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Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhages

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ABSTRACT

Background: Existing research recommends either andexanet alfa (AA) or four-factor prothrombin complex concentrate (4F-PCC) as an antidote for major bleeding events due to apixaban or rivaroxaban. Currently, there is limited published research that directly compares the risks and benefits of the two agents in patients with oral factor Xa inhibitor related traumatic and spontaneous intracerebral hemorrhages. Additional head-to-head data is needed to support favoring either AA or 4F-PCC when it comes to efficacy, safety, and cost.

Methods: A retrospective chart review was conducted to assess patients admitted to a multi-center healthcare system and a stand-alone teaching hospital in central Florida from June 2016 to December 2020. Patients included in the study were at least 18 years of age, taking apixaban or rivaroxaban prior to admission, had radiographical evidence of an intracranial hemorrhage, and received either AA or 4F-PCC as a reversal agent. The primary outcome analyzed was the level of excellent hemostasis achieved, based on a standardized rating system for effective hemostasis defined by the International Society of Thrombosis and Hemostasis (ISTH), after administration of AA or 4F-PCC. Secondary outcomes analyzed included changes in the initial hemorrhage volume as reported on computed tomography (CT) scan and at 12 to 24 h post treatment, rate of thromboembolic events, rate of inpatient mortality, and total cost of treatment after AA or 4F-PCC administration.

Results: A total of 109 patients were included in the study with 47 in the AA group (43.1%) and 62 in the 4F-PCC group (56.9%). There were no statistically significant differences between AA and 4F-PCC in terms of the primary and secondary outcomes with the exception of total cost of treatment. The level of excellent hemostasis achieved after reversal administration of AA was seen in 27 patients (71.1%) and 41 patients (70.7%) after 4F-PCC administration ($p = 1$, p adjusted = 0.654 after controlling for age, ICH score, regional mass effect, and midline shift). There was no statistically significant difference in the median percentage change in hemorrhagic volume from baseline to 12–24 h after reversal treatment (0 [−0.17–-0.24] vs. 0 [−0.021–0.29], $p = 0.439$, adjusted $p = 0.601$) in the AA and 4F-PCC groups, respectively. The total incidence of thromboembolic events (4 [8.5%] vs. 6 [9.7%], $p = 1$, adjusted $p = 0.973$) and rate of inpatient mortality was similar between the two groups (16 [34.0%] vs. 13 [21.0%], $p = 0.134$, adjusted $p = 0.283$). A statistically significant difference was observed with the total cost of reversal treatment: $23,602 for treatment with AA and $6692 for treatment with 4F-PCC.

Conclusions: No statistically significant differences were identified in primary or secondary outcomes between the two agents with the exception of total treatment cost. There is insufficient evidence based on this study to recommend AA over 4F-PCC for patients with intracranial hemorrhages associated with the use of apixaban or rivaroxaban.

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1. Introduction

The use of direct oral anticoagulants for the prevention and treatment of venous thromboembolism (VTE) and for stroke prevention in atrial fibrillation (SPAF) has become a common practice secondary to known favorable safety and efficacy profiles as compared to vitamin K antagonists. These advantages include lower incidence of major bleeding, minor drug and food interactions, convenience of use, rapid onset, short half-life, and minimal need for laboratory monitoring [1]. Historically, the most concerning disadvantage of direct oral anticoagulant use was the lack of a specific antidote for their anticoagulant effects in the setting of life-threatening intracranial bleeding [2].

Four-factor prothrombin complex concentrate (4F-PCC) has been used in adults for the treatment of acute major bleeding secondary to a direct oral anticoagulant. Previous studies concluded that 4F-PCC is effective for treating major bleeding events and found favorable outcomes including low incidence of thromboembolism [3-6]. 4F-PCC is currently FDA approved for the reversal of acute major bleeding induced by vitamin K antagonists only. The Neurocritical Care Society and the Society of Critical Care Medicine guideline panel have recommended 4F-PCC (50 units/kg) if intracranial hemorrhage (ICH) occurs within three to five terminal half-lives of exposure to a direct oral anticoagulant [7].

Andexanet alfa (AA) was approved in the United States in 2018 for the treatment of life threatening or uncontrolled bleeding in patients treated with rivaroxaban or apixaban. In the original studies, the use of AA resulted in excellent or good hemostasis in patients who presented with ICH or gastrointestinal bleeding. The American College of Cardiology in 2020 stated that it is reasonable to use AA for reversal in patients with rivaroxaban- or apixaban-associated critical bleeding; including ICH or life-threatening major bleeding [8].

