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Factor Xa Inhibitor-Related Intracranial Hemorrhage (FiX-ICH): Results from a Multicenter, Observational Cohort Receiving Prothrombin Complex Concentrates

Running Title: *Panos et al.; PCC & Intracranial Hemorrhage from FXa Inhibitors*

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Abstract

Background: Since the approval of the oral factor Xa (FXa) inhibitors, there have been concerns regarding the ability to neutralize their anticoagulant effects after intracranial hemorrhage (ICH). Multiple guidelines suggest using prothrombin complex concentrates (PCC) in these patients based upon research that includes a limited number of patients with ICH. Given this, we aimed to evaluate the safety and efficacy of PCC for FXa inhibitor-related ICH in a large, multicenter cohort of patients.

Methods: This was a multicenter, retrospective, observational cohort study of patients with apixaban or rivaroxaban-related ICH who received PCC between January 1, 2015 and March 1, 2019. The study had two primary analysis groups: safety and hemostatic efficacy. The safety analysis evaluated all patients meeting inclusion criteria for the occurrence of a thrombotic event, which were censored at hospital discharge or 30 days following PCC administration. Patients with intracerebral, subarachnoid, or subdural hemorrhages who had at least one follow-up image within 24 hours of PCC administration were assessed for hemostatic efficacy. The primary efficacy outcome was the percentage of patients with excellent or good hemostasis based upon the modified Sarode criteria. Secondary outcomes included an evaluation of in-hospital mortality, length of stay, infusion-related reactions and thrombotic event occurrence during multiple pre-defined periods.

Results: A total of 663 patients were included and assessed for safety outcomes. Of these, 433 patients met criteria for hemostatic efficacy evaluation. We observed excellent or good hemostasis in 354 patients (81.8%; 95% confidence interval 77.9 – 85.2). Twenty-five (3.8%) patients had a total of 26 thrombotic events, of which 22 occurred in the first 14 days following PCC administration. One patient had documentation of an infusion-related reaction. For the full cohort of patients, in-hospital mortality was 19.0% and the median intensive care unit and hospital length of stay were 2.0 and 6.0 days, respectively.

Conclusions: Administration of PCC after apixaban and rivaroxaban-related ICH provided a high rate of excellent or good hemostasis (81.8%) coupled with a 3.8% thrombosis rate. Randomized, controlled trials evaluating the clinical efficacy of PCC in patients with FXa inhibitor-related ICH are needed.

Key Words: anticoagulation; intracerebral hemorrhage; subarachnoid hemorrhage

Non-standard Abbreviations and Acronyms

4PCC – Four factor prothrombin complex concentrate
aPCC – Activated prothrombin complex concentrate
CT - computed tomography
DVT – deep vein thrombosis
FXa - Factor Xa
ICH – intracranial hemorrhage
ICU – intensive care unit
MRI - magnetic resonance imaging
NCS - Neurocritical Care Society
PE – pulmonary embolism
PCC – prothrombin complex concentrate
REDCap - Research Electronic Data Capture

UPRATE - Unactivated Prothrombin Complex Concentrates for the Reversal of Anti-factor Ten inhibitors

Clinical Perspective

What is new?

- This is the largest multicenter, observational study to date to evaluate the hemostatic efficacy and safety of prothrombin complex concentrate (PCC) administration in patients with an apixaban or rivaroxaban-related intracranial hemorrhage.
- This study demonstrated a high rate (81.8%) of excellent or good hemostasis based upon the modified Sarode criteria, where providers with neuroscience experience reviewed images and independent study personnel adjudicated the primary hemostatic efficacy outcome.
- Administration of PCC was associated with a low rate of thrombotic events (3.8%) occurring during hospitalization with most events occurring within 14 days of PCC administration.

What are the clinical implications?

- This study provides valuable, pragmatic insight into the clinical effectiveness of PCC for apixaban and rivaroxaban-related ICH.
- In the absence of prospective trials and in alignment with several international guideline recommendations, PCC is a reasonable treatment for the management of apixaban or rivaroxaban-related intracerebral hemorrhages when a target-specific antidote is not available.
- Randomized, controlled trials evaluating the clinical efficacy of PCC in patients with FXa inhibitor-related ICH are needed.

