

Supplementary Material

Title:

Idarucizumab for Emergency Reversal of the Anticoagulant Effects of Dabigatran: Final Results of a Japanese Postmarketing Surveillance Study

Authors:

Masahiro Yasaka · Hiroyuki Yokota · Michiyasu Suzuki · Hidesaku Asakura · Teiichi Yamane · Yukako Ogi · Takaaki Kimoto · Daisuke Nakayama

Affiliations:

M. Yasaka

Department of Cerebrovascular Medicine and Neurology, Cerebrovascular Center, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

H. Yokota

Graduate School of Medical & Health Science, Nippon Sport Science University, Kanagawa, Japan

M. Suzuki

Department of Neurosurgery, Yamaguchi University School of Medicine, Yamaguchi, Japan

H. Asakura

Department of Hematology, Kanazawa University Hospital, Ishikawa, Japan

T. Yamane

Department of Cardiology, Jikei University School of Medicine, Tokyo, Japan

Y. Ogi · D. Nakayama

Medicine Division, Nippon Boehringer Ingelheim Co., Ltd., Tokyo, Japan

T. Kimoto

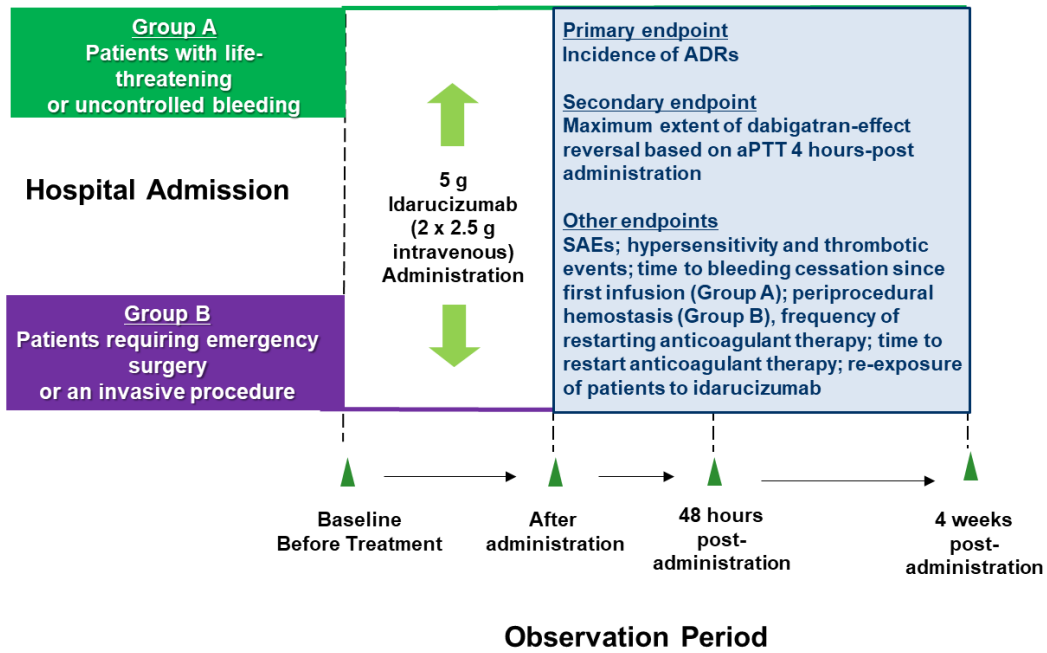
PMS Division, EPS Corporation, Tokyo, Japan

Correspondence:

Dr Masahiro Yasaka

E-mail: yasakamasahiro@gmail.com

Fig. S1 Study design



ADR adverse drug reaction, aPTT activated partial thromboplastin time, SAE serious adverse event