Although previous clinical trials have established the efficacy and safety of 4F-PCC and AA separately for reversal of major bleeding events, there is a need for direct comparison data between the two agents examining efficacy, safety, and cost effectiveness [9,10]. One study directly examined safety and efficacy outcomes between 4F-PCC and AA found no difference in neuroimaging stability, functional outcome, and thrombotic events when comparing AA and 4F-PCC [11]. In addition, a meta-analysis published in May 2021 concluded that available data did not support the clinical effectiveness of AA or 4F-PCC to reverse factor Xa inhibitor-associated acute major bleeding unequivocally, nor does it did it establish potential superiority between the two reversal agents. [12] Another study looked at 29 patients, 11 receiving 4F-PCC and 18 receiving AA and found higher rates of good or excellent hemostasis in the AA group, however patients in the 4F-PCC group had higher ICH volume at baseline and lower GCS [13]. Vestal et al. published a case series composed of 56 patients (21 in the AA group and 35 in the 4F-PCC group) and reported hemostatic efficacy in 54.8% vs 67% of patients who received AA and 4F-PCC, respectively. They reported higher mortality and thromboembolic events in the 4F-PCC group [14].

The hospitals within this retrospective review allow the use of AA or 4F-PCC for ICH, as long as they meet specified criteria (see Supplementary Table 1). The purpose of this study is to compare efficacy and safety of AA versus 4F-PCC for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhage.

2. Methods

2.1. Study design

This was a multicenter, retrospective chart review assessing patients admitted to hospitals within a multi-center healthcare system and a stand-alone teaching hospital in central Florida from June 2016 to December 2020. The dosing for AA and 4F-PCC was evaluated for appropriateness based on the hospitals' protocol. AA was dosed according to the product labeling for life-threatening bleeding associated with factor Xa inhibitors. 4F-PCC dosing protocol was the same across all hospitals in the study: 50 units/kg (max 5000 units) for one dose. Within the multi-center healthcare system, AA was restricted to the following criteria: adult patients with acute, severe neurologic intracranial or spinal bleeding emergencies (ICH, primary or secondary intraventricular hemorrhage, subdural hematoma, epidural hematoma, or subarachnoid hemorrhage), and may only be ordered by neurosurgery, neurology, and critical care physicians, while emergency department physicians may utilize if given approval by above physicians. Within the stand-alone hospital, AA was restricted to the following criteria: patients 18 years of age or older with confirmed acute, life-threatening bleeding, apixaban or rivaroxaban use within the last 18 h, ICH score must be 1 to 4, no use of nonspecific reversal agents within past 24 h or anticipated concomitant use of these agents, and can only be ordered by an attending physician in the following areas: emergency medicine, critical care, neurology, neurosurgery, or hematology. ICH score is often utilized as a risk stratification and outcome prediction scale in the setting of ICH. Factors that are associated with ICH score calculation were Glasgow Coma Score (GCS), age 80 years and older, infratentorial origin of ICH, ICH volume, and presence of intraventricular hemorrhage. Patients were obtained via a search for each reversal agent used within the predefined study period and were screened based on inclusion and exclusion criteria as outlined below. Data was collected via chart review at each site. CT scans were reviewed by two neurosurgeons within the multi-center healthcare system and stand-alone hospital.

2.2. Patient population

Patients were included in the study if they were at least 18 years of age, had documented neuroimaging of an ICH, documented home medication of apixaban or rivaroxaban, and if either AA or 4F-PCC was administered. Patients were excluded if they were less than 18 years of age and if they received both AA and 4F-PCC. Baseline characteristics collected included age, gender, race, weight, prior to admission medication history, indication for anticoagulation, location/type of intracranial bleed, presence of regional mass effect, presence of a midline shift, total bilirubin and INR level at baseline, baseline GCS, and baseline ICH score.

