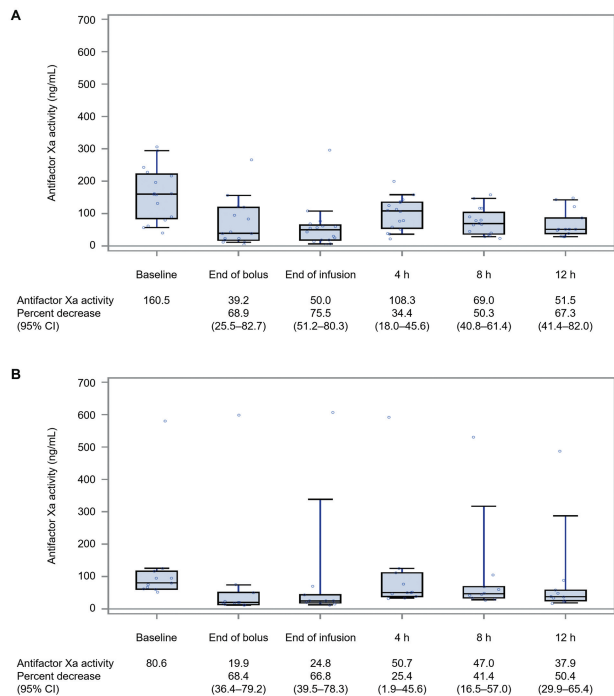


Supplementary Material



Supplementary Fig. S1 Antifactor Xa activity at baseline and after administration of andexanet (patients on edoxaban with baseline antifactor Xa activity ≥ 40 ng/mL). (A) Edoxaban 60 mg. (B) Edoxaban 30 mg. CI, confidence interval.

Supplementary Table S1 Andexanet dosing regimens

Panel A

	Intravenous bolus	Intravenous follow-on infusion
High dose	800 mg at a target rate of 30 mg/min	960 mg at 8 mg/min for 120 min
Low dose	400 mg at a target rate of 30 mg/min	480 mg at 4 mg/min for 120 min

Panel B

Dose	Timing	
	<8 h or unknown	≥8 h
Edoxaban ≤30 mg	Low dose	Low dose
Edoxaban >30 mg or unknown	High dose	

Supplementary Table S2 Rating system for hemostatic efficacy

Bleed type	Excellent (effective)	Good (effective)	Poor/none (not effective)
Visible	Cessation of bleeding ≤ 1 h after the end of infusion <i>and</i> no plasma, coagulation factor, or blood products (excludes pRBCs) ^a	Cessation of bleeding between >1 and ≤ 4 h after the end of infusion <i>and</i> ≤ 2 units of plasma, coagulation factor, or blood products (excludes pRBCs) ^b	Cessation of bleeding >4 h after the end of the infusion <i>and/or</i> >2 units of plasma, coagulation factor, or blood products (excludes pRBCs) ^c
Muscular/skeletal	Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding ≤ 1 h after the end of infusion, and the condition has not deteriorated during the 12-h period	Pain relief or no increase in swelling or unequivocal improvement in objective signs of bleeding >1 and ≤ 4 h after the end of infusion, and the condition has not deteriorated during the 12-h period	No improvement by 4 h after the end of infusion <i>and/or</i> the condition has deteriorated during the 12-h period
Intracerebral hematoma	$\leq 20\%$ increase in hematoma volume compared with baseline on a repeat CT or MRI scan performed at both the 1- and 12-h postinfusion time points	$>20\%$ but $\leq 35\%$ increase in hematoma volume compared with baseline on a repeat CT or MRI scan at +12-h time point	$>35\%$ increase in hematoma volume on a CT or MRI compared with baseline on a repeat CT or MRI scan at +12-h time point
Subarachnoid bleed	$\leq 20\%$ increase in maximum thickness using the most dense area on the follow-up vs. baseline at both the 1- and 12-h postinfusion time points	$>20\%$ but $<35\%$ increase in maximum thickness using the most dense area on the follow-up at +12 h vs. baseline	$>35\%$ increase in maximum thickness using the most dense area on the follow-up at +12 h vs. baseline
Subdural hematoma	$\leq 20\%$ increase in maximum thickness at both the 1- and 12-h postinfusion assessments compared with baseline	$>20\%$ but $<35\%$ increase in maximum thickness at +12 h compared with baseline	$>35\%$ increase in maximum thickness at +12 h compared with baseline
Pericardial	No increase in the size of pericardial effusion on repeat echocardiogram done within 12 h of the end of infusion	$<10\%$ increase in the size of pericardial effusion on repeat echocardiogram done within 12 h of the end of infusion	$\geq 10\%$ increase in the size of pericardial effusion on repeat echocardiogram done within 12 h of the end of infusion
Intraspinal	No increase in hematoma size on repeat CT or MRI scan done within 12 h of the end of infusion	$<10\%$ increase in hematoma size on repeat CT or MRI scan done within 12 h of the end of infusion	$\geq 10\%$ increase in hematoma size on repeat CT or MRI scan done within 12 h of the end of infusion
GI, urinary, or nonvisible bleeding not described above	$\leq 10\%$ decrease in both corrected hemoglobin/hematocrit at 12 h ^{d,e} compared with baseline	$>10\%$ to $\leq 20\%$ decrease in both corrected hemoglobin/hematocrit at 12 h compared with baseline ^{d,e}	$>20\%$ decrease in both corrected hemoglobin/hematocrit ^{d,e}