Table S1 Changing trends in reasons for using idarucizumab in Group A/A+B

	Number of patients, <i>N</i> (%)					
	≤Apr 15, 2017 (<i>N</i> = 70)	Apr 16, 2017, to Nov 15, 2017 (<i>N</i> = 130)	Nov 16, 2017, to Apr 15, 2018 (<i>N</i> = 116)	Apr 16, 2018, to Nov 15, 2018 (<i>N</i> = 118)	Nov 16, 2018, to Apr 15, 2019 (<i>N</i> = 124)	Entire period (<i>N</i> = 558)
Bleeding location						
Intraspinal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.2)
Intramuscular	1 (1.4)	2 (1.5)	3 (2.6)	4 (3.4)	2 (1.6)	12 (2.2)
Retroperitoneal	1 (1.4)	6 (4.6)	3 (2.6)	1 (0.9)	3 (2.4)	14 (2.5)
Intra-articular	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.2)
Intrapericardial	3 (4.3)	15 (11.5)	24 (20.7)	32 (27.1)	32 (25.8)	106 (19.0)
Gastrointestinal	19 (27.1)	38 (29.2)	30 (25.9)	22 (18.6)	24 (19.4)	133 (23.9)
Intracranial	36 (51.4)	52 (40.0)	42 (36.2)	38 (32.2)	40 (32.3)	208 (37.3)
Other	12 (17.1)	24 (18.5)	18 (15.5)	25 (21.2)	30 (24.2)	109 (19.5)

Table S2 ADRs judged by the investigators to be related to idarucizumab^a

	Group A (N = 542)	Group B (N = 240)	Total (N = 804)
No. patients with ADRs	17 (3.1)	12 (5.0)	29 (3.6)
Infections and infestations	1 (0.2)	0	1 (0.1)
Pneumonia aspiration	1 (0.2)	0	1 (0.1)
Nervous system disorders	6 (1.1)	5 (2.1)	11 (1.4)
Cerebral infarction	1 (0.2)	4 (1.7)	5 (0.6)
Cerebral hemorrhage	1 (0.2)	0	1 (0.1)
Embolic stroke	1 (0.2)	0	1 (0.1)
Seizure	0	1 (0.4)	1 (0.1)
Subarachnoid hemorrhage	1 (0.2)	0	1 (0.1)
Spinal cord hemorrhage	1 (0.2)	0	1 (0.1)
Embolic cerebral infarction	1 (0.2)	0	1 (0.1)
Eye disorders	1 (0.2)	0	1 (0.1)
Eye hematoma	1 (0.2)	0	1 (0.1)
Cardiac disorders	1 (0.2)	0	1 (0.1)
Acute myocardial infarction	1 (0.2)	0	1 (0.1)
Vascular disorders	4 (0.7)	1 (0.4)	5 (0.6)
Aortic aneurysm rupture	1 (0.2)	0	1 (0.1)
Shock	1 (0.2)	0	1 (0.1)

Deep vein thrombosis	1 (0.2)	0	1 (0.1)
Hemorrhage	1 (0.2)	0	1 (0.1)
Arterial occlusive disease	0	1 (0.4)	1 (0.1)
Respiratory, thoracic, and mediastinal disorders	1 (0.2)	0	1 (0.1)
Hemothorax	1 (0.2)	0	1 (0.1)
Gastrointestinal disorders	2 (0.4)	2 (0.8)	4 (0.5)
Abdominal discomfort	0	1 (0.4)	1 (0.1)
Melena	0	1 (0.4)	1 (0.1)
Rectal ulcer hemorrhage	1 (0.2)	0	1 (0.1)
Pancreatic enlargement	1 (0.2)	0	1 (0.1)
Skin and subcutaneous tissue disorders	2 (0.4)	0	2 (0.2)
Erythema	1 (0.2)	0	1 (0.1)
Skin discoloration	1 (0.2)	0	1 (0.1)
General disorders and administrative site conditions	0	2 (0.8)	2 (0.2)
Death	0	1 (0.4)	1 (0.1)
Malaise	0	1 (0.4)	1 (0.1)
Investigations	3 (0.6)	0	3 (0.4)
Aspartate aminotransferase increased	1 (0.2)	0	1 (0.1)
Blood pressure decreased	1 (0.2)	0	1 (0.1)
International normalized ratio increased	1 (0.2)	0	1 (0.1)

Injury, poisoning and procedural complications	1 (0.2)	2 (0.8)	3 (0.4)
Subdural hematoma	0	2 (0.8)	2 (0.2)
Extradural hematoma	1 (0.2)	0	1 (0.1)
Subdural hemorrhage	1 (0.2)	0	1 (0.1)

Note: Data are presented as *n* (%)

ADR adverse drug reaction

^a ADRs that occurred in both the treatment and post-treatment periods are reported. ADRs were coded using Version 24.1 of the Medical Dictionary for Regulatory Activities

