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Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage

S.J. Connolly, M. Sharma, A.T. Cohen, A.M. Demchuk, A. Członkowska, A.G. Lindgren, C.A. Molina, D. Bereczki, D. Toni, D.J. Seiffge, D. Tanne, E.C. Sandset, G. Tsivgoulis, H. Christensen, J. Beyer-Westendorf, J.M. Coutinho, M. Crowther, P. Verhamme, P. Amarenco, R.O. Roine, R. Mikulik, R. Lemmens, R. Veltkamp, S. Middeldorp, T.G. Robinson, T.J. Milling, Jr., V. Tedim-Cruz, W. Lang, A. Himmelmann, P. Ladenvall, M. Knutsson, E. Ekholm, A. Law, A. Taylor, T. Karyakina, L. Xu, K. Tsiplova, S. Poli, B. Kallmünzer, C. Gumbinger, and A. Shoamanesh, for the ANNEXA-I Investigators*

ABSTRACT

BACKGROUND

Patients with acute intracerebral hemorrhage who are receiving factor Xa inhibitors have a risk of hematoma expansion. The effect of andexanet alfa, an agent that reverses the effects of factor Xa inhibitors, on hematoma volume expansion has not been well studied.

METHODS

We randomly assigned, in a 1:1 ratio, patients who had taken factor Xa inhibitors within 15 hours before having an acute intracerebral hemorrhage to receive andexanet or usual care. The primary end point was hemostatic efficacy, defined by expansion of the hematoma volume by 35% or less at 12 hours after baseline, an increase in the score on the National Institutes of Health Stroke Scale of less than 7 points (scores range from 0 to 42, with higher scores indicating worse neurologic deficit) at 12 hours, and no receipt of rescue therapy between 3 hours and 12 hours. Safety end points were thrombotic events and death.

RESULTS

A total of 263 patients were assigned to receive andexanet, and 267 to receive usual care. Efficacy was assessed in an interim analysis that included 452 patients, and safety was analyzed in all 530 enrolled patients. Atrial fibrillation was the most common indication for factor Xa inhibitors. Of the patients receiving usual care, 85.5% received prothrombin complex concentrate. Hemostatic efficacy was achieved in 150 of 224 patients (67.0%) receiving andexanet and in 121 of 228 (53.1%) receiving usual care (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003). The median reduction from baseline to the 1-to-2-hour nadir in anti–factor Xa activity was 94.5% with andexanet and 26.9% with usual care (P<0.001). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048); ischemic stroke occurred in 17 patients (6.5%) and 4 patients (1.5%), respectively. There were no appreciable differences between the groups in the score on the modified Rankin scale or in death within 30 days.

CONCLUSIONS

Among patients with intracerebral hemorrhage who were receiving factor Xa inhibitors, andexanet resulted in better control of hematoma expansion than usual care but was associated with thrombotic events, including ischemic stroke. (Funded by Alexion AstraZeneca Rare Disease and others; ANNEXA-I ClinicalTrials.gov number, NCT03661528.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Connolly can be contacted at stuart.connolly@phri.ca or at the Population Health Research Institute, Hamilton Health Sciences, McMaster University, 30 Birge St., Room C3-204, Hamilton ON L8L 0A6, Canada.

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

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CME

A Quick Take is available at NEJM.org

Factor Xa inhibitors are widely used for prevention of thrombotic events, but they increase the risk of hemorrhage.[1] Acute intracerebral hemorrhage is one of the possible consequences of their use and is associated with high morbidity and mortality.[2-6] Furthermore, hematoma expansion is a predictor of poor outcomes.[7,8] Intracerebral hemorrhage in the context of oral anticoagulation use is associated with a poor prognosis,[9] and rapid reversal of anticoagulation could reduce the risk of hematoma expansion. Andexanet alfa is a modified recombinant inactive form of human factor Xa, which binds and sequesters factor Xa inhibitor molecules, rapidly reducing anti–factor Xa activity and restoring thrombin generation.[10,11] A previous study, ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA [Factor Xa] Inhibitors), the initial results of which were published in the *Journal*, was a single-group cohort study of andexanet in patients with acute major bleeding at any site; the results showed that almost 80% of the patients achieved hemostatic efficacy and 10% had a thrombotic event.[12,13] We performed a randomized trial to assess the efficacy and safety of andexanet as compared with usual care in patients with acute intracerebral hemorrhage.

Methods

Trial Design and Oversight

An independent ethics committee at each trial site approved the protocol. Written consent was obtained directly from the patients or by proxy or was deferred in some approved situations. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. An independent data and safety monitoring board monitored the trial.