2.3. Study outcomes

The primary outcome was the level of excellent hemostasis achieved after administration of the reversal agent based on a standardized rating system for effective hemostasis defined by the ISTH [15]. Only patients who had a repeat CT scan after administration of a reversal agent were included in the primary outcome analysis. Criteria for effective clinical hemostasis is summarized in Table 1. The secondary outcomes included: changes in the initial hemorrhage volume as reported on CT scan 12 to 24 h post-treatment, rate of thromboembolic events (stroke, myocardial infarction, arterial thromboembolism, deep vein thrombosis [DVT], or pulmonary embolism [PE]), inpatient mortality, and total cost of treatment. Other data of interest collected include time between order and administration of reversal agent, additional transfusions administered, surgical intervention performed, maximum systolic blood pressure at baseline and 24 h post-treatment, change in hemoglobin from baseline to 12 h post-treatment, resumption of anticoagulation (parenteral or oral), dose of anticoagulant resumed, length of ICU stay, length of hospital stay, and discharge destination. The outcomes data were obtained through retrospective chart review.

2.4. Statistical analysis

Stata 15.1 statistical analysis software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.) was used to perform all Firth logistic regressions of the primary and selected secondary outcome variables against the study's identified predictor variables. The primary outcome and selected secondary outcomes were analyzed using Firth logistic regression analysis, with adjustment for

Table 1
Effective clinical hemostasis

Bleed Type	Excellent	Good	Poor
Intracerebral hematoma	≤ 20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1 & 12 h post infusion time points	> 20% but ≤35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at +12-h time point	> 35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT/MRI scan at +12-h time point
Subarachnoid bleed	≤ 20% increase in maximum thickness using the most dense area on the follow-up vs baseline at both the 1 and 12 h post infusion time points	> 20% but <35% increase in maximum thickness using the most dense area on the follow-up at +12 h vs baseline	> 35% increase in maximum thickness using the most dense area on the +12 h vs at baseline
Subdural hematoma	≤ 20% increase in maximum thickness at both the 1 and 12 h post infusion assessments compared to baseline	> 20% but <35% increase in maximum thickness at +12 h compared to baseline	> 35% increase in maximum thickness at +12 h compared to baseline

Adapted from the International Society of Thrombosis and Hemostasis [15].

age, ICH score greater than or equal to four, regional mass effect, and midline shift. The Firth procedure is a general approach used to reduce small-sample bias in maximum likelihood estimation for regression analysis. Additionally, quantile regression was used to identify any potential differences between the two study groups regarding the difference in the percentage change in hemorrhagic volume. Regression allows simultaneous comparison of multiple variables at one time in relation to a response variable; thus, it addresses the issue of potential confounding since it considers other variables that might influence the response variable.

All other analyses were performed utilizing Minitab 18 (State College, PA). An alpha level of 0.05 was used for all hypothesis testing and a two-sided *p*-value of 0.05 or less was considered statistically significant. A sample size of 277 for each group was calculated to detect a 10% difference at 80% power using a 95% confidence level (alpha = 0.05). Categorical data were analyzed with the Fisher's Exact test, quantitative data were analyzed using Mood's median test, and descriptive statistics were used for baseline characteristics. Mood's median test is a conservative approach for the analysis of quantitative data to determine if there is a difference between the median of two or more groups since it does not rely on any distributional shape assumptions to analyze the data in the study groups. The majority of quantitative data for this study, when comparing the AA and 4F-PCC groups, had distributions that deviated substantially from the standard normal distribution. Therefore, medians and the interquartile ranges [IQRs] were used instead of means and standard deviations to describe the quantitative data because they were more appropriate measures of central tendency in most cases.

3. Results

3.1. Baseline characteristics

The demographic and clinical characteristics were similar between the two treatment groups (Table 2). A total of 109 patients were included in the study: 47 in the AA group (43.1%) and 62 in the 4F-PCC group (56.9%). For the primary outcome analysis, 38 patients in the AA group and 58 patients in the 4F-PCC group were analyzed since they had a follow-up CT after reversal treatment. There was a statistical difference in median weight between the AA group and the 4F-PCC group (9.7 [95% CI: (0.8—14.1)]). There was no difference in the indication for anticoagulation therapy between AA and 4F-PCC with the majority of patients taking a direct oral anticoagulant for SPAF (AA, 39 [83.0%] vs. 4F-PCC, 48 [77.4%]), followed by VTE (6 [12.8%] for the AA group vs. 10 [16.1%] for the 4F-PCC group). Three patients were on an anticoagulant for reasons other than the conventional indications. One patient did not have an indication documented, the second was receiving anticoagulation for DVT prophylaxis while on imatinib, and the third patient was taking anticoagulant for thrombi in arteriovenous shunts. The majority of patients in each group were on apixaban (76.6% of patients in AA group and 71% of patients in 4F-PCC group). Fourteen patients were not on the appropriate anticoagulation dose for their documented indication based on package insert recommendations. The majority of those patients' anticoagulant dose were not adjusted appropriately for SPAF. Fewer patients in the AA group than the 4F-PCC group (AA, 12 [25.5%] vs. 4F-PCC, 22 [35.5%]) had concomitant antiplatelets within the previous seven days, although the difference was not statistically significant. Out of the total 109 patients, 68 (62.4%) were diagnosed with intraparenchymal hemorrhage, 37 (33.9%) with subdural hematoma, 36 (33%) with intraventricular hemorrhage, and 25 (22.9%) with subarachnoid hemorrhage. No difference was found in both treatment groups with regards to presence of regional mass effect or midline shift, total bilirubin, or INR at baseline. The median GCS on admission was 14 and median ICH score was one for both groups.

