reduction in the effects on coagulation with warfarin and a generally more rapid reduction in anticoagulant effects with dabigatran, rivaroxaban, or apixaban. If more rapid reversal of anticoagulant therapy is necessary, pharmacologic intervention in addition to interruption of anticoagulant therapy can be used to hasten the reduction in (i.e., reverse) the effects of oral anticoagulants.

To reverse anticoagulation from warfarin, pharmacologic intervention as a step beyond holding warfarin doses is indicated when the International Normalized Ratio (INR) is greater than 10.<sup>2</sup> Intervention is not warranted when the INR is 10 or less unless the patient is bleeding or requires urgent surgery. Reversal

is indicated for warfarin-treated patients who are bleeding or require urgent surgery regardless of the INR. Pharmacologic reversal of the newer oral anticoagulants may also be attempted in the setting of active bleeding or need for urgent surgery.

### Warfarin reversal options

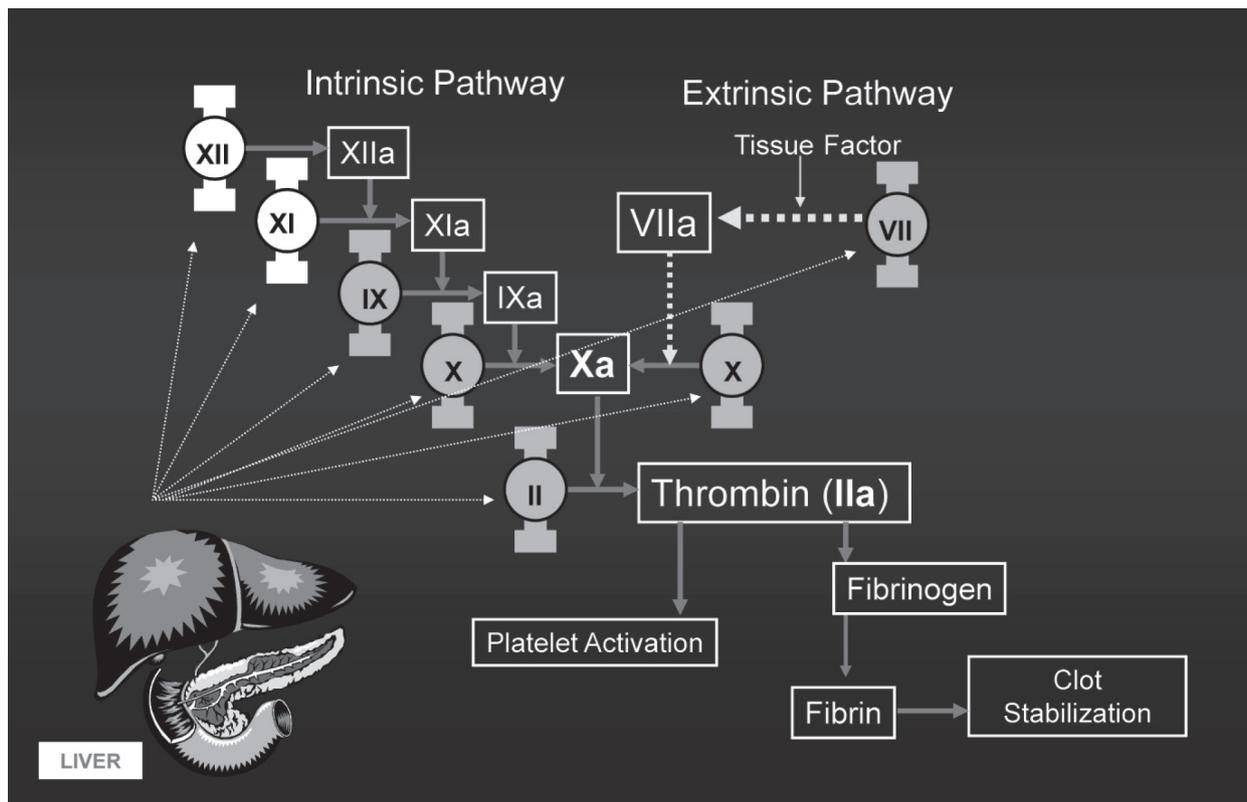
**Phytonadione.** Administration of exogenous vitamin K (phytonadione) reverses the anticoagulant effect of warfarin by promoting hepatic production of vitamin K-dependent clotting factors II, VII, IX, and X. The oral route of administration is preferred for phytonadione unless rapid reversal is needed before surgery or because of bleeding. The risk for anaphylaxis is a concern when phytonadione is administered by the intravenous (i.v.) route; however, the i.v. route is preferred in urgent

situations because it provides earlier onset of action.<sup>3</sup> The intramuscular and subcutaneous routes of phytonadione administration are not recommended in patients requiring warfarin reversal.<sup>2</sup>

Administering an excessive phytonadione dose can result in refractoriness to warfarin when warfarin is restarted. Therefore, the lowest possible dose of phytonadione should be used for warfarin reversal.

Administering phytonadione orally expedites reduction of the INR compared with simply withholding warfarin. Phytonadione given by the i.v. route causes a reduction in the INR within the first six to eight hours after administration.<sup>4</sup> However, the reduction in INR achieved after a 24- to 48-hour period is similar with the i.v. and oral routes. Therefore, there is no advantage to using the i.v.

Figure 1. Clotting cascade.



route when the need for reversal is not urgent. If a patient requires surgery within 12–24 hours, however, a higher dose via the i.v. route is preferred because it produces a faster—although incomplete—reduction in INR.

The American College of Chest Physicians (ACCP) recommends against the routine use of phytonadione for reversal of warfarin anticoagulation in patients with an INR of 4.5–10 and no bleeding; clinical studies have demonstrated that there is no advantage to such intervention.<sup>2</sup> Warfarin should be withheld in these patients until the INR declines. Administering phytonadione 2–2.5 mg orally and withholding warfarin are recommended for patients with an INR greater than 10 and no bleeding. A slow i.v. phytonadione dose of 5–10 mg and withholding warfarin are recommended for patients with bleeding regardless of the INR.

The evidence providing support for most warfarin reversal strategies is weak, because it is based primarily on relatively small observational studies that often evaluate surrogate endpoints (i.e., INR reduction) rather than clinical outcomes (i.e., bleeding) and sometimes do not include a comparator group. In a retrospective analysis of 75 warfarin-treated patients with an INR greater than 10, clinically important bleeding was reported in 3 of 24 patients who had warfarin interrupted but did not receive phytonadione and in 0 of 51 patients who were given single oral 2-mg phytonadione doses.<sup>5</sup> In a case series of 107 warfarin-treated patients with an INR greater than 10 who were given oral phytonadione 2.5 mg as a single dose, 16 patients experienced bleeding within the first seven days after administration of the drug, including 1 patient who experienced major bleeding.<sup>6</sup> Refractoriness to warfarin was not observed in patients treated with low-dose oral phytonadione. These reports suggest that the rates of bleeding are low in warfarin-treated patients with an

INR greater than 10 who are given oral phytonadione.

In warfarin-treated patients who are bleeding or require urgent surgery, i.v. phytonadione is a mainstay in reversing anticoagulation. Phytonadione usually is used in combination with another intervention, such as fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), recombinant factor VIIa (rFVIIa), or activated PCC (aPCC, also known as anti-inhibitor factor complex and factor VIII inhibitor bypassing activity). The duration of action of i.v. phytonadione is longer than that of these other short-acting interventions, with the target INR achieved 24–36 hours after an i.v. phytonadione dose.<sup>4</sup> These short-acting agents have a faster onset of action than i.v. phytonadione because of the time required for formation of vitamin K-dependent clotting factors with phytonadione.

**Fresh frozen plasma.** FFP is obtained from human blood and contains all of the clotting factors found in plasma. Dosing of FFP is based on patient weight and expressed as the volume or number of units of the product. Each unit of FFP contains approximately 200–250 mL. A dosage of 10–20 mL/kg produces a 20–30% increase in plasma levels of clotting factors.<sup>7</sup> In clinical practice, 2 units of FFP is a commonly prescribed fixed dose, although this dose could be inadequate for a patient with a large body weight. Potential disadvantages of FFP include the large volume of fluid administered (often 400 mL or more), which can present a problem for patients with heart failure or other comorbid conditions that are aggravated by excessive fluid.<sup>8</sup> The need for thawing can delay therapy and present a problem when the need for treatment is urgent. Because human blood is the source of FFP, there is a risk for transmission of infectious diseases, although this risk is low as a result of stringent screening of blood donors and blood testing tech-

nology. Transfusion reactions (e.g., transfusion-related acute lung injury, hemolytic reactions due to a blood type mismatch, hypersensitivity) also are associated with FFP.

**Clotting factor concentrates.** Concentrated clotting factor products containing one or more clotting factors are available for use as alternatives to FFP for reversal of warfarin and other oral anticoagulants. There are four major types of products:<sup>9–16</sup>

- rFVIIa (NovoSeven RT, Novo Nordisk Inc., Princeton, NJ);
- Three-factor PCC, which contains factors II, IX, and X in an inactivated form (Bebulin, Baxter Healthcare Corporation, Westlake Village, CA, and Profilnine SD, Grifols Biologicals, Inc., Los Angeles, CA);
- Four-factor PCC, which contains factor VII as well as factors II, IX, and X in an inactivated form (Beriplex P/N, CSL Behring UK Ltd., Marburg, Germany; Cofact, Sanquin Blood Supply, Amsterdam; Kanokad, LFB-Biomedicaments, Paris; Octaplex, Octapharma AG, Vienna, Austria); and
- Activated PCC, which contains factor VII in an activated form and factors II, IX, and X primarily in an inactivated form (FEIBA NF, Baxter Healthcare Corporation, Westlake Village, CA).

The main difference between four-factor PCC products and three-factor PCC products is the presence of factor VII in the former. Bebulin and Profilnine SD are considered three-factor PCC products because they contain a much smaller amount of factor VII than four-factor PCC products. Recombinant factor VIIa and aPCC both contain activated factor VII, but all three-factor PCC products and other four-factor PCC products contain inactivated clotting factors. The inactivated four-factor PCC products are not available in the United States, but aPCC, which contains the same four vitamin K-dependent clotting factors, is available in the United States.

