Reversal of Factor Xa Inhibitor-Related Intracranial Hemorrhage: A Multicenter, Retrospective, Observational Study Comparing the Efficacy and Safety of Andexanet and Prothrombin Complex Concentrates

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OBJECTIVE: To determine the effectiveness and safety of andexanet and prothrombin complex concentrates (PCCs) when administered after intracranial hemorrhage (ICrH) associated with direct oral anticoagulants, specifically apixaban or rivaroxaban.

DESIGN: A multicenter, retrospective, observational study of patients with apixaban or rivaroxaban-related ICrH who received andexanet or PCCs between January 1, 2015, and March 31, 2023. A predefined sensitivity analysis excluding patients with an admission Glasgow Coma Scale score of less than 7 was also performed.

SETTING: Forty-two stroke centers in the United States.

PATIENTS: A total of 1133 patients.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary efficacy outcome was the percentage of patients with excellent or good hemostasis as defined by the modified Sarode criteria. The primary safety outcome was the occurrence of a thrombotic event (TE) during their hospital stay. Of the 1133 patients evaluated, 1096 were included. In the full hemostatic efficacy analysis, patients receiving andexanet (87.8%) had higher odds of achieving excellent or good hemostasis (odds ratio [OR] 1.60; 95% CI, 1.00–2.56; $p = 0.048$) compared with PCCs (81.8%). Patients treated with andexanet (7.9%) had higher odds of a TE (OR 1.91; 95% CI, 1.13–3.20; $p = 0.014$) compared to those treated with PCCs (4.2%). No differences in hemostatic or thrombotic outcomes were observed when the sensitivity analysis was applied.

CONCLUSIONS: Despite statistically higher odds of achieving hemostatic efficacy with andexanet, we also observed higher odds of a TE with no difference in discharge outcomes observed between groups. When those with more severe neurologic injuries were excluded, efficacy and safety outcomes were similar between treatments.

KEYWORDS: andexanet; anticoagulation reversal; factor Xa inhibitors; intracranial hemorrhage; prothrombin complex concentrates

Since oral factor Xa (FXa) inhibitors were approved, there have been concerns regarding the ability to reverse their anticoagulant effects after life-threatening bleeding (1). Before a target-specific antidote became available, guidelines used studies of healthy subjects to suggest the administration of prothrombin complex concentrates (both activated PCCs

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KEY POINTS

Question: Are andexanet and prothrombin complex concentrate (PCC) equally safe and effective for reversing factor Xa (FXa) inhibitor-related intracranial hemorrhage (ICrH)?

Findings: In this observational cohort study of adults treated at 42 stroke centers in the United States, andexanet (87.8%) had higher odds of achieving excellent or good hemostasis compared with PCC (81.8%); however, patients treated with andexanet (7.9%) also had a higher odd of a thrombotic event (TE) compared to those treated with PCC (4.2%).

Meaning: In patients with FXa inhibitor-related ICrH, andexanet resulted in statistically higher odds of achieving excellent or good hemostasis while also leading to a higher rate of TEs.

and four-factor [4PCC]) (2). In 2018, the U.S. Food and Drug Administration (FDA) granted accelerated approval to andexanet (coagulation FXa [recombinant], inactivated-Zhao), a target-specific antidote. Following the approval of andexanet, guidelines published by various organizations continued to suggest PCC as a treatment option for life-threatening bleeding secondary to FXa inhibitors based on clinical experience and supporting reports in the literature (2–6).

In 2019, our group began an observational study comparing andexanet and PCC in a large, multicenter cohort of patients using previously established criteria for determining hemostatic efficacy and safety outcomes (7, 8). Interim results showed that 81.8% of patients receiving PCC following apixaban or rivaroxaban-related intracranial hemorrhage (ICrH) experienced a good or excellent hemostatic efficacy outcome (9). Here, we present the planned second phase analysis results comparing andexanet and PCC.

MATERIALS AND METHODS

This study was approved by the Rush University Institutional Review Board (IRB) with informed consent waived on June 10, 2018 (ORA180441007-IRB01; outcomes of FXa inhibitor-associated ICrH after prothrombin complex concentrate administration). Further amendments were approved on May 14, 2019, to transition to a multicenter study and to include patients receiving andexanet (ORA18041007-IRB01-AM03). Approval letters from study site IRBs were sent to the corresponding author and amended to the Rush University IRB. Procedures were followed under the ethical standards of the IRB on human experimentation and with the Helsinki Declaration of 1975.

