












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

Truman J. Milling Jr , MD*; Saskia Middeldorp , MD*; Lizhen Xu, PhD; Bruce Koch, PharmD; Andrew Demchuk , MD; John W. Eikelboom , MD; Peter Verhamme , MD; Alexander T. Cohen , MD; Jan Beyer-Westendorf, MD; C. Michael Gibson, MD; Jose Lopez-Sendon , MD; Mark Crowther, MD; Ashkan Shoamanesh , MD; Michiel Coppens, MD; Jeannot Schmidt, MD; Pierre Albaladejo, MD; Stuart J. Connolly , MD; on behalf of the ANNEXA-4 Investigators†

BACKGROUND: Andexanet alfa is a modified recombinant inactive factor Xa (FXa) designed to reverse FXa inhibitors. ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) was a multicenter, prospective, phase-3b/4, single-group cohort study that evaluated andexanet alfa in patients with acute major bleeding. The results of the final analyses are presented.

METHODS: Patients with acute major bleeding within 18 hours of FXa inhibitor administration were enrolled. Co-primary end points were anti-FXa activity change from baseline during andexanet alfa treatment and excellent or good hemostatic efficacy, defined by a scale used in previous reversal studies, at 12 hours. The efficacy population included patients with baseline anti-FXa activity levels above predefined thresholds (≥ 75 ng/mL for apixaban and rivaroxaban, ≥ 40 ng/mL for edoxaban, and ≥ 0.25 IU/mL for enoxaparin; reported in the same units used for calibrators) who were adjudicated as meeting major bleeding criteria (modified International Society on Thrombosis and Haemostasis definition). The safety population included all patients. Major bleeding criteria, hemostatic efficacy, thrombotic events (stratified by occurring before or after restart of either prophylactic [ie, a lower dose, for prevention rather than treatment] or full-dose oral anticoagulation), and deaths were assessed by an independent adjudication committee. Median endogenous thrombin potential at baseline and across the follow-up period was a secondary outcome.

RESULTS: There were 479 patients enrolled (mean age, 78 years; 54% male; 86% White); 81% were anticoagulated for atrial fibrillation, and the median time was 11.4 hours since last dose, with 245 (51%) on apixaban, 176 (37%) on rivaroxaban, 36 (8%) on edoxaban, and 22 (5%) on enoxaparin. Bleeding was predominantly intracranial ($n=331$ [69%]) or gastrointestinal ($n=109$ [23%]). In evaluable apixaban patients ($n=172$), median anti-FXa activity decreased from 146.9 ng/mL to 10.0 ng/mL (reduction, 93% [95% CI, 94–93]); in rivaroxaban patients ($n=132$), it decreased from 214.6 ng/mL to 10.8 ng/mL (94% [95% CI, 95–93]); in edoxaban patients ($n=28$), it decreased from 121.1 ng/mL to 24.4 ng/mL (71% [95% CI, 82–65]); and in enoxaparin patients ($n=17$), it decreased from 0.48 IU/mL to 0.11 IU/mL (75% [95% CI, 79–67]). Excellent or good hemostasis occurred in 274 of 342 evaluable patients (80% [95% CI, 75–84]). In the safety population, thrombotic events occurred in 50 (10%) patients; in 16 patients, these occurred during treatment with prophylactic anticoagulation that began after the bleeding event. No thrombotic episodes occurred after oral anticoagulation restart. Specific to certain populations, reduction of anti-FXa activity from baseline to nadir significantly predicted hemostatic efficacy in patients with intracranial hemorrhage (area under the receiver operating characteristic curve, 0.62 [95% CI, 0.54–0.70]) and correlated with lower mortality in patients < 75 years of age (adjusted $P=0.022$; unadjusted $P=0.003$). Median endogenous thrombin potential was within the normal range by the end of andexanet alfa bolus through 24 hours for all FXa inhibitors.

CONCLUSIONS: In patients with major bleeding associated with the use of FXa inhibitors, treatment with andexanet alfa reduced anti-FXa activity and was associated with good or excellent hemostatic efficacy in 80% of patients.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02329327.

Key Words: clinical trials ■ cohort studies ■ factor Xa inhibitors ■ gastrointestinal hemorrhage ■ intracranial hemorrhage

Correspondence to: Truman J. Milling Jr, MD, Seton Dell Medical School Stroke Institute, 1601 Trinity St, 10th Floor, Austin, TX 78712. Email tjmilling@yahoo.com

*T.J. Milling and S. Middeldorp contributed equally.

†A complete list of the ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) investigators is provided in the Appendix.

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.121.057844>.

For Sources of Funding and Disclosures, see page 1037.

© 2023 The Authors. *Circulation* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Treatment with andexanet alfa of 479 patients with major bleeding was associated with reduction in anti-factor Xa (FXa) activity up to 94% and with effective clinical hemostasis in 80%.
- Thrombotic events occurred primarily in patients before restarting anticoagulation or in those who did not restart.

What Are the Clinical Implications?

- Andexanet alfa reverses the anticoagulant effect of FXa inhibitors and is associated with a high frequency of good to excellent clinical hemostasis.
- These data provide preliminary support for the use of andexanet alfa for reversal of FXa inhibitors in patients with life-threatening or uncontrolled bleeding.

Nonstandard Abbreviations and Acronyms

ANNEXA-I	Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor
ANNEXA-4	Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors
FXa	factor Xa
ICH	intracranial hemorrhage

Factor Xa (FXa) inhibitors reduce thrombotic events in patients with nonvalvular atrial fibrillation and venous thromboembolism, but are associated with an increased risk of bleeding. Approximately 6 million people in the United States are taking FXa inhibitors,¹ and the use of direct oral anticoagulants, including FXa inhibitors, has increased substantially in Europe in recent years.² Acute major bleeding on treatment carries considerable morbidity and mortality. In particular, intracranial hemorrhage (ICH) on anticoagulation therapy carries a 30- to 90-day mortality rate of 40% to 65%.³ Andexanet alfa (coagulation FXa [recombinant], inactivated-zhzo) was designed to specifically reverse FXa inhibitor anticoagulation for the treatment of acute bleeding⁴; it has been studied in healthy volunteers and shown to reduce anti-FXa activity and plasma unbound levels of the inhibitor.⁵ 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 under its accelerated approval program. The approval was conditional on performance of an ongoing randomized clinical trial (ANNEXA-I [Andexanet Alfa in Acute

Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor]; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT03661528). The European Medicines Agency also gave conditional approval in April 2019, and full marketing approval was granted in Japan in March 2022, including for the reversal of edoxaban in patients with life-threatening or uncontrolled bleeding.

ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors; URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02329327) was a multicenter, prospective, phase-3b/4, single-group cohort study jointly designed by the Population Health Research Institute (PHRI) at McMaster University and Portola Pharmaceuticals, Inc (now Alexion, AstraZeneca Rare Disease). ANNEXA-4 was designed to assess the safety and efficacy of andexanet alfa in patients with FXa inhibitor-associated major bleeding. The study opened in April 2015 and closed in August 2020, with 479 patients enrolled. The results from 2 analyses of this cohort have been published previously (in 67 and 352 patients, respectively).^{6,7} Here, safety and efficacy outcomes for the final cohort of 479 patients and a secondary analysis on the relationship among anti-FXa activity levels, mortality, and hemostatic efficacy are reported. This final cohort, compared with the full report of 352 patients published in 2019,⁷ provides a larger data set that not only yields greater precision for various estimates, but also enables greater insight into the relationships among anti-FXa level, hemostatic efficacy, and mortality. It is the only prospective FXa inhibitor-associated major bleeding cohort with anti-FXa levels reported at baseline and regular intervals after reversal, in addition to scheduled follow-up imaging for ICH patients, a group that made up two-thirds of the study population.