Table S3 ADRs by bleeding location^a

Bleeding location	Group A	Group A+B	Total
Intracranial (<i>n</i>)	196	12	208
Patients with ADRs	7 (3.6)	0	7 (3.4)
Infections and infestations	1 (0.5)	0	1 (0.5)
Pneumonia aspiration	1 (0.5)	0	1 (0.5)
Nervous system disorders	4 (2.0)	0	4 (1.9)
Cerebral hemorrhage	1 (0.5)	0	1 (0.5)
Cerebral infarction	1 (0.5)	0	1 (0.5)
Embolic stroke	1 (0.5)	0	1 (0.5)
Subarachnoid hemorrhage	1 (0.5)	0	1 (0.5)
Vascular disorders	1 (0.5)	0	1 (0.5)
Hemorrhage	1 (0.5)	0	1 (0.5)
Gastrointestinal disorders	1 (0.5)	0	1 (0.5)
Pancreatic enlargement	1 (0.5)	0	1 (0.5)
Skin and subcutaneous tissue disorders	1 (0.5)	0	1 (0.5)
Skin discoloration	1 (0.5)	0	1 (0.5)
Investigations	1 (0.5)	0	1 (0.5)
International normalized ratio increased	1 (0.5)	0	1 (0.5)
Injury, poisoning, and procedural complications	1 (0.5)	0	1 (0.5)

Extradural hematoma	1 (0.5)	0	1 (0.5)
Subdural hemorrhage	1 (0.5)	0	1 (0.5)
Gastrointestinal (<i>n</i>)	132	1	133
Patients with ADRs	3 (2.3)	0	3 (2.3)
Vascular disorders	1 (0.8)	0	1 (0.8)
Deep vein thrombosis	1 (0.8)	0	1 (0.8)
Gastrointestinal disorders	1 (0.8)	0	1 (0.8)
Rectal ulcer hemorrhage	1 (0.8)	0	1 (0.8)
Skin and subcutaneous tissue disorders	1 (0.8)	0	1 (0.8)
Erythema	1 (0.8)	0	1 (0.8)
Gastrointestinal – lower only (<i>n</i>)	61	0	61
Patients with ADRs	3 (4.9)	0	3 (4.9)
Deep vein thrombosis	1 (1.6)	0	1 (1.6)
Erythema	1 (1.6)	0	1 (1.6)
Rectal ulcer hemorrhage	1 (1.6)	0	1 (1.6)
Gastrointestinal – upper only (<i>n</i>)	52	0	52
Patients with ADRs	0	0	0
Gastrointestinal – lower + upper (<i>n</i>)	5	0	5
Patients with ADRs	0	0	0
Gastrointestinal – unknown (<i>n</i>)	14	0	14

Patients with ADRs	0	0	0
Intrapericardial (<i>n</i>)	104	2	106
Patients with ADRs	1 (1.0)	0	1 (0.9)
Investigations	1 (1.0)	0	1 (0.9)
Aspartate aminotransferase increased	1 (1.0)	0	1 (0.9)
Retroperitoneal (<i>n</i>)	14	0	14
Patients with ADRs	1 (7.1)	0	1 (7.1)
Vascular disorders	1 (7.1)	0	1 (7.1)
Aortic aneurysm rupture	1 (7.1)	0	1 (7.1)
Intramuscular (<i>n</i>)	12	0	12
Patients with ADRs	0	0	0

Note: Data are presented as *n* (%) unless otherwise specified

ADR adverse drug reaction

^a ADRs that occurred in both the treatment and post-treatment periods are reported. ADRs were coded using Version 24.1 of the Medical Dictionary for Regulatory Activities

Table S4 ADRs by type of surgery/procedure^a

Type of surgery/procedure	Group B	Group A+B	Total
Neurological surgery/procedure (<i>n</i>)	103	11	114
Patients with ADRs	6 (5.8)	0	6 (5.3)
Nervous system disorders	3 (2.9)	0	3 (2.6)
Cerebral infarction	2 (1.9)	0	2 (1.8)
Seizure	1 (1.0)	0	1 (0.9)
Vascular disorders	1 (1.0)	0	1 (0.9)
Arterial occlusive disease	1 (1.0)	0	1 (0.9)
Gastrointestinal disorders	1 (1.0)	0	1 (0.9)
Abdominal discomfort	1 (1.0)	0	1 (0.9)
Injury, poisoning, and procedural complications	1 (1.0)	0	1 (0.9)
Subdural hematoma	1 (1.0)	0	1 (0.9)
Vascular surgery/procedure (<i>n</i>)	38	2	40
Patients with ADRs	1 (2.6)	0	1 (2.5)
Nervous system disorders	1 (2.6)	0	1 (2.5)
Cerebral infarction	1 (2.6)	0	1 (2.5)
Abdominal surgery/procedure (<i>n</i>)	37	1	38
Patients with ADRs	1 (2.7)	0	1 (2.6)
Gastrointestinal disorders	1 (2.7)	0	1 (2.6)

