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ORIGINAL RESEARCH ARTICLE

Reversal of apixaban and rivaroxaban with andexanet alfa prior to invasive or surgical procedures

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Abstract

Background: Outcomes following andexanet alfa reversal of factor Xa inhibitors in patients requiring urgent or emergent invasive procedures are lacking. This study aimed to describe efficacy and safety outcomes following andexanet alfa administration within 24 h of an invasive procedure.

Methods: This single-center, observational, retrospective study included patients who received andexanet alfa within 24 h of an invasive or surgical procedure. The primary outcome was hemostatic efficacy graded as excellent, good, or poor using similar definitions to the ANNEXA-4 criteria. Secondary outcomes included hospital discharge disposition, intensive care unit (ICU) and hospital length of stay, 30-day mortality, 30-day thromboischemic event rates, and serum coagulation assay changes pre- and postreversal.

Results: Forty-four patients met inclusion criteria; of these, 27 (62.8%) received apixaban and 16 (37.2%) were treated with rivaroxaban prior to admission. The indications for reversal were categorized as intracranial (n = 20 [45.5%]) or extracranial (n = 24 [54.5%]) sites. Majority of patients required emergent operative procedures (18 [40.9%]), followed by invasive device placement (10 [22.7%]) or arterial embolization (9 [20.5%]). Thirty-eight (86.4%) patients were able to be adequately graded for hemostatic efficacy. Overall, 30 (78.9%) patients achieved excellent or good hemostasis within 24 h after periprocedural administration of andexanet alfa (19 [82.6%] apixaban vs. 11 [78.6%] rivaroxaban; 12 [80.0%] intracranial events vs. 18 [78.3%] extracranial events). Discharge disposition was most often to a short- or long-term care facilities (27 [61.4%]). Thirty-day mortality and thromboischemic complications occurred in 15 (34.1%) and 12 (27.3%) patients, respectively. Prothrombin time and

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antifactor Xa assay results were significantly decreased after andexanet alfa administration ($p < 0.05$) while thromboelastogram assay values (reaction time, kinetic time, and activated clotting time) showed nonsignificant changes pre- versus postreversal. **Conclusion:** Andexanet alfa may be used for urgent or emergent reversal of apixaban and rivaroxaban peri-procedurally with promising hemostatic outcomes. Further prospective, comparative clinical research is warranted.

KEYWORDS
anticoagulation reversal, anticoagulation reversal agents, factor Xa, factor Xa inhibitors, general surgery, recombinant proteins

1 | BACKGROUND

Oral factor Xa inhibitors (FXa-I), such as apixaban and rivaroxaban, continue to increase in use for prophylaxis and treatment for venous thromboembolism as well as stroke prevention in patients with atrial fibrillation since their initial approval by the United States Food and Drug Administration (FDA) in 2011.[1] The positive efficacy outcomes without need for routine coagulation monitoring or dietary restrictions resulted in a recommendation of FXa-I as a first-line medication over vitamin K antagonists for stroke prevention due to atrial fibrillation and treatment of acute venous thromboembolism.[1–4] Although life-threatening bleeding with FXa-I is rare, the need for an effective and rapid-acting antidote remains essential.

Andexanet alfa is a genetically modified factor Xa (FXa) protein that competitively binds to FXa-I. Pharmacodynamically, it acts as a decoy to prevent FXa-I from binding to and inhibiting endogenous FXa. Andexanet alfa also binds to tissue factor pathway inhibitor (TFPI), an endogenous inhibitor of FXa, allowing tissue factor initiation of thrombin generation.[5] The FDA approved andexanet alfa in 2018 for the treatment of life-threatening or uncontrolled bleeding in patients receiving rivaroxaban or apixaban based on the results of the ANNEXA-4 trial.[6] For this indication, andexanet alfa is administered as a bolus up to 30 minutes, followed by a 2-h infusion as either a low-dose or a high-dose regimen depending on the specific FXa-I dose and elapsed time since the last known administration.

The ANNEXA-4 trial, which trended anti-Xa activity and assessed hemostasis after andexanet alfa administration in patients experiencing acute major bleeding within 18 h of a FXa-I, demonstrated a decrease in anti-FXa activity up to 4 h postinfusion with good or excellent hemostasis in 82% of patients.[6] Subsequent smaller, nonrandomized studies specifically addressing intracranial or gastrointestinal hemorrhages demonstrated that 48% to 90% of patients receiving FXa-I therapy achieved excellent or good hemostasis following andexanet alfa administration.[7–13] However, patients requiring invasive or surgical procedures have not been represented in these data. Furthermore, patients suspected to undergo surgical procedures within 12 h of admission were excluded from ANNEXA-4. Only case reports and small case series have described andexanet alfa utilization perioperatively.[14–17] Additional insight is needed to guide the management of FXa-I-mediated bleeding prior to invasive procedures in these vulnerable populations. The purpose of this study was to describe the clinical outcomes of patients who received andexanet alfa for apixaban or rivaroxaban reversal up to 24 h before an invasive or surgical procedure.

2 | METHODS

2.1 | Study design and population

This single-center, observational, retrospective study was conducted at a regional, urban, academic, American College of Surgeons-verified level 1 trauma center. The study was approved by the Institutional Review Board (IRB ID 2020-0971; consent waived). Patients admitted between May 2018 and April 2021 were eligible for inclusion if they received andexanet alfa for reversal of apixaban or rivaroxaban up to 24 h before an invasive or surgical procedure. No exclusion criteria were developed in an effort to maximize inclusion and enhance the pragmatic review of a broader population. Patients were identified through an internal database, which consisted of institutional documentation of compliance with formulary-approved restrictions for andexanet alfa administration.

