Journal of Clinical Pharmacy and Therapeutics

WILEY

RESEARCH ARTICLE OPEN ACCESS

The Selection of Andexanet Alfa vs. 4-Factor Prothrombin Complex Concentrate for the Treatment of Life-Threatening Hemorrhage

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Received: 18 September 2025 | **Revised:** 23 July 2026 | **Accepted:** 7 August 2026

Academic Editor: Fortofoiu Mircea-Catalin

Keywords: 4-factor prothrombin complex concentrate | andexanet alfa | anticoagulation reversal | oral factor Xa inhibitors

ABSTRACT

Andexanet alfa and 4-factor prothrombin complex concentrate (4F-PCC) are used for the reversal of life-threatening hemorrhages associated with oral Factor Xa inhibitors. Limited studies have examined factors influencing reversal agent selection and time to administration. This retrospective, multicenter cohort study evaluated adult patients who presented with a life-threatening hemorrhage associated with oral Factor Xa inhibitors (apixaban or rivaroxaban) and were administered either andexanet alfa or 4F-PCC. The objectives of our study were to analyze whether sociodemographic factors were associated with reversal agent selection, time-to-treatment with the selected reversal agent, and patient outcomes. Among 144 patients (50% andexanet alfa and 50% 4F-PCC), no differences were found in sociodemographic (age, sex, race and ethnicity, insurance, housing status, marital status) or logistical factors (time to reversal agent administration and type of arrival to site hospital) associated with reversal agent selection. There were no differences between andexanet alfa and 4F-PCC for time to reversal agent administration, mortality, mechanical ventilation, length of stay, and thromboembolic events. Factors associated with a longer time to reversal agent administration included patients who were transferred from an outside hospital (RR: 1.27; 95% CI: 1.00, 1.61), patients who received blood products (RR: 1.30; 95% CI: 1.01, 1.68), and patients who were Black compared to non-Hispanic White (RR: 1.34; 95% CI: 1.02, 1.76) after adjusting for age, sex, reversal agent selection (andexanet vs. 4F-PCC), bleeding event type related to Factor Xa inhibitors, insurance, and marital status. In conclusion, there were no statistically significant disparities found in sociodemographic factors associated with the selection of andexanet alfa and 4F-PCC.

1 | Introduction

Factor Xa inhibitors are direct oral anticoagulants (DOACs) used for the treatment and prevention of thromboembolic events associated with atrial fibrillation and/or a history of deep venous thrombosis and pulmonary embolism. While DOACs are considered generally safe, their primary adverse event is the risk of life-threatening intracranial (ICH), gastrointestinal (GI), or traumatic hemorrhages [1]. Rivaroxaban seems to be associated with increased risk of hemorrhagic events compared to apixaban [2–4].

Treatment options for life-threatening hemorrhages occurring in patients taking apixaban or rivaroxaban include andexanet alfa and 4-factor prothrombin complex concentrate (4F-PCC). Andexanet alfa is a recombinant modified Factor Xa protein which received accelerated approval by the U.S. Food and Drug Administration (FDA) in May 2018 to reverse the effects of apixaban and rivaroxaban in patients with life-threatening hemorrhages [5]. Comparative effectiveness studies have yielded mixed results regarding the efficacy and safety of andexanet alfa vs. 4F-PCC in reversing the effects of apixaban and rivaroxaban, though this does seem to correlate to study design and power. Several studies found no differences in achieving hemostatic efficacy between patients who received andexanet alfa and 4F-PCC, though these were limited based on their smaller sample sizes (under 50 patients) and single-center design [6, 7]. Comparatively, in a large observational cohort trial, which included over 4000 patients from multiple hospitals, treatment with andexanet alfa in patients hospitalized with DOAC-related bleeds was associated with 50% lower odds of in-hospital mortality compared to 4F-PCC. However, in this study, the andexanet group was more homogenous with significantly more patients with moderate (GCS 9–12) or severe (GCS < 8) GCS scores compared to the 4F-PCC group [8]. With regard to more secondary outcomes, studies with smaller sample sizes have reported no differences between andexanet alfa and 4F-PCC in hospital length of stay, intensive care unit (ICU) length of stay, and thromboembolic events [9, 10]; however, several studies, including the ANNEXA-I randomized trial, have found a higher incidence of thromboembolic events for andexanet alfa compared to 4F-PCC [11, 12]. In a systematic review with meta-analysis by White and colleagues that adjusted for risk of bias and study quality, there was no significant difference in thrombotic events between andexanet alfa and 4F-PCC, but there was a significantly lower 30-day mortality and improved hemostatic efficacy in patients receiving andexanet alfa versus 4F-PCC [13]. After considering the higher-quality studies such as ANNEXA-I that showed a higher risk of thrombotic events, the FDA communicated to AstraZeneca that the risks of this product outweighed benefits, and AstraZeneca decided to end commercial sales of andexanet alfa on December 22, 2025.

Sociodemographic factors associated with the selection of andexanet alfa or 4F-PCC have not been extensively studied. Several small studies report similar baseline demographic characteristics for those who receive andexanet alfa and 4F-PCC [9–11, 13]. Andexanet alfa is considerably more expensive than 4F-PCC, which may present logistical and sociodemographic barriers to treatment. Most major medical centers have protocols for selection and administration of reversal agents in life-threatening hemorrhages to guide clinicians in standardizing patient care. The primary aim of our study was to analyze if sociodemographic factors were associated with differences in selection of andexanet alfa versus 4F-PCC as the reversal agent for life-threatening hemorrhages in patients on rivaroxaban or apixaban. A secondary objective was to detect whether these factors were associated with different time-to-treatment intervals with the selected reversal agent. The final objective was to evaluate whether these factors affected patient outcomes (length of stay, mechanical ventilation, death).

2 | Methods

This retrospective cohort study was approved by a central institutional review board (IRB), the Western Copernicus Group, and the respective local IRBs at participating sites. The study included patients randomly sampled from four Level 1 trauma centers in urban areas within the Toxicology Investigators Consortium (ToxIC) program. ToxIC is a multicenter research and surveillance network led by medical toxicology physicians at more than 30 major medical centers across the United States [12]. Inclusion criteria were cases between January 2019 and July 2024 that were aged 18 years and older with a history of current apixaban or rivaroxaban use who presented with an acute life-threatening hemorrhage and were treated with either andexanet alfa or 4F-PCC. Exclusion criteria included individuals under 18 years of age, individuals who were incarcerated at the time of the event, and patients who died before receiving treatment for the hemorrhage. Cases were also excluded if race/ethnicity and sex were not documented in the electronic medical record (EMR). However, the case was included if at least one of either race or ethnicity was documented in the EMR. Sampling frames were created by obtaining de-identified patient lists from each institution of individuals who received either andexanet alfa or 4F-PCC. Random number generators were used to conduct proportional sampling from each site. Data on specific a priori parameters were abstracted from the EMR for each randomly selected patient. De-identified data were then entered into Research Electronic Data Capture (REDCap), a secure, web-based software platform [14–16].