We included patients treated with andexanet or PCC from 42 medical centers in the United States between January 1, 2015, and March 31, 2023 (**Table S1**, http://links.lww.com/CCM/H705). The steering committee adjudicated the primary outcome after data validation and before statistical analysis. Eligibility criteria, additional study methodology, and details on efficacy and safety assessments are included in the **Supplemental Methods** (http://links.lww.com/CCM/H705) (9–11). The study had pre-planned hemostatic efficacy and safety analyses. The hemostatic efficacy analysis focused on patients with intracerebral, subarachnoid hemorrhage (SAH), or subdural hemorrhage (SDH) who had at least one follow-up image obtained within 24 hours of reversal agent administration. Patients with primary epidural or intraventricular hemorrhage were excluded from the hemostatic efficacy analysis. The primary efficacy outcome was the percentage of patients with good or excellent hemostasis (hematoma volume change of 35% or less) as defined by Sarode et al (7, 8, 12). An explanation of the hemostatic efficacy criteria and the hemorrhage locations to which they were applied is included in the Supplemental Methods (http://links.lww.com/CCM/H705). The primary safety outcome was a thrombotic event (TE) during hospitalization, and events were censored at hospital discharge or 30 days from admission, whichever occurred first. The safety analysis included all enrolled patients, including those undergoing neurosurgical procedures. TEs included upper and lower extremity deep vein thrombosis, pulmonary embolism, acute ischemic stroke, myocardial infarction, or any other documented thrombosis. Other reported outcomes assessed until hospital discharge included mortality (the combined occurrence of in-hospital death and discharge to hospice), ICU duration, and hospital stay.

Statistical Analysis

Frequency data were described using *n* (%). Data distribution and normality assessment were visually and statistically analyzed. Due to a non-parametric

distribution, all continuous data are reported as median (25–75% interquartile range). A steering committee member performed statistical analyses using R 4.3.1 (R Core Team, 2023; R Foundation for Statistical Computing, Vienna, Austria). A second steering committee member subsequently validated all results using SPSS, Version 29.0 (SPSS, Armonk, NY) to ensure accuracy.

The primary efficacy outcome was first tested for a difference in proportion between groups. Results are reported along with 95% CIs, and a two-sided *p* value of 0.05 was used to determine statistical significance. Then, testing was performed to determine if any difference suggested non-inferiority. Sample size estimation was derived from trials with published efficacy data for andexanet and a meta-analysis for PCC reversal to determine non-inferiority (8, 13, 14). Based on good or excellent hemostatic efficacy rates of 80% andexanet and 77% PCC, a 10% non-inferiority margin was chosen as the maximal difference in efficacy between treatments that would be clinically acceptable by the investigators. Using this margin, 420 patients (210 in the andexanet and PCC groups, respectively) were needed to achieve 90% power with a one-sided α level of 0.025. For the primary outcome of hemostatic efficacy at 24 hours, non-inferiority was established if the upper bound of the one-sided 97.5% CI did not cross the margin of 10%. The Miettinen-Nurminen method determined a one-sided 97.5% CI for proportions.

A sensitivity analysis was applied to the hemostatic efficacy cohort, removing patients who presented with a Glasgow Coma Scale (GCS) score of less than 7. This aimed to homogenize the efficacy and safety populations by removing patients with predictors of worse outcomes. It emulated the same data analysis of previously published randomized control trials studying the same agents (7, 8).

RESULTS

A total of 1133 patients were evaluated for inclusion. After initial exclusions, 1096 patients were included in the safety analysis and 676 in the hemostatic efficacy analysis (**Fig. 1**). Key baseline patient characteristics are summarized in **Table 1**. The primary indication for anticoagulation was atrial fibrillation. Intracerebral bleeding was the most common hemorrhage type in both groups. The median GCS score on presentation was 14 in both groups.

Most patients in the PCC group received 4PCC (78.8%) at a median dose of 44.5 (25.8–50) units per kilogram. Low-dose andexanet was administered to 84.9% of patients in the andexanet cohort. Confirmatory anti-FXa levels were drawn before reversal agent administration in 24.9% of patients treated with andexanet and 10.1% of patients treated with PCC. Further information regarding patient, neurologic, and treatment characteristics is included in **Tables S2–S5** (http://links.lww.com/CCM/H705).

Hemostatic Efficacy Analysis

Of the 676 patients evaluated for hemostatic efficacy, 221 (32.7%) received andexanet, and 455 (67.4%) received PCC. The primary efficacy outcome occurred more frequently in the andexanet group (87.8%) than in the PCC group (81.8%; odds ratio [OR] 1.60; 95% CI, 1.00–2.56; **Fig. 2**). Non-inferiority between the two agents was not observed (97.5% CI, −∞ to 11.61%). A pre-planned subgroup analysis of hemostatic efficacy is included in Figure 2. This analysis is exploratory since the study was not adequately powered to assess hemostatic efficacy differences between subgroups.

