Critical Review Form
Therapy

Dobesh PP, Fermann GJ, Christoph MJ, et al. Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study. Res Pract Thromb Haemost. 2023 Aug 30;7(6):102192.

Objectives: **"The primary objective was to compare in-hospital mortality in patients hospitalized with rivaroxaban- or apixaban-related major bleeding who were treated with andexanet alfa or 4F-PCC [4-factor prothrombin complex concentrate] in routine practice. A secondary objective was to assess potential predictors associated with the risk of in-hospital mortality." (p. 2)**

Methods: **This multicenter, retrospective cohort study sought to identify adults in the US hospitalized with rivaroxaban- or apixaban-related bleeds who received andexanet alfa (AA) or 4F-PCC, with discharge dates between May 2018 and September 2022. Hospital pharmacists and nurse navigators/coordinators with expertise and access to hospitals' electronic health record (EHR) systems were recruited to identify at least 10 and no more than 60 qualifying patients, starting with the most recent patient who met inclusion criteria during the data collection period and working backward.**

Inclusion criteria were age ≥18 years, an ICD-10 code of D68.32 (indicating a hemorrhagic disorder due to extrinsic circulating anticoagulants), use of rivaroxaban or apixaban at the time of the bleeding event, treatment with AA or 4F-PCC during the index hospitalization, and a documented discharge disposition. Patients who received both AA and 4F-PCC were excluded.

The primary outcome was in-hospital mortality across all bleeds and separately for ICH and GI bleeds, after multivariable logistic regression. Patients with missing mental status (n = 187) and those defined as having "other bleeds" (n = 80) were not included in the analysis of mortality. A secondary propensity score-weighted logistic regression was also performed.

A total of 354 institutions in 42 states participated. Of these, 91.8% were Comprehensive Stroke Centers and 44.6% were ACS Level 1 trauma centers. There were 4395 patients, of whom 2122 were treated with AA and 2273 were treated with 4F-PCC. Just over half (58%) of patients had GI bleeds and 30% had ICH.

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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 either based on availability of 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?	Yes. Patients were similar with respect to age, gender, bleed location, presence of altered mental status, presence of a DNR order, initial systolic BP, presence of comorbidities, factor Xa inhibitor used (apixaban vs. rivaroxaban), time since last anticoagulant dose, door-to-needle time, and location and cause of bleeding (traumatic vs. spontaneous) among those with ICH.
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. A higher proportion of patients treated with 4F-PCC than with AA received other treatments, such as IV fluids, packed red blood cells, or fresh frozen plasma (71.6% vs 44.8%).
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?	Yes. The primary outcome, in-hospital mortality, would have been available for all patients in the EHR.
What are the results?	

How large was the treatment effect?	• In-hospital mortality occurred in 6.0% of patients treated with AA and 10.6% of patients treated with 4F-PCC.
	  o Following logistic regression, patients treated with AA had 50% lower odds of death during hospitalization than those treated with 4F-PCC (OR 0.50, 95% CI 0.39 to 0.65).
	• Among those with ICH, in-hospital mortality occurred in 12.6% of patients in the AA group and 23.3% in the 4F-PCC group.
	  o Following logistic regression, odds of death during hospitalization in the AA group were 45% lower than those treated with 4F-PCC for ICH (OR 0.55, 95% CI 0.39 to 0.76).
	• Among patients with GI bleeds, in-hospital mortality occurred in 2.5% of patients treated with AA vs 4.3% of patients treated with 4F-PCC
	  o Following logistic regression, there were 51% lower odds of death during hospitalization in the AA group compared to the 4F-PCC group (OR, 0.49; 95% CI, 0.29 to 0.81).

	• Propensity score weighting resulted in similar findings when compared with logistic regression, with all ORs in favor of AA: o All patients: OR, 0.59; 95% CI, 0.46-0.74; P < .01 o ICH: OR, 0.61; 95% CI, 0.45-0.83; o GI bleeds: OR, 0.61; 95% CI, 0.39-0.96 • In the adjusted logistic regression analysis, the odds of in-hospital mortality were significantly higher for patients with: 1. Spontaneous ICH, traumatic ICH, or critical compartment bleeds when compared with GI bleeds. 2. Increasing age. 3. Impaired mental status or presence of a DNR order compared with those with no impaired mental status or DNR order. 4. And liver disease, CKD, and heart failure.
How precise was the estimate of the treatment effect? (i.e. what 95% CIs were associated with the results?)	See above.
How can I apply the results to patient care?	
Were the study patients similar to my patient?	Yes. This was a multicenter study that included only US institutions. Almost all were Comprehensive Stroke Centers and nearly half were ACS Level 1 trauma centers. There were some centers who had only AA available (6.5%) and some with only 4F-PCC available (18.4%), whereas both are available at our institution.
Were all clinically important outcomes considered?	No. The only outcome measured was in-hospitality. Most importantly, the authors were unable to include measures of functional status (modified Rankin Scale) either at the time of discharge or 30 to 90 days following hospitalization; this would be a more important patient-centered measure for patients with ICH as the indication for anticoagulation reversal.
Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While this study suggests improved in-hospital mortality rates for patients receiving AA vs. 4F-PCC, the retrospective observational nature of the study allows for the introduction of significant bias. The use of logistic regression and propensity matching to try to balance the groups does not replace the need for a randomized controlled trial.

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. While statistical tools—including both multivariable logistic regression and propensity matching— was used to account for differences in baseline prognostic risk, these tools do not replace randomization.**

2. **The authors do not provide details regarding the methodology of the chart review process (Gilbert 1996 and Worster 2004).**

3. **There were some centers who had only AA available (6.5%) and some with only 4F-PCC available (18.4%), whereas both are available at our institution.**

4. **There was no blinding, placing the results at risk of performance bias and observer bias.**

5. The only outcome measured was in-hospitality. The authors were unable to include in-hospital of long-term measures of functional status.

Bottom Line:

This retrospective, multicenter study found that among patients treated with AA or 4F-PCC for reversal of major bleeding in patients taking rivaroxaban or apixaban, there was a 50% lower odds of death during hospitalization among all patients treated with AA vs. 4F-PCC (OR 0.50, 95% CI 0.39 to 0.65) with a 45% lower odds in the subset of patients with ICH (OR 0.55, 95% CI 0.39 to 0.76) and a 51% lower odds of death among those with GI hemorrhage (OR, 0.49; 95% CI, 0.29 to 0.81). These results are limited by the retrospective nature of the study and lack of data on functional outcomes.