2.1 | Study Variables

Sociodemographic variables collected were age, sex, race, ethnicity, marital status, insurance, and housing status. Logistical factors abstracted included arrival time to hospital site and time from hospital arrival to reversal agent administration. Past medical history was obtained. Current apixaban or rivaroxaban treatment was assessed by obtaining characteristics about last dose taken, reason for DOAC treatment, and length of time on DOAC treatment prior to presentation. Clinical signs, symptoms, and treatment received were also documented, including the bleeding event type, non-PCC blood products administered, imaging conducted, specialty services or consultations received, mechanical ventilatory support, length of stay, and vital signs. Bleeding event types were categorized into ICH (spontaneous or traumatic), other trauma (excludes head trauma), GI hemorrhage, and other hemorrhage (e.g., aortic dissection).

2.2 | Outcomes

The primary outcomes for this study included: (1) Reversal agent selection, (2) Time to reversal agent administration after presentation to the initial receiving hospital, (3) Mechanical ventilation (binary—yes/no), (4) Length of stay (measured in days), and (5) In-hospital mortality. For those who were transferred from an outside hospital, time to reversal agent administration was calculated using the time of presentation to the original hospital to time of departure (original hospital length of stay), duration of transport, and time from arrival to second hospital to reversal agent administration. Time was measured in minutes and was transformed prior to fitting a statistical model due to non-normality and several outliers. The transformation that resulted in optimal model fit was operationalized using 30-min segments (e.g., < 29 min, 30–59 min, etc.) up until 319 min. For those who had an administration time of 319 min or more, these subjects were

TABLE 1 | Sociodemographic and past medical history characteristics among patients administered andexanet alfa vs. 4F-PCC ($n = 144$).

	Andexanet alfa *N = 72*	4F-PCC *N = 72*	Total *N = 144*	*p* value
Age in years, Median (IQR)	76.0 (68.0, 80.5)	75.0 (67.0, 81.0)	75.0 (68.0, 81.0)	0.33
Sex				
Male	43 (60%)	45 (63%)	88 (61%)	0.86
Female	29 (40%)	27 (38%)	56 (39%)	
Race and ethnicity				
White (non-Hispanic)	65 (90%)	61 (85%)	126 (88%)	0.45
Black/African-American	5 (7%)	10 (14%)	15 (10%)	
Asian	2 (3%)	1 (1%)	3 (2%)	
Marital status				
Single, never married	11 (15%)	6 (8%)	17 (12%)	0.55
Married	41 (57%)	48 (67%)	89 (62%)	
Divorced/separated	4 (6%)	6 (8%)	10 (7%)	
Widowed	13 (18%)	10 (14%)	23 (16%)	
Unknown	3 (4%)	2 (3%)	5 (4%)	
Housing status				
Stable housing	70 (97%)	71 (99%)	141 (98%)	1.00
Non-criminal supervised care	2 (3%)	1 (1%)	3 (2%)	
Insurance Status				
Medicaid	1 (1%)	2 (3%)	3 (2%)	0.97
Medicare	57 (79%)	54 (75%)	111 (77%)	
Private	6 (8%)	7 (10%)	13 (9%)	
Uninsured	1 (1%)	1 (1%)	2 (1%)	
Other	0	1 (1%)	1 (1%)	
Unknown	7 (10%)	7 (10%)	14 (10%)	

(Continues)

TABLE 1 | (Continued)

	Andexanet alfa *N* = 72	4F-PCC *N* = 72	Total *N* = 144	*p* value
Major past medical/psychiatric history				
Asthma/COPD	14 (19%)	16 (22%)	30 (21%)	0.84
Arrhythmias—atrial fibrillation	56 (78%)	56 (78%)	112 (78%)	1.00
Arrhythmias—other	8 (11%)	3 (4%)	11 (8%)	0.21
Cancer	20 (28%)	22 (31%)	42 (29%)	0.86
Cardiovascular disease	53 (74%)	58 (81%)	111 (77%)	0.43
Congestive heart failure	23 (32%)	33 (46%)	56 (39%)	0.12
Deep venous thrombosis	9 (13%)	12 (17%)	21 (15%)	0.64
Dementia	5 (7%)	1 (1%)	6 (4%)	0.21
Developmental delay	0	0	0	NA
Diabetes mellitus	20 (28%)	27 (38%)	47 (33%)	0.29
Hemorrhagic stroke	3 (4%)	1 (1%)	4 (3%)	0.62
Hepatic disease	2 (3%)	4 (6%)	6 (4%)	0.68
HIV/AIDS	0	2 (3%)	2 (1%)	0.50
Ischemic stroke	17 (24%)	9 (13%)	26 (18%)	0.13
Obesity (BMI > 30)	8 (11%)	10 (14%)	18 (13%)	0.80
Other neurological diagnosis	5 (7%)	0	5 (4%)	0.06
Pulmonary embolism	9 (13%)	11 (11%)	17 (12%)	1.00
Psychiatric illness	14 (19%)	15 (21%)	29 (20%)	1.00
Renal disease	19 (26%)	21 (29%)	40 (28%)	0.85
Transient ischemic attack	5 (7%)	5 (7%)	10 (7%)	1.00
Alcohol use disorder	3 (4%)	4 (6%)	7 (5%)	1.00
Other substance use disorder	1 (1%)	1 (1%)	2 (1%)	1.00
If renal disease, is patient on dialysis?				
Yes	2 (11%)	3 (14%)	5 (12%)	1.00
No	17 (90%)	18 (86%)	36 (88%)	
Was the patient prescribed or taking any of the following anticoagulant or antiplatelet medications at home prior to arrival?				
Aspirin	5 (7%)	11 (15%)	16 (11%)	0.18
Clopidogrel	2 (3%)	3 (4%)	5 (4%)	1.00
Dabigatran	0	0	0	—
Enoxaparin	0	0	0	—
Prasugrel	0	0	0	—
Ticagrelor	0	1 (1%)	1 (1%)	1.00
Ticlopidine	0	0	0	—
Warfarin	1 (1%)	2 (3%)	3 (2%)	1.00
Other	0	0	0	—