This trial was coordinated by the Population Health Research Institute, a joint institute of McMaster University and Hamilton Health Sciences, and was initially funded by Portola, which was purchased by Alexion AstraZeneca Rare Disease. Portola, followed by Alexion, was the trial sponsor and provided the andexanet free of charge. Confidentiality agreements existed between Portola (and then Alexion) and the authors. The statistical analysis was performed by an author who is a statistician at the Population Health Research Institute. The trial was designed primarily by the first author and two employees of Portola. Trial data were collected by and analyzed at the Population Health Research Institute. The first author composed the first draft of the manuscript and vouches for the accuracy and completeness of the data, the fidelity of the trial to the protocol, and the accurate reporting of adverse events. A medical writer whose services were paid for by Alexion assisted with the writing of an earlier version of the Methods section of the manuscript. Although the treatment was unblinded at the trial sites, members of the steering committee were unaware of the patients' group assignments, summary statistics, and trial results; the end points were adjudicated by a committee whose members were unaware of the patients' group assignments. Three amendments to the protocol were added during the trial; these are described in the protocol and in Table S1 in the Supplementary Appendix, both of which are available with the full text of this article at NEJM.org.

Patients

Patients with an intracerebral hemorrhage were eligible if they were receiving a factor Xa inhibitor, with the most recent dose taken within 15 hours before randomization. No patients who had previously received andexanet were enrolled in the current trial. Initially, patients with any acute factor Xa–associated intracranial hemorrhage were eligible for enrollment, but after the protocol was amended, only patients with an acute intracerebral hemorrhage as the main bleeding event (not subdural or subarachnoid hemorrhage), with an estimated hematoma volume of 0.5 to 60 ml and a maximum score on the National Institutes of Health Stroke Scale (NIHSS) of 35 (scores range from 0 to 42, with higher scores indicating worse neurologic deficit), were eligible; another amendment to the protocol changed the eligibility criterion for the time from onset of bleeding symptoms to the baseline imaging scan from 12 hours or less to 6 hours or less. The hematoma needed to be evident in the cerebrum on a computed tomographic (CT) or magnetic resonance imaging (MRI) scan within 2 hours before randomization. Patients were excluded if they had a Glasgow Coma Scale score of less than 7 at the

time of consent (scores range from 3 to 15, with lower scores indicating poor neurologic function) or a score of more than 35 on the NIHSS, if surgery was planned within 12 hours after enrollment, or if they had had a thrombotic event within 2 weeks before enrollment. Hematoma volumes were estimated from cranial CT or MRI by site investigators with the use of local protocols and adjudicated at a central site, with the use of a semiautomated program (Quantomo, Cybertrials), by trained physicians who were unaware of the patients' group assignments. The same imaging method (CT or MRI) was used for baseline and final hematoma volume in all but 7 patients, in whom two different methods were used. These images were read by the core laboratory but referred to the adjudication committee for the blinded final assessment.

RANDOMIZATION AND TREATMENTS

Patients were randomly assigned, in a 1:1 ratio, to receive andexanet or usual care, stratified (after the first amendment to the protocol) according to the intention to use prothrombin complex concentrate in patients who were randomly assigned to receive usual care and according to the time from the onset of symptoms to the performance of baseline imaging (<180 or ≥180 minutes). The randomization scheme was generated by the Population Health Research Institute.

Patients assigned to the andexanet group received either a high-dose bolus or a low-dose bolus over the course of 15 to 30 minutes followed by a continuous infusion over the course of 2 hours. The andexanet formulation included 500 mg of mannitol per vial. The use of a high-dose or low-dose bolus was in accordance with the label approved by the Food and Drug Administration and was based on the type, the amount, and the timing of the most recent dose of the factor Xa inhibitor that was received (for details of the dose-selection algorithm, see Table S1). Usual care was determined by local physicians at their discretion but excluded andexanet and could include prothrombin complex concentrate.

END POINTS

The primary end point was hemostatic efficacy, which was assessed at 12 hours after randomization. The current trial, ANNEXA-I, defined hemostatic efficacy differently from the way it was defined in the ANNEXA-4 study, in which the determination of hemostatic efficacy relied almost entirely on the change in hematoma volume. In the current trial, hemostatic efficacy was achieved if all the following criteria were met: a change in the hematoma volume of 20% or less (excellent hemostatic efficacy) or 35% or less (good hemostatic efficacy) within 12 hours after baseline, an increase in the NIHSS score of less than 7 points at 12 hours, and receipt of no rescue therapies such as andexanet, prothrombin complex concentrate, or surgery to decompress the hematoma within 3 to 12 hours after randomization. The assessment of the NIHSS score at 12 hours was performed by trained health care professionals who were unaware of the patients' group assignments. The secondary end point was the percent change from baseline to nadir in anti–factor Xa activity during the first 2 hours after randomization. Results regarding exploratory end points (the effect of andexanet vs. usual care on thrombin generation, the relationship between anti–factor Xa activity and hemostatic efficacy, neurologic function, immunogenicity of andexanet, health-related quality of life, the incidence of invasive intracranial procedures after randomization, and the incidence of rehospitalization at 30 days) described in the protocol are not included here.

In a post hoc analysis, we assessed the score on the modified Rankin scale at 30 days after randomization, dichotomized as 0 to 3 and 3 to 6 (scores range from 0 to 6, with 0 indicating no deficit and 6 indicating death) because this scale is considered to be of interest to the field and is used in cerebrovascular disease trials; however, our analysis of these data is exploratory. Safety end points were assessed at 30 days and included thrombotic events and death. An end-point adjudication committee whose members were unaware of the patients' group assignments reviewed potential thrombotic events and assessments of hemostatic efficacy. In cases of missing brain scans or assessments of the score on the NIHSS, the committee assessed whether this lack was due to clinical reasons (such as a patient's death) or administrative reasons. A core laboratory in which staff members were unaware of the patients' group assignments reviewed brain imaging to determine the change in hematoma volume.

