Prothrombin Complex Concentrate for Major Bleeding on Factor Xa Inhibitors: A Prospective Cohort Study

Sam Schulman[1,2] Peter L. Gross[1] Bruce Ritchie[3] Susan Nahirniak[4] Yulia Lin[5] Lani Lieberman[6] Marc Carrier[7] Mark A. Crowther[1] Indy Ghosh[8] Alejandro Lazo-Langner[9] Michelle Zondag[10] On Behalf of the Study Investigators*

[1] Department of Medicine, McMaster University and Thrombosis and Atherosclerosis Research Institute, Hamilton, Ontario, Canada
[2] Department of Hematology, Karolinska Institutet, Stockholm, Sweden
[3] Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[4] Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, Alberta, Canada
[5] Department of Clinical Pathology, Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada
[6] Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada
[7] Department of Clinical Pathology, University Health Network, University of Toronto, Toronto, Ontario, Canada
[8] Department of Medicine, The Ottawa Hospital Research Institute at the University of Ottawa, Ottawa, Ontario, Canada
[9] Department of Emergency Medicine, Trillium Hospital, Mississauga, Ontario, Canada
[10] Department of Medicine, Western University, London, Ontario, Canada
[11] Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Address for correspondence Sam Schulman, MD, PhD, Thrombosis Service, HHS-General Hospital, 237 Barton Street East, Hamilton, ON, L8L 2X2, Canada (e-mail: schulms@mcmaster.ca).

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Abstract

Oral factor Xa inhibitors are increasingly used for anticoagulation, but there is no approved reversal agent. Prothrombin complex concentrate (PCC) for the management of Xa-inhibitor–associated bleeding has been described in small case series and one cohort study. Patients on apixaban or rivaroxaban, suffering a major bleed, were treated at nine Canadian hospitals as per existing hospital protocol with a fixed dose of PCC 2,000 units and subsequently recruited for a 30-day follow-up. The treating physician evaluated the haemostatic effectiveness as observed during the first day as good, moderate or poor/none, using an assessment guide. Safety outcomes were thromboembolism or death. We recruited 66 patients with major bleeding who were treated with PCC and who were receiving rivaroxaban (56%) or apixaban (44%). The effectiveness was assessed as good in 65% (95% confidence interval [CI], 53–77), moderate in 20% (95% CI, 10–30) and poor/none in 15% (95% CI, 6–24). For the 36 patients with intracranial haemorrhage, the corresponding ratings were 67, 17 and 17%, and for 16 patients with gastrointestinal bleeding they were 69, 12 and 19%, respectively. There were nine deaths (14%) by 30 days, and five (8%) major thromboembolic events. In a *post hoc* analysis, according to International Society on Thrombosis and Haemostasis criteria, reversal was effective in 68% and ineffective in 32%. For major bleeding associated with oral Xa inhibitors, PCC may have a beneficial effect. The risk of thromboembolism after reversal of anticoagulation in patients with a prothrombotic background has to be taken into account.

Keywords
- antagonists and inhibitors
- haemorrhage
- atrial fibrillation
- rivaroxaban
- apixaban

* *The investigators are listed in Appendix A.*

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Introduction

Major bleeding in patients treated with factor Xa inhibitors occurred at an annual rate of 1.6 to 3.6% per year in the phase III trials in atrial fibrillation.[1–3] These bleeding events were managed almost exclusively with supportive care. Despite this, the outcomes after the bleeds were better among those receiving factor Xa inhibitors than those treated with vitamin K antagonists.[4,5] Major bleeds associated with apixaban had a 50% lower mortality than those associated with warfarin.[6] Similarly, in the trials in venous thromboembolism, major bleeds associated with rivaroxaban had a less severe course than those associated with vitamin K antagonists.[7] Despite favourable outcomes after bleeding, there remains a need for rapid correction of the coagulopathy in Xa-inhibitor–treated patients in certain cases such as a major bleed in a critical organ or before emergency surgery.

Different strategies to mitigate bleeding in patients treated with factor Xa inhibitors are under investigation. A specific antidote for factor Xa inhibitors, andexanet alfa, is under development and interim results from a clinical study were recently published.[8] In a randomized trial, prothrombin complex concentrate (PCC, 25–50 unit/kg), was more effective than plasma to prevent bleeding in patients on vitamin K antagonists requiring emergency surgery.[9] PCC has also been evaluated for possible management of factor Xa-inhibitor–associated bleeds. In healthy volunteers taking twice the therapeutic dose rivaroxaban (40 mg) daily, the laboratory abnormalities (prolonged prothrombin time, reduced endogenous thrombin potential) were reversed by PCC at a dose of 50 unit/kg.[10,11] The duration of bleeding after punch biopsy was shortened in a dose-dependent manner by administration of 4 factor PCC at a dose of 50 unit/kg.[12] In a retrospective case series, 18 patients with intracranial haemorrhage occurring during treatment with rivaroxaban or apixaban received PCC at doses between 2,100 and 4,800 units. The PCC appeared safe with only 1 (5.6%) thromboembolic event.[13] A recent publication from Sweden showed that PCC was deemed effective for the management of rivaroxaban- or apixaban-associated bleeding in the majority of a cohort of 84 cases.[14]

We performed a prospective non-interventional cohort study to evaluate the use of PCC at a dose of 2,000 units for the management of factor Xa-inhibitor–associated major bleeds.