(Continues)

TABLE 1 | (Continued)

	Andexanet alfa $N = 72$	4F-PCC $N = 72$	Total $N = 144$	p value
How did the patient arrive at your sites' facility?				
Ambulatory/walk-in	16 (22%)	9 (13%)	25 (17%)	
EMS	40 (56%)	49 (68%)	89 (62%)	0.23
Transfer from an outside facility	15 (21%)	14 (19%)	29 (20%)	
Other	0	0	0	
Unknown	1 (1%)	0	1 (1%)	
Was the patient taking rivaroxaban or apixaban prior to arrival?				
Rivaroxaban				
Apixaban	13 (18%)	18 (25%)	31 (22%)	0.42
	59 (82%)	54 (75%)	113 (79%)	

Note: M, mean; IQR, interquartile range; ICH, intracranial hemorrhage; GI, gastrointestinal; AIDS, acquired immunodeficiency syndrome.
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; EMS, emergency medical services; 4F-PCC, 4-factor prothrombin complex concentrate; HIV, human immunodeficiency disease; SD, standard deviation.

collapsed into the maximum category. The range of this outcome was 1–12 segments. Length of stay was treated as a continuous variable and measured in days. The outcome of reversal agent type was also included to examine predictors associated with receiving andexanet alfa vs. 4F-PCC.

2.3 | Data Analysis

Data analysis consisted of descriptive statistics computed between those who received andexanet alfa vs. 4F-PCC and bivariate statistical tests (e.g., Chi-square tests or Fisher's exact tests for categorical variables and independent samples *t*-Tests or Wilcoxon rank sum tests for continuous variables). Analyses also consisted of examining bivariate associations between sociodemographic, logistical factors, and clinical characteristics with primary outcomes. Multivariable modeling was conducted to assess statistically significant predictors with the primary outcomes. Logistic regression was used for binary outcomes (e.g., death, mechanical ventilation), and negative binomial regression was used for length of stay and time to reversal agent outcomes due to overdispersion. Model fit statistics were assessed using goodness-of-fit tests and log-likelihood tests for nested models. Odds ratios (OR) and rate ratios (RR) were computed for logistic and negative binomial models, respectively, with corresponding 95% confidence intervals (CIs). Subgroup analyses were conducted excluding those who were transferred from outside hospitals to determine if significant differences existed between those who were transferred and those who were not. Subgroup analyses were also conducted for type of bleeding event. All analyses were conducted in R v4.3.3.

3 | Results

Among the 144 patients included in the study, 50% consisted of patients who received andexanet alfa and 50% received 4F-PCC. The median age was 75 years (interquartile range [IQR]: 68.0, 81.0), 61% were male, and 88% were non-Hispanic White (Table 1). There were no statistically significant differences for sociodemographic variables among those who received andexanet alfa vs. 4F-PCC.

Apixaban and rivaroxaban indication and dosing characteristics among included patients are presented in Table 2; 22% of patients were taking rivaroxaban prior to arrival, and 79% were taking apixaban prior to arrival. There were no statistically significant differences in the choice of reversal agent between those taking apixaban and rivaroxaban ($p = 0.42$). The indication for anticoagulation for the majority of patients taking either apixaban or rivaroxaban was atrial fibrillation (76%), followed by deep venous thrombosis (14%), pulmonary embolism (11%), and ischemic stroke (2%). Over half of patients (54%) were on apixaban or rivaroxaban for more than a year prior to the bleeding event. There were also no statistically significant differences between those who received andexanet alfa vs. 4F-PCC regarding the time of the last known DOAC dose or the time of the "last known well" and arrival at the receiving hospital. Nearly a third of patients had a "last known well" less than an hour prior to arrival at the initial healthcare facility, with 17% having a "last known well" between 1 and 3 h. Individual characteristics stratified by

TABLE 2 | Apixaban and rivaroxaban treatment characteristics among patients receiving andexanet alfa vs. 4F-PCC.

	Andexanet alfa *N* = 72	4F-PCC *N* = 72	Total *N* = 144	*p* value
Was the patient taking rivaroxaban or apixaban prior to arrival?				
Rivaroxaban	13 (18%)	18 (25%)	31 (22%)	0.42
Apixaban	59 (82%)	54 (75%)	113 (79%)	
Reason they were taking apixaban or rivaroxaban[a]				
Arrhythmias—atrial fibrillation	54 (75%)	56 (78%)	110 (76%)	0.84
Deep venous thrombosis	8 (11%)	12 (17%)	20 (14%)	0.47
Ischemic stroke	3 (4%)	0	3 (2%)	0.24
Pulmonary embolism	9 (13%)	7 (10%)	16 (11%)	0.79
Other	3 (4%)	3 (4%)	6 (4%)	1.00
Unknown	1 (1%)	0	1 (1%)	—
How long have they been taking Rivaroxaban/Apixaban prior to arrival?[b]				
Less than 1 month	7 (10%)	10 (14%)	17 (12%)	0.99
1–6 months	7 (10%)	9 (13%)	16 (11%)	
> 6 months–1 year	7 (10%)	9 (13%)	16 (11%)	
> 1 year	36 (50%)	42 (58%)	78 (54%)	
Unknown	15 (21%)	2 (3%)	17 (12%)	
How many hours elapsed between their last rivaroxaban/apixaban dose and arrival at the initial healthcare facility?[b]				
Less than 1 h		0	2 (1%)	0.60
1–3 h	2 (3%)	9 (13%)	15 (10%)	
> 3–6 h	6 (8%)	5 (7%)	10 (7%)	
> 6–12 h	5 (7%)	11 (15%)	22 (15%)	
> 12–24 h	11 (15%)	13 (18%)	18 (13%)	
> 24 h	5 (7%)	5 (7%)	6 (4%)	
Unknown	1 (1%)	29 (40.3%)	71 (49%)	
	42 (58%)			
How many hours elapsed between the patients "last known well" and arrival at the initial healthcare facility?[b]				
Less than 1 h	27 (38%)	19 (26%)	46 (32%)	0.64
1–3 h	12 (17%)	13 (18%)	25 (17%)	
> 3–6 h	6 (8%)	6 (8.3%)	12 (8%)	
> 6–12 h	10 (14%)	7 (9.7%)	17 (12%)	
> 12–24 h	3 (4%)	5 (6.9%)	8 (6%)	
> 24 h	7 (10%)	12 (16.7%)	19 (13%)	
Unknown	7 (10%)	10 (13.9%)	17 (12%)	

Abbreviation: 4F-PCC = 4-factor prothrombin complex concentrate.
[a]Not mutually exclusive categories; percentages may add up to > 100%.
[b]Statistical testing excludes unknown responses.

apixaban or rivaroxaban are displayed in Supporting Tables 1 and 2, respectively.