STATISTICAL ANALYSIS

On the basis of the nearly 80% of patients who achieved hemostatic efficacy with andexanet in the ANNEXA-4 study, we estimated that a total sample size of 900 patients would be required for the trial to have 90% power to detect an absolute difference of 10 percentage points in the percentage of patients with hemostatic efficacy, at a two-sided type I error rate of 5%. The primary end-point analysis assessed the percentage of patients with hemostatic efficacy in the andexanet group as compared with the usual-care group with the use of a Cochran–Mantel–Haenszel test stratified according to the time from symptom onset to the performance of the baseline imaging scan (<180 or ≥180 minutes). The secondary end point of the percent change in anti–factor Xa activity was assessed with the use of the rank analysis of covariance (rank ANCOVA) to compare the two treatment groups, with adjustment for the covariates of the time from symptom onset to baseline imaging scan (<180 or ≥180 minutes), and the baseline anti–factor Xa activity. The efficacy analyses were performed in the intention-to-treat population, and the safety analysis was performed in all patients who received andexanet or usual care; both groups included a few patients with subdural and subarachnoid hemorrhages who were recruited before the change in the protocol was made that did not allow inclusion of patients with these types of hemorrhages.

In accordance with protocol amendment 1, the total enrollment was increased from 440 to 900 patients and an interim analysis of efficacy at the time that 450 patients were enrolled was planned. For the interim analysis or the final analysis, a hierarchical testing procedure was to be used to test the primary and secondary end points to control the overall family-wise type I error rate at 5%. The methods for handling missing data are described in the protocol. The adjudication committee, whose members were unaware of the patients' group assignments, was able to categorize cases with missing scans or missing scores on the NIHSS as nonassessable, poor, good, or excellent on the basis of their complete review of all clinical information.

Before the first amendment was added to the protocol, an interim analysis was planned that could lead to stopping the trial early if a P value of less than 0.001 was observed in favor of andexanet with respect to the primary end point. With the first amendment, a different stopping rule was introduced that would be considered during an interim analysis when 450 patients had been enrolled. This change to the protocol was made without any knowledge of the effect of andexanet on the primary end point. At this interim analysis, the primary end point would be tested at a significance level of 0.031; if the primary end point was statistically significant at this level, the secondary end point would be tested at a significance level of 0.031. The interim analysis was performed by the statistician (who was aware of the patients' group assignments) at the Population Health Research Institute and was reviewed by the data and safety monitoring board, which made the final recommendation of whether to stop the trial on the basis of all the efficacy and safety data available and on the interim P value of less than 0.031 for superiority of andexanet with respect to hemostatic efficacy. The statistical analysis plan is available with the protocol.

RESULTS

PATIENTS

Between June 6, 2019, and May 27, 2023, a total of 550 patients at 131 sites in 23 countries were enrolled and randomly assigned to a trial group (Fig. 1). Irregularities related to deferred and emergency consent were discovered in 20 patients, and their data were removed from the database. On May 31, 2023, the prespecified interim analysis of efficacy, involving the first 452 patients enrolled, met the criterion for efficacy, and the data and safety monitoring board recommended that the trial be stopped. During the period from the database lock for the interim analysis to the time of the stopping recommendation, 78 patients were enrolled. The interim analysis of the data from the first 452 patients enrolled was designated as the primary analysis of efficacy, whereas all 530 patients in the database were included in the safety analyses. In the primary efficacy population (452 patients), 228 patients were assigned to usual care; of these patients, 195 (85.5%) received prothrombin complex concentrate within the first 3 hours after randomization (median dose, 3000 IU; interquartile range, 2000 to 3500). The type of prothrombin complex concentrate used was known in

119 patients (four-factor in 110 patients [92.4%], three-factor in 4 [3.4%], and activated prothrombin complex concentrate or factor VIII inhibitor bypass activity in 5 [4.2%]).

In the primary efficacy population, 224 patients were assigned to receive andexanet. Of these patients, 175 (78.1%) received the low-dose regimen, and the remainder the high-dose regimen. Among the patients assigned to receive andexanet, 4 did not receive it (1 received prothrombin complex concentrate), and among the patients assigned to receive usual care, 3 received andexanet. Hemostatic efficacy was not assessable in 9 patients because of a lack of essential data, such as the follow-up brain scan or the score on the NIHSS. The adjudication committee determined that these data were missing because of administrative errors or because of a clinical reason, such as death or withdrawal of care. In 5 patients (2 of whom were in the andexanet group), hemostatic efficacy was not assessable because of clinical deterioration. All the patients in whom hemostatic efficacy was not assessable were included in the primary efficacy analysis as having poor or no hemostatic efficacy.