3.2. Hemostatic efficacy, safety, and cost outcomes

No significant differences were observed for the primary outcome (Table 3). Excellent hemostasis was achieved in 27 out of 38 patients (71.1%) and 41 out of 58 patients (70.7%) after AA and 4F-PCC administration, respectively ($p = 1$). The result remained non-significant after adjusting for age, ICH score greater than or equal to four, regional mass effect, and midline shift (adjusted $p = 0.654$). Additionally, there was no difference in good hemostasis efficacy (AA, 4 [10.5%] vs. 4F-PCC, 5 [8.6%], $p = 0.737$, adjusted $p = 0.921$) or poor hemostasis efficacy (AA, 7 [18.4%] vs. 4F-PCC, 12 [20.7%], $p = 1.0$, adjusted $p = 0.667$). The median percentage change in hemorrhage volume from baseline to 12–24 h after reversal agent administration was (0 [−0.17–-0.24] vs. 0 [−0.021–0.29], $p = 0.439$, adjusted $p = 0.601$) in the AA and 4F-PCC groups, respectively. The incidence of thrombotic events was similar (AA, 4 [8.5%] vs. 6 [9.7%], $p = 1$, adjusted $p = 0.973$), as well as inpatient mortality prior to discharge (AA, 16 [34.0%] vs. 4F-PCC, 13 [21.0%], $p = 0.134$, adjusted $p = 0.283$). Lastly, the median total cost of treatment with AA was significantly more expensive ($23,602) compared to 4F-PCC ($6692). (See Table 4).

3.3. Other data of interest outcomes

A statistically significant difference was found when comparing the median time (in minutes) between order placement and time of administration for AA and 4F-PCC, respectively (27 [95% CI for difference: (9.0—41.1)])). Fewer patients in the AA group received platelets transfusions than in the 4F-PCC group (2 [4.3%] vs. 11 [17.7%]). Incidence of surgical intervention, changes in maximum systolic blood pressure recorded at baseline and after administration of reversal treatment, and changes in hemoglobin at baseline and 12 h post treatment did not yield statistically significant differences. Resumption of anticoagulation while inpatient was similar between groups (AA, 17 [36.2%] vs. 4F-PCC, 21 [33.9%]). Most patients were resumed on a prophylactic dose of anticoagulation approximately two days after receiving reversal treatment, with only one patient in the study resumed on full dose anticoagulation. The length of stay in ICU and inpatient were similar. Discharge destinations were similar between both groups with the majority of patients being discharged to home (AA, 13 [27.7%] vs. 4F-PCC, 23 [37.1%]), or to a rehabilitation facility (AA, 16 [34%] vs. 4F-PCC, 20 [32.3%]). (See Table 5).

Table 2
Baseline characteristics of all included patients.