Clinical characteristics among patients who received either andexanet alfa or 4F-PCC are displayed in Table 3. There were statistically significant differences in bleeding event type precipitating reversal agent administration between those who were administered andexanet alfa and 4F-PCC. Among those who were administered andexanet alfa, 64% had an ICH compared to only 46% of those who were administered 4F-PCC ($p = 0.04$). A higher percentage of those who received 4F-PCC had a GI hemorrhage compared to those who received andexanet alfa (32% vs. 18%, respectively). This represents an approximately 50% relative difference in agent selection. However, there were no statistically significant differences in bivariate comparisons of length of stay, ICU stay, and patient's disposition between those who were administered andexanet alfa vs. 4F-PCC. The in-hospital mortality rate of those administered andexanet alfa was 19% compared to 15% of those administered 4F-PCC ($p = 0.26$). When comparing those who died with those who survived (Supporting Tables 3 and 4), there were no statistically significant bivariate differences in sociodemographic characteristics or clinical factors. Subgroup analyses for bleeding type showed a slightly higher mortality rate for those with spontaneous ICH (27%) compared to other bleeding types (Supporting Table 5).

TABLE 3 | Clinical characteristics among patients receiving andexanet alfa vs. 4F-PCC.

	Andexanet alfa *N* = 72	4F-PCC *N* = 72	Total *N* = 144	*p* value
What type of bleeding event necessitated apixaban or rivaroxaban reversal?				
Intracranial hemorrhage	46 (64%)	33 (46%)	79 (55%)	**0.04**
Other trauma (nonhead trauma)	5 (7%)	12 (17%)	17 (12%)	0.12
GI bleed	13 (18%)	23 (32%)	36 (25%)	0.08
Other specify bleed	8 (11%)	4 (6%)	12 (8%)	0.37
Other bleeding event				
Aortic dissection	2 (3%)	0	2 (1%)	—
Diffuse alveolar hemorrhage	0	1 (1%)	1 (1%)	
Hemorrhagic liver cyst	0	1 (1%)	1 (1%)	
Left internal iliac artery hemorrhage	1 (1%)	0	1 (1%)	
Perforated small bowel obstruction	1 (1%)	0	1 (1%)	
Pericardial effusion	1 (1%)	0	1 (1%)	
Perihepatic hematoma	1 (1%)	0	1 (1%)	
Recent tongue resection surgery	1 (1%)	0	1 (1%)	
Retroperitoneal hematoma	0	1 (1%)	1 (1%)	
Right groin hematoma	0	1 (1%)	1 (1%)	
Splenic hemorrhage	1 (1%)	0	1 (1%)	
Did the patient receive non-PCC blood products prior to andexanet alfa or 4F-PCC?[a]				
Yes	10 (14%)	26 (36%)	36 (25%)	**0.003**
No	62 (86%)	45 (63%)	107 (74%)	
Unknown	0	1 (1%)	1 (1%)	
Blood products administered prior to andexanet alfa or 4F-PCC administration, ($n = 36$)[b]				
Cellsaver	0	0	0	—
Cryoprecipitate	0	1 (1%)	1 (1%)	
Fresh frozen plasma	1 (1%)	4 (6%)	5 (4%)	
Packed red blood cells	10 (14%)	24 (33%)	34 (24%)	
Platelets	1 (1%)	7 (10%)	8 (6%)	
Whole blood	0	0	0	
Other	0	0	0	
Unknown	0	0	0	
Mechanical ventilation				
Yes	34 (47%)	26 (36%)	60 (42%)	0.24
No	38 (53%)	46 (64%)	84 (58%)	
Was the patient admitted to the ICU?				
Yes	65 (90%)	60 (83%)	125 (87%)	0.33
No	7 (10%)	12 (17%)	19 (13%)	
If yes, total ICU stay, median (IQR)	3.0 (2.0, 8.0)	4.0 (2.0, 7.3)	3.0 (2.0, 8.0)	0.89
Total length of stay, median (IQR)	7.0 (5.0, 15.3)	6.0 (3.0, 11.3)	7.0 (3.0, 14.0)	0.38

(Continues)

TABLE 3 | (Continued)

	Andexanet alfa *N* = 72	4F-PCC *N* = 72	Total *N* = 144	*p* value
Did the patient experience any thromboembolic complications during their hospital stay?[a]				
Yes	3 (4%)	2 (3%)	5 (4%)	1.00
No	69 (96%)	69 (96%)	138 (96%)	
Unknown	0	1 (1%)	1 (1%)	
Was patient restarted on oral anticoagulation after reversal agent administration?				
Yes	25 (35%)	30 (42%)	55 (38%)	0.49
No	47 (65%)	42 (58%)	89 (62%)	
If yes, was the patient restarted on anticoagulation as a prophylactic measure or in response to a thrombotic event that occurred after reversal agent administration ($n = 55$)?				
Prophylaxis	24 (96%)	30 (100%)	54 (98%)	0.45
Treatment	1 (4%)	0	1 (2%)	
What was the patient's disposition?				
Died discharged; home discharged to acute rehab; discharged to psychiatric facility; transferred to another hospital; other	14 (19%)	11 (15%)	25 (17%)	0.26
	22 (31%)	33 (46%)	55 (38%)	
	34 (47%)	26 (36%)	60 (42%)	
	1 (1%)	0	1 (1%)	
	0	0	0	
	1 (1%)	2 (3%)	3 (2%)	
Time from arrival to reversal agent[c] administration in minutes, M (SD) range 2.0–5966.0	333.2 (730.9)	398.2 (771.0)	366.2 (749.4)	0.88
Time from arrival to reversal agent[c] administration in minutes, median (IQR) range 2.0–5966.0	201.0 (124.0, 338.0)	184.0 (90.0, 381.5)	200.5 (101.8, 362.5)	0.88
Time from arrival to reversal agent[d] administration in minutes excluding outliers > 1000 min, mean (SD) range 2.0–927.0	233.1 (168.35)	259.1 (241.15)	246.1 (207.54)	0.63
Time from arrival to reversal agent administration in 30 min blocks, M (SD)	7.1 (3.4)	7.1 (3.8)	7.1 (3.6)	0.85