When sensitivity analysis was performed, we found similar odds of excellent or good hemostasis with andexanet or PCC (OR 1.59; 95% CI, 0.99–2.57) among the 641 patients analyzed; however, non-inferiority was not observed (–0.9% to 12.6%). **Table S6** (http://links.lww.com/CCM/H705) breaks down relevant outcomes for patients in the hemostatic efficacy analysis.

Safety Analysis

Thirty patients (7.9%) in the andexanet and 30 (4.1%) in the PCC groups had a TE documented during hospitalization (**Table 2**). Andexanet patients were found to have higher odds of a TE (OR 1.91; 95% CI, 1.13–3.20; $p = 0.014$) compared with PCC. When sensitivity analysis criteria were applied to the safety cohort, we observed a similar rate of TEs between andexanet (5.6%) and PCC (4.0%).

Clinical outcomes of the safety analysis cohort were also evaluated (**Table 3**). The duration of hospitalization, the length of stay in the ICU, and the discharge disposition location were similar between agents. Mortality was comparable between groups in all analyses. The timing

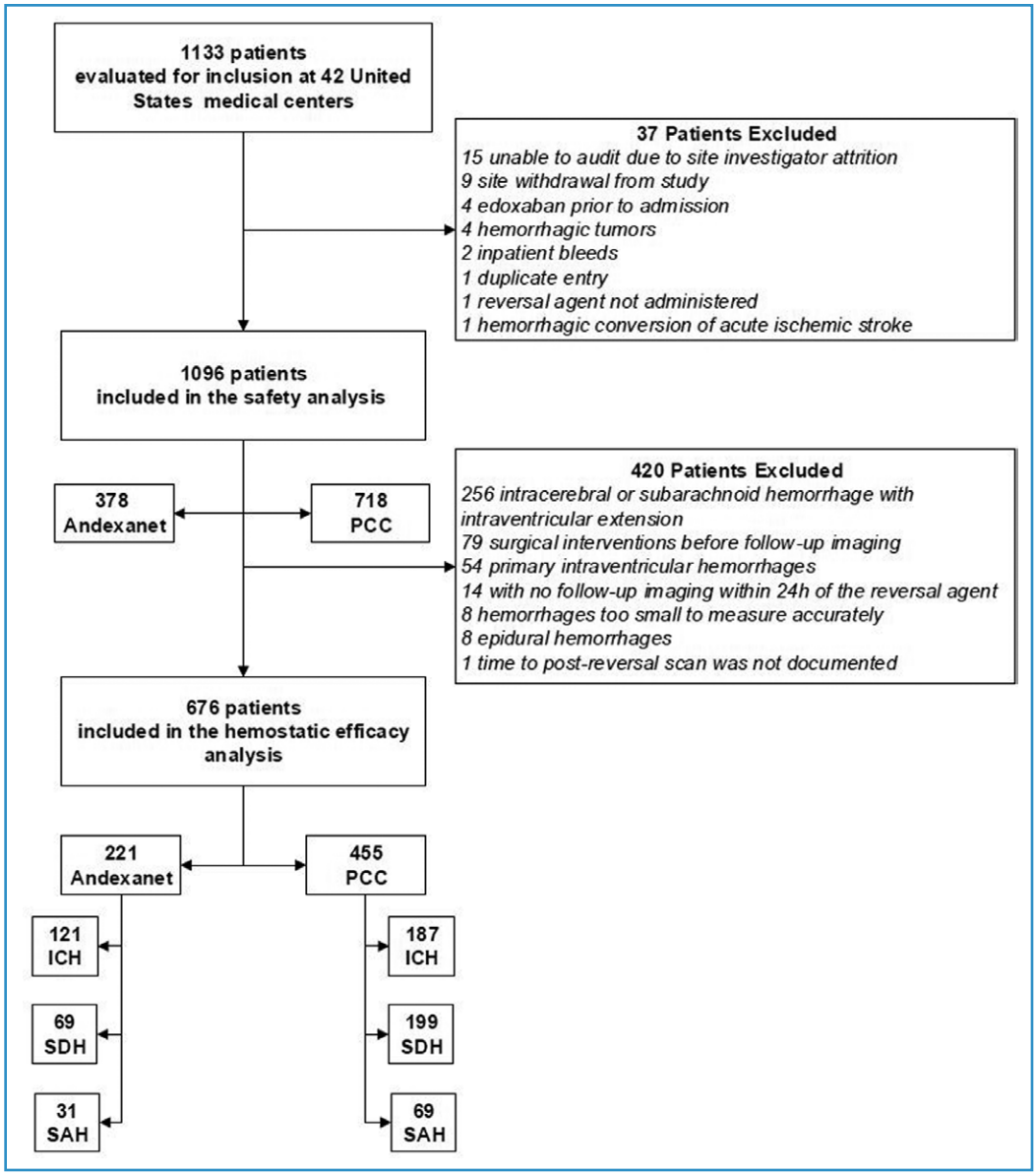

Figure 1. Flow diagram of study design and included patients. Before statistical analysis, all entered data were audited by steering committee members and then re-affirmed by individual investigators at each site; however, at one site, investigator attrition had occurred, and the data were unable to be re-confirmed resulting in these patients being excluded from the analysis. ICH = intracerebral hemorrhage, PCC = prothrombin complex concentrate, SAH = subarachnoid hemorrhage, SDH = subdural hematoma.