The concentrations of clotting factors vary among three- and four-factor PCC products, depending on the manufacturer and lot (Table 1). Dosages are expressed as units of the factor IX component. The use of fixed doses (e.g., 4000 units regardless of body weight) and the use of weight-based doses (e.g., 25 or 50 units/kg) have been reported in the literature.<sup>17,18</sup> Extrapolating results reported in the literature from one product to another is problematic because the content of factors II, VII, and X differs among products when the same amount of factor IX is used.

The prothrombotic potential of clotting factor concentrates, especially activated products (i.e., rFVIIa, aPCC), is a concern. The anticipated benefit must outweigh the prothrombotic risk when these products are used.

### Urgent warfarin reversal

Several clinical studies have addressed the safety and efficacy of options for reversing warfarin in an urgent situation.

**Three-factor PCC.** The efficacy of 25 units/kg and 50 units/kg of a three-factor PCC product (Profilnine SD) for reversing warfarin anticoagulation in 40 patients was compared with that of FFP (approx-

mately 2 units at the discretion of the prescriber) in 42 historical control patients.<sup>18</sup> All patients had an INR greater than 5 and bleeding or a high risk for bleeding at baseline. Patients with intracranial hemorrhage (ICH) were excluded. Phytonadione was administered to 71% of the patients (median dose, 5 mg; range 1–10 mg).

The baseline INR was similar in the three treatment groups, and the target INR was less than 3 within 24 hours after the initial INR measurement.<sup>18</sup> After PCC alone, the mean INR declined from 9.0 at baseline to 4.6 in the low-dose group and from 8.6 at baseline to 4.7 in the high-dose group. When supplemental FFP was given after PCC, the mean INR decreased further to 2.1 and 2.0 in the low- and high-dose group, respectively. In the historical control group treated with FFP alone, the mean INR declined from 9.4 at baseline to 2.3, and 62% of patients achieved an INR less than 3. A similar percentage of patients treated with low- and high-dose PCC (55% and 43%, respectively) achieved the target INR within approximately 24 hours. The addition of FFP to the low- and high-dose PCC groups significantly increased these percentages achieving the target INR to 89% ( $p = 0.01$ ) and 93% ( $p < 0.01$ ), respectively,

compared with PCC alone. The percentage of historical control patients treated with FFP alone who achieved the target INR (62%) was significantly lower than the percentage of patients treated with PCC (either dose) plus FFP ( $p \leq 0.01$ ).

These findings and those from other studies suggest that while the percentage of patients achieving the endpoint of INR less than 3 was similar for FFP and three-factor PCC when used alone, the use of three-factor PCC in addition to FFP can provide even greater INR reduction than either agent alone.<sup>18-21</sup> Conclusions that can be drawn from these studies are limited, however, because of their observational nature and the lack of standardization of the time after PCC administration until measurement of the INR. In most studies of three-factor PCC for warfarin reversal, PCC was used in addition to FFP, which could reduce FFP dosing requirements. Reducing the FFP dosing requirement would be advantageous for patients with heart failure or other conditions in which volume restriction is needed. The dose of three-factor PCC used in most studies was 25–50 units/kg, which reflects the factor IX content, not the content of factor II or factor X. The variable content of products

Table 1.

#### Approximate Clotting Factor Content<sup>a</sup> of Selected Prothrombin Complex Concentrate Products<sup>9,10,13-15,b</sup>

Product	Factor II	Factor VII	Factor IX	Factor X
<i>Three-Factor PCCs</i>				
Bebulin	24–38 units/mL	<5 units/mL	24–38 units/mL	24–38 units/mL
Profilnine SD	NMT 150 units/100 factor IX units	NMT 35 units/100 factor IX units	100 units	NMT 100 units/100 factor IX units
<i>Four-Factor PCCs</i>				
Beriplex P/N	20–48 units/mL	10–25 units/mL	20–31 units/mL	22–60 units/mL
Cofact	14–35 units/mL	7–20 units/mL	25 units/mL	14–35 units/mL
Kanokad	14–35 units/mL	7–20 units/mL	25 units/mL	14–35 units/mL
Octaplex	14–38 units/mL	9–24 units/mL	25 units/mL	18–30 units/mL
<i>aPCC</i>				
FEIBA NF	1.3 units/FEIBA unit	0.9 unit/FEIBA unit	1.4 units/FEIBA unit	1.1 units/FEIBA unit

<sup>a</sup>All concentrations are approximate and vary from one lot to another.

<sup>b</sup>aPCC = activated prothrombin complex concentrate, NMT = not more than, PCC = prothrombin complex concentrate.

from different manufacturers and different lots from the same manufacturer makes comparison and extrapolation of results from studies of different products difficult. Another shortcoming of the studies is the lack of clinical outcomes data, particularly for bleeding. The INR was used as a surrogate endpoint that may or may not reflect bleeding risk.

**Four-factor PCC.** In a case series of 82 warfarin-treated patients who received 85 doses of a four-factor PCC product (Octaplex) with or without phytonadione for immediate reversal, the mean  $\pm$  S.D. INR was significantly reduced from 5.08  $\pm$  5.39 before reversal to 1.43  $\pm$  0.42 ( $p < 0.0001$ ).<sup>22</sup> The mean  $\pm$  S.D. PCC and phytonadione doses were 1792  $\pm$  601 units and 4.9  $\pm$  5.5 mg, respectively. None of the patients received FFP. Seven deaths (4 of 40 patients requiring reversal before surgery and 3 of 36 patients requiring reversal for bleeding) were reported, and thrombosis occurred in three patients. The thrombosis observed in this study highlights the potential risks associated with use of four-factor PCC for warfarin reversal.

Outcomes from use of a four-factor PCC product (Beriplex P/N) were assessed in a randomized, open-label study of 212 patients who required reversal of warfarin therapy because of bleeding.<sup>23,24</sup> Patients were randomly assigned to receive PCC 25–50 units/kg based on the INR or FFP 10–15 mL/kg also based on the INR. The rate of bleeding after 24 hours of treatment was similar in the two treatment groups. The INR was corrected within 30 minutes in more patients receiving PCC (62.2%) than receiving FFP (9.6%), and the frequency of fluid overload was lower in the PCC group (5.0%) than in the FFP group (13.2%).

In these and other studies of four-factor PCC for warfarin reversal, the INR was promptly normalized within minutes or hours.<sup>22–28</sup> In contrast to three-factor PCC pro-

ducts, four-factor PCC products were effective for reducing the INR when used without FFP. The effect of four-factor PCC products on bleeding was similar to that of FFP. Fixed doses (typically 25–50 units/kg) and dosing based on the INR both have been used. The potential for thromboembolic complications during four-factor PCC treatment should be considered, although thromboembolic events have been reported infrequently. As with the three-factor PCC products, most available data for four-factor PCC products evaluate surrogate endpoints (i.e., INR) instead of clinical outcomes (i.e., bleeding). However, the one study of four-factor PCC products that did evaluate clinical outcomes suggested similar efficacy of PCC and FFP and greater tolerability of PCC.<sup>23</sup>

**Recombinant factor VIIa.** In a retrospective, nonrandomized study of 40 warfarin-treated adults with traumatic ICH and an INR greater than 1.3, the effectiveness of rFVIIa (mean dose, 17.7  $\pm$  6.2  $\mu$ g/kg) plus standard treatment for warfarin reversal (FFP with or without phytonadione) was compared with standard treatment alone.<sup>29</sup> All participants received other supportive measures or surgical interventions as needed.

The mean baseline INR was similar in the rFVIIa group (2.87) and the standard treatment group (2.51,  $p > 0.05$ ). The time to an INR less than 1.3 (i.e., normalization) was significantly shorter in the rFVIIa group than the standard treatment group (4.8 hours versus 17.5 hours, respectively,  $p < 0.001$ ).<sup>29</sup> The time to surgery, which may reflect the time until the INR is reduced to a safe level, was lower in the rFVIIa group (5.6 hours; range, 2.1–9.2 hours) than the standard treatment group (74.6 hours; range, 70.5–219.7 hours), although the difference was not significant ( $p = 0.30$ ). There was no difference between the two treatment groups in in-hospital mortality (35% for both groups,  $p = 1.0$ ). The frequency of

thromboembolism was higher with rFVIIa than with standard treatment alone (20.0% versus 5.0%, respectively), although the difference was not significant ( $p = 0.15$ ).

In a retrospective cohort study of 24 adults with warfarin-related ICH, rFVIIa was compared with three-factor PCC (Bebulin).<sup>30</sup> Fifteen patients received rFVIIa (mean dose, 53.4  $\mu$ g/kg; range, 15–78  $\mu$ g/kg), and nine patients received the PCC product (mean dose, 27.8 units/kg; range, 7.6–58 units/kg). The INR decreased from 6.1 to 1.1 after one hour in patients receiving rFVIIa and from 2.3 to 1.48 after one hour in patients receiving PCC. The success rate in achieving an INR of 1.3 or less within one hour was 83% with rFVIIa and 20% with PCC. After six hours, the success rate was 93% with rFVIIa and 50% with PCC.

**Building a four-factor PCC.** Because four-factor PCC products other than aPCC are not available in the United States, a combination of three-factor PCC plus rFVIIa has been used in an effort to build a four-factor PCC that provides the same clotting factors.<sup>17</sup> In a retrospective analysis of 46 patients with warfarin-related ICH and INR values of 1.6 or higher, the efficacy of a reversal strategy involving three-factor PCC (4000 units Profilnine SD) plus rFVIIa 1 mg (as well as phytonadione 5 mg by slow i.v. injection) was compared with that of FFP in 12 historical control patients.<sup>17</sup> Three of the historical control patients received FFP alone, and the other nine historical control patients received a three-factor PCC plus FFP. In the PCC plus rFVIIa group, the mean INR was 3.4 at baseline, 1.0 at the end of the infusion, and 1.2 after 24 hours. In the FFP alone group, the mean INR was 2.6 at baseline and 1.6 both at the end of the infusion and after 24 hours. In the PCC plus FFP group, the mean INR was 3.3 at baseline, 1.4 at the end of the infusion, and 1.3 after 24 hours. The reductions in INR with

PCC plus rFVIIa at end of infusion and at 24 hours were significantly greater than the INR reduction in the FFP alone group ( $p = 0.0036$  and  $p = 0.0056$ , respectively) and in the FFP plus PCC group ( $p = 0.0019$  and  $p = 0.025$ , respectively). Two patients developed thrombotic complications (non-ST segment elevation myocardial infarction) eight hours and three days after treatment with PCC plus a higher dose (2.4 mg) of rFVIIa. Subsequently, the rFVIIa dose was altered to include only low dose.

