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## How I treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage

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**Intracerebral hemorrhage in patients with warfarin-associated coagulopathy is an increasingly common life-threatening condition that requires emergent management. The evolution of therapeutic options in this setting, as well as recently published guidelines, has resulted in some heterogeneity in recommendations by professional societies. This heterogeneity**

**can be attributed to lack of evidence-based support for plasma therapy; the variability in availability of prothrombin complex concentrates; the variability in the coagulation factor levels and contents of prothrombin complex concentrates; ambiguity about the optimal dose and route of administration of vitamin K; and the lack of standardized clinical care**

**pathways, particularly in community hospitals, for the management of these critical care patients. In this review, we summarize the relevant literature about these controversies and present recommendations for management of patients with warfarin-associated coagulopathy and intracerebral hemorrhage.** (*Blood*. 2011; 117(23):6091-6099)

### Introduction

The increasing number of patients receiving chronic vitamin K antagonist (VKA) therapy, along with the expected risks of hemorrhagic complications,<sup>1,2</sup> have underscored the need for well-defined strategies for emergent reversal of warfarin-associated anticoagulation when patients present to small community hospitals as well as to large medical centers with life-threatening bleeding, such as intracranial (subarachnoid, subdural, and intracerebral) hemorrhage. To address this, we review the evolution in therapeutic options, the published guidelines, and emerging controversies about management of patients who have warfarin-associated coagulopathy and intracerebral hemorrhage (ICH).

### Warfarin-induced coagulopathy

Drugs that inhibit the reuse of vitamin K lead to a buildup of vitamin K epoxide at the expense of vitamin K hydroquinone. Warfarin and related VKAs, whether ingested accidentally, factitiously, or as an overdose of oral anticoagulant therapy, lead to a deficiency of vitamin K–dependent proteins, prolongation of the prothrombin time and partial thromboplastin time, and clinical bleeding manifestations. Although such patients are not vitamin K deficient, the clinical and laboratory manifestations because of VKAs are identical to those of vitamin K deficiency. Warfarin inhibits the hepatic synthesis of functional vitamin K–dependent clotting factors by blocking the recovery of the form of vitamin K that is active in the carboxylation for the calcium binding site of these proteins. Warfarin therapy therefore induces functional deficiencies of each of these factors, which can correct within 48 hours after the discontinuation of warfarin if diet and vitamin K absorption are normal. The major determinants of oral vitamin K–induced bleeding are the intensity of the anticoagulant effect, patient characteristics (eg, age), the concomitant use of drugs that interfere with hemostasis (eg, acetylsalicylic acid), and the length

of therapy. In a case-controlled study, the risk of ICH doubled for each increase of approximately 1 in the international normalized ratio (INR).<sup>3</sup>

The antithrombotic/anticoagulant effect of VKA is attributed to its effect on reducing functional levels of 4 vitamin K–dependent clotting factors: prothrombin (factor II), factor VII, Christmas factor (factor IX), and Stuart factor (factor X). The potential management options available to counteract the warfarin effects include vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), and recombinant human factor VIIa (rFVIIa). Cryoprecipitate does not contain sufficient levels of vitamin K–dependent factors and thus is not an option for VKA reversal.

### ICH: the importance of early treatment

ICH is defined as bleeding into the brain parenchyma, which can also involve the ventricles and subarachnoid space. Spontaneous ICH accounts for  $\leq 15\%$  of acute stroke and is the most fatal form of this disease.<sup>4</sup> Early and aggressive treatment after presentation to the emergency department (ED) can make a difference,<sup>5</sup> particularly given the neurologic deterioration because of early hemorrhage expansion and its effect on long-term outcomes.<sup>6</sup> Warfarin use increases both the risk of developing ICH and its mortality.<sup>7</sup> A review of observation studies for patients treated with warfarin reported annual bleeding rates of fatal, major, and minor bleeding of 0.8%, 4.9%, and 15%, respectively.<sup>8</sup> For patients with ICH, hematoma enlargement within 24 hours of admission is associated with incomplete warfarin reversal,<sup>9</sup> and hematoma enlargement within the first 24–48 hours of admission is associated with poor outcome.<sup>10</sup> A retrospective review<sup>9</sup> of 151 patients admitted to 10 (4 university and 6 county) hospitals in Sweden from 1993 to 1996 found striking variability in management (reversal) of

**Table 1. Variability in treatment of patients on oral anticoagulants with spontaneous intracerebral hemorrhage**

	1 hospital, n/N (%)	4 other hospitals, n/N (%)
Plasma	4/7 (60)	2/34 (6)
PCC	19/26 (73)	1/37 (3)
No action taken	2/26 (8)	23/40 (57)

Data were from Sjoblom et al.<sup>8</sup>

PCC indicates prothrombin complex concentrate.

anticoagulation in patients in whom spontaneous ICH was diagnosed. Mortality rates at 30-day and 6-month follow-up were 54% and 64%, respectively. There was a statistically significant variation in choice of treatment between hospitals. Vitamin K was used in 22 of 54 patients (40%) in 4 hospitals, and in only 3 of 61 patients (5%) in 4 other hospitals. Variability in use of plasma and PCC is shown in Table 1. No action to reverse anticoagulation was taken in 25 of 66 patients (40%) treated at 5 of the hospitals reviewed. In a subsequent 2005 survey, only 30% of hospitals had protocols/critical care pathways for management of ICH which included reversal of anticoagulation.<sup>11</sup> The present consensus is that life-threatening bleeding such as ICH requires rapid warfarin reversal to correct warfarin-associated coagulopathy as soon as possible.<sup>12</sup> Studies have not indicated a rebound prothrombotic rate, which has been found to be low when anticoagulation is discontinued temporarily in clinical settings such as patients with atrial fibrillation or mechanical heart valves.<sup>13</sup>