Melena	1 (2.7)	0	1 (2.6)
Orthopedic surgery/procedure (n)	8	0	8
Patients with ADRs	0	0	0
Respiratory surgery/procedure (n)	7	0	7
Patients with ADRs	0	0	0
Gynecological-urological surgery/procedure (n)	6	0	6
Patients with ADRs	0	0	0

Note: Data are presented as *n* (%) unless otherwise specified

ADR adverse drug reaction

^a ADRs that occurred in both the treatment and post-treatment periods are reported. ADRs were coded using Version 24.1 of the Medical Dictionary for Regulatory Activities

TABLE S5 Patients with adverse events leading to death within 5 days of idarucizumab administration

Group	Age (years)	Sex	AE that led to death (PT)	Time from treatment to death (days)	Reason for administration of idarucizumab
A, B	76	F	Pericardial hemorrhage	2	Intrapericardial bleeding, pericardiocentesis
	65	F	Upper gastrointestinal hemorrhage Shock hemorrhagic	1	Gastrointestinal bleeding
	75	M	Brain edema	2	Intracranial hemorrhage, surgery for hematoma
A	74	F	Pneumonia aspiration Cardiac failure congestive Brain herniation Epilepsy	3	Gastrointestinal bleeding
	80	M	Pneumonia bacterial	Unknown	Pulmonary hemorrhage
	83	F	Shock hemorrhagic Mesenteric arterial occlusion	1	Gastrointestinal bleeding
	84	M	Hemorrhage	1	Intracranial, intrathoracic hemorrhage
	81	M	Shock hemorrhagic	2	Intra-abdominal hemorrhage
	75	M	Bronchial hemorrhage Respiratory failure	3	Pulmonary hemorrhage
	83	M	Rib fracture Road traffic accident Spinal fracture Traumatic shock Traumatic hemothorax	1	Intrathoracic hemorrhage
	84	F	Cerebellar hemorrhage	5	Intracranial hemorrhage
	71	F	Cerebral hemorrhage	1	Intracranial hemorrhage
	67	M	Gastrointestinal hemorrhage Pneumonia Pulmonary alveolar hemorrhage	1	Gastrointestinal bleeding, pulmonary hemorrhage
	78	F	Cardiac tamponade	1	Intrapericardial bleeding
	85	M	Subdural hematoma	4	Intracranial hemorrhage
	65	M	Retroperitoneal hemorrhage	2	Retroperitoneal bleeding
	82	M	Shock hemorrhagic	1	Gastrointestinal bleeding

82	F	Cardiac tamponade Ventricle rupture	1	Intrapericardial bleeding
81	F	Cardiac failure congestive Peripheral circulatory failure	4	Retroperitoneal bleeding
82	M	Disseminated intravascular coagulation Shock hemorrhagic	3	Gastrointestinal and urinary tract bleeding
91	M	Subdural hematoma	1	Intracranial hemorrhage
83	M	Subdural hematoma	1	Intracranial hemorrhage
89	M	Embolic stroke	2	Intracranial hemorrhage
80	M	Aortic aneurysm rupture	1	Retroperitoneal bleeding
81	M	Subdural hematoma	2	Intracranial hemorrhage
82	M	Cerebellar hemorrhage	1	Intracranial hemorrhage
78	F	Renal failure Cardiac failure chronic Malignant neoplasm progression	2	Gastrointestinal, intraoral bleeding
76	F	Malignant neoplasm	1	Hematuria
83	M	Subdural hematoma	3	Intracranial hemorrhage
81	M	Cerebral hemorrhage Hypertension	2	Intracranial hemorrhage
83	M	Intra-abdominal hematoma Tumor rupture	1	Intra-abdominal hemorrhage
68	M	Brain edema Brain stem hemorrhage	3	Intracranial hemorrhage
82	F	Multiple organ dysfunction syndrome Shock hemorrhagic Lower gastrointestinal hemorrhage	1	Gastrointestinal bleeding
83	F	Hemorrhage intracranial	4	Intracranial hemorrhage
84	F	Multiple organ dysfunction syndrome Acute coronary syndrome	5	Gastrointestinal, intraoral bleeding
88	F	Death	1	Intracranial hemorrhage
84	M	Subarachnoid hemorrhage	3	Intracranial hemorrhage
60	M	Pyelonephritis Septic shock	2	Gastrointestinal bleeding

