

Rapid Reversal of Warfarin-Associated Hemorrhage in the Emergency Department by Prothrombin Complex Concentrates

Kenneth Frumkin, PhD, MD

Life-threatening warfarin-associated hemorrhage is common, with a high mortality. In the United States, the most commonly used therapies—fresh frozen plasma and vitamin K—are slow and unpredictable and can result in volume overload. Outside of the United States, prothrombin complex concentrates are often used instead; these pooled plasma products reverse warfarin anticoagulation in minutes rather than hours. This article reviews the literature relating to warfarin reversal with fresh frozen plasma, prothrombin complex concentrates, and recombinant factor VIIa and provides elements for a management protocol based on this literature. [Ann Emerg Med. 2013;62:616-626.]

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CLINICAL SCENARIO

A 63-year-old man receiving warfarin for atrial fibrillation presents with a severe right-sided headache and left hemiparesis. Computed tomography shows an acute intracerebral hematoma with slight midline shift. His international normalized ratio (INR) is 3.9. You order vitamin K and 2 units of fresh frozen plasma to be given intravenously, contact your neurosurgeon and intensivist, and wait for the fresh frozen plasma and an ICU bed. While the fresh frozen plasma is being thawed your patient becomes less responsive and requires intubation and mechanical ventilation. Admitted to the ICU, he dies the next morning.

INTRODUCTION

This clinical scenario is familiar to emergency physicians: the bleeding anticoagulated patient who deteriorates despite conventional therapy. I review the literature on treatment options available for these critical patients and present a management protocol based on this literature.

THE PROBLEM

The bleeding risk of warfarin is well known.¹ Anticoagulation can increase the risk of intracranial hemorrhage as much as 7- to 10-fold, with a mortality approximating 60%.² In half of anticoagulated intracranial hemorrhage patients, bleeding continues more than 12 to 24 hours. Such hematoma expansion is an independent predictor of death and poor functional outcome, emphasizing the critical importance of rapid reversal.²⁻⁶ Despite hundreds of references on warfarin reversal, few are in emergency medicine journals.⁷⁻¹⁵

THERAPEUTIC OPTIONS FOR WARFARIN REVERSAL

Warfarin forestalls thrombin generation by inhibiting synthesis of the vitamin K–dependent coagulation factors II,

VII, IX, and X. Treatment of severe warfarin-associated hemorrhage therefore consists of replacing the depleted factors and restoring their native synthesis (vitamin K).

Factor replacement options are contrasted in the Table: fresh frozen plasma, recombinant activated factor VIIa (rFVIIa), and prothrombin complex concentrates.

Vitamin K

Vitamin K restores intrinsic factor production and is required for any sustained reversal of warfarin anticoagulation.¹⁶ Although very effective orally,¹⁷ the intravenous formulation works significantly faster,^{18,19} with 5 to 10 mg intravenously recommended for life-threatening hemorrhage.^{20,21} The intravenous formulation is associated with anaphylaxis in 3 of 10,000 doses (some reactions are anaphylactoid or attributed to the vehicle²²), and thus it is recommended that vitamin K be diluted and administered during 30 minutes or no faster than 1 mg/minute. Intramuscular administration is not recommended because of hematoma formation, and the subcutaneous route appears ineffective.¹⁷

Fresh Frozen Plasma

Despite common use of fresh frozen plasma (usually with vitamin K),²³ the quality of evidence supporting its effectiveness in intracranial hemorrhage and other hemorrhage is low or very low.²⁴ In one study of nearly 5,000 fresh frozen plasma transfusions for a broad range of indications, the median reduction in INR was “generally very small (–0.2).”²⁵

Fresh frozen plasma cannot be administered quickly because it first requires ABO blood group compatibility testing and then needs 30 to 60 minutes to thaw. The recommended initial minimum dose is 15 mL/kg, or approximately 1 L (4 units) in a 70-kg patient. The reliable replacement of factor levels may require more than 30 mL/kg,²⁶ averaging 4 to 12 units for

Table. Therapeutic options for warfarin reversal.

Agent	Vitamin K (Intravenous)	FFP	rFVIIa	PCC	
				3-Factor	4-Factor
Content	Vitamin K1 (phytonadione)	All clotting factors in the usual serum concentrations	rFVIIa	Profilnine SD contains (per 100-U of FIX) no more than 150, 35, and 100 U of FII, FVII, and FX, respectively	Kcentra contains (per 500-U vial) FII (380- 800 U), FVII (200- 500 U), FIX (400-620 U), FX (500-1,020 U), protein C (420-820 U), protein S (240- 680 U), heparin (8- 40 U) AT III (4-30 U)
Source	Manufacture	Donor plasma	Recombinant DNA	Pooled human plasma concentrate	Pooled human plasma concentrate
Brands available	Multiple (generic)	Blood bank	NovoSeven RT (Novo Nordisk Inc., Princeton, NJ)	Profilnine SD Factor IX Complex (Grifols Biologicals, Inc., Los Angeles, CA)*	Kcentra (CSL Behring, King of Prussia, PA) [†]
Mechanism of action	Restores intrinsic clotting factor production	Restores all clotting factors	Triggers the final common pathway of the clotting cascade. Facilitates thrombin generation.	Replaces FII, FIX, FX	Replaces FII, FVII, FIX, FX. Contains proteins C and S
Onset	4-6 h	13-48 h	≤15 min	≤15 min	≤15 min
Dose	10 mg intravenous	15-30 mL/kg	1 mg	25-50 IU/kg	25-50 IU/kg based on INR (not to exceed the 100-kg dose)
Advantages relative to other options	Required for sustained reversal of warfarin. Safer in non-life- threatening bleeding.	No increased risk of thrombosis. Safer in non-life- threatening bleeding.	vs. FFP: Small volume, administered quickly, onset <15 min. Only option with religious objection to blood products. Short half-life when prolonged reversal is problematic.	vs. FFP: Small volume, administered quickly, onset <15 min, documented clinical superiority (speed and completeness of reversal). Preferred over FFP by ACCP ²¹ and others vs. rFVIIa: Longer duration of action, worldwide recommendations and approval, more prospective and randomized studies, lower thrombosis risk, INR reliable.	
Disadvantages relative to other options	Time to maximal effect 4-6 h. Duration of action may be too long for patients needing brief reversal only.	Quality of evidence for efficacy low. Slow preparation, administration, and INR reversal. Volume required may lead to CHF. Transfusion related lung injury. ¹²⁸	Off-label for warfarin reversal. Not approved anywhere for this indication. vs. PCC: Food and Drug Administration black box warning. Thrombosis risk 10%-20%. Short half-life; may require repeated dose or FFP. Weaker (or no) recommendations for use by professional societies. INR unreliable.	Off-label for warfarin reversal. Thrombosis risk 1%-4%. Pooled plasma source increases risk of infection transmission.	Thrombosis risk 1%-4%. Pooled plasma source increases risk of infection transmission. Contains heparin and is contraindicated in patients with known HIT.
Price	\$17.08 for 10 mg [‡]	\$60.70 ¹²⁹	\$1,720 for 1 mg [§] NovoSeven RT [‡]	\$2,160 for 2,000 IU (initial dose for 80- kg patient) Profilnine SD	\$2,540 for 2,000 U (initial dose for 80-kg patient) Kcentra [†]

FFP, Fresh frozen plasma; rFVIIa, recombinant factor VIIa; PCC, prothrombin complex concentrate; FIX, factor IX; FII, factor II; FVII, factor VII; FX, factor X; AT III, anti-thrombin III; ACCP, American College of Chest Physicians; CHF, congestive heart failure; HIT, heparin-induced thrombocytopenia.