Abbreviations: CT, computed tomography; GI, gastrointestinal; MRI, magnetic resonance imaging; pRBCs, packed red blood cells.

Note: Additional factors to be considered during adjudication:

1. Any additional diagnostic data for a particular bleeding site (e.g., nasogastric tube, ultrasound, GI endoscope, echocardiogram, or CT/MRI scans) will be taken into account for the overall assessment.
2. Any uncontrolled bleeding that did not respond to andexanet and was related to an underlying disease will be taken into account for the overall assessment.
3. Pain, swelling, and signs of bleeding are considered to be typical symptoms of musculoskeletal bleeding and are expected to be present at baseline.

^aFor all types of bleeding, no additional plasma, blood products (whole blood products not including pRBCs), and/or coagulation factor products required after initial treatment with andexanet.

^bFor all types of bleeding, no more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet.

^cFor all types of bleeding, more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet. "Blood products" include whole blood but not pRBCs.

^dThe smallest percentage decrease in hemoglobin or hematocrit should be used to determine the efficacy rating of excellent, good, or poor/none. The net change is defined as the difference between the corrected hemoglobin or hematocrit value at baseline and 12 hours after infusion.

^eFor the adjusted hemoglobin and hematocrit calculation, it will be assumed that for each unit of pRBC transfusion there is an increase of 1 g/dL in hemoglobin and a 3% increase in hematocrit.

Supplementary Table S3 Hemostatic efficacy according to HAS-BLED score

	Patients with atrial fibrillation or atrial flutter, with baseline antifactor Xa activity ≥ 40 ng/mL (N = 27)		
	HAS-BLED score 0–2 (N = 17)		
	Patients	Excellent or good hemostasis, n (%)	95% CI (%)
All	17	14 (82.4)	56.6–96.2
Patients with intracranial hemorrhage	15	12 (80.0)	51.9–95.7
Patients with intracerebral bleeding ^a	12	9 (75.0)	42.8–94.5
	HAS-BLED score ≥ 3 (N = 10)		
	Patients	Excellent or good hemostasis, n (%)	95% CI (%)
All	10	8 (80.0)	44.4–97.5
Patients with intracranial hemorrhage	6	6 (100.0)	54.1–100.0
Patients with intracerebral bleeding ^a	4	4 (100.0)	39.8–100.0

Abbreviation: CI, confidence interval.

^aPatients with intracerebral bleeding are a subset of patients with intracranial hemorrhage.