Note: M, mean; IQR, interquartile range; ICH, intracranial hemorrhage; GI, gastrointestinal.
Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; ICU, intensive care unit; SD, standard deviation.
[a]Statistical tests excluded those who were listed as unknown.
[b]Not mutually exclusive categories; percentages may add up to > 100%.
[c]$n = 2$ missing for outside hospital antidotal administration time; $n = 1$ missing for site antidotal administration time. Time to reversal agent includes both those who presented at the initial site hospital and those who were transferred from an outside hospital with complete time documentation of initial arrival to reversal agent.
[d]Excludes additional 6 cases for outliers > 1000 min from arrival to reversal agent administration.

Multivariable models for time to reversal agent administration are displayed in Table 4. Blood product administration (RR: 1.30; 95% CI: 1.01, 1.68), transportation from an outside hospital (RR: 1.27; 95% CI: 1.27, 1.00, 1.61), and Black individuals compared to White/non-Hispanic individuals (RR: 1.34; 95% CI: 1.02, 1.76) were associated with a longer time to reversal agent administration, after adjusting for sociodemographic and DOAC characteristics. Patients who were taking rivaroxaban received the reversal agent 33% faster, on average, compared to those who were taking apixaban (RR: 0.67; 95% CI: 0.53, 0.85). Those who had non-Medicare insurance (e.g., Medicaid, private, uninsured) also had a faster time on average to reversal agent administration compared to those with Medicare insurance (RR: 0.69; 95% CI: 0.54, 0.89). There were no statistically significant predictors associated with mortality in the multivariable model (Table 5). The odds of receiving mechanical ventilation were lower for traumatic ICH (adjusted odds ratio [aOR]: 0.28; 95% CI: 0.09, 0.82) and GI hemorrhage (aOR: 0.06; 95% CI: 0.01, 0.26) compared to those with spontaneous ICH. Those who received blood

TABLE 4 | Time to reversal agent administration among patients receiving andexanet alfa or 4F-PCC after a major bleeding event across 4 sites.

	Time to reversal agent administration	
	Unadjusted rate ratios (95% CI)	**Adjusted rate ratios(95% CI)**
Age (continuous)	1.00 (0.99, 1.01)	1.00 (0.98, 1.01)
Sex		
Male	Ref.	Ref.
Female	0.97 (0.81, 1.17)	1.02 (0.84, 1.25)
Race and ethnicity		
Black	1.23 (0.94, 1.61)	**1.34 (1.02, 1.76)**
White/non-Hispanic	Ref.	Ref.
Initial DOACT		
Apixaban	Ref.	Ref.
Rivaroxaban	**0.74 (0.59, 0.92)**	**0.67 (0.53, 0.85)**
Reversal agent treatment		
Andexanet alfa	1.00 (0.84, 1.20)	0.99 (0.82, 1.18)
4F-PCC	Ref.	Ref.
Bleeding event type		
Spontaneous ICH	Ref.	Ref.
Traumatic ICH	1.03 (0.81, 1.31)	1.07 (0.84, 1.36)
Other trauma (non-head)	0.99 (0.72, 1.37)	0.98 (0.70, 1.38)
GI bleed	0.92 (0.72, 1.19)	0.86 (0.64, 1.16)
Other bleed	1.01 (0.70, 1.47)	0.95 (0.66, 1.36)
Blood products administered		
Yes	1.09 (0.88, 1.34)	**1.30 (1.01, 1.68)**
No	Ref.	Ref.
Arrival type		
Ambulatory/walk-in	1.17 (0.93, 1.47)	1.18 (0.93, 1.49)
Transfer from another hospital	1.22 (0.95, 1.55)	**1.27 (1.00, 1.61)**
EMS	Ref.	Ref.
Insurance		
Medicare	Ref.	Ref.
Other insurance type	**0.77 (0.62, 0.96)**	**0.69 (0.54, 0.89)**
Marital status		
Married	Ref.	Ref.
Single, divorced, widowed, or other	1.02 (0.85, 1.23)	1.10 (0.91, 1.34)

Note: Time to reversal agent = measured in 30-min segments as a count variable (range 1–12). Time of reversal agent administration for times > 319 min were included as a maximum value of 12. Model for length of stay fit statistics: Akaike Information Criterion (AIC) 659.51 and goodness-of-fit test (residual deviance: 130.97, $df = 107$, $p = 0.06$), log-likelihood test statistic between negative binomial and Poisson regression was statistically significant ($p < 0.001$). Asian individuals excluded from these multivariable models because of instability with small cell sizes. Adjusted models included the following variables: age, sex, race and ethnicity, initial DOACT, reversal agent treatment, bleeding event type, blood products administered, arrival type, insurance, and marital status; GI, gastrointestinal; DOACT, direct oral anticoagulant treatment; ICH = intracranial hemorrhage. Bold values indicate $p < 0.05$.

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; CI, confidence interval; EMS, emergency medical services.

TABLE 5 | Sociodemographic and logistical factors associated with death and mechanical ventilation after a bleeding event for patients administered either andexanet alfa or 4F-PCC.