of each TE following reversal agent administration is found in **Table S7** (http://links.lww.com/CCM/H705).

DISCUSSION

Our study assesses the real-world safety and efficacy of andexanet and PCC in patients with FXa inhibitor-related ICrH. Recently, results of a prospective, randomized, controlled trial (ANNEXa-I) comparing andexanet with usual care (typically PCC) demonstrated reduced hematoma expansion and increased thrombosis rate with andexanet use (15). The current study's results are similar to those from ANNEXa-I but also have notable differences. First, we observed higher rates of good or excellent hemostatic efficacy in the andexanet (87.8%) and PCC (81.8%) groups compared with the ANNEXa-I study (74% andexanet vs. 60% receiving usual care) (16). This may be due to differing definitions, timing of imaging assessments, or differences in baseline hematoma volumes between the studies. However, efficacy rates in the current study align with previous reports using the Sarode criteria (7, 9). We observed a greater likelihood of excellent or good hemostasis and TEs in the andexanet cohort. When considering a sensitivity analysis removing subjects with a baseline GCS score less than 7, there was no statistical difference in any outcome between products.

Several differences in the design of ANNEXa-I and the current study merit discussion when considering the results. First, the ANNEXa-I study was prospective and randomized, whereas the current study was retrospective and observational. Second, ANNEXa-I primarily included patients with FXa

TABLE 1.
Baseline Patient Characteristics

Characteristic	Full Safety Cohort		Hemostatic Efficacy Cohort	
	Andexanet (*n* = 378)	PCC (*N* = 718)	Andexanet (*N* = 221)	PCC (*N*= 455)
Age (yr)[a]	76.0 (69.0–83.0)	75.0 (68.5–81.0)	76.0 (70.0–83.0)	78.0 (72.0–84.0)
Male, *n* (%)	219 (57.9)	386 (53.8)	119 (53.8)	242 (53.2)
Race, *n* (%)				
White	299 (79.1)	560 (78.0)	175 (79.2)	372 (81.8)
Black	51 (13.5)	99 (13.8)	25 (11.3)	49 (10.8)
Other	28 (7.4)	59 (8.2)	21 (9.5)	34 (7.5)
Weight (kg)	78.6 (67.8–94.0)	80.0 (66.4–95.3)	78.5 (65.7–94.7)	78.7 (65.1–93.5)
Body mass index[b]	27.1 (23.2–32.9)	27.4 (23.8–31.7)	27.4 (23.2–33.3)	26.9 (23.1–31.7)
Estimated creatinine clearance (mL/min)[c]	59.4 (42.5–80.4)	63.5 (44.9–85.0)	55.3 (40.0–81.4)	58.6 (43.4–80.8)
< 30 mL/min, *n* (%)	38 (10.3)	74 (10.9)	22 (10.1)	45 (10.5)
Factor Xa inhibitor used, *n* (%)				
Apixaban	277 (73.3)	403 (56.1)	166 (75.1)	250 (54.9)
Rivaroxaban	101 (26.7)	315 (43.9)	55 (24.9)	205 (45.1)
Primary intracranial hemorrhage location, *n* (%)				
Intracerebral	213 (56.3)	336 (46.8)	121 (54.8)	187 (41.1)
Subdural	99 (26.2)	240 (33.4)	69 (31.2)	199 (43.7)
Subarachnoid	46 (12.2)	100 (13.9)	31 (14.0)	69 (15.2)
Intraventricular	17 (4.5)	37 (5.2)	–	–
Epidural	3 (0.8)	5 (0.7)	–	–
Multicompartment hemorrhage, *n* (%)	89 (23.5)	171 (23.8)	55 (24.9)	109 (24.0)
Traumatic injury, *n* (%)	169 (44.7)	359 (50.0)	115 (52.0)	277 (60.9)
Admission Glasgow Coma Scale score[d]	14.0 (13.0–15.0)	14.0 (11.0–15.0)	15.0 (14.0–15.0)	15.0 (14.0–15.0)
Anti-factor Xa level measured, *n* (%)	92 (24.9)	71 (9.9)	54 (24.4)	42 (9.2)
Reversal agent administration, *n*				
Low-dose andexanet	321 (84.9)	–	189 (85.5)	–
High-dose andexanet	57 (15.1)	–	32 (14.5)	–
Four-factor PCC	–	566 (78.8)	–	335 (73.6)
Activated PCC	–	152 (21.2)	–	120 (26.4)
Received neurosurgical intervention, *n* (%)	88 (23.3)	145 (20.2)	16 (7.2)	39 (8.6)

PCC = prothrombin complex concentrate.

