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Comparison of 4-factor prothrombin complex concentrate and andexanet alfa for reversal of apixaban and rivaroxaban in the setting of intracranial hemorrhage

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Abstract
The purpose of this study was to evaluate and compare clinical outcomes in patients who experienced intracranial hemorrhage (ICH) while taking apixaban or rivaroxaban and were reversed with four-factor prothrombin complex concentrates (4F-PCC) or andexanet alfa (AA). This retrospective cohort included adult patients that received 4F-PCC or AA for the initial management of an apixaban- or rivaroxaban-associated ICH. A primary outcome of excellent or good hemostatic efficacy at 12 h post-reversal was assessed. Secondary outcomes evaluated were change in hematoma volume size at 12 h, functional status at discharge, need for surgical intervention or additional hemostatic agents post-reversal, new thrombotic event within 28 days, 28-day all-cause mortality, discharge disposition, and hospital and intensive care unit lengths of stay. A total of 70 patients were included (4F-PCC, n = 47; AA, n = 23). For the primary outcome analysis, 21 patients were included in the 4F-PCC group and 12 in the AA group. The rate of effective hemostasis was similar between the 4F-PCC and AA groups (66.7% vs 75%, $p = 0.62$). There were no statistically significant differences between the groups for secondary outcomes, including 28-day mortality (40.4% vs 39.1%, $p = 0.92$) and thrombotic complications within 28 days of reversal (17.0% vs 21.7%, $p = 0.63$). In patients who experienced an ICH while taking apixaban or rivaroxaban, 4F-PCC and AA were found to have similar rates of excellent or good hemostatic efficacy.

Keywords Andexanet alfa · Anticoagulation reversal · Factor Xa inhibitor · Hemostatic efficacy · Intracranial hemorrhage · Prothrombin complex concentrate

Highlights

- The purpose of this retrospective study was to evaluate and compare outcomes in patients who received four-factor prothrombin complex concentrates (4F-PCC) or andexanet alfa (AA) for an intracranial hemorrhage (ICH) in the setting of apixaban or rivaroxaban use.
- The primary outcome evaluated was excellent or good hemostatic efficacy 12 h after the receipt of 4F-PCC or AA.
- In this cohort (n = 70), there was no significant difference in the achievement of excellent or good hemostatic efficacy in patients who were treated with 4F-PCC or AA. The rate of 28-day mortality and thrombotic complications within 28 days were also similar.
- Larger, prospective trials are needed to evaluate the efficacy and safety of 4F-PCC administration for the management of apixaban- or rivaroxaban-associated ICH compared to AA.

Background

Oral factor Xa inhibitors, or direct oral anticoagulants (DOACs), such as apixaban and rivaroxaban, have become the preferred anticoagulation treatment option for venous thromboembolism (VTE) and/or non-valvular atrial fibrillation. DOACs require less therapeutic monitoring, have similar efficacy, and lower rates of major bleeding compared to vitamin K antagonists such as warfarin [1]. The annual rate of anticoagulant-associated ICH in patients taking DOACs is 50% lower (0.1–0.2%) than those patients taking warfarin (0.3–0.6%) [2–4]. Despite relatively low incidence, the 90-day mortality rate of ICH is in excess of

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65% and those patients that survive are at significant risk for severe long-term disability [2]. Rapid achievement of hemostasis is important to prevent progression of ICH and improve patient outcomes.

Prior to FDA approval of andexanet alfa in May 2018, there was no targeted reversal agent for DOACs. Non-specific clotting factors including 4F-PCC had been commonly used off-label to establish hemostasis in DOAC-induced coagulopathy and ICH, despite the lack of robust data regarding safety and efficacy [5, 6]. Andexanet alfa is a recombinant modified factor Xa protein indicated for reversal of life-threatening or uncontrolled bleeding due to apixaban or rivaroxaban [7]. The drug received accelerated approval after phase 1 and 2 studies demonstrated a significant decrease in anti-factor Xa activity from baseline, indicating ability to reverse anticoagulation [8, 9]. After FDA approval, a single-arm cohort study in humans was conducted and found andexanet alfa provided excellent or good hemostatic efficacy in over 80% of cases of acute major bleeding associated with DOAC use [10]. However, because the study was conducted without a comparator group and treatment costs are significantly higher with andexanet alfa [11], its use remains controversial. The limited available data has not identified an agent with superior clinical efficacy.