**Activated PCC.** In a retrospective analysis of patients requiring warfarin reversal because of life-threatening bleeding, 72 patients receiving phytonadione 10 mg by slow i.v. injection plus aPCC (500 units for INR less than 5 or 1000 units for INR of 5 or more) were compared with 69 historical control patients who were treated with FFP (approximately 2 units at the discretion of the prescriber).<sup>31</sup> Administration of aPCC produced lower INR values than did FFP. The median time to an INR of 1.4 or lower (i.e., INR normalization) was significantly shorter with aPCC (2.0 hours) than FFP (25.2 hours,  $p = 0.006$ ). Three of the 72 patients treated with aPCC developed possible cardiac ischemia, and one aPCC-treated patient developed deep vein thrombosis.

**Therapeutic strategy.** In warfarin-treated patients with bleeding, phytonadione 5–10 mg by slow i.v. injection plus a four-factor PCC is recommended for urgent warfarin reversal by ACCP, although no four-factor PCC products currently are available in the United States.<sup>2</sup> In warfarin-treated patients who require surgery within 24 hours, a two-drug combination of phytonadione 5–10 mg slow i.v. injection plus (1) four-factor PCC, (2) rFVIIa, or (3) aPCC will likely be effective for lowering the INR, according to the published literature.<sup>29,31–35</sup> If surgery is needed but can be delayed for more than 24 hours, oral phytonadione alone may suffice for warfarin reversal based on the pharmacodynamics of vitamin K.

Because four-factor PCC products currently are not available in the United States, another strategy must be devised to provide the four vitamin K-dependent clotting factors. FFP can be used in combination with three-factor PCC or rFVIIa in patients who can tolerate the fluid volume associated with FFP. Alternatively, three-factor PCC plus rFVIIa can be used to build a four-factor PCC. Another option would be to use aPCC.

The high cost of clotting factor concentrates is a concern for health-system pharmacists and administra-

tors responsible for managing the drug budget, although the cost for concentrated clotting factor regimens used for anticoagulant reversal is much lower than when these products are used to treat hemophilia. Consideration of the acquisition costs of concentrated clotting factor products (Table 2) may influence the choice among the therapeutic regimens for urgent warfarin reversal.

### Reversal of target-specific oral anticoagulants

Strategies for reversing the effects of the target-specific anticoagulants dabigatran, a direct thrombin (factor IIa) inhibitor, and rivaroxaban and apixaban, direct factor Xa (FXa) inhibitors, currently are largely theoretical and based on limited data obtained primarily from animal models, although some studies in healthy human volunteers and case reports are available. In theory, exogenous administration of the clotting factors that these novel anticoagulants inhibit could overcome (i.e., reverse) the effects of the anticoagulant.

**Animal data.** Animal models have explored the impact of reversal attempts on both laboratory measures of coagulation and actual bleeding. Animal data suggest that four-factor PCC products may reduce bleeding with dabigatran

Table 2.

### Comparative Acquisition Costs of Concentrated Clotting Factor Products for Urgent Warfarin Reversal<sup>a,b</sup>

Agent (dose)	Regimen		
	FFP + Three-Factor PCC	Three-Factor PCC + rFVIIa	aPCC
FFP (15 mL/kg)	\$300	N/A	N/A
Three-factor PCC (25 units/kg)	\$1932	\$1932	N/A
rFVIIa (20 µg/kg)	N/A	\$2820	N/A
aPCC (1000 units)	N/A	N/A	\$1800
Total cost of regimen	\$2232	\$4752	\$1800

<sup>a</sup>aPCC = activated prothrombin complex concentrate, FFP = fresh frozen plasma, N/A = not applicable, PCC = prothrombin complex concentrate, rFVIIa = recombinant factor VIIa.

<sup>b</sup>Costs of medications are for an 80-kg patient based on the suggested wholesale price (three-factor PCC = \$0.97/unit, rFVIIa = \$1410/mg, aPCC = \$1800/1056 units) with doses rounded to nearest vial size and do not reflect the costs of administering the drug or treating adverse effects associated with the drug. Source of medication cost information: Amerisource-Bergen online product catalog; October 2012. <https://passport.amerisourcebergen.com/irj/portal> (accessed 2012 Aug 31). Cost of FFP = approximately \$60 per unit (200–250 mL/unit), available through blood banks.

but not rivaroxaban.<sup>36,37</sup> Laboratory indices were improved when four-factor PCC products were used to counteract rivaroxaban; however, bleeding was not improved.<sup>37</sup> The effects of three-factor PCC products on dabigatran and rivaroxaban are unknown, because data are not available. Data from animals are conflicting regarding the usefulness of rFVIIa for reversing dabigatran and rivaroxaban.<sup>36-39</sup> The effects of both dabigatran and rivaroxaban appear to be reversed by aPCC.<sup>38,39</sup> FFP does not appear useful for reversing dabigatran, and data are not available on the use of FFP for reversing the effects of rivaroxaban. To the author's knowledge, there are no published data from animal studies of the reversal of apixaban; however, *in vitro* data suggest that apixaban may be only partially reversed by aPCC.<sup>40</sup>

**Human data.** Human data for reversal of newer anticoagulants are extremely limited. The usefulness of four-factor PCC (Cofact) for reversing the anticoagulant effects of dabigatran and rivaroxaban was evaluated in a randomized, double-blind, placebo-controlled study of 12 healthy male volunteers.<sup>41</sup> Dabigatran 150 mg twice daily or rivaroxaban 20 mg twice daily was provided for 2½ days before 50 units/kg of PCC or a similar volume of saline placebo was administered. After an 11-day washout period, subjects were crossed over to receive 2½ days of treatment with the other anticoagulant. Dabigatran reversal was assessed using 24-hour serial laboratory monitoring of the activated partial thromboplastin time, ecarin clotting time, and thrombin time. Administration of four-factor PCC had no effect on any of these measures of coagulation in dabigatran-treated subjects. Rivaroxaban reversal was assessed using 24-hour serial laboratory monitoring of prothrombin time (PT) and endogenous thrombin potential (ETP). Administration of four-factor PCC normalized both

the PT and ETP within 15 minutes in rivaroxaban-treated subjects. The fact that laboratory indices were improved for subjects receiving rivaroxaban is consistent with animal data. Findings with dabigatran are less consistent with animal data and might be attributed to use of laboratory tests that are not optimal for monitoring coagulation or to differences in the clotting factor content or dose of four-factor PCC product used. It is also important to note that it is unclear whether correction of laboratory indices, observed with rivaroxaban in this study, will translate to arrest of bleeding in a patient.

An *ex vivo* study was conducted to evaluate the use of four-factor PCC (Kanokad), rFVIIa, and aPCC in reversing dabigatran and rivaroxaban in humans.<sup>42</sup> Venous blood samples were obtained from 10 healthy white male volunteers immediately before and two hours after they received a single 150-mg dose of dabigatran or a 20-mg dose of rivaroxaban. After a two-week washout period, subjects were crossed over to receive the other anticoagulant, and the blood sampling procedure was repeated. Measures of thrombin generation, including ETP, peak thrombin generation, lag time, and time to peak thrombin, were used to assess reversal of the anticoagulants after the blood samples were exposed to several concentrations of four-factor PCC, rFVIIa, and aPCC. The effects of four-factor PCC and rFVIIa on thrombin generation in dabigatran- and rivaroxaban-treated blood samples were inconsistent. By contrast, aPCC had a consistent impact on thrombin generation in rivaroxaban-treated blood and a less consistent impact on thrombin generation in dabigatran-treated blood, although the impact of aPCC on dabigatran-treated blood was greater than that of four-factor PCC and rFVIIa. These findings are fairly consistent with animal data. In addition,

a case has been reported in which aPCC (26 units/kg) was administered to a patient experiencing significant bleeding during an atrial fibrillation ablation.<sup>43</sup> Bleeding was noted to visibly slow after five minutes of aPCC infusion and to stop before the end of the infusion. Thus, aPCC may play a role in reversing dabigatran and rivaroxaban; however, *in vivo* human studies are lacking.

The role of rFVIIa and hemodialysis in reversing dabigatran was described in a case report of a 79-year-old man with renal impairment (creatinine clearance, 36 mL/min) who was receiving dabigatran 150 mg twice daily and required aortic valve replacement and coronary artery bypass graft surgery.<sup>44</sup> Dabigatran therapy was withheld for two days before surgery, an interval that in retrospect may have been too short, given the patient's renal function. The patient subsequently developed massive postoperative bleeding. The bleeding was successfully managed by the administration of five doses of rFVIIa (three 2.4-mg doses and two 7.2-mg doses) and six hours of hemodialysis. Another more recent case report also supports hemodialysis as a viable strategy for treating a patient with dabigatran-induced bleeding.<sup>45</sup>

The contribution of hemodialysis to a successful outcome in these case reports is supported by the results of an open-label pharmacokinetic study in which hemodialysis removed 62% of a single 50-mg dabigatran dose over a two-hour period and 68% of this dose over a four-hour period in six patients with end-stage renal disease.<sup>46</sup> The case report of the 79-year-old man illustrates the importance of considering renal function as well as the type of surgery (i.e., risk for bleeding) in planning surgery for patients receiving dabigatran, because of the importance of the kidneys in eliminating the drug.<sup>47</sup> As renal function deteriorates (i.e., creatinine clearance decreases), the half-life of

dabigatran increases, and the time interval needed between the last dose of dabigatran and the surgery to prevent perioperative bleeding also increases. In addition, the time elapsed between the last dose of dabigatran and surgery should be longer for surgeries associated with a high risk for bleeding than surgeries associated with a lower risk for bleeding. Therefore, discontinuation of dabigatran therapy four days before the 79-year-old man's aortic valve replacement and coronary artery bypass surgery may have been more appropriate, given his age, high bleeding risk associated with the surgery, and underlying renal function.

