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Original research (includes database studies and QI projects)

Title: Andexanet Alfa Is Associated With Lower In-Hospital Mortality Compared To 4-Factor Prothrombin Complex Concentrate In Patients With Factor Xa Inhibitor–Related Major Bleeding

Andexanet Alfa Is Associated With Lower In-Hospital Mortality Compared To 4-Factor Prothrombin Complex Concentrate In Patients With Factor Xa Inhibitor–Related Major Bleeding

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Background:
Factor Xa inhibitors reduce the risk of ischemic events but carry an increased risk of major bleeding. Until andexanet alfa was approved in 2018, options for treating such bleeds were limited. Data comparing andexanet alfa versus 4-factor prothrombin complex concentrate (4F-PCC) in routine clinical practice are needed.

Aim:
To compare in-hospital mortality in patients treated with either andexanet alfa or 4F-PCC while hospitalized for rivaroxaban- or apixaban-associated major bleeding.

Methods:
This multicenter, observational study collected patient chart data from 354 US hospitals with andexanet alfa or 4F-PCC (or both) on formulary. Included patients were aged ≥18 years, treated with andexanet alfa or 4F-PCC during hospitalization for an anticoagulant-related major bleed (ICD-10 code D68.32, indicating bleeding due to extrinsic anticoagulants) between 7/2018 and 9/2022, received apixaban or rivaroxaban prior to hospitalization, and had a documented discharge disposition. In-hospital mortality for andexanet alfa versus 4F-PCC was compared via multivariable logistic regressions overall and by bleed location.

Results:
A total of 4395 patients were identified treated with andexanet alfa (n=2,122) or 4F-PCC (n=2,273). The two main bleed locations were gastrointestinal (58%) and intracranial hemorrhage (30%). Overall, in-hospital mortality occurred in 6.0% of patients treated with andexanet alfa and in 10.6% of the 4F-PCC cohort. Patients treated with andexanet alfa had a 50% lower likelihood of in-hospital mortality compared to 4F-PCC (adjusted OR 0.50 [95% CI

0.38-0.65], p<0.001). In-hospital mortality in patients with ICH was 12.6% with andexanet alfa and 23.3% with 4F-PCC (adjusted OR 0.54 [95% CI 0.39-0.75]). In patients with gastrointestinal bleeds in-hospital mortality was 2.5% with andexanet alfa and 4.3% with 4F-PCC (adjusted OR 0.48 [95% CI 0.28-0.79])..

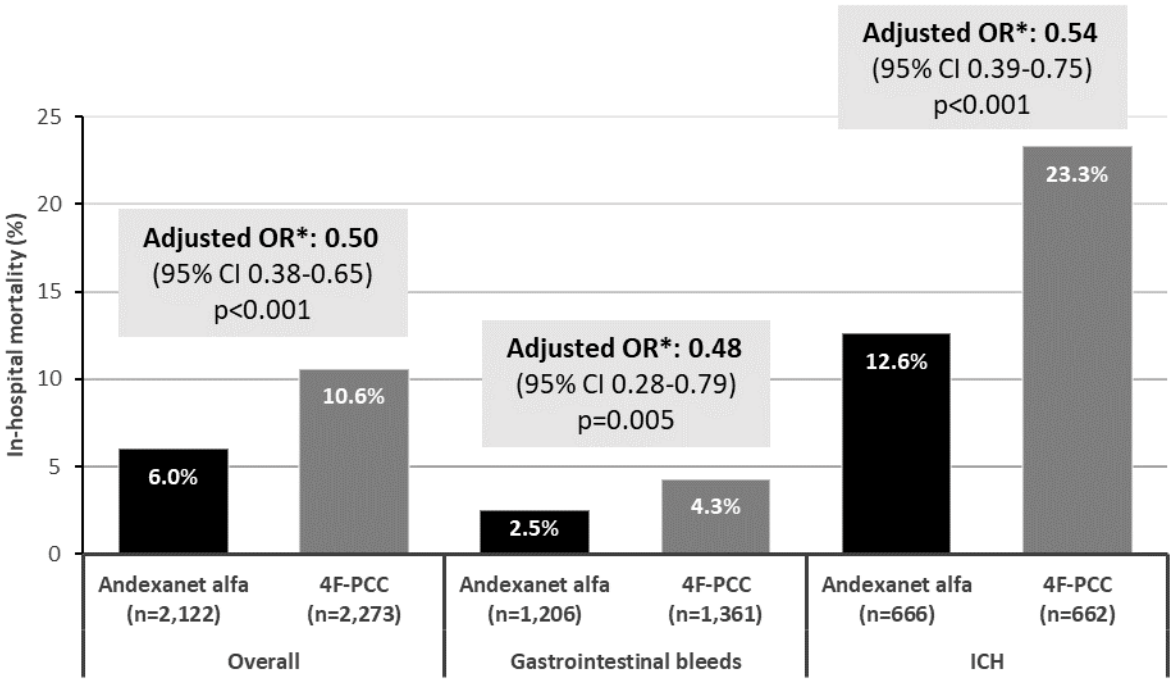
Conclusion:
Andexanet alfa was associated with a 50% lower likelihood of in-hospital mortality compared with 4F-PCC in patients with rivaroxaban- or apixaban-associated major bleeds. This result was similar in gastrointestinal bleeds and ICH.

Table: Demographic and clinical characteristics of patients with rivaroxaban- or apixaban-associated major bleeding treated with andexanet alfa versus 4F-PCC

Characteristic	**Andexanet alfa (n=2,122)**	**4F-PCC (n=2,273)**
Age, mean (SD) years	65.6 (13.1)	66.6 (13.6)
Male sex, n (%)	1,214 (57.2)	1,376 (60.5)
Bleed location, n (%)		
Gastrointestinal bleed	1,206 (56.8)	1,361 (59.9)
ICH	666 (31.4)	662 (29.1)
Traumatic ICH	*327 (49.9)*	*366 (55.3)*
Spontaneous ICH	*339 (50.9)*	*296 (44.7)*
Other	250 (11.8)	250 (11.0)
Time since last Factor Xa inhibitor dose, n (%)		
<8 hours	936 (44.1)	943 (41.5)
8-18 hours	888 (41.8)	934 (41.1)
>18 hours	298 (14.0)	396 (17.4)
Time from hospital arrival to administration, median (IQR) hours	2.5 (1.2, 6.4)	2.3 (1.2, 5.7)

4F-PCC, 4-factor prothrombin complex concentrate; ICH, intracranial hemorrhage; IQR, interquartile range; SD, standard deviation.

Figure: In-hospital mortality with andexanet alfa versus 4F-PCC in patients with rivaroxaban- or apixaban-associated major bleeding overall and separately for gastrointestinal bleeds and ICH



4F-PCC, 4-factor prothrombin complex concentrate; CI, confidence interval; ICH, intracranial hemorrhage; OR, odds ratio.
*Adjusted for age, sex, bleed location (in analyses of overall bleeds), traumatic versus spontaneous ICH (in analyses of overall bleeds and ICH), systolic blood pressure, impaired mental status, do-not-resuscitate order, liver disease, chronic kidney disease, heart failure, diabetes, time since last Factor Xa inhibitor dose, time from arrival to administration, and data collection wave.