METHODS

Study Design and Oversight

This was a multicenter, prospective, open-label, single-cohort study. PHRI and the industry sponsor both selected sites and supervised monitoring. Institutional review boards for each center approved the protocol, consent forms, and ancillary materials. An academic steering committee led the study, and PHRI collected, stored, and analyzed the data. An independent data and safety monitoring board reviewed study data for safety, and an end point adjudication committee assessed whether patients met criteria for major bleeding, and adjudicated the end points of hemostatic efficacy, thrombotic events, and cause of death. A central core laboratory reviewed computed tomography and magnetic resonance imaging of the head. The first authors wrote all drafts of the manuscript. All authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

Study Population

Study enrollment was carried out at 85 centers across a variety of acute care settings, including stroke centers, trauma centers, and large tertiary-care hospitals. Twenty-six centers were in North America (24 in the United States and 2 in Canada), 49 centers were in Europe (35 in Germany, 4 in France, 3 in the United Kingdom, 3 in Belgium, 2 in Spain, and 2 in the Netherlands), and 10 centers were in Japan. Eligibility criteria included those ≥ 18 years of age presenting with acute major bleeding and having received one of the following within 18 hours: apixaban, rivaroxaban, edoxaban, or enoxaparin (the latter at a therapeutic dose of ≥ 1 mg/kg). The steering committee provided guidance to investigators to exclude patients on low-dose FXa inhibitors for coronary or peripheral vascular disease when this indication emerged during the study period. Acute major bleeding was defined as ≥ 1 of the following⁷:

1. Potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise (eg, severe hypotension, poor skin perfusion, mental confusion, or low urine output that could not otherwise be explained);
2. Bleeding associated with a decrease in the hemoglobin level of ≥ 2 g/dL (or a hemoglobin level of ≤ 8 g/dL if no baseline hemoglobin level was available); or
3. Bleeding in a critical area or organ (eg, retroperitoneal, intra-articular, pericardial, epidural, or intracranial or intramuscular bleeding with compartment syndrome).

Full inclusion and exclusion criteria have been published previously.^{6,7} Patients or their legally authorized representatives provided informed consent. Emergency consent was used when permitted.

Study Procedures and Data Collection

Eligible, consenting patients received an andexanet alfa bolus during a period of 15 to 30 minutes, 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; Table S1). The low-dose regimen comprised a 400-mg bolus of IV andexanet alfa during a period of 15 minutes and a follow-up 2-hour infusion of 480 mg. The high-dose regimen comprised an 800-mg bolus of IV andexanet alfa during a 30-minute period and a follow-up 2-hour infusion of 960 mg. A minor modification related to the selection of a low or high andexanet alfa dose was made in a protocol amendment and was published previously⁷; 266 patients were enrolled after implementation of the amendment. 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. Measurement methods for these values were described previously.⁶ Anti-FXa activity was reported in the same units used for the calibrators. For patients with ICH, computed tomography or magnetic resonance imaging of the head was expected within 2 hours before andexanet alfa treatment and at 1 and 12 hours after andexanet alfa treatment.

Study Outcomes

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. An independent adjudication committee assessed hemostatic efficacy based on prespecified criteria (eg, hematoma volume expansion for ICH [excellent or good $\leq 35\%$] and percentage of the hemoglobin/hematocrit drop in gastrointestinal bleeding [excellent or good $\leq 20\%$]; Table S2). The primary safety end points were death, thrombotic events (stratified by occurring before or after restart of either prophylactic [ie, a lower dose for prevention rather than treatment] or full-dose oral anticoagulation), and the development of antibodies to andexanet alfa or to native factor X and FXa to ≥ 30 days. The ANNEXA-4 protocol required routine adverse event and concomitant medication reporting throughout the study. The protocol did not require specific assessments for thrombotic event surveillance. Treating clinicians diagnosed events based on symptoms, signs, and diagnostic imaging according to local standard of care. Monitoring for antibodies to andexanet alfa, factor X, and FXa was performed at baseline and at day 30, or the early termination visit, using validated electrochemiluminescent methods at a central laboratory. For any sample confirmed positive for antibodies against andexanet alfa, the potential for neutralizing antibody activity was further assessed by measuring the functional activity of andexanet alfa in plasma. As implemented in protocol amendment 4, the Bethesda assay was modified to assess the potential presence of neutralizing antibodies to endogenous factor X/FXa (rather than to factor VIII). These tests were performed by central laboratories.

Endogenous thrombin potential at baseline and across the follow-up period was a secondary outcome measured with a tissue factor–dependent assay, as described previously.⁵ Prespecified subgroups were sex, race, age (< 65 , 65–75, and > 75 years), FXa inhibitor type, and bleeding type.

Statistical Analyses

The safety population included all patients given any amount of andexanet alfa. The efficacy population included patients who met the following criteria: baseline anti-FXa activity of ≥ 75 ng/mL (≥ 0.25 IU/mL for patients receiving enoxaparin or > 40 ng/mL for patients treated with edoxaban) and adjudication committee–confirmed major bleeding at presentation. The study initially planned a sample of 250 patients, which would provide 80% power to show that the percentage of patients with excellent or good hemostatic efficacy was $> 50\%$. The target sample size was increased to meet new regulatory requirements for a sufficient number of patients for each FXa inhibitor, with ≥ 120 patients with ICH in the efficacy analysis population. The trial terminated at 479 total patients after enough edoxaban ($n=36$) and Japanese ($n=19$) patients were recruited. Continuous variables are summarized as mean and SD or median and interquartile range. Categorical variables are presented as frequencies. Percent change from baseline anti-FXa activity to nadir was computed with a 2-sided nonparametric CI for the median for each inhibitor to investigate the effect of andexanet alfa. The 95% CI was calculated using order statistics (ranks), as described by Hahn and Meeker in 1991.⁸

The percentage of patients with good or excellent hemostasis is presented with a 95% CI calculated using an exact binomial CI.

Prespecified Anti-FXa Activity and Mortality/Hemostatic Efficacy Correlations

Anti-FXa Activity and Mortality Correlation

First, univariable analyses were performed by comparing the baseline characteristics between 2 groups defined by whether patients died during the study (Table S3). Enoxaparin patients were excluded because of the different units of measure of anti-FXa activity levels. Investigators analyzed all deaths, including those captured after 30 days. Categorical variables were compared using Pearson's χ^2 test or the Fisher exact test. Continuous variables were compared using a *t* test or Wilcoxon rank-sum test if the data were skewed. Second, logistic regression was used to examine the relationship between anti-FXa activity and mortality by setting the anti-FXa activity level at nadir as a covariate of primary interest, adjusting for potential confounders identified in the univariable analyses and a potential clinically relevant variable: the binary indicator of ICH. In the univariable analyses (Table S3), age, CHA₂DS₂-VASc score, and time from presentation to the start of bolus were found to have significant differences in distribution between the no-death group and the death group, with *P* values of <0.001, <0.001, and 0.002, respectively. These variables were thus included in the regression model. Other variables identified to be significantly different between the 2 groups in Table S3 were time length related, along with their binary indicators. These variables were highly correlated with the time from presentation to the start of bolus variable, and thus were not included in the model. The nonlinear association between the nadir anti-FXa level and the logit of mortality rate was explored. Figure S1 shows the restricted cubic spline transformations of the nadir anti-FXa levels, along with their 95% CIs. An EFFECT statement within PROC LOGISTIC in SAS (software v.9.4; SAS Institute) was added, and the restricted cubic spline of the nadir anti-FXa level with 4 knots was specified at 5%, 35%, 65%, and 95%. Two new spline variables were then created and included in the regression model (Table S4). This model was further compared with the other 2 models, in which the nadir anti-FXa level was either in original scale or was log-transformed (Table S5). The final model selected had the smallest Akaike information criterion (AIC) value. Interaction (subgroup) analyses were performed for subgroups of patients defined a priori according to age: <75 years or ≥75 years. A beeswarm plot (Figure 1) and boxplots (Figure 2; Figure S2) were provided to illustrate the distribution of nadir anti-FXa levels stratified by mortality for each age subgroup. The medians were compared by Wilcoxon rank-sum test. Logistic regression was used to examine the relationship between nadir anti-FXa activity (continuous or dichotomized by different thresholds) and mortality adjusted by the confounders of age, CHA₂DS₂-VASc score, and time from hospital arrival to bolus for patients <75 years of age (Figure S3; Table S6).

Anti-FXa Activity and Hemostatic Efficacy Correlation

As in previous analyses,⁷ the association between hemostatic efficacy and change in anti-FXa activity from baseline to nadir with the use of logistic regression, represented by the receiver operating characteristic curve, was examined in the overall

safety population and in the ICH subgroup. Analyses were performed with the use of SAS (v.9.4).

The methods for assessing the anti-FXa activity and mortality/hemostatic efficacy correlations are the same, as they are both using logistic regression. The receiver operating characteristic curve is a graph to assess the prediction of the logistic regression model. In the anti-FXa activity and hemostatic efficacy correlation analyses, there is only one covariate (ie, the absolute change of anti-FXa activity from baseline to nadir), which is consistent with the methods used in the previous article.⁷ In anti-FXa activity and mortality analyses, the correlation is adjusted by other covariates.

