Four-factor Prothrombin Complex Concentrate for the Management of Patients Receiving Direct Oral Activated Factor X Inhibitors

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Direct oral anticoagulants (DOACs) have been approved for the prevention of stroke and systemic embolism in atrial fibrillation, treatment and secondary prevention of venous thromboembolism (VTE), and thromboprophylaxis after major orthopedic surgery. DOACs achieve anticoagulation by inhibiting specific coagulation factors; apixaban, betrixaban, edoxaban, and rivaroxaban inhibit activated factor X, whereas dabigatran inhibits thrombin (factor IIa). In contrast to vitamin K antagonists such as warfarin, DOACs have more predictable pharmacokinetics and pharmacodynamics and fewer interactions with other medications and food, and they are not associated with the problems of a narrow therapeutic window like warfarin.[1–3] This allows for fixed oral dosing once or twice per day, without the need for anticoagulation monitoring or dose adjustments.

Randomized clinical trial data demonstrate that activated factor X inhibitor therapies are noninferior to other anticoagulants such as vitamin K antagonists.[4] DOACs also have favorable safety and efficacy profiles, as demonstrated by evidence from "real-world" cohorts.[5–7] The risk of intracranial hemorrhages was lower with all the DOACs compared with warfarin,[8] although the rate of gastrointestinal bleeding might be increased with rivaroxaban.[9] Other studies have shown that outcomes after bleeding events were similar or less severe for patients receiving DOACs than those receiving vitamin K antagonists.[10,11] The number of patients using DOACs will likely increase due to their advantages over existing therapies, and thus the number of bleeding events in patients on DOAC therapy is also expected to increase. Therefore, for patients presenting with severe or life-threatening bleeding or for patients undergoing urgent surgery, a clear strategy to reverse anticoagulation and to achieve hemostasis is essential.

Management of Patients on DOAC Therapies

While recommendations for the management of vitamin K antagonist-related bleeding are well established,[12–14] guidelines for managing patients on DOACs,[15,16] which were developed more recently, are based on limited evidence. The decision to stop treatment depends on a patient's risk of bleeding *versus* their risk of thromboembolic complications. When deciding to reverse activated factor X inhibitors, their short elimination half-life should also be taken into account[16–19] (table 1); hemostasis is restored approximately 12 to 24 h after cessation of DOACs, assuming normal renal function.[16,20] As DOACs are partially eliminated via the kidney, they can accumulate in patients with impaired renal function.[16,21]

Reversal Strategies in Emergency Cases

Coagulopathy, which is common in trauma and perioperative bleeding, is associated with increased morbidity and mortality, and anticoagulation can further increase a patient's risk of developing coagulopathic bleeding.[14,22] Thus, in cases of life-threatening bleeding, restoration of hemostasis requires prompt reversal of anticoagulation in addition to a multimodal approach using hemostatic agents.[16] In the context of this review, we define severe bleeding according to the International Society on Thrombosis and Haemostasis criteria for major bleeding in nonsurgical patients having a symptomatic presentation.[23]

For reversal of dabigatran, a specific agent is available: idarucizumab, a humanized antibody fragment that specifically binds dabigatran with high affinity and reverses its effects within minutes.[24,25] For reversal of activated factor X inhibitor therapies, andexanet alfa, a recombinant modified human activated factor X protein that specifically binds activated factor X inhibitors, has been developed.[26,27] Although recently approved by the U.S. Food and Drug Administration (Silver Spring, Maryland), its labeled use is currently restricted as clinical evidence for its effectiveness was based on studies in healthy volunteers, whereas improvement in hemostasis in bleeding patients has not been established.[28] Indeed, such improvement has only been demonstrated for four-factor prothrombin complex concentrate (four-factor PCC) *versus* fresh frozen plasma in a randomized clinical trial in surgical patients.[29] In this

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Table 1. Pharmacokinetic Properties of Direct Oral Anticoagulants

	Dabigatran[81]	Apixaban[19]	Rivaroxaban[17]	Edoxaban[18]
Mechanism of action	Direct thrombin inhibitor	Xa inhibitor	Xa inhibitor	Xa inhibitor
Time to peak	2 h	3–4 h	2–4 h	1–2 h
Terminal half-life	11–14 h*	12 h	5–13 h	10–14 h
Renal excretion	85%	27%	~33%	50%

*Longer in patients with renal insufficiency.

trial with 181 patients on vitamin K antagonist, "effective hemostasis" was observed in 90% of patients with PCC *versus* 75% with fresh frozen plasma (difference 14.3%; 95% CI 2.8 to 25.8) and rapid reduction of international normalized ratio was achieved in 55% and 10%, respectively (difference 45.3%; 95% CI, 31.9 to 56.4). In addition, andexanet alfa is not widely available and is expected to be costly (see Economic Considerations for the Use of Prothrombin Complex Concentrate *versus* Andexanet Alfa section).

