SYSTEMATIC REVIEW

blood advances

Management of direct factor Xa inhibitor–related major bleeding with prothrombin complex concentrate: a meta-analysis

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A targeted antidote for reversal of direct factor Xa (FXa) inhibitors is now available for clinical use in the United States, but it is costly and has limited availability. In a systematic review, we evaluated the safety and effectiveness of 4-factor prothrombin complex concentrate (4F-PCC) as an alternative for managing direct FXa inhibitor–related major bleeding. A systematic literature search was conducted using Medline, Embase, and the Cochrane Register of Controlled Trials up to September 2018. No comparative studies were found. Ten case series with 340 patients who received PCC for direct FXa inhibitor–related major bleeding were included. The pooled proportion of patients with effective management of major bleeding was 0.69 (95% confidence interval [CI], 0.61-0.76) in 2 studies using the International Society on Thrombosis and Haemostasis (ISTH) criteria and 0.77 (95% CI, 0.63-0.92) in 8 studies that did not use the ISTH criteria; all-cause mortality was 0.16 (95% CI, 0.07-0.26), and thromboembolism rate was 0.04 (95% CI, 0.01-0.08). On the basis of evidence with very low certainty from single-arm case series, it is difficult to determine whether 4F-PCC in addition to cessation of direct oral FXa inhibitor is more effective than cessation of direct oral FXa inhibitor alone in patients with direct FXa inhibitor–related major bleeding.

Introduction

The options are limited for reversing the direct oral anticoagulant (DOAC) effect in patients who have major bleeding or who urgently need surgery. A targeted reversal agent for anti-factor Xa (anti-FXa) inhibitors, coagulation factor Xa (recombinant), inactivated is now available in the United States[1,2] but it is costly and will initially be available only in a limited number of hospitals. Dabigatran is currently the only DOAC with the widely available direct antidote idarucizumab.[3]

Given the issues relating to coagulation factor Xa (recombinant), inactivated, nonspecific indirect reversal strategies are currently used in clinical practice, including prothrombin complex concentrates (PCCs), activated PCCs, and recombinant FVIIa.[4] PCCs contain vitamin K–dependent coagulation factors and are widely used for reversal of vitamin K antagonists (VKAs).[5] Four-factor PCCs (4F-PCCs) contain FII, FVII, FIX, and FX compared with 3-factor PCCs that lack FVII.[6] PCCs have a lower risk of adverse events (volume overload in particular) than fresh frozen plasma (FFP), with no difference in risk of thromboembolic complications for warfarin reversal.[7] Furthermore, PCCs have a smaller volume and can be administered more rapidly than FFP.[5]

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The efficacy of PCCs in the reversal of direct FXa–related bleeding has been evaluated in healthy volunteers. 4F-PCCs corrected rivaroxaban-induced thrombin generation in 10 healthy volunteers in a dose-dependent manner.[8] In 6 healthy nonbleeding volunteers who received rivaroxaban 20 mg twice per day for 2.5 days, a supratherapeutic plasma concentration was induced, but 4F-PCCs corrected the rivaroxaban-associated prolonged prothrombin time (PT) and increased endogenous thrombin generation potential.[9] Two other studies in healthy volunteers receiving rivaroxaban 20 mg twice per day for 3 to 4 days to reach supratherapeutic steady-state concentrations suggested that 4F-PCCs normalized PT more effectively than 3-factor PCCs[10] and that 4F-PCCs, but not tranexamic acid, reduced PT and increased endogenous thrombin potential.[11] However, neither 4F-PCCs or tranexamic acid reduced bleeding duration or bleeding volume at the punch biopsy site.[11] A phase 1 study evaluated the reversal of the effects of edoxaban on bleeding measures and biomarkers after punch biopsy by 4F-PCCs. 4F-PCCs given at doses of 50, 25, or 10 U/kg after administration of 60 mg edoxaban in a dose-dependent manner reversed the effects of edoxaban on bleeding duration and endogenous thrombin potential, with complete reversal seen at the 50 U/kg dose.[12] Therefore, 4F-PCCs can effectively reverse thrombin generation; however, the effects on bleeding measures are variable as shown by the latter 2 studies in human volunteers of rivaroxaban at supratherapeutic doses and edoxaban at therapeutic doses.[11,12]