The characteristics of the two treatment groups were similar with several exceptions; more patients in the andexanet group than in the usual-care group had atrial fibrillation (90.2% vs. 84.2%), and slightly fewer patients in the andexanet group than in the usual-care group had intracerebral hemorrhage (as differentiated from all types of intracranial hemorrhage). Before the protocol was amended, 34 patients in whom the primary site of hemorrhage was subdural or subarachnoid were enrolled (22 patients [9.8%] in the andexanet group and 12 patients [5.3%] in the usual-care group). Subsequently, only patients with intracerebral hemorrhage were eligible. Baseline characteristics were also similar to those of patients included in registries who had direct oral anticoagulant–associated intracranial hemorrhage (see Table S7).

The most frequently used factor Xa inhibitor was apixaban (62.5% of patients in the andexanet group and 59.2% in the usual-care group). The baseline median hematoma volume was 10.5 ml (interquartile range, 4.1 to 24.9) in the andexanet group and 9.0 ml (interquartile range, 3.1 to 22.8), in the usual-care group. A total of 21.4% of patients in the andexanet group and 21.1% of patients in the usual-care group had a history of stroke, 10.7% and 14.5%, respectively, had a history of myocardial infarction, 7.1% and 9.2% had a history of pulmonary embolism, and 8.0% and 9.6% had a history of deep-vein thrombosis (Table 1). Hemorrhage was preceded by trauma in 11.6% of patients receiving andexanet and in 14.5% of patients receiving usual care. The median baseline score on the NIHSS was 9.0 in both groups. The median time from the onset of symptoms to the performance of the baseline scan was 2.3 hours in the andexanet group and