## Management options

### Vitamin K

Historically, studies suggested that oral vitamin K (2.5-5 mg) or intravenous vitamin K (0.5-5 mg) could be administered for warfarin reversal.<sup>14,15</sup> Guidelines subsequently evolved to recommendations of vitamin K 5 mg orally or intravenously in patients with major bleeding.<sup>13,16,17</sup> More recently, dose recommendations have been increased to 10 mg of vitamin K.<sup>9,18</sup> It has been recommended that intravenous vitamin K be infused slowly (over 30 minutes) because of an estimated 3/100 000 risk of anaphylaxis.<sup>19</sup> Current published guidelines for the management of warfarin-associated ICH, including vitamin K therapy, are detailed in Table 2.<sup>20-24</sup>

Vitamin K therapy alone will require 12-24 hours (reversal begins within 6 hours) to reverse warfarin-associated coagulopathy, and it is not considered adequate treatment for serious life-threatening hemorrhage such as ICH. More recent guidelines<sup>20,21</sup> have called for correction of the INR in these patients as soon as possible. Nevertheless, intravenous administration (given

slowly over 30 minutes) of vitamin K is necessary to ensure that the therapeutic effect is established and maintained after more rapid reversal by additional therapy. INR can usually be normalized by 24 hours,<sup>9,25</sup> but a repeat INR should be determined before then, and, if still prolonged, a second dose of vitamin K should be administered.<sup>21</sup> There is a knowledge gap between the route of administration on the product label for vitamin K and the consensus for route for administration for emergency therapy. Guidelines recommend intravenous infusion for emergent reversal of warfarin-associated coagulopathy, but pharmacies are occasionally reluctant to dispense vitamin K for intravenous infusion because of the risk of anaphylaxis.

### Plasma therapy

In addition to administration of vitamin K, current guidelines state that patients should also receive therapy to replace vitamin K-dependent factors for rapid correction of the INR.<sup>18,20-24</sup> It should be emphasized that, although INR is commonly used in defining indications and goals in reversal of VKA, no published study has directly correlated patient outcomes with individual therapeutic methods or achieved INR levels. Moreover, none of the guidelines specifies which individual therapy should be given to achieve this goal; FFP, PCC, or rFVIIa have each been mentioned as potential therapies (Table 2).

Plasma products currently available from the transfusion service can be FFP (plasma frozen within 8 hours of collection), FP24 (plasma frozen within 24 hours), thawed plasma (thawed FFP or FP24 units relabeled with an extended shelf-life to 96 hours<sup>26</sup> beyond their previous shelf-life after thawing of 24 hours), and liquid plasma (plasma units never frozen; a product with a shelf-life of 28 days at 4°C).<sup>27</sup> The American Association of Blood Banks recommends that transfusion services implement strategies to reduce the risk of transfusion-related acute lung injury (TRALI).<sup>28</sup> As a result, many blood centers no longer collect plasma from female donors (a source of leukocyte-reactive, neutrophilic-specific antibodies and HLA antibodies that can cause TRALI); and the procurement of male-donor plasma only has imposed inventory constraints that have made availability of FFP impractical for many transfusion services. At one of our institutions, we provide FP24 units, which are converted to thawed plasma 24 hours after thawing, and we also provide liquid plasma (blood type AB) for emergency-release support of patients with emergent needs for plasma therapy.<sup>29</sup> Both of these products are therefore available for emergency release and immediate therapy. These plasma products have been approved by our hospital transfusion committee for use as alternatives to FFP for treatment of coagulopathies other than factor VIII deficiency (which is the only temperature-labile clotting factor of clinical concern, not relevant outside the

**Table 2. Published guidelines for reversal of warfarin anticoagulation in patients with intracerebral hemorrhage**

Society (year)	Vitamin K (mg)	Plasma (mL/kg)		PCC (U/kg)	rFVII
Australian (2004) <sup>22</sup>	IV (5-10)	Yes (NS)	AND	Yes (NS)*	NS
British Standards(2005) <sup>13,16,18</sup>	IV (5-10)	Yes (15)	OR	Preferred (50)	NS
EU Stroke (2006) <sup>20</sup>	IV (5-10)	Yes (10-40)	OR	Yes (10-50)	NS
ACCP (2008) <sup>21</sup>	IV (10)	Yes (NS)	OR	Preferred (NS)	Yes†
AHA (2010) <sup>23</sup>	IV (NS)	Yes (10-15)	OR	Yes (NS)	No
French (2010) <sup>24</sup>	Oral or IV (10)	Yes (NS)‡	OR	Preferred (25-50)	No