	Death		Mechanical ventilation	
	Unadjusted odds ratios (95% CI)	Adjusted odds ratios (95% CI)	Unadjusted odds ratios (95% CI)	Adjusted odds ratios (95% CI)
Age (continuous)	0.98 (0.94, 1.02)	0.98 (0.94, 1.03)	0.98 (0.94, 1.01)	0.99 (0.95, 1.03)
Sex				
Male	Ref.	Ref.	Ref.	Ref.
Female	0.56 (0.20, 1.38)	0.72 (0.23, 2.08)	0.67 (0.33, 1.32)	0.80 (0.32, 2.00)
Race and ethnicity*				
Black	0.69 (0.10, 2.73)	0.64 (0.08, 3.57)	0.65 (0.19, 1.93)	1.33 (0.29, 5.85)
White/Non-Hispanic	Ref.	Ref.	Ref.	Ref.
Initial DOACT				
Apixaban	Ref.	Ref.	Ref.	Ref.
Rivaroxaban	1.19 (0.40, 3.15)	2.03 (0.58, 6.80)	0.72 (0.31, 1.62)	0.83 (0.28, 2.45)
Reversal agent treatment				
Andexanet alfa	1.34 (0.56, 3.25)	1.08 (0.40, 2.86)	1.58 (0.81, 3.10)	1.37 (0.59, 3.22)
4F-PCC	Ref.	Ref.	Ref.	Ref.
Time to reversal agent administration in quartiles	0.85 (0.56, 1.26)	0.92 (0.58, 1.44)	0.80 (0.58, 1.09)	0.70 (0.47, 1.02)
Bleeding event type				
Spontaneous ICH	Ref.	Ref.	Ref.	Ref.
Traumatic ICH	0.43 (0.13, 1.33)	0.34 (0.10, 1.17)	**0.32 (0.12, 0.81)**	**0.28 (0.09, 0.82)**
Other trauma (non-head)	0.37 (0.05, 1.68)	0.37 (0.04, 2.14)	0.70 (0.21, 2.26)	0.29 (0.06, 1.37)
GI bleed	0.35 (0.09, 1.20)	0.36 (0.07, 1.61)	**0.30 (0.11, 0.81)**	**0.06 (0.01, 0.26)**
Other bleed	1.39 (0.31, 5.65)	0.93 (0.15, 5.16)	3.95 (0.87, 28.29)	1.21 (0.21, 9.89)
Blood products given				
Yes	0.44 (0.10, 1.40)	0.43 (0.07, 2.10)	1.42 (0.63, 3.16)	**4.40 (1.14, 19.87)**
No	Ref.	Ref.	Ref.	Ref.
Insurance				
Medicare	Ref.	—	Ref.	—
Other insurance type	0.81 (0.25, 2.22)		0.75 (0.33, 1.65)	
Marital status				
Married	Ref.	—	Ref.	—
Single, divorced, widowed, or other	0.72 (0.28, 1.76)		0.54 (0.27, 1.09)	

Note: Model fit statistics for death include Akaike Information Criterion (AIC) 135.38 and for mechanical ventilation AIC: 164.30. Adjusted models included the following variables: age, sex, race and ethnicity, initial DOACT, reversal agent treatment, time to reversal agent administration, bleeding event type, blood products given, insurance, and marital status. Asian individuals excluded from these multivariable models because of instability with small cell sizes. There were no statistically significant differences in model fit when including insurance and marital status, so these variables were dropped from the multivariable model to compensate for other variables and to increase statistical power. Bold values indicate $p < 0.05$.

Abbreviations: 4F-PCC = 4-factor prothrombin complex concentrate, CI = confidence interval, DOACT = direct oral anticoagulant treatment, GI = gastrointestinal, ICH = intracranial hemorrhage.

products were also more likely to require mechanical ventilation (aOR: 4.40; 95% CI: 1.14, 19.87) compared to those who did not receive blood products.

The multivariable model for length of stay results are shown in Table 6. Those with a GI hemorrhage had a 57% shorter length of stay compared to those with spontaneous ICH (RR: 0.43; 95% CI: 0.27, 0.71), after adjusting for sociodemographic and DOAC characteristics. Other insurance type (e.g., Medicaid, private, uninsured) was associated with a 63% longer length of stay compared to Medicare, when adjusting for other covariates (RR: 1.63; 95% CI: 1.07, 2.50).

4 | Discussion

In our retrospective cohort study of 144 patients treated with andexanet alfa or 4F-PCC for life-threatening hemorrhages, the primary aim was to analyze whether sociodemographic factors were associated with selection of andexanet alfa or 4F-PCC for

TABLE 6 | Sociodemographic and logistical factors associated with length of stay after major bleeding event for patients administered either andexanet alfa or 4F-PCC.

	Length of stay	
	Unadjusted rate ratios (95% CI)	**Adjusted rate ratios (95% CI)**
Age (continuous)	1.00 (0.98, 1.02)	**1.01 (1.01, 1.03)**
Sex	Ref.	
Male	0.83 (0.62, 1.10)	Ref.
Female		0.78 (0.56, 1.10)
Race and ethnicity∗		
Black	0.98 (0.64, 1.58)	1.42 (0.88, 2.34)
White/non-Hispanic	Ref.	Ref.
Initial DOACT		
Apixaban	Ref.	Ref.
Rivaroxaban	0.85 (0.61, 1.21)	0.90 (0.61, 1.35)
Reversal agent treatment		
Andexanet alfa	0.85 (0.86, 1.49)	1.12 (0.83, 1.51)
4F-PCC	Ref.	Ref.
Time to reversal agent administration in quartiles	1.12 (0.99, 1.27)	1.09 (0.95, 1.27)
Presentation to site hospital		
Transfer from an outside hospital	1.34 (0.95, 1.91)	1.19 (0.77, 1.85)
Walk-in arrival	0.98 (0.68, 1.45)	0.88 (0.58, 1.35)
EMS	Ref.	Ref.
Bleeding event type		
Spontaneous ICH	Ref.	Ref.
Traumatic ICH	**0.68 (0.47, 0.98)**	0.79 (0.53, 1.16)
Other trauma (nonhead)	0.94 (0.59, 1.51)	0.74 (0.42, 1.30)
GI bleed	**0.53 (0.36, 0.79)**	**0.43 (0.27, 0.71)**
Other bleed	1.18 (0.71, 2.04)	1.41 (0.79, 2.60)
Blood products given		
Yes	1.08 (0.78, 1.52)	1.44 (0.93, 2.21)
No	Ref.	Ref.
Insurance		
Medicare	Ref.	Ref.
Other insurance type	1.08 (0.78, 1.52)	**1.63 (1.07, 2.50)**
Marital status		
Married	Ref.	Ref.
Single, divorced, widowed, or other	0.80 (0.78, 1.52)	1.03 (0.74, 1.45)

Note: Length of stay was measured as a count variable in days. Adjusted models included the following variables: age, sex, race and ethnicity, reversal agent treatment, initial DOACT, time to reversal agent administration, presentation to site hospital, bleeding event type, blood products given, insurance status, and marital status. One outlier excluded in models for length of stay of 337 days. Model for length of stay fit statistics: Akaike Information Criterion (AIC) 815.56 and goodness-of-fit test (residual deviance: 124.36, $df = 105$, $p = 0.10$), log-likelihood test statistic between negative binomial and Poisson regression was statistically significant ($p < 0.001$). Asian individuals excluded from these multivariable models because of instability with small cell sizes; DOACT, direct oral anticoagulant treatment; ICH, intracranial hemorrhage; GI, gastrointestinal. Bold values indicate $p < 0.05$.

