

Critical Review Form Therapy

Pham H, Medford WG, Horst S, et al. Andexanet alfa versus four-factor prothrombin complex concentrate for the reversal of apixaban- or rivaroxaban-associated intracranial hemorrhages. Am J Emerg Med. 2022 May;55:38-44.

Objectives: “to compare efficacy and safety of AA [andexanet alfa] versus 4F-PCC [four factor prothrombin complex concentrate] for the reversal of apixaban- or rivaroxaban- associated intracranial hemorrhage [ICH].” (p. 39)

Methods: This multicenter, retrospective chart review was conducted within a multi-center healthcare system and a stand-alone teaching hospital in central Florida between June 2016 and December 2020. Patients were identified by chart review for use of either AA or 4F-PCC during the study period. Patients aged 18 years or older who received either treatment, had documented neuroimaging of an ICH and documented home medication of apixaban or rivaroxaban were included. Patients who received by AA and 4F-PCC were excluded. Only patients who had a repeat CT scan after administration of a reversal agent were included in the primary outcome analysis.

AA was restricted to the following criteria: adult patients with acute, severe neurologic intracranial or spinal bleeding emergencies (i.e., ICH, primary or secondary intraventricular hemorrhage, subdural hematoma, epidural hematoma, or subarachnoid hemorrhage), and could only be ordered by neurosurgery, neurology, and critical care physicians, while emergency physicians could utilize it with approval by above physicians.

The primary outcome was the level of excellent hemostasis achieved after reversal agent administration, based on the standardized rating system of the [International Society on Thrombosis and Haemostasis \(ISTH\)](#). Secondary outcomes included changes in initial hemorrhage volume on CT 12 to 24 hours post-treatment, rate of thromboembolic events, inpatient mortality, and total cost.

A total of 109 patients were included in the analysis, with 47 in the AA group and 62 in the 4F-PCC group. The median age in the 2 groups was 77 and 81 years, respectively, and 66% and 51.6% were male. Of these, only 38 in the AA group and 58 in the 4F-PCC group underwent repeat CT scanning and were included in the primary outcome analysis.

Critical Review Form: Therapy

Guide

Comments

Are the results valid?

Did experimental and control groups being the study with a similar prognosis?

Were patients randomized?	No. This was a retrospective chart review in which treatment decisions, including reversal agent used, were at the discretion of the treating physicians. There is a high risk for selection bias .
Was allocation concealed? Was it possible to subvert the randomization to ensure a patient would be "randomized" to a particular group?	N/A.
Were patients analyzed in the groups to which they were randomized?	N/A. Patients were analyzed according to whether they received AA or 4F-PCC. Patients who received both reversal agents were excluded, although the authors do not specify how many patients (if any) were excluded for this reason.
Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. Patients were similar with respect to age, weight, anticoagulant used, type of ICH, presence of midline shift, and GCS and INR at presentation. More patients in the AA group were on low-dose (2.5 mg BID) apixaban (25.5% vs. 12.9%) while more patients in the 4F-PCC group were on rivaroxaban 20 mg daily (24.2% vs. 14.9%). Patients in the AA group were more likely to be male (66.0% vs. 51.6%).
Did experimental and control groups retain a similar prognosis after the study started?	
Were patients aware of group allocation?	Perhaps? While this was a retrospective study with no blinding performed, patients would not have been aware of study objectives and may not have been aware of what treatment they were getting. The risk of performance bias on the part of patients is low.
Were clinicians aware of group allocation?	Yes. Treatments were chosen at clinician discretion. While clinicians would not have been aware of study objectives, there is some risk of performance bias .
Were outcome assessors aware of group allocation?	Yes. There is no mention of blinding of outcome assessors, leaving some risk of observer bias .
Was follow-up complete?	No. Of 109 patients included, only 96 (88%) had a repeat CT scan and were hence included in the analysis of the primary outcome. Otherwise, all outcomes were assessed by review of the medical records from the index visit and hence would have been included.
What are the results?	
How large was the treatment effect?	- There were no significant differences in rates of excellent hemostasis (primary outcome) which 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 ($p = 1$; RR 1.0, 95% CI 0.77 to 1.31). - The result remained non-significant after adjusting for age, ICH score greater than or equal to four, regional mass effect, and presence of midline shift. - There was also no difference in rates of "good" hemostasis or "poor" hemostasis. - 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%]; RR 0.88, 95% CI 0.26 to 2.94), as was inpatient mortality prior to discharge (AA, 16 [34.0%] vs. 4F-PCC, 13 [21.0%]; RR 1.62, 95% CI 0.87 to 3.04). - The median total cost of treatment with AA was significantly more expensive (\$23,602) compared to 4F-PCC (\$6692).
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above. The 95% CI for mortality is fairly wide, and a 13% absolute difference in favor of 4F-PCC did not achieve statistical significance.

How can I apply the results to patient care?	
Were the study patients similar to my patient?	Likely yes. This study was conducted within a multicenter system in a large US metropolitan area that included a level I trauma center and satellite hospitals in the community. This would likely result in a similar patient population with similar management as seen in our healthcare system.
Were all clinically important outcomes considered?	The authors primary considered outcomes measurable by chart review, including measures of hemostasis, thrombotic events, and in-hospital mortality. While they reported functional outcomes at discharge for those patients in whom modified Rankin Scores were reported, these were reported in less than half of enrolled patients. No measures of long-term functional status or quality of life were presented.
Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study suggests that treatment with AA did not improve rates of excellent (or good) hemostasis or result in improved mortality, it was a retrospective study at high risk of selection bias. Results will need to be confirmed with randomized clinical trials.

Limitations:

1. This was a retrospective chart review in which treatment decisions, including reversal agent used, were at the discretions of the treating physicians. There is a high risk for [selection bias](#).
2. The authors do not provide details regarding the methodology of the chart review process ([Gilbert 1996](#) and [Worster 2004](#)).
3. There was no blinding, placing the results at risk of [performance bias](#) and [observer bias](#).
4. Despite [calculating a sample size](#) of 277 patients in each group necessary to provide sufficient power to detect a meaningful difference in outcomes, only 109 total patients were included ([The continuing unethical conduct of underpowered clinical trials](#)).
5. Functional outcomes at discharge were reported in less than half of enrolled patients and no measures of long-term functional status or quality of life were presented.

Bottom Line:

This retrospective, multicenter study found that in patients on anticoagulation with rivaroxaban or apixaban suffering intracranial hemorrhage requiring reversal of anticoagulation, AA and 4F-FFP resulted in similar rates of excellent hemostasis (95% CI 0.77 to 1.31) with no significant differences in thrombotic complication rates (RR 0.88, 95% CI 0.26 to 2.94) or mortality (RR 1.62, 95% CI 0.87 to 3.04). The median total cost of treatment with AA was significantly more expensive (\$23,602) compared to 4F-PCC (\$6692).).