Perioperative management of patients with renal impairment may be less problematic when rivaroxaban is used instead of dabigatran, because renal filtration plays a smaller role in elimination of rivaroxaban. Decreases in creatinine clearance prolong the half-life of rivaroxaban to a lesser extent than with dabigatran. Nonrenal routes (i.e., hepatic metabolism, fecal elimination) and renal secretion contribute to the elimination of rivaroxaban, and the drug is highly protein bound.<sup>48,49</sup> Although apixaban has a slightly longer apparent half-life than rivaroxaban, apixaban also has other routes of clearance beyond renal clearance. Therefore, perioperative management issues may be similar for rivaroxaban and apixaban.

**Therapeutic strategy.** Currently available evidence on the effects of clotting factor concentrates in reversing the anticoagulant effects of dabigatran and rivaroxaban in animals and humans is limited, but animal data, ex vivo data, and a case report suggest a possible role for aPCC. The combination of three-factor PCC and rFVIIa, which provides the same four clotting factors as aPCC (in different quantities), might be an alternative. Evidence to support the use of four-factor PCC for reversal of these target-specific oral anticoagulants is conflicting,

and the limited available data suggest that a four-factor PCC may be ineffective for reversal of dabigatran. Data related to the impact of reversal agents on apixaban are even sparser than for dabigatran and rivaroxaban; however, it may be reasonable to expect that apixaban would respond to reversal agents in a manner similar to rivaroxaban, given that both are factor Xa inhibitors.

Larger doses of concentrated clotting factor products often are needed for reversal of the target-specific oral anticoagulants than for warfarin reversal. Determining what dose to use for reversal is difficult, and it may not be possible to extrapolate animal dosing data to humans.

The impact of concentrated clotting factor products may be enhanced by using them in combination with other modalities (e.g., hemodialysis for dabigatran reversal). Administering oral activated charcoal after recent ingestion (<2 hours) of the target-specific oral anticoagulants may be beneficial, as well.<sup>47,50,51</sup>

The lack of evidence of a clear benefit from clotting factor concentrates in patients requiring reversal of target-specific oral anticoagulant therapy suggests that the risks and benefits of these products must be weighed before use for this purpose. Data on the use of clotting factor concentrates to reverse the effects of warfarin suggest that thrombosis is a risk, and one may assume that a prothrombotic risk would also be present if these agents were used for reversal of dabigatran, rivaroxaban, or apixaban. The mostly unproven positive impact of concentrated clotting factor products on bleeding risk may not outweigh the risk of thrombosis, especially in patients in whom thrombosis could be catastrophic (e.g., patients with mechanical valves or left-ventricular assist devices). As such, proper patient selection is vital to optimizing the use of these therapies and patient outcomes.

## Conclusion

Phytonadione and clotting factor concentrates appear to have a role for reversal of warfarin, and limited evidence suggests that clotting factor concentrates could have a role in reversal of target-specific oral anticoagulants in an emergency situation.

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## Developing a management plan for oral anticoagulant reversal

WILLIAM E. DAGER

Oral anticoagulants are widely used for several common conditions, and bleeding is a potential complication. Therapy sometimes must be interrupted temporarily for invasive procedures, including surgery, especially when the procedure is associated with a high risk for bleeding. Ideally, the risk of bleeding during oral anticoagulant therapy or when such therapy is interrupted for an invasive procedure is minimized through preventive strategies. These strategies include proper selection of the anticoagulant agent and dosage before, during, and after the procedure; timing of anticoagulant discontinuation before the procedure; careful patient monitoring for early signs and symptoms of bleeding; and laboratory monitoring when applicable. Additional therapeutic considerations include inter-

**Purpose.** To describe a process for prompt evaluation and management—including reversal of the effects of warfarin and target-specific oral anticoagulants—of patients with or at high risk for bleeding during oral anticoagulant therapy or when such therapy is interrupted for an urgent invasive procedure or surgery.

**Summary.** The use of pharmacologic interventions for anticoagulant reversal may depend on the measured level of anticoagulation, time since the last anticoagulant dose, target level of coagulation, reliability of laboratory tests of coagulation, severity of or risk for bleeding, the agents' mechanism of action and pharmacokinetics, and pharmacodynamics of the reversal agent. The patient's age, weight, renal function, comorbid conditions, and other drug therapy, as well as the risk for thromboembolism and other adverse effects of the reversal therapies, also enter into therapeutic decisions. Hemodialysis may be used to remove the direct throm-

bin (factor IIa) inhibitor dabigatran and reverse its anticoagulant effects. Limited experience with clotting factor concentrates suggests that activated prothrombin complex concentrate may be useful for reversing the anticoagulant effects of dabigatran. The activity of oral factor Xa inhibitors (i.e., rivaroxaban and apixaban) is higher up the common pathway of the coagulation cascade and thus may be easier to reverse than that of direct thrombin inhibitors. Additional clinical experience is needed to identify the optimal reversal agents, dosage, and impact on thrombosis or bleeding outcomes for both classes of agents.

**Conclusion.** A comprehensive plan individualized to each agent should be developed to promptly reverse the effects of oral anticoagulants and optimize outcomes in patients with bleeding or an urgent need for surgery.

**Am J Health-Syst Pharm.** 2013; 70(Suppl 1):S21-31

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Based on the proceedings of a symposium held December 3, 2012, during the 47th ASHP Midyear Clinical Meeting and Exhibition in Las Vegas, Nevada, and supported by an educational grant from CSL Behring.

Dr. Dager received an honorarium for participating in the symposium and preparing this article. Dr. Dager has declared no potential conflicts of interest.

The assistance of Carla J. Brink, M.S., B.S.Pharm., and Susan R. Dombrowski, M.S., B.S.Pharm., in developing the manuscript is acknowledged. Ms. Brink and Ms. Dombrowski have declared no potential conflicts of interest.

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DOI 10.2146/ajhp130042

rupting oral anticoagulant therapy for a sufficient amount of time before any invasive procedure takes place to minimize bleeding complications and determining when to reinstitute therapy afterwards. If anticoagulant therapy cannot be discontinued sufficiently early, the patient may be at increased risk for perioperative and postoperative bleeding complications resulting in morbidity and mortality.

Because bleeding may develop during oral anticoagulant therapy or in emergent situations (e.g., an unanticipated invasive procedure or surgery) despite preventive strategies, a comprehensive plan for prompt reversal of the anticoagulant effect may be necessary to minimize associated morbidity and mortality.

### Patient evaluation and management plan

Acutely ill patients receiving oral anticoagulants who display signs of anemia or other reasons to suspect bleeding after traumatic events or invasive procedures should be evaluated for the presence of bleeding. Internal bleeding may not be accompanied by overt signs, but complete blood counts can be monitored to detect potential blood loss. When a patient receiving an oral anticoagulant presents with bleeding, the site and risk for complications must be assessed. Accumulation of even small amounts of blood at certain sites (e.g., the spine, ocular region) can cause devastating complications. Accumulation of blood in a closed cavity can be more problematic than accumulation at sites that can be drained or managed with adjunctive interventions, such as the application of pressure, cauterization, or suturing. Blood transfusions may be required to maintain adequate levels of hemoglobin and oxygenation of the blood to support vital physiologic functions.

The level (i.e., intensity) of anticoagulation should be measured as part of the evaluation process for

patients receiving anticoagulation therapy. The laboratory assays used for this purpose depend on the type of anticoagulant and the dosage used. Although routine use of laboratory assays is not routinely needed for target-specific oral anticoagulants (e.g., the direct thrombin inhibitor dabigatran, the factor Xa [FXa] inhibitors rivaroxaban and apixaban), these assays can provide potentially useful information in patients with or at high risk for bleeding.

The possibility that a patient may be receiving agents that inhibit platelet function should be considered, because these agents may increase the risk of a bleeding event in patients receiving oral anticoagulants. Citrate in blood transfusions also can contribute to bleeding because of its anticoagulant effect, underlining the importance of co-administering calcium to counteract the citrate.<sup>1</sup>

Various patient characteristics may influence the rate at which the effects of oral anticoagulants decrease when the drug is withheld. The decline in International Normalized Ratio (INR) after warfarin is withheld in patients with elevated values tends to be slower in patients with advanced age, a high initial INR value, decompensated congestive heart failure, active malignancy, or a low weekly maintenance warfarin dose than in patients who are younger with a low initial INR value, high weekly maintenance warfarin dose, and no heart failure or active malignancy.<sup>2</sup>

Withholding the oral anticoagulant and using mechanical interventions (e.g., sutures) may suffice to resolve bleeding, but mechanical interventions often are not feasible because of the site involved or other factors. Pharmacologic interventions (along with withholding the oral anticoagulant) often are needed instead of or in addition to mechanical interventions. The choice of pharmacologic intervention depends on the oral anticoagulant, measured level of

anticoagulation, time since the last oral anticoagulant dose, and degree of anticoagulation needed after reversal. The goal might be partial or complete reversal of anticoagulation. Complete reversal may be needed to minimize severe bleeding complications. Partial reversal may suffice in patients with less severe bleeding concerns. The overall needs of the patient should be considered in any management plan involving reversal therapies, and the plan should be sufficiently flexible to accommodate acute changes in patient status. Oral anticoagulant therapy may need to be reinitiated if the condition for which anticoagulant use was indicated initially (i.e., risk for thrombosis) persists after bleeding resolves. In surgical patients, the postoperative risk for thrombosis as well as for bleeding should be considered in determining the desired intensity of anticoagulation in the early postoperative period. Short- and long-term risks for thrombosis and bleeding should be continually weighed, with management plans revised accordingly. Controlling bleeding is a priority in the short term, but concerns about thrombosis risk often assume increasing importance in the long term.

Reversal of the effects of oral anticoagulants can be achieved by neutralizing or removing the drug or by producing hemostasis independent of direct antagonism of the oral anticoagulant. The duration of the effects of both the anticoagulant and reversal agents should be considered. A rebound anticoagulation effect can occur when the duration of effect of the reversal therapy is shorter than that of the anticoagulant.

The use of clotting factor concentrates for oral anticoagulant reversal may present a challenge because of their prothrombotic effect. The use of long-acting reversal agents also can be problematic because of the risk of thromboembolism as long as the prothrombotic effect persists. Thus, the mechanism of action,

pharmacokinetics, and pharmacodynamics of oral anticoagulant reversal agents are considerations in devising reversal strategies.