Several nonspecific reversal strategies have been studied as potential DOAC reversal agents, including fresh frozen plasma, three-factor PCC or four-factor PCC, activated PCC, and recombinant activated factor VII.[30] Due to its well-documented efficacy and safety in the urgent reversal of vitamin K antagonist, four-factor PCC has emerged as a promising agent to antagonize the effects of activated factor X inhibitors, although the mechanism of action is different, as discussed at the end of the next paragraph.[12–14]

PCCs contain either three or four coagulation factors (factors II, IX, and X, with or without factor VII) and, depending on the formulation, similar proportions of coagulation inhibitors such as protein C, protein S, and low doses of heparin.[31–33] The mechanism of action of PCCs is important for understanding their therapeutic applications. Vitamin K antagonists such as warfarin function by reducing levels of factors II, VII, IX, and X. For acute substitution, for example in severe bleeding, where coagulopathy is caused by consumption and dilution due to massive transfusion, PCCs serve as a source of coagulation factors. In contrast, levels of coagulation factors in bleeding patients on DOAC therapies are not primarily affected by the DOAC but the function of a single factor, either thrombin or activated factor X, is inhibited. The exact mechanism whereby PCC may improve hemostasis under activated factor X inhibition has not been clarified yet. Several animal studies and a phase I trial have indicated that there is a dose-dependent effect,[34–37] but the mechanism of action can probably not be explained by a simple stoichiometric reaction. On a molar basis, the concentration of FX in PCC is not sufficient to overcome the antagonizing effect of the activated factor X inhibitor. Instead, PCCs may restore hemostasis in patients on DOACs as they increase both prothrombin and FX levels at the site of injury and may exert a compensatory prohemostatic effect with increased thrombin generation potential.

There are considerable variations among countries in the availability and licensing status of PCCs. For example, four-factor PCCs have been used for many years in Europe, where their license is not restricted to vitamin K antagonist reversal; thus, PCCs have a broad approval for the "treatment and prophylaxis of bleeding in acquired deficiency of prothrombin complex coagulation factors."[38,39] In the United States, however, four-factor PCC was only approved in 2013 and is currently restricted in use to the urgent reversal of vitamin K antagonist therapy.

PCC in the Reversal of Activated Factor X Inhibitors

The benefit of PCC for management of activated factor X inhibitor–associated bleeds was first explored in animal models of acute hemorrhage using different injury approaches (*e.g.*, kidney incision, hepatosplenic bleeding, mesenteric bleeding, and intracranial hemorrhage)[40–42] and in spiking experiments in blood from human volunteers[42–47] (table 2). These studies provide evidence for improvement of surrogate markers such as partial or full normalization of prothrombin time (useful for rivaroxaban but not for apixaban or edoxaban), endogenous thrombin potential, or thrombin generation.

Phase I studies in human volunteers involved a supratherapeutic dose of rivaroxaban, apixaban, or edoxaban followed by administration of PCC at different doses (10 to 50 IU/kg body weight) and showed similar results in improvement of surrogate markers as was seen for the animal and *ex vivo* studies.[33,37,48–50] There was a dose-dependent response whereby 10 IU PCC/kg body weight was inadequate for activated factor X inhibitor reversal, 25 IU/kg body weight had partial effect, and 37.5 IU/kg body weight gave better reversal but still not complete normalization of coagulation parameters. A randomized placebo-controlled study using a punch biopsy bleeding model in healthy subjects on edoxaban reported reversal to baseline for bleeding duration and a trend toward reduced bleeding volume after administration of four-factor PCC, although CIs for the effect on bleeding duration overlapped with those for placebo.[37] Conversely, a similar study reported that four-factor PCC partially reversed the effects of rivaroxaban on thrombin generation but had no effect on bleeding duration or volume.[51]

Table 2. Overview of *Ex Vivo* Studies and Studies in Healthy Volunteers of the Efficacy of Four-factor PCC