4F-PCCs have a proven efficacy in reversal of VKAs and variable results for reversal of direct FXa inhibitor coagulation assays in healthy human volunteers. In addition, because of high cost, lack of widespread availability of a specific reversal agent for direct FXa inhibitors, and a relatively safe adverse effect profile, 4F-PCCs may be a reasonable option for managing direct FXa-related major bleeding. It is not known whether the reversal effects of 4F-PCCs seen in healthy volunteers accurately reflect effects on clinical outcomes in patients with major bleeding, because no systematic review is available. We performed a systematic review and meta-analysis to address whether cessation of direct FXa inhibitor plus administration of 4F-PCCs vs cessation of direct FXa inhibitor alone can be used in patients with major bleeding while they are receiving apixaban, betrixaban, edoxaban, and rivaroxaban.

Methods

This systematic review was performed as part of the American Society of Hematology (ASH) clinical practice guidelines on venous thromboembolism (VTE), which were developed in partnership with the McMaster University Grading of Recommendations Assessment, Development and Evaluation (GRADE) Centre. Because the ASH guidelines focused on the specific topic of VTE, results and judgments for certainty of the evidence in this systematic review may be somewhat different than what is reported in the guidelines. Review and meta-analysis methodology followed the Cochrane Handbook,[13] and reporting was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14]

Search strategy

We conducted a systematic literature search to identify potential studies in Medline (1996 to week 2 of September 2018), Embase (1974 to week 2 of September 2018), and the Cochrane Central Register of Controlled Trials (until week 2 of September 2018). The search strategy is provided in supplemental Table 1. We also reviewed the references of the included studies for additional potentially eligible studies. There were no restrictions based on language or publication status. The search was performed in blocks to examine the studies separately by design, including observational randomized controlled trials (RCTs) and systematic reviews. Narrative review articles, single case reports, letters to the editor, and editorials were excluded. We aimed to pool the results of these studies in a meta-analysis. The searches retrieved for each study type were combined at the end. Because we did not identify any systematic reviews or RCTs, we focused on observational studies.

Study selection

Two authors (S.P. and R.K.) independently screened the titles and abstracts of articles and then reviewed the full-length version of potentially relevant articlesfor eligibility. Disagreements were resolved by joint review and consensus. RCTs or nonrandomized studies (cohort, case-control, interrupted time series, case series) were eligible if they satisfied all of the following characteristics: involved adult patients (age $\geq$18 years) taking a direct FXa inhibitor (apixaban, betrixaban, edoxaban, rivaroxaban), evaluated the safety and effectiveness of 4F-PCCs in managing major bleeding, reported 1 or more outcomes such as thromboembolic events (including deep vein thrombosis and/or pulmonary embolism), stroke, myocardial infarction, major bleeding, and/or all-cause mortality.

Outcome measures

The effectiveness of major bleeding management was defined according to the International Society on Thrombosis and Haemostasis (ISTH) recommendation for effective management of major bleeding[15] or defined as an absence of progression of hemorrhage on brain imaging by computed tomography in those presenting with intracranial hemorrhage, stabilization of bleeding on endoscopy, or cessation of surgical bleeding. Mortality was defined as death resulting from any cause. Thromboembolic events included deep vein thrombosis and/or pulmonary embolism, stroke, or myocardial infarction.

Risk of bias and indirectness assessment at the study level

Two authors (S.P. and R.K.) assessed the risk of bias using the Joanna Briggs Institute critical appraisal checklist for case series.[16] We considered selection bias given that patients with severe bleeding were likely selected to receive a 4F-PCC and enrollment may not have been consecutive or random. We prespecified potential confounders such as age; alcohol intake; comorbidities such as a history of hypertension, chronic kidney disease, or liver disease; use of antiplatelet agents such as aspirin and/or clopidogrel; and potentially important cointerventions such as fresh frozen plasma, cryoprecipitate, platelets, FVIIa, and tranexamic acid. Although the presence of these confounding factors and cointerventions could not affect the comparison with other bleeding management approaches because only single-arm studies were included, they do provide information regarding how representative the included populations and their outcomes could be for our population of interest. We considered the information on confounding factors and cointerventions in the domain of indirectness.[17]

Table 1. Baseline characteristics of the studies included in the systematic review

