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Retrospective Comparison of Andexanet Alfa and 4-Factor Prothrombin Complex for Reversal of Factor Xa-Inhibitor Related Bleeding

Victoria M. Stevens, PharmD, BCCCP, Toby C. Trujillo, PharmD, FCCP, FAHA, BCPS, Tyree H. Kiser, PharmD, FCCM, FCCP, BCPS, Robert MacLaren, PharmD, MPH, FCCM, FCCP, Paul M. Reynolds, PharmD, BCCCP, and Scott W. Mueller, PharmD, BCCCP, FCCM, FCCP

Abstract

The aim of this retrospective study was to compare andexanet alfa and 4-factor prothrombin complex (4F-PCC) for reversal of factor Xa (FXa)-inhibitor bleeding. Patients that received andexanet alfa for reversal were included. An equivalent number of patients administered 4F-PCC for FXa-inhibitor bleeding were randomly selected as historical controls. The primary outcome was effective hemostasis achievement within 12 h, defined using ANNEXA-4 criteria. Thromboembolic events and mortality within 30 days were also evaluated. A total of 32 patients were included. Baseline characteristics were not statistically different between andexanet alfa (n = 16) and 4F-PCC (n = 16). Intracranial bleeding was the primary reversal indication in 43.8% versus 62.5% of patients, respectively. Effective hemostasis was reached in 75.0% of andexanet alfa patients compared to 62.5% of 4F-PCC patients ($P = .70$). Thromboembolic events occurred in 4 (25.0%) patients and 3 (18.8%) patients, respectively ($P = .99$). Mortality incidence was 12.5% and 31.3%, respectively ($P = .39$). Andexanet alfa and 4F-PCC attained hemostasis in a majority of patients. A high, but a similar rate of thromboembolic events was seen with both treatments. Prospective studies are needed to elucidate comparative risks and benefits of the 2 agents.

Keywords

coagulation factor Xa (recombinant), inactivated-zhzo, andexanet alfa, factor Xa inhibitors, direct-acting oral anticoagulants, hemorrhage, rivaroxaban, apixaban, reversal

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Introduction

Since the approval of oral factor Xa (FXa) inhibitors, such as rivaroxaban and apixaban, their use has grown considerably.[1] Guidelines recommend direct oral anticoagulants, including FXa inhibitors, over warfarin for the treatment of various thromboembolic disorders.[2,3] As the utilization of these agents increases, strategies for management of rare but serious hemorrhagic-related events are of pressing importance. Rapid and aggressive action is necessary to limit the significant morbidity and mortality surrounding these bleeding events.[4-6]

In 2018, coagulation FXa (recombinant), inactivated-zhzo (andexanet alfa) became the first food and drug administration (FDA)-approved agent for the reversal of life-threatening or uncontrolled bleeding in patients receiving apixaban or rivaroxaban.[7,8] Andexanet alfa is an inactivated form of human FXa that binds and sequesters FXa-inhibitor molecules allowing

University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO, USA

Corresponding Author:
Scott W. Mueller, Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, 12850 East Montview Boulevard, C238, Aurora, CO 80045, USA.
Email: scott.mueller@cuanschutz.edu

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for restoration of intrinsic FXa activity and normal hemostasis to occur.[7-9] In the ANNEXA-4 trial, study investigators found that 82% of eligible patients achieved effective hemostasis at 12 h post-andexanet alfa.[8] Thrombotic events and mortality within 30 days were 10% and 14%, respectively.[8] The efficacy of andexanet alfa has also been evaluated in multiple small observational studies, finding effective hemostasis was achieved in 77% to 90.9% of patients, with 1 reporting hemostasis in only 47.6% of patients.[10-13]

Prior to 2018, several pro-hemostatic agents such as 4-factor prothrombin complex concentrate (4F-PCC), activated 4F-PCC, and recombinant factor VIIa were considered for the management of FXa-inhibitor-related bleeding.[14] 4F-PCC emerged as a main therapeutic option for FXa-inhibitor-associated hemorrhage.[14] 4F-PCC contains nonactivated coagulation factors II, VII, IX, and X competing with the effects of FXa inhibitors, increasing thrombin generation, and facilitating clot formation.[14,15] With the exception of Panos et al[16] clinical evaluations of 4F-PCC for reversal of FXa inhibitors are limited to small cohort studies, collectively estimating hemostatic efficacy rates from 60% to 94.7%.[14-28] A meta-analysis of 10 studies evaluating 4F-PCC for FXa-inhibitor reversal found a pooled thrombotic event rate of 4% and a mortality rate of 16%.[22]