	Study Design	No.	Xa inhibitor	PCC Dose(s)	Outcomes
Ex vivo studies					
Fukuda *et al.,* 2012, *Thromb Haemost*[42]	Spiked human plasma	(Pooled)	Edoxaban (up to 300 ng/ml)	0.15, 0.5, 1.5 U/ml	• PCC (0.15, 0.5 and 1.5 U/mL) reduced PT
Marlu *et al.,* 2012, *Thromb Haemost*[46]	Randomized crossover study; spiked human plasma	10	Rivaroxaban (20 mg)	0.25, 0.5, 1 U/ml	• PCC dose-dependently increased ETP AUC and thrombin peak • Slight reduction in lag time • No effect on time to peak
Dinkelaar *et al.,* 2013; *J Thromb Haemost*[43]	Spiked human plasma and whole blood samples	9	Rivaroxaban (up to 800 µg/l)	Up to 4 IU/ml	• PCC normalized thrombin potential • PCC did not normalize PT
Perzborn *et al.,* 2014, *Thromb Res*[41]	Spiked human plasma and whole blood samples	6	Rivaroxaban (200–1,000 ng/ml)	0.2–1.0 U/ml	• PCC significantly reversed PT prolongation • PCC did not reverse CT prolongation • PCC concentration-dependently increased ETP
Escolar *et al.,* 2015, *Circ J*[45]	Spiked steady and circulating human blood	8	Rivaroxaban (230 ng/ml)	50 IU/kg	• PCC shortened prolongation of CT and CFT • PCC restored thrombin generation
Körber *et al.,* 2016, *Blood Transf*[47]	Spiked human blood samples	10	Rivaroxaban (median 603 ng/ml)	25, 50 IU/kg	• 25 and 50 IU/kg PCC did not significantly improve PT • 25 and 50 IU/kg PCC significantly corrected aPTT • 25 IU/kg PCC significantly corrected CT but results did not reach significance with 50 IU/kg
Studies in healthy volunteers					
Eerenberg *et al.,* 2011, *Circulation*[82]	Randomized, double-blind, placebo-controlled crossover study	12	Rivaroxaban (20 mg twice daily for 2.5 d)	50 IU/kg	• PCC normalized PT • PCC normalized ETP
Levi *et al.,* 2014, *J Thromb Haemost*[83]	Open-label, single-center, parallel-group study of 3F-PCC vs four-factor-PCC	35 (3F-PCC=12; four-factor-PCC=11)	Rivaroxaban (20 mg twice daily for 4 d)	50 IU/kg	• PCC reduced prolonged PT (four-factor-PCC>3F-PCC) • PCC increased thrombin generation (3F-PCC>four-factor-PCC) • PCC did not reverse prolonged aPTT
Cheung *et al.,* 2015, *J Thromb Haemost*[48]	Randomized, double-blind, placebo-controlled, crossover study	6	Apixaban (10 mg twice daily for 3.5 d)	25, 37.5 IU/kg	• 25 and 37.5 IU/kg PCC restored PT prolongation • 25 and 37.5 IU/kg PCC increased ETP
Zahir *et al.,* 2015, *Circulation*[37]	Phase I double-blind, randomized, placebo-controlled, two-way crossover study	110	Edoxaban (60 mg)	10, 25, 50 IU/kg	• PCC dose-dependently reversed the effects of edoxaban o 50 IU/kg PCC completely reversed extended bleeding duration and ETP o 50 IU/kg PCC partially reversed PT prolongation
Barco *et al.,* 2016, *Br J Haematol*[83]	Randomized, double-blind, crossover, placebo-controlled study	6	Rivaroxaban (15 mg twice daily for 2.5 d)	25, 37.5 IU/kg	• 25 and 37.5 IU/kg PCC restored PT prolongation • 37.5 IU/kg of PCC led to partial restoration of ETP but 25 IU/kg did not
Nagalla *et al.,* 2016, *Clin Transl Sci*[49]	Phase I randomized, assessor-blinded, two-period crossover study	12	Apixaban (5 mg twice daily for 2.5 d)	25 IU/kg	• PCC increased peak thrombin generation • PCC partially reversed ETP • PCC shortened PT
Song *et al.,* 2017, *J Thromb Haemost*[50]	Open-label, randomized, placebo-controlled, three-period crossover study	15	Apixaban (10 mg twice daily for 3 d)	50 IU/kg	• PCC restored ETP • PCC increased TGA peak height but had little effect on TGA lag time or time to peak • PCC reversed prolonged PT • PCC did not reverse prolonged aPTT
Levy *et al.,* 2018, *J Thromb Haemost*[51]	Randomized, double-blind, parallel-group study of four-factor PCC vs TXA	147 (four-factor-PCC=48)	Rivaroxaban (20 mg twice daily for 3 d)	50 IU/kg	• PCC partially reversed PT prolongation • PCC completely restored ETP • PCC had no effect on bleeding duration or volume

3F, three-factor; 4F, four-factor; aPTT, activated partial thromboplastin time; AUC, area under the curve; CFT, clot formation time; CT, clotting time; ETP, endogenous thrombin potential; PCC, prothrombin complex concentrate; PT, prothrombin time; TGA, thrombin generation assay; TXA, tranexamic acid.