Introduction

Since the approval of the oral factor Xa (FXa) inhibitors, there have been concerns regarding the ability to neutralize their anticoagulant effects after life-threatening bleeding.[1] Guidelines for the treatment of antithrombotic-associated intracranial hemorrhage (ICH) published in 2016 suggested the administration of prothrombin complex concentrates (PCC; both activated [aPCC] and four-factor [4PCC]) based upon evidence available in healthy subjects.[2] However, a target-specific antidote was approved by the United States Food and Drug Administration in 2018. Despite this, recent guidelines published by the American Society of Hematology and the European Stroke Organization continue to suggest PCC administration as a treatment option for life-threatening bleeding during FXa inhibitor treatment. In making these recommendations, the guideline panels cited the lack of comparative trials between available agents to guide decision making.[3,4]

Since PCCs have not been directly evaluated by the United States Food and Drug Administration for this indication, the mechanism by which they exert their hemostatic effect has been the subject of ongoing study. Research performed in healthy volunteers demonstrated that increased thrombin generation through replenishment of coagulation factors, but no changes in FXa activity after PCC administration.[5] Two recent, prospective studies evaluating PCC use in life-threatening hemorrhage from FXa inhibitors demonstrated low rates of hematoma expansion in those with ICH, however, these studies included less than 100 total patients with ICH.[6,7] Other observational studies have been conducted, but their results are limited due to small sample size and a lack of standardized assessment for hemostatic efficacy.[8–14] Given the current gaps in the literature, we aimed to evaluate the safety and efficacy of PCC for apixaban or rivaroxaban-related ICH in a large, multicenter cohort of patients utilizing similar safety and efficacy criteria used in recent anticoagulation reversal trials.[15,16]

Methods

Our study group is currently completing a large, retrospective, multicenter cohort study evaluating clinical outcomes between PCC and andexanet alfa (coagulation factor Xa-[recombinant], inactivated-zhzo). Due to the more limited number of participating sites utilizing andexanet alfa as the preferred agent at this time, data collection for this study is ongoing. The results presented here are from a pre-planned analysis of patients treated with PCC for FXa inhibitor-related ICH. Representatives from the Neurocritical Care Society (NCS) Pharmacy Study Group and the primary site, Rush University Medical Center, coordinated the study. The PCC cohort includes data from 26 participating medical centers, all of which have been designated as a certified stroke center by the American Heart Association / American Stroke Association (3 primary; 23 comprehensive). Each site agreed to participate on a voluntary basis as no funding was obtained to complete the study. The study protocol was approved by institutional review boards at each site and the requirement for informed consent was waived. All study activities were led by a steering committee who solicited sites to participate, coordinated data use agreements, created the study database, evaluated the integrity of the data entered, adjudicated the primary efficacy outcome based upon the recorded hematoma measurements, analyzed the data, and wrote all drafts of the manuscript. The steering committee had access to all complete data and takes responsibility for its integrity and the data analysis. Investigators from the participating sites reviewed and approved the protocol, collected data, and approved the final manuscript. Each is included as members of the NCS Pharmacy Study Group (Supplemental Table 1). The authors declare that all supporting data are available within the article and its online supplementary files. Full data will not be made available to other researchers for purposes of reproducing the results or replicating the procedure until completion

of the ongoing multicenter cohort study evaluating clinical outcomes between PCC and andexanet alfa that was previously discussed is complete.

The analysis includes patients treated with PCC between January 1, 2015 and March 1, 2019. Patients were eligible if they were at least 18 years of age, presented with a spontaneous or traumatic hemorrhage into any intracranial compartment, were determined to have taken a dose of apixaban or rivaroxaban in a time frame prior to hospital presentation that warranted administration of PCC, and received aPCC or 4PCC at the participating hospital. Excluded were patients with hemorrhages associated with other anticoagulant agents or liver disease, known to be pregnant or lactating, with lack of follow-up assessment to assess safety and efficacy due to withdrawal of life sustaining measures within 24 hours of hospital admission, enrolled in any prospective study investigating andexanet alfa, and prisoners. Patients were further excluded from the hemostatic efficacy analysis if they did not have at least one follow-up image of the brain within the first 24 hours of PCC administration.

Data was primarily collected by critical care or emergency medicine pharmacists at each site and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Rush University Medical Center. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.[17,18] Prior to data collection, participants were provided with a training video regarding the protocol and data entry into REDCap to ensure uniform understanding and assessment of data points across each site. Data collected included demographic information, past medical history, pre-admission