Supplementary Table S4 Thrombotic events through day 30 according to CHA₂DS₂-VASc score

	Safety population, including patients with atrial fibrillation or atrial flutter (N = 34)			
	CHA ₂ DS ₂ -VASc score 0–4 (N = 24)			
	Total	Up to 5 days	Days 6–14	Days 15–30
Patients with at least one thrombotic event, n (%)	2 (8.3)	1 (4.2)	1 (4.2)	0 (0)
Myocardial infarction, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Ischemic stroke, n (%)	2 (8.3)	1 (4.2)	1 (4.2)	0 (0)
Transient ischemic attack, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Deep vein thrombosis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Pulmonary embolism, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Systemic embolism, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Cardiovascular, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Noncardiovascular, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
	CHA ₂ DS ₂ -VASc score ≥ 5 (N = 10)			
	Total	Up to 5 days	Days 6–14	Days 15–30
Patients with at least one thrombotic event, n (%)	2 (20.0)	1 (10.0)	0 (0)	1 (10.0)
Myocardial infarction, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Ischemic stroke, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Transient ischemic attack, n (%)	1 (10.0)	1 (10.0)	0 (0)	0 (0)
Deep vein thrombosis, ^a n (%)	1 (10.0)	0 (0)	0 (0)	1 (10.0) ^b
Pulmonary embolism, ^a n (%)	1 (10.0)	0 (0)	0 (0)	1 (10.0) ^b
Systemic embolism, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Death, ^c n (%)	3 (30.0)	2 (20.0)	1 (10.0)	0 (0)
Cardiovascular, n (%)	2 (20.0)	1 (10.0)	1 (10.0)	0 (0)
Noncardiovascular, n (%)	1 (10.0)	1 (10.0)	0 (0)	0 (0)

^aDeep vein thrombosis and pulmonary embolism occurred in the same patient.

^bPatient had been restarted on heparin on day 5, and the deep vein thrombosis/pulmonary embolism occurred on day 15.

^cNone of the patients who died was reported to have experienced a thrombotic event.

Supplementary Table S5 Glasgow Coma Scale score before and after andexanet treatment

Time	Patients with data	Glasgow Coma Scale score, median (IQR)
Within 15 min prior to andexanet bolus	28	15 (12.5–15)
1 h after andexanet bolus	27	15 (11–15)
12 h after andexanet bolus	26	15 (12–15)
Day 30	21	15 (15–15)

Abbreviation: IQR, interquartile range.

Supplementary Table S6 Characteristics and outcomes of patients on edoxaban who did *not* achieve excellent or good hemostasis

A: Baseline characteristics

	Efficacy population, patients with baseline antifactor Xa activity ≥ 40 ng/mL who did not achieve excellent or good hemostasis (N = 6)	Efficacy population, patients with baseline antifactor Xa activity ≥ 75 ng/mL who did not achieve excellent or good hemostasis (N = 5)
Age (y), mean \pm SD	83.5 \pm 5.2	84.2 \pm 5.4
Male sex, n (%)	4 (66.7)	3 (60.0)
White race, n (%)	5 (83.3)	4 (80.0)
Body mass index (kg/m ²), mean \pm SD	23.6 \pm 4.5	22.2 \pm 3.1
Estimated creatinine clearance, ^a n (%)		
<30 mL/min	1 (16.7)	1 (20.0)
30–59.9 mL/min	3 (50.0)	3 (60.0)
≥ 60 mL/min	2 (33.3)	1 (20.0)
Primary indication for anticoagulation, ^b n (%)		
Atrial fibrillation	4 (66.7)	4 (80.0)
Atrial flutter	1 (16.7)	0 (0)
Venous thromboembolism ^c	1 (16.7)	1 (20.0)
Medical history, n (%)		
Myocardial infarction	1 (16.7)	1 (20.0)
Stroke	1 (16.7)	1 (20.0)
Deep vein thrombosis	1 (16.7)	1 (20.0)
Atrial fibrillation	4 (66.7)	4 (80.0)
Heart failure	1 (16.7)	1 (20.0)
Diabetes mellitus	0 (0)	0 (0)
Hypertension	5 (83.3)	4 (80.0)
CHA ₂ DS ₂ -VASc score, median (IQR) ^d	3 (3–5)	4 (2.5–5.5)
HAS-BLED score, median (IQR) ^d	2 (2–3)	2.5 (2–3.5)
Hemoglobin (g/L), mean \pm SD	125.2 \pm 25.4	119.0 \pm 22.7
Platelet count (10 ⁹ /L), mean \pm SD	201.7 \pm 42.3	201.0 \pm 47.3
Primary site of bleeding, n (%)		
Intracranial, any	4 (66.7)	3 (60.0)
Intracranial, associated with trauma ^e	1 (25.0)	1 (33.3)
Gastrointestinal	2 (33.3)	2 (40.0)
Edoxaban dosage, n (%)		
60 mg once daily	2 (33.3)	1 (20.0)
30 mg once daily	3 (50.0)	3 (60.0)