Four-factor PCCs contain a higher content of factor VII than three-factor PCCs, and evidence suggests that four-factor PCCs are a better option for reversing anticoagulation therapies. In a study in healthy volunteers taking rivaroxaban, four-factor PCC reduced mean prothrombin time within 30 min by 2.5 to 3.5 s, *versus* 0.6 to 1.0 s with three-factor PCC.[33]

Based on the available data, PCCs are recommended by international guidelines and used clinically in patients with major or life-threatening bleeding receiving DOAC therapy.[14,16,52] However, it was not known whether reversal in animal models, healthy subjects, and *ex vivo* studies accurately reflects reversal in bleeding patients on DOAC therapy. Therefore, the "An observational multicenter cohort study on efficacy and safety of Unactivated Prothrombin complex concentrate for reversal of oral, direct factor Xa inhibitors Rivaroxaban, Apixaban or edoxaban in Treatment of major bleeding Events" (hereafter referred to as UPRATE) study was initiated to systematically investigate the effectiveness of four-factor PCC to overcome severe bleeding in patients receiving rivaroxaban or apixaban.

Studies with PCC in Patients with Severe Bleeding

A number of cohort studies with PCC for management of activated factor X inhibitor–related bleeds have been published. In addition, there are registries of DOAC-related bleeds, including different aspects and where some patients were reported to receive PCC. An overview of these studies is provided in table 3.[53–61] Published data from the Dresden Registry on patients with DOACs only included 6 cases with PCC for major bleeding.[6] A prospective cohort from the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement—Non-Valvular Atrial Fibrillation (SAMURAI-NVAF) study included 10 cases, but only 9 of those had been on an activated factor X inhibitor.[62] These and other case series with fewer than 10 cases have not been included in the overview. The assessment of effectiveness was done with different methods, with the two UPRATE studies being the only ones that provided assessment according to the International Society on Thrombosis and Haemostasis recommendation.[63] Overall, the effect was considered poor in 6 to 35%. The duration of follow-up varied from "length of stay in hospital" to 180 days, and the thromboembolism event rate was 0 to 8%, whenever specified (crude pooled ratio, 10 of 254 = 4%). Similarly, for mortality, the crude pooled ratio was 56 of 274 = 20%. The two UPRATE studies, which were prospective cohorts with similar design and outcome assessment, will hereafter be described in more detail.

UPRATE Study

The UPRATE study included two cohorts, one in Sweden[55] and one in Canada.[56] PCC was administered according to hospital recommendations (Sweden, 1,500 IU for patients weighing less than 65 kg and 2,000 IU for those weighing 65 kg or more; Canada, 2,000 IU for all patients), with the intention of giving approximately 25 IU/kg. Patients could be treated with any approved four-factor PCC (Sweden: Ocplex; Canada: Octaplex [Octapharma, Switzerland] or Sweden: Confidex; Canada: Beriplex [CSL Behring, USA]). There were differences in data collection between the two cohorts, with respect to time of arrival in hospital, hemoglobin levels after treatment, and follow-up on progression of hematoma volume. Treatment effectiveness was assessed as "effective" or "ineffective," in accordance with the International Society on Thrombosis and Haemostasis recommendation.[63] (In Canada, this was a *post hoc* analysis; effectiveness was initially classified as "good," "moderate," or "poor," according to the Assessment Guide by Sarode *et al.*[64]).

Eighty-four patients were recruited for the Swedish UPRATE cohort, and 66 were recruited for the Canadian cohort (table 4).[55,56] Patient age was similar in the two countries (Sweden, median 75 yr; Canada, mean 77 yr) but, in Sweden *versus* Canada, the percentage of males was lower (57% *versus* 67%) and the median body weight was lower (75 kg *versus* 81 kg). Rivaroxaban was used by more than half of patients in both studies (Sweden, 54%; Canada, 56%). The most common type of hemorrhage necessitating anticoagulation reversal was intracranial bleeding (Sweden, 70% of patients; Canada, 55%), while gastrointestinal bleeding had occurred in 16% of the Swedish patients and 24% of the Canadian patients (table 5).[55,56] Tranexamic acid was added more frequently in Sweden than in Canada (67% *versus* 26% of patients).

Four-factor PCC therapy was found to be "effective" in similar percentages of patients in the two cohorts: 69% in Sweden and 68% in Canada (table 6).[55,56] The percentages of patients receiving additional erythrocyte transfusions were 24% in Sweden and 20% in Canada. Across the two cohorts, there were eight thromboembolic events (5%) within 30 days after PCC administration. No deaths were considered directly related to treatment with PCC; one death (in a patient who had an ischemic stroke 5 days after PCC administration) was assessed as possibly related to treatment with PCC (table 3).[55,56] Overall, the results from the UPRATE study support the use of four-factor-PCCs for treating severe DOAC-associated bleeding, but they should be interpreted with caution due to the absence of a control group.

Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors (ANNEXA)-4 Study

The phase III study with andexanet alfa included 352 patients with major bleeding.[27] Patients had to be within an 18-h window from the last dose of the factor Xa inhibitor and for evaluation of effectiveness, the baseline anti–factor Xa activity had to be at least 75 ng/ml. Thus, 249 patients were evaluable for effectiveness, and 171 (69%) were evaluated as excellent, 33 (13%) as good, and 45 (18%) as poor/

Table 3. Overview of Studies with PCC for Management of Major Factor Xa Inhibitor–related Bleeding*

First Author, Yr, Ref	Design	Cases Treated, No.	Xa inhibitor, No.	Bleeds Included	Follow-up, d	Effectiveness Assessment	Thromboembolic Events, No. (%)	Deaths, No. (%)
Grandhi, 2015[54]	Retrospective	18	riva (16), apix (2)	ICH	90	Effective 94%, not effective 6%	1 (6)	6 (33)
Albaladejo, 2017[53]	Prospective DOAC registry	148	riva (129), apix (19)	Mainly ICH for PCC	30	Totally 44%, partially 27%, not at all 19%	Not specified for PCC	Not specified for PCC
Majeed, 2017[55]	Prospective cohort	84	riva (45), apix (39)	International Society on Thrombosis and Haemostasis major bleeds[23]	30	International Society on Thrombosis and Haemostasis-effective† 69%, not effective 31%	2 (2)	27 (32)
Schulman, 2018[56]	Prospective cohort	66	riva (37), apix (29)	International Society on Thrombosis and Haemostasis major bleeds[23]	30	International Society on Thrombosis and Haemostasis-effective† 68%, not effective 32%	5 (8)	9 (14)
Gerner, 2018[57]	Retrospective of ICH on DOAC, N=146	94	riva (81), apix (13)	ICH	90	Effective 65%, not effective 35%	Not provided	Not specified for PCC
Testa, 2018[59]	Subset of prospective registry	20	riva (15), apix (20)	ICH (90%) and GI bleed (10%)	180	Not specified for PCC	Not specified for PCC	4 (20)
Tellor, 2018[58]	Retrospective	29	riva (18), apix (11)	90% had International Society on Thrombosis and Haemostasis major bleed[23]; 6 ICH	Variable	Not done	1 (3)	6 (21)
Harrison, 2018[60]	Subset of prospective registry	14	Not specified	ICH	Length of hospital stay	Hematoma expansion 7%	0	2 (14)
Tao, 2018[61]	Retrospective	43	riva (49), apix (51)	ICH (37%), GI bleed (40%)	14	Active bleeding despite PCC 7%	1 (2)	In hospital 2 (5)

*Only studies with at least 10 cases treated with PCC have been included. †Effectiveness assessment performed according to the ISTH recommendation.[62]

apix, Apixaban; DOAC, direct oral anticoagulant; GI, gastrointestinal; ICH, intracranial hemorrhage; ISTH, International Society on Thrombosis and Haemostasis; PCC, prothrombin complex concentrate; Ref, reference; riva, rivaroxaban.

Table 4. Baseline Characteristics in the Two UPRATE Cohorts[55,56] and in ANNEXA-4[27]

Characteristic*	Sweden	Canada	ANNEXA-4
N	84	66	352
Age, yr	75.0 ± 10.9	76.9 ± 10.4	77.4 ± 10.8
Male sex, No. (%)	48 (57)	42 (67)	187 (53)
Weight, kg, median (IQR)	75 (66–80)	81 (68–90)	Not available
Creatinine clearance, ml/min, median (IQR)	69.9 (49.6–93.0)	65.3 (51.8–87.2)	
< 30 ml/min, No. (%)	3 (4)	4 (6)	33 (9)
30 to < 60 ml/min, No. (%)	27 (32)	18 (27)	137 (39)
Indication for anticoagulation, No. (%)			
Atrial fibrillation	63 (75)	54 (82)	280 (80)
Venous thromboembolism	18 (21)	8 (13)	61 (17)
Both indications	3 (4)	2 (3)	Not available
Anticoagulant treatment			
Patients on rivaroxaban, No. (%)	45 (57)	37 (56)	128 (36)
Daily dose, mg	19.6 ± 2.3	18.6 ± 3.4	19.3 ± 4.3
Patients on apixaban, No. (%)	39	29 (44)	194 (55)
Daily dose, mg	8.8 ± 2.1	8.1 ± 2.4	7.7 ± 2.7
Concomitant antiplatelet agent, No. (%)*	10 (12)	11 (17)	Not available

Results are provided as mean ± SD unless otherwise stated. *One patient in each study was on concomitant aspirin plus clopidogrel.
IQR, interquartile range.