Andexanet alfa was added to the institutional formulary in 2018 following FDA approval. Use was restricted to patients with known ingestion of apixaban or rivaroxaban within 24 h of a major or life-threatening bleed. For clinical scenarios regarding reversal outside of existing hospital restrictions or FDA approval, such as nonbleeding patients requiring invasive or surgical intervention, the same andexanet alfa dosing scheme was used as for major or life-threatening bleeds depending on specific FXa-I, dose, and timing of last administration.[18] Off-label use was deferred to physician discretion and reviewed by pharmacy retrospectively upon case review. The use of perioperative andexanet alfa in nonbleeding patients is based heavily on the concern for progression to life-threatening bleeding if patients are not reversed before invasive intervention due to the presence of active therapeutic drug. For patients obtunded or unable to provide an accurate past medical history, baseline serum antifactor Xa (anti-Xa) or prothrombin time (PT) were available to help determine whether relevant serum FXa-I was present potentially requiring reversal. An elevated low-molecular-weight heparin (LMWH) calibrated anti-Xa >0.5 units/ml and/or PT >16 s was used as a qualitative surrogate for active FXa-I exposure to promote

efficient decision-making in emergent situations. If clinicians were unable to verify active FXa-I therapy or timing of last apixaban or rivaroxaban dose, then an objective laboratory parameter was needed prior to administration of andexanet alfa per institutional policies. The institutional anti-Xa used was a chromogenic assay (Diagnostica Stago S.A.S, Asniere sur Seine, France) with a hybrid validation curve for unfractionated heparin (UFH) and LMWH. The institution did not have FXa-I-specific assays available and the qualitative threshold of 0.5 units/ml was provided as institutional guidance based on prior literature.[19–21] The assay upper limit of detection was 1.8 units/ml while the lower limit was <0.1 units/ml. Thromboelastography (TEG) was also available to be used clinically to guide resuscitation in the setting of FXa-I reversal. Follow-up coagulation laboratories were ordered at the discretion of the provider.

2.2 | Data collection

Demographic and outcome data were extracted from the electronic medical record (Epic®, Verona, WI) and internal institutional database previously mentioned. Basic demographic information (age, sex, weight, and body mass index [BMI]) was collected in addition to indication for anticoagulation, baseline Glasgow Coma Scale (GCS), trauma versus nontrauma admission, andexanet alfa dose, use of 4-factor prothrombin complex concentrate (PCC) or other blood products (either packed red blood cells [PRBC], whole blood, fresh frozen plasma [FFP], or platelets), and reversal indication. Andexanet alfa doses were categorized as low or high. Low-dose was defined as a 400 mg IV bolus over 13 min followed by a 2-h infusion at 4 mg/min. High-dose was defined as 800 mg IV bolus over 26 min followed by a 2-h infusion at 8 mg/min. Details regarding interventional procedures were also collected, including time from andexanet alfa bolus administration to procedure start, procedure duration, intraprocedure blood product requirements, estimated blood loss, and anesthesia duration, if applicable.

2.3 | Study outcomes and definitions

The primary outcome was hemostatic efficacy graded as excellent, good, or poor using similar definitions to the ANNEXA-4 criteria and evaluated within 24 h after andexanet alfa administration.[6] For patients presenting with intracranial bleeding, hemostasis grading was determined by comparing hematoma volume at baseline to volume on repeat computed tomography (CT) or magnetic resonance imaging (MRI) scan performed up to 24 h after andexanet alfa. "Excellent" hemostasis was defined as a ≤20% increase in hematoma volume; "good" hemostasis was defined as a >20% but ≤35% increase in hematoma volume; and "poor" hemostasis was defined as a >35% increase in hematoma volume. If multiple scans were obtained within 24 h after andexanet alfa administration, then the largest comparative expansion was used for grading. Patients without baseline or repeat neuroimaging were graded as "unable to assess." A single neurointensivist independently and retrospectively reviewed the available neuroimaging for intracranial outcome grading. Hemostasis grading for extracranial bleeding was determined based on change in hemoglobin at baseline compared with lowest hemoglobin recorded and/or receipt of blood product transfusion(s), which included PRBCs, FFP, or whole blood, within 24 h following andexanet alfa administration. "Excellent" hemostasis was defined as a ≤10% decrease in hemoglobin and no more than 2 units of PRBC, FFP, or whole blood transfused; "good" hemostasis was defined as a >10%–≤20% decrease in hemoglobin and no more than 2 units of PRBC, FFP, or whole blood transfused; and "poor" hemostasis was defined as a >20% decrease in hemoglobin or more than 2 units of PRBC, FFP, or whole blood transfused. Patients presenting without active bleeding that required an invasive or surgical intervention necessitating reversal with andexanet alfa had hemostasis graded using the same definitions and hemoglobin thresholds as extracranial bleeds. However, baseline hemoglobin was collected as the closest reported value to procedure start time, and the subsequent 24-h period was reviewed for lowest reported hemoglobin and overall transfusion requirements. In addition, no more than 2 units of PRBC, FFP, or whole blood could be transfused intra-procedurally for "excellent" or "good" hemostasis in nonbleeding patients. Outcomes were assessed for all patients and an exploratory analysis assessed for outcome differences between patients prescribed apixaban versus rivaroxaban. An additional exploratory subgroup separated patients into cohorts of intracranial versus extracranial event types.

Secondary outcomes included the proportion of patients who received any blood product transfusion pre- versus postandexanet alfa, intraprocedural blood transfusion requirements, hospital discharge disposition, 30-day mortality, 30-day thromboischemic event rates, time to ischemic event, resumption of in-hospital therapeutic or prophylactic anticoagulation, intensive care unit and hospital length of stay, change in GCS from admission to discharge for patients surviving an intracranial event, and serum coagulation assay changes immediately pre- and postandexanet alfa administration. Blood product transfusion requirements were compared in the 24-h period pre- and postandexanet alfa administration. Discharge disposition was classified as home, inpatient rehabilitation, skilled nursing facility or long-term acute care hospital, hospice, or deceased. Thromboischemic events included acute ischemic stroke, myocardial infarction, pulmonary embolism, and venous thromboembolism. Diagnosis of acute ischemic stroke required confirmatory imaging with a head CT or MRI. An acute myocardial infarction required the presence of troponin elevation with subsequent cardiac catheterization. Classification of venous thromboembolism required diagnosis of an acute proximal deep vein thrombosis identified on venous duplex and pulmonary embolism required diagnosis on a CT of the pulmonary arteries. Coagulation assays were collected immediately before and in the 24 h after andexanet alfa administration, closest to infusion completion. Coagulation assays included PT, anti-Xa, and TEG parameters, if available. Given the institution anti-Xa upper detection limit was 1.8 units/ml, reported values of >1.8 units/ml were included numerically as 1.8 units/ml for quantitative analyses.

Evaluated TEG values included reaction time (R-time), kinetic time (K-time), and TEG activated clotting time (ACT). Exploratory comparisons between pre- and postandexanet alfa were performed for coagulation parameters for all patients and subgroups of apixaban and rivaroxaban.