*Two other 3-factor PCCs are available in the United States: Bebulin VH (Baxter Healthcare Corporation, Westlake Village, CA) is a 3-factor PCC that also contains small amounts of heparin. FEIBA NH (Baxter International, Inc., Deerfield, IL) is the third 3-factor PCC available in the United States; it does contain FVII (in activated form), as well as factor VIII inhibitor bypassing activity. It carries a Food and Drug Administration black box warning for thrombosis risk.

[†]Kcentra (a 4-factor PCC) was Food and Drug Administration–approved April 29, 2013, for the urgent reversal of anticoagulation in adults with major bleeding.

[‡]McKesson Medical/Surgical, March 21, 2013.

[§]Wholesale price, Novo Nordisk Customer Service, March 3, 2013.

^{||}Average wholesale price \$1.08 per unit, Grifols Customer Service, March 3, 2013.

^{††}Wholesale price \$1.27 per unit, CSL Behring, May 15, 2013.

severe bleeding.^{8,27-32} The correction of INR with fresh frozen plasma typically requires 13 to 48 hours.^{8,27,29,30,33,34} In emergency department (ED) patients with warfarin-associated intracranial hemorrhage, every 30-minute delay in the first dose of fresh frozen plasma was associated with a 20% decreased odds of INR reversal within 24 hours.³⁵

Fresh frozen plasma is a typical treatment element of protocols for life-threatening bleeding, including those that include or favor other agents.³⁶⁻³⁹ Techniques for optimizing the rapid delivery of fresh frozen plasma to patients with warfarin-induced intracranial hemorrhage have been described.⁴⁰⁻⁴²

Rapid Reversal: rFVIIa

rFVIIa (NovoSeven RT, Novo Nordisk, Inc., Princeton, NJ) is approved in the United States only for surgery or bleeding in hemophilic patients with inhibitors; however, 97% of total rFVIIa use is the off-label treatment of hemorrhage in nonhemophilic patients.⁴³ According to a 2012 Cochrane review, its use in patients without preexisting clotting abnormalities “remains unproven.”⁴⁴

rFVIIa use in warfarin reversal. When administered to healthy patients with an INR greater than 2, rFVIIa reverses anticoagulation in less than 1 hour.⁴⁵ When administered to patients with warfarin-induced intracranial hemorrhage, its addition to “standard therapy” resulted in INR normalization in as few as 10 minutes.^{8,29,46} Satisfactory operative hemostasis is commonly reported in case series after rFVIIa. A summary of these reports is found in Appendix E1 (available online at <http://www.annemergmed.com>), with all of these reports limited by one or more of the following: small samples, no randomization, multiple coagulopathy causes, retrospective design, and coadministered therapies. Rosovsky and Crowther⁴⁷ caution that “rFVIIa appears to rapidly correct the INR; however, its clinical impact on bleeding in patients taking warfarin remains unclear.” They recommended “against routine use of rFVIIa in acute warfarin reversal (Grade 2C).”

rFVIIa risks. Complicating thrombosis is uncommon in hemophilic patients (4 per 100,000 doses)⁴⁸; however, it has been reported in 10% to 20% of patients receiving rFVIIa for warfarin reversal (often with coadministered fresh frozen plasma and vitamin K).^{8,31,32,49,50} In the United States, rFVIIa carries a black box warning: “serious thrombotic adverse events are associated with the use of NovoSeven® RT outside labeled indications.”

Dosing of rFVIIa. For warfarin-related intracranial hemorrhage, multiple authors describe their initial use of doses in the range of those recommended for hemophilia (up to 90 µg/kg). Later in their series, they report effective preoperative reversal of warfarin anticoagulation with progressively smaller rFVIIa doses.^{49,51-53} Many successfully used a single 1- or 1.2-mg vial.^{8,28-31,54} (The smallest vial manufactured is now 1 mg.) The efficacy of lower doses is also supported by in vitro studies.⁵⁵ The duration of corrected INR after rFVIIa is dose dependent.^{40,41}

Coagulation versus clotting tests: cautions about rFVIIa. Although INR is the standard marker used to manage warfarin anticoagulation, this test is only a surrogate marker for bleeding risk, sensitive to levels of factors VII and X but not II or IX.⁵⁶ Because rFVIIa does not replace other clotting factors, it may have a much greater effect on the laboratory INR than on actual in vivo hemostasis.^{15,38} A “normal” INR may not mean successful therapeutic reversal of anticoagulation.^{56,57} In one study of healthy subjects administered warfarin, rFVIIa reversed all in vitro clotting measures but failed to decrease bleeding from a punch biopsy.⁵⁸

Interpretation of the INR confounds head-to-head comparisons between rFVIIa and other agents because hemorrhage is harder to quantify than the INR. With a half-life (1 to 2 hours) shorter than the 4 to 6 hours required for intravenous vitamin K to fully take effect, rFVIIa’s coagulant effect can decline whereas effects on the INR persist, placing the patient at unrecognized risk for rebleeding. Repeated doses of rFVIIa or supplementation with fresh frozen plasma is often required. Optimal fresh frozen plasma dosing is challenged by such distortion of the INR by rFVIIa.

Rapid Reversal: Prothrombin Complex Concentrates

Background. Prothrombin complex concentrate is a generic term for multiple products derived from pooled human plasma. Formulations contain factors II, IX, and X, with widely varying amounts of factor VII and proteins C and S. Initially developed to treat hemophilia B, they are licensed and approved in Europe, Australasia, and Canada for warfarin reversal.

Prothrombin complex concentrates are commonly administered in Europe, with pharmacovigilance data for just 3 brands (of an estimated 15 formulations worldwide⁵⁹) documenting nearly 300,000 doses during 8 to 10 years.⁶⁰ Because prothrombin complex concentrates are infrequently used for hemophilia, much of this use must be for warfarin reversal.

Multiple specialty organizations in the United States and around the world (including the American College of Chest Physicians in 2008 and 2012) recommend prothrombin complex concentrates for life-threatening warfarin-associated hemorrhage,^{20,21,36-39,61-64} yet in the United States such use has been off-label and largely unknown.^{65,66} Likely reasons for the relative underuse compared with that of other countries include lack of familiarity, infrequent availability in hospital formularies, and the widespread familiarity and availability of off-label rFVIIa.⁶⁷

Prothrombin complex concentrate formulations and availability. Prothrombin complex concentrates are stored as a powder and can be reconstituted and infused in minutes. Unlike fresh frozen plasma, no ABO compatibility testing is required and administered volumes are generally small (<100 mL).

