

ORIGINAL ARTICLE

Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors

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ABSTRACT

BACKGROUND

Andexanet alfa is a modified recombinant inactive form of human factor Xa developed for reversal of factor Xa inhibitors.

METHODS

We evaluated 352 patients who had acute major bleeding within 18 hours after administration of a factor Xa inhibitor. The patients received a bolus of andexanet, followed by a 2-hour infusion. The coprimary outcomes were the percent change in anti-factor Xa activity after andexanet treatment and the percentage of patients with excellent or good hemostatic efficacy at 12 hours after the end of the infusion, with hemostatic efficacy adjudicated on the basis of prespecified criteria. Efficacy was assessed in the subgroup of patients with confirmed major bleeding and baseline anti-factor Xa activity of at least 75 ng per milliliter (or ≥ 0.25 IU per milliliter for those receiving enoxaparin).

RESULTS

Patients had a mean age of 77 years, and most had substantial cardiovascular disease. Bleeding was predominantly intracranial (in 227 patients [64%]) or gastrointestinal (in 90 patients [26%]). In patients who had received apixaban, the median anti-factor Xa activity decreased from 149.7 ng per milliliter at baseline to 11.1 ng per milliliter after the andexanet bolus (92% reduction; 95% confidence interval [CI], 91 to 93); in patients who had received rivaroxaban, the median value decreased from 211.8 ng per milliliter to 14.2 ng per milliliter (92% reduction; 95% CI, 88 to 94). Excellent or good hemostasis occurred in 204 of 249 patients (82%) who could be evaluated. Within 30 days, death occurred in 49 patients (14%) and a thrombotic event in 34 (10%). Reduction in anti-factor Xa activity was not predictive of hemostatic efficacy overall but was modestly predictive in patients with intracranial hemorrhage.

CONCLUSIONS

In patients with acute major bleeding associated with the use of a factor Xa inhibitor, treatment with andexanet markedly reduced anti-factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours, as adjudicated according to prespecified criteria. (Funded by Portola Pharmaceuticals; ANNEXA-4 ClinicalTrials.gov number, NCT02329327.)

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*A complete list of the ANNEXA-4 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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FACTOR XA INHIBITORS HAVE A FAVORABLE benefit–risk profile for the treatment and prevention of thrombotic events but may cause or worsen acute major bleeding, with substantial morbidity and mortality.^{1–5} Acute major bleeding episodes that are associated with the use of factor Xa inhibitors may be difficult to treat for lack of a specific reversal agent. Andexanet alfa (coagulation factor Xa [recombinant], inactivated-zhzo) is a modified recombinant inactive form of human factor Xa designed specifically to bind and sequester factor Xa inhibitor molecules, thereby rapidly reducing anti–factor Xa activity, a measure of the anticoagulant effect of factor Xa inhibitors.^{6,7} In volunteers receiving either apixaban or rivaroxaban, andexanet rapidly reduced both the unbound fraction of the plasma level of factor Xa inhibitor and anti–factor Xa activity.⁸ Andexanet was approved by the Food and Drug Administration (FDA) in May 2018, under its Accelerated Approval Program, for patients treated with apixaban or rivaroxaban, when reversal of anticoagulation is needed owing to life-threatening or uncontrolled bleeding.

The Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study is a single-group cohort study designed to assess the efficacy and safety of andexanet in patients with acute major bleeding occurring while taking a factor Xa inhibitor. Interim results from the first 67 patients treated in this study were published previously.⁹

METHODS

STUDY DESIGN AND OVERSIGHT

This was a multicenter, prospective, open-label, single-group study. The Population Health Research Institute (PHRI) at McMaster University and the industry sponsor, Portola Pharmaceuticals, jointly designed the study, and both selected sites and supervised monitoring. The protocol, consent forms, and ancillary materials were approved by institutional review boards at each center.

An academic steering committee led the study. The PHRI collected, stored, and analyzed the data. An independent data and safety monitoring board reviewed study data for safety. An endpoint adjudication committee assessed whether patients met criteria for major bleeding and adjudicated hemostatic efficacy as well as throm-

botic events and cause of death (cardiovascular or not). A central core laboratory reviewed all computed tomography (CT) and magnetic resonance imaging (MRI) of the head. The first author wrote all drafts of the manuscript. The steering committee made all decisions regarding submission of the manuscript for publication; the members vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan, which are available with the full text of this article at NEJM.org.