anticoagulation and antiplatelet medication information, neurologic injury information including neurosurgical procedures performed, baseline laboratory values pertaining to coagulation and renal function, resumption of anticoagulation, discharge outcomes, and all information related to hemostatic agents administered. We were unable to record the exact timing of the last apixaban or rivaroxaban dose due to lack of uniform documentation across all participating sites. Following the identification of included patients, a licensed independent provider from each site with specialty experience in neurocritical care, neurology, or neurosurgery reviewed all computed tomography (CT) or magnetic resonance imaging (MRI) scans of the head and recorded hematoma measurements. For patients with hemorrhages into multiple compartments, the largest bleeding component was designated as the primary hemorrhage site. The provider evaluating hematoma size recorded the measurements, but did not adjudicate the hemostatic efficacy outcome at the time of image evaluation. Percent change in hematoma size was calculated by subtracting the baseline hematoma size from the size recorded on each follow-up image obtained within 24 hours of PCC administration, with the difference divided by the original hematoma size and converted to a percentage. The largest percent expansion between each scan was used to adjudicate the primary hemostatic efficacy outcome, which was done by the steering group at the completion of data entry. Patients were classified as having excellent hemostasis if a 0-20.0% increase in hematoma size was seen when each follow-up CT or MRI was compared to baseline imaging, good hemostasis if the increase was 20.1-35.0%, and poor hemostasis if the increase was greater than 35.0%. Further details on the methods used for hematoma assessment are outlined in Supplemental Table 2.

The study had two primary analysis groups: hemostatic efficacy and safety. The hemostatic efficacy analysis included patients with intracerebral, subarachnoid, or subdural

hemorrhages who had at least one follow-up image obtained within 24 hours of PCC administration to assess hematoma size. Patients with primary epidural or any intraventricular hemorrhage were not included in the hemostatic efficacy analysis due to the lack of clear criteria to assess hemostasis in these hemorrhage types in the prespecified criteria used in the study.[16] The primary efficacy outcome was the percentage of patients with excellent or good hemostasis as defined by prespecified criteria developed by Sarode and colleagues that has been used in previous studies.[15,16,19] The primary safety outcome was the occurrence of a thrombotic event during hospitalization, with events censored at 30 days. The safety analysis included all enrolled patients, including those who underwent neurosurgical procedures, to capture the most comprehensive assessment of thrombotic risk associated with PCC use. Thrombotic events included upper and lower extremity deep vein thrombosis (DVT), pulmonary embolism (PE), acute ischemic stroke, myocardial infarction, or any other documented thrombosis. Physician progress notes were assessed to identify the development of thromboembolic events, with relevant documentation of radiologic imaging techniques and laboratory markers assessed, as appropriate. These included doppler ultrasound reports for DVT, CT pulmonary angiography for PE, neuroimaging for acute ischemic stroke, and electrocardiogram and/or troponin elevation for myocardial infarction. Secondary safety outcomes included evaluation of infusion-related reactions and an assessment of thrombotic events during pre-defined periods (post-PCC administration days 0-5, 6-14, and 15-30). Other outcomes reported included in-hospital mortality, as well as duration of intensive care unit (ICU) and hospital stay.

Statistical Analysis

All continuous data are reported as mean (± standard deviation) or median (25-75% interquartile range). Categorical variables are expressed as frequencies (number of patients and percentages).

Percentage of patients with excellent or good hemostasis are presented with a 95% confidence interval calculated with a binomial test and Jeffreys interval.[20] We also conducted an analysis to identify any difference in in-hospital mortality comparing those with poor versus excellent/good hemostatic efficacy using a chi-square test. All tests for statistical significance were two-tailed and statistical significance was established at the $P<0.05$ threshold. All analyses were performed using SPSS, Version 26.0 (SPSS, Inc., Chicago, IL).

Results

A total of 663 patients were included (Figure 1) and followed until hospital discharge. The primary indication for anticoagulation was atrial fibrillation (Table 1). Other prominent medical history included diabetes mellitus (27.6%), ischemic stroke (22.8%), DVT (15.5%), and myocardial infarction (9.4%; Supplemental Table 3). There were 366 patients (55.2%) being treated with apixaban and 297 (44.8%) with rivaroxaban. Intracerebral hemorrhage occurred in 299 (45.1%) patients, subdural hematoma in 229 (34.5%) and subarachnoid hemorrhage in 96 (14.5%). The median GCS score on presentation was 14 [11-15], with 9.2% of patients having scores < 7. Further information regarding patient, neurologic, and treatment characteristics is included in Supplemental Tables 3 through 5.

Overall, 514 patients (77.5%) received 4PCC at a median initial dose of 43.8 [25.6 – 49.8] units per kilogram (kg). The remaining 149 patients (22.5%) received aPCC at a median initial dose of 26.7 [23.8 – 48.3] units per kg. The median time to PCC administration from hospital presentation amongst all 663 patients was 2.6 [1.5-4.3] hours. A second dose of PCC was administered to 34 patients (5.1%). A detailed summary of each repeat dose and the clinical reasoning for repeat dosing is provided in Supplemental Table 6.