	70	M	Cerebral hemorrhage Head injury	3	Intracranial hemorrhage
	76	M	Brain contusion Skull fracture Subdural hematoma Cardiac failure Ventricular fibrillation	5	Intracranial hemorrhage
	89	M	Pulmonary alveolar hemorrhage Respiratory failure	3	Gastrointestinal, pulmonary hemorrhage
	84	M	Acute respiratory distress syndrome Pneumonia aspiration	2	Gastrointestinal bleeding
	84	M	Cardiac failure	4	Gastrointestinal bleeding
	84	M	Subdural hematoma	3	Intracranial hemorrhage
	82	M	Upper gastrointestinal hemorrhage	2	Gastrointestinal bleeding
	73	F	Brain stem hemorrhage	2	Intracranial hemorrhage
	82	M	Road traffic accident Traumatic hemorrhage	4	Intrathoracic hemorrhage
	79	F	Tachycardia Death	2	Unknown
B	86	M	Peritonitis	1	Unknown
	78	M	Peritonitis	5	Sigmoid colectomy
	75	M	Aortic dissection Hemorrhage	1	Aortic prosthetic replacement
	86	M	Death	27	Unknown
	50	M	Hemorrhagic cerebral infarction	3	Decompressive craniectomy
	72	F	Acute myocardial infarction Aortic dissection	2	Aortic prosthetic replacement
	71	F	Septic shock	1	Unknown
	80	M	Sepsis	2	Unknown
	81	M	Hypertension Epilepsy	3	Hematoma drainage
	84	M	Brain herniation Cerebellar hemorrhage	4	Hematoma removal surgery

77	M	Intestinal obstruction Gastrointestinal necrosis Hemorrhage	2	Colostomy
70	F	Hemorrhagic infarction Brain edema	1	Thrombolysis
78	F	Multiple organ dysfunction syndrome Cardiac failure Mitral valve incompetence	5	Mitral valve replacement

AE adverse event, *F* female, *M* male, *PT* preferred term

Table S6 Patients with thrombotic events during the entire study period

Group	Age (years)	Sex	Index event	Thrombotic event	Period from idarucizumab administration to thrombotic event	Outcome	Oral anticoagulation therapy	CHADS ₂ score
A	89	M	Intracranial hemorrhage	Embolic stroke	Unknown	Fatal	No	4
	87	M	Gastrointestinal bleeding	Myocardial infarction	Unknown	Fatal	No	2
	77	M	Prostate gland	Acute myocardial infarction	<24 h	Recovered	No	4
	83	F	Gastrointestinal bleeding	Mesenteric arterial occlusion	<24 h	Fatal	No	3
	70	F	Intracranial hemorrhage by trauma	Cerebral infarction	1 day	Fatal	No	2
	76	M	Retroperitoneal, gastrointestinal, intracranial, intra-abdominal bleeding by trauma	Cerebral infarction	1 day	Recovered	Yes	1
	83	F	Gastrointestinal bleeding	Deep vein thrombosis	3 days	Not recovered	Yes	1
	83	M	Intramuscular, retroperitoneal, intrathoracic bleeding by trauma	Pulmonary embolism	5 days	Fatal	No	3
	63	M	Gastrointestinal bleeding	Peripheral arterial occlusive disease	5 days	Recovered	Unknown	3
	84	F	Gastrointestinal bleeding	Cerebral infarction	6 days	Not recovered	No	5
	80	M	Intracranial hemorrhage by trauma	Cerebral infarction	6 days	Not recovered	Yes	2
	80	F	Intracranial hemorrhage by trauma	Embolic stroke	6 days	Recovered with sequelae	No	1
	80	F	Intra-abdominal	Embolic cerebral infarction	7 days	Recovered with sequelae	No	2
	101	F	Gastrointestinal bleeding	Arterial occlusive disease	9 days	Recovered	Unknown	4
	81	M	Thoracic epidural	Venous thrombosis	9 days	Recovered	Yes	2
	59	M	Subcutaneous bleeding	Pelvic venous thrombosis	9 days	Recovered	Yes	0
	90	F	Intracranial hemorrhage	Embolic stroke	13 days	Not recovered	Yes	1
	83	F	Intracranial hemorrhage by trauma	Pulmonary embolism	16 days	Unknown	Yes	2
	82	M	Intracranial hemorrhage by trauma	Cerebral infarction	17 days	Fatal	No	2