After the complete enrollment of the primary cohort, an extension of the study continued to enroll patients in Germany and is expected to enroll patients in Japan beginning in 2019. The purpose of this extension is to gain experience with patients receiving edoxaban and with Japanese patients.

STUDY POPULATION

Patients were enrolled at 63 centers in North America and Europe. Patients were eligible if they were at least 18 years of age, presented with acute major bleeding, and had received within 18 hours one of the following: apixaban, rivaroxaban, or edoxaban at any dose or enoxaparin at a dose of at least 1 mg per kilogram of body weight per day. Acute major bleeding was defined as bleeding having one or more of the following features: potentially life-threatening bleeding with signs or symptoms of hemodynamic compromise (e.g., severe hypotension, poor skin perfusion, mental confusion, or low cardiac output that could not otherwise be explained); bleeding associated with a decrease in the hemoglobin level of at least 2 g per deciliter (or a hemoglobin level of ≤ 8 g per deciliter if no baseline hemoglobin level was available); or bleeding in a critical area or organ (e.g., retroperitoneal, intra-articular, pericardial, epidural, or intracranial bleeding or intramuscular bleeding with compartment syndrome). Written informed consent was obtained from all the patients, whether directly from the patient, by proxy consent from a legally authorized representative, or by emergency consent (as described in the Supplementary Appendix, available at NEJM.org).

Patients were enrolled from April 2015 through May 2018. From July 2016 through August 2017, only patients with intracranial hemorrhage were enrolled to enrich the study with



A Quick Take is available at [NEJM.org](https://www.nejm.org)

these patients. After August 2017, patients with all types of bleeding except visible, musculoskeletal, or intraarticular bleeding were enrolled. Substantive amendments to the enrollment criteria during the trial are presented in the Supplementary Appendix.

Key exclusion criteria were planned surgery within 12 hours after andexanet treatment (with the exception of minimally invasive operations or procedures); intracranial hemorrhage in a patient with a score of less than 7 on the Glasgow Coma Scale (scores range from 15 [normal] to 3 [deep coma]) or an estimated hematoma volume of more than 60 cc; expected survival of less than 1 month; the occurrence of a thrombotic event within 2 weeks before enrollment; or use of any of the following agents within the previous 7 days: vitamin K antagonist, dabigatran, prothrombin complex concentrate, recombinant factor VIIa, whole blood, or plasma.

STUDY PROCEDURES AND DATA COLLECTION

Eligible, consenting patients received an andexanet bolus over a period of 15 to 30 minutes, followed by a 2-hour infusion of the drug. The following doses were used in the initial protocol: for all patients who had received apixaban and those who had received rivaroxaban more than 7 hours before bolus administration, the bolus dose was 400 mg over a period of 15 minutes and the infusion dose was 480 mg. For patients who had received enoxaparin, edoxaban, or a dose of rivaroxaban 7 hours or less before bolus administration or at an unknown time, the bolus dose was 800 mg over a period of 30 minutes and the infusion dose was 960 mg. With protocol amendment 4, there was a minor modification to this administration plan (see the Supplementary Appendix).

Blood samples were obtained to measure anti-factor Xa activity and the unbound fraction of the plasma level of factor Xa inhibitor before and during andexanet treatment and at 4, 8, and 12 hours after the end of treatment. Methods for measurement of these values have been described previously.^{7,8} For patients with intracranial hemorrhage, CT or MRI of the head was expected to be performed within 2 hours before andexanet treatment and at 1 hour and 12 hours after the end of andexanet treatment.