Hemostatic Efficacy Analysis

A total of 433 patients (65.3%) met criteria for inclusion in the hemostatic efficacy analysis, of which 354 (81.8%) were determined to have an excellent or good hemostasis (Table 2). With each hemorrhage type, the majority of patients were rated as having excellent hemostasis. Of the 79 patients determined to have poor or no hemostasis, 74 cases were identified on the first follow-up imaging and 5 occurred on the second. In-hospital death occurred in 53 (12.2%) patients (Table 3) and was more common in those with poor (16 of 79 cases [20.3%]) versus excellent or good (37 of 354 cases [10.5%]) hemostasis (p=0.02). Median ICU and hospital length of stay in those assessed for hemostasis were 2.0 and 6.0 days, respectively. A breakdown of clinical outcomes by hemorrhage type for patients included in the hemostatic efficacy analysis is found in Supplemental Table 7.

Safety Analysis

Twenty-five (3.8%) of the 663 patients had a thrombotic event documented during hospitalization. The majority of events (22 of 25) occurred within 14 days of PCC administration (Table 4). Fourteen patients with a DVT had a lower extremity thrombus, with the one remaining patient having an upper extremity event. Six DVTs were identified after symptoms (pain, swelling, or fever) prompted a Doppler ultrasound, with the remaining events being asymptomatic in nature and found on surveillance ultrasound. One patient experienced a PE that was diagnosed via ventilation-perfusion scan after worsening respiratory status was noted. Amongst the 10 arterial events, eight patients had an acute ischemic stroke identified on repeat brain imaging. Seven patients experienced alterations in mental status that prompted repeat imaging, while one patient was found to have an event on a routine repeat head CT. All patients with an acute ischemic stroke had a history of atrial fibrillation, with four patients

having documentation that their event was secondary to cardioembolism. Of the remaining four patients, three had documentation that their acute ischemic stroke cause was potentially non-cardioembolic and one the cause was unknown. Amongst the two patients who experienced a myocardial infarction, both were diagnosed based upon elevated troponin levels without the presence of other symptoms and required no cardiac intervention.

When assessed based upon individual PCC agent received, 8 of the 149 patients treated with aPCC experienced a total of 9 thrombotic events (6 DVT, 1 PE, 2 myocardial infarction) and 18 of the 514 patients treated with 4PCC had a total of 18 thrombotic events (9 DVT, 8 ischemic stroke). There was one documented infusion-related reaction in a patient who received aPCC. Anticoagulation was restarted during hospitalization in 39 (5.9%) patients at a median of 8.2 [5.2 – 13.9] days from hospital admission. One thrombotic event (DVT) occurred after anticoagulation was restarted. A total of 126 (19.0%) patients in the safety analysis died during their hospital admission (Table 3). A breakdown of clinical outcomes by hemorrhage type for patients included in the safety analysis is found in Supplemental Table 8.

Discussion

Our study provides the largest, most comprehensive clinical assessment to date regarding the safety and efficacy of PCC use following FXa inhibitor-related ICH. We observed a high rate of excellent or good hemostasis (81.8%) coupled with a 3.8% thrombosis rate. Our results provide support to current guideline recommendations that suggest PCC is a viable treatment option in this population and add valuable insight into the clinical implications of using PCC for treating apixaban and rivaroxaban-induced ICH in the real-word setting.[2,3]

Overall, we observed higher rates of effective hemostasis than seen in previous literature evaluating PCC use in FXa inhibitor-related ICH. We identified numerous studies that previously reported on similar efficacy outcomes in this population.[6–11,13,14,21,22] While several of these studies defined hemostatic efficacy based upon established criteria, their results are limited by a lack of clear methodologic details regarding the method in which hematoma volumes were assessed.[9–11,13,14,22] The remaining studies we identified evaluated hemostatic efficacy using differing sets of established criteria and included less than 300 patients with ICH. First, the Unactivated Prothrombin Complex Concentrates for the Reversal of Anti-factor Ten inhibitors (UPRATE) study reported effective hemostasis in 72.9% of the 59 ICH patients evaluated.[6] Effective hemostasis was defined as less than 35% hematoma expansion between baseline and follow-up imaging combined with no deterioration in neurologic status.[23] A second prospective, observational study included 36 ICH patients and used the same efficacy criteria as our study, observing excellent or good hemostasis in 83.3% of patients.[7] Conversely, Frontera and colleagues used the same criteria in 32 ICH patients, finding a lower rate of excellent or good hemostasis (69%).[21] Finally, a study of 94 intracerebral hemorrhage patients receiving apixaban and rivaroxaban observed that 64.9% of those treated with PCC had their hematoma expand by less than 33% between baseline and follow-up imaging.[8] While a recent meta-analysis on this subject was completed, we are unable to discuss our data in the context of these results because an analysis specific to patients with ICH was not performed.[24] In our assessment of hemostatic efficacy, we also assessed each follow-up image obtained within 24 hours of PCC treatment, with the median time to first follow-up image being 6.1 hours. The timing of repeat imaging in our study is within the 6-24 hours period recommended by the International Society of Thrombosis and Haemostasis and also similar to strategies used in literature evaluating warfarin-