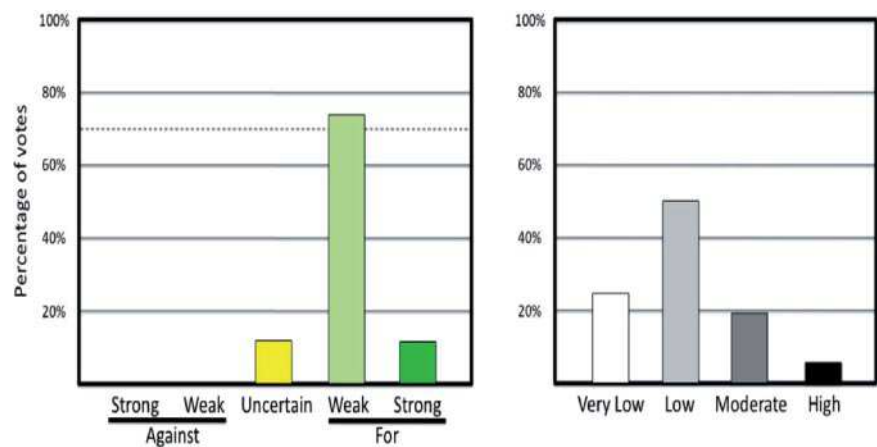
PCC indicates prothrombin complex concentrate; rFVIIa, recombinant human activated factor VII; IV, intravenous; NS, not specified; EU, European Union; ACCP, American College of Chest Physicians; and AHA, American Heart Association.

\*If a 3-factor PCC is administered, fresh frozen plasma is also recommended as a source of factor VII.

†Use of PCCs or rFVIIa may vary, depending on availability.

‡Use of plasma only when PCCs are not available.

**Figure 1. Should plasma transfusion (vs no plasma) be used for patients with warfarin anticoagulation-related intracranial hemorrhage?** (Left) Percentage of panel recommending for or against this intervention. (Right) Quality of evidence supporting this intervention, as rated by the panel. (Reprinted with permission from Roback et al<sup>31</sup>).



treatment of hemophilia A), including reversal of warfarin anticoagulation.<sup>30</sup> Because the terminology “FFP” persists both in the literature and at the bedside, FFP will be used interchangeably with these other products as plasma therapy in this review.

Plasma therapy in the setting of warfarin-associated ICH was recently given a “weak” recommendation in a report from the American Association of Blood Banks Transfusion Medicine Clinical Practice Committee,<sup>31</sup> based on the quality of evidence.<sup>32</sup> The distribution of the panel votes for or against this intervention, along with the rated quality of evidence, are shown in Figure 1. Despite general concerns with evidence quality, the panel thought that the efficacy of plasma to reduce mortality outweighed its potential risks (specified in the report as increased occurrence of TRALI and reduced plasma inventory) in warfarin-treated patients with ICH. However, the level of recommendation and the grading of evidence as “low” are more likely attributable to the delayed administration and inadequate dosing strategies described in the literature for plasma therapy.

Lack of enthusiasm and logistical/technical barriers (listed in Table 3) have led to approaches that are “too little, too late.” First, transfusion services must identify the patient’s blood group type before issuing blood type-compatible plasma; for patients unknown to the institution and without a historic blood type in the patient record, considerable time ( $\leq 60$  minutes) can elapse from presentation until a blood type is ordered, drawn, and determined by the transfusion service. Second, plasma is stored frozen at  $-20^{\circ}\text{C}$ , and further time (30–45 minutes) is required to thaw and issue plasma. Third, the volume for each plasma unit infused ( $\sim 200$ –250 mL) represents a challenge regarding volume overload, which can occur in an elderly population who have preexisting comorbidities such as atrial fibrillation/cardiovascular disease.<sup>8</sup> Finally, the dosing of plasma needed to correct the INR has often been underestimated and therefore subtherapeutic.

A review of consecutive patients with warfarin-related ICH was undertaken to determine whether interventions in the ED were effective in reversing coagulopathy and improving outcomes.<sup>33</sup> Of the interventions and their related parameters, only timing of FFP was associated with successful INR reversal within 24 hours (Table 4); median time to first dose of FFP was 90 minutes (60–205 minutes) for patients with a corrected INR  $\leq 1.4$  within 24 hours and 210 minutes (100–375 minutes) for patients without corrected INR ( $P = .02$ ). Total number of plasma units transfused was not a significant factor. However, successful INR reversal was not found to be associated with improved outcomes in that study.

In another review of patients with ICH on VKA,<sup>34</sup> treatment with FFP ( $n = 7$ ), or PCC ( $n = 10$ ) resulted in mean INR decreases from 3.0 to 1.7 within 7.3 hours versus from 2.8 to 1.2 within 4.8 hours, respectively ( $P < .001$ ). Of note, the average dose of FFP administered in that study was only 8 mL/kg, or 2–3 U for a 70-kg patient. Holland and Brooks<sup>35</sup> showed a linear relationship between the pretransfusion INR and the decrease in the INR per 500 mL ( $\sim 2$  units) of FFP infused in adult patients. The volume of plasma probable to achieve a target INR without a significant change in factor synthesis (ie, in absence of vitamin K), with an initial INR of 5.0 and a target INR of 1.7, was estimated to be 2.3 L (9 U of FFP) or 32 mL/kg.

Chowdhury et al<sup>36</sup> assessed the effects of giving FFP according to existing guidelines<sup>37,38</sup> in 10 consecutive patients compared with higher doses in 12 consecutive critically ill patients. The median volume of FFP infused was 12.2 mL/kg (5.6–22.1 mL/kg) in the standard dose cohort, compared with 33.5 mL/kg (18–51 mL/kg) in the higher-dose cohort. The investigators found that the standard regimen resulted in relatively small, and in most cases inadequate, increments in coagulation factors (median increase of 11% for factor VII and 8% for factor IX); the increased-dose cohort achieved adequate correction of all individual coagulation factors (median increase of 38% for factor VII and 28% for factor IX).