Based on the available literature the American Society of Hematology has suggested the use of either 4F-PCC or andexanet alfa for patients with FXa-inhibitor-associated bleeding.[6] Other guidance forums, including an expert consensus from the American College of Cardiology, have recommended 4F-PCC only if andexanet alfa is unavailable.[5,29,30] Irrespective of these recommendations there is currently limited evidence comparing the 2 agents.[15,31-33] Therefore, the aim of this retrospective cohort is to compare hemostatic efficacy and safety outcomes between andexanet alfa and 4F-PCC for reversal of FXa-inhibitor-related bleeding.

Materials and Methods

Study Design and Patient Selection

This retrospective cohort study identified all adult patients ($\geq$ 18 years old) with a major bleeding event who received andexanet alfa for the reversal of apixaban or rivaroxaban at the University of Colorado Health System Hospital (UCHealth) between June 2018 and August 2020. Some patients have been previously reported.[13] A record of patients that had received 4F-PCC was created for a prior internal quality improvement project that evaluated 4F-PCC use at UCHealth (Colorado Multiple Institution Review Board [COMIRB] # 17-2268). Patients were randomly selected from this record, and if they had received 4F-PCC for the reversal of FXa-inhibitor-related bleeding they were included in this study. Random selection occurred until an equivalent number of 4F-PCC to andexanet alfa patients was reached. Patients presenting after June 28, 2018, were not included in the 4F-PCC group as a way to limit, as much as possible, clinical selection bias that may occur when both agents were available for use. This study was approved by COMIRB (# 19-1610).

Andexanet alfa and 4F-PCC Use

Institutional recommendations for andexanet alfa use and dosing have been described previously.[13] In short, andexanet alfa is approved for patients who present with a life-threatening and/or critical site bleed and have received apixaban or rivaroxaban within the previous 18 h or at an unknown time.[34] A life-threatening bleed was characterized by the presence of hemodynamic instability leading to organ dysfunction. Critical bleeding sites included retroperitoneal, intracranial, epidural, pericardial, or intramuscular with compartment syndrome. The decision to administer 4F-PCC and dosing was at the discretion of the treating provider. Doses were determined by the factor IX content and rounded to the nearest 500-unit vial size. Prior to July 2017, weight-based dosing was used. After this time, the study institution moved to a fixed-dose protocol.[35,36] Concurrent use or repeat doses with either agent was not recommended.

Outcomes

The primary outcome was the difference in the achievement of excellent or good hemostasis within 12 h of andexanet alfa administration as compared to 4F-PCC. Hemostasis was defined based on the ANNEXA-4 study definitions and classified as excellent, good, or poor.[8] Excellent and good hemostasis were combined as "effective" hemostasis for the primary outcome. For an intracranial hemorrhage (ICH), hemostasis was considered excellent if the hematoma volume, or thickness as in the case for subarachnoid hemorrhages and subdural hematomas, increased by $\leq$ 20%, or considered good if >20% but $\leq$ 35%, on repeat imaging. Hematoma expansion >35% was considered poor hemostasis. Evaluation and measurement of the hematoma were performed by a board-certified radiologist. Hematoma volume was calculated using the ABC/2 volume estimation method.[37] Excellent hemostasis for noninntracranial bleeding was achieved if hemoglobin/hematocrit (Hgb/Hct) did not decrease by more than 10% at 12 h, good if Hgb/Hct decreased by >10% but $\leq$ 20%, and poor if there was >20% decrease. Both hemoglobin and hematocrit were corrected based on the amount of packed red blood cells (PRBC) administered.[8] For every 1 unit of PRBC given 1 g/dL was subtracted from the hemoglobin level and 3% from the hematocrit level.[8] For all bleeding types, if patients required more than 2 units of blood products (excluding PRBC) or additional coagulation factors within 12 h after infusion of either drug had finished, they were considered to have poor hemostasis. Additional procoagulants were defined as pro-hemostatic agents such as recombinant factor VIIa, tranexamic acid (TXA), 4F-PCC (andexanet alfa group), or additional 4F-PCC (4F-PCC group), and recombinant thrombin. If data was not available at 12 h the next closest time point was used. Safety outcomes included the rate of thrombotic events and all-cause

mortality within 30 days of andexanet alfa or 4F-PCC administration. Patients discharged before 30 days were evaluated using clinic and readmission notes. If this information was unavailable, then the patient's last known outcomes were carried forward. Lastly, time from presentations to the administration of either andexanet alfa or 4F-PCC was evaluated.