Baseline Characteristics	Andexanet alfa (N = 47)	4F-PCC (N = 62)	Difference with 95% CI
Age (years)	77 [70–86]	81 [71–86]	−4 (−9–5)
Gender, male	31 (66.0)	32 (51.6)	14.3 (−4.0–32.7)
Race			
African American	7 (14.9)	4 (6.5)	8.4 (−3.4–20.3)
Asian	0 (0.0)	1 (1.6)	−1.6 (−4.7–1.5)
Caucasian	36 (76.6)	51 (82.3)	−5.7 (−21.1–9.7)
Hispanic	2 (4.3)	0 (0.0)	4.3 (−1.5–10.0)
Other	2 (4.3)	6 (9.7)	−5.4 (−14.8–3.9)
Weight (kg)	85.0 [68.1–96.9]	75.3 [67.5–89.6)	9.7 (0.8–14.1)
Anticoagulation indication			
Stroke prevention in atrial fibrillation	39 (83.0)	48 (77.4)	7.4 (−7.3–22.1)
Venous thromboembolism	6 (12.8)	10 (16.1)	−3.1 (−16.4–10.3)
Stroke prevention in atrial fibrillation and venous thromboembolism	0 (0.0)	2 (3.2)	−3.2 (−7.6–1.2)
Other	2 (4.3)	2 (3.2)	−1.0 (−6.2–8.3)
Apixaban	36 (76.6)	44 (71.0)	5.6 (−10.9–22.2)
Rivaroxaban	11 (23.4)	18 (29.0)	−5.6 (−22.2–10.9)
Dose of anticoagulation			
Apixaban 5 mg twice daily	23 (48.9)	31 (50)	−1.0 (−20.0–17.9)
Apixaban 2.5 mg twice daily	12 (25.5)	8 (12.9)	12.6 (−2.4–27.6)
Apixaban 10 mg twice daily	1 (2.1)	0 (0.0)	2.1 (−2.0–6.3)
Rivaroxaban 15 mg twice daily	1 (2.1)	0 (0.0)	2.1 (−2.0–6.3)
Rivaroxaban 20 mg daily	7 (14.9)	15 (24.2)	−9.3 (−24.0–5.4)
Rivaroxaban 15 mg daily	0 (0.0)	2 (3.2)	−3.2 (−7.6–1.2)
Rivaroxaban 10 mg daily	2 (4.3)	1 (1.6)	2.6 (−3.9–9.2)
Unknown apixaban or rivaroxaban dose	1 (2.1)	5 (8.1)	−5.9 (−13.9–-2.0)
Medication history			
Other anticoagulant within past 7 days	2 (4.3)	0 (0.0)	4.3 (−1.5–10.0)
Antiplatelets within past 7 days	12 (25.5)	22 (35.5)	−10.0 (−27.2–7.3)
Type of intracranial bleed			
Subdural hematoma	14 (29.8)	23 (37.1)	−7.3 (−25.1–10.5)
Subarachnoid hemorrhage	12 (25.5)	13 (21.0)	4.6 (−11.5–20.6)
Intraventricular hemorrhage	17 (36.2)	19 (30.6)	5.5 (−12.4–23.4)
Intraparenchymal hemorrhage	29 (61.7)	39 (62.9)	−1.2 (−19.6–17.2)
Regional mass effect	26 (55.3)	36 (58.1)	−2.7 (−21.5–16.0)
Midline shift	23 (48.9)	26 (41.9)	7.0 (−11.8–25.8)
Total bilirubin at presentation (mg/dL)	0.7 [0.5–1.0]	0.6 [0.5–0.9]	0.1 (−0.1–0.3)
INR at presentation	1.3 [1.1–1.5]	1.2 [1.1–1.3]	0.1 (0.0–0.2)
Baseline Glasgow Coma Score	14 [10–15]	14 [13–15]	0 (−2–1)
Intracranial Hemorrhage Score	1 [0–3]	1 [0–2]	0 (0–1)

Nominal data presented as n (%) and continuous data as median [IQR].

Modified Rankin Score (mRS) was also collected at discharge only among patients admitted within the multi-center healthcare system, as the stand-alone hospital did not document mRS. There were 18 patients in the AA group and 20 patients in the 4F-PCC group that had a mRS documented at discharge (Table 6). Only the percentage of scores of four showed a statistically significant difference between the AA and 4F-PCC groups, respectively (−35.0 [95% CI for difference: (−55.9–-14.1)]). Patients with mRS of three or less were examined more closely, as the scores indicated good functional outcome. No statistically significant difference was found in the percentage of patients with a mRS of three or less (25.0 [95% CI for difference: (−4.9—54.9)]) in the AA and 4F-PCC groups, respectively.

4. Discussion

In this multi-center, retrospective study, AA and 4F-PC for the reversal of oral factor Xa inhibitors in patients with ICH were assessed. The hemostatic efficacy of these agents was evaluated by comparing baseline and follow-up head CT post-treatment, changes in the hemorrhage volume as reported on the initial CT scan and 12–24 h post-treatment, rate of thrombosis events, inpatient mortality, and total cost of treatment. No statistically significant differences were found in these outcomes between the AA and 4F-PCC with the exception of total cost of treatment. No patients in the study had repeat dosing of either reversal agent. Good to excellent hemostasis in the AA group 10.5% and 71.1%, respectively, are in line with previously reported findings [9,10,13,14]. Good to excellent hemostasis with 4F-PCC of 8.6% to 70.7% was also similar to incidence found in the literature [3,13,14,16-19].