Methods

Study Design

This was a prospective observational multicentre cohort study performed at hospitals in Canada, where PCC is available through the Transfusion Medicine Departments and where a hospital protocol suggests or recommends the use of this concentrate at a standardized dose of 2,000 units for reversal of factor Xa-inhibitor–associated bleeding. Two PCCs are available in Canada; Beriplex (CSL Behring, Pennsylvania, United States) and Octaplex (Octapharma, Lachen, Switzerland), both 4-factor concentrates (containing factor II, VII, IX, and X). Blood transfusion laboratories may stock one or both products and dispense whichever is available without respect to the product that is ordered; over the course of this study, approximately 90% of the PCC used in Canada was Octaplex.

The investigators designed and conducted the study, analysed the results and wrote the article. The study was funded by an unrestricted grant from Octapharma Canada (Toronto, ON, Canada), which had no influence on any parts of the study or the writing of the article. The institutional review boards at each participating centre approved the protocol. All patients or their substitute decision makers provided standard consent for transfusion of blood products before receiving PCC. After the PCC had been given as part of hospital protocol, the patient or next of kin provided specific consent for participation in the study with collection of data and 30-day follow-up. An independent data and safety monitoring board reviewed the safety outcomes (thromboembolism and death) twice during the study and had the mandate to recommend premature discontinuation based on stipulated stopping rules according to the number of major thromboembolic events. The study was coordinated by Thrombosis Service, Hamilton Health Sciences—General Hospital. Since the study was classified as non-interventional, no approval was required from Health Canada.

Study Patients

Patients were eligible for inclusion if (1) they had received infusion per local hospital protocol with PCC (2,000 units), for major bleeding, while on treatment with rivaroxaban or apixaban (edoxaban was not approved in Canada when this study was performed); (2) they had not received other haemostatic agents, including plasma, platelets, activated PCC or recombinant factor VIIa (antifibrinolytic drugs and local haemostatic agents were allowed) prior to administration of PCC and (3) written informed consent had been provided. Major bleeding was defined as recommended by the International Society on Thrombosis and Haemostasis.[15] Exclusion criteria were (1) 'Do not resuscitate' (DNR) orders already given before the treatment with PCC due to the severity of the bleed, (2) drop of haemoglobin without evidence of a source of bleeding or (3) acute coronary syndrome or ischaemic stroke during the past 30 days.

Study Procedures

The Transfusion Medicine service at the different institutions kept and provided the PCC on request by the treating physician in the emergency department or on the ward. According to hospital policy, the order to infuse the concentrate had to be approved either by the physician on call for Transfusion Medicine or for Thrombosis. Any of these physicians could notify the study team that PCC had been given for reversal of rivaroxaban or apixaban. A research assistant or research nurse subsequently obtained informed consent and collected the data from electronic medical records, paper charts, patient, family members and the treating physician—usually from the emergency department. Even if the patient had passed away after receiving the PCC but before study

staff approached, we included the case by obtaining consent from next of kin.

Data regarding the patient, factor Xa inhibitor medication and concomitant drugs that could have influenced the bleeding, the bleeding episode and its related treatment as well as renal function, coagulation tests and haemoglobin levels were captured. The study staff approached the treating physician within 7 days from the event for assessment of haemostatic effectiveness of the treatment with PCC at 24 hours. For this assessment, the treating physician was provided with all haemoglobin results, transfusions, reports from invasive procedures, and from imaging diagnostics, as well as an assessment guide (►**Table 1**). This guide contained criteria for rating the effect as good, moderate or poor/none for four different types of bleeding: (1) visible bleeding, (2) musculoskeletal bleeding, (3) intracranial bleeding and (4) other nonvisible bleeding. Our guide was the one used by Sarode et al;[16] except for the rating of intracranial bleeding we added a change in objective neurological signs to the haematoma volume criterion, as this was an observational study without possibility to mandate repeat diagnostic imaging. We also renamed the first two rating categories from excellent to good and from good to moderate because 'excellent' gives an overly optimistic impression of the result. Intracerebral haematoma volume was calculated from CT scans or MRI scans performed as part of routine clinical practice using the $4/3\,\pi\,abc$ formula, where *a, b* and *c* are the diameters of the three dimensions of the haematoma.[17]

Follow-up

The study team performed the final follow-up at 30 ± 2 days after the treatment with PCC, capturing information from medical records and from the patient on the hospitalization, transfusions, lowest haemoglobin level, invasive procedures, diagnostic imaging, current health status, thromboembolic events and serious adverse events. The same information was captured for patients who had passed away.

Outcome Measures

The primary outcome was the proportion of patients with good effectiveness of PCC as assessed by the emergency physician or most responsible physician, using the assessment guide. Secondary outcomes were other blood products used, decrease in haemoglobin from the first reported level on admission to the lowest level after application of PCC and the length of stay in intensive care unit as well as in hospital. The principal safety outcome was thromboembolic events (symptomatic DVT or pulmonary embolism, ischaemic stroke, heart valve or cardiac chamber thrombosis, symptomatic peripheral arterial thrombosis or myocardial infarction) within 7 days from the application of PCC. The secondary safety outcome was the 30-day event rate of thromboembolic events. In addition, deaths were recorded. The safety outcomes were evaluated by an event adjudication committee consisting of two independent members, who also classified deaths as related to the index bleeding event, to a subsequent bleeding event, to thromboembolism or to none of those. Discrepancies were resolved by consensus.