A study by Makris et al<sup>39</sup> concluded that FFP given at an estimated dose of 12 mL/kg raised factors II, VII, IX, and X by only between 9 and 14 IU/dL. However, for the cohort of 12 patients who received FFP, vitamin K (1–5 mg intravenously) was not administered until 15 minutes after the completion of the FFP infusion (800 mL, or 4 U), at the time of the second determination of the INR. The substantial delay in vitamin K administration in the plasma therapy cohort would now be considered substandard; yet the lower factor IX levels achieved in the plasma therapy cohort

**Table 3. Potential barriers for successful reversal of warfarin anticoagulation in patients with intracerebral hemorrhage with the use of plasma transfusion**

Barrier	Estimated time needed, min
Liquid AB plasma not widely available	
Patient blood type must be determined	$\leq 60$
Plasma units must be thawed	30–45
Plasma volume requires careful management to avoid circulatory overload	30 per unit
Plasma dosing is underestimated	



**Table 4. Management of warfarin-associated coagulopathy in the emergency department**

Characteristics	Correction of INR*		P
	No (n = 12)	Yes (n = 57)	
Door to CT scan time, min	65 (30-90)	40 (25-85)	.5
CT to FFP time, min†	210 (100-375)	90 (60-205)	.02
Dose of FFP, unit	2 (1-5)	4 (2-6)	.1
CT scan to vitamin K time, min	245 (37-361)	87 (25-210)	.2
Any vitamin K given, %	58	81	.1

Data from Goldstein et al.<sup>33</sup> Values are median (range 25%-75%). CT indicates computerized tomography; IQR, interquartile range; and FFP, fresh frozen plasma.

\*INR indicates international normalized ratio to < 1.4 within 24 hours.

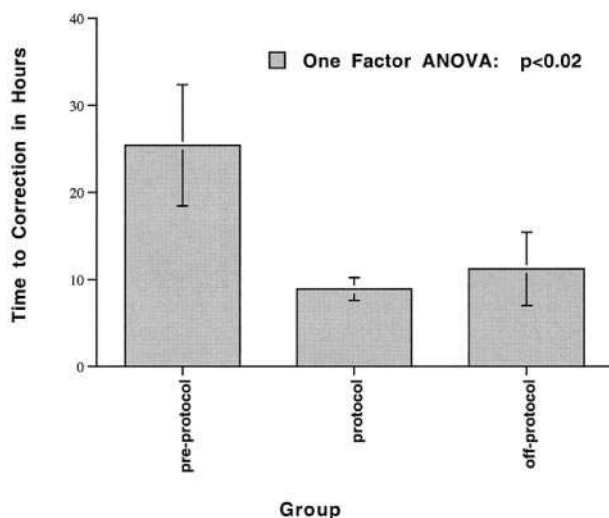
†First dose.

compared with the patients in the other cohort of this study who received PCC, has been noted and cited in subsequent guidelines.<sup>18</sup>

Subsequently, Boulis et al<sup>40</sup> conducted a randomized, controlled study (which also had an uncontrolled cohort component) to compare the speed of correction of INR (to a < 1.3 target) for VKA in patients treated with FFP versus FFP supplemented with PCC. Patients randomly assigned to the FFP group underwent central venous pressure monitoring with rapid FFP infusion and furosemide therapy; both cohorts received vitamin K. As shown in Figure 2, time to correction in the FFP-alone cohort was 25 ± 7 hours for a retrospective cohort (n = 6), compared with 9 ± 1.3 hours for the protocol group (n = 8), and 11 ± 4.2 hours for a subsequent postprotocol group that did not have central venous pressure monitoring (n = 6). Three of 8 patients in the FFP protocol cohort underwent surgery, each with successful hemostasis. The investigators concluded that the improvement in time to correction of VKA was because of physician vigilance to successfully achieve the infusion of 2-3 L of FFP. It should be noted that more than one-third of randomly assigned patients in that study were excluded from analysis because of insufficient data.

### Prothrombin complex concentrates

PCCs are either activated (ie, they include activated coagulation factors to allow for bypassing the factor 8 inhibitor, for treatment of



**Figure 2. Comparison of the time to anticoagulation correction with FFP treatment alone.** Groups included patients treated before protocol initiation (n = 6; 25.4 ± 7 hours), during the protocol (n = 8; 8.9 ± 1.3 hours), and after protocol termination (n = 6; 11.2 ± 4.2 hours). An improvement in the time to correction was observed after protocol initiation and persisted after protocol termination (Reprinted, with permission from Boulis et al<sup>40</sup>).

hemophilia with inhibitors), or nonactivated, which may also be associated with thrombogenicity. Nonactivated PCC products that are currently available and are options for reversal of warfarin-associated coagulopathy are listed in Table 5. The nonactivated PCCs are further categorized on the basis of the presence or absence of sufficient levels of factor VII.<sup>41</sup> PCCs that contain all 4 (including factor VII) of the vitamin K–dependent clotting factors (4-factor PCCs) are approved in the European Union, but are not approved in the United States. The approval status of 4-factor PCCs also varies in other countries such as Canada and Australia (Table 5).<sup>23,26,42</sup> Two 4-factor PCC products are currently undergoing clinical trials in the United States (Beriplex, CSL Behring; and Octaplex, Octapharma).<sup>43,44</sup>

Three-factor PCCs are approved only for the replacement of factor IX; 4-factor PCCs are approved for replacement of the vitamin K–dependent clotting factors (II, VII, IX, X). A number of studies comparing FFP and PCC infusions for reversal of VKA in patients with ICH have been published,<sup>34,39,40,45,46</sup> in addition to studies of PCC with or without concurrent plasma therapy.<sup>47-52</sup> Reviews of the literature focusing on the role of PCC and other options in reversing VKA have been published.<sup>42,53-55</sup> Retrospective chart reviews and case-control studies have reported more rapid correction of INR with vitamin K and PCCs compared with vitamin K and FFP. However, none of the published studies to date have shown any differences in clinical outcomes.<sup>8,25,34,40,45,56</sup> Nevertheless some<sup>11,25,42,53,54,57,58</sup> but not all<sup>55,59</sup> studies have concluded that FFP therapy is less effective than PCC for the reversal of VKA.