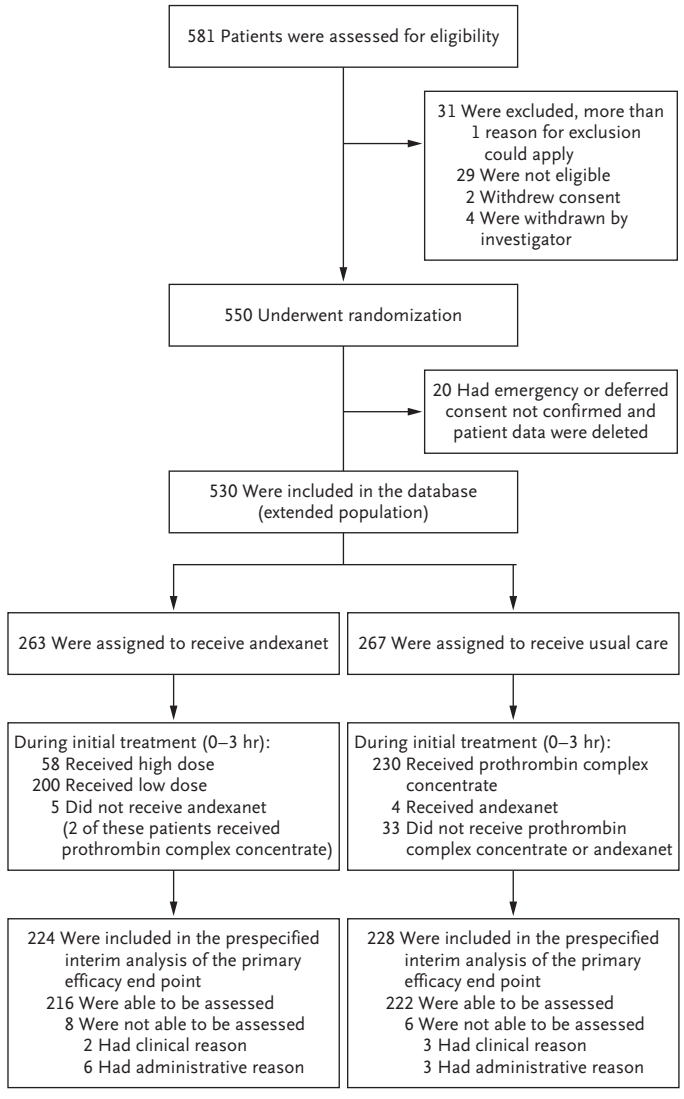

Figure 1. Enrollment, Randomization, and Follow-up.
Patients could have more than one reason to be excluded.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Andexanet (N=224)	Usual Care (N=228)
Age — yr	78.9±8.5	78.9±8.5
Female sex — no. (%)	94 (42.0)	113 (49.6)
Body-mass index†	26.9±5.3	26.3±4.6
Medical history — no. (%)		
Myocardial infarction	24 (10.7)	33 (14.5)
Stroke	48 (21.4)	48 (21.1)
Deep-vein thrombosis	18 (8.0)	22 (9.6)
Pulmonary embolism	16 (7.1)	21 (9.2)
Atrial fibrillation	202 (90.2)	192 (84.2)
Congestive heart failure	34 (15.2)	44 (19.3)
Diabetes	82 (36.6)	59 (25.9)
Creatinine clearance <30 ml/min — no. (%)	10 (4.5)	9 (3.9)
Factor Xa inhibitor used — no. (%)		
Apixaban	140 (62.5)	135 (59.2)
Rivaroxaban	64 (28.6)	65 (28.5)
Edoxaban	20 (8.9)	25 (11.0)
Hemorrhage location — no. (%)		
Intracerebral	198 (88.4)	214 (93.9)
Intraventricular	3 (1.3)	1 (0.4)
Subarachnoid	9 (4.0)	8 (3.5)
Subdural	13 (5.8)	4 (1.8)
Hemorrhage preceded by trauma — no. (%)	26 (11.6)	33 (14.5)
Systolic blood pressure in patients with intracerebral hemorrhage — mm Hg	161.2±27.0	159.8±27.7
Median hematoma volume (IQR) — ml	10.5 (4.1–24.9)	9.0 (3.1–22.8)
Median Glasgow Coma Scale score (IQR)‡	15.0 (13.0–15.0)	15.0 (13.0–15.0)
Median NIHSS score (IQR)§	9.0 (5.0–16.0)	9.0 (4.0–14.0)
Median time from symptom onset to baseline scan (IQR) — hr	2.3 (1.5–4.0)	2.4 (1.4–3.8)
Median time from baseline scan to randomization (IQR) — hr	1.1 (0.7–1.5)	1.2 (0.7–1.7)
Median time from hospital presentation to receipt of treatment (IQR) — hr¶	2.1 (1.5–2.9)	2.3 (1.7–3.1)
Patients receiving high-dose andexanet — no. (%)	45 (20.1)	—
Patients receiving low-dose andexanet — no. (%)	175 (78.1)	—
Patients receiving PCC within 3 hr — no. (%)	—	195 (85.5)

* Plus–minus values are means ±SD. IQR denotes interquartile range and PCC prothrombin complex concentrate.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating a more severe depression of mental status.
§ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating a more severe neurologic deficit.
¶ The median time from hospital presentation to receipt of treatment was assessed only in patients who received andexanet or PCC and excludes patients in the usual-care group who did not receive PCC.

Table 2. Efficacy End Points.

End Point	Andexanet (N=224)	Usual Care (N=228)	Adjusted Difference per 100 Patients (95% CI)*	P Value*
	no./total no. (%)		*percentage points*	
Hemostatic efficacy	150/224 (67.0)	121/228 (53.1)	13.4 (4.6 to 22.2)	0.003
Hematoma volume change ≤35%†	165/215 (76.7)	137/212 (64.6)	12.1 (3.6 to 20.5)	
NIHSS score change <7 points	188/214 (87.9)	181/218 (83.0)	4.6 (–2.0 to 11.2)	
No receipt of rescue therapy between 3 hr and 12 hr	218/224 (97.3)	213/228 (93.4)	3.8 (–7.6 to 0.0)	
Hematoma volume increase ≥12.5 ml‡	24/216 (11.1)	36/214 (16.8)	–5.6 (–12.0 to 0.8)	
Hemostatic efficacy, excluding patients nonevaluable for administrative reasons	150/218 (68.8)	121/225 (53.8)	14.5 (5.7 to 23.4)	

* The between-group difference, P value, and 95% CI were calculated with the use of a Cochran–Mantel–Haenszel test stratified according to the time from symptom onset to the performance of the baseline imaging scan (<180 or ≥180 minutes).
† Patients whose hematoma volume change was nonevaluable are excluded.
‡ Patients who died within 12 hours without follow-up brain imaging are included.

2.4 hours in the usual-care group; the median time from the performance of the scan to randomization was 1.1 hours in the andexanet group and 1.2 hours in the usual-care group.

EFFICACY

Hemostatic efficacy (the primary end point) occurred in 150 of 224 patients (67.0%) in the andexanet group and in 121 of 228 (53.1%) in the usual-care group (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 4.6 to 22.2; P=0.003) (Table 2). With respect to the three components of the primary end point, hematoma volume expansion of 35% or less was observed in 76.7% of patients receiving andexanet and in 64.6% of patients receiving usual care; a change of less than 7 points in the score on the NIHSS was observed in 87.9% and 83.0%, respectively; and no rescue therapy was used in 97.3% and 93.4%. Most of the patients whose results met the criteria for hemostatic efficacy had a hematoma volume expansion of 20% or less. Very large hematoma expansion (defined as an expansion of ≥12.5 ml, as used in other studies) or death within 12 hours after randomization occurred in 24 of 216 patients (11.1%) receiving andexanet and in 36 of 214 (16.8%) receiving usual care.

The median percent change in anti–factor Xa activity between baseline and the 1-to-2-hour nadir (secondary end point) was –94.5% (interquartile range, –96.6 to –88.9) with andexanet and –26.9% (interquartile range, –54.2 to –9.5) with usual care (P<0.001) (Fig. S1). Figure 2 shows results regarding hemostatic efficacy in prespecified subgroups. The trial was not powered for conclusions about subgroups.