[a]Assessed in 1012 patients in the full safety cohort who were younger than 90 yr old; an additional 84 patients (32 andexanet and 52 PCC) were above 89 yr and reported as a dichotomous outcome due to institutional review board requirements; in the hemostatic efficacy cohort, assessed in 615 patients younger than 90 yr old with an additional 61 patients (24 andexanet and 37 PCC) older than 89 yr old.

[b]The body mass index is the actual weight (kilograms) divided by the square of the height (meters) and was missing in 25 patients in the full safety cohort and 10 patients in the hemostatic efficacy cohort.

[c]Calculated using the Cockcroft-Gault equation and was missing in 42 patients in the full safety cohort and 26 patients in the hemostatic efficacy cohort.

[d]Data missing from 26 patients in the full safety cohort and 13 patients in the hemostatic efficacy cohort.

Unless otherwise noted, data are reported as median (25–75% interquartile range).

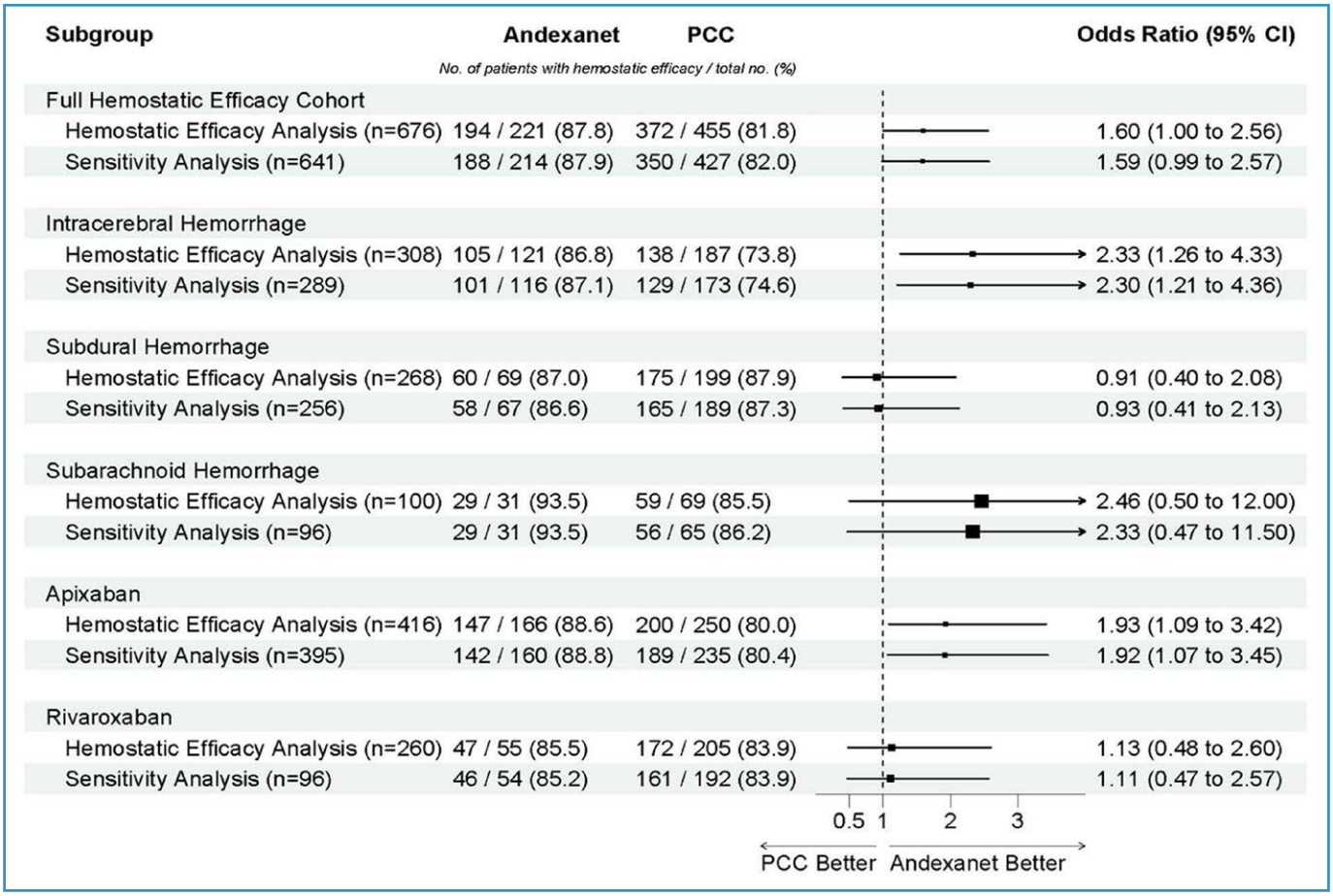

Figure 2. Results of primary efficacy outcome for full cohort and by subgroup. According to the modified Sarode criteria, any hematoma volume change of 35% or less is classified as the primary outcome of good or excellent hemostasis. Odds ratios, *p* value, and 95% CI were calculated using univariable logistic regression; the study was not powered for conclusions about subgroups. Significance testing was only performed on the primary efficacy endpoint and was significant ($p = 0.048$) for the entire hemostatic efficacy cohort. PCC = prothrombin complex concentrate.

inhibitor-associated intracerebral hemorrhage and, through early protocol modifications, excluded patients with other types of intracranial bleeding. The current study included more patients with different types of intracranial bleeding, such as SDH and SAH. These are patients who also may merit emergent reversal of FXa inhibitors when presenting with life-threatening bleeding. They also excluded patients with a planned neurosurgical procedure within 12 hours of randomization, an important subgroup of patients uniquely included in the current study. While the primary efficacy endpoints differed, data from the ANNEXa-I trial is broken down by each part of the composite outcome. This allowed us to compare those results with our study (15). All patients in the current study received known doses of either andexanet or PCC. In contrast, many of the usual care patients in ANNEXa-I received PCC at an unknown dose and formulation or did not receive PCC at all. Thus, the current study provides a more homogeneous comparator group to andexanet than the usual care definition in ANNEXa-I.