One of the concerns with AA prior to its FDA approval in 2018 was the rate of thromboembolism, which was approximately up to 18% [9,10]. In addition to acting as a decoy that binds to factor Xa inhibitors, AA also binds and inhibits tissue factor pathway inhibitor. This mechanism can accelerate the production of factor Xa and thrombin, consequently promoting thrombosis. The FDA had additional concerns

Table 3
Primary outcomes.

Hemostasis Scale	Andexanet alfa (N = 38)	4F-PCC (N = 58)	Difference with 95% CI	p	Adjusted p*
Excellent	27 (71.1)	41 (70.7)	0.4 (−18.2–18.9)	1	0.654
Good	4 (10.5)	5 (8.6)	1.9 (−10.2–14.0)	0.737	0.921
Poor	7 (18.4)	12 (20.7)	−2.3 (−18.4–13.9)	1	0.667

Nominal data presented as *n* (%).
* p-value when adjusted for age, ICH score, regional mass effect, and midline shift.

Table 4
Secondary outcomes.

Outcome	Andexanet alfa (N = 47)	4F-PCC (N = 62)	Difference with 95% CI	p	Adjusted p*
% Change in hemorrhage volume from baseline to 12–24 h after reversal treatment	0 [−0.17–0.24)	0 [−0.021–0.29]	0 (−0.058–0.00)	0.439	0.601
Thromboembolism event	4 (8.5)	6 (9.7)	−1.2 (−12.0–9.7)	1	0.973
Myocardial infarction	1 (2.1)	0 (0.0)	2.1 (−2.0–6.3)	0.431	
Stroke	0 (0.0)	0 (0.0)	0 (*–*)	1	
Deep vein thrombosis	3 (6.4)	5 (8.1)	−1.7 (−11.4–8.1)	1	
Pulmonary embolism	0 (0.0)	1 (1.6)	−1.6(−4.7–1.5)	1	
Inpatient mortality	16 (34.0)	13 (21.0)	13.1(−3.8–30.0)	0.134	0.283
Total cost of reversal treatment ($)	$23,602 [$23,602–$23,602]	$6692 [$5950–$7649]	$16,910 ($16,082–$17,022)	0.000	

Nominal data presented as n (%) and continuous data as median [IQR].
* p-value when adjusted for age, ICH score, regional mass effect, and midline shift.

about the short half-life of AA and the lack of correlation of in vitro activity with clinical efficacy. FDA clinical reviewers initially recommended against approval of AA. They believed the data on safety and efficacy data were not adequate to support approval. However, the Director for the Office of Tissues and Advanced Therapies overrode the recommendation from the review team [20]. In this retrospective study, although no significant difference was detected, fewer thromboembolic events were observed in the AA group (8.5%) than the 4F-PCC group (9.7%). Recent comparison studies between these two agents, with the exception of one study, found a higher percentage of thromboembolic events in AA than 4F-PCC. Nederpelt et al. and Barra et al. reported 10.7% and 16.7% for AA and 3.1% and 9.1% for 4F-PCC. Vice versa, Vesta et al. reported 14.3% with AA and 31.4% thrombotic event with 4F-PCC. This outcome may be an important point to consider when choosing between the two agents.

Although 4F-PCC was less expensive than AA, standard cost-effective analysis is needed to determine if 4F-PCC is truly more cost effective. As of October 1, 2018, all Medicare-qualified acute hospitals that are paid through the Inpatient Prospective Payment System qualified for AA reimbursement through the New Technology Add-on Payment (NTAP). Health systems qualifying for Medicare Part A inpatient cases could receive up to a maximum of $14,062.50 (increased to $18,281) per qualifying case. The NTAP for AA was initially implemented for three years from the approval date and expired September 30, 2021. The manufacturer requested to have this time extended for another year and NTAP granted the one-year extension with a maximum amount of $18,281. Hospitals can apply for NTAP, which can reimburse up to 65% of the cost of new medications, such as AA, when there is no FDA approved alternative [21].

