Circulation

ORIGINAL RESEARCH ARTICLE

Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors

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Background

- Andexanet alfa is a modified recombinant inactive factor Xa (FXa) designed to reverse FXa inhibitors.
- In May 2018, the US Food and Drug Administration approved andexanet alfa for the reversal of anticoagulation with apixaban and rivaroxaban in life-threatening or uncontrolled bleeding.
- The European Medicines Agency also gave conditional approval in April 2019.
- ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) is a multicenter, prospective, phase-3b/4, single-group cohort study that evaluated andexanet alfa in patients with acute major bleeding.

AIM of the study

- To assess the safety and efficacy of andexanet alfa in patients with FXa inhibitor–associated major bleeding.

Methods (I)

- Multicenter, prospective, phase-3b/4, single-group cohort study.
- The study opened in April 2015 and closed in August 2020, with 479 patients enrolled.
- Eligible, consenting patients received an andexanet alfa bolus, followed by a 2-hour infusion.
- There were 2 possible andexanet alfa dosing regimens (low- or high-dose) based on the specific FXa inhibitor received, its dose, and time since patient's last dose (<8 hours, ≥8 hours, or unknown).
- Blood samples were obtained to measure anti-FXa activity and the unbound fraction of the FXa inhibitor plasma level before andexanet alfa treatment, at the end of bolus, at the end of infusion and at 4, 8, and 12 hours after infusion.

Methods (II)

- The study had 2 co-primary efficacy end points: percent change from baseline in anti-FXa activity after andexanet alfa treatment and percentage of patients with excellent or good hemostatic efficacy at 12 hours after andexanet alfa infusion.
- The primary safety end points were death, thrombotic events (stratified by occurring before or after restart of either prophylactic or full-dose oral anticoagulation), and the development of antibodies to andexanet alfa or to native factor X and FXa to ≥30 days.
- Endogenous thrombin potential at baseline and across the follow-up period was a secondary outcome.

Results (I)

- The mean age of patients was 78 years; 54% were male, 81% were anticoagulated for atrial fibrillation.
- Apixaban was used in 245 (51%) patients, rivaroxaban in 176 (37%), edoxaban in 36 (8%), and enoxaparin in 22 (5%).
- In apixaban-treated patients (n=172), median anti-Fxa activity decreased from 146.9 ng/mL at baseline to 10.0 ng/mL at the on-treatment nadir (median reduction, 93%).
- In rivaroxaban-treated patients (n=132), median anti-FXa activity decreased from 214.6 ng/mL at baseline to 10.8 ng/mL at nadir (median reduction, 94%).
- In edoxaban-treated patients (n=28), median anti-FXa activity decreased from 121.1 ng/mL at baseline to 24.4 ng/mL at nadir (median reduction, 71%).

Results (II)

- Hemostatic efficacy was good or excellent in 80% of patients overall and did not vary significantly by subgroups of FXa inhibitor, sex, type of bleeding, age, or andexanet alfa dose.
- In the 30-day follow-up period, 50 (10.4%) patients had ≥1 thrombotic event.
- There were 75 (15.7%) deaths in 30 days.
- The median endogenous thrombin potential in all patients, stratified by type of FXa inhibitor, returned to the normal range by the end of andexanet alfa bolus through 24 hours in all FXa inhibitors.
- Specific to certain populations, reduction of anti-FXa activity from baseline to nadir significantly predicted hemostatic efficacy in patients with intracranial hemorrhage and correlated with lower mortality in patients <75 years of age (adjusted P=0.022; unadjusted P=0.003).