2.4 | Statistical analyses

Descriptive data were used to summarize demographics and clinical outcomes for the entire cohort with comparisons performed between apixaban versus rivaroxaban subgroups. Categorical data were analyzed using Chi-square or Fisher's exact tests and reported as number (percent), as appropriate. Continuous data were analyzed using Student's *t*-test or Wilcoxon Rank Sum and reported as mean (standard deviation [SD]) or median (interquartile range [IQR]), respectively, as appropriate. Continuous coagulation data were analyzed via paired *t*-test or Signed Rank test and reported as mean (SD) or median (IQR), respectively, as appropriate. Statistical analyses were performed using SigmaPlot v.14.0 software (Systat, San Jose, CA). A *p*-value ≤0.05 was used to define statistically significant differences between groups. Due to the lack of existing clinical outcome data in this perioperative subpopulation, an exploratory convenience sample over the 3-year study period was used to optimize patient inclusion and capture a wide variety of complex patient scenarios encountered in real-world utilization of andexanet alfa. The reported outcomes of these unique patients will hopefully strengthen both internal and external validity regarding the use of andexanet alfa for reversal of apixaban and rivaroxaban.

3 | RESULTS

3.1 | Demographics

A total of 115 patients were administered andexanet alfa for reversal of apixaban ($n = 75$) or rivaroxaban ($n = 39$). A total of 44 patients underwent an invasive or surgical procedure up to 24 h after andexanet alfa administration and were included in the primary and secondary outcome analyses. One patient received andexanet alfa that was not actively prescribed oral FXa-I therapy at baseline; therefore, the apixaban and rivaroxaban comparisons are calculated out of a total of 43 patients. Twenty-seven (62.8%) patients were prescribed apixaban and 16 (37.2%) were prescribed rivaroxaban prior to admission. No statistical differences in baseline characteristics were observed between apixaban- and rivaroxaban-treated patients (Table 1).

Thirty-eight (86.4%) patients received andexanet alfa for major or life-threatening bleeding that then required invasive or surgical intervention; however, there were six (13.6%) patients who received andexanet alfa off-label for urgent or emergent surgical intervention without the presence active bleeding. Primary bleed sites for the majority of patients included spontaneous intracranial hemorrhage (10 [22.7%]), hemoperitoneum (9 [20.5%]), or gastrointestinal bleeding (6 [13.6%]). All patients received andexanet alfa prior to invasive or surgical interventions irrespective of the presence or absence of active bleeding. Reversal indications and invasive procedure information are provided in Tables 1 and 2, respectively.

The majority of patients ($n = 38$ [86.4%]) received low-dose andexanet alfa. The median time from andexanet alfa order to bolus administration was 30.0 [IQR 19.8–43.0] min. Andexanet alfa administration occurred a median of 2.6 [IQR 1.2–5.5] h after hospital presentation and 2.8 (0.7–6.6) h prior to documented procedure start time.

No patient received a second dose of andexanet alfa after completion of the first dose. Three (10%) patients received PCC prior to andexanet alfa. Two of those administrations occurred prior to outside hospital transfer. The decision to administer andexanet alfa despite prior PCC use was determined by ongoing evidence of coagulopathy requiring either external ventricular drain placement or craniotomy for intracranial bleeding per chart review documentation. A PCC dose of 25 units/kg was used in two patients and 50 units/kg in one patient, ranging from 2168 to 3267 units.

3.2 | Outcomes

A total of 30 (68.2%) patients achieved excellent or good hemostasis within 24 h after periprocedural administration of andexanet alfa. Excellent or good hemostasis was achieved in 12 (60%) of 20 patients with an intracranial event and 18 (75%) of 24 patients with an extracranial event ($p = 0.46$). Six (13.6%) patients were unable to be assessed for hemostatic efficacy. Specifically, five patients in the intracranial group lacked baseline imaging, and one patient in the extracranial group did not have baseline or postadministration hemoglobin due to patient death. Analyzing only those patients who were able to be adequately assessed, a total of 30 (78.9%) of 38 patients achieved excellent or good hemostasis; 12 (80.0%) of 15 patients with an intracranial event compared to 18 (78.3%) of 23 patients with an extracranial event ($p > 0.99$). No statistical differences in graded hemostatic efficiency were observed between patients prescribed apixaban versus rivaroxaban including combined excellent and good hemostatic efficacy (total: 19/27 [70.4%] vs. 11/16 [68.8%], $p > 0.99$; able to be assessed: 19/23 [82.6%] vs. 11/14 [78.6%], $p > 0.99$), respectively. Additional hemostatic outcomes are presented in Table 3.

No difference in the proportion of patients who required a blood product transfusion 24 h before versus 24 h after andexanet alfa administration (14 [31.8%] vs. 12 [27.2%], $p = 0.82$) was observed. Additionally, there were no differences in blood product administration before versus after reversal in intracranial patients (3 [15%] before reversal vs. 9 [45%] after reversal, $p = 0.08$), but there was a significant decrease in patients requiring blood product administration after reversal in the extracranial subgroup (11 [45.8%] before reversal vs. 3 [12.5%] after reversal, $p = 0.03$). The majority of patients (27 [61.4%]) were discharged to a skilled nursing facility,

TABLE 1 Baseline demographics

	All patients ($n = 44$)	Apixaban ($n = 27$)	Rivaroxaban ($n = 16$)	p-Value[a]
Age, year[b]	69.7 (12.0)	69.5 (12.7)	68 (13.6)	0.71
Sex (male)	28 (63.6)	16 (59.3)	11 (67.8)	0.77
Weight, kg[b]	88.8 (22.7)	86.2 (20.2)	98.4 (25.8)	0.09
BMI, kg/m^2[b]	29.4 (7.1)	28.9 (6.9)	31.7 (7.2)	0.21
Trauma patient	17 (38.6)	9 (33.3)	7 (43.8)	0.72
Admission GCS[c]	10.0 (6.0–14.0)	9.0 (6.0–13.5)	13.0 (7.0–15.0)	0.32
Primary indication for anticoagulation				
Atrial fibrillation	19 (43.1)	12 (44.4)	7 (43.8)	0.78
DVT/PE	19 (43.1)	11 (40.7)	7 (43.8)	0.89
Other[d]	5 (11.4)	4 (14.8)	2 (12.5)	>0.99
Reversal details				
Low-dose regimen	38 (86.4)	25 (92.6)	12 (75.0)	0.17
High-dose regimen	6 (13.6)	2 (7.4)	4 (25.0)	0.17
Patients receiving blood products prior to andexanet alfa administration	14 (31.8)	8 (29.6)	5 (31.3)	>0.99
pRBC	11 (25.0)	7 (25.9)	2 (12.5)	0.45
Whole blood	1 (2.3)	0 (0.0)	1 (6.3)	0.38
FFP	9 (20.5)	6 (22.2)	3 (18.8)	>0.99
Platelets	4 (9.1)	2 (7.4)	2 (12.5)	0.62
4F-PCC prior to andexanet alfa	3 (10.0)	1 (3.7)	2 (12.5)	0.55
Reversal				
Weight-based dose, units/kg	25 (25.0–50.0)	50 (–)	25 (25–25)	-
Dose, units[b]	2566.3 (608.7)	3267 (–)	2216 (67.8)	-
Reversal indications				
Active bleeding	38 (86.4)	24 (88.9)	13 (81.3)	0.66
Nonbleeding	6 (13.6)	3 (11.1)	3 (18.8)	0.66
Intracranial site	20 (45.5)	11 (40.7)	9 (56.3)	0.50
Spontaneous ICH	10 (22.7)	6 (22.2)	4 (25.0)	>0.99
TBI	6 (13.6)	3 (11.1)	3 (18.8)	0.66
Spontaneous SAH	3 (6.8)	2 (7.4)	1 (6.3)	>0.99
Other[e]	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Extracranial site	24 (54.5)	16 (59.3)	7 (43.8)	0.50
Gastrointestinal bleed	6 (13.6)	5 (18.5)	1 (6.3)	0.39
Hemothorax	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Hemoperitoneum	9 (20.5)	7 (25.9)	1 (6.3)	0.22
Lower extremity compartment syndrome	1 (2.3)	1 (3.7)	0 (0.0)	>0.99
Small bowel obstruction/mesenteric ischemia	2 (4.5)	2 (7.4)	0 (0.0)	0.52
Cardiac pacemaker	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Incarcerated ventral hernia	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Thoracic aortic aneurysm	1 (2.3)	1 (3.7)	0 (0.0)	>0.99
Spinal cord compression	2 (4.5)	0 (0.0)	2 (12.5)	0.13