associated ICH.[16,19] It is notable that these recommendations apply to all intracranial bleed types and are not specific to intracerebral hemorrhage, where there is stronger evidence suggesting the time at which peak hematoma expansion occurs.[25] We also included 120 patients who had a second follow-up image during our study period, allowing extra opportunity to capture further hematoma expansion.

In terms of safety, thromboembolic events may occur following PCC administration for multiple reasons. Patients receiving FXa inhibitors have medical conditions that predispose them to the development of thromboembolism, especially when the medication is stopped abruptly. Secondly, PCC contains coagulation factors that promote clot development. A recent meta-analysis of PCC use in FXa inhibitor-related hemorrhage found that 3.0% of patients experienced a thrombotic event when follow-up was limited to 30 days or less.[24] In theory, patients receiving PCC would be at risk for thromboembolism development for approximately 14 days following treatment based upon the pharmacokinetics of the coagulation factors contained in the products. Factor II has the longest half-life (60 hours) and it would take approximately 14 days, or five half-lives, for it to be below levels that would contribute to thromboembolism development.[12] In the current study, the 30-day thrombotic event rate was 3.8%, with 3.3% of patients having an event within 14 days of PCC. A study of 43 patients with multiple hemorrhage types also observed a low thrombotic event rate of 2.1% at 14 days.[12] While the most common type of event in our study was a DVT, we do recognize that PCC administration carries a risk of arterial thrombotic events, as experienced by 10 patients in our study. While all patients who experienced an acute ischemic stroke had a history of atrial fibrillation, only four of these events were presumed to be secondary to cardioembolism. Notably, 6 of the 8 acute ischemic strokes did occur in the first 5 days following PCC administration. Two patients who

had a documented myocardial infarction received this diagnosis based upon elevated myocardial enzymes only, did not require intervention, survived their hospital stay, and were discharged to inpatient rehabilitation for further care.

In-hospital mortality rates have varied greatly in studies of PCC use in FXa inhibitor-related ICH. With a few exceptions, most of the current evidence does not report a mortality rate specific to patients with ICH. The UPRATE trial reported a 22.0% mortality rate in those with ICH, while a retrospective study of patients with traumatic ICH reported 22.9% in-hospital mortality.[26] Additionally, a retrospective, observational study conducted in Germany reported a discharge mortality rate of 20.0% amongst 103 patients with apixaban and rivaroxaban-related intracerebral hemorrhage treated with PCC.[12] In-hospital mortality in our study (19.0%) was similar to the aforementioned studies and is also similar to ICH-specific mortality reported with other agents used for this indication.[27] Notably, the mortality rate observed in our study includes those with an admission GCS < 7, those who underwent neurosurgical procedures within 12 hours, those with baseline hematoma volumes > 60 mL, and those not expected to survive 30 days. When mortality in our study was evaluated only in those with admission GCS 7-15 and at 30 days, it was 11.8%. We also provide additional data related to deaths that may have occurred following discharge by reporting the percentage of patients discharged to hospice.

The most important limitation to our study is that it is an observational cohort study. Due to this, there may have been variability in treatment patterns between each site, including dose and type of PCC used, as well as imaging modalities and overall treatment patterns related to ICH. Additionally, we were unable to evaluate hemostatic efficacy on 230 patients included in the safety analysis for reasons previously discussed. The exclusions of these patients may have impacted the rate of effective hemostasis observed in our cohort. Our ability to assess for the

development of thrombotic events was also limited to hospital discharge, which may have impacted the observed event rate. While we excluded those who made the decision within 24 hours of admission to withdraw aggressive treatment measures, we did not exclude those whose care patterns changed later, which may have influenced our overall mortality rate. As previously discussed, we are unable to report the confirmed time of last FXa inhibitor dose due to challenges faced in clinical practice related to obtaining and consistently documenting this information. While it is possible that patients may have ingested their last dose greater than 24 hours prior to presentation, we feel our approach represents a realistic assessment of the challenges clinicians face when evaluating these patients. Additionally, our study did not evaluate the correlation between hemostatic efficacy and anti-Xa activity levels. In our cohort, 98 (14.8%) patients had anti-Xa activity measured prior to PCC administration. Two medical centers reported using an assay specific to the FXa inhibitors in a total of 8 patients, with the remaining measurements being based upon heparin or low molecular weight heparin anti-Xa activity assays. The lack of FXa inhibitor-specific assay measurements suggests that the clinical outcome of intracranial hematoma enlargement, not changes in laboratory measurements, is used by most of the institutions who participated in our study. In our safety assessment, we did not evaluate agent used or timing of venous thromboembolism prophylaxis initiation and we relied upon documentation in the electronic medical record to assess this outcome. Both of these factors could have impacted the observed rate of thromboembolic events. However, the two prospective studies of PCC use in this population also used retrospective review of hospital records to assess for documentation of thrombotic events.[6,7]