A statistically significant difference was found when examining the difference in median time between the order for the reversal agent and time of administration between the groups (70 min for AA vs. 43 min for 4F-PCC). Reconstituting AA is more labor intensive and time consuming as compared with 4F-PCC. A total of five vials (two vials for the bolus and three vials for the infusion) are needed for the low dose of AA and nine (four vials for the bolus and five vials for the infusion) for the high dose, each vial needing to be reconstituted with 20 mL of sterile water. The shorter time from order to administration may be due to the fact that it takes longer to reconstitute and compound AA than 4F-PCC, making this a considerable advantage for 4F-PCC, although

Table 5
Other Data of Interest

Other Data of Interest	Andexanet alfa (N = 47)	4F-PCC (N = 62)	Difference with 95% CI
Time between order and administration of reversal agent (minutes)	70 [55–87]	43 [31–61.5]	27 (9.0–41.1)
Additional transfusion			
RBC concentrate	1 (2.1)	3 (4.8)	−2.7 (−9.5–4.0))
Plasma	1 (2.1)	3 (4.8)	−2.7 (−9.5–4.0)
Platelets	2 (4.3)	11 (17.7)	−13.5 (−24.6–-2.4)
Vitamin K	2 (4.3)	3 (4.8)	−0.6 (−8.4–7.3)
Surgical intervention	10 (21.3)	14 (22.6)	−1.3 (−17.0–14.4)
Max systolic blood pressure at baseline			
>180 mmHg	15 (31.9)	17 (27.4)	4.5 (−12.9–21.8)
160–180 mmHg	13 (27.7)	10 (16.1)	11.5 (−4.2–27.3)
<160 mmHg	19 (40.4)	35 (56.5)	−16.1 (−34.7–2.7)
Max systolic blood pressure 24 h post-treatment			
>180 mmHg	2 (4.3)	2 (3.2)	1.0 (−6.2–8.3)
160–180 mmHg	6 (12.8)	9 (14.5)	−1.8 (−14.7–11.2)
<160 mmHg	39 (83.0)	51 (82.3)	0.7 (−13.6–15.1)
Change in hemoglobin from baseline to 12 h post-treatment (g/dL)	0.9 [0.2–1.6]	0.7 [0.1–1.6]	0.2 (−0.5–0.7)
Inpatient resumption of anticoagulant	17 (36.2)	21 (33.9)	2.3 (−15.8–20.4)
Time from treatment to anticoagulant resumption (days)	2 [1–3]	2 [1.5–4]	0.0 (−2–1)
Dose of anticoagulant resumed			
Prophylactic dose	17 (36.2)	20 (32.3)	3.9 (−14.1–21.9)
Therapeutic dose	0 (0.0)	1 (1.6)	−1.6 (−4.7–1.5)
Length of stay (LOS) (days)			
Hospital LOS	6.7 [4.0–14.0]	5.1 [3.5–13.4]	1.6 (−3.1–3.0)
ICU LOS	3.0 [1–5.1]	3.0 [2.0–9.1]	0.0 (−2.2–1.2)
Discharge destination			
Home	13 (27.7)	23 (37.1)	−9.4 (−27.0–8.1)
Rehabilitation Facility	16 (34.0)	20 (32.3)	1.8 (−16.1–19.6)
Other Hospital	2 (4.3)	2 (3.2)	1.0 (−6.2–8.3)
Hospice	4 (8.5)	4 (6.5)	2.1 (−8.0–12.1)

Nominal data presented as n (%) and continuous data as median [IQR].

Table 6
Modified Rankin score at discharge among patients in multi-center healthcare system.

Modified Rankin Score at Discharge	Andexanet alfa ($N = 18$)	4F-PCC ($N = 20$)	Difference with 95% CI
0	1 (5.6)	2 (10.0)	−4.4 (−21.3–12.4)
1	3 (16.7)	1 (5.0)	11.7 (−8.0–31.4)
2	2 (11.1)	0 (0.0)	11.1 (−3.4–25.6)
3	3 (16.7)	2 (10.0)	6.7 (−15.0–28.3)
4	0 (0.0)	7 (35.0)	−35.0 (−55.9−14.1)
5	9 (50.0)	8 (40.0)	10.0 (−21.5–41.5)
≤ 3	9 (50.0)	5 (25.0)	25.0 (−4.9–54.9)

Nominal data presented as n (%).

there is no evidence that the additional delay would influence outcomes. It was also observed that fewer patients in the AA group received platelets transfusions than in the 4F-PCC group, which was statistically significant. It is possible that more patients received platelet transfusions in the 4F-PCC group because more patients in this group were on antiplatelet therapy at home.