Statistical Analysis

The initially planned convenience sample size was of 35 patients, which was estimated taking into account the number of available study sites and the intention to achieve results within 2 years. After the addition of four more study sites in 2016, the recruitment rate increased and it was feasible to expand the sample size to approximately 60 patients. Results are reported as means (± standard deviation [SD]) or, in case of skewed distribution, as median and interquartile range (IQR) as appropriate. Comparisons between groups were performed with Mann–Whitney *U*-test.

Results

Between July 2014 and July 2017, a total of 71 consecutive patients were screened at nine sites in Canada, with 4 of those joining only at the end of the study period. Five of the screened patients were not eligible as criteria for major bleeding were not fulfilled (►**Fig. 1**). In ►**Table 2**, the characteristics of the 66 included patients and the antithrombotic treatment are summarized. Sixty-two patients (94%) were seen in the emergency department for the haemorrhage, whereas the remaining 4 had already been hospitalized when the bleeding started. In addition to the antithrombotic medication listed in ►**Table 2**, one patient was receiving rivaroxaban, aspirin and one dose of dalteparin, 5,000 IU, due to suspected myocardial infarction, and one patient was mistakenly taking both rivaroxaban and warfarin (international normalized ratio [INR] on admission: 7.2).

The qualifying bleeding events are described in ►**Table 3**. The intracranial bleeds consisted of 18 intracerebral, 7 subdural, 4 subarachnoid haemorrhages and 7 with combinations thereof. Of the intracerebral haematomas, 11 (48%) had a volume of less than 10 mL, 6 (26%) had a volume of 11 to 44 mL, 5 (22%) had a volume of greater than 44 mL, and 1 (4%) had intraventricular breakthrough. Six (54%) of the subdural haematomas had a maximal thickness of less than 10 mm and the remaining five had a thickness of 13 to 25 mm.

The gastrointestinal bleeds originated from the upper tract in seven cases, the lower tract in six and had an unknown localization in three. The baseline haemoglobin was less than 10 g/dL in 12 of these 16 patients (75%) and 8 of 16 (50%) had received ≥2 units of red cells before PCC infusion. One patient with traumatic pelvic fractures and with haematuria had also received red cell transfusions before the infusion with PCC.

Tranexamic acid, 1,000 mg, was given to 17 patients before or at the time of PCC for intracranial bleeding ($n = 11$), gastrointestinal bleeding ($n = 3$) or other types of bleeding ($n = 3$).

On arrival to the hospital or at the time of the bleed for the inpatients, the INR was available for 62 patients, the prothrombin time was available for 18 of those and for 2 additional patients, and a drug-specific anti-factor Xa level was available for 11 of those with INR, whereas 2 patients had no coagulation tests performed. A prolonged prothrombin time and/or INR above 1.2 and/or anti-Xa level indicating

Table 1 Effectiveness assessment guide, modified from Sarode et al[16]

Rating	Visible bleeding	Non-visible bleeding
Good	Cessation of bleeding ≤1 h after the end of infusion and no additional coagulation intervention required	**1.** Musculoskeletal bleeding: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤1 h after the end of infusion; and the condition has not deteriorated during and after 24 h **2.** ICH: ≤20% increase in haematoma volume compared with baseline on repeat CT scan performed and/or any neurological improvement noted over the following 12 h or—if the patient was progressively deteriorating until the treatment with FEIBA—even a stabilization of the condition **3.** Non-visible bleeding that is not described above (e.g. GI bleeding): ≤10% decrease in both Hb/Hct at 24 h compared with baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤80 ± 1 g/L [i.e. transfuse PRBCs if the Hb ≤80 ± 1 g/L])
Moderate	Cessation of bleeding >1 and ≤4 h after end of infusion and no additional coagulation intervention required	**1.** Musculoskeletal bleeding: pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤4 h after the end of infusion; and the condition has not deteriorated during and after 24 h **2.** ICH: >20%, but ≤35% increase in haematoma volume compared with baseline on a repeat CT scan performed and/or minimal deterioration of neurological condition **3.** Non-visible bleeding that is not described above: >10 to ≤20% decrease in both Hb/Hct at 24 h compared with baseline (initial correction of decrease in Hb with PRBCs, with a transfusion trigger of a Hb ≤80 ± 1 g/L [i.e. transfuse PRBCs if the Hb ≤80 ± 1 g/L])
Poor/None	Cessation of bleeding >4 h after the end of the infusion, and/or additional coagulation intervention required (plasma, whole blood or coagulation factors)	**1.** Musculoskeletal bleeding: no improvement by 4 h after the end of infusion and/or the condition has deteriorated during the 24-h period **2.** ICH: >35% increase in haematoma volume compared with baseline on repeat CT scan performed at the 24-h time point and/or clear deterioration of the condition or death. **3.** Non-visible bleeding that is not listed above: >20% decrease in both Hb/Hct at 24 h compared with baseline (initial correction of decrease in haemoglobin with PRBCs, with a transfusion trigger of a Hb ≤80 ± 1 g/L [i.e. transfuse PRBCs if the Hb ≤80 ± 1 g/L])

Abbreviations: CT, computed tomography; GI, gastrointestinal; ICH, intracranial haemorrhage; PRBCs, packed red blood cells.

the presence of drug (>50 ng/mL) were observed in 33 (50%) of the 66 patients. Nineteen patients on apixaban had normal INR and prothrombin time, but anti-factor Xa, performed in only one of those patients, indicated very high level of drug (1,130 ng/mL). Seventeen patients on rivaroxaban had normal INR and prothrombin time, but anti-factor Xa testing performed in two of them indicated the presence of drug (66–76 ng/mL).