Reference	Study design	PCC type and dose	Cointerventions, no. (%)	No. of patients receiving FXa inhibitor who received PCC	FXa inhibitor	Indication for FXa inhibitor, no. (%)	Follow-up duration, d	Inclusion criteria	Exclusion criteria	Major bleeding definition	Bleeding type
34	Prospective	Type unspecified, dose range, 18-47 IU/kg	FFP alone, 2 (33); FFP and RBCs, 1 (17)	6	Rivaroxaban	Atrial fibrillation, 4 (67); VTE, 2 (33)	90	Planned anticoagulation for at least 3 months; indications included atrial fibrillation, DVT, PE, and others; age older than 18 years; written informed consent; and availability for follow-up by telephone visits	No exclusion criteria applied	ISTH criteria for major bleeding	ICH, 2; upper gastrointestinal bleeding, 2; intraoperative bleeding, 1; spontaneous hemothorax, 1
35	Retrospective	Kcentra, mean dose 3177 U (range, 2124-4770 U)	Platelets, 3 (17)	18	Rivaroxaban, 16 patients; apixaban, 2 patients	Atrial fibrillation alone, 14 (78); atrial fibrillation and DVT, 1 (5.5); atrial fibrillation and mechanical aortic valve replacement, 1 (5.5); mechanical aortic valve replacement, 1 (5.5); lupus anticoagulant, 1 (5.5)	90	Preinjury use of direct oral FXa inhibitors and diagnosis of either spontaneous ICH or blunt traumatic brain injury with evidence of ICH on initial noncontrast CT scan	Patients who had received FFP	Patients with ICH	ICH
36	Retrospective	Profilnine, median dose 40 U/kg	FFP alone, 1 (33.3); FFP and RBCs, 1 (33.3); FFP, platelets, and intravenous iron, 1 (33.3)	3	Rivaroxaban	Atrial fibrillation, 2 (66.7); DVT prophylaxis after hip replacement, 1 (33.3)	180	Age 18 years or older; hemorrhage during admission in those who had received dabigatran or rivaroxaban before this event	If hemorrhage was attributed to other agents or if the etiology of the event was determined to be surgical or caused by other medical conditions	Major bleeding, ISTH criteria; life-threatening bleeding, any fatal bleeding; symptomatic ICH; decrease in hemoglobin ≥50 g/L; ≥4 units of RBCs transfused; required inotropes or surgery	ICH,1; upper gastrointestinal bleeding, 2
37	Retrospective	Beriplex, dose unspecified	FFP and recombinant FVIIa, 1 (17)	3	Rivaroxaban	Atrial fibrillation, 5 (83.3); stents and tachyarrythmia, 1 (16.7)	90	Patients receiving anticoagulation therapy with rivaroxaban or dabigatran 3 days before ICH	NA	Patients with ICH	ICH
39	Prospective	Octaplex or beriplex, median 2000 U (range, 1500-2000 U)	Tranexamic acid, 56 (67); RBCs, 12 (14) before PCC and 18 (21) after PCC; FFP, 5 (6) before PCC and 8 (9.5) after PCC; platelets, 10 (12) after PCC; recombinant FVIIa, 1 (1)	84	Rivaroxaban, 45; apixaban, 39	Atrial fibrillation alone, 63 (75); VTE alone, 18 (21); atrial fibrillation and VTE, 3 (4)	30	Needed treatment with PCC to manage acute and active major bleeding while receiving rivaroxaban or apixaban	Do not resuscitate order, reduced hemoglobin without source of bleeding, perioperative reversal of rivaroxaban or apixaban, acute coronary syndrome or ischemic stroke during the past 30 days if they received other hemostatic agents (recombinant FVIIa or activated PCC)	ISTH criteria for major bleeding	ICH, 59; gastrointestinal , 13; visceral, 5; genitourinary, 4; musculoskeletal, 3
40	Prospective	Freeze-dried human blood coagulation FIX complex, median 1000 U (range, 1000-1125 U)	RBCs and FFP, 1 (0.1)	9	Rivaroxaban, 7; apixaban, 2	Atrial fibrillation, 9 (100)	Median 9 (range, 6-28)	Patients who developed major bleeding while taking NOAC medication and who subsequently received PCC administration were prospectively enrolled	Patients who were judged ineligible for PCC use by physicians in charge or who declined written informed consent were excluded	ISTH criteria for major bleeding	ICH, 8; gastrointestinal, 1

CT, computed tomography; CVA, cerebrovascular accident; DVT, deep vein thrombosis; IQR, interquartile range; NA, not available; NOAC, novel oral anticoagulant; PE, pulmonary embolism; RBC, red blood cell.

