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


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.)
ACTOR 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. 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-zhxo) 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. 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. 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.

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 thrombotic 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, intrarticular, 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
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
Andexanet for Bleeding with Factor Xa Inhibitors

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 previously (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-

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Table 1. Characteristics of the Patients at Baseline.*

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

*  Plus–minus values are means ±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.
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 percent-
ages 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. The 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-

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).
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. Hema-
toma expansion (≥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, NCT03651528) 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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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES


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