Hemostatic Efficacy–Mortality Correlation

The correlation between adjudicated hemostatic efficacy and mortality in the safety population was investigated with the χ^2 test.

Heterogeneity Between FXa Inhibitors

In post hoc analyses, treatment groups by FXa inhibitor were compared for the change from baseline in anti-FXa activity using a mixed model for repeated measures. The observed change from baseline in anti-FXa activity at the end of bolus; at the end of infusion; and at 4, 8, and 12 hours after infusion are the dependent variables that are correlated. Models include the baseline anti-FXa activity and FXa inhibitor groups as fixed-effect covariates, together with visit, the interaction of baseline by visit, and the interaction of FXa inhibitor group by visit. An unstructured covariance pattern is used to estimate the variance–covariance of the within-subject repeated measures.

RESULTS

Patients

The mean age of patients was 78 years; 54% were male, and 86% were White. Additionally, 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%), with a median time since last dose of 11.4 hours. Patients had a significant comorbidity burden at baseline: stroke (23%), heart failure (20%), myocardial infarction (12%), some degree of kidney insufficiency (48%), and diabetes (28%). The sites of bleeding were intracranial (331 [69%] patients), gastrointestinal (109 [23%] patients), or other major bleeding (39 [8%] patients; Table 1). Frequency of FXa inhibitor by center is presented in Table S7.

Anti-FXa Activity

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% [95% CI, 94–93]). 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% [95% CI, 95–93]). In edoxaban-treated patients (n=28),

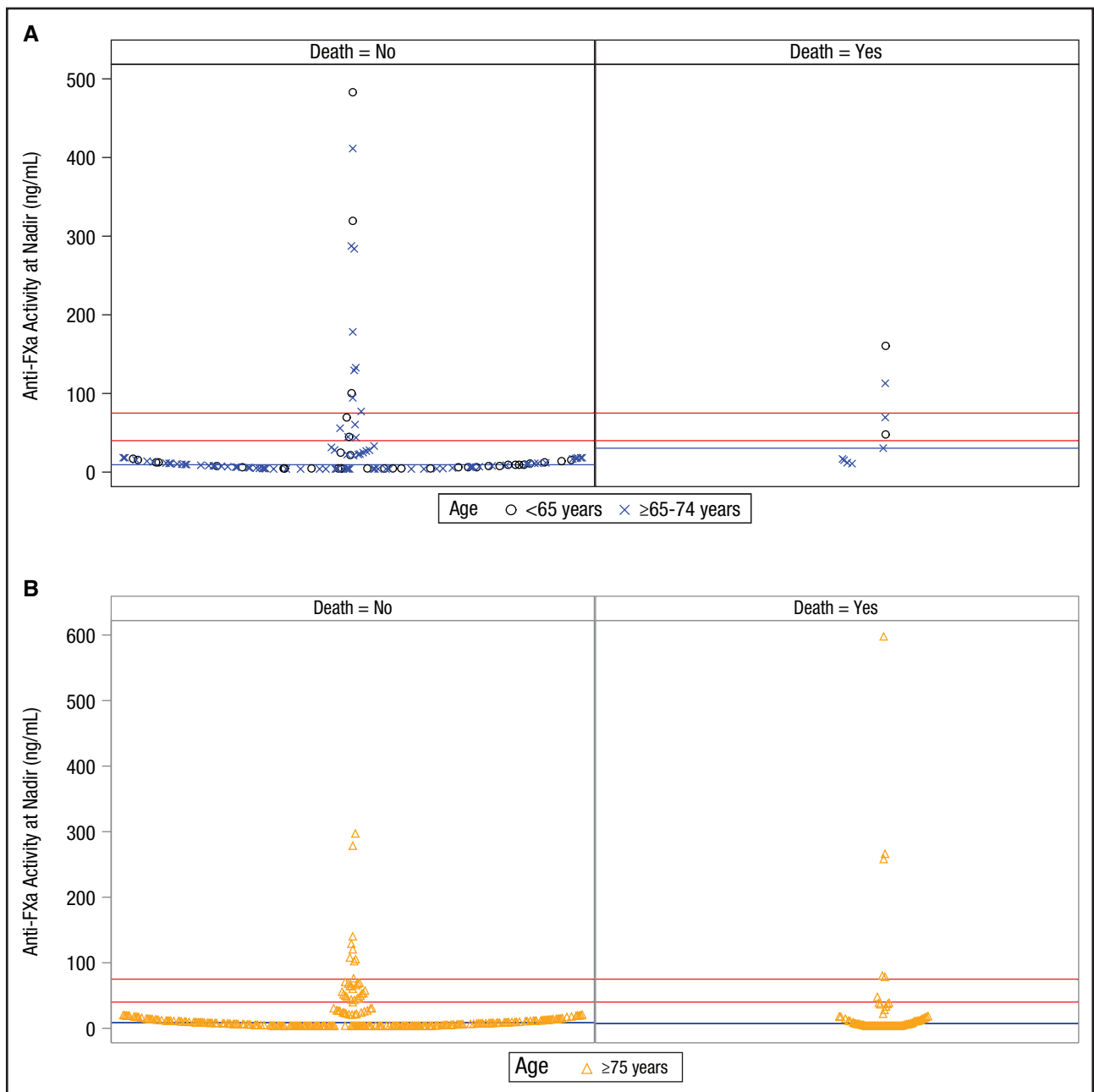


Figure 1. Beeswarm plot of anti-FXa levels at nadir, stratified by age.

The beeswarm plot is a visual explanation of mortality plotted against anti-FXa levels in the <75 years of age group (A) and the ≥75 years of age group (B). From bottom to top, horizontal red lines correspond to nadirs of 40 and 75, respectively. The blue horizontal solid lines represent the medians of the anti-FXa activity level at nadir. A, The death group for patients <75 years of age shows few deaths at low anti-FXa levels, which visualizes why this correlation was significant. B, The death group for patients ≥75 years of age shows the clustering of deaths at low anti-FXa levels, which visualizes why this group confounded the overall association between low anti-FXa levels and survival. FXa indicates factor Xa.

median anti-FXa activity decreased from 121.1 ng/mL at baseline to 24.4 ng/mL at nadir (median reduction, 71% [95% CI, 82–65]); and in enoxaparin-treated patients (n=17), it decreased from 0.48 IU/mL at baseline to 0.11 IU/mL at nadir (median reduction, 75% [95% CI, 79–67]). For all 4 inhibitors, there was decreased anti-FXa activity after andexanet alfa bolus (within 2 minutes after completion), which was sustained through the end of the continuous infusion. There were 9 outliers with high anti-

FXa activity at the end of both bolus and infusion, 8 of which had very high–presentation anti-FXa activity (range, 487 to >950 ng/mL). For the remaining outlier, preinfusion anti-FXa activity was 212 ng/mL; there is no clear explanation for the lack of response. After infusion ended, anti-FXa activity gradually increased back to anticipated normal clearance levels (Figure 3). For all 4 inhibitors, no significant differences in anti-FXa activity were observed across subgroups by race (Table S8).

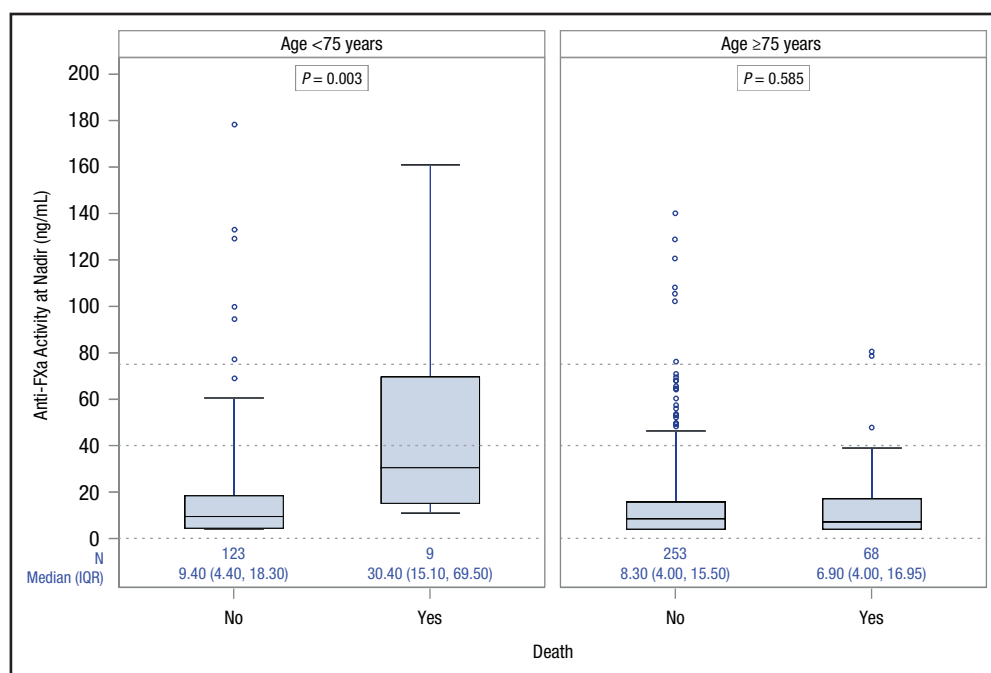


Figure 2. Boxplots of anti-FXa activity at nadir by mortality, stratified by age.

