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ORIGINAL ARTICLE

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

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Abstract

Background: Well-designed studies with sufficient sample size comparing andexanet alfa vs 4-factor prothrombin complex concentrate (4F-PCC) in routine clinical practice to evaluate clinical outcomes are limited.

Objectives: To compare in-hospital mortality in patients hospitalized with rivaroxaban- or apixaban-related major bleeding who were treated with andexanet alfa or 4F-PCC.

Methods: An observational cohort study (ClinicalTrials.gov identifier: NCT05548777) was conducted using electronic health records between May 2018 and September 2022 from 354 U.S. hospitals. Inclusion criteria were age ≥18 years, inpatient admission with diagnosis code D68.32 (bleeding due to extrinsic anticoagulation), a record of use of the factor Xa inhibitors rivaroxaban or apixaban, andexanet alfa or 4F-PCC treatment during index hospitalization, and a documented discharge disposition. Multivariable logistic regression on in-hospital mortality with andexanet alfa vs 4F-PCC was performed. The robustness of the results was assessed via a supportive propensity score-weighted logistic regression.

Results: The analysis included 4395 patients (andexanet alfa, n = 2122; 4F-PCC, n = 2273). There were 1328 patients with intracranial hemorrhage (ICH), 2567 with gastrointestinal (GI) bleeds, and 500 with critical compartment or other bleed types. In the multivariable analysis, odds of in-hospital mortality were 50% lower for andexanet alfa vs 4F-PCC (odds ratio [OR], 0.50; 95% CI, 0.39-0.65; $P < .01$) and were consistent for both ICH (OR, 0.55; [0.39-0.76]; $P < .01$) and GI bleeds (OR, 0.49 [0.29-0.81]; $P = .01$). Similar results were obtained from the supporting propensity score-weighted logistic regression analyses.

Conclusion: In this large observational study, treatment with andexanet alfa in patients hospitalized with rivaroxaban- or apixaban-related major bleeds was associated with

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50% lower odds of in-hospital mortality than 4F-PCC. The magnitude of the risk reduction was similar in ICH and GI bleeds.

KEYWORDS
4-factor prothrombin complex concentrate, andexanet alfa, anticoagulant reversal agents, cerebral hemorrhage, factor Xa inhibitors, gastrointestinal hemorrhage

Essentials

- Andexanet alfa (AA) is a reversal agent for rivaroxaban/apixaban-associated major bleeding.
- We compared in-hospital mortality with AA or 4-factor prothrombin complex concentrate.
- Overall, the odds of in-hospital mortality were 50% lower with AA vs 4-factor prothrombin complex concentrate.
- Risk reduction was similar for intracranial hemorrhage (45%) and gastrointestinal bleeds (51%).

1 | INTRODUCTION

Oral factor Xa (FXa) inhibitors reduce the risk of ischemic events and have a favorable risk-benefit profile compared with warfarin [1]. As with all anticoagulants, oral FXa inhibitors increase patients' risk of major bleeding, which is associated with significant morbidity and mortality [1]. In clinical trials, the annualized rate of major bleeding in patients with atrial fibrillation receiving oral FXa inhibitors ranged from approximately 2% to 6% [2–4], and similar rates have been observed in clinical practice [5,6].

Inactive 4-factor prothrombin complex concentrate (4F-PCC) is approved for the management of bleeding associated with vitamin K antagonists and works by replenishing inactive vitamin K-dependent coagulation factors. 4F-PCC has also been used off-label to manage FXa inhibitor-related major bleeding despite limited clinical trial evidence and lack of regulatory approval [7]. Andexanet alfa is a recombinant protein specifically designed to reverse the anticoagulant effects of oral FXa inhibitors, such as rivaroxaban and apixaban [8]. Andexanet alfa received accelerated approval from the U.S. Food and Drug Administration (FDA) in 2018 and conditional approval from the European Medicines Agency in 2019 as the first specific reversal agent for rivaroxaban- or apixaban-associated, life-threatening or uncontrolled bleeding [9,10]. In the Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXa Inhibitors (ANNEXA-4) trial in patients with oral FXa inhibitor- or enoxaparin-associated major bleeding, andexanet alfa rapidly and significantly reduced anti-FXa activity by more than 90% in apixaban- and rivaroxaban-treated patients and 80% of patients achieved excellent or good hemostatic efficacy at 12 hours [11]. Observational comparative studies with synthetic control arms (ie, external control arms based on patient-level data sourced from previous clinical trials or observational data sets) and case series have also suggested that andexanet alfa may be associated with improved hemostatic effectiveness compared with usual care agents, including 4F-PCC [12–14]. However, data on the direct comparison between andexanet alfa and 4F-PCC for the management of oral FXa inhibitor-related bleeding in routine clinical practice are limited and are primarily based on small, single-center, or single-health system studies [14–16].

The current study included a large data set of more than 4000 patients treated at over 350 hospitals throughout the United States. The primary objective was to compare in-hospital mortality in patients hospitalized with rivaroxaban- or apixaban-related major bleeding who were treated with andexanet alfa or 4F-PCC in routine practice. A secondary objective was to assess potential predictors associated with the risk of in-hospital mortality.

2 | METHODS

2.1 | Study design

This was a multicenter, observational cohort study of adults in the United States hospitalized with rivaroxaban- or apixaban-related bleeds who received treatment with andexanet alfa or 4F-PCC. Patient data were accessed from deidentified electronic health records (EHRs) compliant with the Health Insurance Portability and Accountability Act. A third-party organization identified and recruited U.S. hospital pharmacists and nurse navigators/coordinators with the expertise, access, and permission necessary to query the hospital's EHR system for inpatient visits and to ensure the availability of at least 10 potentially eligible patients, as assessed via a screening questionnaire. Patient record extractors were allowed to include up to 60 qualifying patients, starting with the most recent and working backward. Institutional review board exemption was obtained by Advarra Institutional Review Board Services, Inc, per Department of Health and Human Services regulations found at 45 CFR 46.104(d)(4).