The purpose of this retrospective study is to evaluate and compare clinical outcomes in patients taking apixaban or rivaroxaban, who experienced ICH and were reversed with 4F-PCC or andexanet alfa.

Methods

Study design and population

This single-center, retrospective descriptive cohort was conducted at a level-one trauma center and tertiary referral hospital. Those included were adult patients (≥ 18 years old) that were admitted between January 1, 2015 and February 28, 2021 and received 4F-PCC or AA for apixaban- or rivaroxaban-associated ICH diagnosed via computed tomography (CT) scan. 4F-PCC was administered as a fixed dose of 50 units/kg (up to 5000 units per dose) and AA was dosed according to product labeling for life-threatening bleeding associated with factor Xa-inhibitors. Patients were excluded if ICH was associated with edoxaban or betrixaban, the indication for DOAC reversal was for non-ICH major bleeding, hemostatic agents or clotting factors were administered prior to reversal, or surgical intervention occurred prior to receiving either study drug. The study was reviewed and approved as exempt by the Cooper University Health Care Institutional Review Board.

Data collection

All data was obtained from electronic medical record (EMR) review. Data regarding baseline demographics, CT imaging, clinical, and laboratory information was collected. Hematoma volumes were calculated using the volume estimation method ABC/2 [12]. CT images were independently reviewed by two separate investigators. If inconsistency in the calculated hematoma volume was found, a third investigator was consulted. An initial CT scan was performed at the discretion of the primary provider to evaluate for ICH; once an ICH was identified institutional protocol was followed and repeat imaging was obtained 6–12 h after baseline or intervention and again at 24 h. CT images that were obtained at baseline and 12 h were used in the evaluation of hematoma volume expansion and determine hemostatic efficacy. Information regarding new VTE was obtained via EMR by reviewing Doppler ultrasound and CT angiography results. Mortality was confirmed via death note. In this study, those patients that were discharged to hospice remained inpatient and death notes were available if they expired within 28 days.

Assessment of outcomes

A primary outcome of excellent or good hemostatic efficacy at 12 h post-reversal was assessed. Excellent and good hemostasis were defined as less than 20% increase or greater than 20% but less than 35% increase in hematoma volume compared to baseline computed tomography (CT) imaging at the 12-h time point, respectively [13]. Due to inability to accurately calculate hematoma size for subarachnoid and interventricular hemorrhages, these bleed types were excluded from the primary outcome. Secondary outcomes evaluated were change in hematoma volume size at 12 h, functional status at discharge according to the modified Rankin Scale (mRS) [14], Glasgow Outcome Scale (GOS) [15], and Cerebral Performance Category (CPC) [16], the need for surgical intervention or additional hemostatic agents post-reversal, new thrombotic event within 28 days, 28-day all-cause mortality, discharge disposition, and hospital and intensive care unit (ICU) lengths of stay. The decision to administer additional hemostatic agents was left to the discretion of the treating provider. New thrombotic event was defined as new VTE (deep vein thrombosis and/or pulmonary embolism), cerebrovascular accident or transient ischemic attack, myocardial infarction, or cardiovascular death after AA or 4F-PCC were administered.

Statistical analyses

Baseline characteristics and categorical variables were expressed as counts and percentages and were analyzed using the Chi-square or Fisher's exact test. Parametric,

continuous data was expressed as means and standard deviations and compared using the student's t-test. Non-parametric, continuous data was expressed as medians and interquartile ranges and compared using the Mann–Whitney U test. A binomial logistic regression was performed to determine effects of independent variables on the primary outcome. All statistical tests were two-tailed and statistical significance was set at a p-value < 0.05. Statistical analyses were performed using Microsoft Excel 2016 and IBM® SPSS® Statistics Version 28.0.1.1 (14).