The magnified version of the boxplots shows the range of anti-FXa activity at nadir from 0–200 ng/mL. There are also some outliers that had values ranging from 200 to 600 ng/mL but are not shown in this plot. Note that these outliers are also included in the analysis to get the median (IQR) and *P* values for comparing the medians between groups defined by mortality. To see the whole picture of data distribution and the boxplots, refer to Figure 3 and Figure S2, respectively. Horizontal lines within each box show the median; tops and bottoms of boxes denote the 75th and 25th percentiles (IQR), respectively; whiskers denote the 90th and 10th percentiles; dots indicate outliers. FXa indicates factor Xa; and IQR, interquartile range.

Hemostatic Efficacy

Of the 349 patients in the efficacy analyses, 7 were nonevaluable for hemostatic efficacy related to administrative reasons, leaving 342 patients with evaluable efficacy. Hemostatic efficacy was good or excellent in 80% (95% CI, 75–84) of patients overall and did not vary significantly by subgroups of FXa inhibitor, sex, type of bleeding, age, or andexanet alfa dose (Figure S4). Hemostatic efficacy by FXa inhibitor was 81% (95% CI, 73–87) for patients on rivaroxaban, 79% (95% CI, 72–85) for patients on apixaban, 88% (95% CI, 62–98) for patients on enoxaparin, and 79% (95% CI, 59–92) for patients on edoxaban. Hemostatic efficacy by type of bleeding was 82% (95% CI, 72–90) for gastrointestinal, 79% (95% CI, 74–84) for intracranial, and 82% (95% CI, 60–95) for other types.

Safety Outcomes

In the 30-day follow-up period, 50 (10.4%) patients had ≥ 1 thrombotic event (Figure 4). Among these 50 patients, 19 had their first event within 6 days of treatment, and 31 had their first event at 6 to 30 days after andexanet alfa treatment. There were 15 deep vein thromboses, 7 pulmonary emboli, 22 ischemic strokes, 3 transient ischemic attacks, and 10 myocardial infarctions (Table 2). Investigator-reported adverse

events were listed by severity (unadjudicated results). There were 14 deep vein thromboses in 13 patients: 3 mild in 3 patients, 7 moderate in 7 patients, 3 severe in 2 patients, and 1 life-threatening in 1 patient. There were 12 patients who had deep vein thromboses according to adjudication committee review, but they were not listed by severity.

There was one severe infusion reaction of rigors, severe chills, hypertension, oxygen desaturation, fever, agitation, and confusion beginning 75 minutes after starting andexanet alfa and resolving 80 minutes later with treatment (diphenhydramine, prednisone, haloperidol, paracetamol, and supplemental oxygen). No neutralizing antibodies to factor X, FXa, or andexanet alfa developed. Of the 479 patients in the safety population, 469 had antibody samples at baseline, and 316 patients had samples at day 30/45. The remainder of samples was not obtained because of either death or missing samples at the day-30 or day-45 follow-up.

There were 75 (15.7%) deaths in 30 days. Mortality after ICH was 16.9% (56 of 331); after gastrointestinal bleeding, it was 11.9% (13 of 109); and after other major bleeding, it was 15.4% (6 of 39). Mortality for patients ≥ 75 years of age was 19.6% (65 of 331), and for those < 75 years of age, mortality was 6.8% (10 of 148). Out of the total deaths, 40 were cardiovascular related to index bleeding, 18 were cardiovascular not related to

Table 1. Patient Baseline Characteristics (Safety and Efficacy Populations)

Parameter	Safety population (N=479)	Efficacy population (n=349)
Age, y, mean±SD	77.9±10.7	77.7±10.6
Male sex, n (%)	260 (54.3)	185 (53.0)
White race, n (%)	414 (86.4)	300 (86.0)
Body mass index, kg/m ² , mean±SD	26.6±5.6	26.6±5.8
Estimated creatinine clearance, n (%) [*]		
Missing data	20 (4.2)	15 (4.3)
<30 mL/min	44 (9.2)	35 (10.0)
30 to <60 mL/min	185 (38.6)	138 (39.5)
≥60 mL/min	230 (48.0)	161 (46.1)
Primary indication for anticoagulation, n (%) [†]		
Atrial fibrillation	389 (81.2)	284 (81.4)
Venous thromboembolism [‡]	72 (15.0)	51 (14.6)
Other	18 (3.8)	14 (4.0)
Medical history, n (%)		
Myocardial infarction	59 (12.3)	46 (13.2)
Stroke	110 (23.0)	86 (24.6)
Deep vein thrombosis	80 (16.7)	61 (17.5)
Pulmonary embolism	48 (10.0)	34 (9.7)
Atrial fibrillation	396 (82.7)	288 (82.5)
Heart failure	94 (19.6)	75 (21.5)
Diabetes	132 (27.6)	100 (28.7)
Factor Xa inhibitor, n (%)		
Rivaroxaban	176 (36.7)	132 (37.8)
Apixaban	245 (51.1)	172 (49.3)
Edoxaban	36 (7.5)	28 (8.0)
Enoxaparin	22 (4.6)	17 (4.9)
Primary site of bleeding, n (%)		
Gastrointestinal tract	109 (22.8)	78 (22.3)
Central nervous system/ intracranial	331 (69.1)	249 (71.3)
Other	39 (8.1)	22 (6.3)

^{*}Creatinine clearance estimated according to the Cockcroft–Gault formula.

[†]If >1 primary indication for anticoagulation was recorded, atrial fibrillation was listed as the primary indication if present; in the remaining patients, venous thromboembolism was considered primary if present.

[‡]Venous thromboembolism refers to prevention or treatment of deep vein thrombosis and pulmonary embolism.

index bleeding, 15 were not cardiovascular, and 2 were uncertain or unknown (definitions that were published previously⁶ and used by an independent academic adjudication committee). There were 6 deaths after 30 days (occurring on days 33 [2 deaths], 35, 39, 42, and 44).

There were 323 (67.4%) patients who received at least some parenteral or oral anticoagulant during follow-up. None of the 130 (27.1%) patients who restarted oral anticoagulation had a thrombotic event after restart dur-

ing the 30-day study period, whereas 11 (8.5%) patients had a thrombotic event before restart of oral anticoagulant therapy. Of the 50 patients who had ≥1 thrombotic event, 34 either never restarted any anticoagulant or had the event before restart. Only 16 events occurred after patients restarted anticoagulation with nonoral agents (Tables 2 and 3).

Thrombin Generation

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 (Figure S5).

Anti-FXa, Hemostatic Efficacy, and Mortality Correlations

Anti-FXa Activity and Mortality Correlation

Figure S1 shows some signs of nonlinearity when anti-FXa levels at nadir were low (eg, <10 ng/mL). However, the nonlinearity was not significant, as suggested by a likelihood ratio test comparing models with and without the 2 created spline variables (by comparing models 1 and 2 as defined in Table S5; $P=0.296$). The 4 models being compared varied by format of anti-FXa levels at nadir and by whether an ICH bleeding indicator was included in the model (Table S5). The AIC and negative 2 times log-likelihoods ($-2\log L$) of the 4 compared models are given in Table S5. Among the 3 models (Mortality–Nadir Correlation Models 1–3) that had different formats of anti-FXa levels at nadir but the same confounders, the model with the logarithmic transformation had the smallest AIC (349.11) and was selected as the final model. The final model selected had the logarithmic transformed anti-FXa level at nadir as the covariate of primary interest, adjusting for age, CHA₂DS₂-VASc score, time from hospital arrival to bolus, and ICH bleeding. The parameter estimating results for this model are shown in Table S9.