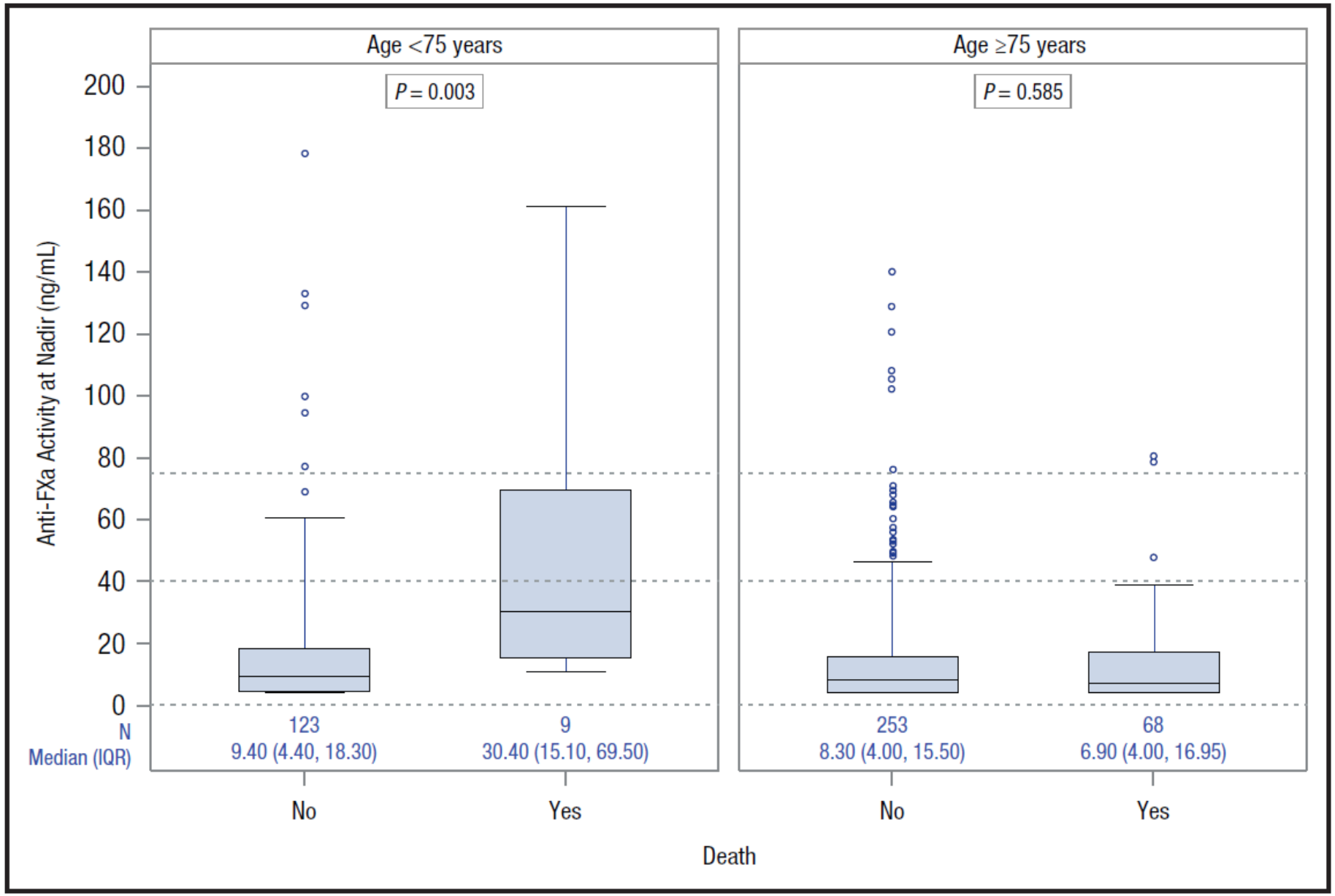
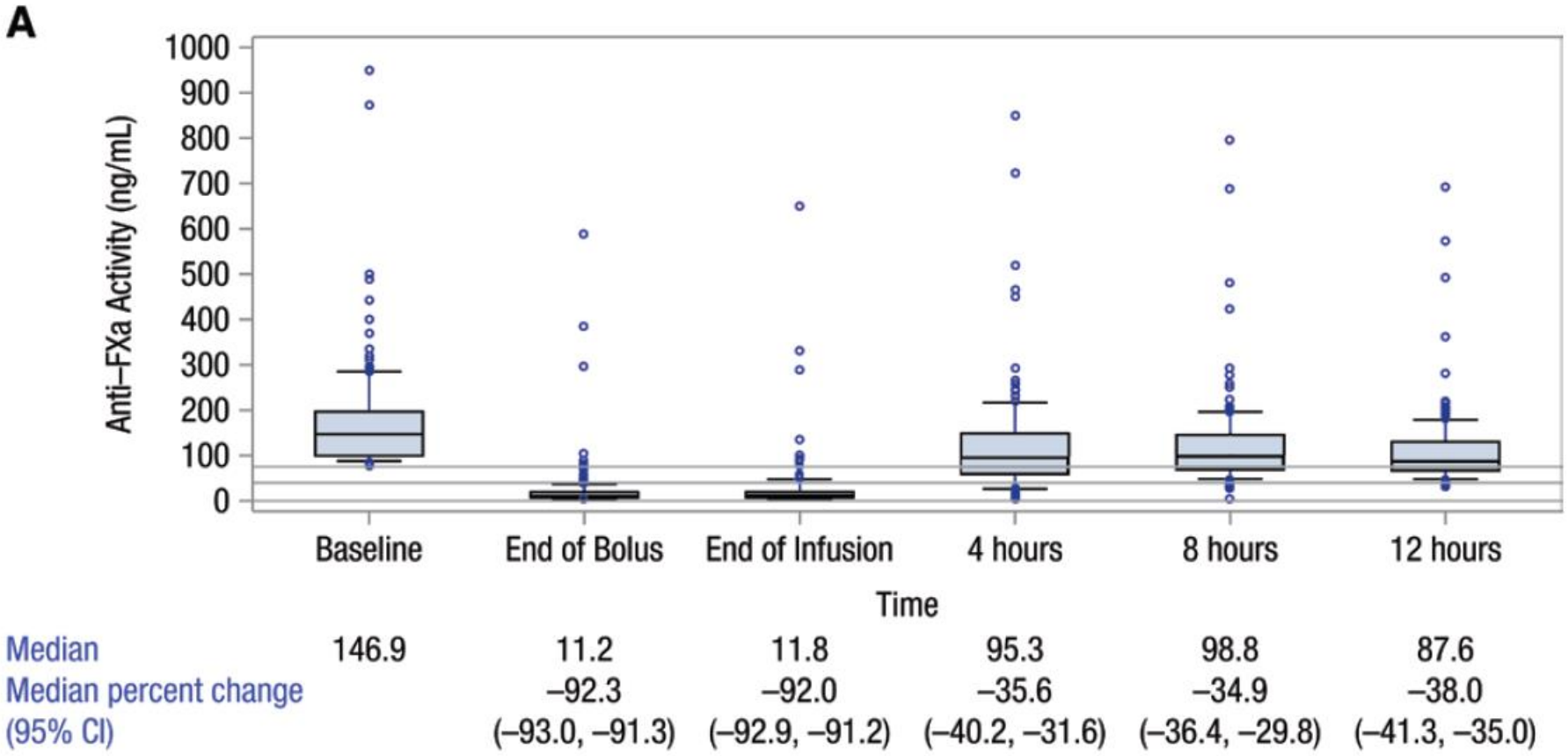