Table 5. Characteristics of Bleeding Events and Treatment With PCC in UPRATE[55,56] and in ANNEXA-4[27]

Characteristic*	Sweden N = 84	Canada N = 66	ANNEXA-4 N = 352
Type of bleeding, No. (%)			
Intracranial	59 (70)	36 (55)	227 (64.5)
Intraspinal	0	2 (3)	NA
Gastrointestinal	13 (16)	16 (24)	90 (25.6)
Retroperitoneal	5 (6)	3 (5)	16 (11)
Intramuscular	3 (4)	2 (3)	NA
Other	4 (5)	7 (11)	NA
Trauma-related bleed, No. (%)	26 (31)	25 (38)	99 (28)
Criteria for major bleeding, No. (%)†			NA
Critical organ	60 (71)	43 (65)	
Overt bleed, transfused ≥ 2 U	11 (13)	12 (18)	
Overt bleed, hemoglobin drop ≥ 20 g/l	17 (20)	28 (42)	
Time from onset of bleed to PCC, h	6 (2–10)	8.6 (5–18)	NA
Time from last dose DOAC to PCC, h	12.5 (9–16)	16.9 (11.9–21.2)	9.5 to 13.1‡
First dose of PCC, IU	2,000 (1,500–2,000)	2,000 (2,000–2,000)	Not applicable
First dose of PCC, IU/kg	26.7 (21.4–29.9)	25.0 (22.2–31.0)	
Second dose of PCC, No. (%)	3 (4)	2 (3)	Not applicable

*Results are provided as median (interquartile range) unless otherwise stated. †Some patients fulfilled more than one criterion. ‡Mean time from last dose to andexanet alfa for the 4 groups of Xa-inhibitors studied (edoxaban 9.5 h, apixaban 12.1 h, rivaroxaban 12.3 h, enoxaparin 13.1 h).
DOAC, direct oral anticoagulant; PCC, prothrombin complex concentrate; NA, not available.

none. The composite outcome of excellent or good was slightly better for gastrointestinal bleeding (85%) than for intracranial hemorrhage (80%). Thromboembolic complications within 30 days were observed in 10%, and 14% died within that time period. Major strengths of the study are that clinically important anti-Xa activity was demonstrated in all cases adjudicated for effectiveness and the larger number of patients than in the UPRATE studies. There were, however, more exclusion criteria in ANNEXA-4—for example, intracranial hemorrhage with a Glasgow Coma Scale score of less than 7, hematoma volume of greater than 60 ml, or estimated survival of less than 1 month.

Benefit–Risk Assessment for the Use of PCC in Anticoagulated Patients

Risk of Thromboembolic Events

Most interventions in acutely ill patients incur a degree of risk as well as expenditures, and in patients receiving anticoagulants, the essential risks are bleeding and

Table 6. Effectiveness Outcomes of DOAC Reversal Management in UPRATE[55,56]

Outcome*	Sweden (n = 84)	Canada (n = 66)
Effectiveness according to ISTH recommendation[63]		
Effective	58 (69)	45 (68)
Ineffective	26 (31)	21 (32)
Hemostatic effectiveness rating†		
Good	46 (55)	43 (65)
Moderate	13 (15)	13 (20)
Poor/None	25 (30)	10 (15)
Transfusions after PCC, patients		
Red cells (1–14 units)	18 (21)	16 (24)
Platelets (1–3 apheresis or pooled units)	10 (12)	8 (12)
Fresh frozen plasma (1–11 units)	8 (10)	4 (6)
Recombinant factor VIIa	1 (1)	0
Length of hospital stay, days, median (IQR)	7 (3–15)	16 (6–30)
Length of stay in ICU, days, median (IQR)	0.5 (0–2)	0 (0–6)

*Results are No. (%) unless otherwise stated. †Evaluated using an Assessment Guide[64] in the Swedish study by two steering committee members and in the Canadian study by the treating physician.

DOAC, direct oral anticoagulant; ICU, intensive care unit; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; PCC, prothrombin complex concentrate.

thromboembolism. In patients with nonvalvular atrial fibrillation, clots in the left atrial appendage were seen in 10% of patients, and twofold to fourfold that proportion were seen in patients who suffered a recent thromboembolic event.[65] The risk of finding these thrombi in the appendage varies from 5 to 17% as inversely correlated to the left atrial appendage flow velocity, and as seen on transesophageal echocardiography.[66] In patients with venous thrombosis, recurrence is prevalent, especially during the first 3 months, before it is resolved or becomes reorganized to a fibrotic scar. Thus, in patients only treated for 6 weeks, the 3-month recurrence rate is 7%,[67] and in patients with venous thromboembolism and cancer, the 3-month recurrence rate while on warfarin is 15%.[68]

When anticoagulant therapy is automatically held after a major bleeding event, the underlying thrombotic risk is exposed. The bleeding event may require surgical intervention and bed rest for at least a few days with ensuing risk of VTE. Furthermore, bleeding initiates hemostatic responses, including stress hormone–induced release of factor VIII and von Willebrand factor from the endothelium and elevated fibrinogen levels.[69] Platelets are also released in premature forms from bone marrow and in mature form from the spleen and lungs.[70] In addition, hemodilution by infusion of crystalloids attenuates procoagulant factors, as well as natural anticoagulants such as antithrombin, resulting in prolonged half-life of activated factor X and thrombin.[70] This can lead to disseminated intravascular coagulation,[70] whereby small clots form in the bloodstream.