Overall, there was no significant association between mortality and anti-FXa activity level at nadir (Table S9). However, the significance in the interaction of age indicator and anti-FXa activity level at nadir suggested the effect of anti-FXa activity levels on mortality in younger patients (<75 years of age) was not the same as that of older patients (≥75 years of age; $P=0.046$; Table S10). In the younger patient group (<75 years of age), the median anti-FXa activity levels at nadir were significantly lower in the no-death group than in the death group ($P=0.003$ by Wilcoxon rank-sum test; Figures 1 and 2; Figure S2). After adjusting for confounders of age, CHA₂DS₂-VASc score, and time from hospital arrival to bolus, the association was still significant ($P=0.022$; Figure S3; Table S6).

Anti-FXa Activity and Hemostatic Efficacy

There was no significant association between hemostatic efficacy and change in anti-FXa activity from

baseline to nadir in the entire cohort, inclusive of all bleeding types. For patients with ICH in the safety population (enoxaparin patients were excluded because

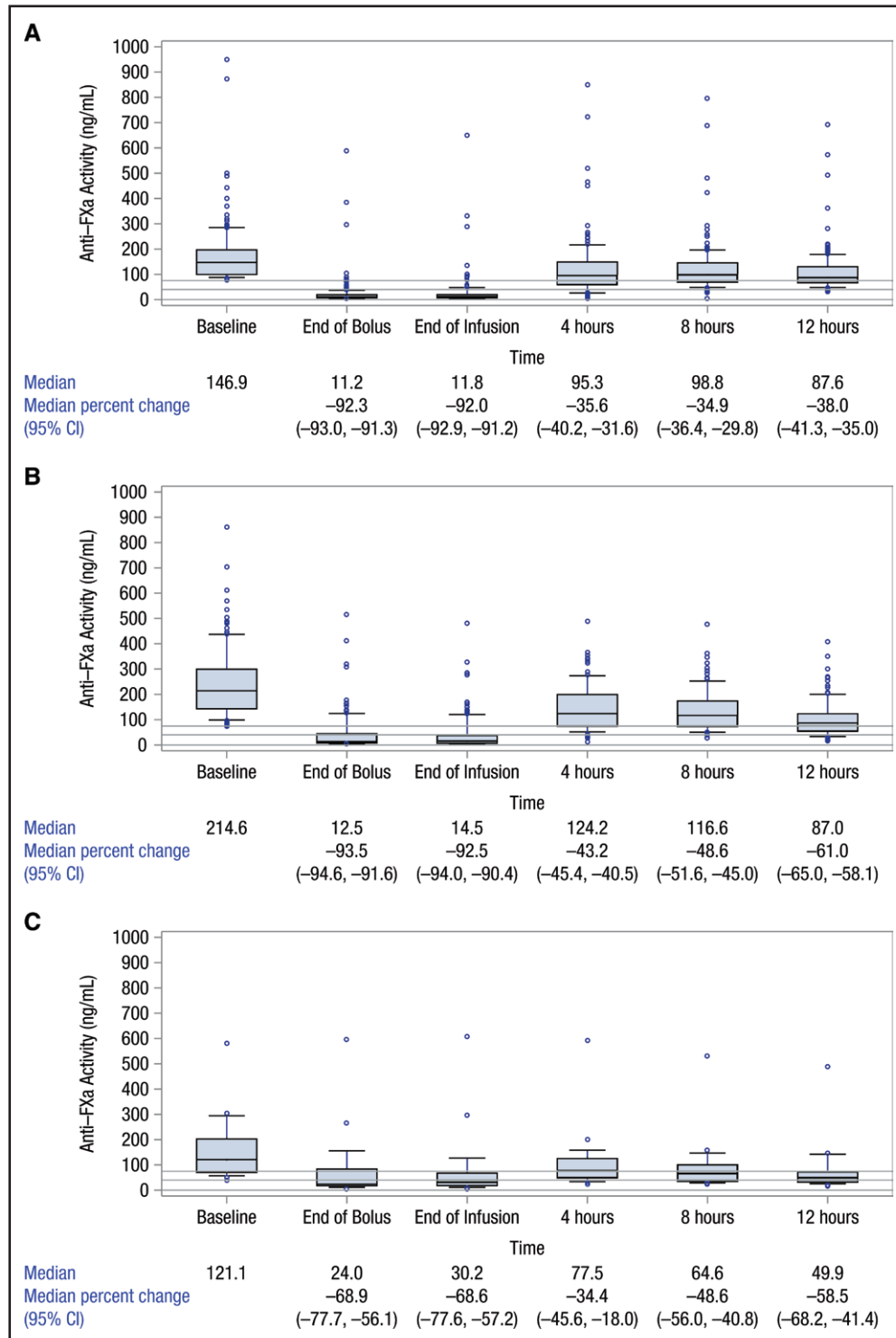


Figure 3. Boxplots of anti-FXa activity in patients receiving apixaban, rivaroxaban, edoxaban, and enoxaparin.

Time course of anti-FXa activity from baseline through 12 hours after treatment is shown for patients receiving apixaban (**A**), rivaroxaban (**B**), edoxaban (**C**), and enoxaparin (**D**). Horizontal lines within each box show the median; tops and bottoms of boxes denote the 75th and 25th percentiles, respectively; whiskers denote the 90th and 10th percentiles; dots indicate outliers. For patients receiving edoxaban, rivaroxaban, and apixaban, 2 horizontal reference lines (40 and 75 mg/mL) are plotted. For patients receiving enoxaparin, a horizontal reference of 0.25 IU/mL is plotted. FXa indicates factor Xa. (Continued)

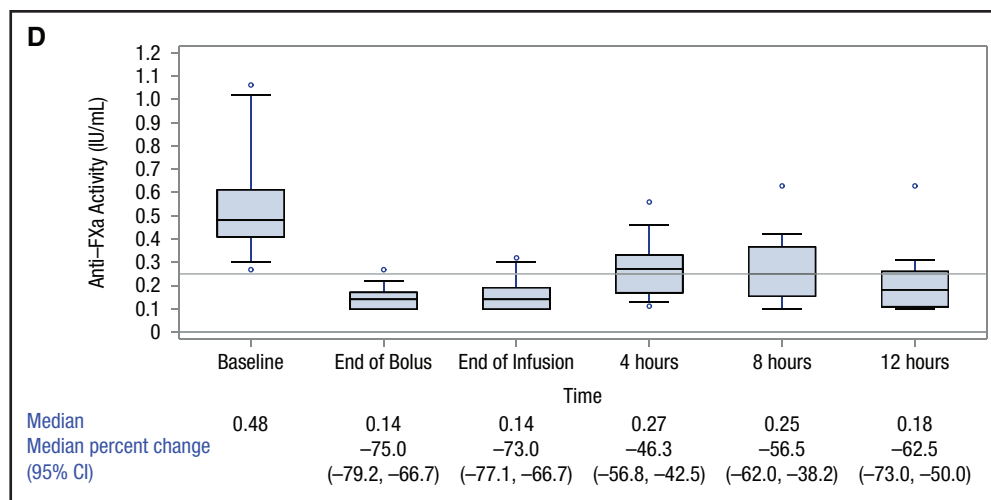


Figure 3 Continued.

of the different units of measure of anti-FXa activity levels), the prediction of absolute change in anti-FXa activity from baseline to nadir for hemostatic efficacy was significant. The area under the receiver operating characteristic curve was 0.62 (95% CI, 0.54–0.70; Figure S6).

Hemostatic Efficacy and Mortality Correlation

There was a significant correlation between hemostatic efficacy and lower mortality in all patients ($P < 0.001$; Table S11).

Heterogeneity During Visit Time Among FXa Inhibitors

In the efficacy population, there were 132, 172, and 28 patients on FXa inhibitors rivaroxaban, apixaban, and edoxaban, respectively. The profile plot of mean change from baseline in anti-FXa activity (ng/mL) versus visit time by FXa inhibitor is shown in Figure S7. The spaghetti plots for each FXa inhibitor group are shown in Figure S8. The variance–covariance matrix of the repeated visits per subject, which is based on the unstructured pattern, is given in Table S12, and the correlation matrix is provided in Table S13. The degrees of freedom and P values for the fixed effects are provided in Table S14. The least square estimated mean changes from baseline for each FXa inhibitor and visit from this interaction term are shown in Table S15 and graphed in Figure S9. The pairwise differences in mean change from baseline in anti-FXa activity among FXa inhibitors are shown in Table S16. The effects of FXa inhibitors on the mean change from baseline in anti-FXa activity at different time points are shown in Table S17. As shown in Table S17, there was heterogeneity among different FXa inhibitors in their effects on the mean change from baseline in anti-FXa activity at 8 and 12 hours after the end of infusion ($P < 0.001$ for both hours).