When analyzing the efficacy of the reversal agents for hemorrhage subgroups, the odds of good or excellent hemostasis were higher for patients with intracerebral hemorrhage treated with andexanet (Table S6, http://links.lww.com/CCM/H705). The results of previous studies determining the hemostatic efficacy of both agents when compared head-to-head have been mixed, with some suggesting no difference, whereas others suggesting andexanet may have improved hemostatic efficacy over PCC (17–22). However, conclusions from these studies should be tempered when considering the study design, heterogeneous populations, and small sample size. An editorial accompanying the publication of ANNEXa-I also called into

TABLE 2.
Safety Analysis of Thrombotic Events

Thrombotic Events	Andexanet Alfa ($n = 378$)	Prothrombin Complex Concentrates ($n = 718$)
Complete safety analysis ($n = 1096$)		
Any thrombotic events, *n* (%)[a]	30 (7.9)	30 (4.2)
Ischemic stroke	12	8
Myocardial infarction	5	2
Deep-vein thrombosis	13	17
Pulmonary embolism	5	3
Therapeutic anticoagulation restarted, *n* (%)[b]	53/378 (14)	48/718 (6.6)
Sensitivity analysis ($n = 725$)		
Thrombotic events, *n* (%)[c]	14/251 (5.6)	19/474 (4.0)
Ischemic stroke, *n*	8	4
Myocardial infarction, *n*	2	1
Deep-vein thrombosis, *n*	3	12
Pulmonary embolism, *n*	2	0
Therapeutic anticoagulation restarted, *n* (%)[b]	31/251 (12.4)	33/474 (7.0)

The percentage of patients with any thrombotic event was calculated using the number of patients with an event divided by the cohort size; For the individual thrombotic event types, the number of each event is reported, and some patients may have experienced multiple event types; A breakdown of thrombotic events based upon the post-reversal day in which they occurred is presented in **Table S7** (http://links.lww.com/CCM/H705) of the online appendix.

[a]Significance testing was performed on the primary safety analyses and was significant (odds ratio [OR] 1.91; 95% CI, 1.13–3.20; $p = 0.014$); five patients experienced more than one thrombotic event (four andexanet, one prothrombin complex concentrate).

[b]Includes the use of therapeutic doses of unfractionated heparin, low-molecular-weight heparin, or any oral anticoagulant (at any dose and for any duration).