Results

A total of 70 patients were deemed appropriate for inclusion (4F-PCC, n = 47; AA, n = 23). There were no significant difference in baseline demographics between groups (Table 1). In general, this cohort included an elderly population with a median age of 81 years. More patients in the AA group were taking apixaban prior to admission (4F-PCC: 53.3%; AA: 87.0%, p = 0.004). Approximately two-thirds of patients were on anticoagulation for atrial fibrillation (4F-PCC: 68.1%; AA: 65.2%). Nearly half of the population was receiving concomitant antiplatelet therapy, with aspirin being the most common agent. Median GCS upon admission was 13 (IQR 6–15) in the 4F-PCC group and 12 (IQR 5–14) in the AA group. Sixty-seven percent of patients presented following traumatic injuries (4F-PCC, 68.1%; AA: 69.6%). The overall incidence of multicompartmental hemorrhage was 48.9% in this cohort (4F-PCC: 46.8%; AA: 52.5%). Initial hematoma volume was evaluable in 47 patients, 27 patients in the 4F-PCC group and 20 in the AA group. There was no significant difference in the median initial hematoma volume (in milliliters), 15.7 (IQR 6.1–33.0) and 18.3 (IQR 7.7–64.0) in the 4F-PPC and AA groups, respectively ($p = 0.25$). The median baseline ICH score was statistically higher in the AA group [3 (IQR 2–3)] compared to the 4F-PCC group [2 (IQR 1–3)], $p = 0.03$. All patients who received 4F-PCC for reversal were administered a 50 units/kg infusion. Approximately 75% of patients who received AA for reversal were given the low dose bolus and infusion.

Twenty-one patients in the 4F-PCC group and 12 in the AA group were included in the primary outcome analysis (Table 2). Patients were excluded from the primary outcome analysis if the hemorrhage was a SAH or IVH, if there were no follow-up CT images for comparison, or if the patient underwent surgical intervention following DOAC reversal (Fig. 1). Excellent or good hemostatic efficacy was achieved in 66.7% of patients in the 4F-PCC group and in 75% of patients in the AA group ($p = 0.62$). Median change in hematoma volume was similar between the 4F-PCC and AA groups (1.0 vs − 0.5 mL, $p = 0.44$). The need for surgical intervention after reversal was similar in the AA group (17.0 vs 30.4%, $p = 0.20$). Functional status at discharge was similar between the groups and reflected severe disability (median mRS = 5, GOS = 3, CPC = 3). Twenty-eight-day mortality was similar between groups, 40.4% for 4F-PCC and 39.1% for AA, $p = 0.92$. Median hospital and ICU lengths of stay were similar between groups—7 and 3 days, respectively. Upon discharge, only 11% of the patients were sent home. More patients in the 4F-PCC group were discharged to a rehabilitation facility compared to AA (36.2% vs 8.7%, $p = 0.02$). The rates of thrombotic complications within 28 days of receiving 4F-PCC or AA were 17.0% and 21.7%, respectively. All 8 patients in the 4F-PCC group who had a thrombotic complication experienced a VTE (DVT/PE). Four of the five patients in the AA group experienced a VTE while one patient died from cardiovascular cause. In patients that experienced a thrombotic complication, average time to initiation of therapeutic anticoagulation or chemical VTE prophylaxis after anticoagulation reversal was numerically longer in the 4F-PCC group (149.9 ± 160.8 vs 51.2 ± 28.3 h), $p = 0.345$.

A binomial logistic regression was performed to ascertain the effects of age, anticoagulant use, baseline ICH score, ICH blood volume, gender, and reversal agent on the likelihood of achieving excellent or good hemostatic efficacy. The logistic regression model was statistically significant, $\chi^2(6) = 13.778$, $p = 0.032$. The model explained 48.3.0% (Nagelkerke R^2) of the variance in good or excellent hemostatic efficacy and correctly classified 84.8% of cases. Sensitivity was 91.3%, specificity was 70%, positive predictive value was 87.5%, and negative predictive value was 77.8%. None of the predictor variables were statistically significant as shown in Table 3.

Discussion

The purpose of this study was to compare outcomes in patients who received 4F-PCC or AA for the management of DOAC-associated ICH. We found no significant difference in the achievement of effective hemostasis at 12 h in patients that were treated with 4F-PCC or AA. Overall achievement of excellent or good hemostasis at 12 h was approximately 70% for this cohort, which is similar to existing literature evaluating hemostasis at 6 and 24 h [17–19]. A binomial logistic regression did not find that age, anticoagulant use, baseline ICH score, ICH blood volume, gender, and reversal agent impacted achievement of excellent or good hemostatic efficacy.