STUDY OUTCOMES

The study had two coprimary efficacy outcomes: the percent change from baseline in anti-factor Xa activity after andexanet treatment and the percentage of patients with excellent or good hemostatic efficacy 12 hours after the andexanet infusion, with hemostatic efficacy assessed by an independent adjudication committee on the basis of prespecified criteria. Information regarding changes to the primary outcome during the trial and details concerning the adjudication of hemostatic efficacy are provided in the Supplementary Appendix. The primary safety outcomes were death, thrombotic events, and the development of antibodies to andexanet or to native factor X and factor Xa. Although some patients had their final safety visit completed up to 45 days after andexanet treatment, all analyses were censored at 30 days.

STATISTICAL ANALYSIS

Safety analyses included all the patients who had received andexanet. The efficacy analysis population included only patients who retrospectively met both of two criteria: baseline anti-factor Xa activity of at least 75 ng per milliliter (or ≥ 0.25 IU per milliliter for patients receiving enoxaparin) and confirmed major bleeding at presentation, as determined by the adjudication committee. Initially, a sample of 250 patients was planned, which would provide 80% power to show that the percentage of patients with excellent or good hemostatic efficacy was more than 50%. The sample was adjusted to 350 patients in protocol amendment 4 (January 2017) to meet new regulatory requirements for sufficient numbers of patients for each factor Xa inhibitor and to have at least 120 patients with intracranial hemorrhage in the efficacy analysis population.

Continuous variables are summarized as mean and standard deviation or median and interquartile range; categorical variables are presented as frequencies. Percent change from baseline in anti-factor Xa activity was computed with a two-sided nonparametric confidence interval for the median.¹⁰ Percentages of patients with effective hemostasis are presented with a 95% confidence interval calculated with the binomial test. The association between hemostatic efficacy and change in anti-factor Xa activity was examined with the use of receiver-operating-characteristic

(ROC) curves.¹¹ Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

We enrolled 352 patients from April 2015 through May 2018, including the 67 patients reported previously⁹ (Fig. S1 in the Supplementary Appendix). All the patients received andexanet and were followed for at least 30 days or until death. Patients had a mean age of 77 years; baseline medical history included myocardial infarction in 48 patients (14%), stroke in 69 (20%), and deep-vein thrombosis in 67 (19%) (Table 1). Atrial fibrillation was the primary indication for anticoagulation in 280 patients (80%). There were 128 patients (36%) receiving rivaroxaban (median daily dose, 20 mg), 194 (55%) receiving apixaban (median daily dose, 10 mg), 10 (3%) receiving edoxaban (daily dose, 30 mg [5 patients] or 60 mg [5 patients]), and 20 (6%) receiving enoxaparin (Table 1, and Table S1 in the Supplementary Appendix). The primary site of bleeding was intracranial in 227 patients (64%) and gastrointestinal in 90 (26%) (Table 1, and Table S2 in the Supplementary Appendix). There were 254 patients (72%) who met the criteria for the efficacy population (adjudicated to meet the criteria for bleeding severity and with baseline anti-factor Xa activity of ≥ 75 ng per milliliter, or ≥ 0.25 IU per milliliter for those receiving enoxaparin).

ANTI-FACTOR XA ACTIVITY

In the efficacy population, among the 134 patients who were receiving apixaban, the median value for anti-factor Xa activity was reduced from 149.7 ng per milliliter at baseline to 11.1 ng per milliliter at the end of the bolus administration, a 92% reduction (95% confidence interval [CI], 91 to 93) (Fig. 1). Among the 100 patients who were receiving rivaroxaban, the median value for anti-factor Xa activity fell from 211.8 ng per milliliter at baseline to 14.2 ng per milliliter at the end of the bolus administration, a 92% reduction (95% CI, 88 to 94). Among the 16 patients who were receiving enoxaparin, the median value for anti-factor Xa activity decreased from 0.48 IU per milliliter at baseline to 0.15 IU per milliliter at the end of the bolus administration, a 75% re-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Safety Population (N = 352)	Efficacy Population (N = 254)
Age — yr	77.4±10.8	77.1±11.1
Male sex — no. (%)	187 (53)	129 (51)
White race — no. (%)†	307 (87)	222 (87)
Body-mass index‡	27.0±5.9	27.0±6.2
Estimated creatinine clearance — no. (%)§		
<30 ml/min	33 (9)	27 (11)
30 to <60 ml/min	137 (39)	104 (41)
≥60 ml/min	167 (47)	113 (44)
Missing data	15 (4)	10 (4)
Primary indication for anticoagulation — no. (%)¶		
Atrial fibrillation	280 (80)	201 (79)
Venous thromboembolism	61 (17)	46 (18)
Other	11 (3)	7 (3)
Medical history — no. (%)		
Myocardial infarction	48 (14)	36 (14)
Stroke	69 (20)	57 (22)
Deep-vein thrombosis	67 (19)	53 (21)
Pulmonary embolism	41 (12)	28 (11)
Atrial fibrillation	286 (81)	204 (80)
Heart failure	71 (20)	56 (22)
Diabetes mellitus	107 (30)	80 (31)
Factor Xa inhibitor — no. (%)**		
Rivaroxaban	128 (36)	100 (39)
Apixaban††	194 (55)	134 (53)
Enoxaparin	20 (6)	16 (6)
Edoxaban	10 (3)	4 (2)
Site of bleeding — no. (%)‡‡		
Gastrointestinal	90 (26)	62 (24)
Intracranial	227 (64)	171 (67)
Other	35 (10)	21 (8)