Note: Categorical data presented as number (percent), unless otherwise specified. Continuous data presented as median (interquartile range), unless otherwise specified.

Abbreviations: 4F-PCC, 4-factor prothrombin complex concentrate; DVT/PE, deep vein thrombosis/pulmonary embolism; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; ICH, intracranial hemorrhage; pRBC, packed red blood cells; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury.

[a]One patient was removed from the apixaban versus rivaroxaban analysis as the patient was not prescribed active oral factor Xa inhibitor therapy prior to admission ($n = 43$).

[b]Data presented as mean (standard deviation).

[c]A total of 19 patients had a baseline GCS assessment all of which had an intracranial event (apixaban, $n = 10$; rivaroxaban, $n = 9$).

[d]$n = 2$ antiphospholipid syndrome with history of deep vein thrombosis; $n = 1$ Factor V Leiden with history of deep vein thrombosis; $n = 2$ central venous sinus thrombosis.

[e]One patient had an acute left middle cerebral artery infarct and right middle cerebral artery and posterior cerebral artery watershed infarction along the right parieto-occipital lobe requiring emergent hemicraniectomy.

TABLE 2 Interventional procedure details

	All patients ($n = 44$)	Apixaban ($n = 27$)	Rivaroxaban ($n = 16$)	p-Value[a]
Invasive device	10 (22.7)	5 (18.5)	5 (31.3)	0.46
External ventricular drain	9 (20.5)	5 (18.5)	4 (25.0)	0.71
Cardiac pacemaker	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Operating room	18 (40.9)	10 (37.0)	7 (43.8)	0.91
Exploratory laparotomy	6 (13.6)	5 (18.5)	0 (0.0)	0.14
Craniotomy	6 (13.6)	4 (14.8)	2 (12.5)	>0.99
Incarcerated hernia repair	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Incision and drainage	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Spinal fusion	2 (4.5)	0 (0.0)	2 (12.5)	0.13
Thoracotomy	1 (2.3)	0 (0.0)	1 (6.3)	0.37
Thoracic endovascular aortic repair	1 (2.3)	1 (3.7)	0 (0.0)	>0.99
Interventional radiology arterial embolization	9 (20.5)	8 (29.6)	1 (6.3)	0.12
Neurointerventional radiology	3 (6.8)	1 (3.7)	2 (12.5)	0.55
Esophagogastroduodenoscopy	4 (9.1)	3 (11.1)	1 (6.3)	>0.99
Time between andexanet alfa bolus and procedure start (hours)	−2.8 (−6.6 to −0.7)	−1.4 (−3.5 to −0.4)	−3.3 (−13.4 to −1.2)	0.23
Procedure duration, hours[b]	2.06 (1.3)	1.7 (1.2)	2.7 (1.4)	0.05
Anesthesia duration, hours[b,c]	3.1 (1.6)	2.4 (1.9–3.4)	3.6 (2.0–4.7)	0.15
Patients requiring blood product during intervention	15 (34.1)	9 (33.3)	6 (40.0)	0.92
Intraprocedure pRBC, units	3.5 (2.0–4.8)	4 (2.5–5.0)	2.0 (1.0–4.0)	0.26
Intraprocedure FFP, units	3.0 (2–3)	3.0 (2.8–3.3)	2.0 (2.0–2.0)	0.14
Intraprocedure platelets, units	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	>0.99
Intraprocedure estimated blood Loss, mL	100 (0–300)	15 (0.0–200)	250.0 (37.5–650)	0.07

Note: Categorical data presented as number (percent), unless otherwise specified. Continuous data presented as median (interquartile range), unless otherwise specified.

Abbreviations: FFP, fresh frozen plasma; IQR, interquartile range; pRBC, packed red blood cells; SD, standard deviation.

[a]One patient was removed from the apixaban versus rivaroxaban analysis as the patient was not prescribed active oral factor Xa inhibitor therapy prior to admission ($n = 43$).

[b]Data presented as mean (SD).

[c]$n = 26$ patients required anesthesia.

long-term acute care center, or inpatient rehabilitation facility. In-hospital mortality occurred in 10 (22.7%) patients and increased to 15 (34.1%) patients by 30 days postreversal. Median discharge GCS for surviving intracranial event patients increased up to 15 (10–15) compared to a GCS of 10 (6–14) at time of admission ($p = 0.15$). Twelve (27.3%) patients experienced a thromboischemic event. Of these, two (16.7%) received PCC prior to andexanet alfa and one (8.3%) received 5 units of FFP prior to reversal. The median time to a thromboischemic event was 3.9 [IQR 2.0–10.5] days after andexanet alfa administration. A total of 40 (90.9%) patients had anticoagulation restarted during hospital admission, most of which was prophylactic doses (79.5%) with median time to initiation of 43.3 [IQR 30.1–64.4] h from andexanet alfa administration. Three (25%) of the 12 patients who experienced a thromboischemic event did not receive any prophylactic or therapeutic anticoagulation prior to the observed occurrence. No differences were observed between secondary outcomes or adverse effects for patients on apixaban versus rivaroxaban prior to admission (Table 4).