Six currently published guidelines (Table 2) recommend that PCC can be given as an alternative to FFP to increase levels of vitamin K–dependent clotting factors, and 3 of these guidelines<sup>18,21,24</sup> indicate that PCC is the preferred treatment. One guideline<sup>22</sup> specifies that if 3-factor PCC is administered, FFP should also be given to provide replacement of factor VII. A recent review of PCCs for reversal of VKA concluded that “PCC should be compared directly in randomized controlled trials [with] other treatment strategies including FFP and rFVIIa, evaluating effect on patient outcomes.”<sup>55</sup> This lack of consensus on the role of PCC therapy relative to plasma therapy may be in part because of the variability in their contents and clotting factor levels<sup>41,60</sup>; their regulatory approval status in different countries; and their irregular availability within hospital formularies, particularly in community hospitals.

Product information for activated PCCs such as FEIBA (VH Immuno Vienna) and Autoplex-T (Baxter) state under warnings that they “must be used only for patients with circulating inhibitors to one or more coagulation factors and should not be used for the treatment of bleeding episodes resulting from coagulation factor deficiencies.”<sup>25,61</sup> Nevertheless, despite the even greater potential risk of thrombogenicity compared with nonactivated PCCs, use of FEIBA was recommended in one publication for reversal of VKA in life-threatening bleeding if 4-factor PCCs are not available.<sup>62</sup> A chart review of 72 patients who received FEIBA for warfarin reversal compared with 69 patients who were treated with FFP in life-threatening bleeding indicated faster and more effective reduction of INR with FEIBA but with similar survival rates and length of hospital stay between the cohorts. Moreover, 7% of the FEIBA-treated patients experienced potentially related adverse events.<sup>62</sup>

Three studies used 3-factor (II, IX, X) PCC plus FFP for reversal of VKA in patients who presented with ICH and reported more rapid and effective correction with PCC.<sup>34,40,45</sup> Two other

**Table 5. Prothrombin complex concentrate (PCC) products available for reversal of warfarin-associated coagulopathy**

Product (manufacturer)	Factor levels			
	II	VII	IX	X
Available in the US				
PCCs, 3-factor (II,IX,X)				
Profilnine SD (Grifols)*,**	≤ 150	≤ 35	≤ 100	≤ 100
Bebulin VH (Baxter)*	24-38	< 5	24-38	24-38
Available outside the US				
PCCs, 4-factor (II, VII, IX, X)				
Beriplex (CSL Behring) †	20-48	10-25	20-31	22-60
Octaplex (Octapharma) ‡	14-38	9-24	25	18-30
Cofact (Sanguin), IU/mL§	14-35	7-20	25	14-35
Prothromplex T (Baxter)	30	25	30	30
PPPSB-HT¶	20	20	20	20
PCCs, 3-factor (II,IX,X)				
Prothromplex HT (Baxter)#	30	—	30	130

\*Product insert specifies: "Indicated for replacement of factor IX in patient with hemophilia B. Not indicated for treatment of factor VII deficiency."

\*\*The values given for factor contents are the number of units present per 100 factor IX units in each vial. For all other values, IU/mL.

†United Kingdom, European Union.

‡United Kingdom, Canada, European Union.

§European Union.

||Austria.

¶Japan.

#Australia.

studies combined the use of 3-factor PCC with factor VII concentrates for emergent reversal of warfarin anticoagulation.<sup>39,56</sup> In a recent study,<sup>63</sup> a 3-factor PCC product used alone was reported to be effective in urgent reversing of warfarin anticoagulation and achieved the target INR in > 90% of the patients. However, only 7 of the 50 patients studied (14%) had INR > 3.5. One study of 40 patients concluded that infusion of low (25 U/kg) or high dose (50 U/kg) of a 3-factor PCC alone achieved suboptimal efficacy compared with FFP in terms of correcting INR, but that additional infusion of a small amount of FFP (mean ~ 2 units) vastly improved the therapeutic effect of PCC.<sup>41</sup> One review concluded that in the presence of major bleeding, treatment with intravenous vitamin K and PCC is the most effective therapy.<sup>54</sup> However, a recently published guideline concluded that dosing for VKA reversal with the use of 3-factor PCCs has not been well established.<sup>23</sup> It remains unproven whether use of PCCs results in improved clinical outcomes compared with plasma therapy.<sup>55</sup>

Four-factor PCCs have been reported to be effective even when used alone in monotherapy (without vitamin K) in a study of 10 patients who presented with major bleeding (none with ICH)<sup>47</sup>; in a study of 42 patients who also were treated with vitamin K, 11 of whom had CNS bleeding or head trauma<sup>48</sup>; in a study of 44 patients, 2 of whom had CNS bleeding<sup>50</sup>; and in a study of 60 patients, none of whom had CNS bleeding,<sup>51</sup> and in whom each showed complete and immediate reversal of anticoagulation. In a retrospective report of 58 patients (36 with CNS hemorrhage) treated with a 4-factor PCC, in which 50% also received plasma therapy as well as vitamin K, the investigators concluded that PCC therapy was an effective treatment method for the correction of VKA in the urgent setting.<sup>49</sup> However, an accompanying editorial stopped short of this conclusion.<sup>59</sup> The 4-factor PCC used in this study (Proplex-T; Baxter) is no longer available in the United States.