Table 1. (continued)

Reference	Study design	PCC type and dose	Cointerventions, no. (%)	No. of patients receiving FXa inhibitor who received PCC	FXa inhibitor	Indication for FXa inhibitor, no. (%)	Follow-up duration, d	Inclusion criteria	Exclusion criteria	Major bleeding definition	Bleeding type
41	Retrospective	Type unspecified, median dose of rivaroxban, 2000 U (IQR, 1500-2600 U); apixaban, 2400 U (IQR, 1500-3000 U)	Rivaroxaban, platelets, 5 (4.5); FFP, 2 (1.8); apixaban, platelets, 2 (9.5); FFP, 1 (4.8); tranexamic acid, 1 (4.8)	94 (total of 146 in the study)	Rivaroxaban, 81; apixaban, 13	Unspecified	90	Patients were treated with a DOAC at onset of ICH	ICH as a result of secondary etiologies such as ICH related to trauma, tumor, arteriovenous malformation, aneurysmal subarachnoid hemorrhage, acute thrombolysis, or other coagulopathies	Patients with ICH	ICH
42	Retrospective	Kcentra, 10 received 50 U/kg, 2 received 35 U/kg, and 2 received 25 U/kg	Unspecified; excluded patients who received FFP	14	Rivaroxaban and apixaban; breakdown was not specified	Atrial fibrillation, 12 (86); VTE, 3 (21); CVA, 2 (14); no. of patients with concomitant indications was not specified	30	If they were age 18 years or older and were admitted with traumatic or nontraumatic oral anticoagulant–associated ICH	Patients who received 4F-PCC without traumatic or nontraumatic oral anticoagulant–associated ICH	Patients with ICH	ICH
38	Prospective	Octaplex or beriplex, mean dose, 2072 U, 2000 U for 54 patients; dose violations from protocol for 12 patients, 2 received 1000 U, 3 received 1500 U, 1 received 2500 U, 4 received 3000 U, 1 received 3500 U, and 1 received 4200 U	Tranexamic acid, 17 (26); transfusions after PCC, second dose PCC, 2 (3); 1 received 1000 U and 1 received 2000 U; RBCs 1-8 units, 13 (20); platelets (1-3 apheresis or pooled units), 8 (12); cryoprecipitate, 1 (2)	66	Rivaroxaban, 37; apixaban, 29	Atrial fibrillation alone, 54 (82); VTE alone, 8 (13); atrial fibrillation and VTE, 2 (3); ischemic stroke, 1 (2)	30	Received infusion per local hospital protocol with PCC (2000 U) for major bleeding on treatment with rivaroxaban or apixaban; did not receive other hemostatic agents including plasma, platelets, activated PCC, or recombinant FVIIa before PCC was administered (antifibrinolytic drugs and local hemostatic agents were allowed); written consent provided	Do not resuscitate orders given before treatment with PCC because of the severity of bleeding; reduction of hemoglobin without evidence of source of bleeding; acute coronary syndrome or ischemic stroke during the past 30 days	ISTH criteria for major bleeding	ICH, 36; gastrointestinal, 16; retroperitoneal, 3; intramuscular, 2; intraspinal, 2; other, 7 with one each of intra-abdominal, pelvic, vaginal, hematuria, hemothorax, chest tube wounds, or carotid artery injury
43	Retrospective	Kcentra, 22 received 25 U/kg, 16 received 50 U/kg, 2 received 25-50 U/kg, 1 received >50 U/kg	FFP, 3 (6.9)	43	Rivaroxaban, 21; apixaban, 22	Atrial fibrillation, 30 (69.8); VTE, 9 (20.9); atrial fibrillation and VTE, 3 (7.0); lower extremity venous bypass graft 1 (2.3)	90	If the patients received 4F-PCC for reversing rivaroxaban, apixaban, or edoxaban for emergency surgery or invasive procedures, or during episodes of major bleeding	If they received 4F-PCC for purposes other than reversing FXa inhibitors or if they were younger than age 18 years	Major bleeding defined as bleeding with hemodynamic instability, decrease in hemoglobin of 2 g/dL, or bleeding requiring blood transfusion	Gastrointestinal bleeding, 17 (39.5); intracranial hemorrhage (nontraumatic), 9 (20.9); intracranial hemorrhage (traumatic), 7 (16.3); trauma, 5 (14.0); other, 5 (11.6)

CT, computed tomography; CVA, cerebrovascular accident; DVT, deep vein thrombosis; IQR, interquartile range; NA, not available; NOAC, novel oral anticoagulant; PE, pulmonary embolism; RBC, red blood cell.