2.2 | Setting and participant selection

Data were retrospectively extracted from EHR records of unique patients with discharge dates between May 2018 and September

2022. In order to collect enough records for each treatment, hospitals that included andexanet alfa and/or 4F-PCC on the formulary were targeted for recruitment. Patient record abstractors were asked to start with the most recent patient who met the inclusion criteria during the data collection period (May 2021-November 2022).

The patient inclusion criteria for these analyses were age ≥18 years, an *International Classification of Diseases, 10th Revision* diagnosis code of D68.32 (indicating a hemorrhagic disorder due to extrinsic circulating anticoagulants) as part of inpatient admission, taking either rivaroxaban or apixaban at the time of the bleeding event (ie, aligned with the FDA-approved indication for andexanet alfa), treatment with either andexanet alfa or 4F-PCC during the index hospitalization, and having a documented discharge disposition. Patients who received both andexanet alfa and 4F-PCC were not included.

Quality control measures were implemented to assess and maximize data integrity during and after data extraction, including real-time flags to respondents in cases of monotonous response patterns, programmed logic checks, and signals for extreme values and outliers.

2.3 | Measures and outcomes

Patient characteristics included age, sex, impaired mental status on admission, do-not-resuscitate (DNR) order, systolic blood pressure, albumin levels (gastrointestinal [GI] bleed only), prothrombin time (GI bleed only), international normalized ratio (INR; GI bleed only), type of oral FXa inhibitor, time from hospital arrival to administration of either andexanet alfa or 4F-PCC (door-to-needle time), time since last anticoagulant dose to hospital admission (<8 hours, 8-18 hours, >18 hours), and a history of liver disease, chronic kidney disease (CKD), heart failure, diabetes mellitus, or stroke. Information on bleed location (intracranial hemorrhage [ICH], GI, critical compartment/noncompressible [non-ICH], and other bleeds), bleed cause for ICH and critical compartment bleeds (spontaneous or trauma), ICH severity (collected from the Glasgow Coma Scale [GCS] and hematoma volume/thickness when available), and specific location of GI bleed (upper, lower, unknown) was also captured. Furthermore, to gain additional information on management approaches, data on mechanical ventilation and procedures were captured for relevant bleed types (hematoma evacuation, decompression surgery, simple aspiration, craniotomy with open surgery, clipping or coiling procedures, stereotactic or endoscopic evacuation, other neurosurgery procedures for patients with ICH, and upper and lower endoscopy, colonoscopy, abdominal angiogram, laparoscopy or laparotomy, arteriography, and nuclear scintigraphy for patients with GI bleeds). The outcome of interest for this study was in-hospital mortality for patients treated with andexanet alfa compared with 4F-PCC.

2.4 | Statistical analysis

Data were summarized as means and SDs, medians and IQRs, or counts and proportions, as appropriate.

Multivariable logistic regression was the predefined primary analytical approach to compare in-hospital mortality for patients treated with andexanet alfa vs 4F-PCC across all bleeds and separately for ICH and GI bleeds. As few patients (n = 80) were categorized as having "other bleeds," which encompassed heterogeneous bleed types, these patients were not included in the analyses of mortality. The model adjusted for bleed location (ICH, critical compartment, GI [reference group]), ICH bleed cause (spontaneous vs traumatic), age (per 10 years), sex, systolic blood pressure (per 10 mm Hg), impaired mental status (yes/no), DNR order (yes/no), comorbidities (liver disease, CKD, heart failure, and diabetes), time since last anticoagulant dose (<8 hours, 8-18 hours, >18 hours [reference group]), door-to-needle time ≥30 minutes, and timing of data collection. Patients with missing mental status (n = 187) were also excluded from the adjusted logistic regression analysis. The covariates were selected based on clinical relevance and anticipated availability of data. A sensitivity analysis was performed that restricted the study population to patients with ICH for whom a GCS score was available.

The robustness of the results from the primary analysis was assessed by also performing propensity score (PS)-weighted logistic regression as a supportive and alternative analytical approach. PSs were estimated within subpopulations by bleed location using logistic regression. The PS-weighted analysis across all bleeds included the same covariates as the primary multivariable logistic regression analysis (Supplementary Methods). In addition, the covariates of bleed cause (spontaneous vs traumatic), GCS score (mild, moderate, and severe), and history of stroke were included for ICH, while bleed location (upper, lower, and other/unknown), history of stroke, INR, and albumin were included for GI bleeds. The PSs were used to create an inverse probability of treatment weights to balance the 2 treatment groups (andexanet alfa and 4F-PCC) with regard to potential confounding factors. The development of the PS models was based on 20 imputations for missing data, conducted within each subpopulation by bleed location. Covariate balance was assessed using standardized mean differences before and after PS weighting for the bleed location subgroups, with values <0.10 regarded as balanced (Supplementary Figure). All statistical analyses were conducted using R (version 4.2 or higher).

3 | RESULTS

3.1 | Hospital characteristics

A total of 354 institutions participated in the study, representing 42 states (Supplementary Table S1). Most participating institutions (91.8%) were Comprehensive Stroke Centers, and 44.6% were American College of Surgeons certified Level 1 trauma centers. Three-quarters (75.1%) of institutions had both andexanet alfa and 4F-PCC on the hospital formulary, 6.5% had andexanet alfa only, and 18.4% had 4F-PCC only.

3.2 | Characteristics of the overall study population

The overall study population comprised 4395 patients with rivaroxaban- or apixaban-associated major bleed events treated with andexanet alfa (n = 2122) or 4F-PCC (n = 2273). Most patients had GI bleeds (andexanet alfa, 56.8%; 4F-PCC, 59.9%), and just under one-third had ICH (andexanet alfa, 31.4%; 4F-PCC, 29.1%). Time since last anticoagulant dose was similar between the andexanet alfa and 4F-PCC cohorts, with more than 80% of patients in both groups having <18 hours between their last dose of oral FXa inhibitor and hospital admission (Table 1). DNR orders were present in 18.3% of andexanet alfa-treated and 19.8% of 4F-PCC-treated patients. As the timing of DNR orders was not captured, it is unclear if these DNR orders were in place prior to the hospitalization for major bleeding or after the diagnosis of major bleeding was established. Approximately 1 in 3 patients in both groups had impaired mental status upon admission.