The dose of PCC deviated from the 2,000 U recommended by the hospital protocols for 12 (18%) patients. Two patients received 1,000 U, three received 1,500 U, one received 2,500 U, four received 3,000 U, one received 3,500 U, and one received 4,200 U (= 50 U/kg).

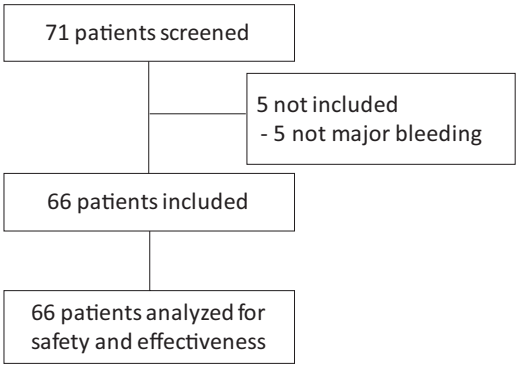

Fig. 1 Study flow.

Anticoagulation was restarted within the 30-day study period in 41 patients (62%) at a median of 5 days (IQR: 2–11.5 days) with low-molecular-weight heparin ($n = 16$), unfractionated heparin ($n = 5$), apixaban ($n = 12$), rivaroxaban ($n = 6$), dabigatran ($n = 1$), or warfarin ($n = 1$).

Haemostatic Effectiveness

The effectiveness of the treatment with PCC on haemostasis was assessed by the treating physician as good for 43 (65%; 95% confidence interval [CI], 53–77), moderate for 13 (20%; 95% CI, 10–30) and poor/none for 10 (15%; 95% CI, 6–24) patients (►**Table 4**), without any significant difference between patients on apixaban versus rivaroxaban. For patients with intracranial haemorrhage, the corresponding assessments were 24 (67%), 6 (17%) and 6 (17%). For patients with gastrointestinal bleeding, the corresponding assessments were 11 (69%), 2 (12%) and 3 (19%). Despite the initial rating of effectiveness as good for 26 patients with intracranial or intraspinal haemorrhage, at the end of the 30-day follow-up, 58% of those had residual neurological deficit or cognitive impairment. For all 38 patients with intracranial or intraspinal bleeding, comparing those with normal

Table 2 Characteristics of the patients and antithrombotic treatment

Characteristic	($n = 66$)
Age, y	76.9 (10.4)
Male sex, no. (%)	42 (67)
Weight, kg, median (IQR)	81 (68–90)
Creatinine clearance, mL/min, median (IQR)	65.3 (51.8–87.2)
< 30 mL/min, no. (%)	4 (6)
30 to <60 mL/min, no. (%)	18 (27)
Indication for anticoagulation, no. (%)[a]	
Atrial fibrillation	54 (82)
Venous thromboembolism	8 (13)
Both indications	2 (3)
Ischaemic stroke	1 (2)
Anticoagulant treatment	
Patients on rivaroxaban, no. (%)	37 (56)
Daily dose, mg, median (IQR)	20 (15–20)
Time from last dose to PCC, h	18.1 (10.3)
Patients on apixaban, no. (%)	29 (44)
Daily dose, mg, median (IQR)	10 (5–10)
Time from last dose to PCC, h	17.8 (9.3)

Abbreviations: IQR, interquartile range; PCC, prothrombin complex concentrate.
Note: Results are mean (standard deviation) unless otherwise stated.
[a]For one patient, the indication was unknown.

Table 3 Characteristics of the bleeding event and its treatment

Characteristic	($n = 66$)
Type of bleeding	
Intracranial	36 (55)
Intraspinal	2 (3)
Gastrointestinal	16 (24)
Retroperitoneal	3 (5)
Intramuscular	2 (3)
Other[a]	7 (11)
Trauma-related bleed	25 (38)
Criteria for major bleeding[b]	
Critical organ	43 (65)
Overt bleed, transfused ≥2 U	12 (18)
Overt bleed, haemoglobin drop ≥20 g/L	28 (42)
Treatment with PCC	
Time from onset of bleed to PCC, h, median (IQR)	8.6 (4.8–18.1)
Time from arrival to PCC, h, median (IQR)[c]	5.4 (3.3–7.8)
First dose of PCC, IU, mean (SD)	2,072 (464)
First dose in IU/kg, mean (SD)	26.4 (7.7)

Abbreviations: IQR, interquartile range; PCC, prothrombin complex concentrate; SD, standard deviation.
Note: Results are *n* (%) unless otherwise stated.
[a]The other qualifying bleeds were one each of intraabdominal, pelvic, vaginal, haematuria, haemothorax, chest stab wounds, carotid artery injury.
[b]Some cases fulfilled more than one criterion.
[c]Four patients were already admitted for another reason when the bleeding started and are not included here.

neurological function versus those with any residual deficit by the end of the 30-day follow-up, there were no significant differences regarding median duration from onset of bleeding, from last dose of Xa inhibitor or from arrival to emergency department to the reversal with PCC. Although those with normal neurological function compared with those with impairment had numerically smaller thickness of the subdural haematoma (median: 7.5 vs. 11 mm) or smaller volume of intracerebral haematoma (median: 11 vs. 29.3 mL), this did not reach statistical significance. Likewise, there was no significant association between interval from onset of bleeding, from last dose of Xa inhibitor or from arrival to emergency department to PCC infusion and the effectiveness outcome (►**Table 5**). The only exception was the shorter interval between arrival and first-dose PCC for patients with poor compared with those with good effectiveness.