Until April 2013, just 3 prothrombin complex concentrate products were approved in the United States, all solely for use in hemophilia: Profilnine SD (Grifols Biologicals, Inc., Los Angeles, CA), Bebulin VH (Baxter Healthcare Corporation,

Deerfield, IL), and FEIBA NH (Baxter Healthcare Corporation). Profilnine SD and Bebulin VH are 3-factor prothrombin complex concentrates containing therapeutic concentrations of factors II, IX, and X and low amounts of factor VII. Bebulin VH also has small amounts of heparin. FEIBA NH does contain factor VII (in activated form) and factor VIII inhibitor bypassing activity.

The “4-factor prothrombin complex concentrates” Beriplex and Octaplex, which contain factor VII in addition to II, IX, and X and proteins C and S, are widely approved for warfarin reversal outside of the United States. Proteins C and S are believed to attenuate the thrombotic risk, whereas the addition of factor VII is believed to enhance effectiveness relative to 3-factor agents.

On April 29, 2013, the Food and Drug Administration approved the 4-factor prothrombin complex concentrate Kcentra (CSL Behring, King of Prussia, PA) “for the urgent reversal of anticoagulation in adults with major bleeding.” Marketed as Beriplex around the world, Kcentra contains all 4 vitamin K–dependent factors (II, VII, IX, and X), as well as antithrombotic proteins C and S and small quantities of heparin.

Prothrombin complex concentrate use in warfarin reversal. The existing literature on prothrombin complex concentrates for warfarin-associated hemorrhage is highly favorable^{42,68-75} and is summarized in Appendix E2 (available online at <http://www.annemergmed.com>). These reports consistently cite rapid reversal of INR within the shortest intervals measured (often 3 to 15 minutes) and note satisfactory (but never quantified) clinical resolution of bleeding. In an observational comparison, Kuwashiro et al⁷⁶ observed a reduced intracranial hemorrhage mortality when prothrombin complex concentrate was part of treatment. All of these reports are limited by one or more of the following: differing prothrombin complex concentrate brands, doses, and adjunctive therapies; retrospective design; small sample size; lack of controls, randomization, or comparisons between therapies; heterogeneous patient populations; and variations in the severity of hemorrhage.

Prothrombin complex concentrate risks. All prothrombin complex concentrate package inserts in the United States warn of thrombosis. FEIBA NH (containing activated factor VII) bears a black box warning like rFVIIa and is described as contraindicated in “bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors” (ie, warfarin). Leissinger et al⁶⁸ reviewed the use of prothrombin complex concentrates in 14 studies of warfarin-related bleeding and found that thrombotic adverse events were uncommon (7/469 cases; 1.5%), similar to the frequency observed in subsequent studies (0.9% to 3.8%).⁷⁷⁻⁷⁹

Unlike recombinant products, prothrombin complex concentrates are derived from pooled donor plasma, with the potential for transmitting infectious agents.

Relative contraindications described for prothrombin complex concentrates include disseminated intravascular

coagulation, decompensated liver disease with antithrombin deficiency,⁵² and warfarin treatment for ongoing acute thrombosis (eg, current myocardial infarction or pulmonary embolism). Bebulin VH and Kcentra contain small amounts of heparin and thus should be avoided when there is a history of heparin-induced thrombocytopenia.

Choice of prothrombin complex concentrate. Profilnine SD (3-factor) has been the agent available in the United States with the most published experience (Appendix E2, available online at <http://www.annemergmed.com>). Bebulin VH use is reported in no more than 17 patients, but it is presumed to behave similarly.^{80,81} Kcentra, the 4-factor prothrombin complex concentrate approved in the United States in April 2013 and expected to be available in July 2013, has been in widespread use worldwide, marketed as Beriplex. Kcentra should likely become the preferred prothrombin complex concentrate for warfarin reversal because of the presence of FVII, Food and Drug Administration approval for this indication, and wider experience (see references to Beriplex in Appendix E2, available online at <http://www.annemergmed.com>).

Dose of prothrombin complex concentrate. Prothrombin complex concentrate dosing is based on the quantity of factor IX administered. Most recommendations are 25 to 50 IU/kg for both 3- and 4-factor prothrombin complex concentrates, adjusting within that range according to clinical features, eg, INR, extent of bleeding.^{15,82-90}

Three-factor versus 4-factor prothrombin complex concentrates—adding factor VII? In a study of 40 patients requiring warfarin reversal, Holland et al⁸⁹ judged a 3-factor prothrombin complex concentrate alone to be “suboptimal,” improving with fresh frozen plasma. However, vitamin K was not consistently administered and important clinical outcomes (eg, cessation of bleeding) were not evaluated.

Guidelines from the Australasian Society of Thrombosis and Haemostasis concur with those of other authors who recommend adding fresh frozen plasma (for its factor VII) to 3-factor prothrombin complex concentrates.^{37,70,91} Cabral et al⁹⁰ report a successful protocol using Profilnine SD (3-factor) plus fresh frozen plasma (for FVII) and vitamin K in 30 patients with intracranial hemorrhage and INR greater than 1.4. Three neurosurgical studies added small quantities of rFVIIa (1 to 1.2 mg) to a 3-factor prothrombin complex concentrate.^{52,92,93} Prothrombin complex concentrates normalize INRs quickly (in ≤ 15 minutes in at least 17 reports; see Appendix E2, available online at <http://www.annemergmed.com>), so a repeated INR 15 minutes after the prothrombin complex concentrate infusion may be used to guide further therapy (repeated prothrombin complex concentrate dose, fresh frozen plasma, rFVIIa).

The degree of anticoagulation affects efficacy because patients with higher initial INRs are less likely to completely reverse after a 3-factor prothrombin complex concentrate.⁹⁴⁻⁹⁶ For Beriplex (a 4-factor prothrombin complex concentrate), 30 IU/kg ex vivo consistently normalized coagulation in

blood samples with INRs greater than or equal to 4.0, whereas 20 IU/kg reversed INRs of 2.0 to 3.9.⁹⁷ Unlike other coagulation factors, endogenous factor VII requires only 10% to 15% of its normal concentration to maintain hemostasis. INR is perceived as a surrogate marker, inversely related to factor VII concentration and extrinsic pathway function.¹⁵ Makris and van Veen⁹⁸ suggested that patients with INRs less than 4.5 have sufficient intrinsic FVII to allow 3-factor prothrombin complex concentrates to be effective, whereas higher INRs reflect FVII concentrations less than 15% and require supplemental FVII. In vitro, 3- and 4-factor prothrombin complex concentrates were equivalent in reversing an INR of 3.0, but an INR of 10.3 was “more effectively corrected” with a 4-factor agent.⁹⁹