Schick et al<sup>64</sup> reviewed 50 surgical patients requiring urgent VKA reversal who received a 4-factor PCC infusion and reported that PCC significantly reduced INR (independent of FFP or

vitamin K administration) and prevented or stopped major surgical bleeding, with no associated thrombotic event. Finally, Demeyere et al<sup>46</sup> in a prospective randomized trial compared a 4-factor PCC with FFP in 44 patients requiring urgent reversal of warfarin anticoagulation to undergo open-heart surgery. Their results showed a faster and more effective outcome with administration of PCC that with FFP: 3 of the 20 FFP-treated patients (15%) were identified to have microvascular bleeding postoperatively, including one patient who needed reoperation, compared with none of the 20 patients in the PCC cohort.

The safety of PCCs in the setting of emergency reversal of warfarin anticoagulation remains a subject of debate. Thrombogenicity is an acknowledged problem,<sup>65,66</sup> in part related to the presence of activated clotting factors that necessitates the concurrent presence of heparin in these preparations and also in part because of the frequent presence of other preexisting thromboembolic risk factors that resulted in initiation of VKA in the first place (eg, atrial fibrillation). We previously reported a patient who was initially successfully treated with rVIIa for refractory, massive hemorrhage while on extracorporeal membrane oxygenation after cardiothoracic surgery but had massive thrombosis after subsequently receiving PCC.<sup>67</sup> Another case of fatal intracardiac thrombosis after rapid administration of activated PCC for urgent warfarin coagulation reversal has been reported.<sup>68</sup> Of note, the patient had also received desmopressin. Reported incidence of thromboembolic events in studies on various PCC products published between 1998 and 2008 ranged from 0% to 7% (overall weighted mean of 2.3%), with higher and repeated dosing potentially associated with higher risk.<sup>55</sup> Multinational trials on patients receiving a 4-factor PCC product at various infusion speeds for urgent VKA reversal have supported the safety and efficacy of rapid infusion of PCC in these patients.<sup>51,69</sup> However, note that it has been recommended that "whenever possible, patients receiving PCCs should be under low-dose heparin prophylaxis."<sup>60</sup> Although this recommendation cannot be followed for patients with ICH, it does underscore that the use of PCCs in this setting is accompanied by risks of thrombosis.

As pooled blood product derivatives, PCCs also have potential risks of transmitting infectious agents.<sup>70</sup> Various processing methods such as nanofiltration, solvent detergent treatment, or vapor heating are used to inactivate pathogens. Nevertheless, cases of parvovirus B19 seroconversion have been reported in recipients of PCCs.<sup>71</sup> The known and potential unknown risks of PCC therapy compared with plasma therapy are summarized in Table 6.

**Table 6. Potential risks and limitations of plasma and prothrombin complex concentrate (PCC) therapy for warfarin-associated coagulopathy**

Product	Risks and limitations
Single-donor plasma	<ol style="list-style-type: none"> <li>1. Longer time to administer</li> <li>2. Volume constraints</li> <li>3. Transmissible disease, known/unknown</li> <li>4. Transfusion-related acute lung injury</li> </ol>
PCC	<ol style="list-style-type: none"> <li>1. Limited availability</li> <li>2. Some preparations lack factor VII</li> <li>3. Donor pools: 3000-20 000</li> <li>4. Transmissible disease, known/unknown (new variant Jakob-Creutzfeldt disease [nvCJ], hepatitis A, parvovirus B19)</li> <li>5. Thrombogenicity</li> </ol>

### Recombinant activated factor VII

Approved indications of rFVIIa in the United States and European Union include treatment of bleeding episodes (or prevention of bleeding from invasive procedures) in patients with hemophilia A or B with inhibitors to factors VIII or IX, patients with congenital factor VII deficiency, and in patients with acquired hemophilia. In addition, it is approved for treatment of Glanzmanns thrombasthenia in the European Union. The manufacturer withdrew an application for a new indication for treatment of acute ICH in 2006.<sup>72,73</sup> Nonetheless, off-label use of rFVIIa in hospitals has been rising rapidly. Use of rFVIIa in patients not on warfarin who had spontaneous ICH increased 8-fold, from 250 cases in 2004 to 2010 cases in 2008, accounting for 11% of all off-label rFVIIa usage.<sup>74,75</sup> Early reports of the off-label use of rFVIIa from one of our institutions as well as others on the successful management of warfarin-associated ICH with rFVIIa therapy led to the development of single-institution policies for oversight of its off-label use.<sup>76-80</sup>