THROMBOTIC EVENTS AND DEATH WITHIN 30 DAYS

Thrombotic events were assessed in the extended population, which included all patients who underwent randomization including those who were enrolled after the database lock for the interim analysis but before the trial was stopped (530 patients). Thrombotic events occurred in 27 of 263 patients (10.3%) receiving andexanet and in 15 of 267 patients (5.6%) receiving usual care (difference, 4.6 percentage points; 95% CI, 0.1 to 9.2; P=0.048). Ischemic stroke occurred in 17 patients (6.5%) receiving andexanet and in 4 patients (1.5%) receiving usual care (difference, 5.0 percentage points; 95% CI, 1.5 to 8.8). Death occurred in 73 patients (27.8%) receiving andexanet and in 68 patients (25.5%) receiving usual care (adjusted difference, 2.5 percentage points; 95% CI, –5.0 to 10.0; P=0.51). The trial did not have sufficient information or power to draw conclusions about the effect of treatment (either usual-care treatment or andexanet) on death. Results regarding thrombotic events and death

Subgroup	Andexanet	Usual Care	Adjusted Difference (95% CI)
	no. of patients with hemostatic efficacy/ total no. (%)		
Overall	150/224 (67)	121/228 (53)	13.4 (4.6 to 22.2)
Age			
<65 yr	10/13 (77)	10/15 (67)	9.9 (–23.3 to 43.1)
65 to <75 yr	28/45 (62)	19/46 (41)	20.3 (0.0 to 40.7)
≥75 yr	112/166 (67)	92/167 (55)	12.5 (2.3 to 22.6)
Sex			
Male	82/130 (63)	51/115 (44)	18.3 (6.1 to 30.5)
Female	68/94 (72)	70/113 (62)	9.6 (–2.9 to 22.1)
Race			
Asian	1/3 (33)	1/3 (33)	—
Black	1/5 (20)	1/3 (33)	—
White	137/202 (68)	114/213 (54)	13.8 (4.7 to 22.9)
Other	5/7 (71)	5/8 (62)	9.6 (–38.6 to 57.8)
Geographic location			
North America	13/26 (50)	13/25 (52)	–3.2 (–32.3 to 25.9)
Europe	137/198 (69)	108/203 (53)	15.6 (6.4 to 24.9)
Previous FXa inhibitor treatment			
Apixaban	98/140 (70)	76/135 (56)	13.7 (2.6 to 24.9)
Rivaroxaban	36/64 (56)	30/65 (46)	8.7 (–8.4 to 25.7)
Edoxaban	16/20 (80)	14/25 (56)	23.4 (–2.8 to 49.6)
Indication for previous FXa inhibitor			
Atrial fibrillation or flutter	132/196 (67)	103/193 (53)	13.0 (3.5 to 22.5)
Venous thromboembolism	10/16 (62)	16/28 (57)	8.6 (–22.2 to 39.5)
Other	8/12 (67)	2/7 (29)	37.9 (–5.1 to 80.9)
Anti-FXa activity at baseline			
<30 ng/ml	8/14 (57)	9/13 (69)	–13.3 (–49.2 to 22.5)
≥30 ng/ml	132/195 (68)	95/190 (50)	17.1 (7.6 to 26.6)
<75 ng/ml	48/69 (70)	30/53 (57)	13.5 (–3.6 to 30.7)
≥75 ng/ml	92/140 (66)	74/150 (49)	15.3 (4.2 to 26.3)
ICH score at baseline			
<3	129/193 (67)	112/198 (57)	10.2 (0.8 to 19.6)
≥3	19/28 (68)	9/29 (31)	34.4 (9.5 to 59.3)
Volume of hematoma at baseline			
<30 ml	125/180 (69)	109/192 (57)	12.0 (2.4 to 21.6)
≥30 ml	25/44 (57)	12/35 (34)	22.8 (1.5 to 44.1)
<0.5 ml	5/7 (71)	6/9 (67)	14.1 (–26.1 to 54.2)
≥0.5 ml	145/217 (67)	115/218 (53)	13.7 (4.7 to 22.6)
Hemorrhage location at baseline			
Intracerebral	131/198 (66)	111/214 (52)	13.8 (4.5 to 23.1)
Intraventricular	2/3 (67)	0/1 (0)	—
Subdural	9/13 (69)	4/4 (100)	–24.6 (–51.2 to 2.0)
Subarachnoid	8/9 (89)	6/8 (75)	15.1 (–19.4 to 49.5)
Time to randomization since last administration of FXa			
<8 hr	51/86 (59)	43/99 (43)	14.6 (0.4 to 28.8)
≥8 hr	96/133 (72)	78/129 (60)	12.2 (0.9 to 23.4)
Andexanet dose			
Low	126/175 (72)	121/228 (53)	18.2 (9.0 to 27.4)
High	24/45 (53)	121/228 (53)	0.8 (–14.9 to 16.5)
Usual care received			
PCC	150/224 (67)	101/195 (52)	14.7 (5.5 to 23.9)
Non-PCC	150/224 (67)	18/30 (60)	6.8 (–11.5 to 25.1)

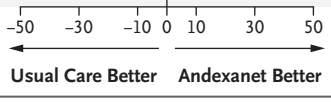

Figure 2 (facing page). Subgroup Analysis for Hemostatic Efficacy.