Among patients treated with andexanet alfa, the lower dose (initiated on a 400 mg bolus) was administered to 68.8% of patients (Table 1). For 4F-PCC, a mean (SD) of 2510.1 (1073.1) total units were administered per patient, and of those with 4F-PCC dosing data available, 6.2% received multiple doses.

3.3 | Characteristics of patients with ICH

The most common site for ICH was subdural, followed by subarachnoid (Table 2), with similar occurrences in both cohorts. The occurrences of intracerebral bleeds (just under 1 in 5 patients for both groups), multicompartment bleeds (<10%), and intraventricular hemorrhage (≤5%) were also generally similar across the 2 groups. Approximately half of all ICH bleeds were categorized as traumatic. Patients in the andexanet alfa group had higher average systolic blood pressure at baseline than those treated with 4F-PCC (147.6 mm Hg vs 139.9 mm Hg).

Hematoma volume was reported for 52/666 (7.8%) andexanet alfa-treated patients and 30/662 (4.5%) 4F-PCC-treated patients, and hematoma thickness was reported for 96/666 (14.4%) and 106/662 (16.0%) patients, respectively. Among patients with available data, hematoma volume was smaller in patients in the andexanet alfa cohort than in patients in the 4F-PCC cohort (mean baseline of 22.6 mL vs 27.5 mL, respectively); however, hematoma thickness was comparable between the 2 arms (mean baseline of 7.1 mm vs 6.2 mm, respectively). Among patients with GCS scores available (347/666 [52.1%] andexanet alfa-treated patients and 369/662 [55.7%] 4F-PCC-treated patients), the proportion of patients with moderate (9-12) or severe (≤8) GCS scores at baseline was higher in the andexanet alfa group (70.9%) vs the 4F-PCC group (61.0%).

A higher proportion of patients with ICH in the andexanet alfa cohort received hematoma evacuation (21.8% vs 16.2%, respectively) and decompression surgery (14.6% vs 9.5%, respectively) compared with the 4F-PCC cohort. The proportion of patients receiving other neurosurgical procedure types was similar across the 2 treatment cohorts. These data are unadjusted for baseline differences and bleed severity between groups and, thus, do not indicate effects of treatment.

3.4 | Characteristics of patients with GI bleeds

Upper GI bleeds were the most common GI bleed location in both treatment cohorts (Table 3). The average systolic blood pressure in both groups was similar (andexanet alfa, mean, 130.5 mm Hg; 4F-PCC, mean, 128.0 mm Hg). Among those with an available AIMS65 score (830/1206 [68.8%] andexanet alfa-treated patients and 979/1361 [71.9%] 4F-PCC-treated patients), most patients in both groups (andexanet alfa, 57.8%; 4F-PCC, 61.7%) had an AIMS65 score ≥2. Approximately half of patients with GI bleeds underwent a surgical or diagnostic procedure. Endoscopy was the most common type of procedure in both treatment groups, recorded for 34.2% of andexanet alfa-treated patients and 38.1% of 4F-PCC-treated patients. The types of other surgical procedures performed were similar across the 2 treatment groups. As with ICH, these data are unadjusted for baseline differences between the 2 groups.

3.5 | Characteristics of patients with critical compartment bleeds

Retroperitoneal bleeds were the most common type of non-ICH critical compartment/noncompressible bleed and were less frequent in patients receiving andexanet alfa (27.4%) than those receiving 4F-PCC (41.3%; Supplementary Table S2). Pericardial (17.9% vs 11.1%, respectively) and intraocular (13.7% vs 7.2%, respectively) bleeds were more prevalent in the andexanet alfa group than the 4F-PCC group.

3.6 | Clinical outcomes and in-hospital mortality

In the overall study population, a higher proportion of patients treated with 4F-PCC than with andexanet alfa received other treatments, such as intravenous fluids, packed red blood cells, or fresh frozen plasma (71.6% vs 44.8%; Table 4). Anticoagulation (oral anticoagulants or unfractionated or low-molecular-weight heparin) was restarted prior to discharge in approximately 30% of patients in both treatment cohorts, the majority of whom restarted oral anticoagulation (Table 4). In patients discharged alive, the median (IQR) duration of hospitalization was the same in both treatment cohorts (6.0 [4.0, 8.0] days). Half of all patients in the overall population were discharged home, and approximately 40% were discharged to another facility or unknown location, with similar rates between the groups (Table 4).

In-hospital mortality occurred in 6.0% of patients treated with andexanet alfa and 10.6% of patients treated with 4F-PCC (Table 4, Figure 1, and Supplementary Table S3). In the adjusted logistic regression analysis, which accounted for various clinical factors, including bleed location and type, patients treated with andexanet alfa

TABLE 1 Patient characteristics of the overall study population.

Variable		Andexanet alfa (n = 2122), n (%)[a]	4F-PCC (n = 2273), n (%)[a]
Age (y) mean; median (IQR)		65.6; 66.0 (56.0, 75.0)	66.6; 67.0 (58.0, 77.0)
Sex	Male	1214 (57.2)	1376 (60.5)
	Female	908 (42.8)	897 (39.5)
Bleed location	GI	1206 (56.8)	1361 (59.9)
	ICH	666 (31.4)	662 (29.1)
	Critical compartment/noncompressible (non-ICH) bleed	212 (10.0)	208 (9.2)
	Other	38 (1.8)	42 (1.8)
Alteration in mental status (yes)[b]		674 (33.2)	806 (37.1)
DNR order (yes)		388 (18.3)	449 (19.8)
Systolic BP (first measurement), mm Hg, mean; median (IQR)		135.3; 136.0 (110.0, 160.0)	131.1; 132.0 (108.0, 155.0)
Comorbidities	Hypertension	1312 (61.8)	1391 (61.2)
	Diabetes	910 (42.9)	1001 (44.0)
	Heart failure	491 (23.1)	510 (22.4)
	CKD	485 (22.9)	527 (23.2)
	Prior stroke	440 (21.0)	470 (20.9)
	Peptic ulcer disease	294 (13.9)	301 (13.2)
	Liver disease	261 (12.3)	295 (13.0)
Oral FXa inhibitor	Apixaban	1271 (59.9)	1417 (62.3)
	Rivaroxaban	851 (40.1)	856 (37.7)
Time since last anticoagulant dose[c]	<8 h	936 (44.1)	943 (41.5)
	8-18 h	888 (41.8)	934 (41.1)
	>18 h	298 (14.0)	396 (17.4)
Door-to-needle time, h, mean; median (IQR)		8.2; 2.5 (1.2, 6.4)	7.3; 2.3 (1.2, 5.7)
Andexanet alfa initial dose	Low dose[d]	1460 (68.8)	–
	High dose[e]	658 (31.0)	–
	Other	4 (0.2)	–
4F-PCC total units, mean; median (IQR)		–	2510.1; 2200.0 (1900.0, 3000.0)
4F-PCC dosing	Single[f]	–	2050 (93.8)
	Multiple[f]	–	135 (6.2)
	Missing	–	88 (3.9)