Certainty of body of evidence

We assessed the certainty of the body of evidence from all included studies in the domains of risk of bias, indirectness, imprecision, inconsistency, and publication bias using the GRADE approach.[18] In accordance with the Cochrane Handbook,[13] we could not use funnel plots to assess for publication bias given that we had <10 included studies in the systematic review. We then created a GRADE evidence profile using GRADEpro software (www.gradepro.org).

Statistical analyses

Because the included studies were single arm only, we pooled the single-arm event rates using a random effects generic inverse variance method. We assessed heterogeneity using the I^2 index, χ^2 test, and visual inspection. Calculations were performed using RevMan version 5.3.

Results

Study selection

The study selection process is shown in supplemental Figure 1. We identified 1410 citations in our literature search and found 58 potentially eligible studies. Forty-two studies were excluded: 33 were abstracts, 1 was a review article,[19] 4 articles were not related to DOAC-associated major bleeding,[20-23] outcomes for patients treated with PCCs were not reported in 2 articles,[24,25] and the bleeding outcome for each type of DOAC was unspecified in 8 studies.[26-33] The remaining 10 studies were included in the systematic review and meta-analysis.

Patient and study design characteristics

The baseline characteristics of the included studies are listed in Table 1. A total of 340 patients were included in the 10 studies,[34-43] all of which were single-arm case series (no comparison group) that included only patients who received 4F-PCCs for direct FXa inhibitor–related major bleeding. Follow-up duration had a median of 9 days in 1 study,[40] 30 days in 3 studies,[38,39,42] 90 days in 5 studies,[34,35,37,41,43] and 180 days in 1 study.[36] In 9 studies, atrial fibrillation was the most common indication for a direct oral FXa inhibitor therapy. One study did not specify the indication for anticoagulation.[41] Most patients were receiving rivaroxaban at the time of bleeding except for 107 patients who received apixaban. Cointerventions were used in 9 studies, including FFP, platelets, or recombinant FVIIa. Two of the 10 studies excluded patients who had received FFP.[35,42] None of the patients received activated PCCs.

Risk of bias and certainty of evidence

All the included studies were rated as having very serious risk of bias because they lacked a control group and had a high risk of confounding and selection bias. Only 2 studies included consecutive patients (supplemental Table 2).[38,39] Furthermore, outcome assessors in all 10 studies were not blinded. The risk of evidence imprecision was rated as very serious, given that the included studies had small sample sizes and very few events. Overall, the certainty of evidence was rated as very low (Table 2).

Table 2. Assessment of quality of evidence using GRADE approach

No. of studies	Quality assessment						No. of patients		Pooled event rate (95% CI)	Quality	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outcome	Total			
Effective management of major bleeding using the ISTH criteria											
2	Observational	Very serious*	Not serious	Not serious	Very serious†	None	103	150	0.69 (0.61-0.76)	⊕◯◯◯ Very low	Critical
Effective management of major bleeding not using the ISTH criteria											
8	Observational	Very serious*	Not serious	Not serious	Very serious†	None	143	190	0.77 (0.63-0.92)	⊕◯◯◯ Very low	Critical
Mortality											
9	Observational	Very serious*	Not serious	Not serious	Very serious†	None	50	249	0.16 (0.07-0.26)	⊕◯◯◯ Very low	Critical
Thromboembolic complications											
7	Observational	Very serious*	Not serious	Not serious	Very serious†	None	10	240	0.04 (0.01-0.08)	⊕◯◯◯ Very low	Critical

*All studies were single-arm case series, the outcome assessors were not blinded, and the studies are at risk of selection bias.
†Studies included very few patients and very few events.