Strengths of this study include the multicenter design and large number of patients included. Additionally, all patient information was abstracted directly from the medical record

and did not rely on coding or claim data. We included patients treated at medical centers from multiple geographic regions of the United States, as well as multiple patient populations of interest that were excluded from previous studies of anticoagulation reversal. Notably, all of the participating medical centers (23 of 26 being a comprehensive stroke center) are designated as a stroke center by the American Heart Association / American Stroke Association, which aids in reducing variations in care between sites. All of these factors aid in increasing the generalizability of our results to a broad population of patients in the United States with FXa inhibitor-related ICH. We also employed several strategies into the study design to reduce bias associated with the study results. While we were unable to have a single provider review each image in a centralized database, we attempted to minimize bias by having each individual image assessed by site-specific providers with specialty experience in neurocritical care, neurology, or neurosurgery. The outcome of hemostatic efficacy was then adjudicated by the steering group based upon the recorded measurements and the predefined criteria used. Furthermore, the primary investigator at each site was provided with a training video regarding the protocol to ensure uniform understanding and assessment of data points across each site.

Conclusions

PCC administration after apixaban and rivaroxaban-related ICH achieved an 81.8% rate of effective hemostasis with a thrombosis rate of 3.8%. This study also provides valuable, pragmatic insight into the clinical effectiveness of PCC that are observed in current practice. Finally, randomized, controlled trials evaluating the clinical efficacy of PCC in patients with FXa inhibitor-related ICH are needed.

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Table 1. Baseline Patient Characteristics

Characteristic	Safety Analysis N=663	Hemostatic Efficacy Analysis N=433
Age group (years), n (%)		
<65	97 (14.6)	54 (12.5)
65-75	175 (26.4)	106 (24.5)
>75	391 (59.0)	273 (63.0)
Male, n (%)	361 (54.4)	231 (53.3)
Caucasian race, n (%)	522 (78.7)	356 (82.2)
Weight, kilograms	82.2 ± 21.6	80.6 ± 21.3
Body mass index*	28.1 ± 6.5	27.6 ± 6.3
Estimated creatinine clearance†	70.4 ± 34.2	67.2 ± 32.9
< 30 ml/min, n (%)	52 (7.8)	37 (8.5)
30 – 60 ml/min, n (%)	199 (30.0)	146 (33.7)
≥60 ml/min, n (%)	339 (51.1)	197 (45.5)
Missing data, n (%)	73 (11.0)	53 (12.2)
Primary anticoagulation indication, n (%)		
Atrial fibrillation	521 (78.6)	337 (77.8)
Venous thromboembolism prophylaxis	12 (1.8)	11 (2.5)
Venous thromboembolism treatment	102 (15.4)	69 (15.9)
Other‡	28 (4.2)	16 (3.7)
Factor Xa inhibitor, n (%)		
Apixaban	366 (55.2)	234 (54.0)
Rivaroxaban	297 (44.8)	199 (46.0)
Primary intracranial hemorrhage site, n (%)		
Intracerebral	299 (45.1)	172 (39.7)
Subarachnoid	96 (14.5)	68 (15.7)
Subdural	229 (34.5)	193 (44.6)
Epidural	5 (0.8)	--
Intraventricular	34 (5.1)	--
Multicompartment hemorrhage, n (%)	155 (23.4)	103 (23.8)
Traumatic injury, n (%)	339 (51.1)	265 (61.2)
Admission GCS score§	14 [11-15]	15 [14-15]
3-6	61 (9.2)	21 (4.8)
7-15	585 (88.2)	404 (93.3)
Missing data	17 (2.6)	8 (1.8)
PCC administered		
Activated PCC	149 (22.5)	118 (27.3)
Four-factor PCC	514 (77.5)	315 (72.7)