The need for replacement of blood loss is a consideration in managing active bleeding from oral anticoagulants. The citrate content of blood products administered and the risk of transfusion reactions are potential concerns. Comorbid conditions that could contribute to coagulopathies and bleeding (e.g., sepsis) should be managed to the extent possible. Administration of calcium may be needed to counteract the anticoagulant effects of citrate in blood products and maintain hemostasis.<sup>1,3,4</sup> A comprehensive management plan with appropriate follow-up should be devised to address patient needs and concerns associated with the reversal of oral anticoagulants in patients with bleeding. The risk for complications, including continued bleeding or thrombosis, should be addressed in this plan.

### Warfarin reversal

Therapeutic options for warfarin reversal include phytonadione, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), activated PCC (aPCC), and recombinant factor VIIa (rFVIIa). Phytonadione administration promotes hepatic production of vitamin K-dependent clotting factors II, VII, IX, and X, which are depleted by warfarin. Because the onset of effect of phytonadione is not immediate, products containing clotting factors (e.g., PCC, FFP, rFVIIa) are used to expedite hemostasis. PCC products include three-factor PCCs, which primarily contain clotting factors II, IX, and X (with only minimal factor VII) in an inactivated form, and four-factor PCCs, which contain factors II, VII, IX, and X in an inactivated form. Activated PCC contains clotting factor VII in an activated form and clotting factors II, IX, and X primarily in an inactivated form.

Recombinant activated factor VII contains only clotting factor VII. Because these products promote hemostasis independent of the anticoagulant, their use is also associated with a risk for thrombosis; thus, clinicians should use the lowest possible dose to achieve treatment goals.

**PCC dosing.** The dosing of three- and four-factor PCCs typically is based on patient weight, current INR, and severity of bleeding. The three-factor PCC products currently approved by the Food and Drug Administration (FDA) are indicated for prevention and control of bleeding in patients with factor IX-deficient hemophilia. With the availability of selective factor IX products, PCC product use has shifted to include use for the reversal of vitamin K antagonists such as warfarin. The doses typically used for warfarin reversal (25–50 units of the factor IX component per kilogram of body weight) are lower than those used for patients with hemophilia.<sup>5,6</sup> Higher doses (i.e., more than 25 units/kg) might be considered in patients with elevated INR values and severe bleeding (i.e., the potential to impair a vital body function). Lower doses (25 units/kg or less) may be considered in patients with a lower INR and a lesser concern or urgency related to bleeding. One example based on the INR alone is to consider a PCC dose of 35 units/kg for an INR value of 4–6 and 50 units/kg if the INR exceeds 6.<sup>7</sup> It is noteworthy, however, that as the INR climbs, the reduction in the concentration of clotting factors present becomes smaller. Thus, at very high INR values (over 6), a small change in the concentration of clotting factors can lead to a notable reduction in the subsequent INR. Whether to use ideal body weight or total body weight to determine the PCC dose in morbidly obese patients is unclear.

The onset of INR reversal and the induction of hemostasis are rapid, occurring within minutes after infusion of the PCC product, which

allows titrating to response when bleeding sites can be visualized. The vial size is a practical consideration; the dose should be rounded to use the entire vial contents because of the high cost of the products and need to minimize waste in dose preparation.

**PCC development.** Four-factor PCC products, which are recommended for warfarin reversal in current guidelines, are not available in the United States.<sup>8–10</sup> Recent experience in the United States, including use in patients with intracranial hemorrhage (ICH), has shown limited ability of three-factor PCC products to reverse the INR completely.<sup>11,12</sup> Several four-factor PCC products are in development; they are either under review by FDA or have received orphan drug status for reversal of vitamin K antagonists such as warfarin.<sup>13,14</sup>

In abstracts describing a Phase III, randomized, open-label study of 212 warfarin-treated patients with an elevated INR (2 or higher) and acute major bleeding, the hemostatic efficacy of a four-factor PCC product (Beriplex P/N, CSL Behring UK Ltd., Marburg, Germany) designed to reinstate factors specifically reduced by warfarin (25–50 units of the factor IX component per kilogram, depending on the INR) was compared with FFP (10–15 mL/kg based on the INR).<sup>15–17</sup> The rate of success in achieving hemostasis after 24 hours was similar (72.4% and 65.4%, respectively; difference 7.1%; 95% confidence interval [CI], –5.8–19.9). The four-factor PCC product was more effective than FFP in achieving the target INR within 30 minutes; success rates were 62.2% for four-factor PCC and 9.6% for FFP (difference, 52.6; 95% CI, 39.4–65.9). The risk of fluid overload or similar cardiac events was lower with PCC (4.9%) than with FFP (12.85%).<sup>17</sup> In Phase III studies, this four-factor PCC product was given in combination with phytonadione (orally or by slow intravenous [i.v.] infusion); doses were based on the

INR (25 units/kg for INR of 2 to less than 4, 35 units/kg for INR of 4–6, and 50 units/kg for INR greater than 6).<sup>16</sup> The frequency of treatment-related adverse events was similar with PCC and FFP, although less fluid overload was associated with PCC than with FFP.<sup>18</sup> The relative benefits of weight-based dosing versus fixed dosing of PCC have not been established.

**aPCC.** Activated PCC has also been explored for reversing the effects of warfarin. A retrospective chart review of patients with warfarin-related life-threatening bleeding showed that target INR values below 1.5 were achieved in approximately half of 72 patients receiving an aPCC product (FEIBA NF, Baxter Healthcare Corporation, Westlake Village, CA) in doses of 500 units for baseline INR values below 5 or 1000 units for INR values of 5 or more, compared with one third of 69 patients receiving FFP (median dose 2 units) ( $p = 0.017$ ).<sup>19</sup> No difference in survival was noted between aPCC and FFP, however. In the 72 patients receiving aPCC, 5 potentially related thromboembolic events were noted.

**rFVIIa.** The doses of rFVIIa used for lowering the INR during warfarin therapy (53  $\mu\text{g}/\text{kg}$  on average in one retrospective study) are considerably lower than those used for prevention and treatment of bleeding in patients with hemophilia (90  $\mu\text{g}/\text{kg}$ ), the FDA-approved indications for the drug.<sup>20,21</sup> Data are available suggesting that rFVIIa doses as low as 1–2 mg (i.e., 14–28  $\mu\text{g}/\text{kg}$  for a 70-kg person) are effective for warfarin reversal using the INR as a surrogate endpoint.<sup>22–24</sup> The optimal rFVIIa dose and the impact on bleeding complications are uncertain. The onset of effect for reducing both bleeding and the INR appears to be rapid, with the lowest effective dose sought primarily because of concerns about thrombosis.

**Phytonadione.** Administration of phytonadione promotes hepatic production of the four vitamin

K-dependent clotting factors depleted by warfarin. The route of administration (oral or i.v.) of phytonadione depends on the INR and the presence of bleeding.<sup>8</sup> Phytonadione should not be given by subcutaneous (s.c.) or intramuscular (i.m.) injection for warfarin reversal, because the oral and i.v. routes have a more rapid and predictable onset of effect.<sup>25</sup> Other interventions with a more rapid onset of action on the INR than phytonadione, including three-factor PCC, rFVIIa, FFP, and aPCC, may be added to phytonadione in patients with serious and life-threatening bleeding.

The maximum recommended i.v. infusion rate for phytonadione is 1 mg/min.<sup>26</sup> Most infusions are administered over 15–20 minutes. Doses usually are diluted in 50 mL of fluid. Diluting the drug in larger volumes may delay delivery and the onset of action. The drug is sensitive to and must be protected from light.<sup>26</sup>

Hypersensitivity reactions to phytonadione are rare, but potentially serious adverse effects have been associated with rapid i.v. infusion, with a frequency of 3 per 10,000 i.v. doses, according to a retrospective review of more than 6,000 doses over a five-year period.<sup>27</sup> Administering phytonadione by slow i.v. injection reduces the risk of a hypersensitivity reaction.

Up to 10 mg of phytonadione is recommended for reversing the effects of warfarin in patients with life-threatening bleeding.<sup>8</sup> Because vitamin K is fat soluble and excess amounts can be stored in tissues, the effects of phytonadione on coagulation may be prolonged, which can be a concern once bleeding has resolved and reestablishment of anticoagulation with a vitamin K antagonist is sought. In a retrospective chart review of 114 patients who received i.v. phytonadione alone for warfarin reversal, increasing the i.v. phytonadione dose beyond 2 mg did not influence the rate or extent of INR reduction beyond what was achieved

using 2 mg after 12 hours, 24 hours, or 48 hours.<sup>28</sup> Doses as large as 10 mg were used. However, doses larger than 2 mg were associated with a trend toward increased need for and duration of bridging therapy (i.e., dual anticoagulation with another anticoagulant plus warfarin to prevent thrombosis once bleeding resolved) compared with smaller doses, which may reflect warfarin refractoriness (i.e., resistance to the effects of warfarin when the drug was restarted). These findings suggest that large i.v. phytonadione doses do not have an advantage for urgent warfarin reversal over smaller doses in patients without life-threatening bleeding who expect to need to restart warfarin therapy promptly.