Several authors report satisfactory warfarin reversal with a 3-factor product alone, specifically questioning recommendations for supplemental factor VII.^{80,87,88,100-102} A dose of less than 25 IU/kg of a 3-factor prothrombin complex concentrate was “effective” in 74 patients without fresh frozen plasma.¹⁰¹

COMPARISONS

Prothrombin Complex Concentrate Versus Fresh Frozen Plasma

Speed (minutes versus hours). Prothrombin complex concentrates produce more rapid and complete anticoagulation reversal than fresh frozen plasma,^{10,14,71,80,103-110} with most studies showing prothrombin complex concentrate reversal of the INR to less than 1.5 in 10 to 30 minutes.¹¹¹ Prothrombin complex concentrates are reconstituted at the bedside and can be infused rapidly. Time to INR correction is 3 to 5 times faster with prothrombin complex concentrates than fresh frozen plasma.^{103,105} Improvements in neurologic status¹⁰³ and hematoma growth¹⁰⁷ have also been observed with prothrombin complex concentrates versus fresh frozen plasma. One in vitro study noted that even as much as 20% volume replacement with fresh frozen plasma was inferior to prothrombin complex concentrates for warfarin reversal.⁹⁹

Safety. Prothrombin complex concentrates mitigate concerns about fluid volume associated with fresh frozen plasma.⁶⁹ Preliminary data from recent phase III trials suggest a similar incidence of thromboembolism and other adverse events between fresh frozen plasma and a 4-factor prothrombin complex concentrate for warfarin-related bleeding.¹¹²

rFVIIa Versus Fresh Frozen Plasma

In a historical comparison, warfarin reversal with fresh frozen plasma took more than twice as long as with rFVIIa.⁸⁰ Multiple authors describe decreased fresh frozen plasma requirements or time to INR reversal in patients also administered rFVIIa.^{28,29,31,32} Like prothrombin complex concentrates, rFVIIa demonstrates benefits over fresh frozen plasma in speed of administration and limiting infusion volume.

Prothrombin Complex Concentrate Versus rFVIIa

Comparative data. In a retrospective comparison of patients treated with either prothrombin complex concentrate or rFVIIa for warfarin-related intracranial hemorrhage, Pinner et al⁸¹ found more rapid INR correction but also more frequent hematoma expansion in patients administered rFVIIa. Not all were treated with fresh frozen plasma or vitamin K. In their retrospective review of patients treated for warfarin-related intracranial hemorrhage with rFVIIa or prothrombin complex concentrate (plus vitamin K), Woo et al⁸⁰ found no significant difference in reversal times between agents but more frequent INR rebound with rFVIIa. The only direct comparisons are in animal and in vitro models of anticoagulant-related hemorrhage, in which prothrombin complex concentrates are more effective than rFVIIa.¹¹³⁻¹¹⁷

Level of evidence. Of 60 prothrombin complex concentrate reports including 3,117 patients, 31 (52%) were prospective and 6 were randomized and controlled. Of the 37 rFVIIa reports including 881 patients, 7 (19%) were prospective and none randomized. (See Appendices E1 [rFVIIa] and E2 [prothrombin complex concentrate], available online at <http://www.annemergmed.com>.)

Thrombosis risk. Thrombotic events are more common with rFVIIa (10% to 20%) versus 1% to 4% for prothrombin complex concentrate. Prothrombin complex concentrates are widely recommended and approved for warfarin reversal, whereas rFVIIa is not. Unlike rFVIIa, there are no black box warnings for 3 of the 4 prothrombin complex concentrates available in the United States.

National and international guidelines and recommendations. The majority of published guidelines favor prothrombin complex concentrate over rFVIIa or do not mention rFVIIa at all.^{20,21,36,37,39,62-64} Others actively discourage use of rFVIIa.^{38,47,61}

Duration of action. In the absence of major continuing blood loss, prothrombin complex concentrates reverse anticoagulation for 6 to 8 hours. Because vitamin K takes effect within 4 to 6 hours, repeated prothrombin complex concentrate dosing after initial INR correction is not likely to be required. With rFVIIa half-life as short as 60 minutes,¹¹⁸ repeated rFVIIa dosing or other factor replacement may be necessary.⁹¹

WARFARIN REVERSAL PROTOCOLS

Adoption of Rapid Reversal Protocols

Despite the theoretical advantages and clinical evidence supporting prothrombin complex concentrates, they are not widely used in the United States and elsewhere.¹¹⁹⁻¹²¹ Prothrombin complex concentrates are used in less than half of British neurosurgical ICUs,¹²² likely a result of limited availability.⁷⁴ They are administered to just 6% of Italian ED patients with oral anticoagulant-associated intracranial hemorrhage.¹²³ In the United States, of 56 patients with warfarin-related intracranial hemorrhage transferred from community hospital EDs to one stroke referral center, 36 (64%) received no acute reversal of any kind.⁶⁶ Even when

- A. Define “life-threatening” bleeding in the warfarin-anticoagulated patient.
Consider:
1. Intracranial hemorrhage
 2. Hemorrhage into the spinal canal
 3. Dissecting or rupturing aortic aneurysm
 4. Other acute life-threatening hemorrhage in a patient
 - a. needing immediate INR correction, or
 - b. who cannot tolerate the volume associated with fresh frozen plasma therapy
- B. Consider mechanical, surgical, or other interventional means of hemorrhage control, along with conventional reversal therapy (vitamin K, fresh frozen plasma).
- C. Replace blood and blood components as needed. Consider “massive transfusion protocol.”
- D. Give vitamin K intravenously (10 mg) to all
- E. Factor replacement options (will depend on consultant preferences and availability); treat INR >1.5
1. Optimized fresh frozen plasma:
 - a. Streamlined blood bank procedures
 - b. Thawed or liquid universal donor (AB) plasma (15 mL/kg)
 2. rFVIIa (neurosurgeons may prefer, often combined with fresh frozen plasma)
 - a. 1 mg rFVIIa
 - b. Consider fresh frozen plasma
 - c. INR inaccurate after rFVIIa
 3. 4-Factor prothrombin complex concentrate (Kcentra)
 - a. For INR 2–<4, give 25 U/kg
 - b. For INR 4–6, give 35 U/kg
 - c. For INR >6, give 50 U/kg
 - d. Do not exceed the 100-kg dose at any INR
 4. 3-Factor prothrombin complex concentrate (Profilnine SD)
 - a. Give 25 IU/kg
 - b. Recheck INR 15 min after administration
 - c. If repeated INR is >1.5, consider a second 25 IU/kg dose
 - d. Recheck INR 15 min after completion of second dose
 - e. If repeated INR is >1.5, give fresh frozen plasma or rFVIIa
- F. Consent for rFVIIa or 3-factor prothrombin complex concentrate (Profilnine SD): Both are off-label in the United States for warfarin reversal. Thrombosis risk for both PCC and rFVIIa (Food and Drug Administration black box warning for rFVIIa).