Data are reported as mean + standard deviation unless otherwise noted; ESRD = end stage renal disease; GCS = Glasgow Coma Scale; min= minute; mL = milliliters; PCC=Prothrombin Complex Concentrate; *Weight in kilograms divided by the square of the height in meters; †Estimated according to the Cockcroft-Gault formula; ‡Other indications documented included mechanical heart valve, peripheral arterial disease, embolic stroke of unknown source, cardiac stents, heart failure, portal vein thrombosis, hypercoagulable disorder, and unknown; §Data reported as median [25-75% interquartile range]

Table 2. Hemostatic Efficacy Assessment

Subgroup	Percent with Excellent or Good Hemostasis (95% Confidence Interval)
Overall (n=433)	81.8 (77.9 – 85.2)
Factor Xa inhibitor	
Apixaban (n=234)	79.5 (74.0 – 84.3)
Rivaroxaban (n=199)	84.4 (78.9 – 88.9)
Sex	
Male (n=231)	81.8 (76.5 – 86.4)
Female (n=202)	81.7 (75.9 – 86.5)
Primary intracranial hemorrhage site	
Intracerebral (n=172)	73.3 (66.3 – 79.4)
Subarachnoid (n=68)	85.3 (75.5 – 92.2)
Subdural (n=193)	88.1 (83.0 – 92.1)
Hemorrhage mechanism	
Traumatic (n=265)	81.9 (76.9 – 86.2)
Spontaneous (n=168)	81.5 (75.2 – 86.8)
Age (years)	
<65 (n=54)	77.8 (65.4 – 87.2)
65-75 (n=106)	87.7 (80.5 – 92.9)
>75 (n=273)	80.2 (75.2 – 84.6)
PCC administered	
Activated PCC (n=118)	88.1 (81.4 – 93.0)
Four-factor PCC (n=315)	79.4 (74.6 – 83.6)
Receiving concurrent antiplatelet agents prior to hospital presentation (n=171)	83.0 (76.9 – 88.1)

GCS = Glasgow Coma Scale; PCC= prothrombin complex concentrate

Table 3. Overall Clinical Outcomes for All Hemorrhage Types

	Safety Analysis (N=663)	Hemostatic Efficacy Analysis (N=433)
Hospital discharge disposition, n (%)		
Home	156 (23.5)	132 (30.5)
Inpatient rehab facility	171 (25.8)	110 (25.4)
Skilled nursing facility	136 (20.5)	99 (22.9)
Long-term acute care hospital	23 (3.5)	12 (2.8)
Hospice	51 (7.7)	27 (6.2)
Death	126 (19.0)	53 (12.2)
ICU length of stay (days)	2.8 [1.1-6.8]	2.0 [1.0–4.5]
Hospital survivors	2.5 [1.0-5.7]	2.0 [0.9–4.0]
Hospital non-survivors	4.0 [2.0-8.5]	4.0 [2.0-9.1]
Hospital length of stay (days)	7.0 [3.7-12.0]	6.0 [3.3–10.0]
Hospital survivors	7.0 [3.9-12.6]	6.0 [3.5-9.9]
Hospital non-survivors	6.0 [2.4-10.4]	6.0 [2.3-11.4]

ICU = intensive care unit; All data are presented as median [25-75% interquartile range] unless otherwise noted