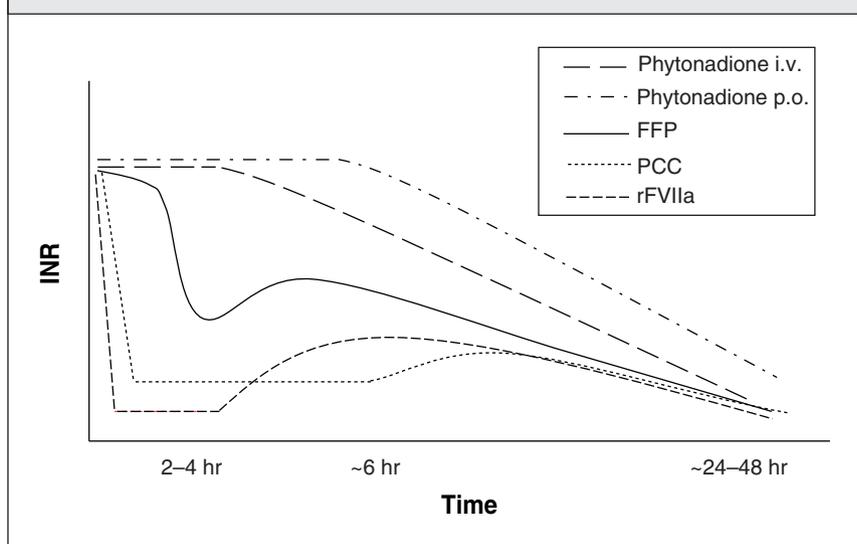
**Pharmacodynamics.** There is a delay before the INR decreases in response to i.v. or oral phytonadione administration in warfarin-treated patients with an elevated INR because of the lag time needed for production of vitamin K-dependent clotting factors, although the INR decrease occurs sooner after i.v. administration than after oral administration (Figure 1).<sup>23</sup> Administering a clotting factor concentrate, such as a PCC product or rFVIIa, to a warfarin-treated patient with an elevated INR provides an immediate drop in INR, but this drop is followed several hours later by a rebound increase due to the short elimination half-life of factor VII. Because the other clotting factors in PCC products (i.e., factors II, IX, and X) have longer half-lives than factor VII, the rebound increase in INR occurs later than after rFVIIa administration.<sup>29</sup> The onset of action of FFP is delayed because of the time required for thawing and administration of the product, which involves infusion of a large volume. Warfarin reversal by FFP is only partial, and a rebound increase in INR begins shortly after the end of the infusion. Combination therapies (e.g., phytonadione plus either PCC or rFVIIa or all

three agents) may be used to avoid rebound increases in INR.

**Role of surgery and pharmacologic intervention.** Questions have arisen about the role of pharmacologic interventions in improving clinical outcomes in patients with warfarin-related ICH. In 141 such patients, the INR was reduced from a median of 2.6 to less than 1.5 (i.e., normalized) within one hour after administration of a four-factor PCC product (Octaplex, Octapharma AG, Vienna, Austria) in 79.5% of the patients.<sup>30</sup> However, the in-hospital mortality rate was high (42.3%), substantial hematoma expansion occurred in nearly half the patients (45.5%), and the median modified Rankin scale was 5, reflecting severe disability. In a review of a protocol using a three-factor PCC product (Profilnine, Grifols Biologicals, Inc., Los Angeles, CA; mean dose, 47 units/kg) in 70 patients for urgent reversal of warfarin in the setting of ICH, correction of the INR (target <1.4) was incomplete (the mean INR was reduced from 3.36 to 1.96), and PCC-related serious adverse events occurred in 10% of patients.<sup>12</sup>

Pharmacologic intervention may play an important role in prompt reduction of the INR to a value considered safe enough for surgical intervention. In an analysis of seven patients with warfarin-related ICH, administration of a three-factor PCC product (Profilnine) halted hematoma expansion and expedited surgical intervention.<sup>31</sup> The effects of PCC and rFVIIa on INR reported in retrospective studies were prompt, although the times to measurement of INR were not standardized to allow comparison among products.<sup>32</sup> In the Surgical Trial in Intracerebral Haemorrhage (STICH), which compared early surgical intervention with initial conservative treatment of spontaneous supratentorial intracerebral hematomas ( $n = 1033$ ), no benefit from early surgery was noted.<sup>33</sup> In the 80 patients receiving

**Figure 1.** Onset and duration of effect on International Normalized Ratio (INR) of various warfarin reversal therapies. FFP = fresh frozen plasma, PCC = prothrombin complex concentrate, rFVIIa = recombinant factor VIIa. Adapted from reference 23.



an oral anticoagulant, there was a nonsignificant trend toward fewer unfavorable outcomes; the trial used a prognosis-based outcome that incorporated a Glasgow outcome score at six months with early surgery (fixed OR, 0.51; 95% CI, 0.17–1.46)].

**Risks to consider.** The potential for INR rebound after administration of PCC or rFVIIa to patients with warfarin-related ICH needs to be considered. Administering i.v. phytonadione with these agents may prevent or delay INR rebound, and early phytonadione administration is needed because of the lag time before clotting factors are replenished by vitamin K. The INR needs to be closely monitored, and adjunctive therapies (e.g., PCC or rFVIIa) may be needed if rebound occurs.

The risk for thromboembolism is a serious concern with the administration of clotting factor concentrates. The administration of these products when endothelial damage, tissue factor expression, or underlying disease processes (e.g., coronary artery disease) are present may increase the risk for thrombosis, including acute coronary syndrome and sudden death from pulmonary

embolism.<sup>12,29</sup> In a retrospective analysis of 69 patients who received rFVIIa for various off-label uses (i.e., non-hemophilia patients), 36 possible thromboembolic adverse events were identified in 29 patients, including 12 patients with events judged related to rFVIIa.<sup>34</sup> The mean rFVIIa dose was 8.2 mg (i.e., 117  $\mu\text{g}/\text{kg}$  for a 70-kg person). On average, the events were identified 8.8 days after exposure to the drug. None of the 48 physicians who cared for these patients and later completed questionnaires about the care provided were aware of the thromboembolic events, perhaps because the patient moved to a different care setting before the event occurred. These findings suggest that such events may be underreported in patients receiving rFVIIa (especially at higher doses) for off-label uses, and clinicians need to be aware of the risk for thromboembolism, especially while anticoagulation therapy is being withheld.

In warfarin-treated patients with elevated INR values requiring reversal because of bleeding or an urgent need for surgery, the frequency of thromboembolism after use of three-factor PCC products (0.7%) was low-

er than after use of four-factor PCC products (approximately 1.8%).<sup>35</sup> However, rates of thromboembolism higher than these reported values for both three-factor PCC and four-factor PCC products have recently been observed.<sup>36-38</sup>

Adding rFVIIa to three-factor PCC (Profilnine) has been proposed for warfarin-treated patients with INR values exceeding 4.5 to enhance the INR reduction.<sup>39</sup> In one assessment of combining a three-factor PCC and low-dose rFVIIa in 46 patients, two cases of thromboembolism were observed.<sup>40</sup> In another study of 70 patients with warfarin-related ICH, adding FFP either before or concomitant with a three-factor PCC product (Profilnine) did not appear to improve the INR correction, compared with three-factor PCC alone.<sup>12</sup> Additional concerns associated with the use of PCC products include the presence of unfractionated heparin (UFH) in some three- and four-factor PCC products. These PCC products should not be given to patients with heparin-induced thrombocytopenia (HIT), an immune-mediated effect of heparin therapy that increases the risk for thrombosis.

Patients with antithrombin III deficiency, a rare hereditary disorder that results in a hypercoagulable state, should not receive PCC products because these products may increase the risk for thrombosis.<sup>39</sup>

Low levels of the natural regulatory anticoagulant protein C and protein S are present in some warfarin-treated patients who require reversal. Some four-factor PCC products (e.g., Beriplex P/N; Octaplex; Cofact, Sanquin Blood Supply, Amsterdam) contain these proteins, and administering these four-factor PCC products (an approach referred to as balanced PCC therapy) could in theory reduce the risk for thromboembolic complications.<sup>34,41</sup>

**Interpreting laboratory test results.** The reliability of laboratory

tests used to monitor warfarin therapy should be considered in interpreting test results, because of the risk of inappropriate clinical conclusions. Isolated values or a series of rapidly rising or falling values that are inconsistent with prior trends and expectations based on warfarin dosing should be questioned. Clinicians should understand the implications of a change in the INR. There is little difference in the concentration of clotting factors present between an INR of 6 and an INR of 12, but a much larger difference between an INR of 1 and an INR of 2.<sup>42</sup>

The method by which the blood sample is obtained also can affect the reliability of the results. If the sample is obtained from a venous site too close to the site where i.v. fluids are administered or withdrawn from a recently flushed i.v. line, the results may reflect hemodilution. Hemodilution can result in falsely elevated INR and activated partial thromboplastin time (aPTT) values and a low hematocrit value, misleading clinicians to suspect internal bleeding. Falsely elevated aPTT values also may occur if a syringe is used to obtain the blood sample and there is a delay in transferring the sample to a collection tube containing citrate.

The INR may not be a reliable measure of the degree of anticoagulation during the initial days of warfarin therapy.<sup>42,43</sup> A rising INR during this period primarily reflects the depletion of factor VII before depletion of the more potent factor II. Therefore, the INR during early warfarin therapy exaggerates the degree of anticoagulation.

Similarly, the declining INR is not a reliable measure of anticoagulation when warfarin therapy is withheld, because levels of factor VII recover before factor II levels do. A falling INR in the early days after warfarin discontinuation may suggest a greater degree of anticoagulation due to the lag time for hepatic production of factor II.

Interpretation of changing INR values requires consideration of the context. A person with a falling INR of 1.8 shortly after warfarin is withheld might have a greater degree of anticoagulation than a person with a rapidly rising INR of 2.2 during initial warfarin therapy.

Warfarin therapy sometimes overlaps treatment with UFH or the target-specific oral anticoagulants, and these agents can independently elevate the INR. Some laboratories neutralize the UFH to avoid test interference. The INR accurately reflects the effect of warfarin only after the direct thrombin inhibitor has been discontinued and effects (measured by aPTT) have dissipated, which requires hours to days.<sup>44</sup> Patients who have reduced dabigatran, rivaroxaban, or apixaban daily dosing requirements for a given indication to maintain desired anticoagulation may have a low rate of drug clearance; thus, interference with the INR test can persist for a longer period after drug discontinuation than in patients with normal clearance.