Two patients required a second dose of PCC. An additional dose of PCC, 1,000 U, was given 1 day after the first dose to the patient that took warfarin together with rivaroxaban, as the INR was 2.7 (baseline INR: 7.2). A second dose of 2,000 U was given as a last effort to a patient with large intracerebral, subdural and subarachnoid haemorrhage after the second CT scan showed further expansion. Thirteen patients required additional red cell transfusions (1–8 units) for the index bleed, 9 of which were from the gastrointestinal tract. Six patients received red cell transfusions (1–4 units) 7 to 25 days after the index bleed for recurrent bleeding events (gastrointestinal—2, haematuria—1), for anaemia (subdural haematoma—2), or for surgery ($n = 1$). Five of those events were after antithrombotic treatment had been restarted. Additional drops in haemoglobin after treatment with PCC, invasive procedures required by the bleeding event, length of stay and discharge destinations are summarized in ►**Table 4**.

Post Hoc Analyses

In a *post hoc* analysis of effectiveness in the 33 patients with prolonged prothrombin time or elevated INR or anti-factor Xa at baseline, the assessments were good in 22 (67%), moderate in 7 (21%) and poor/none in 4 (12%). The corresponding ratings were separately for apixaban 10 (91%), 1 (9%) and 0, and for rivaroxaban 12 (55%), 6 (27%) and 4 (18%).

In another *post hoc* analysis, we rated the patients according to the original assessment guide by Sarode et al,[16] so that instead of the neurological status assessed by the treating physician for patients with intracranial haemorrhage, we compared the volume of the haematoma (for subdural, subarachnoid or intraspinal haematoma, the thickness) between the diagnostic imaging performed before the

Table 4 Outcomes of the reversal management

Outcome	($n = 66$)
Haemostatic effectiveness rating[a]	
Good	43 (65)
Moderate	13 (20)
Poor/None	10 (15)
Transfusions after PCC for the index bleed, patients	
Second-dose PCC (1,000 U and 2,000 U)	2 (3)
Red cells (1–8 U)[b]	13 (20)
Platelets (1–3 apheresis or pooled units)	8 (12)
Cryoprecipitate	1 (2)
Drop in haemoglobin after PCC, g/L, median (IQR)	18 (3–34)
Invasive procedures performed	10 (29)
Evacuation of intracranial haematoma	8
Coiling of intracranial aneurysm	2
Endo-/colonoscopy with cauterization	5
Chest tube for haematoma evacuation	2
Laparotomy for dissecting aneurysm repair	2
Pericardial window	1
Cystoscopy for clot evacuation	1
Embolization for lower gastrointestinal bleed	1
Length of hospital stay, d, median (IQR)	16 (5.3–30)[c]
Length of stay in ICU, d, median (IQR)	0 (0–6)[c]
Final known discharge destination (actual or planned)	
Home	27 (41)
Institution with increased assistance	18 (27)
Unknown because still hospitalized	12 (18)
Death	9 (14)
Thromboembolism day 0–7 (primary safety outcome)	2 (3)
Thromboembolism day 8–30 (secondary safety outcome)	3 (5)[d]

Abbreviations: IQR, interquartile range; ICU, intensive care unit; PCC, prothrombin complex concentrate.
Note: Results are *n* (%) unless otherwise stated.
[a]Evaluated by the treating physician using an assessment guide.
[b]Three of these 13 patients and 3 additional patients received 1–4 red cell units 8–21 days after the PCC treatment for new bleeds.
[c]Seventeen patients were still in the hospital and 4 patients were still in ICU by the end of the 30-day follow-up.
[d]In addition, there was one late minor event, a thrombophlebitis in the cephalic vein.

reversal and on the first occasion after that. An increase of $\leq$20% is rated, according to Sarode et al,[16] as excellent, >20 to $\leq$35% as good and >35% as poor/none. Thirty of 38 patients had a follow-up scan and we also included three without repeat scan, and who had large bleeds resulting in death, with rating as poor/none. Thus, based on comparison with the second scan, performed after a median of 15 hours (which is close to the time point recommended by Sarode et al[16]), we identified 24 cases as excellent, 1 as good and 8 as poor/none. A comparison of these results with those based on the same rating system in other studies is presented in ►**Table 6**.

Table 5 Delays from onset of bleeding, from last dose of anticoagulant, or from arrival to reversal and effectiveness ratings

Delay from	Good h, median (IQR)	Moderate h, median (IQR)	Poor/None h, median (IQR)
Onset of bleed	12 (6–26)	11 (5–18)	4 (2–25)
Last dose[a]	18 (11–26)	17 (12–21)	15 (11–18)
Arrival in ED[b]	6.1 (3.9–12.4)[c]	5.4 (4.4–6.3)	3.4 (2.0–5.0)[c]

Abbreviations: ED, emergency department; IQR, interquartile range.
Note: Difference between medians is significant (Mann–Whitney, $p = 0.03$).
[a]Time of last dose of rivaroxaban/apixaban was unknown for six cases.
[b]Not applicable for four patients who were already admitted.
[c]Difference between this pair of medians is significant (Mann–Whitney, $p = 0.03$).