* Plus-minus values are means \pm SD. Percentages may not total 100 because of rounding.

† Race was reported by the investigators.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Creatinine clearance was estimated according to the Cockcroft-Gault formula.

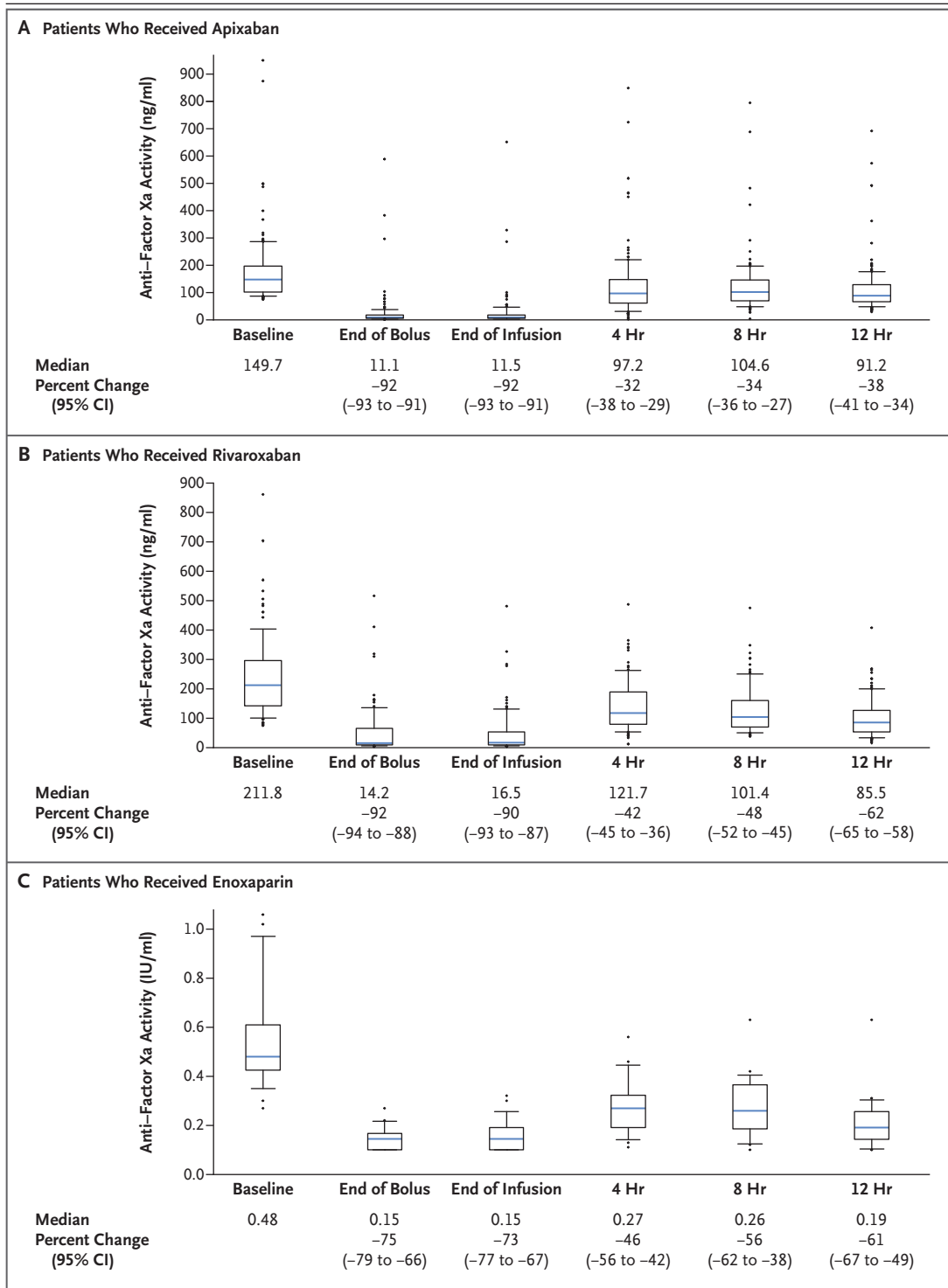
¶ For some patients, more than one primary indication was recorded. If atrial fibrillation was present, it was considered primary. Venous thromboembolism, if recorded, was considered primary in the remaining patients.