3F-PCC, 3-factor prothrombin complex concentrate; 4F-PCC, 4-factor prothrombin complex concentrate; BP, blood pressure; CKD, chronic kidney disease; DNR, do-not-resuscitate; FXa, factor Xa; GI, gastrointestinal; ICH, intracranial hemorrhage.

[a]Unless otherwise specified.

[b]Andexanet alfa, n = 2032; 4F-PCC, n = 2174.

[c]Time from last FXa inhibitor dose to hospital admission.

[d]A 400 mg bolus (delivered at a target rate of 30 mg/min, followed by a 4 mg/min infusion over 120 min).

[e]An 800 mg bolus (delivered at a target rate of 30 mg/min, followed by an 8 mg/min infusion over 120 min).

[f]Based on available data (n = 2185).

TABLE 2 Characteristics of patients with intracranial hemorrhage by treatment subgroup.

Variable		Andexanet alfa (n = 666), n (%)[a]	4F-PCC (n = 662), n (%)[a]
Subtype	Subdural	217 (32.6)	214 (32.3)
	Subarachnoid	151 (22.7)	141 (21.3)
	Intracerebral	110 (16.5)	129 (19.5)
	Epidural	56 (8.4)	58 (8.8)
	Multicompartment	41 (6.2)	60 (9.1)
	Intraventricular	33 (5.0)	29 (4.4)
	Infratentorial	4 (0.6)	2 (0.3)
	Unknown	94 (14.1)	90 (13.6)
Bleed cause	Trauma	327 (49.1)	366 (55.3)
	Spontaneous	339 (50.9)	296 (44.7)
Systolic BP (first measurement), mm Hg, mean; median (IQR)		147.6; 154.0 (123.2, 175.0)	139.9; 142.0 (113.2, 165.0)
Hematoma volume (epidural, intracerebral, multicompartment, intraventricular, infratentorial), mL, mean; median (IQR)		(n = 52)	(n = 30)
		22.6; 14.5 (5.8, 30.0)	27.5; 22.5 (10.0, 38.8)
Hematoma thickness (subdural, subarachnoid), mm, mean; median (IQR)		(n = 96)	(n = 106)
		7.1; 5.5 (4.0, 10.0)	6.2; 4.0 (3.0, 8.0)
Baseline GCS score		(n = 347)	(n = 369)
	Severe (≤8)	107 (30.8)	130 (35.2)
	Moderate (9-12)	139 (40.1)	95 (25.7)
	Mild (13-15)	101 (29.1)	144 (39.0)
Mechanical ventilation (yes)		224 (33.6)	252 (38.1)
Neurosurgical procedure	Any type	298 (44.7)	219 (33.1)
	Hematoma evacuation	145 (21.8)	107 (16.2)
	Decompression surgery	97 (14.6)	63 (9.5)
	Craniotomy with open surgery	51 (7.7)	37 (5.6)
	Simple aspiration	29 (4.4)	16 (2.4)
	Clipping or coiling procedures	28 (4.2)	24 (3.6)
	Stereotactic or endoscopic evacuation	9 (1.4)	6 (0.9)
	Other procedure	1 (0.2)	4 (0.6)

4F-PCC, 4-factor prothrombin complex concentrate; BP, blood pressure; GCS, Glasgow Coma Scale.
[a]Unless otherwise specified.

had 50% lower odds of death during hospitalization than patients treated with 4F-PCC (odds ratio [OR], 0.50; 95% CI, 0.39-0.65; P < .01; Figure 1 and Supplementary Table S3).

Among patients with ICH, in-hospital mortality occurred in 12.6% of patients in the andexanet alfa cohort compared with 23.3% of patients in the 4F-PCC cohort (Figure 1 and Supplementary Table S3). The odds of death during hospitalization were 45% lower with andexanet alfa compared with 4F-PCC in patients presenting with ICH (OR, 0.55; 95% CI, 0.39-0.76; P < .01). The sensitivity analysis restricted to patients with ICH with an available GCS score resulted in an adjusted OR of 0.62 (95% CI, 0.39-0.99; P = .04; Supplementary Table S4), similarly showing 38% lower odds of in-hospital mortality associated with andexanet alfa compared with 4F-PCC. In those with GI bleeds, in-hospital mortality occurred in 2.5% vs 4.3% of patients, respectively, with 51% lower odds of death during hospitalization for GI bleeds (OR, 0.49; 95% CI, 0.29-0.81; P = .01; Figure 1 and Supplementary Table S3).

Similar results were obtained from the supporting PS-weighted logistic regression analyses. As shown in Supplementary Figure, all covariates were balanced after PS weighting. When pooled across all bleed types, the odds of in-hospital mortality were 41% lower in patients treated with andexanet alfa compared with 4F-PCC (OR, 0.59; 95% CI, 0.46-0.74; P < .01). The Q statistic was 1.28 (P = .53). The odds of death during hospitalization were 39% lower with andexanet alfa vs 4F-PCC for both ICH (OR, 0.61; 95% CI, 0.45-0.83; P < .01) and GI bleeds (OR, 0.61; 95% CI, 0.39-0.96; P = .03).