Table 3. Outcomes of the studies included in the systematic review

Reference	Effective management of major bleeding	ISTH criteria used (Y/N)	Patients with effective vs ineffective management of major bleeding, no. (%)	Mortality definition	Mortality rate, no. (%)	Thromboembolic complications definition	Thromboembolic rate, no. (%)
34	Absence of progression of ICH on CT of the head, stabilization of bleeding on endoscopy, or cessation of surgical bleeding	N	Effective, 5 (83.3); ineffective, 1 (16.7) had progression of ICH with fatal ICH	90-day mortality	2 (33.3); 1 sepsis, 1 fatal ICH	PE, DVT, MI, or CVA	0 (0)
35	Absence of progression of ICH on CT of the head or bleeding complication after neurosurgical intervention	N	Effective, 17 (94.5); ineffective, 1 (5.5) had progression of ICH	In-hospital mortality and 90-day Modified Rankin Scale (0 = no symptoms to 6 = dead)	6 (33); 2 pneumonia, 4 withdrawal of care	PE, DVT, or MI	1 (5.5) PE
36	Absence of progression of ICH on CT of the head or stabilization of bleeding on endoscopy	N	Effective, 3 (100); ineffective, 0(0)	In-hospital mortality and mortality within 180 days after discharge	0 (0)	Not reported	NA
37	Intraoperative surgical assessment of bleeding during neurosurgical intervention (strong bleeding vs normal)	N	Effective, 1 (33.3) normal intraoperative bleeding; ineffective, 2 (66.7) strong intraoperative bleeding; intraoperative bleeding was unspecified in 3 patients	Glasgow Outcome Scale (5 = low disability to 1 = death)	2 (33.3)	Not reported	NA
39	Bleeding rated as effective or ineffective based on ISTH criteria for 4 different types of bleeding: visible, musculoskeletal, intracranial, or nonvisible	Y	Effective, 58 (69); ineffective, 26 (31)	30-day mortality	27 (32); 18 ICH, 7 sepsis and multiorgan failure, 1 cardiac rrhythmia, 1 cardiac arrest	Objectively verified arterial (stroke, MI or arterial thromboembolism) or VTE (DVT or PE)	2 (2) ischemic stroke; 1 patient 5 days after and the other 10 days after PCC
40	Absence of progression of ICH on CT of the head or the need for surgical evacuation	N	Effective, 3 (33); ineffective, 6 (67)	In-hospital mortality and mortality within 7 days after PCC administration; Modified Rankin Scale (0 = no symptoms to 6 = dead) at discharge	0 (0)	Not defined	0 (0)
41	The primary outcome measure was occurrence of hematoma enlargement defined as a relative parenchymal volume increase of >33% from the initial follow-up imaging	N	Effective, 61 (65); Ineffective, 33 (35)	In-hospital mortality, 3-month mortality and 3-month Modified Rankin Scale score were reported for all patients and not for patients receiving direct FXa inhibitors	Mortality rate among all patients: 29 (19.9) of 146 at discharge; 43 (29.5) of 146 at 3 months; mortality rate not reported separately for the 94 patients receiving direct FXa inhibitor who received PCC	Not reported	NA
42	Hematoma expansion rate	N	Effective, 13 (93%); Ineffective, 1 (7%)	In-hospital mortality	2 (14)	MI, DVT, PE, and ischemic stroke within 30 days	0 (0)
38	Bleeding rated as good, moderate, or poor using an effectiveness assessment guide. In post hoc analysis, bleeding was also rated as effective or ineffective based on ISTH criteria for 4 different types of bleeding: visible, musculoskeletal, intracranial, or other nonvisible	Y	Good for 43 (65) patients (95% CI, 53-77), moderate for 13 (20) (95% CI, 10-30), and poor/none for 10 (15) (95% CI, 6-24). Post hoc analysis using the ISTH criteria: effective: 45 (68); ineffective: 21 (32)	30-day mortality	9 (14): 8 had ICH, 7 of these deaths were adjudicated as a result of the index ICH event, 1 died as a result of self-inflicted stab wounds to the chest	Primary safety outcome: symptomatic DVT, PE, ischemic stroke, heart valve or cardiac chamber thrombosis, symptomatic peripheral arterial thrombosis or myocardial infarction within 7 days after PCC administration; secondary safety outcome: 30-day thromboembolic event rate	5 (8) major thromboembolic event 7-day rate, 2 (3); 8- to 30-day rate, 3 (5)

MI, myocardial infarction; N, no; Y, yes.