Figure. Warfarin reversal protocols: elements.

administered, prothrombin complex concentrates may be given at an incorrect dose or timing up to 74% of the time.¹²⁴ Emergency medicine knowledge translation remains a challenge.¹²⁵

A Warfarin Reversal Protocol

Institutions should work with their relevant specialists to create and implement specific protocols for managing life-threatening warfarin-associated hemorrhage. According to the literature reviewed, I present elements to be considered for such protocols in the Figure.

Agents and availability. Vitamin K should be stored in the ED and administered early by the intravenous route for nearly all patients for whom warfarin reversal of life-threatening bleeding is required. Fresh frozen plasma should be used when rFVIIa and prothrombin complex concentrate are not available. If rFVIIa is available, it may be considered a feasible treatment

option for patients with religious objections to blood products, when prothrombin complex concentrate is not available, or when prolonged warfarin reversal with vitamin K is problematic (artificial heart valve). If prothrombin complex concentrate is available, arguments favoring its use include worldwide acceptance and use, more data, small volume, lower thrombosis risk than rFVIIa without black box concerns, and evidence of clinical superiority (speed and completeness of reversal) compared with fresh frozen plasma.¹⁰³⁻¹⁰⁸

A 4-factor prothrombin complex concentrate is preferable and now approved in the United States for warfarin reversal. Given the lack of FVII in 3-factor prothrombin complex concentrates, adding fresh frozen plasma or rFVIIa to these remains a consideration in locations or institutions where 4-factor prothrombin complex concentrates are not yet available. An INR obtained quickly post-prothrombin complex concentrate infusion can help determine the need

for a repeated prothrombin complex concentrate dose, fresh frozen plasma if available, or both. A persistently elevated INR after (3-factor) prothrombin complex concentrate infusion at an optimal dose implies persistent FVII deficiency, which can be treated with fresh frozen plasma or rFVIIa. Volume status, response to initial prothrombin complex concentrate therapy, relative thrombosis risk, and concerns about accuracy of subsequent INRs should influence the decision to supplement 3-factor prothrombin complex concentrates with rFVIIa versus fresh frozen plasma.

Cost. rFVIIa and prothrombin complex concentrates are expensive (Table). In a large integrated health care delivery system, the estimated average treatment cost for warfarin reversal with rFVIIa was more than \$10,000 USD. The average prothrombin complex concentrate treatment was approximately 32% the cost of rFVIIa, whereas the average cost of fresh frozen plasma was approximately 7% the cost of rFVIIa.⁸⁰ rFVIIa has been described as cost-effective when the use of fresh frozen plasma, hospital and ICU lengths of stay, and other variables are considered.¹²⁶ In a decision model analysis for the UK National Health Service, prothrombin complex concentrate appeared to be more cost-effective than fresh frozen plasma for emergency warfarin reversal.¹²⁷

Informed consent. Given the off-label status and thrombosis risk associated with rFVIIa and 3-factor prothrombin complex concentrates, ideally the risks and benefits should be discussed with patients and their families before administration.

CONCLUSIONS AND RECOMMENDATIONS

Warfarin-related hemorrhage results in substantial mortality, and traditional reversal with fresh frozen plasma is slow and unpredictable and often requires substantial fluid volume. Prothrombin complex concentrates are widely used instead of fresh frozen plasma outside of the United States, and clinical evidence supports their more rapid and superior efficacy. This article reviews the literature relating to warfarin reversal and provides elements for a management protocol based on this literature.

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Supervising editor: Steven M. Green, MD

Author affiliations: From the Emergency Medicine Department, Naval Medical Center Portsmouth, VA.

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Address for correspondence: Kenneth Frumkin, PhD, MD, E-mail Kenneth.Frumkin@med.navy.mil.

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Appendix E1. Reports: rFVIIa and warfarin reversal.

Reference	Study Population	Intervention	Outcome	Thrombotic Complications
A. Case Reports				
Veshchev et al., 2002 ¹	SDH; INR 6.39	rFVIIa only; immediate surgery	INR 1.25 in 1 hr, good hemostasis	Died
Islam et al., 2003 ²	Nosebleed; INR 14.2	K ineffective, rFVIIa added	INR normal; bleeding resolved	None reported
Sanchis Cervera et al., 2003 ³	GI bleed; INR 6.5	FFP, plasma substitute, K, then rFVIIa	INR 1.7 in 70 min; bleeding stopped	None reported
Carnazzo et al., 2005 ⁴	Emergency surgery; INR 2.84	rFVIIa only x2	No bleeding	Died
Conti et al., 2005 ⁵	ICH; INR 3.22	rFVIIa + K	INR corrected in 15 min; full recovery	None found
Ionita et al., 2005 ⁶	ICH; INR 4.9	rFVIIa	INR 0.8 in < 30 min	Ventriculostomy thrombosed
Talkad et al., 2005 ⁷	Stroke, rtPA planned; INR 2.2	rFVIIa	Stroke score back to baseline	None found
Morante et al., 2006 ⁸	C-section; INR 3.2	rFVIIa	INR 0.8 at 30 min; C-section "uneventful"	None reported
Goldberg & Drummond, 2008 ⁹	Jehovah's Witness, SDH; INR 3.7	rFVIIa	INR 1.0; successful surgery	None reported
Kalainov & Valentino, 2008 ¹⁰	Rotator cuff surgery; INR 2.7	rFVIIa	Successful surgery	None found
Testerman et al., 2009 ¹¹	Retroperitoneal hematoma; INR 5.6	FFP, PRBC, then rFVIIa	"Hemodynamic profile & INR normal in 4 hrs"	None reported
B. Retrospective Case Series				
Lin et al., 2003 ¹²	2 SCH, 2 SDH; INR 1.9-5.6	rFVIIa + FFP	INR normal in 2 hrs; blood loss <100 ml	None found
Park et al., 2003 ¹³	3 ICH; INR \geq 9.6	rFVIIa + FFP	INR \leq 1.0	None found
Sorensen et al., 2003 ¹⁴	6 ICH, 1 post trauma; INR 1.7-6.6	rFVIIa + K; 3 + FFP	INR <1.5 in 10 min; hemostasis	None found
Freeman et al., 2004 ¹⁵	7 ICH; Mean INR 2.7	rFVIIa; 6 + K 6 + FFP	Mean INR 1.08	None found
Zupancic-Salek et al., 2005 ¹⁶	4, bleeding; INR >7	rFVIIa + K	INR normal; bleeding stopped	None found
Da'as et al., 2006 ¹⁷	7, ICH; Mean INR 3.7	rFVIIa; 6 + (FFP + K + PLT)	Mean INR 0.87	1 PE
Ingerslev et al., 2007 ¹⁸	3, bleeding	rFVIIa; + multiple other Rx	2 bleeding "stopped", 1 "decreased"	None reported
McQuay et al., 2009 ¹⁹	18, TBI, 7 on warfarin; Median INR 1.4	rFVIIa	Median INR 0.98; "complete reversal in 17"	1 MI
Robinson et al., 2010 ²⁰	101, ICH or SDH; Mean INR 3.04	rFVIIa + K + FFP	Mean INR 1.03	12.8% thrombosis in 90 days, mostly DVT
Sarode et al., 2012 ²¹	See Web Appendix B			
C. Retrospective Cohort Series				
Brody et al., 2005 ²²	27, ICH	FFP + K; 2 + rFVIIa	INR <1.3 in: (a) 8.8 hrs w rFVIIa w ½ the FFP; (b) 32.2 hrs w FFP	1 DIC and clotting of dialysis graft
Ilyas et al., 2008 ²³	54, ICH; Mean INR 3.0	FFP + K; 30 + rFVIIa	Mean INR \leq 1.3 in: (a) 2.4 hrs + 4 u FFP w rFVIIa; (b) 13.7 hrs + 7.7 u FFP alone	1 MI

Appendix E1. Continued.