The value of rFVIIa in patients with spontaneous ICH who were not on warfarin anticoagulation underwent scrutiny in clinical trials in which it was shown to reduce growth of hematoma if administered within 4 hours of onset,<sup>81</sup> but it did not improve survival or functional outcome.<sup>82</sup> A subsequent post hoc analysis of these trials suggested that the use of rFVIIa was most beneficial and associated with improved outcomes in patients  $\leq 70$  years old who had lower baseline hemorrhage volume and shorter time from onset to treatment.<sup>83</sup> Another trial compared escalating doses of rFVIIa with placebo in patients with traumatic ICH who were not on VKAs.<sup>84</sup> No significant difference was observed in mortality or adverse events among treatment groups, although asymptomatic deep vein thrombosis was more frequent in patients who received any dose of rFVIIa. Higher rFVIIa dose was associated with lower hemorrhage volume and less hematoma progression, but the association was not statistically significant. A meta-analysis of these and other randomized controlled trials concluded that, although rFVIIa could reduce hemorrhage progression in ICH, there is no significant improvement in mortality or function status and that it was associated with increased risk of thromboembolic events.<sup>85</sup> Note that patients on VKA were frequently excluded in rFVIIa trials mentioned earlier.

In contrast, case reports have described the successful use of rFVIIa in patients with warfarin-associated anticoagulation and ICH,<sup>86-88</sup> and studies have indicated that doses of 15-20  $\mu\text{g}/\text{kg}$  rFVIIa can normalize INR values when used to treat warfarin-associated deficiencies of functional vitamin K-dependent clotting factors.<sup>89</sup> Nonetheless, concerns have been raised whether the effect goes beyond mere normalization of INR and whether patient outcomes are improved.<sup>53</sup> A study by Tanaka et al<sup>90</sup> showed that in rodents with VKA-induced anticoagulation, rFVIIa infusion performed worse than PCC infusion in an in vivo assay of thrombin generation. This group has also developed a porcine model for spleen trauma, and in a pilot study they have showed that PCC accelerated hemostasis and augmented thrombin generation compared with rFVIIa.<sup>91</sup> Recently, Skolnick et al<sup>92</sup> used a punch biopsy model in healthy subjects to explore whether rFVIIa reversed warfarin effects with the use of thromboelastography, thrombin generation, and clotting assays. The study was able to show the warfarin reversal effects of rFVIIa in the in vitro clotting assays but not in the in vivo punch biopsy bleeding model. However, this is not a validated model, and it may be no more predictive of hemostasis than the clinical bleeding time test.<sup>93</sup> Finally, the uncertainty on whether the demonstrable effects of rFVIIa on INR correction are accompanied by adequate restoration of thrombin generation compared with PCCs is the cited reason why one guideline has recommended against the routine use of rFVIIa for warfarin reversal in patients with ICH.<sup>23,94</sup>

**Table 7. Published guidelines/recommendations for the off-label use of recombinant human activated factor VII, including warfarin-associated coagulopathy**

Society (year)	Recommendations
SABM/UHC (2005) <sup>99</sup>	Appropriate for spontaneous or traumatic intracranial bleeding in patients on warfarin
EU societies (2006) <sup>100</sup>	Patients on warfarin anticoagulation not addressed
Northern Ireland (2007) <sup>101</sup>	If on-going significant hemorrhage after correction of clotting factor deficiencies
ASH (2008) <sup>94</sup>	Not indicated

SABM/UHC indicates Society for Advancement of Blood Management/University Hospitals Consortium; EU, European Union; and ASH, American Society of Hematology.

Published reports have indicated effective in vivo hemostasis after administration of rFVIIa in several clinical settings. Jeffers et al<sup>95</sup> randomly assigned 71 patients with liver disease who underwent laparoscopic liver biopsy to receive 1 of 4 doses (5, 20, 80, and 120  $\mu\text{g}/\text{kg}$ ) of rFVIIa given adjuvantly before biopsy. Time of correction of prothrombin time to normal ( $< 13.1$  seconds) for the 4 study groups was a median of 9.6, 29.4, 287, and 84 minutes, respectively. Forty-eight patients (78%) were observed to have satisfactory hemostasis within 10 minutes; however, there was no control arm for comparison. Friederich et al<sup>96</sup> conducted a prospective, randomized double-blinded study of perioperative adjuvant rFVIIa (placebo, 20  $\mu\text{g}/\text{kg}$ , and 40  $\mu\text{g}/\text{kg}$ ) therapy in 36 men who underwent open radical prostatectomy and showed significantly reduced estimated surgical blood losses in the patients treated with rFVIIa compared with placebo. Finally, 2 case series of patients with ICH who received rFVIIa for normalization of INR also had subgroups of patients who underwent neurosurgical procedures with adequate hemostasis.<sup>76,97</sup> Recently, Nishijima et al<sup>98</sup> studied 40 patients receiving warfarin who were admitted to the ED for traumatic ICH and reported that administration of rFVIIa was associated with shorter time to normal INR; however, there was no difference in mortality (or in thromboembolic complications) among patients who received rFVIIa and patients who did not.