[c]Significance testing was performed on the sensitivity safety analyses (OR 1.41; 95% CI, 0.69–2.87; $p = 0.34$); one patient that was treated with andexanet experienced more than one thrombotic event.

question the choice of hemostatic efficacy, highlighting the importance of clinical and functional outcomes instead (23). In our study, andexanet showed only a marginal statistical difference for hemostatic efficacy, with the primary outcome having a calculated fragility index of zero. More research may be needed to determine if there is a more tangible clinical benefit to andexanet than a slight improvement in hematoma size, especially for those with intracerebral hemorrhage. The Sarode criteria were initially validated in a small sample of patients with intracerebral hemorrhage, SDH, and SAH (7). Subsequently, the ANNEXA trials were designed to include the same three hemorrhage types, but protocol amendments later resulted in intracerebral hemorrhage patients making up the majority of patients randomized (8, 15). Due to this imbalance in hemorrhage types, there remains debate regarding the applicability of these criteria to bleeding outside the intracerebral compartment. With intracerebral hemorrhage, the Sarode criteria may be more accurate in determining changes in blood volume since the shape of the hemorrhage more closely resembles a sphere. However, if the hemorrhage extends into the ventricle, changes in blood volume here would not be captured by the criteria. With SDH and SAH, the area where the blood is the thickest is used, which may not wholly capture volume changes. Because SAH may also extend into the ventricles, the same challenges exist regarding assessing whether blood volume has increased. Although no other scales have been proposed in randomized trials, further research may be needed to determine the applicability of the Sarode criteria to all three hemorrhage types. Scales that are more sensitive to changes in blood volume may be

TABLE 3.
Clinical Outcomes of All Patients

	Full Safety Analysis		Sensitivity Analysis	
Outcome	**Andexanet Alfa, *n* = 378**	**PCC, *n* = 718**	**Andexanet Alfa, *n* = 251**	**PCC, *n* = 474**
Hospital length of stay, d	7.0 (4–13.3)	6.80 (3.7–11.9)	6.0 (4.0–11.5)	6.0 (3.6–11.0)
ICU	2.70 (1.5–6)	2.85 (1.1–6.4)	2.0 (1.0–4.0)	2.0 (1.0–5.0)
Discharge disposition, *n* (%)				
Home	88 (23.3)	169 (23.5)	79 (31.5)	146 (30.8)
Inpatient rehabilitation facility	93 (24.6)	183 (25.5)	69 (27.5)	126 (26.6)
Skilled nursing facility	72 (19.0)	144 (20.1)	56 (22.3)	107 (22.6)
Long-term acute care hospital	23 (6.1)	29 (4.0)	10 (4.0)	14 (3.0)
In-hospital death or hospice	102 (27.0)	193 (26.9)	37 (14.7)	81 (17.1)
Hospice	43 (11.4)	55 (7.7)	18 (7.2)	29 (6.1)
In-hospital death	59 (15.6)	138 (19.2)	19 (7.6)	52 (11.0)

Unless otherwise noted, all data are presented as median (25–75% interquartile range). The study was not powered to conclude clinical outcomes, and significance testing was not reported.

required if this outcome continues to be used to validate reversal products.

Mortality rates after FXa inhibitor-associated ICrH continue to vary between 15% and 70% after the administration of a reversal agent (9, 24–31). We defined mortality as in-hospital death or discharge to hospice and observed no difference with either agent (Table 3) despite including those with an admission GCS of less than 7, those who underwent neurosurgical procedures within 12 hours, those with baseline hematoma volumes greater than 60 mL, and those not expected to survive 30 days. When sensitivity analysis was applied, overall rates of the outcome dropped substantially, and there remained no difference in discharge status or mortality. A limitation of our assessment of discharge disposition is that we could not capture functional outcomes at discharge from the hospital or at 90 days. Therefore, more questions remain regarding the long-term effect on functional outcomes when using these reversal agents, and data on mortality should be evaluated as hypothesis-generating only.

When considering the reversal effect of the available agents, the prothrombotic effect of these agents should be considered. When administering andexanet, tissue factor-initiated thrombin generation can last up to 22 hours after the infusion stops (14). This may be due to andexanet binding to the tissue factor pathway inhibitor, which reduces its activity and increases thrombin formation with transient increases in D-dimer and prothrombin fragments 1 and 2 (14, 32). Patients receiving reversal agents have medical conditions that predispose them to the development of thromboembolism, especially when the medication is stopped abruptly. A recent meta-analysis of the low-moderate risk of bias studies suggested a non-significant risk of TEs associated with andexanet (33). In ANNEXa-I, researchers noted an increased risk of thromboembolic complication after receiving andexanet (10.3%) compared with usual care (5.6%) (15). Notably, data presented at a recent FDA public hearing revealed that the TE rate for patients who received PCC in the ANNEXa-I trial was lower than 5.6% in the full usual care cohort (4.8%) (34). Our study found a similar thrombotic risk (7.9% andexanet vs. 4.1% PCC). We also observed more TEs with andexanet (4.5%) than PCC (2.6%) within 6 days of agent administration. It is also worth noting that the fragility index for TEs was six, much higher than the index calculated for the hemostatic efficacy. Finally, recently presented data from ANNEXa-I revealed that mortality secondary to TEs was three times higher (2.5% vs. 0.9%) in patients treated with andexanet compared to usual care. Overall mortality in our study was numerically higher in andexanet patients who experienced a TE (36.7% with an event vs. 26.1% without a TE) compared with patients in the PCC group (26.7% with an event vs. 26.9% without a TE).