In a third *post hoc* analysis, we evaluated the effectiveness of reversal according to the recommendation by ISTH from 2016,[18] which specifies separate criteria for non-visible bleeding, visible bleeding, musculoskeletal bleeding and intracranial bleeding and uses a binary classification. For the 66 cases, the outcome of reversal was classified as effective in 45 (68%) and ineffective in 21 (32%). Three patients with gastrointestinal bleeding and effectiveness graded as moderate or poor in the primary assessment by the treating physician were assessed as effective according to the ISTH definition, because endoscopy within hours after PCC showed that the bleeding had stopped ($n = 2$) or that there was no further drop in haemoglobin and no additional transfusion ($n = 1$).

Safety

There were six centrally confirmed thromboembolic events, of which five were major (three ischaemic strokes, one peripheral arterial occlusion, one venous thromboembolism) and the remaining one was a superficial thrombophlebitis. The five major events were diagnosed 1, 2, 9, 12 and 22 days after PCC and the thrombophlebitis 22 days after PCC. The four events between days 1 and 12 occurred before resumption of anticoagulation.

Nine patients died (14%), eight with intracranial haemorrhage as index event, corresponding to 22% of the intracranial bleeds. Seven of the deaths were adjudicated as 'a result of the index (intracranial) bleeding event'. The ninth death was in a patient with self-inflicted stab wounds to the chest. There were eight additional serious adverse events, all among patients with initial intracranial bleeding; six with prolonged hospitalization due to extracranial bleeding (gastrointestinal—

Table 6 Comparison with other studies on management of anticoagulant-associated bleeds

Study (Ref.) Characteristic or outcome	Sarode et al[16] ($N = 104$)	Sarode et al[16] ($N = 98$)	ANNEXA-4[8] ($N = 67$)	Majeed et al[14] ($N = 84$)	This study ($N = 66$)
Anticoagulant	Warfarin	Warfarin	Xa inhibitors	Xa inhibitors	Xa inhibitors
Reversal agent	Plasma	PCC	Andexanet alfa	PCC	PCC
Exclusion for poor prognosis	Expected survival <3 d	Expected survival <3 d	Expected survival <1 mo	DNR order given	DNR order given
Age, mean (SD)	69.8 (13.9)	69.8 (12.8)	77.1 (10.0)	75 (10.9)	76.9 (10.4)
Male sex	51 (49)	50 (51)	35 (52)	48 (57)	42 (67)
ICH	12 (12)	12 (12)	28 (42)	59 (70)	36 (55)
GI bleed	64 (62)	63 (64)	33 (49)	13 (16)	16 (24)
Time last dose Xa inhibitor to PCC, median (IQR)	N.A.	N.A.	(Mean ± SD) R: 12.8 ± 4.2 A: 12.1 ± 4.7	12.5 (9–16)	16.9 (12–21)
Effectiveness assessment according to Sarode et al[16] for CNS bleeds					
Excellent or Good[a]	7 (58)	5 (42)	16 (80)	Not done	25 (76)[b]
Effectiveness assessment according to ISTH criteria[18] for CNS bleeds					
Effective[a]	Not done	Not done	Not done	43 (73)	25 (69)
Safety outcomes during 30 d					
Thromboembolism	7 (6)	8 (8)	12 (18)	3 (4)	5 (8)
Death	5 (5)	6 (6)	10 (15)	27 (32)	9 (14)

Abbreviations: A, apixaban; CNS, central nervous system; DNR, do not resuscitate; GI, gastrointestinal; ICH, intracranial haemorrhage; IQR, interquartile range; ISTH, International Society on Thrombosis and Haemostasis; N.A., not applicable; PCC, prothrombin complex concentrate; R, rivaroxaban; SD, standard deviation.

Note: Results are *n* (%) unless otherwise noted.

[a]The remainder of the patients in the effectiveness assessments were assessed as poor/none (Sarode et al) and ineffective (ISTH), respectively.

[b]Only patients with repeat computed tomography ($n = 30$) or with large CNS bleeds resulting in early death ($n = 3$, outcome poor/none) are included in this analysis.

1; gross haematuria—2), and one patient each with cellulitis, infection + hypernatremia + delirium, neurological deterioration due to expansion of previously evacuated subdural haematoma; and two with re-hospitalizations for gastrointestinal bleeding.