|| Venous thromboembolism includes the treatment or prevention of deep-vein thrombosis and pulmonary embolism.

** Additional details are provided in Table S1 in the Supplementary Appendix.

†† In one patient who reported receiving apixaban, analysis of plasma indicated a high concentration of rivaroxaban.

‡‡ Additional details are provided in Table S2 in the Supplementary Appendix.



duction (95% CI, 66 to 79). At 4, 8, and 12 hours after andexanet infusion, the median value for anti-factor Xa activity was reduced from baseline by 32%, 34%, and 38%, respectively, for apixaban and by 42%, 48%, and 62%, respectively, for rivaroxaban.

Figure 1 (facing page). Anti-Factor Xa Activity in the Efficacy Population.

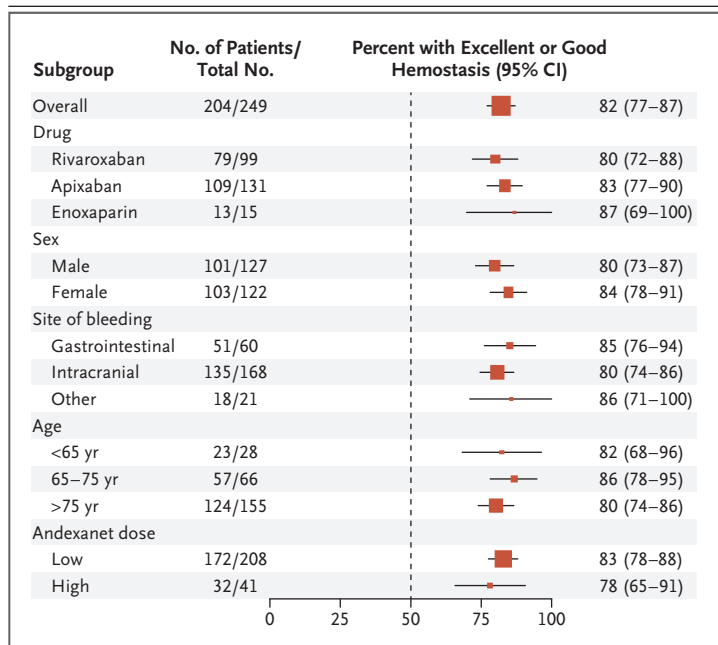
The median for each level of anti-factor Xa activity at each time point is marked as a horizontal line within the box. The top and bottom of the box denote the 75th and 25th percentiles, respectively, and the whiskers indicate the 90th and 10th percentiles. Outliers are shown as dots. The bolus of andexanet was delivered over a period of 15 to 30 minutes, and the drug infusion lasted 2 hours. Subsequent time points are measured from the end of the infusion. The plots for the 134 patients who received apixaban, the 100 who received rivaroxaban, and the 16 who received enoxaparin are shown in Panels A, B, and C, respectively. (The 4 patients in the efficacy analysis who received edoxaban are not shown.) The numbers below the graphs show the median values, the percentage change in median values from baseline, and the 95% confidence intervals (CI) for this change.