In general, baseline characteristics between the two groups were similar. The majority of patients in both groups were on therapeutic anticoagulation for atrial fibrillation. Apixaban use was more common among patients in the AA group compared to the 4F-PCC group (87.0% vs 51.1%,

Table 1 Baseline characteristics

	4F-PCC n = 47	Andexanet alfa n = 23	*p*-value
Age, median years [IQR]	81 [74–87]	80 [73–85]	0.46
Male, n (%)	30 (63.8)	10 (43.5)	0.11
Height, mean cm ± SD	170.2 ± 11.4	168.5 ± 11.9	0.29
Weight, mean kg ± SD	80.5 ± 23.3	85.8 ± 26.8	0.17
BMI, mean kg/m^2 ± SD	27.7 ± 6.5	29.7 ± 6.5	0.07
Anticoagulant, n (%)			
Apixaban	24 (51.1)	20 (87.0)	0.004
Rivaroxaban	23 (48.9)	3 (13.0)	0.004
Anticoagulant dose, n (%)			
Apixaban	**n = 24**	**n = 20**	
2.5 mg PO twice daily	5 (20.8)	3 (15.0)	0.71
5 mg PO twice daily	11 (45.8)	17 (85.0)	0.01
10 mg PO twice daily	1 (4.2)	0 (0)	1.00
Unknown	7 (29.2)	0 (0)	0.01
Rivaroxaban	**n = 23**	**n = 3**	
15 mg PO daily	6 (26.1)	2 (66.7)	0.22
20 mg PO daily	11 (47.8)	1 (33.3)	1.00
Unknown	6 (26.1)	0 (0)	0.56
Indication for anticoagulation, n (%)			
Atrial fibrillation	32 (68.1)	15 (65.2)	0.81
Venous thromboembolism	12 (25.5)	6 (26.1)	0.96
Unknown	3 (6.4)	2 (8.7)	0.66
Concurrent antiplatelet therapy, n (%)			
Aspirin	21 (44.7)	11 (47.8)	1.00
P2Y12 inhibitor	2 (4.3)	1 (4.3)	1.00
Other	1 (2.1)	0 (0)	1.00
GCS on admission, median [IQR]	13 [6–15]	12 [5–14]	0.43
Mechanism of injury, n (%)			
Traumatic	32 (68.1)	16 (69.6)	0.90
Spontaneous	15 (31.9)	7 (30.4)	0.90
Multicompartment hemorrhage, n (%)	22 (46.8)	12 (52.2)	0.67
Initial hematoma volume[a], median mL [IQR]	**n = 27** 15.7 [6.1–33.0]	**n = 20** 18.3 [7.7–64.0]	0.25
Baseline ICH[a,b], median score [IQR]	**n = 27** 2 [1–3]	**n = 20** 3 [2, 3]	0.03
Reversal agent dosing, n (%)			
Andexanet alfa[c]			
Low dose	–	17 (73.9)	
High dose	–	6 (26.1)	
4F-PCC: 50 units/kg infusion	47 (100)	–	

BMI body mass index, *GCS* Glasgow coma scale, *ICH* intracerebral hemorrhage, *SD* standard deviation, *IQR* interquartile range

[a]Excluded patients with primary intraventricular and subarachnoid hemorrhages

[b]Intracerebral hemorrhage score is used to estimate mortality based on GCS, age, and CT imaging; scores of 2 and 3 approximate 26% and 74% mortality, respectively

[c]Low dose—400 mg bolus followed by 4 mg/min infusion for up to 120 min; high dose—800 mg bolus followed by 8 mg/min infusion for up to 120 min

Table 2 Outcomes and safety endpoints

	4F-PCC n = 47	Andexanet alfa n = 23	*p*-value
Primary outcome			
Excellent or good hemostatic efficacy at 12 h[a], n (%)	**n = 21** 14 (66.7)	**n = 12** 9 (75)	0.62
Secondary outcomes			
Change in hematoma volume at 12 h[a], mean mL ± SD	**n = 21** 1.0 ± 11.8	**n = 12** − 0.5 ± 5.5	0.44
Receipt of other hemostatic agents, n (%)	2 (4.3)	1 (4.3)	1.00
Need for surgical intervention after reversal, n (%)	8 (17.0)	7 (30.4)	0.20
Modified Rankin Scale, median [IQR]	5 [3–6]	5 [4–6]	0.24
Glasgow Outcome Scale, median [IQR]	3 [1–4]	3 [1–3]	0.37
Cerebral Performance Category, median [IQR]	3 [3–5]	3 [3–5]	0.29
28-day mortality, n (%)	19 (40.4)	9 (39.1)	0.92
ICU length of stay, median days [IQR]	3 [1–8]	3.5 [1–10]	0.75
Hospital length of stay, median days [IQR]	7 [3–11]	7 [4–12]	0.61
Discharge disposition, n (%)			
Home	7 (14.9)	1 (4.3)	0.26
Rehabilitation facility	17 (36.2)	2 (8.7)	0.02
LTACH, SNF	3 (6.4)	10 (43.5)	0.0004
Hospice	7 (14.9)	3 (13.0)	1.00
Expired	13 (27.7)	7 (30.4)	0.81
Safety outcome			
New thrombotic event within 28 days, n (%)	8 (17.0)	5 (21.7)	0.63
Cardiovascular death	0 (0)	1 (20)	0.38
Venous thromboembolism (DVT/PE)	8 (100)	4 (80)	0.38