Statistical Analysis

Categorical variables were expressed as values and percentages. Comparisons of categorical variables between andexanet alfa and 4F-PCC groups were analyzed using Fisher's exact test. Continuous variables were expressed as either mean ± standard deviation (SD) or median and interquartile range (IQR). Student *t*-test or Mann-Whitney *U*-test was used to compare continuous variables between 2 groups. Statistical significance was defined as a 2-sided *P*-value of $< .05$. All statistical analyses were conducted using JMP® Pro software and verified in version 15.0.0 (SAS Institute Inc., Cary, NC, 2019).

Results

Baseline Characteristics

A total of 32 patients were included in the analysis. Sixteen patients received andexanet alfa, all of which were included. Of note, 13 of those patients were a part of a prior analysis of andexanet alfa at the study institution.[13] No significant differences in baseline characteristics were observed between groups (Table 1). Mean age was 69 ± 13.6 years, body mass index 31.2 ± 9.1 kg/m^2, and median length of hospital stay was 8.5 days (IQR: 5.4 - 20.5). Apixaban (68.8%) was most common in the andexanet alfa group compared to rivaroxaban (56.3%) in the 4F-PCC group. For both groups, the median dose of rivaroxaban was 20 mg/day. The median dose of apixaban was 10 mg/day in the andexanet alfa group and 5 mg/day in the 4F-PCC cohort. Last known FXa-inhibitor exposure occurred at a median 11.4 h (IQR: 9.5 - 12.9) and 14.5 h (IQR: 13.8 - 15.3) in andexanet alfa and 4F-PCC groups, respectively ($P = .12$). In each group, there were 7 patients (43.8%) where the time of the last FXa-inhibitor dose was unknown. No patients had a known last FXa-inhibitor dose >18 h prior to reversal administration. A total of 5 patients (31.3%) that received andexanet alfa were on antiplatelet therapy. The 1 patient was on both clopidogrel and aspirin therapy, the other 4 patients were on aspirin only. A total of 3 patients (18.8%) in the 4F-PCC group were on concomitant aspirin therapy.

Intracranial bleeding was the indication for FXa-inhibitor reversal in 43.8% of the andexanet alfa group and 62.5% of the 4F-PCC group. Severe nonintracranial bleeding in the andexanet alfa cohort included retroperitoneal bleed, iliacus/psoas hematoma, uterine hemorrhage, flank hematoma, lower extremity muscular bleed, pericardial effusion, intraabdominal bleeding, and 2 patients with aortic dissection. Types of severe nonintracranial bleeding in the 4F-PCC group included retroperitoneal bleed, pericardial effusion, intraabdominal bleeding, and 3 patients with gastrointestinal bleeding (GIB).

Table 1. Baseline Characteristics.[a]

Characteristic	Andexanet alfa (N = 16)	4F-PCC (N = 16)
Age—year	69.1 ± 9.4	69.0 ± 17.2
Male	8 (50.0)	11 (68.8)
Weight—kg	94.4 ± 26.0	86.4 ± 30.1
Body mass index—kg/m^2	32.7 ± 9.1	29.6 ± 9.2
Estimated creatinine clearance		
<30 mL/min	2 (12.5)	3 (18.8)
30 to 60 mL/min	6 (37.5)	5 (31.3)
>60 mL/min	8 (50.0)	8 (50.0)
Primary indication for anticoagulation		
Atrial fibrillation	11 (68.8)	14 (87.5)
Venous thromboembolism	5 (31.3)	2 (12.5)
Past medical history		
Myocardial infarction	3 (18.8)	1 (6.3)
Stroke	0 (0)	3 (18.8)
Deep-vein thrombosis	5 (31.3)	1 (6.3)
Pulmonary embolism	1 (6.3)	1 (6.3)
Heart failure	4 (25.0)	6 (37.5)
Diabetes mellitus	3 (18.8)	5 (31.3)
Concomitant antiplatelet therapy	5 (31.3)	3 (18.8)
FXa inhibitor		
Apixaban	11 (68.8)	7 (43.8)
Rivaroxaban	5 (31.3)	9 (56.3)
Time since last FXa-inhibitor dose		
<8 h	3 (18.8)	1 (6.3)
8-18 h	6 (37.5)	8 (50.0)
Unknown	7 (43.8)	7 (43.8)
Heparin exposure within 12 h prior to reversal agent	3 (18.8)	0 (0)
Site of bleeding		
Intracranial	7 (43.8)	10 (62.5)
Nonintracranial	9 (56.3)	6 (37.5)
GCS score[b]	15 [8-15]	13 [11-15]
ICH GCS score[c]	8 [6-12]	13 [11-14]
Non-ICH GCS score[d]	15 [15-15]	14 [11-15]
Hemodynamically unstable[e]	6 (37.5)	4 (25.0)