To place the risk of thromboembolic events with PCC in context, a meta-analysis found that thromboembolic events occurred in 4.2% of patients who had warfarin reversed with PCC *versus* 4.8% in patients treated with fresh frozen plasma.[71] Fresh frozen plasma has not been considered a thrombogenic substance. In eight uncontrolled studies using PCC for activated factor X inhibitor–associated major bleeds, the crude pooled incidence of thromboembolic events was 5%.[72] It therefore seems likely that an intrinsic thromboembolic event rate of 4 to 5% in these specific patients has to be accepted when oral anticoagulants are reversed for major bleeding. This risk has been reported as 10% for andexanet alfa.[27]

Evaluation of Available Evidence

The benefit of PCC for management of activated factor X inhibitor–associated bleeds has been explored in animal models and healthy human volunteers, as discussed earlier in the PCC in the Reversal of Activated Factor X Inhibitors section. However, the ultimate evidence for hemostatic efficacy comes from studies in the target population—patients with major bleeding. Fully conclusive data must come from randomized controlled trials, which have not been performed so far, neither with PCC for reversal of activated factor X inhibitors, nor with the specific antidotes against any of the DOACs. When the effectiveness of reversal is evaluated in uncontrolled studies, several possible scenarios can occur. First, the efficacy of the DOAC reversal agent could be adjudicated as poor because this is truly the case or because the case was not informative. For example, this could occur with a large intracranial hemorrhage where the patient is already moribund due to brain herniation, or in active spurting gastric bleeding (rated 1A or 1B according to the Forrest classification[73]), when reversal of the anticoagulant should not be expected to have effect. Second, the efficacy could be adjudicated as good/excellent because there was no further increase in hematoma volume or drop in hemoglobin levels; however, without serial measurements before reversal, it is not known if bleeding had already stopped by the time the reversal agent was provided. It would obviously be unethical to delay reversal in patients with acute intracranial hemorrhage to obtain serial brain scans or in patients with hemodynamically unstable gastrointestinal bleeding to obtain serial hemoglobin levels. Third, the effectiveness of reversal could be rated as good/excellent because the bleeding stopped but concomitant procedures were performed (external ventricular drain, endoscopic cauterization, therapeutic embolization). These cases should be classified as nonevaluable unless it can be shown that the bleeding stopped or decreased significantly before the procedure. Fourth, the efficacy is rated as good/excellent and it was indeed observed by the treating physician that an overt bleeding ceased with PCC. Cases of this last kind have been described, but it would difficult to perform a study solely on patients with overt and observable major bleeding.

Comparison of the effectiveness of DOAC reversal agents between different studies and therapies is problematic due to variations in the inclusion and exclusion

criteria, as well as in the definition of effectiveness. The criteria for effectiveness recommended by the International Society on Thrombosis and Haemostasis was used in the two UPRATE cohorts, which showed remarkably similar results (PCC was rated as 68% and 69% "effective"), despite independent assessments.[55,56] Another way to address the question of effectiveness is to understand the mechanism of action. Specific antidotes neutralize (idarucizumab) or compete with (andexanet alfa) the anticoagulant effect of the thrombin or activated factor X inhibitor, which can be directly appreciated as a reduction or normalization of anti-Xa levels. Conversely, PCC has a more general prohemostatic effect with elevation of the vitamin K–dependent factor levels, which compensate for the impaired activation of the prothrombinase complex. Furthermore, some PCCs contain clinically significant concentrations of the anticoagulants protein C and protein S,[31] which may contribute to maintaining hemostatic equilibrium under bleeding conditions and thereby reduce the risk of thrombotic events.