Table 3. (continued)

Reference	Effective management of major bleeding	ISTH criteria used (Y/N)	Patients with effective vs ineffective management of major bleeding, no. (%)	Mortality definition	Mortality rate, no. (%)	Thromboembolic complications definition	Thromboembolic rate, no. (%)
43	The hemostatic efficacy was determined by the treating physician on the basis of clinical measures, including patient hemodynamics, trend of hemoglobin and hematocrit, and active bleeding as seen on imaging or with invasive procedures	N	Effective, 40 (93); ineffective, 3 (7) continued to have active bleeding. Two patients (4.6) died as a result of hemorrhage and 1 required surgery to achieve hemostasis	Not reported	Two patients (4.6) died as a result of hemorrhage	Acute DVT, PE, MI, or acute coronary syndrome, transient ischemic stroke, cerebral vascular accidents, and arterial thrombosis of limb or mesentery	2 (4.6); 1 (2.3) had a DVT within 14 days after PCC administration, 1 (2.3) had a subsegmental PE 3 months after receiving PCC

MI, myocardial infarction; N, no; Y, yes.

Outcomes

Outcomes of interest are listed in Table 3. Two studies used the ISTH effective major bleeding management criteria,[38,39] and 8 studies did not.[34-37,40-43] Therefore, a pooled meta-analysis of the effectiveness of management of all 10 studies was not performed. All of the studies except for 1[41] reported mortality outcomes and were included in the pooled crude proportion analysis for overall mortality. Three studies did not report thromboembolic events,[36,37,41] and we did not include these in the pooled crude proportion analysis for thromboembolic complications.

Pooled analysis of outcomes

Forest plots of the pooled outcome proportions are provided in supplemental Figures 2-5. The pooled proportion of effective major bleeding management using the ISTH criteria was 0.69 with a 95% confidence interval (CI) of 0.61 to 0.76, meaning that 69% of patients achieved successful bleeding management using 4F-PCCs. This was pooled from 2 studies involving 150 patients.[38,39] The pooled proportion of effective management of major bleeding that did not use the ISTH criteria was 0.77 (95% CI, 0.63-0.92). This was pooled from 8 studies involving 190 patients.[34-37,40-43] The crude mortality pooled proportion was 0.16 (95% CI, 0.07-0.26), meaning that 16% of patients died during the specified follow-up period. This was pooled from 9 studies involving 249 patients.[34-40,42,43] The crude pooled proportion of thromboembolic events was 0.04 (95% CI, 0.01-0.08), meaning that 4% of patients experienced a thromboembolic event during follow-up. This was pooled from 7 studies involving 240 patients.[34,35,38-40,42,43] In a subanalysis, we separated the effect on short-term thromboembolic complication only for 5 studies that had a follow-up of ≤30 days (supplemental Figure 6).[38-40,42,43] The short-term pooled proportion of thromboembolic complications was 0.03 (95% CI, 0.0-0.06). There was no statistical heterogeneity between the studies for most outcomes (I^2 = 0%) except for effective management of major bleeding not using the ISTH criteria (I^2 = 85%) and crude mortality (I^2 = 74%).

Discussion

We found 10 nonrandomized, unblinded, single-arm case series in which all patients received 4F-PCC for management of direct FXa-related major bleeding. Therefore, these data were pooled to determine the proportion of patients who experienced benefits and harms after receiving 4F-PCC. Because there was no comparator group, it was difficult to determine whether administration of 4F-PCC in addition to cessation of direct oral FXa inhibitor was more likely to achieve hemostasis and improve important outcomes than cessation of direct oral FXa inhibitor alone.

Our study is the first systematic review to examine the safety and effectiveness of 4F-PCC for managing major bleeding in patients receiving FXa inhibitors to treat VTE or atrial fibrillation. The search was systematic and comprehensive and consisted of searches in multiple electronic databases. Our study has limitations. First, the included studies had a high risk of bias and small sample sizes. All were case series that lacked a control group and likely suffered from selection bias. Only 2 studies minimized the selection bias by including consecutive patients.[38,39] In addition, there may also be a risk of confounding biases because

of differences in the baseline characteristics or cointerventions between study populations. For example, cointerventions such as tranexamic acid, FFP, platelets, or recombinant FVIIa were used in all studies, which could have influenced the bleeding outcome. The certainty of evidence was rated very low because of the high risk of bias and imprecision resulting from small sample sizes and few events. Furthermore, we could not assess publication bias using funnel plots because we had <10 studies. In addition, there was a high degree of heterogeneity for the pooled outcomes of effective major bleeding management not using the ISTH criteria and crude mortality. This is most likely because of differences in baseline characteristics in the individual studies. For example, in 1 study, a tertiary care center received patient referrals from other hospitals in which previous supportive measures had failed.[39] Second, we combined patients with different types and doses of 4F-PCC. Finally, the definition of outcome events was not uniform between studies. The recent ISTH criteria for effective management of major bleeding were used in only 2 studies.[15]