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; FXa, factor Xa.
[a]Data presented as mean ± SD, no. (%), or median [IQR]. No significant differences between the groups were observed at baseline.
[b]Baseline GCS scores were not reported for 2 patients in the andexanet alfa group.
[c]Median GCS scores for 7 andexanet alfa patients and 10 4F-PCC patients.
[d]Median GCS scores for 7 andexanet alfa patients and 6 4F-PCC patients.
[e]Hemodynamically unstable defined as mean arterial pressure (MAP) <65 mm Hg and/or requiring vasopressor support.

Hemostatic Outcomes

Effective hemostasis within 12 h of drug administration was achieved in 12 patients (75%) in the andexanet alfa group compared to 10 patients (62.5%) in the 4F-PCC group ($P = .70$). In both groups, 62.5% were categorized as having an excellent hemostasis (Table 2). In the andexanet alfa group, 12.5% had good hemostasis and 25% had a poor hemostatic outcome.

Table 2. Treatment Outcomes.[a]

	Andexanet alfa (N = 16)	4F-PCC (N = 16)	*P*-value
Effective hemostasis overall	12 (75.0)	10 (62.5)	.70
Excellent	10 (62.5)	10 (62.5)	
Good	2 (12.5)	0 (0)	
Poor	4 (25.0)	6 (37.5)	
Effective hemostasis for ICH	4/7 (57.1)	7/10 (70.0)	.64
Excellent	3/7 (42.9)	7/10 (70.0)	
Good	1/7 (14.3)	0 (0)	
Poor[b]	3/7 (42.9)	3/10 (30.0)	
Effective hemostasis for non-ICH	8/9 (88.9)	3/6 (50.0)	.24
Excellent	6/9 (66.7)	3/6 (50.0)	
Good	2/9 (22.2)	0 (0)	
Poor[c]	1/9 (11.1)	3/6 (50.0)	
ICU length of stay—days	4.5 [3-10.5]	3 [2-11]	.36
Total hospital length of stay—days	10.5 [6.5-20.5]	6 [4.5-21]	.44

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; ICH, intracranial hemorrhage; ICU, intensive care unit.
[a]Data presented as mean ± SD, no. (%), or median [IQR].
[b]Two andexanet alfa patients and 1 4F-PCC patient experienced > 35% hematoma expansion. One andexanet alfa patient developed clinical manifestations of severely elevated intracranial pressure within 12 h of administration and died. Two 4F-PCC patients required > two additional units of blood products/procoagulants within 12 h following 4F-PCC administration.
[c]The andexanet alfa patient experienced both > 20% Hgb/Hct drop and required > 2 additional units of blood products/procoagulants. One 4F-PCC patient had > 20% Hgb/Hct drop, and the other two patients required > two additional units of blood products/procoagulants.

No patients in the 4F-PCC were classified as having a good hemostatic outcome and 37.5% were identified as having poor hemostasis.

In patients with ICH, effective hemostasis was seen in 4 of 7 (57.1%) that received andexanet alfa, compared to 7 of 10 (70%) that received 4F-PCC ($P = .64$). There was 1 patient in the andexanet alfa group with an ICH that did not have a post-treatment imaging. This patient died within 12 h of andexanet alfa administration with clinical findings consistent with elevated intracranial pressure and was determined by study investigators to a poor hemostatic outcome. Median pre-intervention Glasgow Coma Scale (GCS) scores for patients with an ICH were 8 (IQR: 6 - 12) verses 13 (IQR: 11 - 14) for andexanet alfa and 4F-PCC groups, respectively ($P = .24$). For nonintracranial bleeding, effective hemostasis was achieved by 8 of 9 patients (88.9%) receiving andexanet alfa, compared to 3 of 6 patients (50%) receiving 4F-PCC ($P = .24$). Median preintervention GCS scores for patients with a nonintracranial bleed were 15 (IQR: 15 - 15) versus 14 (IQR: 11 - 15) for andexanet alfa and 4F-PCC groups, respectively ($P = .053$). The 2 patients in the andexanet alfa group with nonintracranial bleeding did not have a reported GCS score preandexanet alfa administration as both underwent immediate surgery.