Discussion

In this non-interventional cohort study with prospective follow-up, we investigated the use of PCC at a dose of 2,000 units for the management of major bleeding in association with oral anti-factor Xa inhibitors. This is of interest in view of the recent publication of interim data from the 'Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors' (ANNEXA-4) study,[8] which evaluated a class-specific antidote, andexanet alfa that has not yet been approved. PCC is available in many hospitals for reversal of anticoagulation with vitamin K antagonists. The relatively low dose of 2,000 units corresponds to 25 unit/kg for a person weighing 80 kg, and in an ex vivo study, this concentration of PCC corrected the rivaroxaban-induced decrease of area under the curve for the endogenous thrombin potential.[19] However, in a randomized study in healthy volunteers receiving twice the therapeutic dose of rivaroxaban, a dose of PCC 50 unit/kg normalized the endogenous thrombin potential.[11] It can be reasoned that heavier patients will have a lower plasma concentration of rivaroxaban, as it is given at a fixed dose, and therefore a relatively lower plasma concentration of PCC might suffice and vice versa for leaner patients. Our assumption could be wrong, as in pharmacokinetic studies the area under the curve (AUC) was unaffected by body weight in healthy volunteers taking rivaroxaban,[20] the volume of distribution was moderately influenced by weight in patients on rivaroxaban,[21] a mean increase of body weight of 83% resulted in only a 23% decrease of the AUC in volunteers taking apixaban[22] and only the non-renal clearance was significantly affected in patients on edoxaban.[23] Furthermore, a study in human volunteers given rivaroxaban 15 mg twice daily showed that PCC at 37.5 or 50 unit/kg partially reversed the depressed endogenous thrombin potential, but 25 unit/kg did not.[24] Therefore, a future study should compare two doses, for example 25 with 50 unit/kg. We had chosen a fixed dose of PCC for simplicity, but that might not be adequate for all patients.

Our study illustrates several of the problems with reversal in clinical practice. The door-to-PCC delay—5.4 hours in this study—is too long, especially for intracerebral haemorrhages

(5.0 hours) but similar to what has been reported in clinical practice for reversal of warfarin-associated intracerebral bleeds—4.5 hours.[25] We also noted that despite knowing that the anticoagulant was an oral factor Xa inhibitor and having specific anti-Xa tests available at the participating hospitals, this test was only done in a small proportion of patients (17%). It might be a widespread misconception that prothrombin time or INR are informative in this setting. Anti-Xa levels, on the other hand, will likely reflect trough levels in a substantial proportion of patients admitted with a bleed 12 to 18 hours after the last dose of apixaban or rivaroxaban. This could imply that reversal with a specific antidote like andexanet alfa is not required. However, if PCC has a mechanism of action that is not an elimination of the anticoagulant activity but rather a general haemostatic effect on current bleeding, it might still be of benefit. Nevertheless, there are cases where haemostatic agents will not have effect, for example intracranial haemorrhage where detrimental organ damage already has occurred, haemorrhagic shock with multiorgan failure or arterial bleeding.

The recommended classification of outcomes of reversal according to ISTH was published in 2016, toward the end of recruitment of the cases in this study. The criteria and the binary outcome classification differ from what has been used in other publications on reversal of anticoagulants, with one recent exception.[14] The *post hoc* analysis results presented here therefore are mainly intended for future comparisons.

Our results of effectiveness with 15% assessed as poor/none are similar to the 21% in the ANNEXA-4 study[8] and 27.6% with PCC for warfarin reversal.[16] The other two categories in our study, good (65%) and moderate (20%), were similar to the rates seen in the ANNEXA-4 study, where they were rated as excellent (66%) and good (13%).[8] The three-category assessment guides in both studies were, however, based on the principles used by Sarode et al in the trial comparing PCC with plasma for warfarin-associated bleeding.[16] We had renamed the first two categories already in the initial protocol, because we felt that the term excellent gave an overly optimistic impression of the result. Indeed, 58% of our patients with central nervous system haemorrhage and top rating for effectiveness still had neurological deficits at 30 days.

The patients in both our study and the ANNEXA-4 trial had to qualify for inclusion with a major bleed according to similar criteria. Although we had DNR order as an exclusion criterion, there was no such case because whenever DNR was ordered, it happened after recruitment. We did not have restrictions for inclusion based on intracerebral haematoma volume or Glasgow coma scale score.

There were additional differences between the two studies. Due to the non-interventional design, we could not mandate testing for drug levels or repeat diagnostic imaging at specific time points. The patients in our study had a longer interval between the last doses of rivaroxaban or apixaban and the treatment with PCC (18.1 and 17.8 hours, respectively) than in the ANNEXA-4 study (12.0 and 11.0 hours, respectively, in the efficacy population).[8] Accordingly, elevated INR levels or prolonged prothrombin times (albeit not very sensitive methods for this purpose) or elevated anti-Xa levels were observed only in 50% of the patients in our study. This does not mean that all the remaining patients did not have clinically important levels of drug in circulation, as anti-Xa levels were done only in 11 patients. In fact, in our *post hoc* analysis of patients with laboratory tests indicating that circulating levels of rivaroxaban or apixaban were present, the effectiveness was similar to that for the entire study population.

The similar effectiveness results in our study and in ANNEXA-4 could, if true, be because both methods are effective or alternatively because reversal has minimal or no effect on the outcome. The latter could, in turn, be due to too late administration (intracranial haemorrhage—the damage is already done) or that the anticoagulation effect is rapidly vanishing with the short half-life of the Xa inhibitors.

Safety outcomes in different reversal studies are compared in ►**Table 6**. Resumption of prophylactic or therapeutic anticoagulation occurred after a median of 5 days in 62% of our patients versus 27% in ANNEXA-4.[8] It is unclear if this reflects a lesser concern for recurrent bleeding among Canadian physicians than among colleagues in other countries.

A recent Swedish cohort study with 84 patients with Xa-inhibitor–associated major bleeds, treated with 25 U/kg of PCC, showed very similar results to our study[14] (►**Table 6**).