	72	M	Intracranial hemorrhage	Embolic stroke	20 days	Fatal	No	3
	86	F	Intracranial hemorrhage	Deep vein thrombosis	20 days	Recovered	Yes	2
	78	M	Intracranial hemorrhage by trauma	Cerebral infarction	23 days	Unknown	No	3
B	78	F	Unknown	Cerebral infarction	Unknown	Recovered with sequelae	No	2
	86	F	Aortic prosthetic replacement	Cerebral infarction	Unknown	Not recovered	Yes	1
	72	F	Aortic prosthetic replacement	Acute myocardial infarction	Unknown	Fatal	No	1
	68	M	Aortic prosthetic replacement	Arterial occlusive disease	<24 h	Recovered with sequelae	Unknown	1
	77	F	Hematoma removal surgery	Cerebral infarction	1 day	Recovered with sequelae	Yes	2
	74	F	Craniotomy clipping	Cerebral infarction	1 day	Fatal	No	1
	70	M	STA-MCA bypass	Cerebral infarction	1 day	Not recovered	Unknown	3
	81	F	Thrombolysis	Cerebral infarction	2 days	Recovered with sequelae	Yes	5
	57	M	Thrombolysis	Arterial occlusive disease	2 days	Recovered	Unknown	4
	74	M	Thrombectomy	Carotid artery occlusion	3 days	Recovered with sequelae	Unknown	4
	71	M	Thrombolysis	Cerebral infarction	5 days	Not recovered	Yes	3
	80	F	Unknown	Cerebral infarction	8 days	Recovered with sequelae	No	1
	69	M	Aortic prosthetic replacement	Cerebral infarction	12 days	Not recovered	No	0
	67	M	Aortic prosthetic replacement	Celiac artery occlusion	13 days	Recovered	Yes	1
	84	M	Ventricular drainage	Cerebral infarction	18 days	Recovered with sequelae	Yes	5
	74	M	Thrombectomy	Carotid artery occlusion	21 days	Not recovered	Unknown	4

CHADS₂ Congestive heart failure, Hypertension, Age (>65 = 1 point, >75 = 2 points), Diabetes, previous Stroke /transient ischemic attack (2 points), *F* female, *M* male, *STA-MCA* superficial temporal artery to middle cerebral artery

Table S7 Thrombotic events and hypersensitivity by bleeding location^a

Bleeding location	Group A/A+B
Intracranial (<i>n</i>)	208
Thrombotic event	11 (5.3)
Cerebral infarction	5 (2.4)
Embolic stroke	4 (1.9)
Pulmonary embolism	1 (0.5)
Deep vein thrombosis	1 (0.5)
Hypersensitivity	1 (0.5)
Circulatory collapse	1 (0.5)
Gastrointestinal (<i>n</i>)	133
Thrombotic event	7 (5.3)
Cerebral infarction	2 (1.5)
Mesenteric arterial occlusion	1 (0.8)
Myocardial infarction	1 (0.8)
Deep vein thrombosis	1 (0.8)
Peripheral arterial occlusive disease	1 (0.8)
Arterial occlusive disease	1 (0.8)
Hypersensitivity	0
Intrapericardial (<i>n</i>)	106
Thrombotic event	0
Hypersensitivity	0
Retroperitoneal (<i>n</i>)	14
Thrombotic event	2 (14.3)
Cerebral infarction	1 (7.1)
Pulmonary embolism	1 (7.1)
Hypersensitivity	0
Intramuscular (<i>n</i>)	12
Thrombotic event	1 (8.3)
Pulmonary embolism	1 (8.3)
Hypersensitivity	0

Note: Data are presented as n (%)

^a Events that occurred in both the treatment and post-treatment periods are reported. Adverse events were coded using Version 24.1 of the Medical Dictionary for Regulatory Activities