HEMOSTATIC EFFICACY

Of the 254 patients in the efficacy analysis, 249 could be evaluated for hemostatic efficacy, and 204 (82%) were adjudicated as having excellent or good hemostatic efficacy at 12 hours (95% CI, 77 to 87) (Fig. 2). Of these, 171 were adjudicated as having excellent hemostatic efficacy and 33 as having good hemostatic efficacy. The percentages of patients with excellent or good efficacy were 85% (95% CI, 76 to 94) for gastrointestinal bleeding and 80% (95% CI, 74 to 86) for intracranial bleeding. Data for patients with poor or no hemostatic efficacy are provided in Tables S3 and S4 in the Supplementary Appendix. Data for outliers with very high baseline anti-factor Xa activity are provided in the Supplementary Appendix. Results for thrombin generation are presented in Table S5 in the Supplementary Appendix.

SAFETY OUTCOMES

There were 34 patients (10%) with a thrombotic event during the 30-day follow-up period (Table 2). Of these patients, 11 had an event within 5 days after andexanet therapy, 11 had an event between 6 and 14 days, and 12 had an event between 15 and 30 days. Myocardial infarction occurred in 7 patients, ischemic stroke in 14, deep-vein thrombosis in 13, and pulmonary embolus in 5. There were 2 patients with infusion reactions, neither of which was severe (as described in the Supplementary Appendix). Antibodies to factor X or Xa developed in no patients after andexanet treatment, and no neutralizing anti-

**Figure 2. Hemostatic Efficacy.**

Shown are the percentages of patients in the efficacy analysis who had excellent or good hemostatic efficacy at 12 hours, as assessed by the independent adjudication committee on the basis of prespecified criteria. The size of the red squares is proportional to the number of patients included in the subgroup analysis. The study hypothesis was that the rate of excellent or good hemostatic efficacy would exceed 50% (indicated by the vertical dashed line). There were five patients in the efficacy population in whom hemostatic efficacy could not be adjudicated owing to administrative reasons (see Fig. S1 in the Supplementary Appendix for details). The four patients in the efficacy population who received edoxaban are not shown for the subgroup according to drug.

bodies to andexanet developed. There were 49 patients (14%) who died within 30 days after enrollment, 35 of cardiovascular causes, 12 of non-cardiovascular causes, and 2 of unknown causes.

REINITIATION OF ANTICOAGULATION AND THROMBOTIC EVENTS

Factor Xa inhibitor therapy was immediately stopped in all patients at the time of enrollment. In the 30 days after andexanet treatment, 220 patients (62%) received at least one dose of either parenteral or oral anticoagulant therapy; of these patients, 8 (2%) had a thrombotic event after restarting anticoagulation. Of the 220 patients, 100 (28%) were restarted on oral anticoagulation during follow-up. No thrombotic events occurred after oral anticoagulation had been restarted (Table 2).

Table 2. Timing of Thrombotic Event and Restarting of Anticoagulation.*

Variable	Safety Population (N = 352)			
	Total	<6 Days after Bolus	6–14 Days after Bolus	15–30 Days after Bolus
	number of patients (percent)			
≥1 Thrombotic event within 30 days†	34 (10)	11	11	12
Myocardial infarction	7	6	1	0
Ischemic stroke or stroke of uncertain classification	14	5	6	3
Transient ischemic attack	1	0	0	1
Deep-vein thrombosis	13	1	5	7
Pulmonary embolism	5	1	0	4
Death within 30 days‡	49 (14)	8	21	20
Cardiovascular cause	35	7	15	13
Noncardiovascular cause	12	1	5	6
Uncertain cause	2	0	1	1
Restart of any anticoagulation§	220 (62)	145 (41)	46 (13)	29 (8)
Thrombotic event before restart¶	26 (7)			
Thrombotic event after restart	8 (2)			
Restart of oral anticoagulation	100 (28)	31 (9)	37 (11)	32 (9)
Thrombotic event before restart¶	34 (10)			
Thrombotic event after restart	0			

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

† Some patients had more than one thrombotic event.