Reference	Study Population	Intervention	Outcome	Thrombotic Complications
Stein et al., 2008 ²⁴	63, TBI w coagulopathy, 11 on warfarin; Mean INR 2.1	29 rFVIIa, 13 rFVIIa + FFP, 34 FFP only	rFVIIa: Mean INR 0.8, less FFP & time to intervention, equal mortality	18.7%, no difference among groups
Stein et al., 2008 ²⁵	81, trauma w coagulopathy, 18 on warfarin; Mean INR 1.9	rFVIIa + FFP + K	Mean INR 0.8; less FFP & PRBC after rFVIIa	12 thrombotic events, 4 attributed to rFVIIa
Stein et al., 2009 ²⁶	179, TBI w coagulopathy; Mean INR 1.9	68 rFVIIa, 111 "conventional Rx"	Total hospital charges & costs less w rFVIIa for ICU subset	17%, no difference between groups
Brown et al., 2010 ²⁷	28, TBI w coagulopathy, 10 on warfarin; INR >1.3	FFP; 14 + rFVIIa	rFVIIa: lower INR, less FFP & PRBC	None found
Nishijima et al., 2010 ²⁸	40, traumatic ICH, ED; INR ≥1.3	FFP + K; 20 + rFVIIa	INR <1.3 in: (a) 4.8 hrs w rFVIIa, ½ the FFP; (b) 17.5 hrs for FFP alone;	12.5%, no difference between groups
Pinner et al., 2010 ²⁹ / Bebulin(3F)	24, ICH Mean INR 5.6 in rFVIIa group, 2.6 in PCC group	15 PCC 9 rFVIIa 21 + K; 19 + FFP	INR ≤1.3 w/in 1 hr: (a) 83% w rFVIIa (b) 20% w PCC Hematoma expansion: (a) 20% w rFVIIa (b) 11% w PCC	rFVIIa: 1 stroke PCC: 1 DVT, 1 PE
Woo, et al., 2013 ³⁰	63, ICH Group mean INR 2.7-4.6	9 rFVIIa + K 8 PCC + K 46 FFP + K	Time to INR 1.3-1.5: FFP twice as long as PCC = rFVIIa INR rebound w rFVIIa	None found
D. Prospective Cohort Series				
Muleo et al., 1999 ³¹	4, for surgery, 3 on warfarin; INR 3.6-9.8	rFVIIa	INR < 1.3	None reported
Deveras & Kessler, 2002 ³²	13, for reversal; INR ≥1.85	rFVIIa + K	INR "reduced" in 10 min	None found
Dutton et al., 2004 ³³	81, trauma w coagulopathy, 9 on warfarin; INR >1.4 or PLT <100,000	rFVIIa, FFP, K, PRBC, PLT; historical controls	Coagulopathy "reversed" in 61; Mean PT 19.6 => 10.8	3 bowel infarction, questionably related
Roitberg et al., 2005 ³⁴	29, for neurosurgery w coagulopathy, 14 on warfarin; Mean INR 2.2 after FFP	FFP + K, then rFVIIa; historical controls	Mean INR 1.12	None found
Dager et al., 2006 ³⁵	16, "major bleeding"; Mean INR 2.8	rFVIIa + FFP + K	Mean INR 1.07 in 10-30 min	1 of 6 deaths possibly from thrombosis
Bartal et al., 2007 ³⁶	15, traumatic SDH, 7 on warfarin; Mean INR 1.5 after Rx	FFP + K + PLT, then rFVIIa	Mean INR 0.92	None found
Cusick et al., 2009 ³⁷	See Web Appendix B			

ABBREVIATIONS: DIC = Disseminated Intravascular Coagulation, ED = Emergency Department, FFP = Fresh Frozen Plasma, GI = Gastrointestinal, hrs = Hours, ICH = Intracerebral Hemorrhage, INR = International Normalized Ratio, K = Vitamin K, MI = Myocardial Infarction, min = Minutes, "None found" = thrombotic complications specifically sought and "none found", "None reported" = no mention of thrombotic complications either sought or found, PE = Pulmonary Embolism, PLT = Platelets, PRBC = Packed Red Blood Cells, PT = Prothrombin Time, pt = Patient, pts = Patients, rFVIIa = Recombinant Factor VIIa, rTPA = Recombinant Tissue Plasminogen Activator, Rx = Treatment, SCH = Spinal Canal Hemorrhage, SDH = Subdural Hematoma, TBI = Traumatic Brain Injury, u = unit(s), w = with, w/o = without.

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Appendix E2. Reports: Prothrombin complex concentrates (PCC) and warfarin reversal.