Achievement of hemostatic efficacy in prespecified subgroups is shown. Hemostatic efficacy was defined in the trial as an expansion of the hematoma volume of 35% or less at 12 hours, an increase of less than 7 points on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with higher scores indicating worse neurologic deficit), and no receipt of rescue therapy. The trial was not powered for conclusions about subgroups. Race was reported by the patients. The intracerebral hemorrhage (ICH) scale estimates the risk of death in patients with ICH and ranges from 0 to 6, with a score of 6 estimating a 100% risk of death from the ICH. FXa denotes factor Xa, and PCC prothrombin complex concentrate.

in the extended population (all enrolled patients) according to treatment group are shown in Table 3; results regarding thrombotic events and death that were assessed on the basis of the trial intervention actually received can be found in Table S5. In the andexanet group, 69 of 246 patients (28.0%) had a score on the modified Rankin scale of 0 to 3 at 30 days, and in the usual-care group, 79 of 255 patients (31.0%) had a score of 0 to 3.

DISCUSSION

Among patients with acute intracerebral hemorrhage who were receiving a factor Xa inhibitor, a larger proportion of patients receiving andexanet than patients receiving usual care met the criteria for hemostatic efficacy, defined in the trial as an expansion of the hematoma volume of 35% or less at 12 hours, an increase of less than 7 points on the NIHSS, and no receipt of rescue therapy. These criteria included hemostatic efficacy categorized in the trial as "good" (≤35% hematoma volume expansion) and "excellent" (≤20% hematoma expansion). The between-group difference with respect to the primary end point appeared to be driven by differences in hematoma volume expansion, given that the results for the two other components of the primary end point did not differ appreciably between the groups. Among patients with acute intracerebral hemorrhage, hematoma expansion is considered a modifiable risk factor that has an influence on morbidity and mortality. In INTERACT1 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial),[8] each 1 ml of hematoma

Table 3. Thrombotic Events and Deaths at 30 Days.*

Event	Andexanet (N=263)	Usual Care (N=267)	Increase per 100 Patients (95% CI)†	P Value†
	no. of patients (%)		*percentage points*	
≥1 Thrombotic event	27 (10.3)	15 (5.6)	4.6 (0.1 to 9.2)	0.048
Transient ischemic attack	0	0	—	
Ischemic stroke	17 (6.5)	4 (1.5)	5.0 (1.5 to 8.8)	
Myocardial infarction	11 (4.2)	4 (1.5)	2.7 (–0.2 to 6.1)	
Deep-vein thrombosis	1 (0.4)	2 (0.7)	–0.4 (–2.4 to 1.5)	
Pulmonary embolism	1 (0.4)	6 (2.2)	–1.9 (–4.5 to 0.2)	
Arterial systemic embolism	3 (1.1)	2 (0.7)	0.4 (–1.7 to 2.7)	
Death	73 (27.8)	68 (25.5)	2.5 (–5.0 to 10.0)	0.51

* The safety analysis is based on the intention-to-treat extended population (all patients, including those who were enrolled after the database lock for the interim analysis but before the trial was stopped).

† In the analysis of the number of patients with at least one thrombotic event, the increase with andexanet per 100 patients is estimated from the between-group difference, the 95% confidence interval is a Wald confidence interval, and the P value is derived from a chi-square test. In the analysis of death at 30 days, the estimated increase with andexanet per 100 patients, the 95% confidence interval, and the P value were calculated with the use of a Cochran–Mantel–Haenszel test stratified according to the time from symptom onset to the performance of the baseline imaging scan (<180 or ≥180 minutes). For the specific thrombotic events, the unconditional exact confidence intervals based on the Farrington–Manning relative risk score are given.

growth was associated with a 5% higher chance of death or dependency at 90 days. Hematoma expansion of 12.5 ml or more has also been associated with poor outcomes in patients with intracerebral hemorrhage, with an 80% positive predictive value for substantial disability or death.[3,14] However, in the current trial, multiplicity unadjusted results for death and a good outcome on the modified Rankin scale did not differ appreciably between groups; the trial was not designed to have sufficient power to detect differences in these outcomes.

A rapid reduction in anti–factor Xa activity was observed with andexanet, as compared with a minimal reduction with usual care. This effect is consistent with the mechanism of action of the drug, which is to rapidly sequester factor Xa inhibitor molecules to allow normalization of natural hemostatic mechanisms.[11]

The percentage of patients with thrombotic events in the andexanet group, approximately 10%, was similar to the percentage observed with andexanet among patients in the single-group ANNEXA-4 study.[12] Possible mechanisms by which andexanet increases the risk of thrombotic events include rapid reversal of anticoagulation in patients at risk for cardioembolic stroke. It is also possible that andexanet has a direct procoagulant effect through the binding of tissue factor pathway inhibitor, an endogenous inhibitor of factors Xa and VIIa that transiently increases D-dimer and prothrombin fragment levels.[15] In other studies, no thrombotic events were reported in older healthy volunteers who received andexanet.[10,16] The mechanism of thrombotic events with andexanet is uncertain.