However, we did not assess individual causes of mortality in our study and are unable to provide a direct comparison to the data presented in ANNEXa-I (16).

Restarting therapeutic anticoagulation is an important, challenging method of reducing the thrombosis risk after reversal. In the current study, two times more patients had anticoagulation restarted after receiving andexanet compared with the PCC group, but the majority were after 15 days. Within 6 and 14 days, a similar percentage of patients within each group was restarted on anticoagulation (Table 2). Why patients in either group did not begin anticoagulation sooner is unknown. Andexanet has been shown to inactivate unfractionated heparin and low-molecular-weight heparins but not synthetic pentasaccharides like fondaparinux (35). Therefore, patients cannot be immediately anticoagulated with a heparin product after administering andexanet. Nevertheless, providing any agent to reverse the effect of anticoagulants should include a risk-benefit discussion. A more nuanced approach regarding the type of reversal agent offered to patients may be necessary to provide the most effective therapy without causing harm and provide an avenue for the timely re-initiation of anticoagulation when it is safe.

The most important limitation of our study that has not yet been noted is that it is an observational cohort study. Confounding due to known or unknown factors cannot be excluded as an explanation for the results. Our study included enough patients to assess non-inferiority based on our original analysis; however, because we observed only a 6% difference in proportions, our study is likely underpowered to assess non-inferiority between agents truly. We could not evaluate hemostatic efficacy on 421 patients included in the safety analysis due to a lack of follow-up imaging to assess hematoma size. The exclusion of these patients may have impacted our cohort's effective hemostasis rate. We also do not know the effect of time on treatment after the symptom onset of intracranial bleeding. We could not report the confirmed time of the last FXa inhibitor dose due to challenges faced in clinical practice related to obtaining and consistently documenting this information. Although patients may have ingested their last dose more than 24 hours before presentation, our approach represents a realistic assessment of clinicians' challenges when evaluating these patients. Our study did not assess the correlation between hemostatic efficacy and anti-Xa activity levels, which was infrequently evaluated in both groups. Due to challenges with blood pressure documentation between the 42 medical centers, we could not report information on these measurements between groups. Our ability to assess for the development of TEs was also limited to hospital discharge or 30 days, which may have impacted the observed event rate. Although we excluded those who decided to withdraw aggressive treatment measures within 24 hours of admission, we did not exclude those whose care patterns changed later, which may have influenced our overall mortality rate. However, including these patients reflects the natural course of intracranial bleeding, lending credibility to the real-world nature of the current study. Our safety assessment did not evaluate the agent used for venous thromboembolism prophylaxis or the timing of initiation. We relied upon documentation in the electronic medical record to assess the safety outcomes. Both factors could have impacted the observed rate of thromboembolic events. Finally, we could not evaluate long-term functional status due to inconsistent real-world documentation across the participating centers.

The strengths of this study include the multicenter design, which uses a heterogeneous sample of community and academic medical centers, and the large sample size. We included patients treated at medical centers from multiple geographic regions of the United States and numerous patient populations of interest excluded from previous studies of anticoagulation reversal. Notably, all participating medical centers are designated as stroke centers by the American Heart Association/American Stroke Association, The Joint Commission, or Det Norske Veritas, which aids in reducing variations in care between sites. All these factors help increase the generalizability of our results to a broad population of patients in the United States with FXa inhibitor-related intracranial bleeding. We also used strategies to reduce bias associated with the study results. Although we could not have a single provider review each image in a centralized database, we attempted to minimize bias by assessing each image by site-specific providers with specialty experience in neurocritical care, neurology, or neurosurgery. The steering group then adjudicated the outcome of hemostatic efficacy based on the recorded measurements and the predefined criteria. Furthermore, the primary investigator at each site was provided with a training

video regarding the protocol to ensure uniform understanding and assessment of data points across each site. Finally, we used a study protocol that was only modified to account for changes in participating sites and the date range of patients that could be included.

CONCLUSIONS

Despite statistically higher odds of achieving hemostatic efficacy with andexanet, we also observed higher odds of a TE with no difference in discharge outcomes observed between groups. When those with more severe neurologic injuries were excluded, efficacy and safety outcomes were similar between treatments. Further studies are needed to confirm the utility of hemostatic efficacy using a protocolized approach in the hyperacute phase of ICrH.

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