Interventions

A total of 8 patients (50%) in each group underwent a surgical intervention or procedure within 12 h of andexanet alfa or 4F-PCC initiation (Table 3). In the andexanet alfa group, interventions included aortic arch repair (n = 2), craniotomy, external ventricular drain (EVD) placement, lower extremity hematoma evacuation, catheter embolization, exploratory laparotomy, and sternotomy for pericardial effusion repair. Both patients that underwent aortic arch repair were given heparin for cardiopulmonary bypass with cessation of heparin administration 4.5 and 3.5 h prior to andexanet alfa. The patients received andexanet alfa for ongoing bleeding complicating surgical completion when other therapeutic anticoagulation

Table 3. Interventions.[a]

	Andexanet alfa (N = 16)	4F-PCC (N = 16)
Andexanet alfa dosing		
High dose[b]	2 (12.5)	–
Low dose[c]	14 (87.5)	–
4F-PCC administration		
Patients	4 (25.0)	16 (100.0)
Initial dose—units	1500 ± 0	2310 ± 1125
Initial dose—units/kg	14.3 ± 2.7	27.9 ± 11.7
Second 4F-PCC dose within 12 h	1 (6.3)	1 (6.3)
Time from order entry to administration—min	42 [30-50]	30 [22-54]
ED presentation to administration—min	145 [91-269]	123 [79-275]
Recombinant factor VIIa	2 (12.5)	0 (0)
Tranexamic acid	3 (18.8)	0 (0)
Blood product transfusions		
PRBC prereversal—no.	5 (31.3)	3 (18.8)
PRBC prereversal—units[d]	2 [1-3]	1 [1-2]
PRBC within 12 h postreversal—no.	4 (25.0)	6 (37.5)
PRBC within 12 h postreversal—units[d]	1 [1-2]	1.5 [1-3]
FFP prereversal—no.	3 (18.8)	0 (0)
FFP prereversal—units[d]	4 [1-9]	0
FFP within 12 h postreversal—no.	4 (25.0)	4 (25.0)
FFP within 12 h postreversal—units[d]	1.5 [1-2.5]	2 [2-3]
Platelets prereversal—no.	1 (6.3)	1 (6.3)
Platelets prereversal—units[d]	3	0.5
Platelets within 12 h postreversal—no.	2 (12.5)	2 (12.5)
Platelets within 12 h postreversal—units[d]	1.5 [1-2]	1 [1-1]
Emergent surgery or intervention	8 (50.0)	8 (50.0)

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; ED, emergency department; PRBC, packed red blood cells; FFP, fresh frozen plasma.
[a]Data presented as mean ± SD, no. (%), or median [IQR].
[b]High dose 800 mg intravenous (IV) bolus followed by 960 mg IV infusion over 2 h.
[c]Low dose 400 mg IV bolus followed by 480 mg IV infusion over 2 h.
[d]Includes only those who received the blood product.

reversal failed. These patients met criteria for excellent and good hemostasis. A patient that went for an exploratory laparotomy within 1 h after andexanet alfa infusion finished was noted to have procedural bleeding that was more than would be expected. This patient had a poor hemostatic outcome by Hgb/Hct decrease criteria. The other 7 patients in the andexanet alfa group were judged to have normal or expected procedural-related bleeding. In the 4F-PCC group, interventions included EVD placement (n = 4), esophagogastroduodenoscopy (n = 2), catheter embolization, and thoracotomy for pericardial effusion repair. All patients were documented to have normal or expected procedural-related bleeding.

At least 1 additional procoagulant was used in 5 (31.3%) andexanet alfa patients versus 1 (6.3%) 4F-PCC patient, $P = .17$ (Table 3). In the andexanet alfa group, adjunctive procoagulants included 4F-PCC (n = 4), recombinant factor VIIa (n = 2), and TXA (n = 3). The 4 of the 5 patients received 2 or more other procoagulant agents, including 1 patient that received 2 doses of 4F-PCC (4.5 h prior to and 3 h after andexanet alfa infusion). With the exception of the aforenoted patient, all procoagulants were administered prior to or during andexanet alfa infusion. One patient received desmopressin after andexanet alfa infusion.