DVT deep vein thrombosis, *ICU* intensive care unit, *IQR* interquartile range, *LTACH* long-term acute care hospital, *PE* pulmonary embolism, *SD* standard deviation, *SNF* skilled nursing facility

[a]Patients were excluded if the primary hemorrhage was a subarachnoid or intraventricular hemorrhage, if there was lack of follow-up imaging, or if the patient had neurosurgical intervention (e.g. hematoma evacuation) after receiving a study drug

$p = 0.004$). This is likely reflective of the change in provider preference in the community to use apixaban over rivaroxaban due to its reduced bleeding risk and dosing options for patients with renal impairment throughout the study period. Patients who received AA presented with numerically larger ICH volumes (18.3 vs 15.7 mL) and lower GCS scores at baseline (12 vs 13); however, these were not statistically significant. More than two-thirds of the study population experienced a traumatic ICH and nearly half presented with multicompartmental bleeds. Intracerebral hemorrhage scores for evaluable patients in the AA group (3) was significantly higher than the 4F-PCC (2), which may represent more severe injury at baseline. In the AA group, 40% of the evaluable patients had an ICH volume ≥ 30 mL whereas only 29% of patients in the 4F-PCC group met this threshold. However, none of the individual components of the ICH score (age, baseline GCS, ICH volume ≥ 30 mL, presence of IVH, or infratentorial origin of hemorrhage) were statistically significant between groups. When the composite of all ICH score components was evaluated, there was a statistical difference between groups. The ICH score is a clinical grading tool and predictor of 30-day mortality; scores of 3 and 2 correlate with predicted 30-day mortality of 72% and 26%, respectively [20]. Despite this, 28-day mortality was similar between the groups at around 40%. A higher mortality was reported in our cohort than in previously published literature (26–38%) [17–19] which may be due to selection bias as our level 1 trauma center serves as a tertiary referral center and treats a more severely ill population. These findings differ from those described by Costa and colleagues, where a propensity-score overlap weighted analysis found AA to associated with 2.7-fold higher odds of achieving effective hemostasis and greater than 60% reduced relative odds of 30-day mortality when compared to 4F-PCC [21]. A notable difference between analyses was the inclusion criteria for each. We included patients with GCS < 7 and admission ICH volumes ≥ 30 mL; however, these patients were excluded from the analysis by Costa et al. Additionally, they included patients with primary SAH in the analysis of the composite primary outcome, while those individuals were