Reference/PCC (Type*)	Study Population	Intervention	Outcome	Thrombotic Complications
A. Case Reports				
Yasaka et al., 2003 ¹ / PPSB-HT(4F)	2 bleeding, procedure; INR >10, 6.69	PCC + K	INR 1.12, 1.85 in 10 min	None found
Warren & Simon, 2009 ² / ProfilNine(3F)	Pericardial tamponade, ED; INR >12.8	PCC + K + Desmopressin	Successful pericardiocentesis, INR still >12.8	Death, right ventricle thrombus
Morimoto et al., 2010 ³ / PPSB-HT(4F)	2, dental extraction, Hx HIT, INR ≥4.5	PCC	INR <2 in 15 min	None reported
Wong, 2011 ⁴ /Beriplex(4F)	SDH; INR 4.1	PCC + K	INR 1.0 in “minutes”	None reported
B. Retrospective Case Series				
Nitu et al., 1998 ⁵ /FIX + FVII concentrates(4F)	20, bleeding or procedures; INR >4.3	Factors IX/VII; 3 + K	Mean INR 1.3 in 15 min	None found
Sjoblom et al., 2001 ⁶ / Prothromplex-T(4F)	151, ICH	PCC, FFP, K or nothing, varying combinations	Case fatality studied; no treatment superior	None reported
Bruce & Nokes, 2008 ⁷ / Beriplex(4F)	24, bleeding, 8 on warfarin; Mean PT 52.7	PCC + K; after FFP, RBC, PLT, and/or cryo	Mean PT 14.7	None Found
Chiu et al., 2009 ⁸ / Prothrombinex-HT(3F)	50, vascular surgery or angiography; INR 2.0-3.9	PCC	INR 1.0-1.3	None found
Safaoui et al., 2009 ⁹ /FIX Complex(3F)	28, ICH; Mean INR = 5.1	PCC; most +K + FFP	Mean INR 1.9; Mean correction time 13.5 min	None found
Schick et al., 2009 ¹⁰ / Beriplex(4F)	12, surgery and/or bleeding; Mean INR 2.8	PCC; 7 + K, 1 + PLT, PRBC	Mean INR 1.5 in 31 min	None found
Chong et al., 2010 ¹¹ / ProfilNine(3F)	7, ICH; Median INR 3.0	PCC + FFP; 6 + K 1 + rFVIIa	Median INR 1.3	1 DVT with PE
Cabral et al., 2012 ¹² / ProfilNine(3F)	30 ICH; INR >1.4, Median INR 2.3	PCC + K + FFP	Median INR 1.4	3 thrombotic events
Sarode et al., 2012 ¹³ / ProfilNine(3F) + rFVIIa = (4F)	46, ICH; Mean INR 3.4	PCC + rFVIIa + K	Mean INR 1.0	2 NSTEMI
Song et al., 2012 ¹⁴ /Octaplex(4F)	82; Mean INR 5.08	PCC; 69 + K	Mean INR 1.43	3 thrombotic events
Switzer et al., 2012 ¹⁵ / ProfilNine(3F)	70, ICH; Mean INR 3.36	PCC; 39 + FFP	Mean INR 1.96; 63% <1.4	3 thrombotic events, 2 sudden death
C. Retrospective Cohort Series				
Fredriksson et al., 1992 ¹⁶ /Preconativ(3F)	17, ICH	10 PCC + K, 7 FFP + K	PCC: 4.6x faster w lower INR than FFP	1 renal infarction
Makris et al., 1997 ¹⁷ /9A, BPL, UK(4F), or Prothromplex T(4F)	41, hemorrhage or reversal	29 PCC + K, 12 FFP + K	15 min after Rx: (a) PCC: Mean INR 5.8 =>1.3 (b) FFP: Mean INR 10.2 => 2.3	None reported
Yasaka et al., 2003 ¹⁸ / PPSB-HT(4F)	17, “major hemorrhage”	11 PCC + K, 2 PCC only, 4 K only	PCC + K: INR 2.7 =>1.3 in 10 min	None found
Crawford & Augustson, 2006 ¹⁹ /Prothrombinex- VF(3F)	105, bleeding or procedures	74 PCC, 31 PCC + FFP; + K in 70%	All w hemostasis; FFP not needed	None reported
Huttner et al., 2006 ²⁰ / PCC not identified	55, ICH	31 PCC w or w/o FFP, K; 18 FFP w or w/o K; 6 K only	Less hematoma growth w PCC	None reported
Lankiewicz et al., 2006 ²¹ /Proplex-T(4F)	58, 62% ICH; Median INR 3.8	PCC + K; 50% + FFP	Median INR 1.3 “immediately”	2 MI, 2 DVT
Junagade et al., 2007 ²² / Beriplex(4F)	21, “various, 10 life-threatening”; INR > 2.0	PCC, 1 of 3 doses; 3 + FFP	INR <2.0 in 88% in median of 2.5 hrs	None found
Siddiq et al., 2008 ²³ / ProfilNine(3F)	19, ICH; Mean INR 2.16	FFP + K; 10 + PCC	Mean INR 1.34 in both groups: (a) PCC + FFP in 4.25 hrs; (b) FFP alone in 8.52 hrs	None found

Appendix E2. Continued.

Reference/PCC (Type*)	Study Population	Intervention	Outcome	Thrombotic Complications
Wójcik et al., 2009 ²⁴ / FEIBA(4F)	141, "life-threatening bleeding", ED; Median INR 2.9-3.3	72 PCC + K, 69 FFP, historical controls	Median INR \leq 1.4 in: (a) 51% w PCC; (b) 33% w FFP	5 events "possibly" related
Pinner et al., 2010 ²⁵ / Bebulin(3F)	24, ICH Mean INR 5.6 in rFVIIa group, 2.6 in PCC group	15 PCC 9 rFVIIa 21 + K; 19 + FFP	INR \leq 1.3 w/in 1 hr: (a) 83% w rFVIIa (b) 20% w PCC Hematoma expansion: (a) 20% w rFVIIa (b) 11% w PCC	rFVIIa: 1 stroke PCC: 1 DVT, 1 PE
Chapman et al., 2011 ²⁶ / ProfilNine(3F)	31, trauma; Mean INR 2.88	FFP + K; 13 + PCC	INR \leq 1.5 in 90%: (a) PCC + FFP in 17 hrs; (b) FFP alone in 30 hrs	2 in PCC, 1 in no PCC
Baggs et al., 2012 ²⁷ / ProfilNine(3F)	50, INR >2	PCC; Some + K, FFP, PRBC	INR \leq 1.5 in 58%; less likely if initial INR 3.5 vs. 2.5	None reported
Barillari et al., 2012 ²⁸ / Uman Complex(3F)	47; 23 TBI, 24 spontaneous bleeding	PCC; 15 + K 20 + FFP 18 + PRBC	Mean INR: TBI group 2.7 => 1.4; spontaneous bleeding group 6.58 => 1.9	None found
Woo et al., 2013 ²⁹ /Profilnine(3F) or Bebulin(3F)	63, ICH Group mean INR 2.7-4.6	8 PCC + K 9 rFVIIa + K 46 FFP + K	Time to INR 1.3-1.5: FFP twice as long as PCC = rFVIIa INR rebound w rFVIIa	None found
D. Prospective Case Series				
Sandler et al., 1973 ³⁰ / Konyne(4F)	5, "life-threatening bleeding"; Mean PT 40.9	PCC; + K after 1 hour	Mean PT 13.7 in 30 min	None found
Staudinger et al., 1999 ³¹ /Beriplex(4F)	16, bleeding or procedures	PCC	PT "normalized"	None found
Cartmill et al., 2000 ³² / FIXaBPL(3F)	12, ICH	6 PCC + K, 6 FFP + K, historical controls	Mean INR in 15 min (correction time): (a) PCC: INR 4.86 => 1.32 (41 min) (b) FFP: INR 5.32 => 2.3 (115 min)	None reported
Evans et al., 2001 ³³ /Beriplex(4F)	10, bleeding; Median INR >20	PCC + K	Median INR 1.1 in 30 min, "immediate cessation of bleeding"	None found
Preston et al., 2002 ³⁴ / Beriplex(4F)	42, reversal; Median INR 3.98	PCC + K	33 INR <1.3 in 20 min; 9 w INR 1.3-1.9	1 stroke
Lubetsky et al., 2004 ³⁵ / Octaplex(4F)	20, bleeding or surgery; Mean INR 6.1	PCC; 7 + K	Mean INR 1.5 in 10 min	None found
Lavigne-Pardonge et al., 2006 ³⁶ /PPSD-SD(4F)	12, bleeding or surgery; Mean INR 5.5	PCC + K; + FFP prn	11 Mean INR 1.2 in 15 min	None found
Lorenz et al., 2007 ³⁷ / Beriplex(4F)	8, bleeding, surgery, or procedures; Mean INR 3.4	PCC; 5 + Antithrombin III 2 + heparin 1 + K	INR \leq 1.4 in 10 min	None found
Riess et al., 2007 ³⁸ /Octaplex(4F)	56, bleeding or procedures	PCC	Median INR 2.8 => 1.1 in 10 min	None found
Vigue et al., 2007 ³⁹ /Kaskadil(4F)	18, ICH; Mean INR 4.0	PCC + K	Mean INR 1.2 in 3 min, "immediate" surgery	None found
Imberti et al., 2008 ⁴⁰ / Prothromplex(3F)	92, ICH; Median INR 3.3	PCC + K; 1 + FFP	Median INR 1.4 in 30 min	None found
Kalina et al., 2008 ⁴¹ / Proplex T(4F)	111, ICH	46 PCC + FFP + K, 65 FFP + K, historical controls	PCC improved: time to INR \leq 1.5, % of patients reversed, & time to OR	3 DVT
Pabinger-Fasching, 2008 ⁴² /Beriplex(4F)	43, bleeding or surgery; Median INR 3.3	PCC; "most" + K	Mean INR 1.18 in 30 min	1 thrombotic event "possibly related"