In the 4F-PCC group, 1 patient received a repeat dose of 4F-PCC 4 h after the initial dose. No patients in the 4F-PCC received recombinant factor VIIa or TXA. Two patients received a dose of desmopressin prior to 4F-PCC and 3 patients received intravenous (IV) vitamin K within 12 h of the 4F-PCC dose.

Drug Dosing and Administration

Treatment regimens can be seen in Table 3. Among the 4 patients in the andexanet alfa group that received 4F-PCC, the initial dose of 4F-PCC was 1500 units (14.3 ± 2.7 units/kg). One patient was given a second dose of 4F-PCC to a total of 3000 units (32.1 units/kg). The average initial 4F-PCC dose in the 4F-PCC group was 2310 ± 1125 units (27.9 ± 11.7 units/kg). One patient was administered a second dose of 4F-PCC to a total of 5000 units (51 units/kg).

There was no statistically significant difference in time of order entry by the provider to time of drug administration for andexanet alfa versus 4F-PCC. Median times were 42 min (IQR: 30 - 50) and 30 min (IQR: 22 - 54), respectively ($P = .44$). For patients that presented to the ED with a major bleeding event, the mean time from patient arrival to drug administration was 145 (IQR: 91 - 269) minutes versus 123 (IQR: 79 - 275) minutes for andexanet alfa and 4F-PCC, respectively ($P = .68$).

Safety Outcomes

Thrombotic events were not statistically different between andexanet alfa (25%) and 4F-PCC 18.8%, $P = .99$ (Table 4). In the andexanet alfa group, a total of 5 thromboembolic events occurred across 4 patients. Two of the 4 patients also received 4F-PCC ± factor VIIa. One patient exposed to factor VIIa, 4F-PCC, and andexanet alfa for ongoing bleeding following cardiopulmonary bypass experienced an ischemic stroke within 1 day and a pulmonary embolism (PE) on day 26. Other events included deep vein thrombosis (DVT), myocardial infarction (MI), and superficial venous thrombosis. The median time to event was 6.5 days (IQR: 1 - 26). Of the 5 thrombotic events, 4 occurred before prophylactic, or therapeutic anticoagulation was restarted. In all, 6 patients (37.5%) were not re-started on either prophylactic or therapeutic anticoagulation during their hospital admission following andexanet alfa administration. In those restarted on a form of anticoagulation, the median time to initiation was 4 days (IQR: 2.3 - 5).

Table 4. Safety Outcomes.[a]

Variable	Andexanet alfa (N = 16)	4F-PCC (N = 16)	*P*-value
≥1 Thrombotic event within 30 days	4 (25.0)	3 (18.8)	.99
Myocardial infarction	1 (6.3)	0 (0)	
Ischemic stroke	1 (6.3)	0 (0)	
Deep-vein thrombosis	1 (6.3)	2 (12.5)	
Pulmonary embolism	1 (6.3)	1 (6.3)	
Superficial venous thrombosis	1 (6.3)	0 (0)	
Death within 30 days	2 (12.5)	5 (31.3)	.39
Restart of any AC	10 (62.5)	9 (56.3)	.99
Prophylactic AC	6 (37.5)	6 (37.5)	
Therapeutic AC	4 (25.0)	3 (18.8)	
Thrombotic event after AC restarted	1/5 (20)	4/4 (100)	

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; AC, anticoagulation.
[a]Data presented as no. (%).

In the 4F-PCC group, a total of 4 thrombotic events occurred across 3 patients. One patient experienced a PE and a renal thrombosis causing acute kidney injury. The remaining 2 patients both experienced DVTs. The median time to event was 13 days (IQR: 11.5 - 15.6). All thrombotic events in the 4F-PCC cohort were diagnosed after the initiation of prophylactic or therapeutic anticoagulation. In all, 7 patients (42.8%) were not re-started on anticoagulation (prophylactic or therapeutic) during their hospital admission following 4F-PCC administration. In those restarted on a form of anticoagulation, the median time to initiation was 3 days (IQR: 3 - 5).