Management of major bleeding according to the ISTH criteria was effective in 103 (69%) of the 150 patients in 2 studies. This is similar to the results of the ANNEXA-4 trial: coagulation factor Xa (recombinant), inactivated reduced the anti-FXa activity in patients with acute major bleeding and achieved good or excellent hemostasis in 109 (83%) of 132 patients.[2] Without a control group, it is unclear whether coagulation factor Xa (recombinant), inactivated is more effective in achieving hemostasis than supportive care alone. Because of the high cost and limited availability of coagulation factor Xa (recombinant), inactivated, many clinicians may continue to choose 4F-PCC for managing direct FXa-related major bleeding.

The crude pooled proportion of thromboembolic complications in patients who received 4F-PCCs in our meta-analysis (4%) was higher than the incidence of 1.8% for 4F-PCC-associated thromboembolic complication for managing VKA-related bleeding[32] but far below that of the reported rate when using coagulation factor Xa (recombinant), inactivated (11%).[2] The difference may be explained by differences in baseline characteristics, the timing of re-initiation of anticoagulation after administering the reversal agent, the intrinsic properties of the reversal agent, or the combination. Transient elevations in D-dimer and prothrombin fragments 1 + 2 levels were observed in healthy volunteers after administration of andexanet alfa,[44] which is thought to be mediated by interaction between andexanet and tissue factor pathway inhibitor. As with the case series included in our meta-analysis, a controlled study is required to determine whether the reported rate of thromboembolic events exceeds the expected rate in patients who are already at increased risk of thromboembolic complications at baseline.

The crude all-cause mortality pooled proportion was higher than that reported in the ANNEXA-4 trial (18% vs 12%, respectively).[2] The mortality rate observed in our meta-analysis is likely influenced by selection bias whereby sicker populations were selected across studies. Furthermore, 251 (74%) of the 340 patients included in our meta-analysis had intracranial hemorrhage (ICH) compared with 61% of the patients in the ANNEXA-4 study.[2] Anticoagulant-related ICH is generally known to have a high mortality rate.[45-48] The mortality rate in patients with warfarin-related ICH treated with PCC has been reported as 45%,[49,50] which is higher than the rate observed in our study (25.5% [36 of 141 ICH patients in 8 studies]). A recent observational study of 42 patients with oral anticoagulant–associated ICH (28 taking VKAs and 14 taking an FXa inhibitor) were treated with 4F-PCC.[42] Although the sample size is small, the outcomes were similar in both groups, with no significant difference in in-hospital mortality (32.1% in the VKA group vs 14.2% in the FXa inhibitor group) or rates of hemorrhagic expansion, thromboembolic complications, or length of stay.[42]

In conclusion, our systematic review and meta-analysis is the first of its kind to examine safety and effectiveness outcomes of 4F-PCC for managing direct FXa inhibitor–related major bleeding. However, in light of the absence of a comparator group, it is impossible to know whether 4F-PCC is more effective than supportive care alone. For example, if there is no change in hematoma volume in patients with ICH, without a control group it cannot be determined whether this would have occurred without administering 4F-PCC. In addition, gastric bleeding from deep ulcers with a visible blood vessel may not be amenable to treatment with 4F-PCC or coagulation factor Xa (recombinant), inactivated. For such bleeding types, invasive interventions are required. The rate of thromboembolic events must be taken into consideration when evaluating the harms and benefits associated with administration of 4F-PCC. Given the quick offset of DOAC anticoagulant effects in patients with adequate renal function and a low but clinically relevant rate of thromboembolic complications after administration of 4F-PCC, clinicians should reserve this intervention for life-threatening bleeding only. Because of the high cost and lack of widespread availability of a specific reversal agent for direct FXa inhibitors, 4F-PCC may be a reasonable option for managing direct FXa-related major bleeding. Because of the high risk of bias and small sample sizes across studies, the quality of the evidence is very low. Future studies with a control group are needed to determine whether reversal with 4F-PCC is more effective than supportive care alone.

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Authorship

Contribution: S.P. contributed to study design, study selection, collection of data, statistical analyses, and writing the initial draft of the manuscript; R.K. contributed to study design, study selection, and collection of data; S.S. and A.M. interpreted the data and provided vital reviews of the manuscript; and A.H., D.M.W., W.W., H.J.S., and R.N. contributed to study design, interpreted the data, and provided vital reviews of the manuscript.

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