3.3 | Laboratory parameters

A total of 41 (93.1%) patients had at least one serum coagulation parameters assessed pre- and postandexanet alfa, including either PT, anti-Xa, or TEG. Combining draw times for all measured parameters, baseline coagulation assays were drawn 1.1 [IQR 0.61–1.9] h prior to andexanet alfa bolus administration and follow-up labs were obtained 2.1 [IQR 0.9–7.7] h after infusion completion. These times are also reported per specific coagulation assay below.

Prothrombin time and anti-Xa results were significantly different before versus after andexanet alfa administration (Figure 1). For all patients, the median PT was reduced from 17.7 [IQR 16.2–21.9] to 16.8 [IQR 15.3–18.6] s ($p < 0.001$) and anti-Xa decreased from 1.8 [IQR 1.4–1.8] to 1.4 [IQR 0.9–1.8] units/ml ($p = 0.008$) after andexanet alfa. Nineteen (52.8%) of the 36 patients who had a baseline anti-Xa drawn resulted at >1.8 units/ml versus only 6 (24.0%) of 25 patients who had anti-Xa results available up to 24 h after reversal ($p = 0.05$). Median PT was significantly reduced for both apixaban

TABLE 3 Hemostatic outcome data

	All patients ($n = 44$)	Apixaban ($n = 27$)	Rivaroxaban ($n = 16$)	p-Value[a]
All				
Excellent	22 (50.0)	14 (51.9)	8 (50.0)	0.84
Good	8 (18.2)	5 (18.5)	3 (18.8)	>0.99
Poor	8 (18.2)	5 (18.5)	3 (18.6)	>0.99
Unable to assess	6 (13.6)	4 (14.8)	2 (12.5)	>0.99
Intracranial event	20 (45.5)	11 (40.7)	9 (56.3)	0.50
Excellent	8 (18.2)	6 (22.2)	3 (18.8)	>0.99
Good	4 (9.1)	1 (3.7)	2 (12.5)	0.55
Poor	3 (6.8)	1 (3.7)	2 (12.5)	0.55
Unable to assess	5 (11.4)	3 (11.1)	2 (12.5)	>0.99
Extracranial event	24 (54.5)	16 (59.3)	7 (43.8)	0.50
Excellent	14 (31.8)	7 (25.9)	5 (31.3)	0.74
Good	4 (9.1)	4 (14.8)	1 (6.3)	0.64
Poor	5 (11.4)	4 (14.8)	1 (6.3)	0.64
Unable to assess	1 (2.3)	1 (3.7)	0 (0.0)	>0.99

Note: All data presented as number (percent).

[a]One patient was removed from the apixaban versus rivaroxaban analysis as the patient was not prescribed active oral factor Xa inhibitor therapy prior to admission ($n = 43$).

(before, 17.4 [IQR 16.1–20.8] vs. after, 16.2 [IQR 15.3–17.9] s; $p = 0.01$) and rivaroxaban (before, 21.3 [IQR 16.9–30.8] vs. after, 18.5 [IQR 15.6–26.1] s; $p = 0.02$) (Figure 1). The anti-Xa concentration was not significantly reduced in the apixaban and rivaroxaban groups (Figure 1).

Thromboelastogram assays were drawn 0.9 [IQR 0.6–1.5] h and 2.1 [IQR 0.9–4.7] h pre- and post-andexanet alfa administration, respectively. No statistical differences were observed between TEG parameters for the entire cohort or the apixaban and rivaroxaban subgroups (Figure 2). All reported TEG parameters were within normal and detectable ranges for rapid TEG testing.

4 | DISCUSSION

This study demonstrates that andexanet alfa may be used effectively for periprocedural reversal of apixaban and rivaroxaban in patients requiring invasive or surgical intervention. The majority of patients achieved excellent or good hemostasis within 24 h of intervention or surgery. However, achievement of hemostasis is weighed against the 27% of patients who experienced an ischemic or thrombotic event within 30 days of reversal. These findings represent the largest cohort of patients that received andexanet alfa prior to procedural intervention, including patients who would have been excluded from ANNEXA-4.[6]

Several andexanet alfa real-world case reports and case series have included small numbers of procedural patients who were assessed for hemostasis up to 12 or 24 h after intervention.[7,10–12,14–17,22–23] However, robust and generalizable data are lacking. We found a comparable overall incidence of effective (good or excellent) hemostasis of 78.9% in patients who were able to be assessed compared to the 82% found in ANNEXA-4.[6] The ANNEXA-4 study did not demonstrate any differences in hemostasis between intracranial (80%) and gastrointestinal (85%) bleeding, but it is unknown if the introduction of procedural intervention may lead to differences in outcomes between primary bleeding sites. The findings of this study suggest there are no observable differences in clinical outcomes when comparing intracranial versus extracranial events in a procedural patient population. Furthermore, a case series of 21 patients who received andexanet alfa for extracranial bleeding that included 13 procedural interventions found a lower effective hemostasis rate at 47.6% using the same definitions for hemostatic efficacy as ANNEXA-4 compared with the 75% in our extracranial cohort.[10] We also investigated an exploratory analysis into differences in achieved clinical outcomes of apixaban versus rivaroxaban cohorts, which has previously not been reported. No differences in efficacy, morbidity, or safety were observed between groups although the study was not powered to detect such findings. The timing of reversal in conjunction with surgical and other hemostatic interventions, including administration of blood products, likely influenced hemostatic effectiveness observed in this study.

Our finding of a 27% incidence of ischemic or thrombotic events despite early anticoagulation is comparable to rates reported by other andexanet alfa case series ranging from 0% to 33%.[6–7,11–13,23–24,26,27] It is substantially higher than the 10% incidence reported in ANNEXA-4, however, and contradicts the findings that only 2% of patients experienced thrombotic events after resumption of anticoagulation.[6] Our findings represent a different population than those analyzed in ANNEXA-4 in regard