The reduction in hematoma expansion with andexanet as compared with usual care was accompanied by an increase in thrombotic events, including stroke; determining the potential net benefit of andexanet treatment in acute intracerebral hemorrhage is challenging because the relative clinical effects are difficult to assess. In a trial involving patients with intracerebral hemorrhage who had taken a factor Xa inhibitor within the previous 15 hours, andexanet rapidly reduced anti–factor Xa activity and resulted in better control of hematoma expansion on a composite measure than usual care but was associated with thrombotic events.

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APPENDIX

The authors' full names and academic degrees are as follows: Stuart J. Connolly, M.D., Mukul Sharma, M.D., Alexander T. Cohen, M.D., Andrew M. Demchuk, M.D., Anna Członkowska, M.D., Arne G. Lindgren, M.D., Carlos A. Molina, M.D., Daniel Bereczki, M.D., Danilo Toni, M.D., David J. Seiffge, M.D., David Tanne, M.D., Else Charlotte Sandset, M.D., Georgios Tsivgoulis, M.D., Hanne Christensen, D.M.Sci., Jan Beyer-Westendorf, M.D., Jonathan M. Coutinho, M.D., Mark Crowther, M.D., Peter Verhamme, M.D., Pierre Amarenco, M.D., Risto O. Roine, M.D., Robert Mikulik, Ph.D., Robin Lemmens, M.D., Roland Veltkamp, M.D., Saskia Middeldorp, M.D., Thompson G. Robinson, M.D., Truman John Milling, Jr., M.D., Vitor Tedim-Cruz, M.D., Wilfried Lang, M.D., Anders Himmelmann, M.D., Ph.D., Per Ladenvall, M.D., Ph.D., Mikael Knutsson, Ph.D., Ella Ekholm, M.D., Ph.D., Andrew Law, M.B.B.S., Amanda Taylor, B.Sc., Tetyana Karyakina, B.Sc., Lizhen Xu, Ph.D., Kate Tsiplova, M.Sc., Sven Poli, M.D., Bernd Kallmünzer, M.D., Christoph Gumbinger, M.D., and Ashkan Shoamanesh, M.D.

The authors' affiliations are as follows: the Population Health Research Institute, McMaster University, Hamilton, ON (S.J.C., M.S., M.C., A.T., T.K., L.X., K.T., A.S.), and the Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, AB (A.M.D.) — both in Canada; Guy's and St. Thomas' Hospital, King's College London (A.T.C.), and Imperial College (R.V.), London, NIHR Biomedical Research Centre and College of Life Sciences, University of Leicester, Leicester (T.G.R.), and Alexion Pharmaceuticals UK, Uxbridge (A.L.) — all in the United Kingdom; the Second Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland (A.C.); the Department of Clinical Sciences Lund, Neurology, Lund University, and the Department of Neurology, Skåne University Hospital, Lund (A.G.L.), and AstraZeneca Biopharmaceuticals Research and Development, Late-stage Development, Cardiovascular, Renal, and Metabolism, Gothenburg (A.H., P.L., M.K., E.E.) — all in Sweden; Vall d'Hebron University Hospital, Barcelona (C.A.M.); Semmelweis University, Budapest, Hungary (D.B.); Sapienza University of Rome, Rome (D. Toni); the Department of Neurology, Inselspital University Hospital and University of Bern, Bern, Switzerland (D.J.S.); Rambam Health Care Campus, Technion, Israel Institute of Technology, Haifa (D. Tanne); the Department of Neurology, Oslo University Hospital, and the Norwegian Air Ambulance Foundation — both in Oslo (E.C.S.); the Second Department of Neurology, National and Kapodistrian University of Athens, "Attikon" University Hospital, Athens (G.T.); Copenhagen University Hospital, Bispebjerg Hospital, Copenhagen (H.C.); the Department of Medicine 1, Division "Thrombosis and Hemostasis," University Hospital Dresden, Dresden (J.B.-W.), Alfried Krupp Krankenhaus, Essen (R.V.), the Department of Neurology and Stroke (S.P.) and the Hertie Institute for Clinical Brain Research (S.P.), Eberhard-Karls University, Tübingen, the Department of Neurology, Universitätsklinikum Erlangen, Erlangen (B.K.), and the Department of Neurology, Heidelberg University Hospital, Heidelberg (C.G.) — all in Germany; the Department of

Neurology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam (J.M.C.), and Radboud University Medical Center, Nijmegen (S.M.) — both in the Netherlands; University Hospitals Leuven, University of Leuven (P.V.), the Department of Neurosciences and Experimental Neurology, KU Leuven (R.L.), and the Department of Neurology, University Hospitals Leuven (R.L.) — all in Leuven, Belgium; Bichat Claude-Bernard Hospital, Paris (P.A.); Turku University Hospital, Turku, Finland (R.O.R.); Tomas Bata Regional Hospital, Zlín, Czech Republic (R.M.); Dell Medical School, University of Texas, Austin, and the University of Houston, Houston (T.J.M.); University of Porto, Porto, Portugal (V.T.-C.); and Hospital of St. John of God, Sigmund Freud University, Medical Faculty, Vienna (W.L.).

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