Taken together, there is reason to believe that the use of 25 IU/kg PCC for management of activated factor X inhibitor–associated bleeding has a positive effect without significantly increasing the risk of thromboembolic events. To understand how PCC performs in comparison with a specific antidote, the effectiveness of PCC in the Canadian UPRATE cohort and the effectiveness of andexanet alfa in the interim report from ANNEXA-4[26] were compared in a *post hoc* analysis.[56] The assessment rules from the ANNEXA-4 study for intracranial hemorrhage were applied to a similar subset from UPRATE, and were based on change in hematoma volume and/or thickness. After treatment with andexanet alfa or PCC, the outcome was classified as excellent or good in a similar percentage of patients (80% and 76% of patients, respectively). In the full report on andexanet alfa, 171 patients with intracranial hemorrhage were evaluable for efficacy, and the excellent/good classification remained at 80%.[27]

Restarting Anticoagulant Therapy

Irrespective of the strategy used for management of bleeding, it is important to restart prophylaxis against VTE as early as possible. Mechanical prophylaxis can be provided while the patient is still bleeding except in case of lower limb injuries. Pharmacologic prophylaxis can be started 2 to 4 days after an intracranial hemorrhage.[74] Pharmacologic stroke prophylaxis for patients with atrial fibrillation unfortunately requires a longer interval due to the higher dose. For patients with additional risk factors for recurrent intracranial or other life-threatening bleeds, one should consider left atrial appendage closure.[75]

Economic Considerations for the Use of PCC *versus* Andexanet Alfa

Finally, economic considerations influencing the use of anticoagulation reversal agents should be taken into account. For the dose of PCC used in most participants of the UPRATE study (2,000 IU, *i.e.*, 26 IU/kg body weight), the price is €800 (France), US$2,540 (United States),[76] or approximately Can$1,500 (Canada). In comparison, initial pricing of andexanet alfa (Andexxa, Portola, USA) is US$3,300 for a vial of 100 mg.[77] The recommended dose based on the ANNEXA-4 study protocol is a 400-mg bolus, followed by 480 mg as a 2-h infusion (nine vials=$29,700), but for reversal of rivaroxaban, edoxaban, or enoxaparin within 7 h from last dose or unknown interval, the bolus should be 800 mg, followed by a 960-mg infusion (18 vials=$59,400).[77] Thus for reversal of activated factor X inhibitors, PCC compares favorably to andexanet alfa, at least in terms of direct costs, as well as demonstrating comparable effectiveness and a low level of thromboembolic complications when used for reversal of activated factor X inhibitors in clinical trials so far. Nevertheless, it should be kept in mind that there were differences between the ANNEXA-4 and the UPRATE studies regarding design, patient characteristics, and effectiveness assessments. Only a head-to-head comparison between andexanet alfa and PCC, as requested by U.S. Food and Drug Administration and now being initiated, can demonstrate whether there are significant differences in effectiveness and safety between the products.

Areas for Further Research

Results from the UPRATE studies provided estimates of the effectiveness of PCC in activated factor X inhibitor reversal, but further studies are needed to optimize treatment. The selection of PCC dose for DOAC reversal requires finding the optimal balance between effectiveness and thrombotic risk. It cannot be excluded that higher doses of PCC may increase the risk of thromboembolic events. A careful increase of the dose of PCC might improve the effectiveness without increased risk and is worth exploring, preferably in a randomized controlled study with two doses.

Another open question is whether PCC should be given at a fixed dose based on body weight. The fixed dose is easy to remember and was used in the Canadian UPRATE cohort with almost identical effectiveness results as in the Swedish cohort, which used a quasi–weight-based regimen (1,500 or 2,000 IU for body weight less than or more than 65.0 kg).[55] However, it should be noted that as patient body mass increases, plasma volume gets larger. Whereas the area under the curve for oral activated factor X inhibitors is minimally influenced by body mass, a larger dose of PCC would be required to achieve the same plasma level as in patients with a lower body mass. Thus, a weight-based regimen for PCC would be more in accordance with the pharmacokinetic data.[78–80]

Outcomes for bleeding patients might be improved further by use of adjunctive therapies. Use of tranexamic acid for patients with mucosal bleeding, although contraindicated for urinary tract bleeding, and desmopressin

or platelet transfusion in case of concomitant antiplatelet therapy, should be explored. This could initially be done by hypothesis-generating subgroup analyses of previous studies.

Finally, the management of nonbleeding patients on activated factor X inhibitors before emergency surgery is of particular interest. If it can be shown that PCC provides normal or almost normal hemostasis during surgery for patients with a clinically important plasma level of anti-Xa, we would obtain crucial evidence for effectiveness. The assessment of effectiveness should include the evaluation by the surgeon, blood loss volume, and postoperative complications.

Future studies of PCC and of DOAC reversal agents must include instructions regarding aggressive thromboprophylaxis. The effectiveness of these agents should be assessed according to the recommendation by International Society on Thrombosis and Haemostasis, with or without other assessment rules, to facilitate comparisons between studies.

Conclusions

Current data including recent results from the UPRATE study support the use of PCC for the reversal of activated factor X inhibitors in bleeding patients and suggest that PCC could become a useful and relatively affordable option for management of DOAC-associated bleeding. Further studies are needed to investigate the optimal dosing of PCC to maintain the balance between procoagulant effectiveness and low thrombotic risk.

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Competing Interests

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