Guidelines that address the off-label use of rFVIIa specifically in patients with ICH and warfarin-associated coagulopathy have been published and are summarized in Table 7.<sup>94,99-101</sup> In 2005, guidelines that used the Rand/UCLA appropriateness method were developed jointly by the Society for Advancement of Blood Management and the University Hospitals Consortium.<sup>99</sup> The consensus panel agreed that rFVIIa was appropriate for reversal of warfarin anticoagulation in patients with either spontaneous or traumatic intracranial bleeding. In 2006, a consortium of European Union societies used a modified Delphi method to address use of rFVIIa as an adjuvant treatment for massive bleeding, but patients on VKA were not specifically addressed.<sup>100</sup> In 2007, the Northern Ireland Advisory Committee on Blood Safety published guidelines for off-license use of rFVIIa in acquired coagulopathy<sup>101</sup> and concluded that rFVIIa was indicated in patients with on-going significant hemorrhage, if correction of other clotting factor deficiencies had been adequately addressed; reversal of VKA was not reviewed or addressed here. As in guidelines for plasma and PCC therapy, there has been a diversity of recommendations about the role of rFVIIa in management of VKA-associated ICH (Table 2). However, the most recent guidelines on management of these patients proscribe against use of rFVIIa in the treatment of warfarin-associated ICH or limit its use in circumstances when PCC and plasma are not available.<sup>23,24</sup> An updated Cochrane review of hemostatic drug therapies for acute spontaneous (nontraumatic) ICH concluded that rFVIIa did not reduce death or improve functional status and that it was associated with a higher risk of



thromboembolic serious adverse events (albeit not statistically significant).<sup>102</sup>

The safety profile of rFVIIa in controlled trials in patients with spontaneous ICH suggests that an increased risk of thrombotic arterial events may be underreported by treating physicians<sup>75</sup>; a careful case review showed that 27 of 285 trauma patients (9.4%) had thromboembolic complications after administration of rFVIIa, including 3 patients who were treated for warfarin reversal.<sup>103</sup> Thromboembolic events associated with rFVIIa were reported to the Food and Drug Administration in ~2% of treated patients (for both approved and off-label use), but sufficient data were not available to identify the incidence in patients who received rFVIIa for VKA reversal.<sup>104</sup> Levi et al<sup>105</sup> recently analyzed 35 randomized trials with 4468 subjects and found that 11.1% had thromboembolic events. Rates of venous thromboembolic events were similar for subjects who received rFVIIa compared with placebo (5.3% and 5.7%, respectively); arterial events, however, were significantly higher (5.5% vs 3.2%;  $P < .003$ ) in subjects receiving rFVIIa than in subjects receiving placebo, particularly for older patients or higher doses or both.

## Summary

Considering the present state of heterogeneity in consensus guidelines by professional societies (Table 3), the irregular availability of PCCs, the variability in content of clotting factor levels in PCCs (Table 5), and the need for more standardized clinical care pathways in the critical care of patients with warfarin-associated ICH, we recommend that the following management strategies for patients in this clinical setting be implemented as a clinical treatment pathway:

1. Early diagnosis and initiation of therapy to replenish levels of functional vitamin K–dependent clotting factors are of paramount importance.
2. Initial diagnostic laboratory evaluation should include determination of patient ABO/Rh blood type as well as INR.
3. Vitamin K therapy (10 mg) should be administered immediately by slow intravenous infusion over 30 minutes, and a repeat dose should be considered at 12 hours.
4. For plasma therapy
  - A. A minimum of 15 mL/kg and  $\leq 30$  mL/kg unless the patient is unable to tolerate the volume (4–8 U in an adult patient) should be infused. Careful attention must be paid to patient volume status, including use of diuretic therapy when needed.
  - B. The initial plasma units should be emergency-released AB plasma, pending the patient's blood type determination and thawing frozen plasma that will allow conversion to blood type-specific plasma therapy.
5. Three-factor PCC therapy is approved only for the replenishment of factor IX among the vitamin K–dependent clotting

factors, and it is not indicated for replenishment of factor VII. Its use is therefore off label in this setting. Its clinical benefits in reversal of warfarin-associated coagulopathy, compared with plasma, have not been established. In some countries, 4-factor PCC therapy is available and approved for reversal of VKA. Recommended doses are generally 25 IU/kg for patients with ICH whose INRs are within therapeutic range or 35–50 IU/kg for patients whose INRs exceed therapeutic range. The thromboembolic and other potential risks of PCCs need to be taken into consideration when used in this setting.

6. rFVIIa therapy has not been approved for reversal of warfarin-associated coagulopathy. Its use is therefore off-label in this setting, and dosage recommendations are currently unresolved. Fixed vial dosing of 2 mg would provide 20–40  $\mu$ g/kg for patients between 100 kg and 50 kg of body weight. Clinical benefits in this setting have not been established, and its risks of arterial thrombotic complications, particularly in the elderly or at higher doses, must be taken into consideration.

## Conclusions

Institutional clinical care pathways are needed to successfully manage patients with ICH in the context of warfarin-associated coagulopathy. Patients with this life-threatening condition present not only at medical centers that have coagulation clinics to support cardiovascular programs but also frequently at local community hospitals. Limitations to successful management include unfamiliarity with the need for intravenous administration of vitamin K by clinicians and hospital pharmacies and the challenging inventory management strategies for providing emergency plasma therapy. In addition, approval status and availability of 4-factor PCCs is limited, whereas 3-factor PCCs are not approved for replacement of the vitamin K–dependent clotting factors except for factor IX. Close collaboration between treating physicians and ED personnel, critical care specialists, or hematology, transfusion medicine, and neurology/neurosurgery services, as well as pharmacy, is of utmost importance to achieve timely normalization of the INR and to control bleeding. Short- and long-term clinical outcomes related to initial management modalities and INR values are necessary to improve the care of patients in this critical care setting.

## Authorship

Contribution: L.T.G. and A.S. contributed to the research, writing, and editing of the manuscript.

Conflict-of-interest disclosure: L.T.G. declares competing financial interests from CSL Behring; and A.S. declares competing financial interests from Baxter, Bayer, and NovoNordisk.

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