Table S8 Thrombotic events and hypersensitivity by type of surgery/procedure^a

Type of surgery/procedure	Group B/A+B
Neurological surgery/procedure (<i>n</i>)	114
Thrombotic event	8 (7.0)
Cerebral infarction	6 (5.3)
Carotid artery occlusion	1 (0.9)
Arterial occlusive disease	1 (0.9)
Hypersensitivity	2 (1.8)
Circulatory collapse	1 (0.9)
Rash	1 (0.9)
Vascular surgery/procedure (<i>n</i>)	40
Thrombotic event	5 (12.5)
Cerebral infarction	2 (5.0)
Acute myocardial infarction	1 (2.5)
Arterial occlusive disease	1 (2.5)
Celiac artery occlusion	1 (2.5)
Hypersensitivity	0
Abdominal surgery/procedure (<i>n</i>)	38
Thrombotic event	0
Hypersensitivity	1 (2.6)
Circulatory collapse	1 (2.6)
Orthopedic surgery/procedure (<i>n</i>)	8
Thrombotic event	0
Hypersensitivity	1 (12.5)
Drug eruption	1 (12.5)
Respiratory surgery/procedure (<i>n</i>)	7
Thrombotic event	0
Hypersensitivity	0
Gynecological-urological surgery/procedure (<i>n</i>)	6
Thrombotic event	0
Hypersensitivity	0

Note: Data are presented as n (%)

^a Events that occurred in both the treatment and post-treatment periods are reported. Adverse events were coded using Version 24.1 of the Medical Dictionary for Regulatory Activities

Table S9 Blood product use

	Group A (N = 542)	Group B (N = 240)	Group A+B (N = 16)	Other (N = 6)	All (N = 804)
Blood products/transfusions					
Yes	261 (48.2)	81 (33.8)	7 (43.8)	2 (33.3)	351 (43.7)
No	273 (50.4)	154 (64.2)	9 (56.3)	4 (66.7)	440 (54.7)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Missing	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.3)
Fresh frozen plasma					
Yes	114 (21.0)	50 (20.8)	4 (25.0)	2 (33.3)	170 (21.1)
No	421 (77.7)	186 (77.5)	12 (75.0)	4 (66.7)	623 (77.5)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Packed red blood cells					
Yes	200 (36.9)	61 (25.4)	3 (18.8)	1 (16.7)	265 (33.0)
No	335 (61.8)	175 (72.9)	13 (81.3)	5 (83.3)	528 (65.7)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Platelets					
Yes	35 (6.5)	34 (14.2)	2 (12.5)	1 (16.7)	72 (9.0)
No	500 (92.3)	202 (84.2)	14 (87.5)	5 (83.3)	721 (89.7)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Cryoprecipitate					
Yes	1 (0.2)	0 (0.0)	1 (6.3)	0 (0.0)	2 (0.3)
No	534 (98.5)	236 (98.3)	15 (93.8)	6 (100.0)	791 (98.4)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Whole blood					
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	535 (98.7)	236 (98.3)	16 (100.0)	6 (100.0)	793 (98.6)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Prothrombin complex concentrate					
Yes	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
No	534 (98.5)	236 (98.3)	16 (100.0)	6 (100.0)	792 (98.5)

Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Factor VIIa					
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	535 (98.7)	236 (98.3)	16 (100.0)	6 (100.0)	793 (98.6)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Volume expanders					
Yes	4 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	5 (0.6)
No	531 (98.0)	235 (97.9)	16 (100.0)	6 (100.0)	788 (98.0)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Tranexamic acid					
Yes	65 (12.0)	17 (7.1)	2 (12.5)	0 (0.0)	84 (10.4)
No	470 (86.7)	219 (91.3)	14 (87.5)	6 (100.0)	709 (88.2)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Other					
Yes	37 (6.8)	20 (8.3)	1 (6.3)	0 (0.0)	58 (7.2)
No	498 (91.9)	216 (90.0)	15 (93.8)	6 (100.0)	735 (91.4)
Unknown	7 (1.3)	4 (1.7)	0 (0.0)	0 (0.0)	11 (1.4)
Dialysis					
Yes	12 (2.2)	8 (3.3)	0 (0.0)	1 (16.7)	21 (2.6)
No	527 (97.2)	230 (95.8)	16 (100.0)	5 (83.3)	778 (96.8)
Unknown	3 (0.6)	2 (0.8)	0 (0.0)	0 (0.0)	5 (0.6)

Note: Data are presented as *n* (%)