DISCUSSION

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. A global randomized controlled trial of andexanet alfa versus usual care in ICH patients is ongoing (ANNEXA-I).

The correlation between lower anti-FXa activity levels and lower mortality in andexanet alfa–treated patients < 75 years of age is intriguing, although exploratory. It was hypothesized that removing the anticoagulant with andexanet alfa in acute bleeding will reduce mortality, and these data provide some support for this idea.⁹ Overall mortality within 30 days in this study was 15.7%, which is lower than in some cohorts of patients with FXa inhibitor–associated major bleeding.^{10–13} When comparing different cohorts, consideration should be given to differences in baseline patient characteristics, as well as the proportion of patients with ICH, which comprise the majority of patients within ANNEXA-4 (69%). It is possible that the association between anti-FXa levels and mortality was only seen in younger patients because the signal was confounded by concomitant frailty, other comorbidity, and withdrawal of active care because of early do-not-resuscitate orders in older patients.^{14–17} These factors contribute to a much higher in-hospital mortality, regardless of the presenting disease.^{14–17}

A reduction in anti-FXa activity predicted hemostatic efficacy in the ICH subgroup in previous analyses,⁷ although there was no prediction in the total safety population. In these analyses, there was also a modest prediction (area under the receiver operating characteristic curve, 0.62 [95% CI, 0.54–0.70]) in the ICH subgroup but not in the overall safety population. As expected, higher hemostatic efficacy correlated with lower mortality.

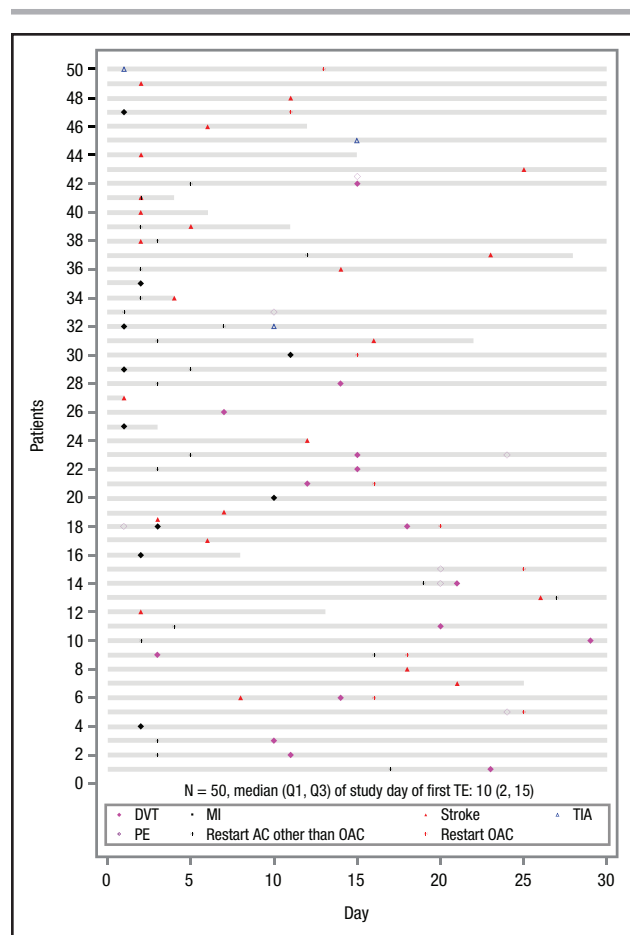


Figure 4. Timing frequency plot with distribution of all thrombotic events.

AC indicates anticoagulation; DVT, deep vein thrombosis; MI, myocardial infarction; OAC, oral anticoagulation; PE, pulmonary embolism; TE, thrombotic event; and TIA, transient ischemic attack.

The thrombotic event incidence was 10.4%. Thrombotic events occurring after major bleeding may be attributable to patients' intrinsic thrombotic risk, activation of coagulation concomitant with bleeding, withdrawal of the anticoagulant, or the reversal agent itself.¹⁸ Patients with ICH are at particularly high thrombotic risk, and the percentage of patients with ICH at enrollment in the studies of andexanet alfa, idarucizumab, and prothrombin complex concentrate was 64%, 33%, and 12%, respectively.¹⁸ The ongoing ANNEXA-I study will prospectively evaluate thrombotic events against usual care in patients with ICH, at which time comparisons between reversal strategies will be possible.

These data suggest the importance of prompt resumption of anticoagulation, when indicated, after major bleeding in these highly prothrombotic patients. Although some patients did experience thrombosis after prophylactic parenteral anticoagulants (routinely administered low-dose heparins or heparinoids for venous thromboembolism prevention in hospitalized patients) were restarted, no patient had a throm-

botic event after restart of oral anticoagulation, as noted previously.¹⁹ Four ongoing phase-3 randomized trials are testing when and whether to restart anticoagulation: 3 are studying restarting anticoagulation treatment after spontaneous ICH (ENRICH AF [Edoxaban for Intracranial Hemorrhage Survivors With Atrial Fibrillation]; ASPIRE [Aspirin to Prevent Recurrent Venous Thromboembolism]; PRESTIGE-AF [Prevention of Stroke in Intracerebral Haemorrhage Survivors With Atrial Fibrillation]) and one is looking at restarting anticoagulation treatment after traumatic ICH (Restart TICrH [Restarting and Timing of Oral Anticoagulation After Traumatic Intracranial Hemorrhage]).²⁰

Although anti-FXa levels fell significantly in patients treated with each inhibitor studied, there was heterogeneity in the degree of decline between inhibitors. Whether this is explained by the pharmacodynamic and pharmacokinetic differences between the inhibitors or the interaction between andexanet alfa and the various drugs cannot be determined with certainty in a single cohort, but will again be evaluated against usual care in ANNEXA-I. Importantly, thrombin generation was maintained for all inhibitors, which might lessen concern for this heterogeneity. Also, clinical hemostatic efficacy was not significantly different by FXa inhibitor type.

Limitations

This study lacks a comparator group; all of the findings are observational. This lack of a randomized comparator means the findings are correlations that could be confounded in multiple ways, particularly with selection bias. The lower mortality in this study, compared with other anticoagulant reversal cohorts, may be related to selection bias, or it may have been mitigated by the reversal agent, but confirmation of this via randomized controlled study (eg, ANNEXA-I) is necessary. Expert panels recommend exclusion of larger intracranial hematomas, generally >30 to 60 mL, from clinical trials of medical therapies, as there is little potential for survival and meaningful recovery.²¹ ANNEXA-4 excluded patients with Glasgow coma scale scores <7 or with a hematoma volume >60 mL, although few patients with large hematomas were enrolled. The median volume of all spontaneous ICH has been estimated at 13.76 mL,²² and the median in ANNEXA-4 was 14 mL. Compared with previous ICH studies, the hematoma volumes of patients enrolled in ANNEXA-4 appear consistent. For example, the ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) trial median was ≈10 mL, whereas the VISTA-ICH (Virtual International Stroke Trials Archive), i-DEF (Deferoxamine Mesylate in Patients With Intracerebral Hemorrhage), and TICH-2

Table 2. Thrombotic Events and Deaths Within 30 Days and After Restarting Anticoagulation* (Safety Population)

	Safety population (N=479)			
	Total	<6 days after bolus	6–14 days after bolus	15–30 days after bolus
Thrombotic event† within 30 days	50 (10.4)	19 (4.0)	15 (3.1)	16 (3.3)
Myocardial infarction	10 (2.1)	8 (1.7)	2 (0.4)	0
Ischemic stroke	22 (4.6)	10 (2.1)	6 (1.3)	6 (1.3)
Stroke of uncertain classification	1 (0.2)	0	1 (0.2)	0
Transient ischemic attack	3 (0.6)	1 (0.2)	1 (0.2)	1 (0.2)
Deep vein thrombosis	15 (3.1)	1 (0.2)	6 (1.3)	8 (1.7)
Pulmonary embolism	7 (1.5)	1 (0.2)	1 (0.2)	5 (1.0)
Arterial systemic embolism	0	0	0	0
Death within 30 days	75 (15.7)	16 (3.3)	28 (5.8)	31 (6.5)
Death, cardiovascular	58 (12.1)	14 (2.9)	21 (4.4)	23 (4.8)
Death, noncardiovascular	15 (3.1)	2 (0.4)	6 (1.3)	7 (1.5)
Death, uncertain cause	2 (0.4)	0	1 (0.2)	1 (0.2)
Restart of any anticoagulation‡	323 (67.4)	226 (47.2)	65 (13.6)	32 (6.7)
Thrombotic event before restart (or never restarted)	34 (7.1)	–	–	–
Thrombotic event after restart	16 (3.3)	–	–	–
Restart of any oral anticoagulation§	130 (27.1)	40 (8.4)	53 (11.1)	37 (7.7)
Thrombotic event before restart (or never restarted)	50 (10.4)	–	–	–
Thrombotic event after restart	0	–	–	–

All data are expressed as n (%).