TABLE 3 Characteristics of patients with gastrointestinal bleeds by treatment subgroup.

Variable		Andexanet alfa (n = 1206), n (%)[a]	4F-PCC (n = 1361), n (%)[a]
Subtype	Upper GI bleed	475 (39.4)	550 (40.4)
	Lower GI bleed	402 (33.3)	434 (31.9)
	Other/unknown	329 (27.3)	377 (27.7)
Systolic BP (first measurement), mm Hg, mean; median (IQR)		130.5; 130.0 (108.0, 154.0)	128.0; 130.0 (105.0, 150.0)
PT, sec, mean; median (IQR)		(n = 631)	(n = 792)
		21.1; 16.9 (13.0, 25.0)	25.4; 22.0 (14.0, 33.0)
INR, mean; median (IQR)		(n = 895)	(n = 1048)
		2.7; 2.2 (1.3, 3.4)	2.5; 1.9 (1.2, 3.3)
AIMS65 score (complete cases only)		(n = 830)	(n = 979)
	≥2	480 (57.8)	604 (61.7)
	0 or 1	350 (42.2)	375 (38.3)
GI procedure	Any type	592 (49.1)	730 (53.6)
	Endoscopy	412 (34.2)	518 (38.1)
	Colonoscopy	272 (22.6)	329 (24.2)
	Abdominal angiogram	34 (2.8)	37 (2.7)
	Laparoscopy or laparotomy	26 (2.2)	20 (1.5)
	Arteriography	17 (1.4)	20 (1.5)
	Nuclear scintigraphy	13 (1.1)	11 (0.8)
	Other procedure	1 (0.1)	5 (0.4)

4F-PCC, 4-factor prothrombin complex concentrate; BP, blood pressure; GI, gastrointestinal; INR, international normalized ratio; PT, prothrombin time.
[a]Unless otherwise specified.

3.7 | Predictors of in-hospital mortality

In the adjusted logistic regression analysis, the odds of in-hospital mortality were significantly higher for patients with spontaneous ICH, traumatic ICH, or critical compartment bleeds than GI bleeds (Figure 2). Further, the odds of mortality were higher with increasing age and were higher for patients with impaired mental status and those with a DNR order vs those with no impaired mental status or DNR order. In terms of comorbidities, an increased risk of mortality was associated with the presence of liver disease, CKD, and heart failure.

4 | DISCUSSION

In this study, the largest observational study to date of patients admitted with rivaroxaban- or apixaban-related major bleeding, treatment with andexanet alfa was associated with an observed 50% lower odds of in-hospital mortality compared with 4F-PCC. Risk reductions were consistent for both ICH (45%) and GI bleeds (51%). The results from the PS-weighted analyses were statistically significant and similar to the primary multivariable logistic regression analysis, although with slightly lower point estimates, supporting the robustness of the findings.

The results from this study are consistent with an additional, nonoverlapping observational study in 255 U.S. veterans admitted with oral FXa inhibitor-related bleeds, which showed significantly lower in-hospital mortality for those managed with andexanet alfa compared with 4F-PCC (10.6% vs 25.3%; P = .01; weighted hazard ratio, 0.31; 95% CI, 0.14-0.71) [17]. Similar results were also reported in an indirect comparison study, which included patients treated with andexanet alfa from the ANNEXA-4 trial and a synthetic control arm based on EHR data from patients treated with 4F-PCC admitted to 3 hospitals within a U.S. health care system [13]. In the PS-overlap weighted analysis, andexanet alfa was associated with lower odds of 30-day mortality vs 4F-PCC in patients with apixaban- or rivaroxaban-associated ICH (7.9% vs 19.6%; OR, 0.36; 95% CI, 0.13-0.98) [13]. Prior systematic reviews and meta-analyses, primarily based on single-arm, observational studies, have attempted to compare hemostatic efficacy and/or mortality for patients treated with andexanet alfa compared with 4F-PCC for FXa inhibitor-related bleeding [18–21]. These reviews have noted many limitations with the included studies, such as heterogeneity in the definition of hemostatic effectiveness, differences in the proportion of patients with ICH compared with other bleed types, lack of reporting on the time since the last dose of FXa inhibitor or anti-FXa levels, different follow-up times in assessing mortality (30-day vs in-hospital), and small sample sizes yielding limited statistical power and precluding the ability to adjust for

TABLE 4 Outcomes for the overall study population.

Variable		Andexanet alfa (*n* = 2122), *n* (%)[a]	4F-PCC (*n* = 2273), *n* (%)[a]
Other treatment strategies	i.v. fluids	336 (15.8)	461 (20.3)
	Packed red blood cells	191 (9.0)	285 (12.5)
	Fresh frozen plasma	148 (7.0)	342 (15.0)
	Vitamin K	143 (6.7)	354 (15.6)
	Protamine sulfate	69 (3.3)	55 (2.4)
	Tranexamic acid	31 (1.5)	73 (3.2)
	Desmopressin	18 (0.8)	38 (1.7)
	rFactor VIIa	10 (0.5)	10 (0.4)
	FEIBA NF	5 (0.2)	8 (0.4)
	3F-PCCs	0	1 (<0.1)
Restart of anticoagulation[b]	Oral anticoagulation	450 (21.2)	443 (19.5)
	Unfractionated or low-molecular-weight heparin	117 (5.5)	152 (6.7)
	Anticoagulation not restarted	1555 (73.3)	1678 (73.8)
Length of hospital stay (d), mean; median (IQR)[c]		7.1; 6.0 (4.0, 8.0)	6.9; 6.0 (4.0, 8.0)
Discharge disposition	In-hospital death	128 (6.0)	241 (10.6)
	Home	1061 (50.0)	1167 (51.3)
	Other/unknown destination	933 (44.0)	865 (38.1)

3F-PCC, 3-factor prothrombin complex concentrate; 4F-PCC, 4-factor prothrombin complex concentrate; i.v., intravenous.
[a]Unless otherwise specified.
[b]Anytime during the hospitalization.
[c]For patients discharged alive.

baseline bleed severity, particularly for patients with ICH. Our study addresses several of these limitations by providing direct comparative data in a large sample of U.S. hospitals while accounting for baseline bleed location, severity, and time since last dose of oral FXa inhibitor.