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; CI, confidence interval.

reversal of life-threatening hemorrhages in patients on rivaroxaban or apixaban. There were no differences in sociodemographic factors associated with reversal agent selection between patients who received andexanet alfa compared to patients who received 4F-PCC. Additionally, there were no differences in logistical factors associated with reversal agent selection between andexanet alfa and 4F-PCC (e.g., type of arrival, insurance, time to reversal agent administration) in this analysis. The lack of differences in sociodemographic and logistical factors in reversal agent selection at these four major medical centers may be due to clinicians primarily utilizing hospital protocols for selection of reversal agent. Patients with an ICH were more likely to receive andexanet alfa compared to 4F-PCC in our study, which is consistent with the approved indication for andexanet alfa. Outcomes for those with ICH are more favorable for patients who receive andexanet alfa compared to 4F-PCC in previous research,

which may have influenced providers' selection of andexanet alfa for these patients [8, 12]. Selection of reversal agent for ICH may be influenced by studies demonstrating superiority in hemostatic control for andexanet alfa over 4F-PCC [12, 13, 16]. In the recent ANNEXA-I trial, andexanet alfa had better control in hematoma expansion in patients with ICH compared to standard therapies [12].

Patient characteristics that were associated with a delay in administration of reversal agents include interhospital transfer, other blood product administration, and those who identify as Black compared to non-Hispanic White. The delay from interhospital transfer may be related to the availability of reversal agents and specialists at the initial receiving hospital. In a retrospective cohort study by Nichols et al., interhospital transfers were associated with a 6.26-fold increase in time to neurosurgical admission [17]. The current study found racial differences in the time to reversal agent administration. Other research has shown longer time to emergency treatment for chest pain and stroke for non-Hispanic Black individuals compared to White individuals [18, 19]. However, the current study did not find racial disparities associated with reversal agent selection, mortality, or mechanical ventilation. Site differences were examined in bivariate analysis, and there were no statistically significant differences in insurance status or race/ethnicity with regard to site. Future research should examine systemic barriers associated with longer time to reversal agent administration. Although some factors were associated with faster reversal agent administration, further investigation with larger samples is needed to clarify the role of insurance status' impact on time to treatment.

Additionally, there were no statistically significant differences between andexanet alfa and 4F-PCC with regard to mortality, mechanical ventilation, and length of stay. Mortality has previously been shown to be lower in patients who received andexanet alfa compared to 4F-PCC in the treatment of life-threatening hemorrhages; however, we did not detect this association in our study, which may be due to the smaller sample size [8, 13, 16]. In the ANNEXA-I study, there was also found to be no difference in mortality between andexanet alfa as compared to standard of care [12].

Several studies have shown an increase in the incidence of thromboembolic events in patients treated with andexanet alfa compared to 4F-PCC [7, 12, 20]. In a meta-analysis published by Orso et al., the rate of thromboembolic events after treatment for ICH was higher in the andexanet alfa group compared to 4F-PCC [20]. The ANNEXA-4 multicenter, prospective study of 171 patients documented a thromboembolic complication rate of 10% after administration of andexanet alfa compared to the 4.2% in the 72 patients analyzed in this study [21]. In our study, there was a relatively low risk of thromboembolic events in the andexanet alfa cohort (4%) compared to the 4F-PCC cohort (3%), which was not statistically different. This is more consistent with the meta-analysis by White and colleagues which did not detect a statistically significant difference in thrombotic events between andexanet alfa and 4F-PCC [12].

4.1 | Limitations

The limitations of this study are primarily related to its retrospective study design and smaller sample size of only 144 patients. While proportional sampling strategies were implemented to obtain balanced groups of patients receiving andexanet alfa and 4F-PCC, there were a limited number of cases receiving andexanet alfa. This may have reduced the ability to detect small to moderate differences in sociodemographic and logistical factors associated with reversal agent selection. Additionally, because data were extracted from the EMR, data are limited by the availability and completeness of documentation at the time of care. Important clinical details may have been missing or inconsistently recorded across sites.

5 | Conclusion

Despite possible concerns about sociodemographic and logistical barriers to accessing andexanet alfa compared to 4F-PCC, there were no differences in these variables between those who received andexanet alfa compared to those who received 4F-PCC. This may indicate that factors such as race and ethnicity, sex, marital status, and housing status did not factor into clinicians' decisions for selecting a reversal agent. Likewise, despite the more recent use of andexanet alfa for bleeding reversal compared to 4F-PCC, and possible familiarity with 4F-PCC, there were no differences in length of time to reversal agent administration. Factors that were associated with longer times to reversal agent administration included patients transferred from outside hospitals, patients receiving blood products, and patients who were Black compared to non-Hispanic White. Finally, there were no differences in sociodemographic factors with regard to patient outcomes.

Funding

This research was supported by an investigator-initiated grant through AstraZeneca (ESR-22–22013).

Disclosure

The sponsor had no role in the study design, data collection, analysis, or interpretation of the results, or in the decision to submit the manuscript for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. S. Ballestri, E. Romagnoli, D Arioli, et al., "Risk and Management of Bleeding Complications With Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Venous Thromboembolism: A Narrative Review," *Advances in Therapy* 40, no. 1 (2023): 41–66, https://doi.org/10.1007/s12325-022-02333-9.

2. W. A. Ray, C. P. Chung, C. M Stein, et al., "Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation," *Jama* 326, no. 23 (2021): 2395–2404, https://doi.org/10.1001/jama.2021.21222.

3. W. C. Y. Lau, C. O. Torre, K. K. C Man, et al., "Comparative Effectiveness and Safety Between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban Among Patients With Atrial Fibrillation: A Multinational

Population-Based Cohort Study," *Annals of Internal Medicine* 175, no. 11 (2022): 1515–1524, https://doi.org/10.7326/M22-05114.

4. L. A. Castellucci, V. M. Chen, M. J Kovacs, et al., "Bleeding Risk With Apixaban vs. Rivaroxaban in Acute Venous Thromboembolism," *New England Journal of Medicine* 394, no. 11 (2026): 1051–1060, https://doi.org/10.1056/NEJMoa2510703.