Patients taking an oral factor Xa inhibitor therapy at home have underlying disease states that predispose them to thromboembolic events. Reversing oral factor Xa inhibitor therapy may expose patients to the thrombotic risk of their underlying disease. To reduce the risk of thrombosis, resumption of anticoagulation should be considered as soon as medically appropriate following treatment with reversal agents. Compared to the previous direct comparison between AA and 4F-PCC studies that have been published, this study is the first to collect data on the time from treatment with a reversal agent to resumption of anticoagulation. Anticoagulation was resumed in 33–36% of patients, on average. The median days from treatment to anticoagulant resumption for both reversal agents were approximately two days, although a statistically significant difference was not observed with this endpoint. The majority of patients that were resumed on an anticoagulant received doses for VTE prophylaxis and only one patient was resumed on their home anticoagulant dose. Without enough high-quality evidence to guide clinical decision-making, it is imperative for clinicians to balance the risks of thromboembolism and recurrent ICH in each patient. The optimal timing of anticoagulation resumption after an ICH is still unknown and should be explored in future studies.

One of the previous studies, by Ammar et al., used mRS of less than or equal to three as a marker for good functional outcome at discharge [11]. This study also looked the mRS at discharge, but only in patients admitted to one of the multi-center healthcare systems. The mRS were not documented at the stand-alone teaching hospital. A total of 20 patients in the 4F-PCC group and 18 in the AA group had a mRS documented at discharge. Only the score of four was statistically significant ($p = 0.009$), but this may be due to the 4F-PCC group having seven patients while AA had none. Although more commonly used to measure the degree of disability or dependence of patients who have suffered a stroke, mRS can also be a useful tool to assess for patients' disability after an ICH event. This is another endpoint that is worth expanding on in larger studies. No differences between discharge destinations were found between groups, although interestingly, there was a trend towards more patients being discharged to a rehabilitation facility in the AA group and more patients being discharged to home in the 4F-PCC group.

This study has the fundamental limitations of a retrospective chart review. Although this study has the largest sample size to date, a larger sample size would contribute significantly to being able to detect a difference between AA and 4F-PCC. Another limitation of this study is the lack of resources to collect some variables that may influence outcomes in ICH, such as time from last dose of DOAC and time from symptom onset to CT and treatment, which were unfortunately not routinely documented in the EMR. Additionally, presence of CT angiography, spot sign, and the limitation of early care due to shared decision making, were not documented and thus could not be assessed. Future prospective studies with these variables included would be beneficial.

Having patient data from a multi-center healthcare system and a large stand-alone hospital was a strength of the study. This study has the largest sample size to date, directly comparing AA and 4F-PCC. Moreover, imaging was analyzed by two neurosurgeons, one for each hospital system, to determine type of ICH, confirm the presence of regional mass effect and/or midline shift, and identify the size and volume of the hemorrhages. A validated hemostasis scale was utilized to assess for hemostatic efficacy which offers a more reliable rating for effective hemostasis in all patients compared to provider judgement, which could be considered subjective and infers inherent risk of bias. This study also includes binomial logistic regression to adjust for confounding variables. In terms of excellent hemostasis, regional mass effect and ICH score greater than or equal to four were negatively correlated, while the choice of reversal agent had no impact. To address concern for possible prescribing bias of restricting AA for more severe cases, a regression was performed on reversal agent and ICH greater than or equal to four, which had to be dichotomized due to small sample size, and found no relationship between choice of reversal agent and ICH score.

5. Conclusions

No significant difference was found in efficacy or safety between AA and 4F-PCC when used for ICH. There is insufficient evidence to recommend one reversal agent over the other for patients with ICHs associated with the use of apixaban or rivaroxaban. Further studies with a larger patient population to assess whether there is truly a difference between AA and 4F-PCC in hemostatic efficacy are needed.

CRediT authorship contribution statement

Haithuy Pham: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Whitney Gibson Medford:** Writing – review & editing, Methodology, Conceptualization, Data curation. **Spencer Horst:** Conceptualization, Data curation, Methodology, Writing – review & editing. **Melissa Levesque:** Investigation, Data curation, Conceptualization. **David Ragoonanan:** Conceptualization, Data curation, Investigation. **Christine Price:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Harold Colbassani:** Investigation. **Keaton Piper:** Investigation. **Keith Chastain:** Formal analysis, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2022.02.029.

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