Many of the previously published comparisons between andexanet alfa and 4F-PCC treatment in single-center or single-health systems have suggested no difference in outcomes [14,16,22–24]. Notably, these studies ranged in size from 29 to 109 patients and were therefore significantly underpowered for a comparison between these treatments. Our data provide an approximately 40-fold increase in the patient population compared with previously published analyses, allowing for the inclusion of a broader population of patients who might have been excluded from smaller studies. Moreover, there are very limited data evaluating treatment of oral FXa-related GI bleeds, with most studies including <10 patients with GI bleeds or patients with ICH only. With >2500 GI bleeds, the current study represents the first evaluation of the impact of these agents in the treatment of oral FXa-related bleeding.

Among the 54% of patients with ICH with baseline GCS scores available, a smaller proportion of patients who received andexanet alfa vs 4F-PCC had scores ≤8 or ≥13. Among patients with available data (6% for hematoma volume and 15% for hematoma thickness), hematoma volume was smaller in patients in the andexanet alfa cohort than in patients in the 4F-PCC cohort; however, hematoma thickness was comparable between the 2 arms. The low frequency with which intracerebral hematoma volume and subdural/subarachnoid hematoma thickness were reported, which is an inherent limitation of retrospective analysis, prevents comparisons or adjustment for these factors. However, the observed patterns could indicate that patients in the 4F-PCC group may have had heterogeneous bleeds (both more and less severe bleeds), whereas the andexanet alfa cohort was more homogeneous, with the greatest proportion of patients having moderate GCS scores of 9 to 12. Further data are needed to fully account for these indicators of severity, in addition to the timing of computed tomography scans. Given that hematoma expansion is one of the key modifiable factors associated with mortality risk [25], preventing hematoma expansion via rapid treatment with specific reversal agents may be critical to lowering mortality in this population. The need for mechanical ventilation was generally similar across treatment groups for patients with ICH, although a higher proportion of patients treated with andexanet alfa underwent hematoma evacuation and decompression surgery compared with patients treated with 4F-PCC. This may be explained by baseline differences between the treatment groups, including the aforementioned differences in baseline GCS scores. However, the findings were consistent when GCS scores were accounted for, both in the adjusted logistic regression sensitivity analysis restricted to patients with ICH with available GCS scores and in the PS-weighted analyses.

Among the 70% of patients with GI bleeds for whom an AIMS65 score could be calculated, the proportion with a score ≥2, a predictor