Appendix E2. Continued.

Reference/PCC (Type*)	Study Population	Intervention	Outcome	Thrombotic Complications
Cusick et al., 2009 ⁴³ / ProfilNine(3F) + rFVIIa = (4F)	14, ICH	PCC + rFVIIa + K	Mean INR 1.0	1 multiple thromboses
Holland et al., 2009 ⁴⁴ / ProfilNine(3F)	40, bleeding or reversal; INR>5	PCC; some + FFP some + K historical controls (FFP, some + K)	INR <3 in: (a) ≤55% w PCC; (b) ≥89% w PCC + FFP	None reported
Khorsand et al., 2010 ⁴⁵ / Cofact(4F)	67, bleeding or procedures; Median INR 4.7	PCC + K; fixed dose vs. historical controls (individualized dose)	Median INR 1.8	1 MI, 2 PE
Pabinger et al., 2010 ⁴⁶ / Beriplex(4F)	43, bleeding, surgery or procedures; INR>2	PCC	INR ≤1.4 in 30 min	1 PE
Rizos et al., 2010 ⁴⁷ /Beriplex(4F)	10, SDH; Median INR 3.0	PCC + K	INR ≤1.4	None found
Tran et al., 2010 ⁴⁸ / Prothrombinex(3F)	50, reversal; Mean INR 3.5-5.6	PCC; 42 PCC + K	91-93% target INR in 30 min	None found
Imberti, et al., 2011 ⁴⁹ / Uman Complex(3F)	46, ICH; Median INR 3.5	PCC + K	Median INR 1.3 in 30 min	None found
Desmettre et al., 2012 ⁵⁰ / Kaskadil or Octaplex(4F)	256, bleeding, surgery, or procedure	PCC; w or w/o K, FFP, PRBC	INR < 1.5 in 65%	None found
E. Prospective Cohort Series				
Yasaka et al., 2005 ⁵¹ / PPSB-HT(4F)	42, hemorrhage or procedure; INR>2	PCC, 3 doses; 31 + K	At 500 IU: Median INR 2.49 => <1.5 in 96% in 10 min	None found
Kuwashiro et al., 2011 ⁵² / PPSB-HT(4F)	37, ICH; INR>2	19 PCC, 18 no PCC; Some +K, + FFP	PCC better outcome (Rankin) and less mortality	None reported
Khorsand et al., 2012 ⁵³ / Cofact(4F)	240, non-intracranial bleeding	PCC + K 101 fixed PCC dose 139 variable PCC dose (by weight and INR)	INR < 2.0 in 91.7% of fixed dose and 94.7% of variable dose PCC. Clinical outcomes were =	3 thrombotic events
Majeed et al., 2012 ⁵⁴ / Prothromplex, Octaplex, or Beriplex(4F)	160, bleeding or surgery; Median INR 3.5	PCC; 74% + K 34% + FFP	Median INR 1.4	9 thrombotic events
F. Prospective Randomized Controlled				
Taberner et al., 1976 ⁵⁵ / Prothromplex (3F)	18, reversal	9 PCC, 9 IV K	PCC corrected in 30 min; K some effect at 2 hrs	None noted
Boulis et al., 1999 ⁵⁶ / Konyne(4F)	13, ICH; PT>17sec	FFP; 5 + PCC 8 + SC K	PCC: faster time to INR ≤1.3 & less FFP	None found
Van Aart et al., 2006 ⁵⁷ / Cofact(4F)	93, bleeding or surgery; INR>2.2	PCC + K; PCC dose fixed vs. individualized	In 15 min: target INR in 43% w fixed dose & 89% w individualized dose	2 CVA
Demeyere et al., 2010 ⁵⁸ / Cofact(4F)	40, surgery; INR≥2.1	20 PCC, 20 FFP	INR≤1.5 in 15 min in 7/16 w PCC; 0/16 w FFP	None reported
Sarode et al., 2012 ⁵⁹ / Beriplex(4F)	212, major bleeding; 114, emergency surgery	159 PCC + K, 167 FFP + K	Phase III safety study. Adverse events and deaths: PCC = FFP	PCC = 6.3%; FFP = 7.8% (No difference)
Goldstein 2012 ⁶⁰ /Beriplex(4F)	202, acute bleeding	202, PCC or FFP, + K	INR in 1 hr ≤1.3 in 70% w PCC; <5% w FFP	7.8% PCC, 5% FFP

ABBREVIATIONS: cryo = cryoprecipitate, DVT = Deep Venous Thrombosis, ED = Emergency Department, FFP = Fresh Frozen Plasma, FIX = Factor IX, FVII = Factor VII, GI = Gastrointestinal, HIT = Heparin-Induced Thrombocytopenia, Hx = History, ICH = Intracerebral Hemorrhage, hr = hour, hrs = hours, INR = International Normalized Ratio, IV = intravenous, K = Vitamin K, MI = Myocardial Infarction, min = minutes, NSTEMI = Non-ST Segment Elevation Myocardial Infarction, "None found" = Thrombotic complications specifically sought and "none found", "None reported" = No mention of thrombotic complications either sought or found, PE = Pulmonary Embolism, PLT = Platelets, PRBC = Packed Red Blood Cells, prn = as needed, PT = Prothrombin Time, pt = patient, pts = patients, R = right, rFVIIa = Recombinant Factor VIIa, rPA = Recombinant Tissue Plasminogen Activator, Rx = Treatment, SC = subcutaneous, SCH = Spinal Canal Hemorrhage, SDH = Subdural Hematoma, TBI = Traumatic Brain Injury, u = unit(s), w = with, w/in = within; w/o = without, x = times.

*PCC TYPE: 3F = 3-Factor PCC; 4F = 4-Factor PCC.

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