TABLE 4 Secondary outcomes

	All patients ($n = 44$)	Apixaban ($n = 27$)	Rivaroxaban ($n = 16$)	p-Value[a]
ICU LOS, days	7.0 (5.0–15.5)	6.0 (5.0–10.8)	9.0 (5.0–19.0)	0.15
Hospital LOS, days	11.5 (6.0–19.0)	10.0 (6.0–17.0)	14.5 (7.5–22.5)	0.29
Hospital discharge disposition				
Deceased	9 (20.5)	6 (22.2)	2 (12.5)	0.69
Home	6 (13.7)	2 (7.4)	4 (25.0)	0.17
Hospice	2 (4.5)	1 (3.7)	1 (6.25)	>0.99
Inpatient rehabilitation	9 (20.5)	7 (25.9)	2 (12.5)	0.45
SNF/LTAC	18 (40.9)	11 (40.7)	7 (43.8)	0.89
Discharge GCS[b]	15.0 (10.0–15.0)	14.0 (10.5–15.0)	15.0 (10.0–15.0)	>0.99
30-day mortality	15 (34.1)	11 (40.7)	3 (18.8)	0.25
30-day thromboischemic events	12 (27.3)	8 (29.6)	3 (18.8)	0.49
VTE	5 (11.4)	4 (14.8)	1 (6.3)	0.64
PE	1 (2.3)	0 (0.0)	1 (6.3)	0.37
VTE and PE	2 (4.5)	1 (3.7)	1 (6.3)	0.99
STEMI	2 (4.5)	1 (3.7)	0 (0.0)	0.99
AIS	2 (4.5)	2 (7.4)	0 (0.0)	0.52
In-hospital anticoagulation Reinitiation	40 (90.9)	24 (88.9)	15 (93.8)	>0.99
Prophylactic	35 (79.5)	22 (81.5)	13 (81.3)	>0.99
Therapeutic	5 (11.4)	2 (7.4)	2 (12.5)	0.62

Note: Categorical data presented as number (percent), unless otherwise specified. Continuous data presented as median (interquartile range), unless otherwise specified.

Abbreviations: AIS, acute ischemic stroke; GCS, Glasgow Coma Scale; IQR, interquartile range; LOS, length of stay; LTAC, long-term acute care; PE, pulmonary embolism; SNF, skilled nursing facility; STEMI, ST-elevation myocardial infarction; VTE, venous thromboembolism.

[a]One patient was removed from the apixaban versus rivaroxaban analysis as the patient was not prescribed active oral factor Xa inhibitor therapy prior to admission ($n = 43$).

[b]A total of 15 patients were able to be assessed for discharge GCS following intracranial event (apixaban, $n = 8$; rivaroxaban, $n = 7$).

to the introduction of invasive or surgical manipulation that may alter rates of thromboischemic events. Additionally, the majority of patients in this study were initiated on prophylactic rather than restarting therapeutic anticoagulation. Several real-world case series offer conflicting results regarding the incidence of thrombotic events in patients who have received concomitant PCC or FFP prior to andexanet alfa, which applies to 12 (27.2%) of the patients included in this study.[12,26,28] Andexanet alfa has been suggested to induce hypercoagulability through inhibition of TFPI, the main regulator of the tissue factor pathway.[24,25] This along with the upregulation of tissue factor incurred in surgical endothelial manipulation and the observed thrombotic rate suggests needed balance when weighing andexanet alfa use and anticoagulation reinitiation.[29–30] Despite the high rate of thromboischemic events, obtained postreversal TEG parameters did not detect or suggest hypercoagulability in the current study. It may also be worth noting that two of the six patients presenting without active bleeding who received andexanet alfa as an off-label indication developed a thromboischemic complication.

Determination of appropriate patient selection for reversal relies heavily on confirmation of active FXa-I therapy. Verbal confirmation of FXa-I adherence is not always possible resulting in the use of laboratory parameters to confirm the presence of drug in the serum. Institutions may rely on standard assays such as PT or UFH/LMWH-calibrated anti-Xa if drug-specific assays are not available. Several studies have found a strong linear correlation between serum FXa-I concentrations and UFH/LMWH-calibrated anti-Xa.[19–21] Prothrombin time has shown a poor correlation with FXa-I concentrations but may be used as a sole qualitative assessment of serum drug presence if elevated.[31] This study is the first to describe real-world application of these assays by comparing baseline and follow-up coagulation assays in patients undergoing FXa-I reversal. We observed a significant decrease in PT and anti-Xa concentrations pre- versus postandexanet alfa administration suggesting an intended pharmacodynamic effect from reversal to normalize coagulation hemostasis. Observations of anti-Xa concentration rebound after cessation of andexanet alfa from the ANNEXA-4 trial are noted, but intrinsic FXa-I clearance also plays a vital part in determination of anti-Xa trends postreversal.[6] The findings of ANNEXA-4 concluded that there was no significant relationship between hemostatic efficacy and a reduction in antifactor Xa activity. Despite the cited