*Thrombotic events that occurred on the day of restarting anticoagulation were considered to have occurred before the restart.

†Some patients had >1 thrombotic event.

‡Including any form of heparin or low-molecular-weight heparin, fondaparinux, argatroban, and any oral anticoagulant (vitamin K antagonist or direct oral anticoagulation [eg, apixaban, rivaroxaban, dabigatran, and edoxaban] of any dose and any duration).

§Including any oral anticoagulant (vitamin K antagonist or direct oral anticoagulation of any dose and any duration).

(Tranexamic Acid for Hyperacute Primary Intracerebral Hemorrhage) medians were 12 to 13 mL.^{23–26} The FAST (Factor Seven for Acute Hemorrhagic Stroke) trial was an outlier, with a median of ≈24 mL.²⁷ Hematoma volumes in ICH studies tend to skew to the lower end, at least partly because of the difficulty in enrolling larger hematoma volumes and the inherent delays of study team coordination, obtaining informed consent, and preparing the study drug. Clinicians facing these high-mortality presentations understandably feel compelled to intervene quickly, often in ways that may make the patient ineligible for the study.

Hematoma expansion in ICH cases could be biased because of the time between enrollment (and index scan) and the start of drug infusion (2–3 hours per protocol), leading to undetected expansion, which would be incorrectly attributed to treatment failure. The follow-up scan after andexanet alfa measures the hematoma expansion before andexanet alfa plus any expansion that happens after andexanet alfa. Anticoagulant restarting behavior is subject to confounding by indication, making milder cases more likely to be restarted and have better outcomes.

Additionally, 86% of the enrolled patients were White, meaning data on non-White patients are needed.

Table 3. Adjudicated Thrombotic Events Within 30 Days

Variable	All patients (N=479)	Gastrointestinal (n=109)	Intracranial hemorrhage (n=331)	Other (n=39)	P value*
Patients restarting oral anticoagulants	130 (27.1)	50 (45.9)	58 (17.5)	22 (56.4)	<0.001
Thrombotic event before restart†	11 (8.5)	3 (6.0)	5 (8.6)	3 (13.6)	0.535
Thrombotic event after restart†	0	0	0	0	–
Patients restarting any anticoagulants	323 (67.4)	64 (58.7)	227 (68.6)	32 (82.1)	0.021
Thrombotic event before restart†	17 (5.3)	3 (4.7)	9 (4.0)	5 (15.6)	0.031
Thrombotic event after restart†	16 (5.0)	0	15 (6.6)	1 (3.1)	0.063

All data are expressed as n (%), except for P values. The academic adjudication committee was independent.

*Fisher exact test was used if the smallest cell count was <5; otherwise, a χ^2 test was used.

†Denominator is number of patients anticoagulated.

CONCLUSIONS

In this prospective cohort of FXa inhibitor-associated major bleeding patients, andexanet alfa reduced anti-FXa levels and was associated with good or excellent hemostatic efficacy in 80% of patients. Specific to certain populations, 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.

ARTICLE INFORMATION

Received October 26, 2021; accepted January 19, 2023.

Affiliations

Seton Dell Medical School Stroke Institute, Dell Medical School, University of Texas at Austin (T.J.M.). Department of Internal Medicine and Radboud Institute of Health Sciences, Nijmegen, the Netherlands (S.M.). Population Health Research Institute (L.X., A.S., S.J.C.) and Department of Medicine (J.W.E., M. Crowther), McMaster University, Hamilton, Ontario, Canada. Alexion, AstraZeneca Rare Disease, Boston, MA (B.K.). Departments of Clinical Neurosciences and Radiology, Cumming School of Medicine, University of Calgary, Alberta, Canada (A.D.). Center for Molecular and Vascular Biology, University of Leuven, Belgium (P.V.). Guy's and St. Thomas' Hospitals, London, UK (A.T.C.). Department of Medicine I, Division of Hematology and Hemostasis, University Hospital Dresden, Germany (J.B.-W.). Harvard Medical School, Boston, MA (C.M.G.). Instituto de Investigación Hospital Universitario, La Paz, Madrid, Spain (J.L.-S.). Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Centers, University of Amsterdam, the Netherlands (M. Coppens). Centre Hospitalier Universitaire de Clermont-Ferrand, France (J.S.). Grenoble-Alpes University Hospital, France (P.A.).

Acknowledgments

Drs Milling, Middeldorp, and Xu drafted the manuscript, and all other authors made significant contributions, including subsequent revisions of the manuscript.

Sources of Funding

Support was provided by Portola Pharmaceuticals, Inc, now Alexion, AstraZeneca Rare Disease, after acquisition of Portola by Alexion.

Disclosures

Dr Milling has consulted for and served on scientific advisory boards of Alexion, CSL Behring, Octapharma, and Cellphire Therapeutics; and reports honoraria from Alexion and a research grant from CSL Behring. Dr Middeldorp reports personal fees from Daiichi Sankyo, Bayer, Pfizer, Boehringer Ingelheim, Portola/Alexion, AbbVie, Bristol Myers Squibb, Sanofi, and Viatrix, all paid to his institution; and grants from Daiichi Sankyo, Bayer, Pfizer, and Boehringer Ingelheim. Dr Koch is an employee of Alexion, AstraZeneca Rare Disease. Dr Demchuck has consulted for Medtronic, HLS Therapeutics, Inc, and Boehringer Ingelheim; received compensation from Philips for data and safety monitoring services; and has a patent issued for stroke-imaging software licensed to Circle NVI. Dr Eikelboom reports consulting for/honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Pfizer, Janssen, Sanofi-Aventis, and Servier; and grants and/or in-kind support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Pfizer, Janssen, and Sanofi-Aventis. Dr Verhamme reports honoraria for lectures and/or consultancy from Alexion, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Bristol Myers Squibb, Leo Pharma, Janssen, and Pfizer; and research support from Bayer, Bristol Myers Squibb, Daiichi Sankyo, and Pfizer. Dr Cohen reports fees for serving on adjudication committees for Boehringer Ingelheim and AbbVie; grant support and fees for serving on committees from Bristol Myers Squibb, Daiichi Sankyo, and Pfizer; consulting fees from Janssen, Portola Pharmaceuticals, and Ono Pharmaceuticals; and fees for serving on a steering committee and consulting fees from Bayer. Dr Beyer-Westendorf reports personal honoraria (lectures and advisory boards) and travel support from Bayer, Daiichi Sankyo, and Alexion; and institutional research support from Bayer, Daiichi Sankyo, Pfizer, and Alexion. Dr Gibson has consulted for Alexion, AstraZeneca, Bayer, Janssen, and CytoSorbents. Dr Lopez-Sendon has

consulted for Alexion. Dr Crowther reports grants from Bayer AG; and personal fees from Servier Canada, Asahi Kasei, Precision Biologics, Hemostasis Reference Laboratories, Syneco Health, Pfizer Canada, CSL Behring, and Diagnostica Stago. Dr Shoamanesh has consulted for Alexion, Octapharma, Bayer, Daiichi Sankyo, Bristol Myers Squibb, and Servier Canada. Dr Coppens reports research support from Bayer, uniQure, Novo Nordisk, and Roche; and personal fees from CSL Behring, Daiichi Sankyo, Portola/Alexion, Roche, Sanquin Blood Supply, uniQure, Novo Nordisk, Pfizer, and Sobi. Dr Schmidt has consulted for Bayer, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim, and Daiichi Sankyo. Dr Albaladejo has consulted for Pfizer, Sanofi, and Bristol Myers Squibb. Dr Connolly has consulted for Alexion, Bristol Myers Squibb, Bayer, and Daiichi Sankyo. Dr Xu reports no conflicts.