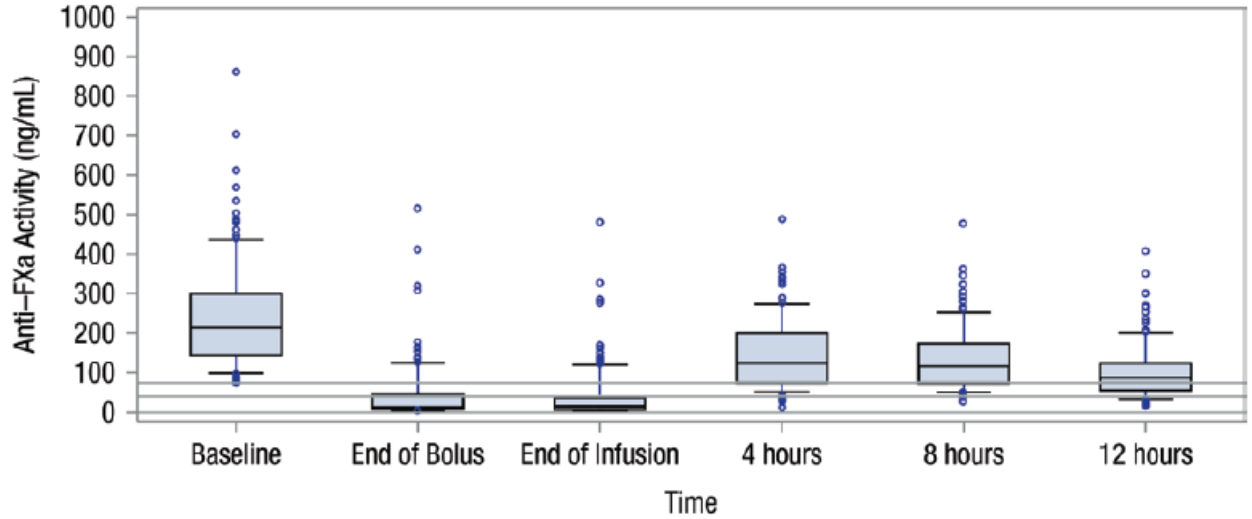