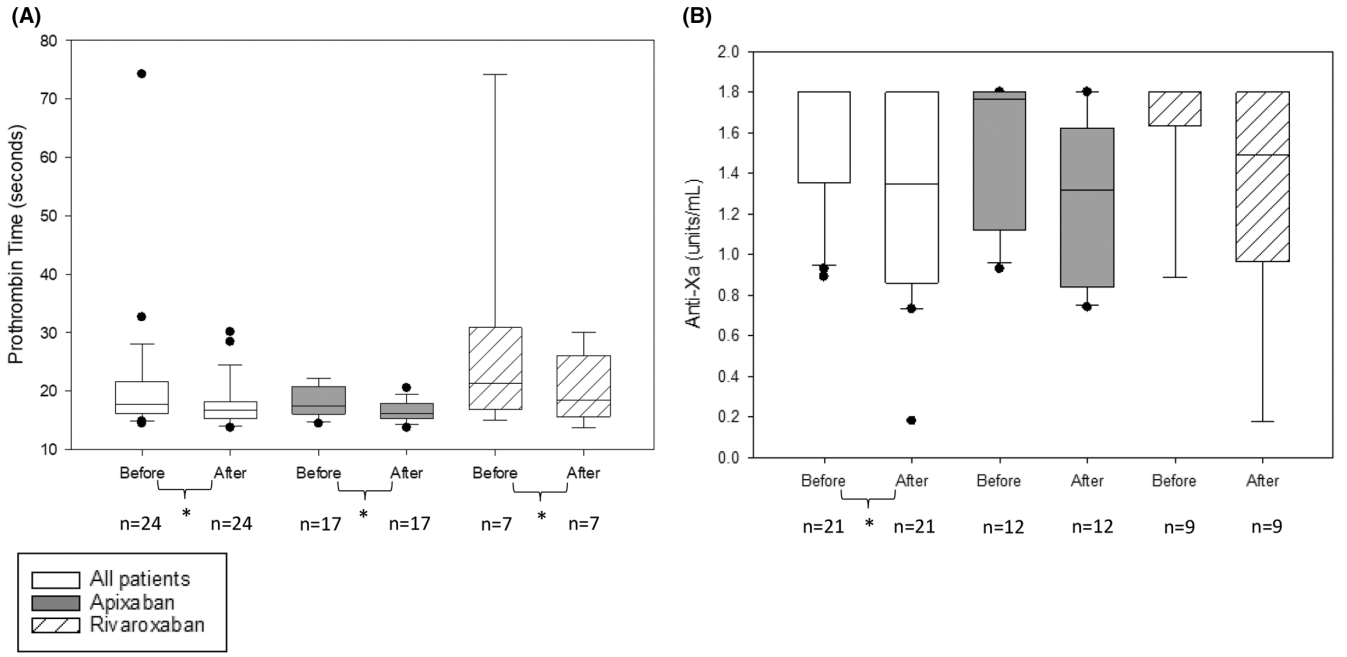

FIGURE 1 Prothrombin time (PT) and anti-Xa assay results compared pre- and post-andexanet alfa administration for all patients combined and then divided out into cohorts of apixaban patients and rivaroxaban patients. Plots represent median line with in each box. Upper and lower limits of each box represent 25th and 75thpercentile, respectively. Error bars represent the 10th and 90th percentile. Dots represent outliers. *Signifies statistical significance with $p < 0.05$. (A) PT for all patients, $n = 24$: PT of 17.7 (IQR 16.2–21.9) seconds drawn 1.5 (IQR 2.3–0.8) hours prior to bolus versus 16.8 (IQR 15.3–18.6) seconds drawn 1.9 (IQR 0.6–5.2) hours after infusion completion; $p < 0.001$); $n = 17$ for apixaban patients: PT of 17.4 (IQR 16.1–20.8) seconds drawn 0.9 (IQR, 0.3–1.8) hours prior to bolus versus 16.2 (IQR, 15.3–17.9) seconds drawn 1.9 (IQR, 0.5-6.9) hours after infusion completion; $p = 0.01$), $n = 7$ for rivaroxaban patients: PT of 21.3 (IQR, 16.9–30.8) seconds drawn 3.1 (SD, 2.3) hours prior to bolus versus 18.5 (IQR, 15.6–26.1) seconds drawn 1.9 (SD, 2.6) hours after infusion completion; $p = 0.02$). (B) Anti-Xa assay results for all patients, $n = 21$: anti-Xa 1.8 (IQR, 1.4–1.8) units/ml drawn 1.1 (IQR, 0.5–2.0) hours prior to bolus versus 1.4 (IQR, 0.9–1.8) units/ml drawn 5.9 (IQR, 1.8–12.1) hours after infusion completion; $p = 0.008$; $n = 12$ for apixaban patients, anti-Xa 1.8 (IQR, 1.1–1.8) units/ml drawn 0.6 (IQR, 0.1–1.7) hours prior to bolus versus 1.3 (IQR, 0.8–1.6) units/ml drawn 6.7 (IQR, 1.6–19.6) hours after infusion completion; $p = 0.08$; $n = 9$ for rivaroxaban patients: anti-Xa 1.8 (IQR, 1.6–1.8) units/ml drawn 1.9 (IQR, 0.9–2.7) hours prior to bolus versus 1.5 (IQR, 0.9–1.8) units/ml drawn 6.4 (IQR, 3.2–8.1) hours after infusion completion; $p = 0.06$.

correction in LMWH-calibrated anti-Xa and PT results in this current study, there was no analysis to assess correlation to hemostatic efficacy. Therefore, laboratory results alone should not be used to assess reversal efficacy. Thromboelastography has not been validated to assess therapeutic or quantitative effects of FXa-I; however, it may be used to guide resuscitation or detect other complex coagulopathies requiring targeted intervention outside of FXa reversal.[31–32] We found no observed statistical change in R-time, K-time, or ACT times pre- versus postandexanet alfa suggesting TEG may not provide an additional surrogate assessment of achieved reversal.

There are multiple strengths of this study. The broad inclusion criteria allowed for a diverse, real-world cohort and delivers essential data to guide clinical practice of FXa-I reversal in the periprocedural population. Uniquely, our study also included six patients who presented without active bleeding but required an invasive intervention. This population has been entirely excluded from prior literature reporting clinical outcomes associated with off-label andexanet alfa administration. The median time to administration of andexanet alfa was 30 min from the time of order placement and 2.6 h from hospital admission in this study, which is substantially faster than the 1.7 h from time of consent and 4.8 h from presentation seen in ANNEXA-4.[6] Other strengths included tracked clinical outcomes up to 30 days, inclusion of severe intracranial events requiring invasive intervention, and use of definitions that aligned with prior literature for hemostatic efficacy and safety. This study also provides important and unique insight into the coagulation effects of andexanet alfa by evaluating paired laboratory data pre- and post-andexanet alfa administration.

This study also has notable limitations. First, several patients received blood products or PCCs after initial laboratory analysis which could affect post-reversal coagulation assays and potentially increase the thrombotic risk. The institutional anti-Xa was calibrated for LMWH and had an undetectable threshold of >1.8 units/ml, which limited investigators in providing an objective and quantitative reversal effect of andexanet alfa on anti-Xa trends. Despite this upper limit threshold, our observation of a significant decrease in anti-Xa concentrations after reversal is likely strengthened due to the capping of undetectably high anti-Xa concentrations at 1.8 units/ml. Researchers were not blinded to coagulation lab results prior to retrospectively grading hemostatic efficacy. The use of consistent objective thresholds for hemostatic