### Reversal of target-specific oral anticoagulants

Although antidotes are in development for both dabigatran and the direct FXa inhibitors rivaroxaban and apixaban, no such antidotes currently are available.<sup>45,46</sup>

In patients with normal renal function, the anticoagulant effect of dabigatran, rivaroxaban, and apixaban diminishes within a day or two after stopping the drug.<sup>47</sup> The elimination half-life and anticoagulant effect of all three agents are prolonged in patients with kidney dysfunction. The greatest effect of renal impairment is observed with dabigatran because the kidneys have a greater role in its elimination, compared with the FXa inhibitors. Age-related decreases in renal function may be responsible for the prolonged elimination half-life of these agents in the elderly.<sup>48</sup>

**Role of hemodialysis.** Hemodialysis can be used to remove dabigatran because of low protein binding.<sup>44</sup> Hemodialysis is not expected to remove rivaroxaban or apixaban because the drugs are highly protein bound (92–95% and 87%, respectively).<sup>48,49</sup> In six patients with stage V chronic kidney disease (i.e., end-stage renal disease), approximately two thirds of a single 50-mg oral dabigatran dose was removed by hemodialysis over a two-hour period.<sup>50</sup> These observations should be interpreted with caution because they reflect the use of single 50-mg doses instead of the multiple 150-mg doses typically used in practice, and the measured plasma concentrations in these six patients do not reflect the distribution of the drug into tissues in patients with renal impairment receiving multiple 150-mg doses. The plasma drug concentration measured after a first dose may reflect initial drug distribution from the plasma to the tissues, suggesting a higher clearance rate than that seen after equilibrium between plasma and tissues has been established.<sup>51</sup>

In a case report, hemodialysis was used to reverse the effects of dabigatran 150 mg orally twice daily in a 59-year-old woman with moderate renal impairment (creatinine clearance, 40 mL/min) who was planning to undergo heart transplantation.<sup>52</sup> Her thrombin time (TT, a measure of thrombin activity in plasma) was elevated (90.6 seconds) before hemodialysis. After 2.5 hours of hemodialysis using a blood flow rate of 500 mL/hr, which is considered robust to promote the adequacy of hemodialysis, the TT was only marginally reduced to 60.2 seconds, an elevated level that suggests that appreciable amounts of the drug remained after hemodialysis.

In another case report, a 94-year-old man with normal renal function who was receiving dabigatran 150 mg orally twice daily developed a life-threatening ICH after a fall.<sup>53</sup> After a brief delay, hemodialysis was initiated

to reverse the anticoagulant effect. The plasma dabigatran concentration decreased substantially during the three-hour hemodialysis session, but a marked increase in concentration was observed after hemodialysis ended. This rebound probably reflects redistribution of the drug from tissues to plasma. These observations suggest that a longer period of hemodialysis may be needed to provide a sustained reduction in plasma concentrations of dabigatran and reverse its anticoagulant effect.

**Coagulation tests.** The results of many common coagulation tests used as quantitative estimates of the intensity (i.e., level) of anticoagulation can vary among the target-specific oral anticoagulants for multiple reasons, including differences in the agents' site of action.<sup>41</sup> The TT is often used as a very sensitive qualitative test to detect the presence of dabigatran.<sup>28,54</sup> Quantitative assays (e.g., chromogenic ecarin clotting time [ECT], dilute prothrombin time) under development may be useful for monitoring coagulation during dabigatran therapy. Chromogenic anti-FXa assays can be used to provide qualitative and quantitative information about rivaroxaban and apixaban.<sup>41</sup> The ECT and TT are not useful for monitoring coagulation during treatment with the FXa inhibitors.

For the target-specific oral anticoagulants, assay sensitivity may depend on the class of agents. The prothrombin time (PT) is a more sensitive test than aPTT for the FXa inhibitors, whereas the aPTT is a more sensitive test than PT for the direct thrombin inhibitors.<sup>54,55</sup> The INR is derived from the PT, and point-of-care INR test results during dabigatran therapy tend to be higher than those obtained from clinical laboratories.<sup>56</sup> Therefore, the use of point-of-care INR tests to measure coagulation in patients receiving dabigatran is not recommended. The INR is not an easily used method for

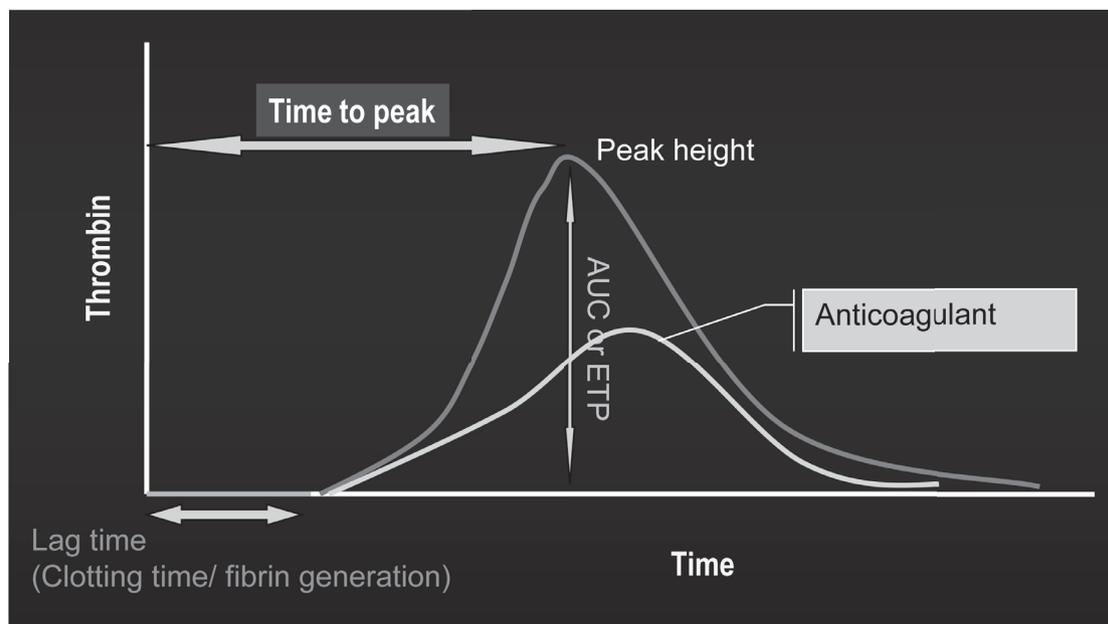
monitoring coagulation during treatment with FXa inhibitors because the assay would need to be calibrated for the specific agent being measured, and differences in the international sensitivity index and available assays may further influence values.<sup>41,57</sup>

The implications of abnormal coagulation assay results are unclear. Normal values may not indicate loss of anticoagulant effects, and elevated values may occur for multiple reasons, making it difficult to quantify the degree of anticoagulation. When excessively high coagulation test values are observed in the absence of other explanations, clinicians should consider potential causes of the excessive effects, such as acute organ dysfunction or drug interactions that reduce elimination of the anticoagulant. Elevated INR values from sources other than warfarin (e.g., a target-specific oral anticoagulant or liver disease) may make transitioning to warfarin problematic, since it may be difficult to know when the target INR value solely attributed to warfarin has been achieved.

Thrombin generation tests reflect the inhibition of thrombin (factor IIa) production by an anticoagulant, the administration of which leads to a delay before thrombin production is detected (i.e., lag time), delay in the peak thrombin generation (i.e., increase in the time to peak thrombin activity), and reduction in the peak thrombin activity (Figure 2). The area under the plasma thrombin concentration–time curve (AUC) is diminished by anticoagulants. The endogenous thrombin potential (ETP) reflects this AUC and is one test that is being explored for assessment of the ability of various reversal agents to reduce anticoagulant activity. The test, however, has not been validated in controlled trials with bleeding patients receiving reversal agents.

In making decisions about oral anticoagulant dosages and invasive procedures or surgery, coagulation

Figure 2. Thrombin generation. AUC = area under the concentration–time curve, ETP = endogenous thrombin potential.



test results should be interpreted in the context of the clinical status of the patient. Test results indicating when changes in anticoagulant dosages are needed or when invasive procedures or surgery are safe have not been defined.

**Clotting factor concentrates.** Various clotting factor concentrates have been used to reverse target-specific oral anticoagulants. Limited data are available on the use of these products in humans.

In a randomized, double-blind, placebo-controlled, crossover study of 12 healthy male volunteers, dabigatran 150 mg twice daily for 2½ days increased the aPTT, ECT, and TT.<sup>58</sup> A four-factor PCC (Cofact) given in a dose of 50 units/kg did not fully reverse these anticoagulant effects. However, when the volunteers were crossed over to receive rivaroxaban 20 mg twice daily for 2½ days (an 11-day washout period between anticoagulants was provided), four-factor PCC normalized the ETP and PT. The ETP was 92% of the normal value at baseline, 51% of the normal

value after rivaroxaban treatment, and 114% of the normal value after PCC treatment (i.e., 14% higher than normal, possibly reflecting a hypercoagulable state). Reversal of the PT was immediate and was sustained for 24 hours. The degree of hemostasis and the dose necessary to manage active bleeding have not been established.

The effects of four-factor PCC (Kanokad, LFB-Biomedicaments, Paris), rFVIIa, and aPCC in reversing dabigatran and rivaroxaban were evaluated in an ex vivo, crossover study of blood samples obtained immediately before and two hours after a single 150-mg dose of dabigatran or 20-mg dose of rivaroxaban in 10 healthy white male volunteers.<sup>59</sup> A two-week washout period was provided between anticoagulant doses. Measures of thrombin generation, including ETP, peak thrombin generation, lag time, and time to peak thrombin, were used to assess reversal of the anticoagulant effects after the addition of a concentrated clotting factor product. Both rFVIIa

and aPCC (but not four-factor PCC) corrected the dabigatran-induced prolongation of the lag time.<sup>59</sup> Four-factor PCC increased (i.e., corrected) the ETP in dabigatran-treated blood to a greater extent than rFVIIa, suggesting a greater antagonist effect. Four-factor PCC strongly corrected the rivaroxaban-induced reduction in ETP, but rFVIIa did not (although rFVIIa corrected the lag time). By contrast, aPCC corrected all measures of thrombin generation in rivaroxaban-treated blood. These results should be interpreted with caution because the doses of reversal agents used were high, especially for aPCC, and the tests were performed ex vivo, not in vivo. The investigators expressed interest in the potential usefulness of low-dose aPCC.

Case reports provide additional insight into the use of clotting factor concentrates for reversal of target-specific oral anticoagulants. Large doses of rFVIIa (three 2.4-mg doses and two 7.2-mg doses) and six hours of hemodialysis were required to manage massive postoperative

bleeding in a 79-year-old man with renal impairment who was receiving dabigatran 150 mg twice daily and underwent coronary artery bypass graft surgery.<sup>60</sup> Dabigatran therapy had been withheld for two days before surgery. This case report demonstrates the need for early discontinuation of dabigatran before surgery, especially in patients with renal impairment, and the limited usefulness of rFVIIa for urgent reversal of the drug. In another case report of a patient receiving dabigatran with acute kidney injury and gastrointestinal bleeding, FFP, rFVIIa (30 µg/kg), and cryoprecipitate provided no apparent benefit.<sup>61</sup> As noted in two other case reports, a three-factor PCC (Profilnine) had little effect on measured coagulation parameters.<sup>62,63</sup> In each of these cases, hemodialysis was part of the management plan.