Figure 2. **Boxplots of anti-FXa activity at nadir by mortality, stratified by age.**

Figure 3. Boxplots of anti-FXa activity in patients receiving apixaban, rivaroxaban, edoxaban.
Time course of anti-FXa activity from baseline through 12 hours after treatment is shown for patients receiving apixaban (**A**), rivaroxaban (**B**), edoxaban (**C**).

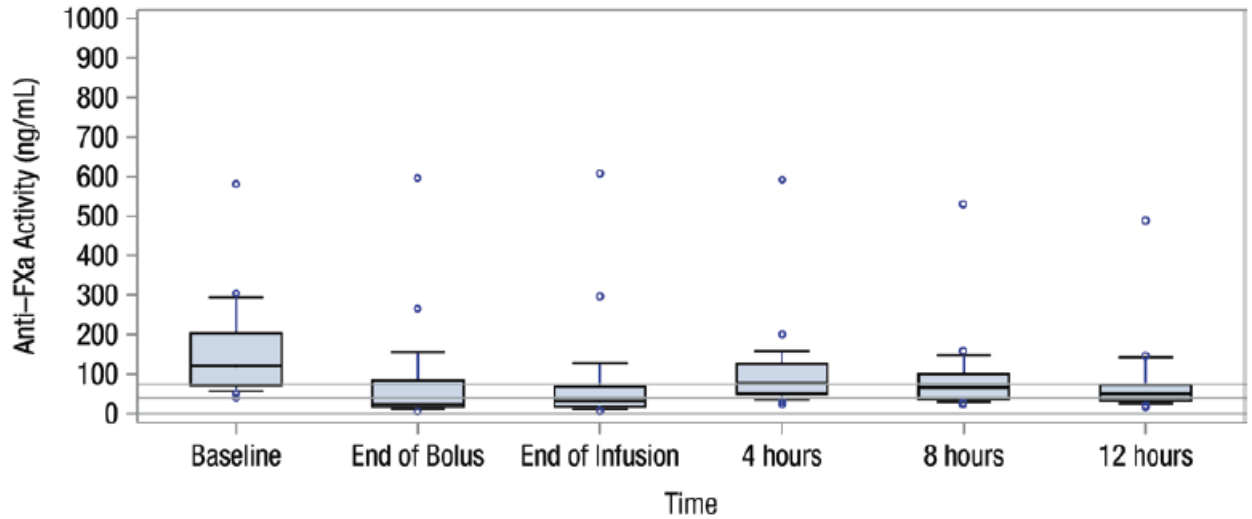


B



Median	214.6	12.5	14.5	124.2	116.6	87.0
Median percent change		−93.5	−92.5	−43.2	−48.6	−61.0
(95% CI)		(−94.6, −91.6)	(−94.0, −90.4)	(−45.4, −40.5)	(−51.6, −45.0)	(−65.0, −58.1)

C



Median	121.1	24.0	30.2	77.5	64.6	49.9
Median percent change		−68.9	−68.6	−34.4	−48.6	−58.5
(95% CI)		(−77.7, −56.1)	(−77.6, −57.2)	(−45.6, −18.0)	(−56.0, −40.8)	(−68.2, −41.4)

Conclusions

- In this final ANNEXA-4 cohort of 479 patients with major bleeding, andexanet alfa lowered anti-FXa activity, and was associated with good or excellent hemostatic efficacy in 80% of patients.
- Reduction of anti-FXa activity from baseline to nadir significantly predicted hemostatic efficacy in patients with ICH and correlated with lower mortality in patients <75 years of age.
- These results support the use of andexanet alfa as a specific reversal agent for Fxa inhibitor–associated acute major bleeding.
- However, in clinical practice, andexanet alfa use is currently limited by high costs and poor handling.
- A global randomized controlled trial of andexanet alfa versus usual care in ICH patients is ongoing (ANNEXA-I).