Table S10 Restart of anticoagulation therapy by bleeding location

Bleeding location	Group A/A+B
Intracranial (<i>n</i>)	208
Restarted any anticoagulant therapy, <i>n</i> (%)	111 (53.4)
Time to restart any anticoagulant therapy, days	
No. of patients	62
Median (IQR)	6.7 (3.5–11.8)
Gastrointestinal (<i>n</i>)	132
Restarted any anticoagulant therapy, <i>n</i> (%)	66 (50.0)
Time to restart any anticoagulant therapy, days	
No. of patients	46
Median (IQR)	4.8 (2.7–9.3)
Intrapericardial (<i>n</i>)	106
Restarted any anticoagulant therapy, <i>n</i> (%)	89 (84.0)
Time to restart any anticoagulant therapy, days	
No. of patients	63
Median (IQR)	1.7 (0.9–3.6)
Retroperitoneal (<i>n</i>)	14
Restarted any anticoagulant therapy, <i>n</i> (%)	7 (50.0)
Time to restart any anticoagulant therapy, days	
No. of patients	4
Median (IQR)	5.5 (1.7–12.9)
Intramuscular (<i>n</i>)	12
Restarted any anticoagulant therapy, <i>n</i> (%)	8 (66.7)
Time to restart any anticoagulant therapy, days	
No. of patients	4
Median (IQR)	5.9 (1.7–11.9)

IQR interquartile range

Table S11 Restart of anticoagulation therapy by type of surgery/procedure

Type of surgery/procedure	Group B/A+B
Neurological surgery/procedure (<i>n</i>)	112
Restarted any anticoagulant therapy, <i>n</i> (%)	80 (71.4)
Time to restart any anticoagulant therapy, days	
No. of patients	53
Median (IQR)	1.8 (1.2–6.7)
Vascular surgery/procedure (<i>n</i>)	40
Restarted any anticoagulant therapy, <i>n</i> (%)	31 (77.5)
Time to restart any anticoagulant therapy, days	
No. of patients	20
Median (IQR)	2.8 (1.5–4.1)
Abdominal surgery/procedure (<i>n</i>)	38
Restarted any anticoagulant therapy, <i>n</i> (%)	28 (73.7)
Time to restart any anticoagulant therapy, days	
No. of patients	21
Median (IQR)	3.4 (1.7–8.9)
Orthopedic surgery/procedure (<i>n</i>)	8
Restarted any anticoagulant therapy, <i>n</i> (%)	5 (62.5)
Time to restart any anticoagulant therapy, days	
No. of patients	3
Median (IQR)	0.9 (0.8–3.6)
Respiratory surgery/procedure (<i>n</i>)	7
Restarted any anticoagulant therapy, <i>n</i> (%)	6 (85.7)
Time to restart any anticoagulant therapy, days	
No. of patients	2
Median (IQR)	13.0 (12.1–13.9)
Gynecological-urological surgery/procedure (<i>n</i>)	6
Restarted any anticoagulant therapy, <i>n</i> (%)	3 (50.0)
Time to restart any anticoagulant therapy, days	
No. of patients	3
Median (IQR)	5.9 (5.9–36.9)

IQR interquartile range

Table S12 Patients who were re-exposed to idarucizumab

No.	No. of doses	Group	Reason for administration	Age	Sex	Dose (g)	Period until readministration of idarucizumab (days)	AEs of hypersensitivity
1	1	A	Gastrointestinal hemorrhage	88	M	5.0	6	No
	2	A	Gastrointestinal hemorrhage	88		5.0		No
2	1	B	McVay method, partial bowel resection	85	F	5.0	14	No
	2	A	Gastrointestinal hemorrhage	85		5.0		No
3	1	B	Perforation drainage	89	M	5.0	51	No
	2	B	Perforation drainage	89		5.0		No
4	1	B	Laparoscopic cholecystectomy	73	M	5.0	39	No
	2	B	ERCP	73		5.0		No
5	1	A	Gastrointestinal hemorrhage	89	M	5.0	8	No
	2	A	Gastrointestinal hemorrhage	89		5.0		No
6	1	A	Gastrointestinal hemorrhage	75	M	5.0	10	No
	2	A	Gastrointestinal hemorrhage	75		5.0		No
7	1	A	Gastrointestinal hemorrhage	63	F	5.0	532	No
	2	A	Intracranial hemorrhage, epidural hemorrhage	64		5.0		No

AE adverse event, ERCP endoscopic retrograde cholangiopancreatography, F female, M male