‡ Two deaths occurred during study follow-up, but after 30 days.

§ Restart of any anticoagulation includes the use of any form of heparin or low-molecular-weight heparin, fondaparinux, or argatroban, or any oral anticoagulant, including vitamin K antagonists and non-vitamin K antagonists (at any dose and for any duration).

¶ Included are thrombotic events that occurred in patients who never restarted anticoagulation.

|| Restart of oral anticoagulation includes only the use of vitamin K antagonists or non-vitamin K oral anticoagulants (at any dose and for any duration).

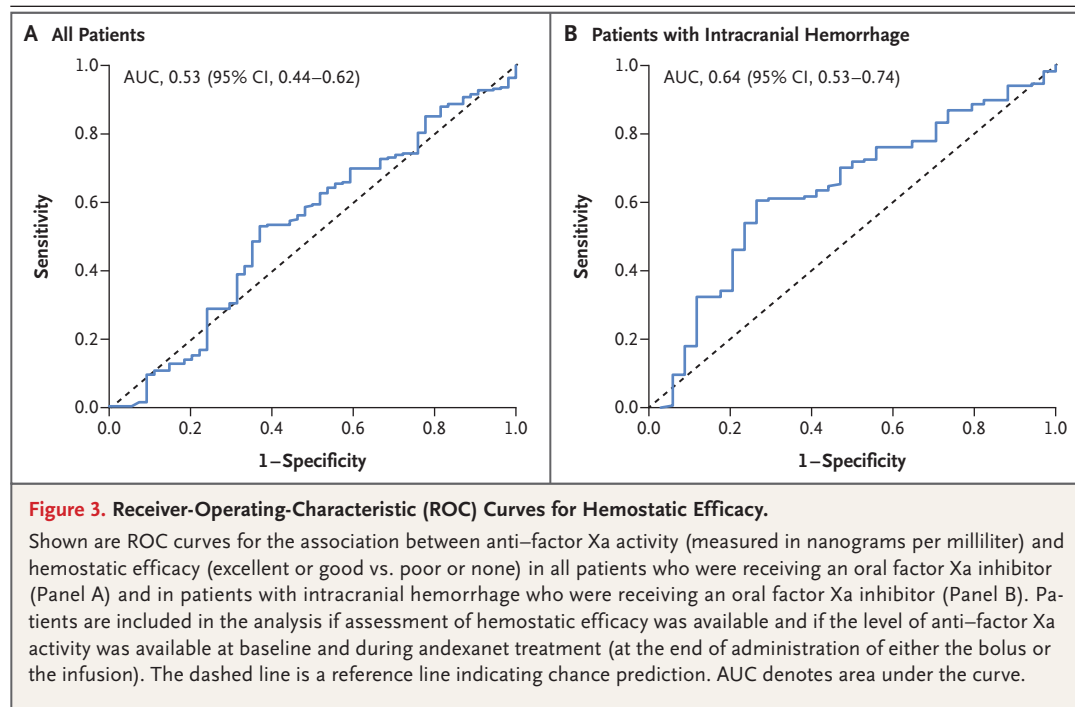
BIOMARKER—EFFICACY CORRELATION

The relationship between change in anti-factor Xa activity during andexanet therapy and adjudicated hemostatic efficacy was evaluated by means of ROC curves. Overall, there was no significant relationship between hemostatic efficacy and a reduction in anti-factor Xa activity during andexanet treatment (Fig. 3). For patients with intracranial hemorrhage, the magnitude of the reduction in anti-factor Xa activity from baseline to nadir during treatment was a predictor of hemostatic efficacy, with an area under the ROC curve of 0.64 (95% CI, 0.53 to 0.74).

DISCUSSION

Acute major bleeding that is associated with the use of factor Xa inhibitors can be a medical emergency with a poor prognosis.¹² There are limited treatment options for such patients. We administered andexanet to patients with acute major bleeding associated with factor Xa inhibitors; 64% of the patients had acute intracranial hemorrhage. The percentage of patients with excellent or good hemostatic efficacy at 12 hours, adjudicated according to prespecified criteria, was 82%, with consistent effects across all subgroups.