A limitation of our study is that patients were recruited after treatment with PCC had been provided, and the decision of the responsible physician whether to treat resulted in selection bias with the worst cases possibly excluded. Conversely, desperate cases could be more likely to receive PCC as a last resort. The study design also precluded the possibility to mandate testing for anti-factor Xa levels, but our *post hoc* analysis of the patients with coagulation parameters demonstrating some degree of anticoagulant effect showed similar results for effectiveness. Third, we did not have a control group, similar to the design of the studies with andexanet alfa and idarucizumab,[8,26] and it is therefore impossible to know if the reversal with any of these agents made a difference of clinical importance. Fourth, we cannot say if 2,000 units PCC is the optimal dose or if a higher dose could have improved the outcome, for example with fewer neurological deficits after intracranial haemorrhage. Finally, the method we used for the assessment of effectiveness, relying on the treating physician, can be criticized as subjective. We tried to minimize this effect by asking the physician to follow the assessment guide, which includes objective parameters. Conversely, this method could be considered a strength, as the first-hand observations of clinical effect in combination with results of repeat diagnostic imaging, haemoglobin levels and transfusions might be more valuable than the decisions by an off-site event adjudication committee.

Conclusion

Management of oral factor Xa-inhibitor–associated major bleeding using PCC to achieve initial haemostasis was assessed by the treating physician as good in 65% of the cases, with 67% for intracranial and 69% for gastrointestinal bleeding. For

another 20% of the cases, it was assessed as moderate. Despite these ratings, patients still had significant morbidity and mortality, mainly after intracranial bleeding on anticoagulation. The risk of thromboembolism after reversal must be remembered and anticoagulation with at least a prophylactic dose should be started when bleeding has been controlled.

What is known about this topic?

- There is no approved reversal agent for factor Xa inhibitors.
- Prothrombin complex concentrate reverses Xa-inhibitor–associated bleeding in some animal models.
- One published prospective cohort study showed promising results for the utility of PCC for mitigating bleeding in factor Xa-inhibitor–treated patients.

What does this paper add?

- This prospective cohort of 66 patients had effectiveness of PCC for Xa inhibitor reversal assessed by the treating physician.
- The effectiveness in major bleeding control was assessed as good in 65%, moderate in 20% and poor in 15%.
- There were five (8%) major thromboembolic events during 30 days after PCC use.

Authors' Contribution

S. Schulman, B. Ritchie and M. Carrier conceived and designed the study; S. Schulman analysed and interpreted the data; all authors provided study patients, collected data, wrote and gave final approval of the manuscript.

Conflict of Interests

Dr. Schulman has received grant support/honoraria from Boehringer Ingelheim, Octapharma, Baxter, Bayer, Sanofi and Bristol-Myers-Squibb; Dr. Carrier has received grant support/honoraria from Bristol-Myers-Squibb, Leo Pharma, Boehringer Ingelheim, Pfizer and Bayer; Dr. Gross has received speaker honoraria from Bayer, Pfizer and Bristol Myers Squibb and has intellectual property on a method to test direct oral anticoagulants; Dr. Lin has received grant support from Novartis; consulting fees from Boehringer Ingelheim, Genzyme, Pfizer; unrestricted educational grants from CSL Behring, Grifols; Dr. Lieberman has received grant support from CSL Behring and honoraria from Grifols; Dr. Crowther is on the Board of Directors or on an advisory committee for CSL Behring, Asahi Kasei Pharma America, Bayer, Boehringer Ingelheim, LEO Pharma, Octapharma, Pfizer and Portola Pharmaceuticals; has consulted for CSL Behring, Alexion Pharmaceuticals, Bayer AG, LEO Pharma, Octapharma, Pfizer and Portola Pharmaceuticals; has received honoraria from Ortho Clinical Diagnostics, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Celgene, Daiichi Sankyo, LEO Pharma and Pfizer; and has been affiliated with the Speaker's Bureau for CSL Behring, Alexion, Bayer and Leo Pharma. Dr. Lazo-Langner has received honoraria from Pfizer and Bayer and grant support from Pfizer, Bayer and Alexion. The other authors report no conflict of interest.

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Appendix A: Committee Members and Study Investigators

Steering Committee: S. Schulman (chair), M. Carrier, P. L. Gross, S. Nahirniak, B. Ritchie, Y. Lin, L. Lieberman, M. Crowther, I. Ghosh, A. Lazo-Langner.

Data Safety Monitoring Board: D. Garcia, R. Roberts (statistician).

Independent Event Adjudication Committee: Clive Kearon, Menaka Pai.

Study Coordinator: M. Zondag.

Investigators: *Hamilton General Hospital*: S. Schulman, M. Zondag, N. Bedek. *Juravinski Hospital*: P. Gross, P. Stevens, S. Dodds. *University of Alberta Hospital*: B. Ritchie, S. Nahirniak, H. Blain, A. Ramell, J. Skripitsky, A. Strilchuk. *Sunnybrook Health Sciences Centre:* Y. Lin, J. Callum, C. Armali. *University Health Network:* L. Lieberman, C. Cserti-Gazdewich, J. Pendergrast, N. Parmar. *The Ottawa Hospital*: M. Carrier, A. Giulivi, E. Saidenberg, A.M. Clement, M. Tokessy, N. Cober, S. Reddie. *St. Joseph's Healthcare*: M. Crowther, D. Siegal, A. Glushchenko. *Trillium Hospital*: I. Ghosh, S. Futers. *London Health Sciences Center*: A. Lazo-Langner, L. Pallaveshi.