Data Transparency

Alexion will consider requests for disclosure of clinical study participant-level data if participant privacy is assured through methods like data de-identification, pseudonymization, or anonymization (as required by applicable law), and if such disclosure was included in the relevant study informed consent form or similar documentation. Qualified academic investigators may request participant-level clinical data and supporting documents (statistical analysis plan and protocol) pertaining to Alexion-sponsored studies. Further details regarding data availability and instructions for requesting information are available in the Alexion Clinical Trials Disclosure and Transparency Policy at <https://alexion.com/our-research/research-and-development>. (Data request form: <https://alexion.com/contact-alexion/medical-information>.)

Supplemental Material

Tables S1–S17

Figures S1–S9

Appendix

REFERENCES

- Coleman CI, Dobesh PP, Danese S, Ulloa J, Lovelace B. Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study. *Future Cardiol*. 2021;17:127–135. doi: 10.2217/fca-2020-0073
- Ibáñez L, Sabaté M, Vidal X, Ballarín E, Rottenkolber M, Schmiel S, Heeke A, Huerta C, Merina EM, Montero D, et al. Incidence of direct oral anticoagulant use in patients with nonvalvular atrial fibrillation and characteristics of users in European countries (2008–2015): a cross-national drug utilization study. *Br J Clin Pharmacol*. 2019;85:2524–2539. doi: 10.1111/bcp.14071
- Steiner T, Weitz JI, Veltkamp R. Anticoagulant-associated intracranial hemorrhage in the era of reversal agents. *Stroke*. 2017;48:1432–1437. doi: 10.1161/STROKEAHA.116.013343
- Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, Luan P, Hutchaleelaha A, Inagaki M, Conley PB, et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med*. 2013;19:446–451. doi: 10.1038/nm.3102
- Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, Mathur VS, Castillo J, Bronson MD, Leeds JM, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373:2413–2424. doi: 10.1056/NEJMoa1510991
- Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, Bronson MD, Lu G, Conley PB, Verhamme P, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375:1131–1141. doi: 10.1056/NEJMoa1607887
- Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, Yue P, Bronson MD, Lu G, Conley PB, et al; ANNEXA-4 Investigators. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380:1326–1335. doi: 10.1056/NEJMoa1814051
- Hahn GJ, Meeker WQ. *Statistical Intervals: A Guide for Practitioners*. John Wiley & Sons; 1991.
- Fernando SM, Mok G, Castellucci LA, Dowlatshahi D, Rochweg B, McIsaac DI, Carrier M, Wells PS, Bagshaw SM, Fergusson DA, et al. Impact of anticoagulation on mortality and resource utilization among critically ill patients with major bleeding. *Crit Care Med*. 2020;48:515–524. doi: 10.1097/CCM.00000000000004206
- Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, Hempel EL, Magnusson M, Frisk T, Schulman S. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017;130:1706–1712. doi: 10.1182/blood-2017-05-782060

11. Schulman S, Gross PL, Ritchie B, Nahiriak S, Lin Y, Lieberman L, Carrier M, Crowther MA, Ghosh I, Lazo-Langner A, et al; Study Investigators. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemost*. 2018;118:842–851. doi: 10.1055/s-0038-1636541
12. Panos NG, Cook AM, John S, Jones GM; Neurocritical Care Society (NCS) Pharmacy Study Group. Factor Xa inhibitor-related intracranial hemorrhage: results from a multicenter, observational cohort receiving prothrombin complex concentrates. *Circulation*. 2020;141:1681–1689. doi: 10.1161/CIRCULATIONAHA.120.045769
13. Milling TJ Jr, Clark CL, Feronti C, Song SS, Torbati SS, Fermann GJ, Weiss J, Patel D. Management of factor Xa inhibitor-associated life-threatening major hemorrhage: a retrospective multi-center analysis. *Am J Emerg Med*. 2018;36:396–402. doi: 10.1016/j.ajem.2017.08.042
14. Becerra-Muñoz VM, Núñez-Gil IJ, Eid CM, García Aguado M, Romero R, Huang J, Mulet A, Ugo F, Rametta F, Liebetrau C, et al. Clinical profile and predictors of in-hospital mortality among older patients hospitalised for COVID-19. *Age Ageing*. 2021;50:326–334. doi: 10.1093/ageing/afaa258
15. Inglis T, Banaszek D, Rivers CS, Kurban D, Evaniew N, Fallah N, Waheed Z, Christie S, Fox R, Thiong JM, et al. In-hospital mortality for the elderly with acute traumatic spinal cord injury. *J Neurotrauma*. 2020;37:2332–2342. doi: 10.1089/neu.2019.6912
16. Al Rajeh S. Stroke in the elderly aged 75 years and above. *Cerebrovasc Dis*. 1994;4:402–406. doi: 10.1159/000108520
17. Brizzi M, Abdul-Kasim K, Jalakas M, Selariu E, Peeah-Rasmussen H, Zia E. Early do-not-resuscitate orders in intracerebral haemorrhage; frequency and predictive value for death and functional outcome. A retrospective cohort study. *Scand J Trauma Resusc Emerg Med*. 2012;20:36. doi: 10.1186/1757-7241-20-36
18. Milling TJ Jr, Connolly SJ, Conley P. Andexanet alfa for bleeding with factor Xa inhibitors. Reply. *N Engl J Med*. 2019;381:192–193. doi: 10.1056/NEJMc1906058
19. Milling TJ Jr, King B, Yue P, Middeldorp S, Beyer-Westendorf J, Eikelboom JW, Crowther M, Xu L, Verhamme P, Siegal DM, et al; ANNEXA-4 Investigators. Restart of anticoagulant therapy and risk of thrombosis, rebleeding, and death after factor Xa inhibitor reversal in major bleeding patients. *Thromb Haemost*. 2021;121:1097–1106. doi: 10.1055/a-1400-6159
20. Milling TJ Jr, Warach S, Johnston SC, Gajewski B, Costantini T, Price M, Wick J, Roward S, Mudaranthakam D, Dula AN, et al. Restart TICrH: an adaptive randomized trial of time intervals to restart direct oral anticoagulants after traumatic intracranial hemorrhage. *J Neurotrauma*. 2021;38:1791–1798. doi: 10.1089/neu.2020.7535
21. Hemorrhagic Stroke Academia Industry (HEADS) Roundtable Participants; Second HEADS Roundtable Participants. Recommendations for clinical trials in ICH: the Second Hemorrhagic Stroke Academia Industry Roundtable. *Stroke*. 2020;51:1333–1338. doi: 10.1161/STROKEAHA.119.027882
22. Robinson D, Van Sanford C, Kwon SY, Coleman E, Sekar P, Murphy R, Flaherty ML, Demel SL, Aziz Y, Moomaw CJ, et al. What is the median volume of intracerebral hemorrhage and is it changing?. *Int J Stroke*. 2022;17:576–582. doi: 10.1177/17474930211032594
23. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, et al; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med*. 2016;375:1033–1043. doi: 10.1056/NEJMoa1603460
24. Al-Shahi Salman R, Frantziadis J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, et al; VISTA-ICH Collaboration; ICH Growth Individual Patient Data Meta-Analysis Collaborators. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol*. 2018;17:885–894. doi: 10.1016/S1474-4422(18)30253-9
25. Selim M, Foster LD, Moy CS, Xi G, Hill MD, Morgenstern LB, Greenberg SM, James ML, Singh V, Clark WM, et al; i-DEF Investigators. Deferoxamine Mesylate in Patients with Intracerebral Haemorrhage (i-DEF): a multicentre, randomised, placebo-controlled, double-blind phase 2 trial. *Lancet Neurol*. 2019;18:428–438. doi: 10.1016/S1474-4422(19)30069-9
26. Sprigg N, Flaherty K, Appleton JP, Al-Shahi Salman R, Bereczki D, Beridze M, Christensen H, Ciccone A, Collins R, Czlonkowska A, et al; TICH-2 Investigators. Tranexamic Acid for Hyperacute Primary Intracerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial. *Lancet*. 2018;391:2107–2115. doi: 10.1016/S0140-6736(18)31033-X
27. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358:2127–2137. doi: 10.1056/NEJMoa0707534