Death within 30-days occurred in 2 (12.5%) andexanet alfa patients versus 5 (31.3%) 4F-PCC patients ($P = .39$). In the andexanet alfa group, mortality occurred at 1.5 and 2.5 days. Both patients had intracranial bleeds with a GCS score of 8 and 4. In the andexanet alfa cohort, 1 patient was lost to follow-up and their last known outcomes at day 24 were carried forward. For 4F-PCC patients, the median time to mortality was 8.5 days (IQR: 5.5 - 19). The 4 of the 5 patients had intracranial bleeds, median GCS of these 4 patients was 12 (IQR: 10 - 13), and 1 patient had a GIB. A total of 4 patients were lost to follow-up and their last known outcomes were carried forward. There was no difference in mortality rates

among patients who achieved effective hemostasis compared to those who did not (22.7% [5 of 22] vs 20% [2 of 10], respectively, $P = .99$).

Discussion

In this retrospective cohort study, there was no statistically significant difference in the achievement of effective hemostasis at 12 h between andexanet alfa and 4F-PCC for FXa-inhibitor-related bleeding. Though some study definitions differ, in general, these rates are within the ranges of effective hemostasis seen in previously published reports, which range from 47.6% to 90.9% for andexanet alfa,[8,10-12,15,38] and 60% to 94.7% for 4F-PCC.[14-28,38] A recent meta-analysis of real-world use estimated weighted mean effectiveness of 82% and 88% at 12 h for andexanet alfa and 4F-PCC, respectively.[38] When looking exclusively at patients with an ICH, andexanet alfa, although lower, was not statically different in achievement of effective hemostasis compared to 4F-PCC in our cohort. This contrasts with estimates from a retrospective study by Barra et al who reported a numerically higher incidence of excellent or good hemostasis with andexanet alfa compared to 4F-PCC for ICH (88.9% vs 60%, respectively).[15] As with our study, changes in proportional estimates are strongly influenced by a small sample size. The aforementioned meta-analysis evaluated patients with ICH at 12 and 24 h. The estimated mean hemostatic effectiveness was 57% and 89% with andexanet alfa and 88% and 73% for 4F-PCC, respectively.[38] In ICH, a low GCS is a poor prognostic factor.[39,40] Barra et al reported median GCS scores of 15 and 10 for andexanet alfa and 4F-PCC, respectively. Median GCS scores for patients with ICH in our cohort were 8 for andexanet alfa and 13 for 4F-PCC. Thus, groups with a lower median GCS score had worse outcomes suggesting the benefit of either therapy may be limited by the severity of ICH. The differences in baseline GCS scores could have also had a strong influence on our results.

Optimal dosing of 4F-PCC for reversal of FXa-inhibitor-related bleeding is not well defined. Animal studies and data in healthy subjects indicate a dose-dependent effect of 4F-PCC on the correction of coagulation markers in the presence of FXa inhibitors.[41,42] However, clinical data in patients with FXa-inhibitor-related acute hemorrhage have shown lower doses (25-35 units/kg) of 4F-PCC are effective at achieving hemostasis.[15,17,18,21,24,26,28] In our study the average initial 4F-PCC dose was 27.9 units/kg. Wilsey et al compared 4F-PCC 25 units/kg to 50 units/kg and found no difference in hemostatic efficacy outcomes.[28] This is the only study to date comparing different doses of 4F-PCC for FXa-inhibitor-associated bleeding. As such, it remains unclear if the doses used in our study were sufficient for optimal 4F-PCC efficacy. More data comparing 4F-PCC doses for FXa-inhibitor-related bleeding is required to guide clinicians.

Thrombotic event rates were high in both andexanet alfa and 4F-PCC groups (25% and 18.8%, respectively). These percentages are greater than those reported in most prior studies. Previously reported rates of thrombotic events range 0% to 19% for andexanet alfa[8,10-12,15,38,43,44] and 0 to 12.9% for 4F-PCC.[14-18,20-28,38,45-47] Numerically more patients in the andexanet alfa cohort had venous thromboembolism (VTE) indication for FXa inhibitor use compared to 4F-PCC in our cohort. Those who received andexanet alfa with a baseline VTE indication had a 40% (2 of 5) incidence of new thrombosis development. This is relevant in the context that the overwhelming majority of thromboembolic events in the andexanet alfa group experienced these events remote from the administration of the antidote (median 6.5 days), as well as prior to the implementation of any prophylactic or therapeutic anticoagulation. This is consistent with observations from other reports[8] and likely reflects the underlying propensity for thromboembolism in these patients when anticoagulation therapy is removed. Importantly, 2 of the 4 andexanet alfa patients who developed a thrombosis also received 4F-PCC, 1 received both 4F-PCC and factor-VIIa.[13] Andexanet alfa is not considered to be a prothrombotic agent and has been shown to return thrombin generation back to preanticoagulation levels in healthy volunteers.[9,48] However, factor VIIa and 4F-PCC both carry an independent thrombotic risk.[49,50] Since andexanet alfa brings thrombin generation back to baseline the administration of these other products could push patients into a prothrombotic state.[9]