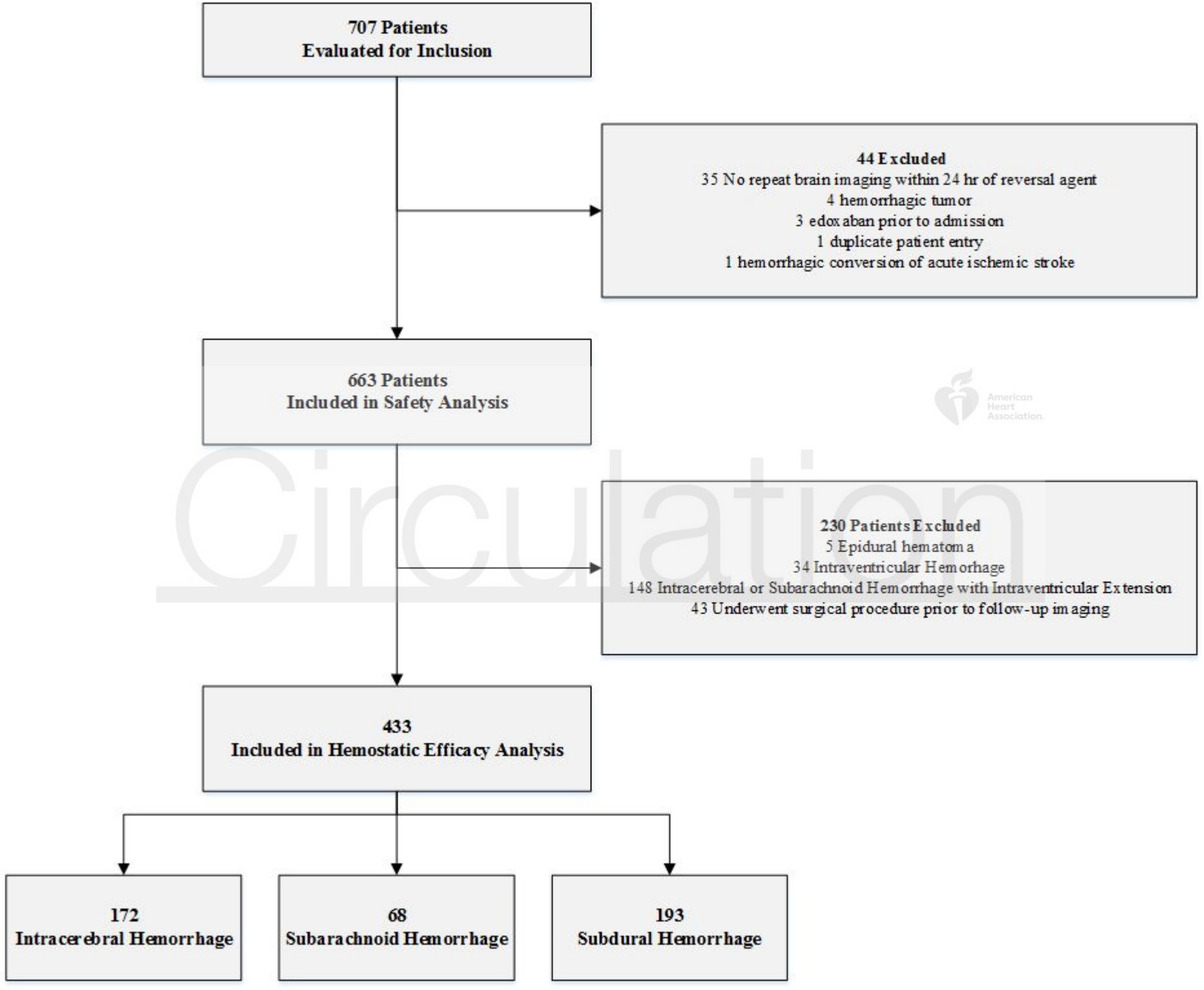
Table 4. Timing of thrombotic events, anticoagulation initiation, and in-hospital death in the safety analysis

Variable	Total	Days after PCC		
		0-5	6-14	15-30
Patients with any thrombotic event, n (%)[*]	25 (3.8)	13 (2.0)[†]	9 (1.4)[†]	4 (0.6)
Deep-vein thrombosis, n	15	6	5[‡]	4
Pulmonary embolism, n	1	0	1	0
Acute ischemic stroke, n	8	6	2	0
Myocardial infarction, n	2	1	1	0
Patients with therapeutic anticoagulation restarted, n (%)[§]	39 (5.9)	13 (2.0)	17 (2.6)	9 (1.4)
In-hospital death, n (%)[‖]	126 (19)	60 (9.0)	49 (7.4)	13 (2.0)

*Patients may have experienced more than one thrombotic event; [†]Number of patients with thrombotic events during three time periods equals 26 because 1 patient experienced a myocardial infarction on hospital day 2 and a pulmonary embolism on hospital day 6; [‡]All thrombotic events occurred prior to restarting therapeutic anticoagulation with the exception of 1 patient who experienced a deep-vein thrombosis on post-PCC day 6 after therapeutic anticoagulation had been restarted for 48 hours; [§]Includes the use of therapeutic doses of unfractionated heparin, low-molecular-weight heparin, or any oral anticoagulant at any dose and for any duration; [‖]Four patients (0.6%) expired after 30 days

Figure Legend

Figure. Flow Diagram of Included Patients


707 Patients
Evaluated for Inclusion
44 Excluded
35 No repeat brain imaging within 24 hr of reversal agent
4 hemorrhagic tumor
3 edoxaban prior to admission
1 duplicate patient entry
1 hemorrhagic conversion of acute ischemic stroke
663 Patients
Included in Safety Analysis
230 Patients Excluded
5 Epidural hematoma
34 Intraventricular Hemorhage
148 Intracerebral or Subarachnoid Hemorrhage with Intraventricular Extension
43 Underwent surgical procedure prior to follow-up imaging
433
Included in Hemostatic Efficacy Analysis
172
Intracerebral Hemorrhage
68
Subarachnoid Hemorrhage
193
Subdural Hemorrhage