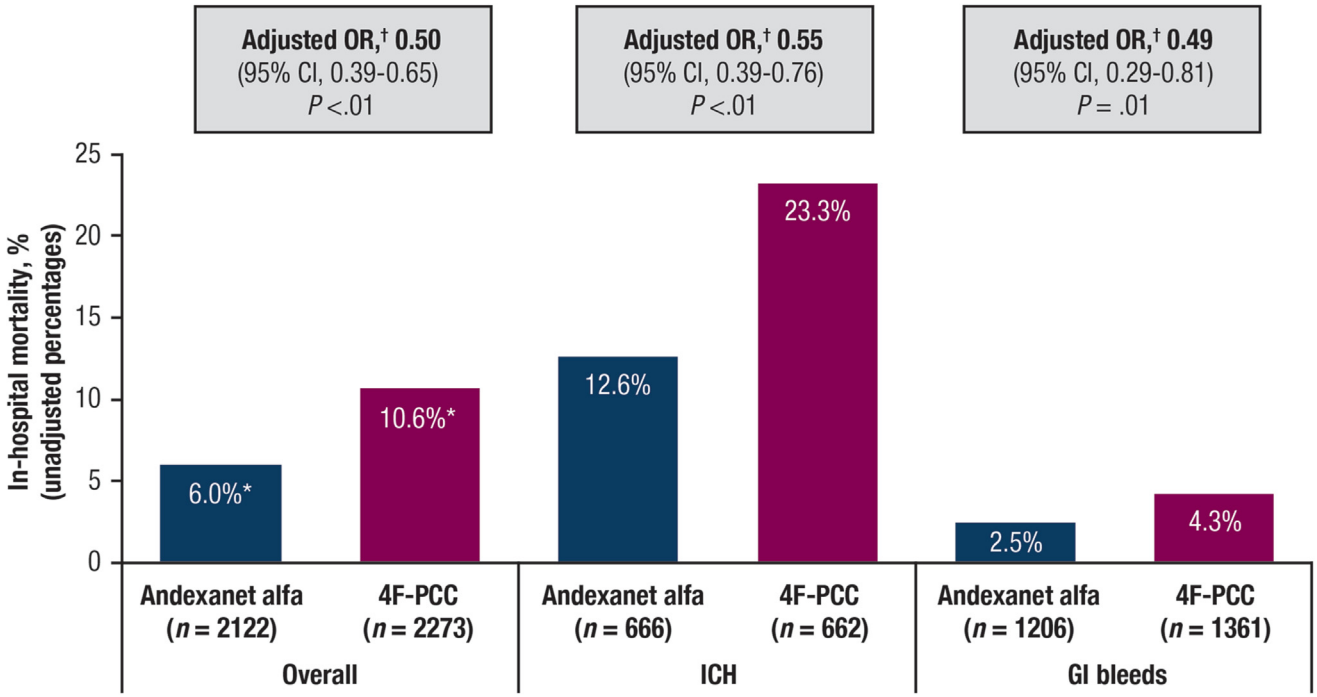

FIGURE 1 In-hospital mortality with andexanet alfa vs 4-factor prothrombin complex concentrate (4F-PCC) in patients with rivaroxaban- or apixaban-associated major bleeding overall and separately for gastrointestinal (GI) bleeds and intracranial hemorrhage (ICH). *Unadjusted percentages of in-hospital mortality were calculated in the overall population, including those with "other bleed" types and missing mental status (*N* = 4395). †Adjusted for age, sex, bleed location (in analyses of overall bleeds), traumatic vs spontaneous ICH (in analyses of overall bleeds and ICH), systolic blood pressure, impaired mental status, do-not-resuscitate order, liver disease, chronic kidney disease, heart failure, diabetes, time since last factor Xa inhibitor dose, time from arrival to administration, and timing of data collection. Patients with "other bleed" types (*n* = 80) were excluded from the overall bleeds category in the adjusted logistic regression analysis. Patients with missing mental status were also excluded (*n* = 187 in the overall bleeds category; *n* = 45 in ICH; *n* = 110 in GI bleeds). Thus, the resulting patient counts (and number of events) in the adjusted logistic regression analyses were as follows: overall, *N* = 4128 (352 events); ICH, *N* = 1283 (235 events); GI bleeds, *N* = 2457 (85 events). OR, odds ratio.

of high in-hospital mortality [26], was similar across both treatment groups. Components of the AIMS65 were included as covariates in both the logistic regression analysis (eg, age, systolic blood pressure, and impaired mental status) and PS-weighted analysis (eg, albumin levels and INR), and the results of both analyses were consistent among patients with GI bleeds. The proportion of patients undergoing GI procedures was slightly lower in the andexanet alfa group compared with the 4F-PCC group. Given that the reported data on interventional procedures are unadjusted for baseline confounders, no conclusions can be drawn regarding treatment effects on the requirement of these procedures. Furthermore, the differences in patients undergoing procedures may be impacted by different bleed subtypes or origins, as each would be associated with different treatment pathways.

The odds of mortality were significantly higher among those with ICH and critical compartment bleeds than GI bleeds. This result aligns with prior research that has reported a higher likelihood of mortality associated with FXa inhibitor-associated ICH compared with GI bleeds [27–29]. Additionally, the odds of mortality were substantially higher for patients with impaired mental status and those with a DNR order. These findings align with clinical experience and prior research, as impaired mental status could contribute to lower GCS scores, which is a well-characterized predictor of mortality within ICH [25]. DNR orders upon admission have also been previously identified as a risk factor for mortality among patients with ICH [30]. In terms of comorbidities, the odds of mortality were significantly related to the presence of liver disease, CKD, and heart failure; prior research has found poor prognoses and high mortality among patients with these diseases who experience ICH [31–34]. By controlling for key confounders, including comorbidities and GCS scores, in the ICH-specific sensitivity analysis and PS-weighted analysis, we addressed a key gap identified by Chaudhary et al. [18] in their systematic review comparing patients with ICH treated with andexanet alfa vs 4F-PCC, which noted the lack of head-to-head studies controlling for comorbidities.

This study used a large EHR data set that included laboratory and clinical variables not commonly available in other data sources (eg, administrative claims). Compared to several recent single-center/system, observational cohort studies [14–16,35], the present study represents the largest multicenter U.S. data set to date. Similar to a previously published large EHR study that assessed the management of oral FXa inhibitor-related bleeds [29], the ICD-10 diagnosis code D68.32 was used for patient selection in both the andexanet alfa and 4F-PCC cohorts. The use of various bleed location-specific ICD-10 codes to identify eligible patients via EHRs was not deemed feasible