Our reported mortality rates in the andexanet and 4F-PCC groups were within the ranges seen in previous studies, which span 10.3% to 40% for andexanet alfa[8,10-12,15,38,43,44] and 4.7% to 63.6% for 4F-PCC.[14-28,38,45-47] Barra et al[15] reported a lower incidence of mortality in the andexanet alfa group compared to 4F-PCC (22.2% vs 63.6%, respectively). The observed 4F-PCC mortality rate in this study was likely influenced by the lower GCS scores and larger initial intracranial hematoma volumes in the 4F-PCC group. Two other retrospective analyses have associated a decreased incidence of mortality with andexanet alfa compared to 4F-PCC.[31,32] However, a meta-analysis associated andexanet alfa with a nonsignificantly increased hospital mortality yet a numerically lower 30-day mortality.[38] A randomized prospective study is needed to further examine these associations. A prospective, randomized, open-label phase 4 study will compare andexanet alfa to usual care for FXa-inhibitor reversal in ICH (NCT03661528) and hopefully provide more information in this area.

Limitations of this study include its small sample size and retrospective design. The sample size limits the comparative interpretation of our report as confounding and outliers may have a greater impact on outcome estimates. Patients in the 4F-PCC group were randomly selected from a list of historical patients that received 4F-PCC for FXa-inhibitor reversal. Only patients that presented before the date when andexanet alfa was available at study institutions were included in the 4F-PCC group. However, selection bias and confounding cannot be eliminated. Prior to 2018, there was limited information on the use of 4F-PCC for FXa-inhibitor reversal. This could have influenced the higher number of ICH patients in the 4F-PCC group. Since ICH is known to have worse mortality

outcomes, providers may have initially reserved 4F-PCC for this indication. The pragmatic design allowed for the use of additional procoagulants. This may have influenced both hemostatic efficacy and thromboembolic outcomes, especially for the andexanet alfa group since 5 patients received other procoagulants. In addition, the timing of repeat imaging and laboratory monitoring could not be controlled so the closest available time point was used for assessment. A total of 5 patients were lost to follow-up and therefore could not be fully assessed for thromboembolic complication or death (1 patient in the andexanet alfa group and 4 patients in the 4F-PCC group). Their last known values and outcomes were carried forward. Lastly, the time of last FXa-inhibitor dose was unknown in 43.8% of patients and anti-Xa levels were not routinely performed. Therefore, the presence and magnitude of FXa-inhibitor activity were not confirmed for many patients prior to administration of a reversal agent. This may be an important consideration given the results of an in vitro investigation noting insufficient tissue factor initiated thrombin generation with 4F-PCC at apixaban and rivaroxaban concentrations above 75 ng/mL.[51] Similarly, in healthy volunteers with an average rivaroxaban trough concentration of 130 ng/mL, punch biopsy bleeding was not reduced following 4F-PCC (50 units/kg) although endogenous thrombin potential did increase compared to saline controls.[52] Nevertheless, our cohort represents our observations in a real-world setting of FXa-inhibitor-related bleeding.

Conclusions

Andexanet alfa and 4F-PCC both achieved effective hemostasis in a majority of the patients. However, both groups also had a high incidence of thromboembolic events. A small sample size, co-administration of other procoagulants, and delay in restarting anticoagulation may have contributed to thromboembolic risk. A prospective randomized trial is required to better elucidate differences between outcomes with andexanet alfa and 4F-PCC for FXa-inhibitor-related major hemorrhage.

Declaration of Conflicting Interests

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ORCID iDs

Victoria M. Stevens https://orcid.org/0000-0002-2312-0297
Tyree H. Kiser https://orcid.org/0000-0001-7415-3999

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