5. M. Reed, P. Tadi, and D. Nicolas, in *Statpearls* (StatPearls Publishing, March 2025), http://www.ncbi.nlm.nih.gov/books/NBK519499/.

6. C. Troyer, W. Nguyen, A. Xie, and D. Wimer, "Retrospective Review of Andexanet Alfa Versus 4-Factor Prothrombin Complex Concentrate for Reversal of DOAC-Associated Intracranial Hemorrhage," *Journal of Thrombosis and Thrombolysis* 55, no. 1 (2023): 149–155, https://doi.org/10.1007/s11239-022-02715-4.

7. V. M. Stevens, T. Trujillo, S. W. Mueller, R. MacLaren, P. M. Reynolds, and T. H. Kiser, "Coagulation Factor Xa (Recombinant), Inactivated-Zhzo (Andexanet Alfa) Hemostatic Outcomes and Thrombotic Event Incidence at an Academic Medical Center," *Clinical and Applied Thrombosis/Hemostasis* 25 (2019): 1076029619896619, https://doi.org/10.1177/1076029619896619.

8. P. P. Dobesh, G. J. Fermann, M. J Christoph, et al., "Lower Mortality With Andexanet Alfa vs 4 Factor Prothrombin Complex Concentrate for Factor Xa Inhibitor-Related Major Bleeding in a U.S. Hospital-Based Observational Study," *Research and Practice in Thrombosis and Haemostasis* 7, no. 6 (2023): 102192, https://doi.org/10.1016/j.rpth.2023.102192.

9. W. B. Hays, K. Billups, J Nicholson, et al., "3-Factor Prothrombin Complex Concentrate Versus 4-Factor Prothrombin Complex Concentrate for the Reversal of Oral Factor Xa Inhibitors," *Journal of Thrombosis and Thrombolysis* 58, no. 2 (2025): 276–283, https://doi.org/10.1007/s11239-024-03052-4.

10. A. A. Ammar, M. A. Ammar, K. A Owusu, et al., "Andexanet Alfa Versus 4-Factor Prothrombin Complex Concentrate for Reversal of Factor Xa Inhibitors in Intracranial Hemorrhage," *Neurocritical Care* 35, no. 1 (2021): 255–261, https://doi.org/10.1007/s12028-020-01161-510.

11. M. E. Barra, A. S. Das, B. D Hayes, et al., "Evaluation of Andexanet Alfa and Four-Factor Prothrombin Complex Concentrate (4F-PCC) for Reversal of Rivaroxaban-and Apixaban-Associated Intracranial Hemorrhages," *Journal of Thrombosis and Haemostasis* 18, no. 7 (2020): 1637–1647, https://doi.org/10.1111/jth.14838.

12. S. J. Connolly, M. Sharma, A. T Cohen, et al., "Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage," *New England Journal of Medicine* 390, no. 19 (2024): 1745–1755, https://doi.org/10.1056/NEJMoa2313040.

13. C. M. White, K. S. Caroti, Y Bessada, et al., "Andexanet Alfa Versus PCC Products for Factor Xa Inhibitor Bleeding: A Systematic Review With Meta-Analysis," *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy* 44, no. 5 (2024): 394–408.

14. A. Hughes, A. Amaducci, S. L Campleman, et al., "The Toxicology Investigators Consortium 2023 Annual Report," *Journal of Medical Toxicology* 20, no. 4 (2024): 350–380, https://doi.org/10.1007/s13181-024-01033-w.

15. P. A. Harris, R. Taylor, B. L Minor, et al., "The Redcap Consortium: Building an International Community of Software Platform Partners," *Journal of Biomedical Informatics* 95 (2019): 103208, https://doi.org/10.1016/j.jbi.2019.103208.

16. P. A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, and J. G. Conde, "Reserach Electronic Data Capture (REDCap)-A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support," *Journal of Biomedical Informatics* 42, no. 2 (2009): 377–381, https://doi.org/10.1016/j.jbi.2008.08.010.

17. L. Nichols, C. Stirling, J. Stankovich, and S. Gall, "Time to Treatment Following an Aneurysmal Subarachnoid Hemorrhage, Rural Place of Residence and Inter-Hospital Transfers," *Australas Emergerncy Care* 23, no. 4 (2020): 225–232, https://doi.org/10.1016/j.auec.2020.05.004.

18. C. Allamby, T. Scott, J. Krizo, K. Consing, C. Mangira, and E. L. Simon, "Do Racial Disparities Exist at Various Time Points During an Emergency Department Visit for Chest Pain," *The American Journal of Emergency Medicine* 58 (2022): 1–4, https://doi.org/10.1016/j.ajem.2022.04.029.

19. S. J. Karve, R. Balkrishnan, Y. M. Mohammad, and D. A. Levine, "Racial/Ethnic Disparities in Emergency Department Waiting Time for Stroke Patients in the United States," *Journal of Stroke and Cerebrovascular Diseases* 20, no. 1 (2011): 30–40, https://doi.org/10.1016/j.jstrokecerebrovasdis.2009.10.006.

20. D. Orso, F. Fonda, A Brussa, et al., "Andexanet Alpha Versus Four-Factor Prothrombin Complex Concentrate in Doacs Anticoagulation Reversal: An Updated Systematic Review and Meta-Analysis," *Critical Care* 28, no. 1 (2024): 221, https://doi.org/10.1186/s13054-024-05014-x.

21. T. J. Milling, S. Middeldorp, L Xu, et al., "Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors," *Circulation* 147, no. 13 (2023): 1026–1038, https://doi.org/10.1161/CIRCULATIONAHA.121.057844.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supporting Information 1.** Supporting Table 1 Rivaroxaban characteristics among patients receiving andexanet alfa vs. 4F-PCC. Supporting Table 2 Apixaban characteristics among patients receiving andexanet alfa vs. 4F-PCC. Supporting Table 3 Descriptive statistics or patients who died among those who received andexanet alfa or 4F-PCC after a major bleeding event. Supporting Table 4 Descriptive statistics of patients who died among those who received andexanet alfa or 4F-PCC after a major bleeding event excluding those who were transferred from an outside hospital. Supporting Table 5 Descriptive characteristics of clinical events by bleeding events among patients who received andexanet alfa vs. 4F-PCC. **Supporting Information 2.** STROBE Statement—checklist of items that should be included in reports of observational studies.