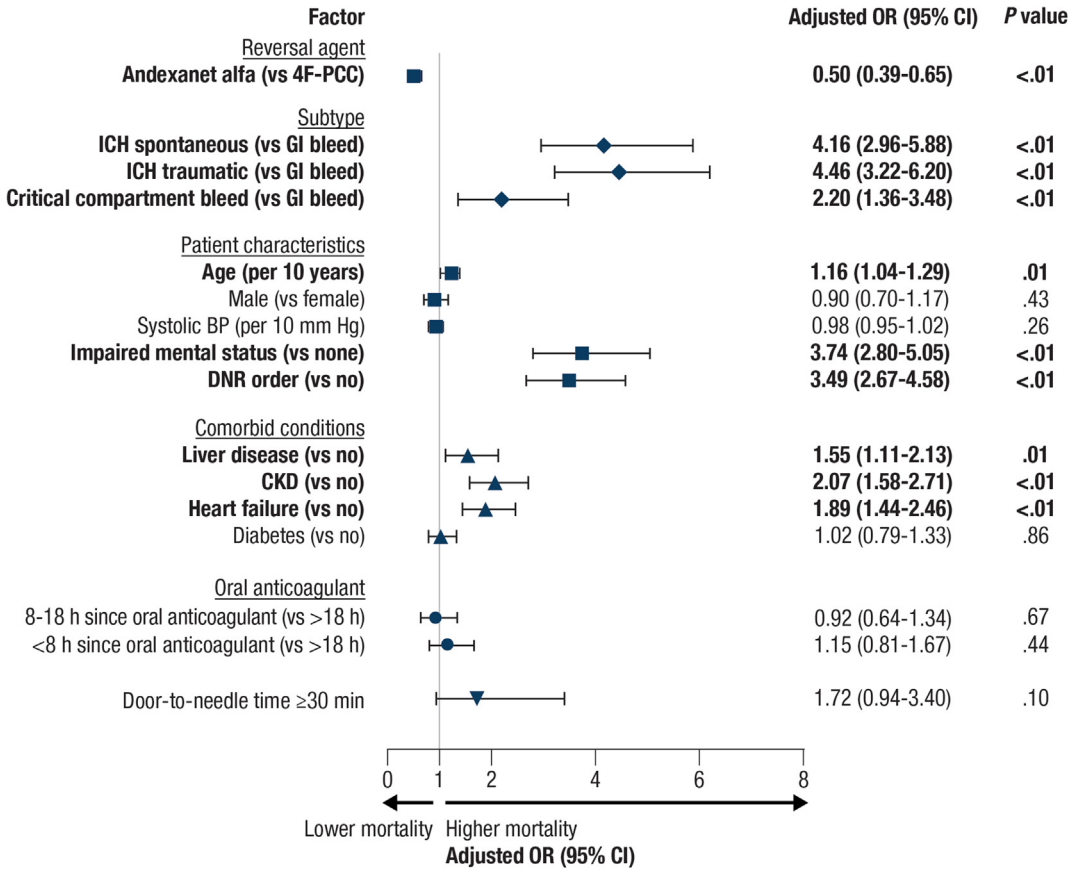

FIGURE 2 Adjusted logistic regression analysis of clinical factors associated with odds of in-hospital mortality. Models were adjusted for bleed location, intracranial hemorrhage (ICH) bleed cause (trauma vs spontaneous), age, sex, systolic blood pressure (BP), mental status, do-not-resuscitate (DNR) status, comorbid liver disease, chronic kidney disease (CKD), heart failure, and diabetes, time since last anticoagulant dose, door-to-needle time, and timing of data collection. Patients with "other bleed" types (n = 80) and missing mental status (n = 187) were excluded from the adjusted logistic regression analysis, resulting in N = 4128; events = 352. 4F-PCC, 4-factor prothrombin complex concentrate; GI, gastrointestinal; OR, odds ratio.

given the large number of records screened. While potentially eligible patients who did not have the D68.32 code recorded may have been missed, it is unlikely to have resulted in any bias due to differential selection between the cohorts.

Limitations of this study include its nonrandomized design and that the data obtained were dependent on the quality and accuracy of routine EHR documentation. While the analyses controlled for as many confounding variables as possible, some covariates could not be assessed due to lack of data, with some risk of residual confounding. For example, data on the initial indication for and dose of anticoagulation, certain laboratory parameters (eg, anti-FXa levels), and the time interval between treatment with andexanet alfa or 4F-PCC and neurosurgical procedures were underreported, as were some baseline characteristics (eg, race or ethnicity). Further, we did not adjust for clustering at the hospital level; however, clustering was unlikely to have an impact on standard errors due to the large number of hospitals included (>350) and relatively small number of patients coming from each hospital. GCS scores were only reported for approximately 50% of the ICH sample, and among patients with GI bleeds, a full AIMS65 score was unavailable for approximately 30% of patients. Other outcomes, such as hemostatic efficacy, timing of anticoagulation restart, thrombotic events (including venous and arterial locations), longer-term mortality, and functional neurologic outcomes (eg, Modified Rankin Scale scores), were beyond the design of this study and were not possible to assess within this study due to the limited reporting, the need for endpoint adjudication, and/or because patient follow-up ended at hospital discharge. Thromboembolic events would need to have been evaluated beyond the hospitalization period, as the majority of events occurred 6 to 30 days after treatment with andexanet alfa in ANNEXA-4 [11]. In the present study, the focus was on in-hospital mortality as the primary outcome of interest. Although >350 hospitals across the United States were included in this analysis, which may improve external validity compared with single-center studies, other institutions beyond those included in the current study may have different patient populations, which may impact the generalizability of the results.

5 | CONCLUSIONS

In conclusion, treatment with andexanet alfa in patients hospitalized with rivaroxaban- or apixaban-related major bleeds was associated

with 50% lower odds of in-hospital mortality compared with 4F-PCC when adjusted for identified risk factors of mortality. The risk reduction was similar in both ICH and GI bleeds. Other factors associated with higher odds of death included ICH and critical compartment bleeds (vs GI bleed), increasing age, presence of liver disease, CKD, or heart failure, impaired mental status, and a DNR order. While hemostatic efficacy and thrombotic event data are important, in-hospital mortality as a primary outcome was considered the most relevant, robust, and measurable objective endpoint for this evaluation. The randomized controlled ANNEXA-I trial was designed to assess the effects of andexanet alfa compared with usual care, including 4F-PCC, in patients with intracerebral hemorrhage receiving an oral FXa inhibitor. In June 2023, the early stop of ANNEXA-I was announced after the prespecified criteria of superior hemostatic efficacy and ability to limit life-threatening intracerebral hemorrhage expansion were met with andexanet alfa treatment compared with usual care [36]. Improving patient outcomes is key, given the high morbidity and mortality for patients experiencing FXa inhibitor-related bleeding. Although randomized controlled trials are typically considered the "gold standard" for generating clinical evidence, real-world studies, including the present observational cohort study, provide critical complementary data on the impact of therapeutic agents on patient outcomes in a large, heterogeneous population encountered in the routine clinical setting. The findings from the present study support guideline recommendations of andexanet alfa as the preferred agent for treating FXa inhibitor-related bleeds over 4F-PCC [1,37–40].

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AUTHOR CONTRIBUTIONS

P.P.D., G.J.F., M.J.C., B.K., B.L., T.D., M.D., J.U., S.D., and C.I.C. conceptualized the study. J.U. and S.D. collected the data. M.D., J.U., and S.D. analyzed the data. P.P.D., G.J.F., M.J.C., B.K., E.L., H.C., B.L., T.D., M.D., J.U., S.D., and C.I.C. critically reviewed and evaluated the results. P.P.D., G.J.F., M.J.C., B.K., E.L., H.C., B.L., T.D., M.D., J.U., S.D., and C.I.C. wrote, reviewed, and edited the paper. P.P.D., G.J.F., M.J.C., B.K., E.L., B.L., T.D., and C.I.C. supervised the study. All authors read and approved the final version of the manuscript for submission.

RELATIONSHIP DISCLOSURE

P.P.D. has served as a consultant for Pfizer/Bristol Myers Squibb Alliance and Janssen Pharmaceuticals. G.J.F. has served on a speakers bureau for Janssen Pharmaceuticals and AstraZeneca has served, as a consultant for Milestone Pharmaceuticals, and has received research funding from Siemens, PCORI, and the NIH. B.K., E.L., H.C., and T.D. are employees of AstraZeneca. M.J.C. and B.L. are previous employees of AstraZeneca. M.D., J.U., and S.D. are employees of Outcomes Insights, which has received research funding related to cardiovascular disease from Amgen and Boston Scientific. C.I.C. has received research funding and/or consulting honoraria from Janssen Pharmaceuticals, Bayer AG, and AstraZeneca.

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SUPPLEMENTARY MATERIAL

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