In another case report, a 67-year-old man receiving dabigatran 150 mg twice daily for atrial fibrillation experienced life-threatening bleeding during a cardiac ablation procedure.<sup>64</sup> His last dabigatran dose was administered seven hours before the procedure. Transseptal perforation occurred, and blood losses exceeded 3 L through the pericardial window. Administration of FFP, protamine, and packed red blood cells failed to reduce the bleeding. Low-dose aPCC (3159 units, which is 26 units/kg actual body weight) therapy was administered over 15 minutes. Hemostasis was noted within minutes after initiation of the infusion, with cessation of bleeding observed at the time administration was complete. A limited impact on TT, ECT, INR, and aPTT was observed, suggesting that aPCC produced hemostasis through a mechanism independent of dabigatran reversal. This case report suggests that low doses of aPCC may be effective for urgent reversal of dabigatran, although such therapy should be used with caution because experience with this approach is limited to this single case report.

### Institutional system support

Institutions should establish a plan for managing patients who require oral anticoagulant reversal because of life-threatening bleeding or an urgent need for an invasive procedure or surgery. The management plan should include guidelines for laboratory testing, clinical assessment of coagulation, use of hemodialysis, and selection among the available pharmacologic agents for reversal, with appropriate dosing strategies for each oral anticoagulant. The institutional system should facilitate rapid guideline implementation and order entry. The guidelines should be updated as additional clinical data become available. Policies and procedures should be established to provide for swift administration of reversal agents and transfer of patients requiring hemodialysis to a setting where it is available. The management plan should be readily available around the clock to facilitate prompt implementation and avoid delays.

### Conclusion

A comprehensive plan individualized to each agent should be developed to promptly reverse the effects of oral anticoagulants and optimize outcomes in patients with bleeding or an urgent need for surgery.

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## New approaches to reversing oral anticoagulant therapy

Article 0204 -0000-13-442-H01-P

Knowledge-based activity

Qualifies for 2.5 hours (0.25 CEU) of continuing-education credit

### Learning objectives

After studying these articles, the reader should be able to

1. Compare and contrast the mechanisms of action, pharmacokinetics, and rate of bleeding complications from warfarin and target-specific oral anticoagulants.
2. Assess the risks for thromboembolism and bleeding in patients receiving oral anticoagulation therapy, including patients who require temporary interruption of such therapy to undergo an elective invasive procedure or surgery.
3. Describe the pharmacologic agents and therapeutic strategies used in patients receiving oral anticoagulant therapy who experience severe bleeding or require temporary interruption of such therapy to undergo an elective or urgent invasive procedure or surgery.
4. Describe the potential usefulness of coagulation assays for monitoring the effects of oral anticoagulant therapy.
5. Outline a plan for prompt evaluation and management of patients with or at high risk for bleeding when receiving oral anticoagulants or interrupting such therapy for an urgent invasive procedure or surgery.

### Self-assessment questions

For each question there is only one best answer.

1. Which of the following patient characteristics or conditions is most likely to affect the pharmacokinetics of target-specific oral anticoagulants and increase the risk for bleeding?
  - a. Diastolic heart failure.
  - b. Female sex.
  - c. Renal impairment.
  - d. Active cancer.
2. Which of the following target-specific oral anticoagulants is least dependent on the kidneys for elimination?
  - a. Dabigatran.
  - b. Rivaroxaban.
  - c. Apixaban.
  - d. Edoxaban.
3. Which of the following is a potentially reversible component of the HAS-BLED scoring system for bleeding risk assessment in patients with atrial fibrillation receiving oral anticoagulant therapy?
  - a. Stroke.
  - b. Genetic factors.
  - c. Uncontrolled hypertension.
  - d. Concomitant use of central nervous system drugs.

4. Which of the following procedures is associated with a high risk for perioperative bleeding (two-day risk of major bleeding 2–4%)?
  - a. Coronary artery bypass graft surgery.
  - b. Cholecystectomy.
  - c. Abdominal hysterectomy.
  - d. Dental extraction.
5. The time during which dabigatran should be withheld before an elective invasive procedure or surgery and the time until resumption of therapy after the procedure depends on
  - a. Renal function but not type of procedure.
  - b. Type of procedure but not renal function.
  - c. Both type of procedure and renal function.
  - d. Neither renal function nor type of procedure.
6. Which of the following coagulation assays is most useful for monitoring therapy with rivaroxaban?
  - a. Ecarin clotting time.
  - b. International Normalized Ratio (INR).
  - c. A chromogenic anti-factor IIa assay.
  - d. A chromogenic anti-factor Xa assay.
7. According to the American College of Chest Physicians, which of the following phytonadione doses should be given together with an order to withhold warfarin in a warfarin-treated patient with an INR of 11 and signs of bleeding?
  - a. 2–2.5 mg orally.
  - b. 5–10 mg orally.
  - c. 2–2.5 mg by subcutaneous injection.
  - d. 5–10 mg by slow intravenous (i.v.) injection.

8. Which of the following are disadvantages of using fresh frozen plasma (FFP) for urgent warfarin reversal?
  - a. Delay due to need for thawing and large fluid volume administered.
  - b. Delay due to need for thawing and lack of clotting factor VII.
  - c. Large fluid volume administered and high risk of transmission of infectious diseases.
  - d. Large fluid volume administered and lack of clotting factor VII.
9. Which of the following clotting factors is present in substantial amounts in four-factor prothrombin complex concentrate (PCC) products but not to an appreciable extent in three-factor PCC products?
  - a. II.
  - b. VII.
  - c. IX.
  - d. X.
10. Which of the following statements about the efficacy of three-factor PCC and four-factor PCC with and without FFP for urgent warfarin reversal (i.e., INR reduction) is correct?
  - a. Three-factor PCC is effective only when used without FFP.
  - b. Adding FFP to three-factor PCC could reduce PCC dosing requirements.
  - c. Four-factor PCC is effective when used without FFP.
  - d. Four-factor PCC is effective only when used with FFP.
11. Which of the following clotting factor concentrates have been used in combination to build a four-factor PCC product for urgent reversal in patients with warfarin-related intracranial hemorrhage (ICH) and elevated INR values in the United States where four-factor PCC products currently are not available?
  - a. FFP plus activated PCC (aPCC).
  - b. FFP plus recombinant factor VIIa (rFVIIa).
  - c. rFVIIa plus three-factor PCC.
  - d. aPCC plus rFVIIa.
12. When determining a therapeutic strategy for the reversal of target-specific oral anticoagulants, which of the following statements best describes the potential risks and benefits of concentrated clotting factors?
  - a. Proven benefits outweigh the cost.
  - b. Proven benefits outweigh potential risk for thrombosis.
  - c. Anticipated but unproven benefits should be weighed against potential risk for thrombosis.
  - d. Anticipated but unproven benefits outweigh potential risk for thrombosis.
13. Which of the following statements about the process for detecting bleeding in a patient receiving dabigatran is correct?
  - a. The absence of overt signs and symptoms of bleeding suffices to exclude the possibility of bleeding.
  - b. Complete blood counts should be monitored for decreases reflecting blood loss.
  - c. Laboratory coagulation assays do not provide useful information.
  - d. Patient monitoring for bleeding is unnecessary because this complication is rare.
14. The dosage of three-factor PCC products used for urgent warfarin reversal depends on
  - a. Patient weight alone.
  - b. INR alone.
  - c. Patient weight and INR, regardless of the severity of bleeding.
  - d. Patient weight, INR, and severity of bleeding.
15. Use of the lowest effective rFVIIa dose for urgent warfarin reversal is sought primarily because of concerns about
  - a. Cost.
  - b. Thrombosis.
  - c. Bleeding.
  - d. Warfarin refractoriness after warfarin therapy is resumed.
16. Which of the following interventions for urgent warfarin reversal has the slowest onset of action but the most sustained effect on INR?
  - a. Three-factor PCC.
  - b. aPCC.
  - c. I.V. phytonadione.
  - d. rFVIIa.
17. Differences in the time to rebound increases in INR during use of the clotting factor concentrates rFVIIa and PCC for urgent warfarin reversal primarily reflect differences in
  - a. Amount of clotting factors in the concentrated clotting factor product.
  - b. Half-lives of the clotting factors in the concentrated clotting factor product.
  - c. Time to administration of the concentrated clotting factor product.
  - d. Duration of infusion of the concentrated clotting factor product.
18. Which of the following statements about i.v. phytonadione administration in combination with PCC or rFVIIa in patients with warfarin-related ICH is correct?
  - a. Phytonadione may decrease the risk for thrombosis from PCC or rFVIIa.
  - b. Phytonadione may prevent or delay INR rebound after administration of PCC or rFVIIa.
  - c. Early phytonadione administration is needed because of the lag time before clotting factors are depleted by vitamin K.
  - d. Early phytonadione administration is needed to reduce the risk of refractoriness after warfarin therapy is resumed.
19. Rebound increases in the plasma concentration of dabigatran after completion of hemodialysis to reverse its anticoagulant effects probably reflect
  - a. The limited renal clearance of the drug.
  - b. The increased renal clearance of the drug.

- c. The lack of distribution of the drug into tissues.
  - d. The redistribution of the drug from tissues to plasma.
20. Which of the following statements best describes the usefulness of PT as a coagulation test to measure the intensity of anticoagulation for the target-specific anticoagulants?
- a. PT may be a more sensitive test than aPTT for rivaroxaban and apixaban.
  - b. PT may be a more sensitive test than aPTT for dabigatran.
  - c. aPTT may be a more sensitive test than PT for rivaroxaban and apixaban.
  - d. INR may be easier to obtain than PT for rivaroxaban and apixaban.

## AJHP Continuing Education

### Supplement: New approaches to reversing oral anticoagulant therapy

Activity Number: 0204-0000-13-442-H01-P

CE Credit: 2.5 hours (0.25 CEU)

Activity Type: Knowledge-based

**CE Release Date:** May 15, 2013

**CE Expiration Date:** May 15, 2016

Enrollment Code: 13442

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