Rapid specific reversal of factor Xa inhibition



to hasten hemostatic control should improve clinical outcomes. The hemostatic efficacy of 82% in our trial compares well with the hemostatic efficacy of 72% observed in a previous study of prothrombin complex concentrate involving patients with major bleeding who were treated with vitamin K antagonists, which used similar criteria for assessment of anticoagulation reversal.¹¹

Small cohort studies that evaluated the management of major bleeding associated with factor Xa inhibitors, some of which enrolled patients receiving prothrombin complex concentrates (which are not approved for this indication), have included hemostatic outcomes assessed by diverse methods. Gerner et al.¹³ retrospectively measured hematoma expansion in 146 patients with intracranial hemorrhage associated with a direct oral anticoagulant; 83% of bleeding episodes were associated with factor Xa inhibitors, and 71% of patients with a bleeding episode received prothrombin complex concentrate. Hematoma expansion ($\geq 33\%$ from baseline) occurred in 34% of the patients. In a prospective evaluation of the use of prothrombin complex concentrate in patients with acute major bleeding associated with factor Xa inhibitors (intracranial hemorrhage

in 70% of patients), Majeed et al.¹⁴ reported that effective hemostasis occurred in 69% of patients. Schulman et al.¹⁵ reported hemostatic effectiveness from a registry describing the use of prothrombin complex concentrate in patients with acute major bleeding associated with factor Xa inhibitors. Of 36 patients with intracranial hemorrhage who underwent repeat brain imaging or had early death, 11 (31%) had an increase in hematoma volume of more than 35% or died.

Patients receive factor Xa inhibitors because they are at high risk for thrombotic events. Abrupt discontinuation of anticoagulation, coincident with acute bleeding, accentuates this risk. In the study by Majeed et al., involving 84 patients with acute major bleeding associated with factor Xa inhibitors, the 30-day mortality was 32%, with three thrombotic events.¹⁴ In the study by Schulman et al., involving 66 patients with acute major bleeding associated with factor Xa inhibitors, there were nine deaths (14%) by 30 days and five major thromboembolic events (8%).¹⁵ In our study, 14% of the patients died and there were thrombotic events in 10%. Not surprisingly, a majority of events occurred in patients in whom resumption of oral anticoagulation was delayed or in patients who did not restart anti-

coagulation. After restarting of oral anticoagulation, no patient had a thrombotic event during the 30-day follow-up.

We hypothesized that a reduction in anti-factor Xa activity was a predictor of clinical response. In the overall population, this was not the case, perhaps because of confounding by variation in bleeding source (venous or arterial), in platelet function, in type of factor Xa inhibitor, and in other patient characteristics. We assessed hemostatic efficacy most objectively in the patients with intracranial hemorrhage, in whom we were able to directly measure the change in hematoma volume or thickness over a period of 12 hours, using serial scans interpreted by a core laboratory. This is perhaps why a relationship was observed between a decrease in anti-factor Xa activity and hemostatic efficacy in the patients with intracranial hemorrhage. However, this relationship was not robust; in clinical practice, measurement of a change in anti-factor Xa activity is not likely to be useful for prediction of clinical response.

The most important limitation of this trial is that it did not include a randomized comparison with a control group. At the time of study initiation, it was determined that a randomized, controlled trial would have logistic and ethical challenges, given the perceived risks of placebo assignment in this highly vulnerable population. However, continued use of unapproved agents, despite a lack of rigorous clinical data, has changed the equipoise for a trial. Thus, under the guidance of the FDA and as a condition of accelerated approval in the United States, the sponsor is conducting a randomized trial (ClinicalTrials.gov number, NCT03661528) that is expected to begin later this year.

In conclusion, we treated patients with factor Xa inhibitor–associated acute major bleeding with the reversal agent andexanet alfa. Treatment with andexanet markedly reduced anti-factor Xa activity, and 82% of patients had excellent or good hemostatic efficacy at 12 hours, as adjudicated according to prespecified criteria.

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APPENDIX

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