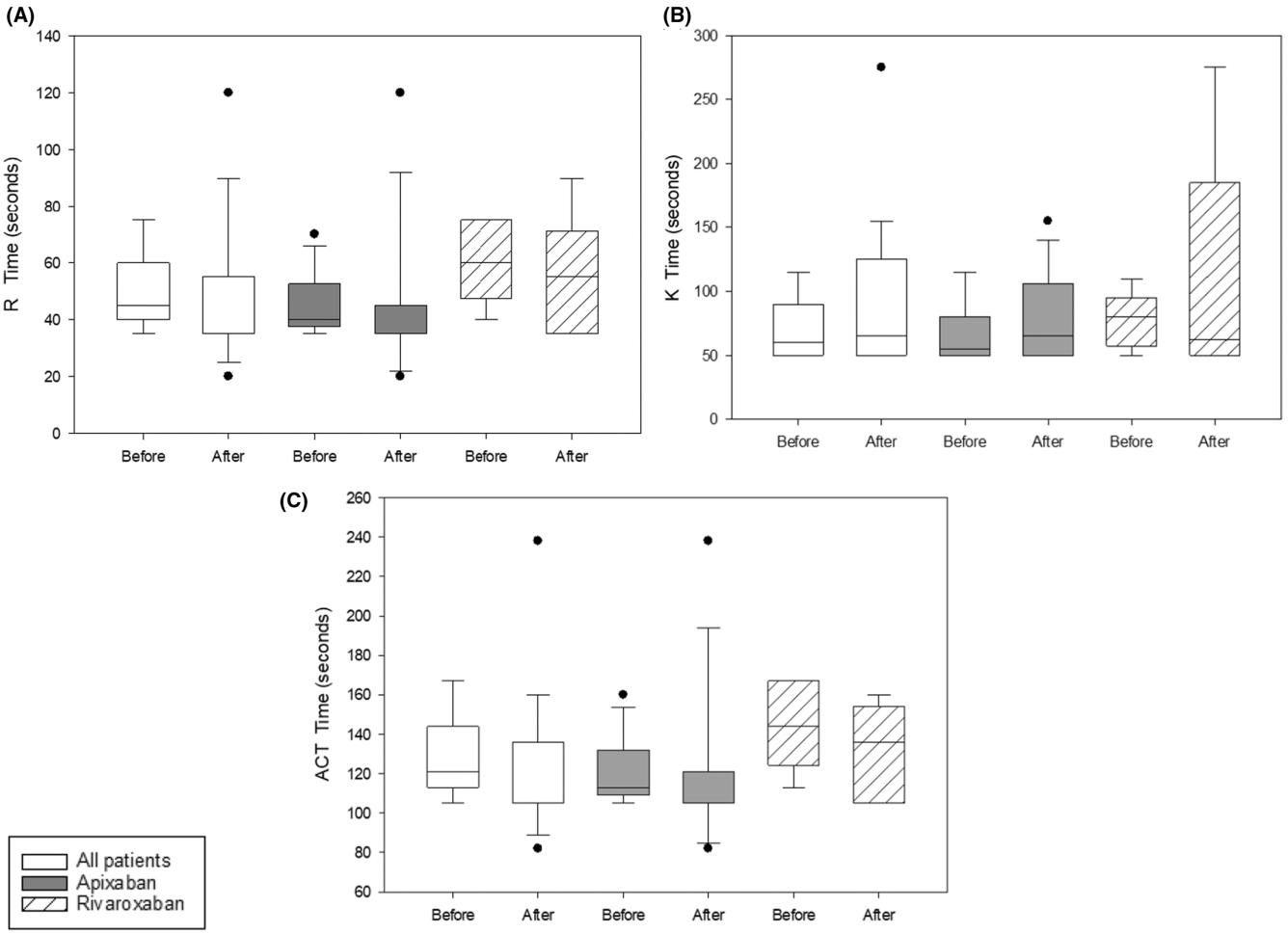

FIGURE 2 Thromboelastogram assay results (reaction time [R time], kinetic time [K time]), and activated clotting time (ACT time) were compared before versus after andexanet alfa administration for all patients combined and then divided into cohorts of apixaban patients and rivaroxaban patients. Plots represent median line within each box. Upper and lower limits of each box represent 25th and 75th percentile, respectively. Error bars represent the 10th and 90th percentile. Dots represent outliers. TEG parameters for all patients ($n = 19$) were drawn 0.9 (IQR, 0.6–1.5) hours and 2.1 (IQR, 0.9–4.7) hours pre-bolus and post-infusion of andexanet alfa, respectively. A total of 13 patients receiving apixaban had TEG assays drawn 0.8 (IQR, 0.4–1.3) hours and 2.2 (IQR, 1.3–5.4) hours pre-bolus and post-infusion of andexanet alfa, respectively. A total of six patients receiving rivaroxaban had TEG assays drawn 2.1 (SD 2.0) hours and 2.4 (SD 1.7) hours pre-bolus and post-infusion of andexanet alfa, respectively. (A) All patients TEG R time before reversal of 45.0 (IQR, 40.0–60.0) seconds versus after of 35.0 (IQR, 35.0–55.0) seconds, $p = 0.38$;apixaban patients TEG R time before of 40.0 (IQR, 37.5–52.5) seconds versus after of 35.0 (IQR, 35.0–45.0) seconds, $p = 0.32$; rivaroxaban patients TEGR time before of 60.0 (IQR, 47.5–75.0) seconds versus after of 55.0 (IQR, 35.0–71.3) seconds, $p = 0.81$. (B) All patients K time before reversal of 60.0 (IQR, 50.0–90.0) seconds versus after of 65.0 (IQR, 50.0–125.0) seconds, $p = 0.17$;apixaban K time before of 55.0 (IQR, 50.0–80.0) seconds versus after of 65.0 (IQR, 50.0–106.5) seconds, $p = 0.09$; rivaroxaban patients K time before of 80.0 (IQR, 57.5–95.0) seconds versus after of 62.5 (IQR, 50.0–185.0) seconds, $p = 0.81$. (C) All patients TEG-ACT before reversal of 121.0 (IQR, 113.0–144.0) seconds versus after of 105.0 (IQR, 105.0–136.0) seconds; $p = 0.30$; apixaban patients TEG-ACT before of 113.0 (IQR, 109.0–132.0) seconds versus after of 105.0 (IQR, 105.0–121.0) seconds; $p = 0.43$; rivaroxaban patients TEGACT before of 144.0 (IQR, 124.5–167.0) seconds versus after of 136.0 (IQR, 105.0–154.0) seconds; $p = 0.63$.

efficacy grading attempted to control for potential biases regarding unblinded analysis. The use of paired pre- and postandexanet alfa infusion assays allowed for an evaluation of the effect of andexanet alfa, but standardized times were not used due to the retrospective design of the study.

In conclusion, andexanet alfa provided promising hemostasis in perioperative patients on FXa-I therapy. There were no statistical differences in outcomes for patients prescribed apixaban versus rivaroxaban or in those experiencing an intracranial versus extracranial event. Ongoing consideration regarding the high postprocedural thromboischemic risk in this patient population is warranted. These findings provide more thorough insight on complex patient populations that frequently require anticoagulant reversal while carrying both bleeding and thrombotic complication risks. Prospective data are needed for conclusive management of patients requiring periprocedural reversal of FXa-I.

AUTHOR CONTRIBUTION

PGB—primary research idea generator, IRB submission, data collector, statistician, and manuscript writer/reviewer. SK—co-idea generator, methodology input, and manuscript review. MD—methodology input, critical manuscript review and subsequent revisions. NE—manuscript composition. MF—data collection and manuscript composition. NH—data collection and manuscript writing. AM—manuscript composition and review. EM—methodology input, manuscript and statistic review. CP—methodology input, data collection and manuscript composition. VS—CT head readings and grading of hemostatic efficacy for ICH population. JW—data collection, figure and table configuration reviewer, manuscript composition. *MG—critical manuscript review and TEG analysis expert. *CD—methodology input, critical manuscript and statistic review, senior author research mentorship. *Co-senior authorship.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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