(Continued)

Supplementary Table S6 (Continued)

	Efficacy population, patients with baseline antifactor Xa activity ≥ 40 ng/mL who did not achieve excellent or good hemostasis (N = 6)	Efficacy population, patients with baseline antifactor Xa activity ≥ 75 ng/mL who did not achieve excellent or good hemostasis (N = 5)
15 mg once daily	1 (16.7)	1 (20.0)
Baseline antifactor Xa activity (ng/mL), median (IQR)	162.4 (80.6–294.4)	208.0 (116.8–294.4)
Time from last dose of edoxaban to andexanet bolus (h), median (IQR)	9.3 (8.6–12.8)	9.5 (8.6–12.8)
Time from presentation at the emergency department to andexanet bolus (h), median (IQR)	2.3 (1.4–3.3)	1.8 (1.3–15.0)

Abbreviations: INR, international normalized ratio; IQR, interquartile range; SD, standard deviation.

^aCreatinine clearance estimated according to the Cockcroft–Gault formula.

^bIf >1 primary indication for anticoagulation recorded: if atrial fibrillation was present, this was listed as the primary indication; if present, venous thromboembolism was considered primary in the remaining patients.

^cVenous thromboembolism refers to prevention or treatment of deep vein thrombosis and pulmonary embolism.

^dReported for patients with atrial fibrillation or atrial flutter. The CHA₂DS₂-VASc score ranges from 0 to 9 (congestive heart failure [1], hypertension [1], age ≥ 75 years [2], diabetes [1], prior stroke or transient ischemic attack [2], vascular disease [1], age 65–74 years [1], female sex [1]). A modified HAS-BLED score is reported, ranging from 0 to 7 (hypertension [systolic blood pressure >160 mm Hg at baseline [1], abnormal kidney function [1], abnormal liver function [1], prior stroke [1], bleeding history [not including the qualifying bleeding event] or anemia [1], age >65 years [1], concomitant use of antiplatelet agents or nonsteroidal anti-inflammatory drugs [1]). As opposed to the original HAS-BLED score, the categories labile INR (not applicable) and alcohol use (data not available) were not considered.

^eDenominators for percentage with traumatic intracranial hemorrhage are all patients with any intracranial hemorrhage.

B: Safety outcomes through 30 days after andexanet administration (there were no thrombotic events in patients who did not achieve excellent/good hemostasis at 12 hours)

	<i>Efficacy population, patients with baseline antifactor Xa activity ≥ 40 ng/mL who did not achieve excellent/good hemostasis (N = 6)</i>			
	<i>Total</i>	<i>Up to 5 days</i>	<i>Days 6–14</i>	<i>Days 15–30</i>
Death, n (%)	2 (33.3)	1 (16.7)	0 (0)	1 (16.7)
Cardiovascular, n (%)	1 (16.7)	0 (0)	0 (0)	1 (16.7)
Noncardiovascular, n (%)	1 (16.7)	1 (16.7)	0 (0)	0 (0)
	<i>Efficacy population, patients with baseline antifactor Xa activity ≥ 75 ng/mL who did not achieve excellent/good hemostasis (N = 5)</i>			
	<i>Total</i>	<i>Up to 5 days</i>	<i>Days 6–14</i>	<i>Days 15–30</i>
Death, n (%)	2 (40.0%)	1 (20.0)	0 (0)	1 (20.0)
Cardiovascular, n (%)	1 (20.0%)	0 (0)	0 (0)	1 (20.0)
Noncardiovascular, n (%)	1 (20.0%)	1 (20.0)	0 (0)	0 (0)

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