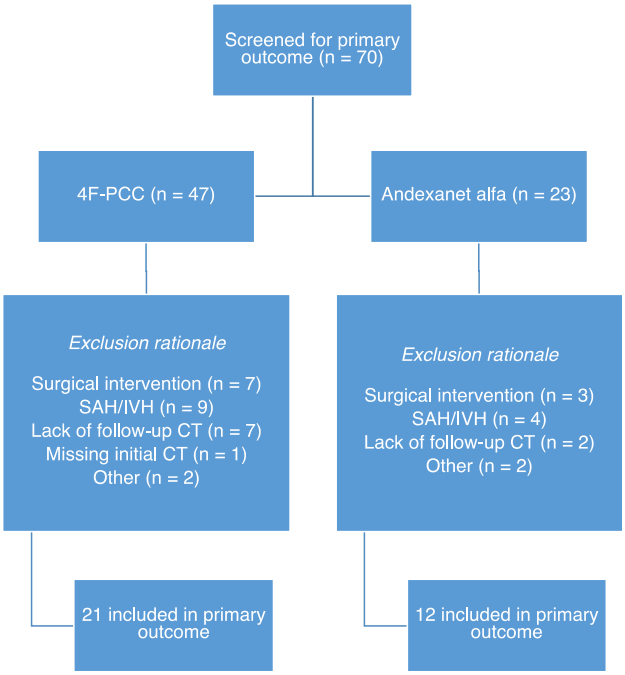

Fig. 1 Patient selection for primary outcome analysis

excluded from our analysis of hemostatic efficacy. Dosing of 4F-PCC also differed between studies. All patients who received 4F-PCC in our study were dosed at 50 units/kg, while only 13.9% of patients in Costa et al. received that same weight-based dose with the majority receiving lower doses of 25 units/kg [21].

Patients that survive an ICH often have significant morbidity [2]. The median mRS, GOS, and CPC scores for this cohort were 5, 3, and 3, respectively. Each of these are indicative of severe disability in which patients are unable to carry out activities of daily living without nursing care and attention [14–16]. More than half of the patients that were discharged alive were sent to rehabilitation centers or skilled nursing facilities (SNF) and long-term acute care hospitals (LTACH). Patients in the AA group were more likely to be discharged to a SNF/LTACH (43.5% vs 6.4, $p = 0.0004$) whereas patients in the 4F-PCC were more likely to be discharged to a rehabilitation facility (36.2 vs 8.7, $p = 0.02$). According to the Centers for Medicare and Medicaid services, a rehabilitation facility is that which provides comprehensive rehabilitation services under the supervision of a healthcare provider to patients with physical disabilities. Patients requiring higher levels of care are often more appropriately placed at a SNF which is a facility with specific regulatory certification requirements that offers skilled nursing care including medical, nursing, and/or rehabilitative services that does not meet the level of care in an inpatient hospital. [22] These findings may be explained by the higher ICH scores observed in the AA group. There are additional confounding variables that contribute to a patient's discharge disposition including insurance coverage and placement availability that we were unable to account for in this study.

This small, exploratory study is not without limitations. The study included a small sample size and was not powered to detect a difference in the primary outcome. The inability to calculate accurate hematoma volumes for SAH and IVH and lack of follow-up CT imaging limited the number of patients evaluated in the primary outcome. We were unable to collect information regarding blood products and quantities administered after DOAC reversal due to documentation limitations in the EMR. Additionally, data was pulled from the EMR at our institution alone. Missing or incomplete information may have impacted our results including readmissions to outside institutions affecting accuracy of long-term outcomes or thrombotic complications. Finally, our findings are representative of a patient population that received anticoagulation reversal for ICH associated with apixaban or rivaroxaban use, thus limiting

Table 3 Binomial logistic regression predicting likelihood of good or excellent hemostatic efficacy based on age, anticoagulant use, baseline ICH score, ICH blood volume, gender, and reversal agent

	B	*SE*	*Wald*	*df*	*p*	Odds ratio	95% CI for Odds ratio	
							Lower	Upper
Age	0.037	0.037	0.986	1	0.321	1.037	0.965	1.115
Anticoagulant[a]	0.250	1.093	0.052	1	0.819	1.284	0.151	10.949
Baseline ICH score	0.123	0.638	0.037	1	0.848	1.130	0.324	3.945
ICH blood volume	0.103	0.064	2.640	1	0.104	1.109	0.979	1.256
Gender[b]	0.907	1.135	0.638	1	0.424	2.477	0.268	22.920
Reversal agent[c]	0.327	1.386	0.056	1	0.814	1.386	0.092	20.985
Constant	-4.450	3.471	1.644	1	0.200	0.012		

ICH intracranial hemorrhage

[a]Anticoagulant is for rivaroxaban compared to apixaban

[b]Gender is for females compared to males

[c]Reversal agent is for andexanet alfa compared to 4-factor prothrombin complex concentrates

the generalizability of findings to other life-threatening indications (e.g. gastrointestinal hemorrhages) or bleeding associated with edoxaban or betrixaban.

Conclusion

There was no significant difference found in the rate of effective hemostasis when patients with DOAC-associated ICH were treated with 4F-PCC or andexanet alfa. However, due to the limited number of patients evaluated and retrospective nature of our study, further research with larger, prospective randomized controlled trials is needed.

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Declarations

Conflict of interest The authors have no potential conflicts of interest to declare with respect to research, authorship, and/or publication of this manuscript.

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